

Indian Journal of Medical and Paediatric Oncology

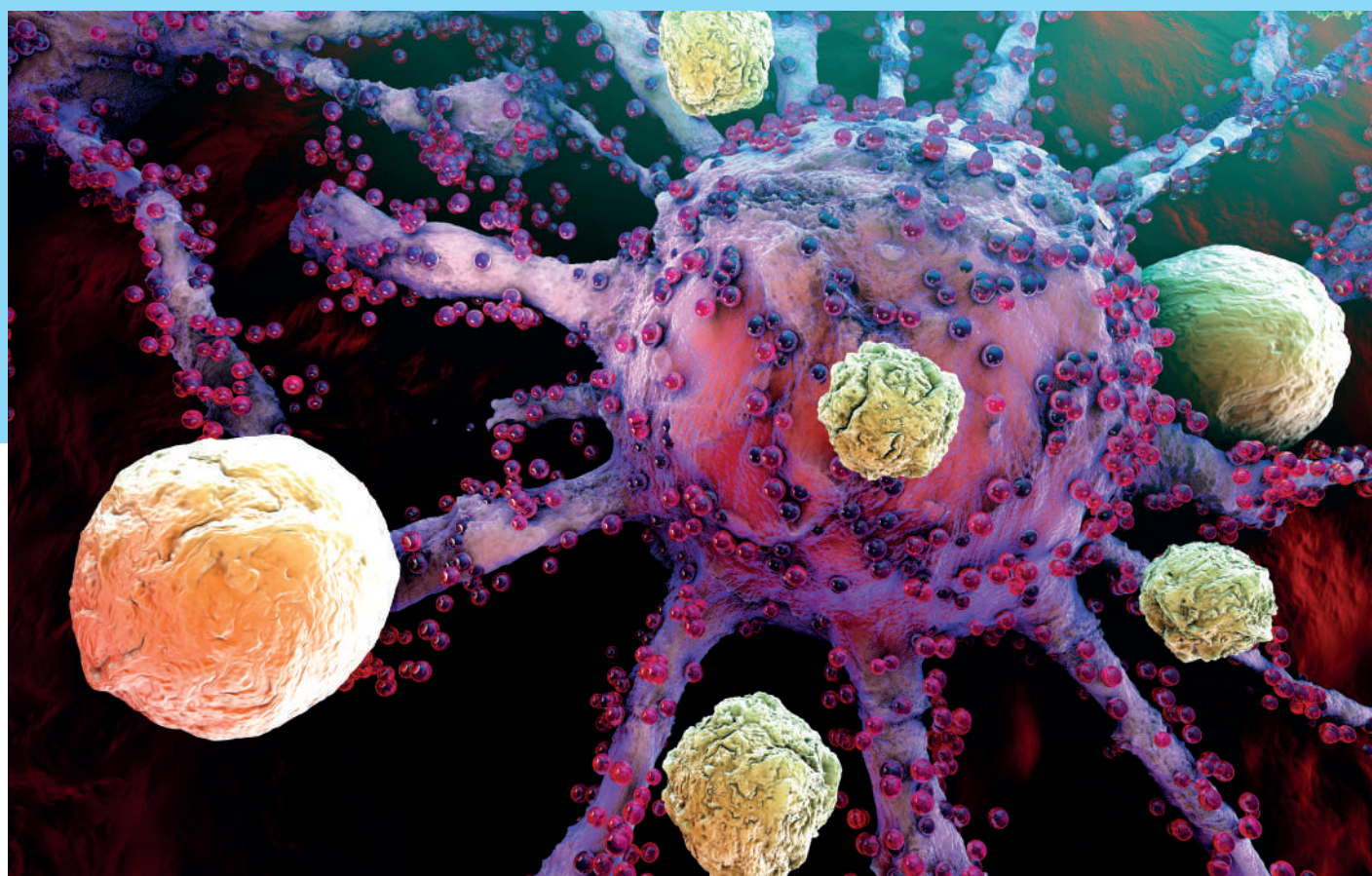
ISSN 0971-5851
eISSN 0975-2129

Number 2 • Volume 44 • Pages 149–286 • April 2023

Emeritus, Editor-in-Chief: Dr. Padmaj S. Kulkarni, MD, DM

Editor-in-Chief: Dr. Seema Gulia, MD, DM

Guest Issue Editor: Dr. Abhishek Mahajan, MD



Special Issue: Imaging Guidelines: Part—1



OPEN
ACCESS

CASPA
Scopus®



 Thieme

Indian Journal of Medical and Paediatric Oncology

Volume 44 • Number 2 • Pages 149–286 • April 2023

STAY TUNED

IJMPO

is coming up with
2 special issues in 2023



Hematopathology



Current Status of Psycho-Oncology in India

Indian Journal of Medical and Paediatric Oncology

Editor-in-Chief Emeritus

Dr. Padmaj S. Kulkarni, MD, DM
Department of Medical Oncology,
Deenanath Mangeshkar Hospital
and Research Center, Pune,
Maharashtra, India

Editor-in-Chief

Dr. Seema Gulia, MD, DM
Department of Medical Oncology,
Tata Memorial Centre, Mumbai,
Maharashtra, India

Guest Issue Editor

Dr. Abhishek Mahajan
Department of Radiodiagnosis,
The Clatterbridge Cancer Centre NHS
Foundation Trust, Liverpool, UK

Associate Guest Editor

Dr. Nivedita Chakrabarty
Tata Memorial hospital, India

Associate Guest Editor

Dr. Jinita Majitha
Tata Memorial Hospital, India

Immediate Past Editor-in-Chief

Raghunadharao Digumarti, MD, DM
Department of Medical Oncology,
KIMS Icon Hospital,
Vishakhapatnam, Andhra Pradesh, India

Joint Editors

Jyoti Bajpai, MD, DM
Department of Medical Oncology,
Tata Memorial Centre,
Mumbai, Maharashtra, India

TVSVGK Tilak, MD, DNB, DM, FRCP,
Department of Medical Oncology,
Armed Forces Medical College,
Pune, Maharashtra, India

Prashant Mehta, MD, DM
Department of Haematology/Medical
Oncology and BMT,
Amrita Institute of Medical Sciences,
Faridabad, Haryana, India

Editorial Advisor

Sudeep Gupta, MD, DM
Department of Medical Oncology,
Tata Memorial Centre,
Parel, Mumbai, Maharashtra, India

Section Editors

Bharatsinha Bhosale, MD, DM
Department of Medical Oncology,
Bombay Hospital Medical and
Research Institute,
Sunrise Oncology Day Care,
Fortis Hospital, Jaslok Hospital,
H N Reliance Hospital and Raheja Hospital,
Mumbai, Maharashtra, India

Kaustav Talapatra, MD
Department of Radiation Oncology,
Nanavati Max Super Speciality Hospital,
Mumbai, Maharashtra, India

TVSVGK Tilak, MD, DNB, DM, FRCP,
Department of Medical Oncology,
Armed Forces Medical College,
Pune, Maharashtra, India

Deepti Mutreja, MD, DNB
Department of Pathology,
Armed Forces Medical College,
Pune, Maharashtra, India

Pradeep Kulkarni, MD
Consultant in Palliative Care,
Private Practice,
Pune, Maharashtra, India

Reetu Jain, MD
Department of Medical Oncology,
Jaslok Hospital and Research Centre,
Mumbai, Maharashtra, India

Gaurav Prakash, MD, DM
Department of Clinical Haematology and
Medical Oncology,
Post Graduate Institute of Medical
Education & Research,
Chandigarh, Punjab, India

Deepak Dabkara, MD, DM
Department of Medical Oncology,
CHL Hospital,
Indore, Madhya Pradesh, India

Venkatraman Radhakrishnan, MD, DM
Department of Medical Oncology,
Cancer Institute (WIA),
Chennai, Tamil Nadu, India

Bivas Biswas, MD, DM
Department of Medical Oncology,
Tata Medical Center,
Kolkata, West Bengal, India

Priyanka Srivastava, MD, DNB
Department of Medical Oncology,
M.S. Patel Cancer Center, Shree Krishna
Hospital, Karamsad, Gujarat, India

Suresh Babu MC, MD, DM
Department of Medical Oncology,
Kidwai Memorial Institute of Oncology,
Bengaluru, Karnataka, India

Joydeep Ghosh, MD, DM

Department of Medical Oncology,
Tata Medical Centre,
Kolkata, West Bengal, India

Manikandan Dhanushkodi, MD, DM, DNB

Department of Medical Oncology,
Thoothukudi Cancer Care, Thenmani
Hospital,
Thoothukudi, Tamil Nadu, India

Prasanth Ganesan, MD, DM

Department of Medical Oncology,
Jawaharlal Institute of Postgraduate
Medical Education and Research,
Puducherry, India

Amol Patel, MD, DM

Department of Medical Oncology,
INHS Asvini, Mumbai, Maharashtra, India

Sujith Kumar Mullapally, MBBS, MD, DNB, DM

Department of Medical Oncology,
Apollo Proton Cancer Centre,
Chennai, Tamil Nadu, India

Venkata Pradeep Babu Koyyala, MD, DrNB Medical Oncology, ECMO, MNAMS

Department of Medical Oncology,
Tezpur Cancer Centre,
Assam Cancer Care Foundation,
Assam, India

Sandip Ganguly, MD, DM

Department of Medical Oncology,
Tata Medical Centre,
Kolkata, West Bengal, India

Sunil Kumar Polipalli, MSc, PhD

Department of Cytogeneticist,
Lok Nayak Hospital & Maulana
Azad Medical College, New Delhi, India

Anupriya Kaur, MD, DM

Department of Pediatrics (Genetics),
Post Graduate Institute of Medical
Education & Research,
Chandigarh, Punjab, India

Parathan Karunakaran, MD, DM

Department of Medical Oncology,
Cancer Institute WIA,
Chennai, Tamil Nadu, India

Smita Kayal, MD, DM

Department of Medical Oncology,
Jawaharlal Institute of Postgraduate
Medical Education & Research,
Puducherry, India

Akash Kumar, MD, DM

Department of Medical Oncology,
NCI-All India Institute of Medical Sciences,
New Delhi, India

Section Advisors

Hemant Malhotra, MD, FRCP, FRCP, FACP, ECMO, MNAMS, FUICC, FICP, FIMSA

Department of Medical Oncology,
Shri Ram Cancer Center, Mahatma Gandhi
Hospital,
Mahatma Gandhi University of Medical
Sciences & Technology,
Jaipur, Rajasthan, India

Shripad D. Banavali, MD, BC, BE

Department of Medical Oncology,
Tata Memorial Centre,
Mumbai, Maharashtra, India

K. Govind Babu, MD, DM

Department of Medical Oncology,
St. John's Medical College Hospital and
HCG Hospital, Bengaluru, Karnataka, India

Purvish M. Parikh, MD, DNB, FICP, PHD, ECMO, CPI

Department of Clinical Hematology,
Mahatma Gandhi University of Medical
Sciences and Technology,
Jaipur, Rajasthan, India

Manish Agarwal, MS, DNB

Department of Surgical Oncology
(Orthopaedics),
Nanavati Max Super Speciality Hospital,
Mumbai, Maharashtra, India

Rajiv Sarin, MD, FRCR

Department of Radiation Oncology and
Cancer Genetics Unit,
Tata Memorial Centre,
Mumbai, Maharashtra, India

Kumar Prabhash, MD, DM, ECMO, PDCR

Department of Medical Oncology,
Tata Memorial Centre,
Mumbai, Maharashtra, India

Chirag Jyotiker Desai, MD, DM (Oncology)

Hemato-Oncology Clinic,
Vedanta Institute, Ahmedabad,
Gujarat, India

Senthil J. Rajappa, MD, DNB, DM

Department of Medical Oncology,
Basavatarakam Indo American Cancer
Hospital and Research Center,
Hyderabad, Telangana, India

Rakesh Jalali, MD

Department of Radiation Oncology,
Apollo Proton Cancer Centre,
Chennai, Tamil Nadu, India

Nita Nair, DNB, MRCs (Ed), MCh

Department of Surgical Oncology,
Tata Memorial Centre,
Mumbai, Maharashtra, India

Special Content Editors

Parikshit Prayag, MD, ABIM, ABMS

Department of Transplant Infectious
Diseases,
Deenanath Mangeshkar Hospital and
Research Center,
Pune, Maharashtra, India

Sujit Nilegaonkar, MBBS, DRM, DNB, LLB

Department of Nuclear Medicine,
Deenanath Mangeshkar Hospital and
Research Center,
Pune, Maharashtra, India

Sanjay Desai, MD, DNB, MNAMS, FVIR, FRCR

Department of Radiation Oncology,
Deenanath Mangeshkar Hospital and
Research Center,
Pune, Maharashtra, India

Sampada Patwardhan, MBBS, MD

Department of Microbiology and Hospital
Infection Control
Deenanath Mangeshkar Hospital and
Research Center,
Pune, Maharashtra, India

Sunil Pasricha, MD, Fellowship (Oncopathology)

Department of Pathology,
Rajiv Gandhi Cancer Institute &
Research Centre,
New Delhi, India

Ankush Jajodia, MBBS, DMRD, DNB

Department of Radiology,
Rajiv Gandhi Cancer Institute and
Research Center, New Delhi, India

Web Editor

Prashant Mehta, MD, DM

Department of Haematology/Medical
Oncology and BMT,
Amrita Institute of Medical Sciences,
Faridabad, Haryana, India

Associate Editors

Mahesh M. Mandolkar, MD, DNB

Department of Pathology,
Deenanath Mangeshkar Hospital and
Research Center,
Pune, Maharashtra, India

Ravi Sekhar Patnaik, MBBS, MD, DM, ECMO

Department of Medical Oncology,
The Brunei Cancer Centre, Brunei,
Pantai Jerudong Specialist Centre, Brunei
UBD PAPRSB Institute of Health Sciences,
Brunei

Ravi Jaiswal, MD, MRCP, ECMO, DNB

Department of Medical Oncology,
BALCO MEDICAL Centre,
Raipur, Chhattisgarh, India

Hemant Dadhich, MD, DM

Department of Medical Oncology,
Sudha Hospital & Medical Research Centre,
Kota, Rajasthan, India
Cancer Research Centre,
Kota, Rajasthan, India

Urmi Sitanshu Sheth, MBBS, DNB

Medicine Fellowship of Royal College
of Pathology- Clinical Haematology,
Department of Medical Oncology,
Deenanath Mangeshkar Hospital and
Research Center,
Pune, Maharashtra, India

Vineet Govinda Gupta, MD, DM

Department of Medical Oncology,
Artemis Hospital,
Gurugram, Haryana, India

Zonal Editors

Bhaves B Parekh, MD, DM, MBA

Department of Medical Oncology,
Shalby Multispeciality Hospital,
Ahemdabad, Gujarat, India

Tarini Prasad Sahoo, MD, DM

Department of Medical Oncology,
Silverline Hospital,
Bhopal, Madhya Pradesh, India

Linu Abraham Jacob, MD, DM

Department of Medical Oncology,
Kidwai Memorial Institute of Oncology,
Bengaluru, Karnataka, India

Randeep Singh, MD, DM, ECMO, FCCP

Department of Medical Oncology,
Narayana Superspeciality Hospital,
Oncomed Clinic,
New Delhi, India

Deepak Dabkara, MD, DM

Department of Medical Oncology,
CHL Hospital,
Indore, Madhya Pradesh, India

Student Editor

Sneha Bothra Jain, MD, MRCPI, DNB, ECMO

Department of Medical Oncology,
Mittal Bhilai Hospital,
Bhilai, Chattisgarh, India

Sub-Editors

Amrita Prayag, MBBS, MS, Master of Science (Pharmacology)

Department of Clinical Research Unit,
Deenanath Mangeshkar Hospital and
Research Center,
Pune, Maharashtra, India

Vinayak Deshpande, MScs

Department of Statistics,
Sankhya Analytical Research Pvt. Ltd.,
Medicounts Lifesciences Pvt. Ltd.,
Mumbai, Maharashtra, India

Ganesh Divekar, MBBS, MBA

Department of Clinical Operations and
Medical Services,
SIRO Clinpharm Pvt. Ltd.,
Thane, Maharashtra, India

Domain Experts

Karthik Bommannan, MBBS, MD, DM

Department of Oncopathology,
Cancer Institute (WIA),
Chennai, Tamil Nadu, India

Aditi Dastane, MD

Department of Molecular Diagnostic Lab
and Cancer Genetics Clinic,
Deenanath Mangeshkar Hospital and
Research Center,
Pune, Maharashtra, India

Mahati Chittam, BA, MSc Health Psychology, PhD

Department of Psychology,
Indian Institute of Technology
Hyderabad, Hyderabad, Telangana,
India

Anand Raja, MS, MCh

Department of Surgical Oncology,
Cancer Institute (WIA),
Chennai, Tamil Nadu, India

Senior Editorial Assistant

Yogesh Kumbhavi, MBA, CHR, CTM, DHA, PMP, DCR

Department of Administration,
Tata Memorial Centre,
Mumbai, Maharashtra, India

Editorial Assistant

Devika Joshi, MSc (Biochemistry)

Pune, Maharashtra, India

National Advisory Board

Lalit Kumar, MD, DM

Department of Medical Oncology,
All India Institute of Medical Sciences,
New Delhi, India

Rajendra Badwe, MS

Department of Surgical Oncology,
Tata Memorial Centre,
Mumbai, Maharashtra, India

B. K. Smruti, MBBS, MD (Medicine)

Department of Medical Oncology,
Lilavati Hospital & Research Centre,
Bombay Hospital Institute of
Medical Sciences, Asian Cancer Institute,
Mumbai, Maharashtra, India

Narayanankutty Warriar, MD, DM

Department of Medical Oncology,
MVR Cancer Centre and Research Institute,
Kozhikode, Kerala, India

Lalit Mohan Sharma, MD

Department of Medical Oncology,
Sriram Cancer Centre, Mahatma Gandhi
Medical College and Hospital,
Jaipur, Rajasthan, India

Ajay Bapna, MD

Department of Medical Oncology,
Bhagwan Mahaveer Cancer Hospital &
Research Centre, Jaipur, Rajasthan, India

Surendra Beniwal, MD, DM

Department of Medical Oncology,
Acharya Tulsi Regional Cancer Treatment
and Research Centre,
Bikaner, Rajasthan, India

Rejiv Rajendranath, DM, DNB

Department of Medical Oncology,
Integrated Cancer Care Group, Apollo Cancer
Institute, Chennai, Tamil Nadu, India

Aju Mathew, MBBS, MD, MPhil, FACP

Department of Medical Oncology,
Trivandrum Institute of Palliative Sciences,
Thiruvananthapuram, Kerala, India

Amit Agarwal, MBBS, MD, DM, MRCP

Department of Medical Oncology,
Dr B L Kapur Hospital, New Delhi, India

Arun Seshachalam, MD, DNB, DM

Department of Medical and Pediatric Oncology,
Dr GVN Cancer Institute,
Trichy, Tamil Nadu, India

Sourav Kumar Mishra, MD, DM, ECMO

Department of Medical Oncology,
APOLLO Cancer Centre,
Bhubaneswar, Odisha, India

Vivek Agarwala, MD, DM, DNB, ECMO, MRCP

Department of Medical Oncology,
Narayana Superspeciality Hospital and Cancer
Institute, Kolkata, West Bengal, India

Vinayak V. Manka, MD, DM

Department of Medical Oncology,
Ramaiah Medical College and Hospitals,
Bengaluru, Karnataka, India

Soumya Surath Panda, MD, DM

Department of Medical Oncology,
IMS & SUM Hospital (SOA University),
Bhubaneswar, Odisha, India

Krishna Mohan Mallavarapu, DNB, DM

Department of Medical Oncology,
Basavataarakam Indo American Cancer
Hospital, Hyderabad, Telangana, India

Rushabh Kothari, MD, DM, ECMO

Department of Medical Oncology,
Narayana Multispeciality Hospital, Oncowin
Cancer Center Ahmedabad, Gujarat, India

Anita Ramesh (Chandra), DCH, MD, DNB, DM, MSc Oncology, MBA

Department of Medical Oncology,
Saveetha University,
Saveetha Medical College and Hospital,
Thandalam Saveetha Medical Centre,
Apollo Speciality Hospital and Kauvery
Hospital, Chennai, Tamil Nadu, India

Chetan Deshmukh, MD, DM

Department of Medical Oncology,
Deenanath Mangeshkar Hospital and
Research Centre, Jehangir Hospital,
Orchids Breast Health, Sassoon General
Hospital and B J Medical College,
Pune, Maharashtra, India

Kushal Gupta, MD, DM, ECMO

Post Graduate Institute of Medical
Education & Research,
Chandigarh, Punjab, India

Shweta Bansal, DNB, Fellowship PHO-BMT

Department of Pediatric Hemato-Oncology,
Sir HN Reliance Foundation Hospital,
Mumbai, Maharashtra, India

Raju Titus Chacko, MBBS, MD

Department of Medical Oncology, Christian
Medical College, Vellore, Tamil Nadu, India

Sandeep Batra, MD, DNB

Department of Medical Oncology,
Max Hospital, Gurgaon, Haryana, India

Maheboob Basade, MD

Department of Medical Oncology,
Jaslok Hospital, Mumbai, Maharashtra, India

Bharath Rangarajan, MD, DM, ECMO, PDCR

Department of Medical Oncology,
Kovai Medical Center and Hospital,
Coimbatore, Tamil Nadu, India

Prasad Narayanan, MD, DM, ECMO

Department of Medical Oncology,
Cytecancer Cancer Hospital,
Bengaluru, Karnataka, India

Nikhil Ghadyalpatil, MD, DNB, MNAMS, PDCR, DM, ECMO

Department of Medical Oncology,
Yashoda Cancer Institute,
Hyderabad, Telangana, India

Chandrashekhar V. Pethe, MD, DM

Department of Medical Oncology,
Hope Cancer Institute,
Nasik, Maharashtra, India
Pravara Institute Of Medical Sciences,
Loni, Maharashtra, India

M. Vamshi Krishna, MD, DM

Department of Medical Oncology,
Apollo Cancer Institute,
Hyderabad, Telangana, India

Prakash G. Chitalkar, MD, ECMO, PDCR

Department of Medical Oncology,
Sri Aurobindo Institute of Medical
Sciences, Indore,
Madhya Pradesh, India

Amish D. Vora, MD, DNB, DM

Department of Medical Oncology,
PSRI Hospital, New Delhi, India

International Advisory Board

Chassan Abou-Alfa, MD, MBA

Department of Medical Oncology,
Memorial Sloan Kettering Cancer Center,
New York, United States of America

Ajit Venniyoor, MD, DNB, DM

Department of Medical Oncology,
National Oncology Centre,
Royal Hospital Center,
Muscat, Oman

Paul Mitchell, MBBS, MD, PhD, FRANZCO, FRACS, FROphth, FAFPHM

Department of Clinical Ophthalmology &
Eye Health, Westmead
Clinical School, University of Sydney,
Sydney, Australia

Rakesh M. Jamkhandikar MD, FRCR, M Med

Department of Radiology, Armed Forces
Hospital, Muscat, Oman

Apar Kishor Ganti, MD, MS

Department of Internal Medicine, Division
of Oncology/Hematology,
University of Nebraska Medical Center,
Omaha, Nebraska

Amit Khot MBBS, MD, MRCP, FRCPath, FRACP

Department of Haematology and Bone
Marrow Transplant, Peter MacCallum
Cancer Centre, Melbourne, Australia

David James Kerr, CBE, MA, MD, DSc, FRCP, FRCGP, FMedSci

Department of Cancer Medicine,
University of Oxford, Oxford, England
Department of Oncology, Sichuan,
Xiamen and 2nd Military Universities,
China Honorary Professor,
Seoul National University,
Seoul, South Korea
Korea Nuffield Division of Clinical and
Laboratory Sciences,
Oxford, England

Soe Aung, MB, BS, DCH, FRACGP

Independent Medical Practice
Professional, Myanmar

Sanjeev Sewak, MBBS, FRACP

Department of Medical Oncology,
South Eastern Private Hospital,
Melbourne, Victoria, Australia

Ravindran Kanesvaran, MRCP, BSc, MD, FAMS

Department of Medical Oncology, National
Cancer Centre Singapore,
Duke-NUS Graduate Medical School,
Singapore

Fatima Cardoso, MD, MS

Director Breast Unit, Champalimaud
Clinical Center Lisbon, Portugal

Christopher Steer, MBBS, FRACP

Department of Medical Oncology,
Albury Wodonga Private Hospital,
New South Wales, Australia

Alex A. Adjei, MD, PhD

Department of Medical Oncology and
Pharmacology, Mayo Clinic,
Rochester, United States

Alexandru Eniu, MD, PhD

Department of Breast Tumors,
Cancer Institute "Ion Chiricuta",
Cluj-Napoca, Romania

Premal H. Thaker, MD, MS

Division of Gynecologic Oncology,
Washington University School of Medicine
Saint Louis, United States

Etienne Brain, MD, PhD

Department of Medical Oncology,
Institut Curie/Saint-Cloud, France

© 2023. The Author(s). All rights, including the rights of publication, distribution, and sales, as well as the right to translation, are reserved. No part of this work covered by the copyrights hereon may be reproduced or copied in any form or by any means — graphic, electronic, or mechanical, including photocopying, recording, taping, or information and retrieval systems — without written permission of the publisher.

Indian Journal of Medical and Paediatric Oncology is published 6 times a year in February, April, June, August, October, and December by Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India. Tel: +91-120-4556600, Fax: +91-120-455-6649.

Subscription: Open access journals available online for free at <http://open.thieme.com>.

Advertisers contact: Marketing, Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India, marketing@thieme.in.

Indian Journal of Medical and Paediatric Oncology is indexed in *Emerging Sources Citation Index* and SCOPUS. Thieme Medical Publishers is a member of the CrossRef initiative.

Editorial comments should be sent to journals@thieme.com. The content of this journal is available online at www.thieme-connect.com/products. Visit our Web site at www.thieme.com and the direct link to this journal at www.thieme.com/ijmpo.

Typesetting: Thomson Digital, Noida, India

Printing and Binding: Replika Press Pvt. Ltd.

Printed in India



CALLING MEDICAL PROFESSIONALS

to join one of the Emerging &
Fastest growing Healthcare Group

Manipur Cancer Control Mission



Karkinos Healthcare Private Limited, is a purpose driven technology-led oncology platform, focused on a mission to create "**cancer centers without walls**" with a primary aim of addressing the accessibility and affordability gaps in cancer care.

Karkinos Healthcare (NE) Pvt. Ltd. is partnering with Govt. of Manipur under Public Private Partnership (PPP) and coming up with:

- Comprehensive Cancer Care Hospital at Imphal.
- Under the Hub and Spoke model, Karkinos will establish Centres with Imphal Hospital and JNIMS as Hub and Health and Wellness centers (HWCs), Primary Healthcare Centers (PHCs) and District Hospitals (DHs) across the state as Spoke (as screening and diagnostic partner centers).

The State-of-the-Art Hospital will have the following treatment facilities:



Linac



Gamma Camera + SPECT



Major OT



Brachytherapy



PET CT



Endoscopy Suites



State of the art Onco Lab including
Molecular Oncology

We invite applications for the following positions at Imphal, Manipur:

- | | | |
|--|--|--|
| • MEDICAL ONCOLOGY
DM/ DNB Medical Oncology | • SURGICAL ONCOLOGY
M.Ch/ DNB Surgical Oncology | • RADIATION ONCOLOGY
MD/ DNB Radiation Oncology |
| • PREVENTIVE ONCOLOGY
MD General Medicine/
MD Community Medicine | • HEAD & NECK ONCOLOGY
MS/ DNB ENT; Fellowship in Oncology | • DIAGNOSTIC RADIOLOGY
MD/ DNB Radiodiagnosis |
| • GENERAL MEDICINE
MD/ DNB General Medicine with
experience in ICU management | • BREAST ONCOLOGY
MS/ DNB General Surgery; Fellowship
in Breast Oncology | • INTERVENTIONAL RADIOLOGY
MD/ DNB Radiodiagnosis; Fellowship
in Interventional Radiology |
| • MEDICAL OFFICER
MBBS | • GYNECOLOGICAL/ GI ONCOLOGY
DGO/ MD/ MS/ DNB OBGY; Fellowship in Oncology
MS/ DNB General Surgery; Fellowship in GI Oncology | |
- | | | |
|--|--|--|
| • MICROBIOLOGY
MD Microbiology | • HISTOPATHOLOGY
MD Pathology with domain expertise
in Histopathology | • BIOCHEMISTRY
MD Biochemistry |
|--|--|--|

INVESTORS



APPLY ONLINE AT: careers.khne@karkinos.in

www.karkinos.in



In HER2+, EBC and MBC

UJVIRA

Trastuzumab emtansine 20 mg/mL IV Inj.

— CHOICE SHE DESERVES —

More than 25 analytical assays done to ensure¹



- Similar ADC binding and MoA
- Highly comparable drug-antibody ratio of 3.5
- Highly similar drug distribution with no unmodified trastuzumab
- Highly similar level of purity ($\geq 98\%$) and size variant profile
- Up to 36 months of stability[#]

Proven biosimilarity¹

- Robust drug development program spanned over 7 years including a prospective, multicenter, randomized phase III clinical trial

Abridged Prescribing Information - UJVIRA™

PHARMACEUTICAL FORM AND COMPOSITION: UJVIRA™ Injection is lyophilized powder for concentrate for solution for infusion, 160 mg single dose lyophilized powder for infusion & 100 mg single dose lyophilized powder for infusion. **THERAPEUTIC INDICATION:** UJVIRA™ is indicated for the treatment of patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who had previously received trastuzumab and a taxane, separately or in combination. It is also indicated for the adjuvant treatment of patients with HER2-positive early breast cancer with residual invasive disease in the breast and/or lymph nodes after receiving neo-adjuvant taxane-based and HER2-targeted therapy. **POSLOGY AND METHOD OF ADMINISTRATION:** UJVIRA™ should be administered as an intravenous infusion. Do not administer as an intravenous push or bolus. It should be given at a dose of 3.6 mg / kg body weight with 3 weekly intervals (21 Day cycle). The first dose should be administered over 90 minutes intravenous infusion. Patients should be observed for fever and chills or other symptoms related to infusion. **SUBSEQUENT DOSES:** If the previous dose was well tolerated, the 3.6 mg / kg body weight dose can be administered over 30 minutes intravenous infusion. If dose reduction is done due to drug related adverse effect, then the dose should not be re-escalated in subsequent cycles. **CONTRAINDICATIONS:** There are no known contraindications to UJVIRA™. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE:** Infusion-related reactions and hypersensitivity characterized by one or more of the following symptoms have been reported with trastuzumab emtansine- flushing, chills, pyrexia, dyspnoea, hypotension, wheezing, bronchospasm and tachycardia. It is recommended to monitor serum transaminases and bilirubin prior to initiate the treatment with UJVIRA™ as hepatotoxicity risk is associated. UJVIRA™ administration may lead to reductions in left ventricular ejection fraction. Evaluate left ventricular function in all patients prior to and during treatment with UJVIRA™. It is recommended that platelet counts are monitored prior to each trastuzumab emtansine dose. Patients with significant thrombocytopenia should be monitored closely while on trastuzumab emtansine treatment. **PREGNANCY:** UJVIRA™ should be avoided during pregnancy as it can cause fetal harm when administered to a pregnant woman. **NURSING MOTHERS:** Women should discontinue breast-feeding prior to initiating treatment with trastuzumab emtansine. Women may begin breast-feeding 7 months after concluding treatment. **ADVERSE EVENTS:** Some reported adverse events included vomiting, pyrexia, cough, thrombocytopenia, aspartate aminotransferase increased and pain. **STORAGE:** Store vials between +2°C and +8°C. **RECONSTITUTED SOLUTION:** It is recommended to use immediately. If not used, it can be stored between +2°C and +8°C up to 24 hours. Do not freeze. Please refer to the full Prescribing Information before using UJVIRA™.

[#]Based on analysis from R&D batches

IV: Intravenous, ADC: Antibody-Drug Conjugate, MoA: Mode of Action HER2+: Human Epidermal growth factor Receptor 2 positive, EBC: Early Breast Cancer, MBC: Metastatic Breast Cancer, Reference: 1. Data on file.

Zydus Lifesciences Ltd.,

Zydus Corporate Park, 4th Floor, C Wing, Scheme No. 63, Survey No. 536, Near Vaishnodevi Circle, Khoraj (Gandhinagar),
Ahmedabad - 382481, Gujarat.

zydus
Dedicated To Life

BIO/ING/04/06/2021/06

Indian Journal of Medical and Paediatric Oncology

Editor's Note

- 149 Editor's Note
Abhishek Mahajan

Review Articles

- 150 Imaging Recommendations for Diagnosis, Staging, and Management of Oral Cancer
Abhishek Mahajan, Ujjwal Agarwal, Nandakumar PG, Richa Vaish, Shreya Shukla, Arpita Sahu, Ashu Seith Bhalla, Vasundhara Patil, Suman Kumar Ankathi, Sarbani Ghosh Laskar, Vijay Patil, Vanita Noronha, Nandini Menon, Kumar Prabhash, Diva Shah, Asawari Patil, Ankita Ahuja, Pankaj Chaturvedi, Prathamesh S. Pai, A K Dcruz, MS
- 159 Imaging Recommendations for Diagnosis, Staging, and Management of Cancer of the Thyroid, Parathyroid, and Salivary Glands
Abhishek Mahajan, Shreya Shukla, Suman Kumar Ankathi, Anuradha Shukla, Richa Vaish, Shubham Suryavanshi, Ujjwal Agarwal, Vasundhara Patil, Arpita Sahu, Shubham Padashetty, Sarbani Ghosh Laskar, Vijay Patil, Vanita Noronha, Nandini Menon, Kumar Prabhash, Asawari Patil, Pankaj Chaturvedi, Prathamesh S. Pai, Swapnil Rane, Munita Bal, A. K. Dcruz
- 175 Imaging Recommendations for Diagnosis, Staging, and Management of Nasopharynx Carcinoma
Chirag Kamal Ahuja, Vivek Agarwal, Chirag Jain, Sameer Vyas, Jyoti Kumar, Paramjeet Singh
- 181 Imaging Recommendations for Diagnosis, Staging, and Management of Lung Cancer
Aparna Irodi, Ashu Seith Bhalla, Leena Robinson Vimala, Taruna Yadav, Subathra Adithan, Harish Bhujade, Parang Sanghavi, Alok Kale, Mandeep Garg, Abhishek Mahajan, Yvette Kirubha Jaykar David Livingstone, Sudha Kiran Das, Geethi M. H., Balukrishna Sasidharan, Balamugesh Thangakunam, Simon Pavamani, Rajesh Isiah, Anjana Joel, Tameem Ahmad Bhat
- 194 Imaging Recommendations for Diagnosis, Staging, and Management of Carcinoma of Unknown Origin (Lymph Node, Pulmonary, Liver, Skeletal, and Brain) with Emphasis on the Current Position of PET-CT in Carcinoma of Unknown Origin (CUP)
Sarvesh Loharkar, Sandip Basu
- 207 Imaging Recommendations for Diagnosis, Staging, and Management of Breast Cancer
Meenakshi Thakur, Suma Chakrabarthi, Purvi Haria, Smriti Hari, Palak Popat, Aparna Katdare, Kunal Gala, Sonal Chouhan, Nita Nair, Jyoti Bajpai, Rima Pathak, Tanuja Shet, Gauravi Mishra, Sneha Shah, Shalaka Joshi, Soujanya Mynalli, Anne Srikanth, Suyash Kulkarni
- 229 Imaging Recommendations for Diagnosis, Staging, and Management of Esophageal Cancer
Nivedita Chakrabarty, Abhishek Mahajan, Prachi Patil, Manoranjan Chowhan, Naveen Munmmudi, Devayani Niyogi, Deepak Dabkara, Suryaveer Singh, Ajaykumar Singh, Sanjana Devarmani, Varun Singh Dhull, Kumar Prabhash



Thieme

Delhi • Stuttgart • New York • Rio de Janeiro

Copyright © 2023 Thieme Medical and Scientific Publishers Private Limited
A - 12, Second Floor, Sector - 2, Noida - 201 301,
Uttar Pradesh, India
Tel: +91-120-4556600

online www.thieme-connect.com/products

- 241 Imaging Recommendations for Diagnosis, Staging, and Management of Hepatic and Biliary Tract Cancer
Argha Chatterjee, Sumit Mukhopadhyay, Priya Ghosh, Diva Shah, Anisha Gehani, Akshay Baheti, Bharat Gupta, Aditi Chandra, Arvind K. Chaturvedi, Jeevitesh Khoda, Anurima Patra, Dayananda Lingegowda, Saugata Sen
- 251 Imaging Recommendations for Diagnosis, Staging, and Management of Peritoneal Malignancies
Amit Kumar Choudhari, Anuradha Chandramohan, Nitin Shetty, Suyash Kulkarni, Shailesh Shrikhande, Avanish Saklani, Rohin Mittal, Kedar Deodhar, Subhash Yadav, Reena Engineer, Vikas Ostwal, Prachi Patil
- 257 Imaging Recommendations for Diagnosis, Staging, and Management of Bone Tumors
Amit Janu, Anurima Patra, Mahesh Kumar, Ashish Gulia, Suyash Kulkarni, Nitin Sudhakar Shetty, Ajay Puri, Prakash Nayak, Manish Pruthi
- 261 Imaging Recommendations for Diagnosis, Staging, and Management of Soft Tissue Sarcomas
Kenneth Lupton, Manjusha Salins, Bill Pass, Raj Negi, Harun Gupta
- 268 Imaging Recommendations for Diagnosis, Staging, and Management of Bladder and Urethral Malignancies
Jinita Majithia, Gagan Prakash, MH Thakur, Palak Popat, Nilesh Sable, Aparna Katdare, Suyash Kulkarni, Daksh Chandra
- 275 Imaging Recommendations for Diagnosis, Staging, and Management of Testicular Cancer
Aparna Katdare, Palak Popat, Rachel Sequeira, Nilesh Sable, Kunal Gala, Daksh Chandra, Archi Agrawal, Gagan Prakash, Vedang Murthy, Santosh Menon, Amit Joshi, Ajaykumar Singh, Suyash Kulkarni
- 281 Imaging Recommendations for Diagnosis, Staging, and Management of Penile Cancer
Rachel Sequeira, Aparna Katdare, Palak Popat, Nilesh Sable, Kunal Gala, Daksh Chandra, Archi Agrawal, Gagan Prakash, Vedang Murthy, Santosh Menon, Amit Joshi, Ajaykumar Singh, Suyash Kulkarni

Cover design: © Thieme

Cover image source: © Spectral-Design/stock.adobe.com

Some of the product names, patents, and registered designs referred to in this publication are in fact registered trade marks or proprietary names even though specific reference to this fact is not always made in the text. Therefore, the appearance of a name without designation as proprietary is not to be construed as a representation by the Publisher that it is in the public domain.

All rights, including the rights of publication, distribution, and sales, as well as the right to translation, are reserved. No part of this work covered by the copyright hereon may be reproduced or copied in any form or by any means – graphic, electronic, or mechanical, including photocopying, recording, taping, or information and retrieval systems – without written permission of the Publisher.

Important Note: Medical knowledge is ever-changing. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy may be required. The authors and editors of the material herein have consulted sources believed to be reliable in their efforts to provide information that is complete and in accord with the standards accepted at the time of publication. However, in view of the possibility of human error by the authors, editors, or publisher

of the work herein, or changes in medical knowledge, neither the authors, editors, or publisher, nor any other party who has been involved in the preparation of this work, warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from use of such information. Because of rapid advances in the medical sciences, independent verification of diagnoses and drug dosages should be made. Readers are encouraged to confirm the information contained herein with other sources. For example, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this publication is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this journal does not constitute a guarantee or endorsement of the quality or value of such product or of claims made by its manufacturer.

IMFINZI

has shown significant
Overall Survival Benefits
in stage III NSCLC* & ES-SCLC**

IMFINZI™
durvalumab
Injection for Intravenous Use 50 mg/mL

IN UNRESECTABLE STAGE III NSCLC

The **1st** and only
approved immunotherapy
to provide remarkable
5-year OS of
42.9%¹

A Remarkable
advancement
in curative
intent setting

Sustained and durable
PFS of
33.1% at
5 years¹

In Extensive stage SCLC

The **1st** and only
approved immunotherapy
to demonstrate sustained
and durable **3-year OS**
of **17.6%** in
ES-SCLC²

3 X
patients were alive at
3 years
with Durvalumab+
EP vs EP alone²

Imfinzi + Etoposide-Platinum
combination has promising
Median Overall Survival,
safety and efficacy **regard-**
less of baseline brain
metastases.²



***This Image is for display and doesn't correlate the original product for representation.

API Details

<https://az.box.com/s/94qerykvp6c7uadcm7k9iv47phj0kym>

Reference:

1. Spigel, David R., et al. "Five-year survival outcomes from the PACIFIC trial: Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer." *Journal of Clinical Oncology* 40.12 (2022): 1301.
2. Paz-Ares, L., et al. "Durvalumab, with or without Tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN." *ESMO open* 7.2 (2022): 100408.

Disclaimer: Intended for use by Healthcare Practitioner

IMFINZITM is a trademark of the AstraZeneca group of companies. © 2017 AstraZeneca. All rights reserved. TM: Trademark Applied For

*Unresectable Stage-III NSCLC post CRT **In 1st line Extensive stage SCLC in combination with CT



Approval ID: IN-11105 | Approved Date: 07/02/2023 | Expiry Date: 07/02/2025

AstraZeneca Pharma India Limited, Block N1, 12th Floor, Manyata Embassy Business park, Rachenahalli, Ring Road, Bangalore - 560045 WWW.astrazenecaindia.com



Submit your manuscripts

The Indian Journal of Medical and Paediatric Oncology is inviting potential authors to submit their engaging content

Official journal of Indian Society of Medical and Paediatric Oncology

Scopus®



OPEN
ACCESS

CASPA

Scopus®

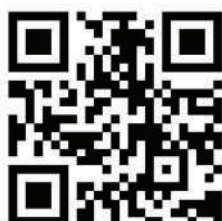


Thieme



Top Reasons to Publish in IJMPO

- 1 | Fast and fair double-blinded peer review
- 2 | High quality editorial services
- 3 | Abstracted and indexed in Emerging Sources Citation Index/Web of Science, SCOPUS, and more...
- 4 | Easy and free global online access which gives maximum exposure, readership and citations.



Submit your
articles here

Scan the QR Code



Thieme

Editor's Note

Abhishek Mahajan¹

¹ Department of Radiodiagnosis, The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, United Kingdom

Ind J Med Paediatr Oncol 2023;44:149.

Address for correspondence Abhishek Mahajan, MD, Fellowship in Cancer Imaging, MRes (KCL, London), FRCR (UK), Department of Radiodiagnosis, The Clatterbridge Cancer Centre NHS Foundation Trust, Pembroke Place Liverpool, Liverpool L7 8YA, United Kingdom (e-mail: drabhishek.mahajan@yahoo.in).

The *Indian Journal of Medical and Paediatric Oncology* (IJMPO) is an international journal published by Thieme Medical Publishers on behalf of the Indian Society of Medical and Paediatric Oncology (ISMPO). Over more than four decades, the journal has strived to contribute to the academic discourse surrounding all aspects of oncology.

This year, under the leadership of Guest Editor (of the current issue) Dr. Abhishek Mahajan and Editor-in-Chief Dr. Padmaj Kulkarni, IJMPO strives to continue its mission of advancing the knowledge and understanding of oncology. The idea of having an exclusive edition dedicated to imaging guidelines in oncology was conceived by Dr. Abhishek Mahajan, Consultant Radiologist at Clatterbridge Cancer Centre, Liverpool, United Kingdom, and ex-Consultant Radiologist at Tata Memorial Hospital, Mumbai, Maharashtra, India, having more than 15 years of experience in oncoimaging, with the aim of providing a comprehensive one-stop reference guide to the clinicians and radiologists alike on practical aspects of site-specific imaging in oncology. We express personal gratitude to associate editors Dr. Nivedita Chakrabarty and Dr. Jinita Majithia for the effort and extra time you both have contributed toward this special edition.

This special issue offers themed content with an important focus on imaging. This themed issue covers "Imaging Guidelines in Oncology" from authoritative and recognized oncology groups and societies, aimed at providing scientific

statements on various tumors relevant to diagnosis, staging, and management. The thought behind this composite theme was to have a concise and simplified overview of various cancers and what a radiologist must know about the imaging in cancer. Our aim is to present a diverse selection of stimulating articles.

The authors have devoted countless hours in trying to bring forward well-researched and eloquent articles. Each author has delved into the details of site-specific cancers with focus on global and national epidemiology, the risk factor and etiopathogenesis as well as clinical and diagnostic workup. Elaborate discussions on the imaging guidelines regarding screening, diagnosis, staging and surveillance, and follow-up have been presented. A summary of recommendations and synoptic reporting templates have been provided at the end of each article so as to follow standard guidelines throughout. The content has been double-blind peer reviewed by experts in the field.

It is the undying support of our esteemed authors, round-the-clock hard work of the editorial staff, and the keen interest of the readers that have helped IJMPO to successfully contribute to this issue. And it is this continued involvement and contribution by all that will help us strive better each time for our medical fraternity.

Conflict of Interest

None declared.

DOI <https://doi.org/10.1055/s-0043-1766139>.
ISSN 0971-5851.

© 2023. The Author(s).
This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)
Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Imaging Recommendations for Diagnosis, Staging, and Management of Oral Cancer

Abhishek Mahajan¹ Ujjwal Agarwal² Nandakumar PG²^{ID} Richa Vaish³^{ID} Shreya Shukla²^{ID}
 Arpita Sahu⁴ Ashu Seith Bhalla⁵ Vasundhara Patil⁴ Suman Kumar Ankathi⁴ Sarbani Ghosh Laskar⁶^{ID}
 Vijay Patil⁷ Vanita Noronha⁷ Nandini Menon⁷^{ID} Kumar Prabhash⁷ Diva Shah⁸ Asawari Patil⁹^{ID}
 Ankita Ahuja¹⁰ Pankaj Chaturvedi³ Prathamesh S. Pai³ A K Dcruz, MS¹¹

¹ Department of Radiodiagnosis, The Clatterbridge Cancer Centre, Liverpool, United Kingdom

² Department of Radiodiagnosis, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, Maharashtra, India

³ Department of Head and Neck Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, Maharashtra, India

⁴ Department of Radiodiagnosis and Imaging, Tata Memorial Hospital, Homi Bhabha National Institute, Parel, Mumbai, Maharashtra, India

⁵ Department of Radiodiagnosis and Interventional Radiology, All India Institute of Medical Sciences, New Delhi, India

⁶ Department of Radiation Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, Maharashtra, India

⁷ Department of Medical Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, Maharashtra, India

Address for correspondence Abhishek Mahajan, MD, Fellowship in Cancer Imaging, MRes (KCL, London), FRCR (UK), Department of Radiodiagnosis, The Clatterbridge Cancer Centre NHS Foundation Trust, Pembroke Place Liverpool, Liverpool L7 8YA, United Kingdom (e-mail: drabhishek.mahajan@yahoo.in).

⁸ Department of Radiodiagnosis, HCG Cancer Centre, Ahmedabad, Gujarat, India

⁹ Department of Pathology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, Maharashtra, India

¹⁰ Department of Radiodiagnosis, Innovision Imaging, Mumbai, Maharashtra, India

¹¹ Apollo Hospitals, Belapur, Mumbai, India

Ind J Med Paediatr Oncol 2023;44:150–158.

Abstract

Oral cavity cancers contribute to a majority of cancers in India. Clinical examination alone cannot determine the deeper extent of the disease; therefore, need for cross-sectional imaging including computed tomography and magnetic resonance imaging becomes indispensable for pre-treatment evaluation to decide optimal plan of management. Oral cavity squamous cell cancers (OSCC) can be treated with surgery alone, whereas deep muscle, neurovascular, osseous, or nodal involvement on imaging suggests advanced disease that requires a combination of surgery, radiation, and/or chemotherapy. Because of the complex anatomy of the oral cavity and its surrounding structures, imaging is crucial for locoregional staging and early detection of distant metastases. Imaging plays indispensable role not only in diagnosis but also in planning the management. An optimal guideline paper for developing countries like India is lacking that not only helps standardize the management but will also assist oncologists make reasonable decisions and reduce the unnecessary imaging. This imaging guideline paper will discuss the optimal imaging in diagnosis and management OSCC for Indian subcontinent.

Keywords

- computed tomography
- guidelines
- magnetic resonance imaging
- oral cancer
- imaging

The article is not under consideration for publication elsewhere. Each author participated sufficiently for the work to be submitted. Publication is approved by all authors.

DOI <https://doi.org/10.1055/s-0042-1760314>.
 ISSN 0971-5851.

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)
 Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Head and neck cancers are the sixth most common cancer worldwide, with oral cavity squamous cell carcinoma (OSCC) being the most common and having the high morbidity and fatality rates.¹ For proper management, timely diagnosis and correct tumor staging are vital. Radiologic imaging is routinely used to assess the disease extension in supplementation with clinical examination. The most common histology is SCC, which accounts for the vast majority of oral cancers.² The symptoms of malignancy, the methods by which it spreads, and the prognosis are all highly variable, and are largely determined by the anatomic region where the initial tumor develops. For diagnostic assessment and appropriate treatment planning, it is of utmost importance to understand the oral anatomy and most typical pathways of dissemination of OSCC.³

Risk Factors and Etiopathogenesis

Risk factors for OSCC include quid chewing, poor oral hygiene, tobacco, alcohol consumption, and sharp tooth/denture.^{4,5} The World Health Organization describes the oral potentially malignant disorders that may transform into carcinoma later in life. These include leukoplakia, erythroplakia, erythroleukoplakia, oral submucous fibrosis, smokeless tobacco keratosis, lichen planus, and discoid lupus erythematosus.⁶ The morphological spectrum of oral potentially malignant disorders varies from acanthosis, hyperkeratosis, to dysplasia and carcinoma in situ.⁷

Epidemiology and Clinical Presentation in India and Global

Oral cancer constitutes sixth most frequent malignancies in Asia with approximately 274,300 new cases occurring each year.⁸ Age standardized incidence rate (ASIR) in Sri Lanka, Taiwan, Bangladesh, India, and Pakistan, is far more than the world ASIR (10.5 for men and 4.02 for women). In India, ASIR of 12.7/100,000 in men (Bombay) and 10.0/100,000 in women (Bangalore) has been reported.⁹ The plausible reason is the rampant use of chewed tobacco and common custom of chewing beetle quid containing areca nut along with slaked lime. Patients usually present with nonhealing ulcer, pain, bleeding, poorly fitting dentures, speech alteration, and neck lymph nodes.¹⁰ Examination includes inspection of the oral cavity along with palpation of the lesion under anesthesia to assess the submucosal extent of disease. The neck is thoroughly palpated to detect lymph node metastasis that is large in size, hard in consistency, and may be fixed to surrounding structures.¹¹ The upper aerodigestive tract should be examined for any synchronous second primary. Biopsy of tumor and/or lymph nodes is done to establish the diagnosis and further workup is planned after histological confirmation.

Imaging Referral Guidelines

The American Joint Committee on Cancer/International Union Against Cancer staging method is a tool that allows

physicians all over the globe to stage cancer before any therapy, after surgical resection, and at the time of recurrence.¹² Staging divides patients into prognostic groups, making it easy to choose the best treatment strategy, schedule treatment, and predict prognosis based on the stage of the disease. Updates in the 8th edition are as shown in ►Table 1.¹³

Clinical/Diagnostic Workup Excluding Imaging

Oral cavity lesions tend to present with classical history of long-standing nonhealing ulcers associated with pain and are easily accessible to visual and bimanual examinations; hence majority of the oral cavity malignancies are diagnosed clinically.¹⁴ Examination also permits evaluation of the local extent of the tumor. Apart from physical examination, endoscopic examination also plays an important in deep-seated lesions or lesion involving the larynx or pharynx. Punch biopsies of the oral cavity lesions or ulcers can be performed per orally in most of the cases.¹⁵ Majority of these tumors are SCCs. There is no defined role of tumor markers in head and neck malignancy apart from the human papilloma virus and Epstein-Barr virus statuses.¹⁶

Imaging Guidelines

While local examination provides an idea of the local extent, evaluation of detailed extension of the tumor and presence of bony erosion, perineural spread, nodal and distant metastases require cross-sectional examination.¹⁷ All the above findings have implications on the treatment and outcome of the patient. The various subsites of oral cavity include lips, buccal mucosa, oral or anterior two thirds of tongue, upper and lower alveolus with gingiva, retromolar trigone (RMT), floor of mouth (FOM), and hard palate. The various diagnostic modalities employed are ultrasonography (USG), contrast-enhanced computed tomography (CECT), contrast-enhanced magnetic resonance imaging (CE-MRI), and fluorodeoxyglucose positron emission tomography (FDG-PET). Imaging-guided interventions like biopsy and fine-needle aspiration cytology (FNAC) are also essential for tissue diagnosis in deep-seated or recurrent lesions. We will further discuss these modalities and their relevance below. The preferred imaging modality in various settings, CT and MRI protocols, are summarized in ►Tables 2 to 4.^{18,19}

Screening

There are no studies supporting the benefit of imaging-based screening tests in the diagnosis of oral cavity cancers. Since oral cavity is easily accessed by visual examination, the need for imaging screening is not defined till date. However, as there are high rates of malignant transformation with the premalignant lesion like leukoplakia, erythroplakia, oral submucous fibrosis, and lichen planus, these lesions are kept on clinical follow-up and biopsy can be performed to detect malignant transformation at an earlier stage.²⁰

Table 1 Difference in 7th and 8th edition of American Joint Committee on Cancer clinical staging for oral cancers¹³

	Seventh edition	Eighth edition
T1	Tumor < 2 cm	Tumor ≤ 2 cm, ≤ 5 mm depth of invasion
T2	Tumor 2–4 cm	Tumor ≤ 2 cm, >5 mm and ≥ 10 mm depth of invasion or tumor > 2 cm but ≤ 4 cm and depth of invasion ≤ 10 mm
T3	Tumor > 4 cm	Tumor > 4 cm and depth of invasion < 10 mm or tumor <4cm and depth of invasion >10 mm
T4a	Moderately advanced local disease Lip: tumor invades through the cortical bone or involves inferior alveolar nerve, floor of mouth, or skin of face Oral cavity: tumor involves adjacent structures such as cortical bone of maxilla or mandible, maxillary sinus or skin of face, or extrinsic muscles of tongue	Extrinsic muscles of tongue removed, included extensive tumors with bilateral tongue involvement or tumor > 4cm and depth of invasion > 10mm
T4b	Very advanced local disease; tumor invades masticator space, pterygoid plates, skull base and/or encases the internal carotid artery	No change
N1	Metastases to single lymph node, 3 cm or less in greatest dimension	Same, except node must be extranodal extension negative
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension	Same, except node must be extranodal extension negative
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension	Same, except nodes must be extranodal extension negative
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension	Same, except nodes must be extranodal extension negative
N3	Metastases to node > 6 cm	Subdivided into 3a: Same as N3 before, but extranodal extension negative 3b: any node with extranodal extension

Table 2 Preferred imaging modality in various setting

Imaging setting	Preferred imaging modality
Screening	CECT or CE-MRI ^a (no proven role)
Diagnosis:	
a) Diagnostic	For gingivobuccal cancer—CECT PNS and thorax For tongue carcinoma—CE-MRI ^a plus NCCT thorax FDG-PET-CT
b) Intervention	CT-guided biopsy/FNAC for deep-seated lesions USG-guided biopsy/ FNAC for nodes and superficially seated lesions
Management	
a) Post-surgery	CECT/ CE-MRI ^a (OR) FDG-PET-CT
b) Neoadjuvant, adjuvant or palliative chemotherapy	CECT/CE-MRI ^a (OR) FDG-PET-CT
Follow-up	FDG-PET-CT (OR) CECT/CE-MRI ^a

Abbreviations: CECT, contrast-enhanced computed tomography; CE-MRI, contrast-enhanced magnetic resonance imaging; FDG-PET-CT, fluorodeoxyglucose positron emission tomography-computed tomography; FNAC, fine-needle aspiration cytology; NCCT, noncontrast CT, PNS, para nasal sinus; USG, ultrasonography.

^aCECT—for majority of oral cavity subsites, CE-MRI—oral tongue and floor of mouth.

Table 3 CT oral cavity imaging protocol

Parameter	Characteristics
Scanner type	Helical scanner
Slice thickness	0.75 mm
Intravenous contrast	Iodine-based contrast agent at 3 to 5mL/sec flow rate (total volume—80 mL)
Maneuvers	Puffed-cheek technique
Acquisition time	40–50 seconds
Reconstruction	Bone algorithm reconstruction Multiplanar reconstruction in coronal plane or parasagittal plane
Anatomical coverage	Pituitary fossa to arch of aorta. Include thorax and upper abdomen in venous phase—staging

Abbreviation: CT, computed tomography.

Diagnosis

Imaging plays a key role in the disease assessment of oral cavity cancer. The current modality of choice for primary diagnosis of oral cavity lesions (excluding oral tongue and hard palate) is CECT head and neck with puffed cheek technique and bone algorithm reconstruction. For oral tongue and FOM lesions, MRI head and neck is the preferred modality. FDG-PET-CT can also be employed for diagnosis in appropriate settings.¹⁸ The role, advantage, and drawback of each modality have been briefly explained below.^{21,22}

Table 4 MRI oral cavity imaging protocol

Sequence	Plane of acquisition	Slice thickness
T1W FS-FSE	Coronal	4 mm
STIR	Coronal	4 mm
T2W FS-FSE	Sagittal	4 mm
T2W FS-FSE	Axial	4 mm
T1W FS-FSE	Axial	4 mm
DWI	Axial	4 mm
Postgadolinium contrast T1W FS-FSE	Axial, coronal, and sagittal planes	4 mm

Abbreviation: DWI, diffusion-weighted imaging; FS-FSE, fat-saturated fast spin echo; MRI, magnetic resonance imaging; STIR, short tau inversion recovery; T1W, T1-weighted.

Oral cavity: CECT head and neck with puffed cheek technique enables detailed evaluation of the oral cavity. Puffed cheek technique improves the contour and margin delineation as compared to the conventional CECT.²³ Also, this technique separates the mucosal surface from alveolus enabling better assessment of subtle lesions that may otherwise be missed in routine imaging. With puffed cheek technique structures like buccal mucosa, gingival, buccal vestibule and RMT are better delineated (►Fig. 1).²⁴ Bone algorithm reconstruction is routinely performed in all oral cavity malignancies to assess for bony erosion. Patterns of bony erosion affect the surgical technique; hence, it is mandatory to perform and report the bony erosion (►Fig. 2 and ►Supplementary Table S1).²⁵ CECT enables identification of the depth of invasion (DOI), local and regional extent of the tumor, presence of bony erosion, and perineural spread. Surgical resection is possible in disease with involvement of low infratemporal fossa (ITF) or retroantral ITF and superficial or deep cortical bony erosion.^{18,26} Detailed explanation of the all the above entities is beyond the scope of this article. CECT has its own disadvantages like less soft tissue resolution compared to CE-

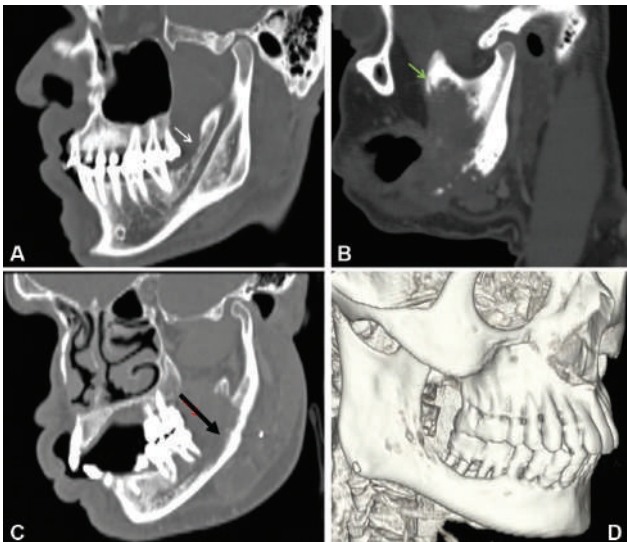


Fig. 2 (A) Oblique sagittal reformatted images showing superficial cortical erosion (white arrow) of the mandible, (B) erosion of the coronoid process of the mandible (Green arrow), (C) cortical and medullary erosion with involvement of inferior alveolar canal (black arrow) of mandible. (D) Shaded surface display image shows erosion of mandible and important in planning surgical reconstruction.

MRI, which can be used as a problem-solving tool in detecting subtle lesions, or for demonstrating perineural or intracranial spread. MRI is not an ideal initial modality for oral cavity imaging as it is time consuming and can have motion artefacts.

Tongue: CE-MRI has better soft tissue resolution and hence it is the modality of choice for evaluation of tongue. MRI better defines the DOI, muscles of tongue involvement, midline extension, FOM, neurovascular structure, and posterior third tongue involvement.²⁷ However, for the evaluation of mandibular cortical bone involvement CECT is preferred to MRI.

Artefacts: Both CT and MRI images are susceptible to artefacts in the presence of dental implants or amalgams. However, CT has its advantage in this aspect, as it permits

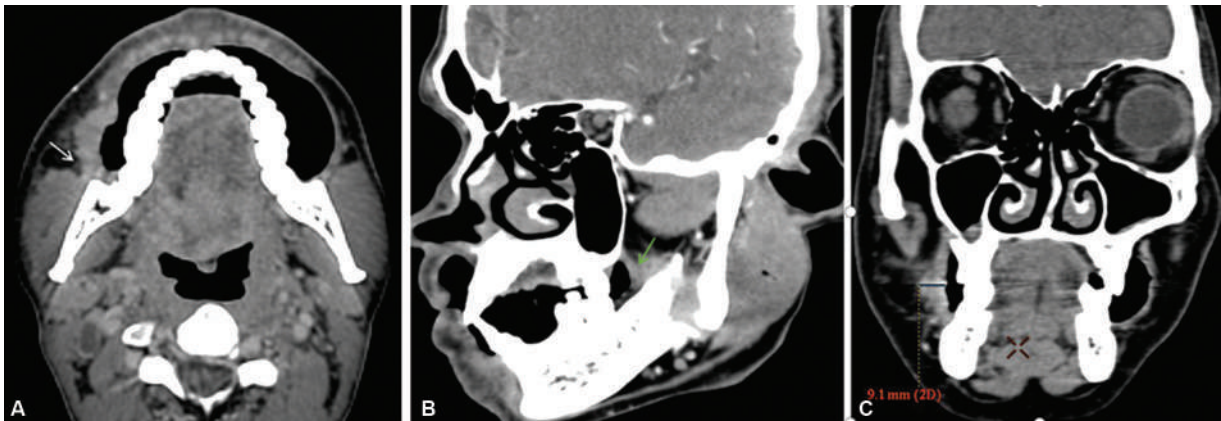


Fig. 1 (A) Axial section shows an ill-defined thickening involving right buccal mucosa buccinator complex with loss of fat planes with masseter muscle (white arrow). (B) Sagittal oblique shows an ill-defined thickening involving retromolar trigone region (green arrow) highlighting importance of oblique reformation. (C) Coronal reformatted images show technique to measure depth of invasion.

Table 5 Imaging findings of perineural spread

Direct signs	Indirect signs
1.Nerve enhancement 2.Nerve enlargement 3.Foramina fat plane obliteration 4.Foramina enlargement and destruction 5.Intracranial spread	1. Denervation atrophy. 2. Denervation enhancement In acute or subacute phase, T2 hyperintense edema in the corresponding muscle develops postcontrast enhancement. In chronic phase, muscle atrophy shows hyperintense signal on T1 and T2-weighted sequences due to fatty replacement

artefact reduction via employment of tube angulation and algorithms like metal artefact reduction.¹⁸

Interventions: Oral cavity lesions are usually sampled per orally in clinical setting; however, image guidance is required if the lesion is deep seated as in masticator space, ITF, parapharyngeal or retropharyngeal space. Generally, CT-guided sampling is preferred in these deep-seated subsites.²⁸ FDG-PET-CT has major advantage in guiding the sampling to the site of FDG avidity. USG can be employed for sampling of superficial seated lesions, lymph nodes, etc.

Staging

The role of imaging in staging relies on identifying locoregional extent and nodal and distant metastases. CECT whenever performed for initial workup should include thorax and upper abdomen as part of staging evaluation. Involvement of the ITF, masticator space, and presence of perineural spread are important predictors of locoregional staging. Perineural spread (► **Supplementary Table S2**) of disease can be identified as thickening, enhancement of nerve, and widening of neural foramina as shown in ► **Tables 5** and **6**.^{18,29,30} Even though CECT can detect the presence of perineural spread, MRI is more sensitive as it can depict even subtle perineural spread. The most commonly involved nerve being mandibu-

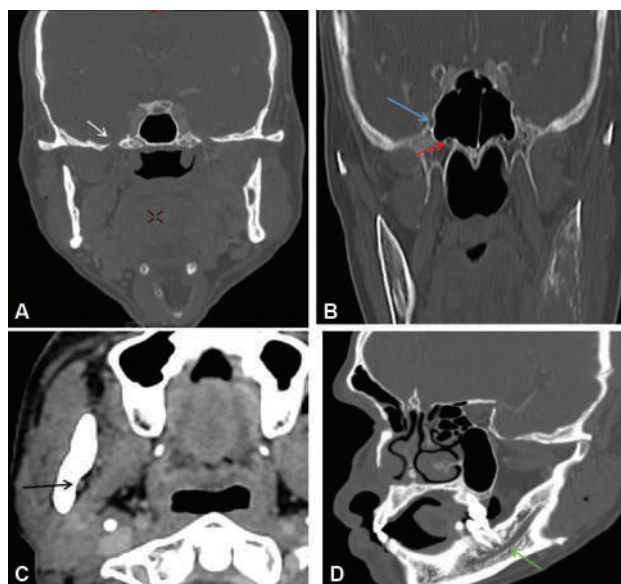


Fig. 3 Multiplanar reformatted images showing normal structures acting as conduit for perineural spread (A–D) foramen ovale (white arrow), foramen rotundum (blue arrow), vidian canal (red arrow), mandibular foramen (black arrow), and inferior alveolar canal (green arrow).

lar in gingivobuccal cancer and maxillary division of trigeminal nerve in carcinoma hard palate is shown in ► **Figs. 3** and **4**. ITF involvement (► **Supplementary Table S3**) can be subdivided as high and low ITF, based on the presence of disease involvement above or below the level of the sigmoid notch of mandible.^{18,31–34} Regional metastasis is common to the cervical lymph nodes. The frequent sites of distant metastases in oral cavity cancers are lungs, liver, bones, and mediastinal nodes. Cervical lymph node metastases can be detected by USG as it better depicts the morphology, shape, presence of cystic change, and nature of fatty hilum. Also, USG guidance can be used for sampling of these nodes for FNAC or biopsy. CECT and CE-MRI both equally depict the extranodal extension (ENE), an important prognostic marker

Table 6 Key points in evaluation of each nerve

Nerves	Key findings
1. Ophthalmic branch of trigeminal nerve(V1)	Obliteration of the orbital fat pad and enhancement of V1 in the orbit and the cavernous sinus
2. Maxillary branch of the trigeminal nerve(V2)	Obliteration of the fat pads in the pterygopalatine fossa; enlargement of the infraorbital fissure and thickening and enhancement of V2 in the round foramen and cavernous sinus
3. Mandibular branch of the trigeminal nerve(V3)	Obliteration of the fat pads of the mental or mandibular foramen and of the parapharyngeal fat below the foramen ovale; enlargement or erosion of foramina; thickening and enhancement of V3 in the parapharyngeal space and foramen ovale; abnormal bone marrow in the jaw; signs of denervation of the masticatory muscles
4. Trigeminal nerve	Obliteration of Meckel's cave
5. Facial nerve	Obliteration of the fat pad of the stylomastoid foramen and abnormal enhancement
6. Geniculate ganglion	Enlargement, obliteration and sclerosis of the geniculate fossa
7. Greater superficial petrosal nerve	Obliteration of the fat pad and enlargement or erosion of the vidian canal
8. Auriculotemporal nerve	Tumor growth in the posterior mandible

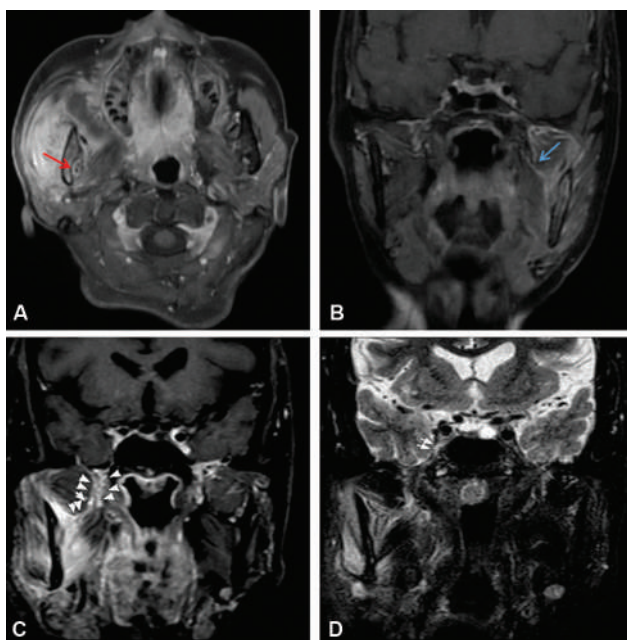


Fig. 4 (A) Axial postcontrast magnetic resonance imaging showing right upper Guillain-Barre syndrome mass with associated enhancement along right mandibular nerve in mandibular foramen suggesting perineural spread (red arrow). (B) Coronal postcontrast image showing enhancement along the infratemporal fossa component of the left mandibular (blue arrow). (C and D) Coronal postcontrast image showing enhancement and thickening of the right mandibular nerve involving foramen and suspicious intracranial extension superiorly (white arrowheads and arrow).

in predicting advanced nodal disease and local recurrence and are considered the best imaging modality for nodal metastases (**►Fig. 5**).^{35,36} Usually, the imaging modality that is used to assess the primary lesion can also evaluate the regional metastases. Most frequent site of distant metastases is lung and many times they tend to cavitate. Routine chest radiograph can detect overt lung metastases, while for detection of smaller or subpleural lesions, CECT is mandatory.³⁷ Furthermore, one can miss lesions in the hidden areas of radiograph. FDG-PET-CT has incremental value in detection of subtle metastases and detecting extrathoracic metastases. In addition, it also provides the standardized uptake value.³⁸

Management

The various treatment modalities available for oral cavity cancers are surgery, chemotherapy, and radiation therapy either as single modality or in combination. Response assessment in neoadjuvant, adjuvant, and palliative settings aims at the detection of the residual disease and documents increase or decrease in disease burden and presence of new metastases.¹⁷ Response assessment in most of the oral cavity cancers is best done with CECT as it can better detect the presence of residual disease (**►Fig. 6**). CE-MRI is the ideal modality for assessing response for oral tongue lesions. Surgical resection or radiation therapy is known to cause various post-treatment changes in the tissue distortion and these changes should be kept in mind while reporting.^{39,40} There are some key findings in gingivobuccal sulcus and

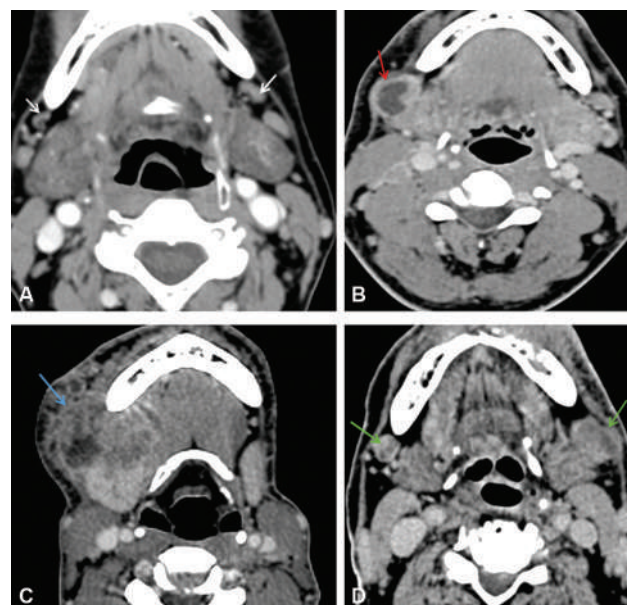


Fig. 5 (A) Bilateral reactive nodes are seen with maintained fatty hilum (white arrow). (B) Necrosis is seen in the right level IB node (red arrow). (C) Right level IB node with extranodal extension is seen (blue arrow). (D) Metastatic bilateral necrotic IB nodes are seen with capsular irregularity in the left IB node suspicious for extranodal extension (green arrow).

tongue cancers on imaging that have vital implications for the management plan. Gingivobuccal sulcus cancers with low ITF involvement on imaging are resectable. High ITF involvement is a relative contraindication for surgery with posterior high ITF (pterygopalatine fossa and pterygomaxillary fissure) involvement requiring palliative care, while anterior high ITF (retroantral fat) involvement is still amenable for surgery. Superficial/cortical bone erosion does not alter the T stage of the disease. Mandible preserving surgery can be done if anteroposterior extent of paramandibular soft tissue is less than 1 cm and directs marginal mandibulectomy if it is more than 1 cm. Deep cortical erosion or marrow involvement upstages the disease to T4a and requires segmental mandibulectomy. Perineural spread of disease is resectable if limited to infra-notch compartment but warrants palliative management if supra-notch extension is present. In tongue cancers, when tumor thickness is more than 4 mm elective neck dissection is done in view of the greater risk of nodal metastases. DOI of more than 10 mm is a marker of poor prognosis for which adjuvant treatment is recommended. When disease crosses the midline contralateral neck, dissection and radiation are warranted. Total glossectomy with flap reconstruction has to be done when bilateral neurovascular bundles get involved. Bone erosion in tongue cancers requires mandibulectomy with reconstruction and invasion of FOM reconstruction with flaps. Involvement of vallecula, pre-epiglottic space, and hyoid are relative contraindications for surgery. Extension to masticator space deems the disease nonresectable. Imaging in a clinically node-negative disease helps to pick up occult/skip nodal metastases that warrants elective neck dissection. High

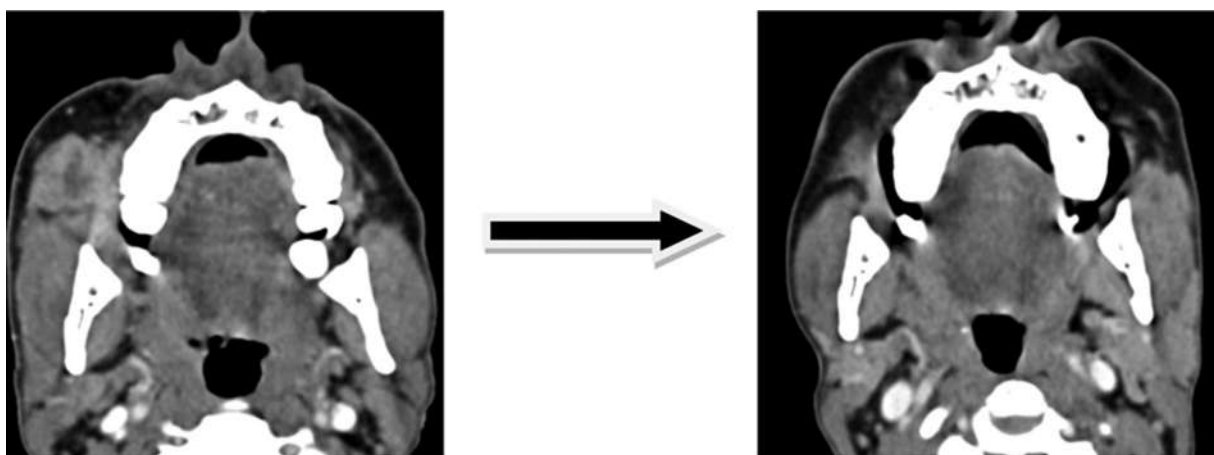


Fig. 6 Axial multidetector computed tomography images showing downstaging of T4b disease post induction chemotherapy.

nodal burden on CT warrants PET-CT/CT thorax in view of increased risk of distant metastases. Adjuvant treatment is required if ENE is present.

Follow-Up

Follow-up or surveillance in post-treatment setting aims at the detection of recurrence at the earliest. The timeline for first post-treatment surveillance imaging is usually 3 months post-treatment. However, the National Comprehensive Cancer Network criteria suggest that first surveillance imaging should be performed between 3 and 6 months of completion of therapy.⁴¹ While CECT is preferred for majority of the oral cavity subsites, CE-MRI is preferred for tongue imaging. Radiologists need to be aware of the possible post-treatment appearance following surgeries or radiation therapy in head and neck as they cause distortion of normal anatomy and fibrosis that make detection of residual or recurrent disease challenging. FDG-PET-CT can be used as a problem-solving tool in distinguishing recurrent tumor from post-treatment changes.^{42,43}

Principles of Management

The mainstay of treatment for oral cancers is surgery with or without adjuvant therapy. For early-stage disease (stages I and II), the treatment is single modality, whereas for advanced stage disease (stages III and IVA), the treatment is multi-modality.¹⁷ The primary disease is excised with adequate margin of more than 5 mm all around the tumor. Neck dissection is performed in all cases. Elective neck dissection clearing level I to III is performed for node negative neck. Modified radical neck dissection clearing level I to IV or V is performed preserving all the nonlymphatic structures namely internal jugular vein, spinal accessory nerve, and sternocleidomastoid muscle that are sacrificed only if involved by the disease. For advanced disease (stages III and IV), it is surgical resection followed by radiation therapy with or without concurrent chemotherapy. Inoperable cases are directly treated with radiation therapy with or without concurrent chemotherapy.⁴⁴ Best supportive care is recommended if the general condition of the patient is poor precluding any treatment.

The stage-wise prognosis (5-year survival rate) in oral cavity cancers is 85.2, 82.9, 56.3, and 42.6% for stages I, II, III, and IV respectively.⁴⁵

Follow-Up Imaging and Management of Recurrent Disease Including Specific Interventional and Palliative Measures

The main aim of follow-up imaging is diagnosing and treating the recurrent disease at the earliest. Most cases of oral cavity malignancy recur either in the postoperative bed or in the cervical lymph nodes. Image-guided tissue sampling plays an important role in documenting these recurrences. Surgery should be offered to the patients if the recurrence is excisable. However, when the recurrence cannot be excised with clear margins or in the presence of distant metastasis, nonsurgical treatment should be offered that includes chemotherapy or chemoradiation. These recurrent tumors tend to be resistant to many conventional chemotherapeutic drugs and immunotherapy and targeted therapies could be the options for such patients. There is some emerging data that oligometastatic cases with solitary lung recurrence can be treated with radio frequency or microwave ablation, metastasectomy, or stereotactic body radiotherapy; however, the practice varies across the globe.^{46,47}

Summary of Recommendations

1. Oral cavity cancers have better outcomes if detected early and treated with timely surgery.
2. Imaging plays a crucial role in diagnosing, staging the disease, treatment planning on case-to-case basis, and surveillance of disease.
3. Modality of choice for majority of oral cavity cancers is CECT, while for oral tongue and FOM, CE-MRI is performed.
4. FDG-PET-CT is used as a problem-solving tool and in the setting of recurrent or residual disease.

Conflict of Interest

None declared.

References

- Starzyńska A, Sobocki BK, Alterio D. Current challenges in head and neck cancer management. *Cancers (Basel)* 2022;14(02):358
- Goel B, Tiwari AK, Pandey RK, et al. Therapeutic approaches for the treatment of head and neck squamous cell carcinoma—an update on clinical trials. *Transl Oncol* 2022;21:101426
- Kato H, Matsuo M. Imaging findings of oral cancers. In *Inflammation and Oral Cancer*. Academic Press; 2022:55–77
- Asthana S, Labani S, Kailash U, Sinha DN, Mehrotra R. Association of smokeless tobacco use and oral cancer: a systematic global review and meta-analysis. *Nicotine Tob Res* 2019;21(09):1162–1171
- Epstein JB, Barasch A. Oral and dental health in head and neck cancer patients. In *Multidisciplinary Care of the Head and Neck Cancer Patient*. Springer, Cham; 2018:43–57
- Haider T, Yousaf Z, Khan AG, Fatima S. Awareness and practice of oral hygiene and its relation to socio-demographic factors among patients attending general OPD: Oral Hygiene & its Relation to Socio-Demographic Factors. *Pakistan BioMedical Journal*. 2022;5(02):80–83
- Woo SB. Oral epithelial dysplasia and premalignancy. *Head Neck Pathol* 2019;13(03):423–439
- Sarode G, Maniyar N, Sarode SC, Jafer M, Patil S, Awan KH. Epidemiologic aspects of oral cancer. *Dis Mon* 2020;66(12):100988
- Krishna Rao SV, Mejia G, Roberts-Thomson K, Logan R. Epidemiology of oral cancer in Asia in the past decade—an update (2000–2012). *Asian Pac J Cancer Prev* 2013;14(10):5567–5577
- Wong T, Yap T, Wiesenfeld D. Common benign and malignant oral mucosal disease. *Aust J Gen Pract* 2020;49(09):568–573
- Acharya B, Rayamajhi A. Imaging modalities in squamous cell carcinoma of head and neck: a review article. *J Can Res Adv Ther*. 2020;1(02):19–23
- Zanoni DK, Patel SG. New AJCC: how does it impact oral cancers? *Oral Oncol* 2020;104:104607
- Zanoni DK, Patel SG, Shah JP. Changes in the 8th edition of the American Joint Committee on Cancer (AJCC) staging of head and neck cancer: rationale and implications. *Curr Oncol Rep* 2019;21(06):52
- Grégoire V, Boisbouvier S, Giraud P, Maingon P, Pointreau Y, Vieilleveigne L. Management and work-up procedures of patients with head and neck malignancies treated by radiation. *Cancer Radiother* 2022;26(1–2):147–155
- Borse V, Konwar AN, Buragohain P. Oral cancer diagnosis and perspectives in India. *Sens Int* 2020;1:100046
- Yete S, D'Souza W, Saranath D. High-risk human papillomavirus in oral cancer: clinical implications. *Oncology* 2018;94(03):133–141
- D'Cruz AK, Vaish R, Dhar H. Oral cancers: current status. *Oral Oncol* 2018;87:64–69
- Mahajan A, Ahuja A, Sable N, Stambuk HE. Imaging in oral cancers: a comprehensive review. *Oral Oncol* 2020;104:104658
- Jeyaraj PR, Samuel Nadar ER. Computer-assisted medical image classification for early diagnosis of oral cancer employing deep learning algorithm. *J Cancer Res Clin Oncol* 2019;145(04):829–837
- Ilhan B, Lin K, Guneri P, Wilder-Smith P. Improving oral cancer outcomes with imaging and artificial intelligence. *J Dent Res* 2020;99(03):241–248
- Junn JC, Soderlund KA, Glastonbury CM. Imaging of head and neck cancer with CT, MRI, and US. In *Seminars in Nuclear Medicine*. WB Saunders 2021 Jan 1 (Vol. 51, No. 1, pp. 3–12)
- Murakami R, Shiraishi S, Yoshida R, et al. Reliability of MRI-derived depth of invasion of oral tongue cancer. *Acad Radiol* 2019;26(07):e180–e186
- Maraghehli D, Pietragalla M, Calistri L, et al. Techniques, tricks, and stratagems of oral cavity computed tomography and magnetic resonance imaging. *Appl Sci (Basel)* 2022;12(03):1473
- Eneva MI, Nedevska M. MDCT amplified by the “puffed-cheek” maneuver in the radiological assessment of oral cavity tumors—a technical guide and a pictorial review of imaging findings. Vienna: European Congress of Radiology-ECR; 2018
- Lee YC, Jung AR, Kwon OE, et al. Comparison of computed tomography, magnetic resonance imaging, and positron emission tomography and computed tomography for the evaluation bone invasion in upper and lower gingival cancers. *J Oral Maxillofac Surg* 2019;77(04):875.e1–875.e9
- Mahajan A, Dhone N, Vaish R, et al. Prognostic impact of pattern of mandibular involvement in gingivo-buccal complex squamous cell carcinomas: marrow and mandibular canal staging system. *Front Oncol* 2022;11:752018
- Mao MH, Wang S, Feng ZE, et al. Accuracy of magnetic resonance imaging in evaluating the depth of invasion of tongue cancer. A prospective cohort study. *Oral Oncol* 2019;91:79–84
- Aiken AH. Image-guided biopsies in the head and neck: practical value and approach. *AJNR Am J Neuroradiol* 2020;41(11):2123–2125
- Baulch J, Gandhi M, Sommerville J, Panizza B. 3T MRI evaluation of large nerve perineural spread of head and neck cancers. *J Med Imaging Radiat Oncol* 2015;59(05):578–585
- Hanna E, Vural E, Prokopakis E, Carrau R, Snyderman C, Weissman J. The sensitivity and specificity of high-resolution imaging in evaluating perineural spread of adenoid cystic carcinoma to the skull base. *Arch Otolaryngol Head Neck Surg* 2007;133(06):541–545
- Mahajan A, Smriti VM. Masseter pars coronioidea: Gateway between the masticator space and infratemporal fossa. *Cancer Res Stat Treat* 2022;5(01):185
- Mohiyuddin SMA, Harsha P, Maruvala S, et al. Outcome of compartment resection of locally advanced oral cancers extending to infratemporal fossa: a tertiary rural hospital experience. *Eur Arch Otorhinolaryngol* 2018;275(11):2843–2850
- Arya S, Chaukar D, Pai P. Imaging in oral cancers. *Indian J Radiol Imaging* 2012;22(03):195–208
- Liao CT, Ng SH, Chang JT, et al. T4b oral cavity cancer below the mandibular notch is resectable with a favorable outcome. *Oral Oncol* 2007;43(06):570–579
- Pantvaidya G, Rao K, D'Cruz A. Management of the neck in oral cancers. *Oral Oncol* 2020;100:104476
- Abdel-Halim CN, Rosenberg T, Dyrvig AK, et al. Diagnostic accuracy of imaging modalities in detection of histopathological extranodal extension: A systematic review and meta-analysis. *Oral Oncol* 2021;114:105169
- Irani S. Distant metastasis from oral cancer: A review and molecular biologic aspects. *J Int Soc Prev Community Dent* 2016;6(04):265–271
- Ishikawa S, Hiraka T, Kirii K, et al. Relationship between standard uptake values of positron emission tomography/computed tomography and salivary metabolites in oral cancer: a pilot study. *J Clin Med* 2020;9(12):3958
- Dhar H, Vaish R, D'Cruz AK. Management of locally advanced oral cancers. *Oral Oncol* 2020;105:104662
- Geiger JL, Adelstein DJ. Chemotherapy in the definitive management of oral cancers: where do we stand today? *Oral Oncol* 2020;102:104584
- Strauss SB, Aiken AH, Lantos JE, Phillips CD. Best practices: application of NI-RADS for posttreatment surveillance imaging of head and neck cancer. *AJR Am J Roentgenol* 2021;216(06):1438–1451
- Dinkelborg P, Ro SR, Shnayien S, et al. Retrospective evaluation of NI-RADS for detecting postsurgical recurrence of oral squamous cell carcinoma on surveillance CT or MRI. *AJR Am J Roentgenol* 2021;217(01):198–206
- Jung AR, Roh JL, Kim JS, Choi SH, Nam SY, Kim SY. Post-treatment ¹⁸F-FDG PET/CT for predicting survival and recurrence in patients with advanced-stage head and neck cancer undergoing curative surgery. *Oral Oncol* 2020;107:104750

- 44 Koefman SA, Ismail N, Crook D, et al. Management of the neck in squamous cell carcinoma of the oral cavity and oropharynx: ASCO clinical practice guideline. *J Clin Oncol* 2019;37(20):1753–1774
- 45 Bobdey S, Sathwara J, Jain A, Saoba S, Balasubramaniam G. Squamous cell carcinoma of buccal mucosa: an analysis of prognostic factors. *South Asian J Cancer* 2018;7(01):49–54
- 46 Szturcz P, Vermorken JB. Management of recurrent and metastatic oral cavity cancer: raising the bar a step higher. *Oral Oncol* 2020;101:104492
- 47 Swain M, Ghosh-Laskar S. Stereotactic body radiotherapy (SBRT) for primary non-metastatic head and neck cancer: when less is enough. *Oral Oncol* 2021;116:105265

Imaging Recommendations for Diagnosis, Staging, and Management of Cancer of the Thyroid, Parathyroid, and Salivary Glands

Abhishek Mahajan¹ Shreya Shukla² Suman Kumar Ankathi³ Anuradha Shukla² Richa Vaish⁴
Shubham Suryavanshi² Ujjwal Agarwal² Vasundhara Patil³ Arpita Sahu² Shubham Padashetty²
Sarvani Ghosh Laskar⁵ Vijay Patil⁶ Vanita Noronha⁶ Nandini Menon⁶ Kumar Prabhash⁶
Asawari Patil⁷ Pankaj Chaturvedi⁴ Prathamesh S. Pai⁴ Swapnil Rane⁷ Munita Bal⁷ A. K. Dcruz⁸

¹Department of Radiodiagnosis, The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, United Kingdom

²Department of Radiodiagnosis, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India

³Department of Radiodiagnosis and Imaging, Tata Memorial Hospital, Mumbai. Homi Bhabha National Institute, Parel, Mumbai, India

⁴Department of Head and Neck Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India

⁵Department of Radiation Oncology, Tata Memorial Hospital, Mumbai. Homi Bhabha National Institute Location: Mumbai

Address for correspondence Abhishek Mahajan, MD, Fellowship in Cancer Imaging, MRes (KCL, London), FRCR (UK), Department of Radiodiagnosis, The Clatterbridge Cancer Centre NHS Foundation Trust, Pembroke Place Liverpool, Liverpool L7 8YA, United Kingdom (e-mail: drabhishek.mahajan@yahoo.in).

⁶Department of Medical Oncology, Tata Memorial Hospital, Mumbai. Homi Bhabha National Institute, Mumbai, India

⁷Department of Pathology, Tata Memorial Hospital, Mumbai. Homi Bhabha National Institute Location: Mumbai, India

⁸Department of Head and Neck Oncosurgery, Oncology Apollo Hospitals, India

Ind J Med Paediatr Oncol 2023;44:159–174.

Abstract

Keywords

- Computed tomography
- cross-sectional imaging
- guidelines
- head and neck cancer
- magnetic resonance imaging
- parathyroid imaging
- salivary gland tumor
- thyroid cancer
- thyroid gland
- ultrasound
- thyroid gland
- ultrasound

Thyroid cancer ranks as the leading endocrine malignancy in adults. The foundation for primary diagnosis of thyroid cancer is a high-resolution ultrasound (US) of the thyroid gland including US-guided fine-needle biopsy (FNB) of suspected thyroid nodules. Advanced cross-sectional imaging, including computed tomography (CT), magnetic resonance imaging, and positron emission tomography, can be useful in selected patients. The mainstay of treatment of thyroid cancer is surgery. It may be supplemented by radioactive iodine ablation/therapy in high-risk differentiated thyroid cancer. Radiology plays a crucial role in both diagnostic and posttreatment follow-up imaging. Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder with single parathyroid adenoma being its most common cause. The radiologist's aim in parathyroid imaging is to provide the clinician with an illustrative picture of the neck, locating lesions with respect to landmarks. Imaging helps in the detection of solitary versus multiglandular disease, ectopic and supernumerary glands with precise localization. US, nuclear imaging, and four-dimensional CT are the most commonly used imaging modalities for the preoperative localization of the parathyroid disease. Salivary gland tumors account for approximately 0.5% of all neoplasms, the most common location being the parotid gland (70%). Imaging is crucial in salivary gland tumors by defining its location, detecting malignant features, assessing local extension and invasion, staging the tumors according to the tumor-node-metastasis classification, and assessing the feasibility of surgery.

DOI <https://doi.org/10.1055/s-0042-1760403>.
ISSN 0971-5851.

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)
Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Thyroid Gland, Introduction, Risk Factors, and Etiopathogenesis

Thyroid cancer ranks as the leading endocrine malignancy in adults.¹ Thyroid cancer can arise from two chief cell types: follicular and parafollicular or C-cells. Papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) are grouped together as differentiated thyroid cancer (DTC) as they both arise from thyroid follicular cells. Medullary thyroid cancer arises from parafollicular cells. Anaplastic carcinomas (ATC) are the most undifferentiated type of thyroid cancer.² Papillary microcarcinoma (PMC) refers to papillary cancer smaller than 1 cm.³

Exposure to radiation, family history of thyroid cancer, and inherited genetic syndromes are some of the risk factors for thyroid cancer. Other risk factors include high iodine intake, increased thyroid-stimulating hormone (TSH) levels, obesity, and exposure to nitrate.⁴ Sources of radiation exposure may be environmental nuclear disasters, radiological tests (e.g., computed tomography [CT] scans, X-rays), and medical treatment, including radiation therapy for head and neck cancer and radioactive iodine (RAI) treatment.⁵ Thyroid cancer is known to have a high hereditary predisposition; however, more than 90% is sporadic in nature.^{6,7} The autosomal dominant hereditary syndromes associated with thyroid cancer include familial adenomatous polyposis, Cowden syndrome, and Carney complex. The familial form of medullary thyroid carcinoma (MTC) is present in 20 to 25% of cases and is usually a component of MEN 2A or 2B or a part of familial medullary thyroid carcinoma syndrome.⁸

Epidemiology, Clinical Presentation in India and Global

The GLOBOCAN 2020 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer show that there were 586,202 new cases of thyroid cancer with an estimated 43,646 deaths worldwide with an estimated incidence rate of 1.4 per 100,000 in India.⁹ DTC accounts for 90% of all cases with PTC accounting for approximately 70 to 80% and FTC accounting for 10 to 15% of all cases.¹⁰ PMC accounts for approximately 24% of thyroid cancer cases in the United States.¹¹ Most cases of DTC occur in adults ages 30 to 50 years.¹² The DTCs usually present as thyroid nodules which can be single or multiple. These cancers are more common in females. The findings which should alert the physician to thoroughly investigate the patients include extremes of age (<16 years and >55 years), male patients, history of radiation exposure, family history, and symptoms of involvement of surrounding structures like hoarseness, breathing difficulty, and hemoptysis.

Imaging Referral Guidelines

The 2015 American Thyroid Association (ATA) management guidelines for adult patients with thyroid nodules are widely popular for DTC and MTC. The ATA guidelines for manage-

ment of patients with ATC have been revised in 2021. Korean Society of Thyroid Radiology (KSThR) through a collaboration with the National Evidence-based Healthcare Collaborating Agency has developed the 2020 Imaging guidelines for thyroid nodules and DTC using an adaptation process and has identified four clinical situations which mandate thyroid imaging.¹² They reviewed the previous existing guidelines including the 2015 ATA management guidelines for adult patients with thyroid nodules and DTC, American Association of Clinical Endocrinologists (AACE)/Italian Association of Clinical Endocrinologists/the European Thyroid Association medical guidelines for clinical practice for diagnosis and management of thyroid nodules, British Thyroid Association guidelines for the management of thyroid cancer, U.S. Diagnosis and Imaging-based Management of Thyroid Nodules: Revised KSThR Consensus Statement and Recommendations, American College of Radiology (ACR) Appropriateness Criteria Thyroid Disease, Revised Korean Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Thyroid Cancer and National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Thyroid Carcinoma, Version 1. 2019.^{13–18} After a thorough discussion and comparison of the recommendations and the evidence in the literature for the selected guidelines, recommendations were prepared by the guideline committee.

The recommendations in four typical clinical situations include (1) *evaluation of known or suspected thyroid nodules*—neck US is usually appropriate for the evaluation of suspected thyroid nodules. US-guided biopsy of thyroid nodules is also appropriate for initial diagnostic workup. Contrast-enhanced CT or magnetic resonance imaging (MRI) of the neck can be additionally performed in advanced thyroid cancer. (2) *Preoperative evaluation of DTC*—neck US is usually appropriate for the preoperative evaluation of DTC. For the preoperative assessment of DTC, washout thyroglobulin (Tg) for neck lymph nodes (LNs) and/or ultrasound (US) guided biopsy are typically appropriate. In advanced disease, neck CT or MRI with IV contrast may be appropriate as an adjunct to US. Contrast-enhanced CT (CECT) chest may be appropriate to evaluate the lung parenchyma or the advanced mediastinum disease. (3) *Early imaging after surgery for DTC*—neck US is appropriate for the postoperative evaluation of DTC after definitive treatment. CECT neck may be appropriate for early imaging after definitive treatment of DTC. When the response to therapy cannot be adequately assessed by US and serum Tg, it may be taken into consideration in individuals with a high risk of persistent pathology. (4) *Suspected recurrence of DTC*—neck US is usually appropriate when recurrence of DTC is suspected. US-guided biopsy and/or washout Tg for neck LNs are usually appropriate when recurrence of DTC is suspected on imaging. Contrast-enhanced neck CT or MRI may be appropriate as a second-line imaging modality in cases of widely distributed recurrent disease, when aerodigestive tract invasion is suspected, or in cases of discrepancy between serum Tg and US results. Chest CT with or without IV contrast may be appropriate in high-risk patients with elevated serum Tg or rising anti-Tg antibodies.¹²

2015 ATA guidelines for MTC: US examination of the neck should be performed in all patients with MTC. Patients with significant neck disease and signs or symptoms of local or distant metastases might as well have CECT of the neck and chest, three-phase contrast-enhanced multidetector liver imaging, contrast-enhanced MRI of the liver, axial MRI, and bone scintigraphy. These studies should also be conducted in all patients with a serum Ctn level greater than 500 pg/mL. (C)¹⁹

2021 ATA guidelines for ATC: Initial radiological tumor staging should include cross-sectional imaging, in particular, CT neck, chest, abdomen, and pelvis with contrast (or MRI), and, if available, fluorodeoxyglucose positron emission tomography (FDG PET)/CT. If clinically necessary, contrast-enhanced brain imaging using an MRI should also be performed.²⁰

Clinical/Diagnostic Work-Up Excluding Imaging

The physical examination with neck palpation and US are the two techniques to screen for thyroid cancer. Neck palpation can identify palpable nodules, while US can identify both palpable and nonpalpable nodules. The clinical examination comprises meticulous palpation of the gland along with the neck nodes. Signs of extrathyroidal extension like the involvement of straps and retrosternal extension should be assessed. Determination of Tg in the case of DTC and calcitonin in the case of MTC is of vital significance.²¹ The incidence of malignancy in this scenario is low. The ATA guidelines for the assessment of thyroid nodules recommend serum TSH measurement. DTC is more commonly associated with the euthyroid or hypothyroid state. If the TSH is below normal limits, thyroid scintigraphy should be done. Focal FDG uptake in >1 cm thyroid nodule raises concern and fine-needle aspiration (FNA) should be performed. If it measures <1 cm, the nodule may be monitored.²² The 2015 ATA guidelines for MTC suggest that family history should be thoroughly elicited in suspected medullary thyroid cancers as 25% are hereditary. Fine-needle aspiration cytology (FNAC) from the thyroid nodule establishes the diagnosis in corroboration with serum calcitonin and CEA levels. Genetic testing and counseling should be performed to identify the RET germline mutation. The extent of the disease is established on imaging along with serum calcitonin levels. The family should be screened for the mutation and if present then prophylactic thyroidectomy should be offered to these patients.^{23,24} Somatic alterations of BRAF are common in ATC with an incidence of 40 to 70%. Immunohistochemical detection of the most common BRAF mutation (BRAFV600E) is necessary novel mutation-specific therapies that are now available.²⁰

Imaging Guidelines

Diagnosis (Including Interventions)

Imaging Thyroid Nodule

The foundation for primary diagnosis of thyroid cancer is a high-resolution US of the thyroid gland including US-guided

FNB of suspected thyroid nodules.⁴ The US scanning technique involves the use of a high-frequency linear array probe. The scan is performed in the hyperextended position of the neck. The neck is scanned from the submental area to the sternal notch. The evaluation of the primary thyroid lesion is done along with the assessment of lateral and central compartment lymph nodes. The head is turned away from the side of interest to scan the tracheoesophageal groove. The transducer is angled inferiorly to examine the mediastinum and laterally to study lateral compartment lymph nodes (levels 2, 3, and 4). Neck is studied from mandible to clavicle and the transducer is angled inferiorly towards clavicle to image infraclavicular nodes at the base of level 4. Sweep laterally along the clavicle to posterior border of the sternocleidomastoid muscle, then trace posterior border superiorly to the mastoid process to image the posterior compartment nodes (level 5).

There are five criteria to identify malignancy on brightness-mode US that help identify malignancy in thyroid nodules: composition, hypoechogenicity, taller than wide shape (anterior-posterior diameter larger than the width in an axial scan), irregular margin, and macro- and microcalcification.²⁵ Many simple classification systems have been lately developed for thyroid nodules on thyroid US. The most popular include the classifications proposed by the ATA²⁶ and AACE,²⁷ and the thyroid imaging reporting and data systems (TIRADS) released by the KSThR,²⁸ the European Thyroid Association,²⁹ and the American College of Radiology (ACR-TIRADS).³⁰ ►Table 1 describes the US features of high, intermediate, and mild suspicion of malignancy according to ATA guidelines. ►Table 2 describes the ACR-TIRADS US-based thyroid nodule reporting system (discussed in ►Table 2). The performance of the TIRADS was compared in a recent meta-analysis, wherein categories 4 and 5 had a sensitivity of approximately 90% for the detection of DTC with specificities between 50 and 60% and ACR-TIRADS was found to be the most specific system in a recent prospective study.³¹ From a size of 10 mm and above, every suspicious thyroid nodule should undergo US-guided FNB.¹³ ATA and AACE guidelines recommend performing thyroid scintigraphy in addition to ultrasound in all patients evaluated for thyroid nodules who have subnormal serum thyrotropin (TSH).^{13,27}

The American College of Radiology proposed ACR-TIRADS which is an US -based thyroid nodule reporting system.³² Five categories of US findings are used to score each thyroid nodule. The likelihood of malignancy increases with an increase in the TR (TIRADS) level with an increase in the cumulative score. TIRADS levels include TR1: 0 points (benign), TR2: 2 points (not suspicious), TR3: 3 points (mildly suspicious), TR4: 4 to 6 points (moderately suspicious), and TR5: ≥7 points (highly suspicious). Based on the TIRADS levels and the size of the thyroid nodule, recommendations are given to the patient: TR1: no FNA required; TR2: no FNA required; TR3: ≥1.5 cm follow up at 1, 3, and 5 years, ≥2.5 cm FNA; TR4: ≥1.0 cm follow up at 1, 3, and 5 years, ≥1.5 cm FNA; and TR5: ≥0.5 cm annual follow-up for up to 5 years, ≥1.0 cm FNA.³²

Table 1 Thyroid nodules with ultrasound features of high, intermediate, and mild suspicion of malignancy according to the American Thyroid Association guidelines.

Risk of malignancy	Ultrasound features
Benign pattern (0% risk)	Completely cystic nodules with well-defined walls
Very low suspicion pattern (<3% risk)	Spongiform nodules and nodules with interspersed cystic spaces, without any of the features in more suspicious patterns
Low suspicion pattern (5–10% risk)	Isoechoic or hyperechoic nodule partially cystic nodule with a peripheral solid component none of the following features: microcalcifications (see other points below*) irregular margins extrathyroidal extension taller than wide
Intermediate suspicion pattern (10–20% risk)	Hypoechoic solid nodule with smooth margins none of the following features: microcalcifications (see other points below*) irregular margins extrathyroidal extension taller than wide
High suspicion pattern (>70–90% risk)	Solid hypoechoic nodule (or solid hypoechoic component of a partially cystic nodule), with at least one of these features: microcalcifications (see other points below*) irregular margins (infiltrative, microlobulated) extrathyroidal extension taller than wide rim calcifications with an extrusive soft tissue component lymphadenopathy * Other points: - Dystrophic calcifications (e.g. coarse macrocalcification, rim calcifications) other than microcalcifications increase risk, but to a lesser degree than microcalcifications. - The cervical lymph nodes must be studied in all neck ultrasounds.

Cross-sectional imaging: Additional cross-sectional imaging, including CT, MRI, and PET, can be useful in a minority of select patients. The four common conditions in which cross-sectional imaging of thyroid carcinoma may be performed are as follows: detection of the incidental thyroid nodule, evaluation of thyroid nodal metastases, presurgical imaging for invasive disease, and evaluation for recurrence in the posttreatment neck. FDG-PET/CT is useful in the initial (postthyroidectomy) staging of high-risk patients with less differentiated (and thus less iodine-avid and clinically more aggressive) subtypes, such as tall cell variant and Hürthle cell carcinoma, poorly differentiated, and anaplastic carcinoma. FDG-PET/CT may help in defining the extent of disease in some patients with medullary thyroid carcinoma and rising postoperative calcitonin levels.³³

Imaging Nodal Metastases

Metastasis to cervical nodes is common in papillary carcinoma with a reported incidence varying from 30 to 90%.³⁴ Spread to neck nodes is also common in medullary carcinoma (50%) and anaplastic carcinoma (40%), while lymphatic spread is less common with follicular carcinoma (10%).³⁵ US remains the imaging modality of choice for the evaluation of nodal metastases. It can be combined with US-guided FNAC, and the nodes and primary tumor can be evaluated in the same examination. US features of metastatic nodes from thyroid cancer are similar to those from other head and neck

cancers and include a round shape, loss of the nodal hilum, peripheral vascularity, necrosis, and extranodal tumor spread, the latter two features are commonly seen in metastatic nodes from anaplastic carcinoma.³⁶ Calcification (50–69%), increased echogenicity (87%), and cystic composition (20%) are the characteristic of metastatic nodes from papillary carcinoma with latter being the dominant feature.³⁷

Ultrasound-Guided Fine-Needle Aspiration of Thyroid Nodule/Cervical Lymph Nodes

The criteria developed by the ATA (2015) are often used in clinical practice.¹³ The ACR TIRADS system recommends FNA for TR3 lesions >25 mm, TR4 lesions >15 mm, and TR5 lesions >10 mm.³² FNA is recommended for any nonbenign lesion (i.e., U3, U4, or U5) by the British Thyroid Association Ultrasound classification.¹⁵ FNA is recommended for nodules <10 mm whenever clinical information or US features raise suspicion for malignancy. Additional recommendations for FNA by the American Association of Clinical Endocrinologists includes nodule of any size with patient history of neck irradiation in childhood or adolescence; papillary thyroid carcinoma, medullary thyroid carcinoma, or multiple endocrine neoplasia type 2 in first-degree relatives; previous thyroid surgery for cancer; increased calcitonin levels in the absence of interfering factors.¹⁴ According to 2021 ATA guidelines, for the initial evaluation of anaplastic carcinoma, FNA cytology can play an important role, but a parallel core

Table 2 The ultrasound-based thyroid nodule reporting system (TIRADS) proposed by the American College of Radiology including the five categories of ultrasound findings and the point given for each finding. A cumulative score determines the likelihood of malignancy.

Category	Ultrasound finding	Points
Composition (choose one)	Cystic or completely cystic	0
	Spongiform	0
	Mixed cystic and solid	1
	Solid or almost completely solid	2
Echogenicity (choose one)	Anechoic	0
	Hyper- or isoechoic	1
	Hypoechoic	2
	Very hypoechoic	3
Shape (assessed on the transverse plane; choose one)	Wider than tall	0
	Taller than wide	3
Margin (choose one)	Smooth	0
	Ill-defined	0
	Lobulated/irregular	2
	Extra-thyroidal Extension	3
Echogenic foci (choose one or more)	None	0
	Large comet-tail artifact	0
	Macrocalcifications	1
	Peripheral/rim calcifications	2
	Punctate echogenic foci	3

biopsy may be necessary for definitive diagnosis and to obtain a sufficient sample for molecular workup.¹³ Once ATC diagnosis is confirmed, assessment of BRAF mutation should be expeditiously performed by IHC and confirmed by molecular testing.²⁰ Assuming that each thyroid nodule >1 cm carries an independent risk of malignancy and those numerous nodules may necessitate FNA, patients with multiple thyroid nodules >1 cm should be assessed in the same way as patients with a single nodule >1 cm. When multiple nodules >1 cm are present, those with suspicious US features should be aspirated preferentially.¹³ It is reasonable to aspirate only the largest nodules (>2 cm) or to continue surveillance without FNA while monitoring the other nodules with serial US examinations if none of the nodules have a high or moderately suspicious sonographic pattern and multiple sonographically similar very low or low suspicion pattern nodules coalesce with no intervening normal parenchyma. In patients with numerous nodules, a low or low-normal serum TSH levels may imply that one or more nodules may be autonomous. To establish the functionality of any nodule larger than 1 cm in such circumstances, a radioactive thyroid scan should be considered and directly compared with the US pictures. FNA should then be considered only for those iso-functioning or nonfunctioning nodules, among which

those with high-suspicion sonographic pattern should be aspirated preferentially.¹³

Procedure

To ensure accuracy, the needle tip must be visualized within the target thyroid nodule/lymph node during the FNA. If the entire nodule/lymph node is morphologically abnormal on US, then the FNA specimen can be obtained by moving the needle tip throughout the lymph node. Else, the needle tip should be targeted to the suspicious component of the nodule/node. For solid/cystic nodules/lymph nodes, a solid vascular portion should be targeted (unless fluid is required for Tg analysis). For US-guided FNA, a parallel or a perpendicular approach can be employed. In the parallel approach, the needle is visualized along its entire length as it enters the lymph node. Only the needle's tip can be visible when using a perpendicular approach. Either a 25-gauge or a 27-gauge needle can be used. Confirm that the needle tip is within the suspicious component of the nodule/node and then obtain the cytology specimen by either the capillary or the aspiration technique. The needle tip is moved back and forth through the diameter of the target without suction, in the capillary technique. Suction is used in the aspiration technique as the needle tip is moved. For thyroid nodule FNA, the recent literature has shown low nondiagnostic rates using smaller gauge needles and the capillary action technique.^{38,39} The cytology specimen can be prepared using a liquid preparation or by creating a slide smear. If on-site adequacy assessment by a trained cytologist is not available, the preferred number is three to four passes.⁴⁰ In addition to cytology analysis, Tg measurement from the FNA needle washout (FNA-Tg) has been shown to improve the sensitivity of US FNA cytology alone.⁴¹ Published reports have suggested a cut-off FNA-Tg level in the 1 ng/mL range for washouts prepared with up to 1 mL of diluent, though the serum Tg level, which may be higher in patients with a large volume of residual cancer or an intact thyroid gland, must be considered.⁴² The use of FNA-Tg is especially vital for cystic lymph nodes, only macrophages and no epithelial cells may be seen in cytology. FNA washout for calcitonin measurement can also be performed in MTC for the diagnosis of metastatic lymph nodes.²²

For reporting thyroid cytopathological results, the Bethesda System for Reporting Thyroid Cytopathology developed a standardized, category-based reporting system for thyroid FNA specimens. The 2017 revision reaffirms that every thyroid FNA report should begin with one of six diagnostic categories: (1) nondiagnostic or unsatisfactory; (2) benign; (3) atypia of undetermined significance or follicular lesion of undetermined significance; (4) follicular neoplasm or suspicious for a follicular neoplasm; (5) suspicious for malignancy; and (6) malignant.⁴³

Staging

The American Joint Committee on Cancer (AJCC) have developed different tumor-node-metastasis (TNM) classification for differentiated, anaplastic and for medullary thyroid cancer which have been discussed in ►Table 3–5 and 6.^{44–46}

Table 3 T (Tumor) classification of TNM classification for differentiated, medullary, and anaplastic thyroid cancer

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor is found
T1	Tumor size ≤ 2 cm in greatest dimension and is limited to the thyroid
T1 a	Tumor ≤ 1 cm, limited to the thyroid
T1 b	Tumor > 1 cm but ≤ 2 cm in greatest dimension, limited to the thyroid
T2	Tumor size > 2 cm but ≤ 4 cm, limited to the thyroid
T3	Tumor size > 4 cm, limited to the thyroid or any tumor with gross extrathyroidal extension invading only strap muscles
T3 a	Tumor size > 4 cm, limited to the thyroid
T3 b	Any size tumor with gross extrathyroidal extension invading only strap muscles (e.g., extension to sternothyroid, sternohyoid, thyrohyoid, or omohyoid muscles)
T4 a	Any size tumor with gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4 b	Any size tumor with gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels

Abbreviation: TNM, tumor-node-metastasis.

Table 4 N (Regional lymph nodes) classification of TNM Classification for differentiated, medullary, and anaplastic thyroid cancer: N include central compartment, lateral cervical, and upper mediastinal lymph nodes

NX	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N0a	One or more cytologically or histologically confirmed benign lymph nodes
N0b	No radiologic or clinical evidence of locoregional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastases to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian or upper mediastinal) lymph nodes; can be unilateral or bilateral disease
N1b	Metastases to unilateral, bilateral, or contralateral neck lymph nodes (levels I, II, III, IV, or V) or retropharyngeal lymph nodes
NX	Regional nodes cannot be assessed

Abbreviation: TNM, tumor-node-metastasis.

Table 5 M (Distant metastasis) classification of TNM classification for differentiated, medullary and anaplastic thyroid cancer

M0	No distant metastasis is found
M1	Distant metastasis is present

Abbreviation: TNM, tumor-node-metastasis.

Management

The mainstay of treatment of thyroid cancer is surgery. It may be supplemented by RAI ablation/therapy in high-risk DTC. Many risk stratification systems have been developed for patients with DTC including GAMES (grade, age, metastases, extrathyroidal extension, size) which was developed in the 1990s and is still used to predict cancer mortality.⁴⁷ Age, presence of distant metastases, presence of gross extrathyroidal extension, and aggressive histological features are some of the criteria used to prognosticate disease outcomes. A recent large cohort of patients from the National Cancer Data Base (NCDB) has suggested that nodal disease is also associated with poorer overall survival in young patient.⁴⁷

Principles of Management

2015 ATA guidelines for DTC¹³: Hemithyroidectomy is recommended for low-risk tumor that are less than or equal to 1 cm. Diagnostic lobectomy should be considered for patients with a solitary, cytologically indeterminate nodule, as an initial surgical approach. The high-risk cases and tumors more than 4 cm in size should undergo total thyroidectomy. The incidence of regional metastasis is high in DTC, and the first draining node is level VI. Therapeutic neck dissection involves clearing level VI nodes in central compartment node-positive patients. Prophylactic central compartment dissection is not recommended routinely in low risk and T1/T2 tumors due to the associated morbidity of RLN injury or hypoparathyroidism. ATA recommends prophylactic central compartment dissection for locally advanced tumors, when the lateral compartment has metastasis or if such clearance helps in decision-making. Lateral compartment dissection involves clearing level II–V nodes in positive regional metastasis. Total thyroidectomy is preferred in patients with lesions > 4 cm in size, multifocal disease,

Table 6 Stage groups for DTC, ATC and MTC

Stage	T	N	M
Differentiated thyroid cancer (DTC)			
If age at diagnosis <55 y:			
I	Any T	Any N	M0
II	Any T	Any N	M1
If age at diagnosis ≥55 y:			
I	T1, T2	N0, Nx	M0
II	T1, T2	N1	M0
	T3	Any N	M0
III	T4a	Any N	M0
IV A	T4b	Any N	M0
IV B	Any T	Any N	M1
Anaplastic thyroid cancer (ATC)			
IV A	T1, T2, T3a	N0, Nx	M0
IV B	T1, T2, T3a	N1	M0
	T3b, T4	Any N	M0
IV C	Any T	Any M	M1
Medullary thyroid cancer (MTC)			
I	T1	N0	M0
II	T2, T3	N0	M0
III	T1, T2, T3	N1 a	M0
IV A	T1, T2, T3	N1 b	M0
	T4a	Any N	M0
IV B	T4b	Any N	M0
IV C	Any T	Any N	M1

positive for known mutations specific for carcinoma, cases of familial thyroid carcinoma or history of radiation exposure, and in cases with regional or distant metastasis which will be followed by RAI administration. Patients with indeterminate nodules who have the bilateral nodular disease, those with significant medical comorbidities, or those who prefer to undergo bilateral thyroidectomy to avoid the possibility of requiring a future surgery on the contralateral lobe, may undergo total thyroidectomy, assuming completion thyroidectomy would be recommended if the indeterminate nodule proved malignant following lobectomy. Surgery may be considered for growing nodules that are benign after repeat FNA if they are large (>4 cm), causing compressive or structural symptoms, or based upon clinical concern. Benign recurrent cystic thyroid nodules should be considered for surgical removal or percutaneous ethanol injection based on compressive symptoms and cosmetic concerns. Asymptomatic cystic nodules may be followed conservatively.¹³ Management of MTC and ATC is as per the 2015 ATA guidelines for MTC and 2021 ATA guidelines for ATC.^{19,20} The minimum surgery recommended for MTC is total thyroidectomy along with central compartment clearance. Therapeutic neck dissection clearing level II–V should be performed in cases with

regional metastasis. In the absence of regional metastasis, the decision regarding prophylactic neck dissection should be based on the calcitonin levels. For patients with confined (stage IVA/IVB) ATC in whom RO/R1 resection is anticipated, surgical resection is strongly recommended. Given the poor prognosis of ATC, radical resection (such as laryngectomy, tracheal/esophageal resections, and/or major vascular resections) is typically not advised and should only be considered very selectively after thorough discussion by the multidisciplinary team, as well as considering new information based upon present mutations and the availability of targeted therapies.

Follow-up

Cases with raised Tg level should undergo US of the neck to detect any locoregional recurrence which is then confirmed by performing the FNAC. However, Tg antibodies cause falsely low serum Tg level that can mask the presence of recurrent disease.⁴⁹ The stimulated Tg testing for recurrent thyroid cancer generally provides effective surveillance against disease recurrence, with a high negative predictive value (NPV) of 99%.⁵⁰ US is a very sensitive modality for detecting abnormal lymph nodes and masses in the thyroid bed and may also demonstrate persistent disease despite a negative stimulated Tg measurement. Thus, the ATA guidelines have emphasized the role of neck US in the follow-up of patients with PTC.¹³ The combination of stimulated Tg and neck US has been found to have a 96.3% sensitivity in detecting locoregional disease, as well as an NPV of 99.5%.⁵¹ The US finding of nodularity in the post-thyroidectomy bed is generally suspicious. Benign lesions causing nodules in the thyroid bed may be due to postoperative fibrosis, suture granulomata, reactive lymph nodes, parathyroid adenoma, and remnant thyroid tissue.⁴⁹

Follow-up Imaging and Management of Recurrent Disease Including Specific Interventional and Palliative Measures

A patient's response to initial therapy is measured with careful clinical assessment and review of serial Tg and antibody levels and can be classified into four categories: excellent, biochemically incomplete, structurally incomplete, or indeterminate. Six monthly nonstimulated Tg measurements and 12-monthly neck US is done for low-risk patients. Tg values have the highest sensitivity and specificity for the detection of recurrent disease after total thyroidectomy and RAI ablation. Serum Tg levels should be very low after total thyroidectomy with (<1 to 2 ng/mL) or without RAI ablation (<5 ng/mL). A progressive increase in serum Tg concentrations suggests recurrence and raises the need to perform imaging. High-resolution neck US can detect nodules as small as 2 to 3 mm in diameter. Only nodules 8 to 10 mm in size should be considered for biopsy. The sample should be sent for cytology and Tg measurement from the needle washout fluid. Suspicious lymph nodes less than 8 to 10 mm can be followed without biopsy with consideration for FNA or intervention if there is growth or if the node threatens vital structures such as a

functional recurrent laryngeal nerve. If there are no abnormalities within the first 2 years, patients are deemed to have an excellent response to therapy with a very low risk of recurrence and no additional surveillance is required. For the small group of patients with biochemical or structural persistent disease, surveillance beyond 2 years is needed. Surveillance of the intermediate-risk patients is 2 years in the absence of suspicious findings. Follow-up is similar to the low-risk group with the additional diagnostic RAI scan at 18 months to detect potential regional or distant disease. Routine cross-sectional imaging is limited to high-risk patients and those with raised Tg or abnormalities on the neck US. CECT of the neck and chest is advised for high-risk individuals and those who have growing Tg levels without obvious neck disease. MRI is recommended where CECT is contraindicated. Surveillance RAI scans can be useful in select patients if further RAI therapy is warranted. FDG-PET may be considered in patients in whom there is a suspicion of dedifferentiated disease.⁵²

Management of Recurrent Disease

Small volume suspicious nodes on US can be managed with serial follow-up US. FNA should be performed when there is evidence of disease progression or proximity to vital structures such as the recurrent laryngeal nerve with a view to revision surgery. For LNs more than 10 mm in size, in the previously undissected neck, a comprehensive neck dissection with preservation of uninvolved vital structures should be done. In the previously dissected neck, a limited neck dissection is performed in selected patients. Surgical resection in combination with RAI therapy is recommended for palpable nodal disease. At 5 years, subsequent nodal and distant recurrence-free survival are 89.2 and 93.7%, respectively.⁵²

Role of Ultrasound in Active Surveillance in Papillary Microcarcinoma

The recent update of the ATA guidelines (2015) incorporated active surveillance in management guidelines making it an acceptable option for appropriately selected patients with low-risk thyroid cancers to prevent overtreatment for PMCs.¹³ Patients with low-risk PMC are those lacking the high-risk characteristics as outlined by Ito and Miyauchi, such as tumors next to the trachea, tumors on the thyroid lobe's dorsal surface, tumors that may have invaded the recurrent laryngeal nerve, high-grade malignancy suggested by FNA biopsy results, presence of regional node metastasis, or presence of distant metastasis. Additionally, the ATA 2015 guideline update includes a few other criteria including patients with multiple comorbid conditions and high surgical risk, patients with short life expectancy (significant cardiopulmonary disease, other malignancies, and advanced age), and patients with concurrent medical or surgical issues needing to be addressed prior to thyroid surgery.¹³

Summary of Recommendations

- US is the imaging modality of choice for the evaluation of thyroid nodules.
- The American College of Radiology proposed ACR TI-RADS is a widely popular US-based thyroid nodule reporting system.
- ATA guidelines aid in classifying thyroid nodules based on US features into nodules with high, intermediate, and mild suspicion of malignancy.
- The detection of incidental thyroid nodules, assessment of thyroid nodal metastases, presurgical imaging for invasive disease, and evaluation for recurrence in the posttreatment neck are the four frequent circumstances in which cross-sectional imaging of thyroid cancer may be undertaken.

Synoptic reporting formats for radiograph, US, CT and MRI has been provided as ► **Supplementary Appendix 1** and **2** at the end of the text.

Parathyroid Gland, Introduction, Risk factors and Etiopathogenesis

PHPT is characterized by an abnormality in the parathyroid gland which causes excess production of parathyroid hormone and leads to an increase in serum calcium levels.⁵³ PHPT accounts for the leading cause of hypercalcemia. It is the third most prevalent endocrine condition.⁵⁴ A single parathyroid adenoma is the most common cause (85–90%) of PHPT. It may also result from multiglandular hyperplasia (approximately 6%), double parathyroid adenoma (approximately 4%), and parathyroid carcinoma (<1%) in the decreasing order of frequency.⁵⁵ The only definitive treatment for this condition remains surgical excision of the abnormal parathyroid.

Women are affected two to three times more often than men.⁵⁶ It is caused by the overproduction of PTH. Approximately, 5% of PHPT are part of hereditary syndromes, such as multiple endocrine neoplasia types 1, 2, and 4 (MEN-1, MEN-2, and MEN-4) and hyperparathyroidism-jaw tumor syndrome or as part of nonsyndromic familial pHPT. The rest (95%) are sporadic.⁵⁷ Radiation exposure has also been proposed as an etiology of pHPT, and this association was observed in subjects exposed to radiation fallout following the bombing in Hiroshima and the nuclear power plant accident in Chernobyl.⁵⁸

Epidemiology, Clinical Presentation in India and Global

Asymptomatic hypercalcemia diagnosed in routine blood investigations is the most common presentation of PHPT. “Bones, stones, abdominal moans, and psychic groans”—best describe the spectrum of clinical manifestations.⁵⁸ Skeletal disease, nephrolithiasis, and neurocognitive effects make the classic clinical presentations of PHPT.⁵⁹ Leading questions in otherwise asymptomatic subjects identify symptoms like

fatigue, decreased appetite, slowed cognition, and depression.⁵⁸ Symptoms including constipation, polydipsia, polyuria, and a decrease in appetite occur due to raised serum calcium levels. There is an association between hypertension, hyperlipidemia, diabetes, obesity, and PHPT.⁵⁵ There is an associated increased risk of cardiovascular disease, cerebrovascular disease, renal disease, fractures, and mortality.^{60–65} PHPT, hence, poses a significant threat to overall health.^{66,67}

Imaging Referral Guidelines

Clinical/ Diagnostic Work-Up Excluding Imaging

The evaluation of these patients comprises laboratory tests and localization which are based on imaging. PHPT is essentially diagnosed biochemically. Raised serum calcium levels along with high parathormone levels establish the diagnosis. However, these tests may be complemented with tests to confirm pHPT and rule out other causes of hypercalcemia. Serum phosphate levels are lowered in severe pHPT; 1,25-dihydroxyvitamin D levels either on the higher side of normal or slightly increased and few patients may develop hypomagnesemia. All patients who undergo imaging should have biochemically proven PHPT.⁶⁷

Imaging Guidelines

The goal of imaging is to allow the precise localization of the adenoma not diagnosis. US, nuclear imaging, and multiphase (four-dimensional [4D]) CT are the most commonly used imaging modalities for the preoperative localization of the parathyroid disease.⁵³ Most comparative studies have shown the superiority of 4D CT over other imaging modalities including higher diagnostic accuracy. 4D CT can help locate the disease in challenging scenarios when US and/or nuclear medicine imaging cannot give definitive results in cases of multiglandular disease (MGD), and recurrent PHPT.^{68–73} Minimally invasive parathyroidectomy (MIP) can be performed if single adenoma can be accurately localized on imaging. If on imaging MGD is diagnosed, bilateral neck

exploration (BNE) should be planned. If the disease cannot be localized on imaging, surgery can still be performed, but performing BNE might become necessary. Ectopic parathyroid glands have an incidence of approximately 16%.⁶³ There can be supernumerary glands which are known to exist in 3 to 13% of individuals with the total number of glands varying from 5 to 8.^{64,65} The European Association of Nuclear Medicine issued the first edition of the guideline on parathyroid imaging, and several new insights and techniques have been developed since then.

Parathyroid Four-Dimensional Computed Tomography Imaging

Radiologists play a crucial role in the surgical planning by helping clinicians in identifying and localizing the disease/ abnormal gland. The aim is to provide the clinician with an illustrative picture of the neck, locating lesions with respect to various surgical landmarks.

Image Acquisition

A three-phase protocol is used, consisting of noncontrast material-enhanced, arterial (beginning 30 seconds after the start of contrast material injection), and venous (beginning 60 seconds after the start of contrast material injection) phases. To reduce beam-hardening artifacts which may obscure small lesions in the lower neck and upper mediastinum, the use of 140 kVp instead of 120 kVp is suggested. The recommended acquisition parameters for 4D CT are listed in ►Table 7.

Imaging Findings

Parathyroid adenomas are lower in attenuation compared with the normal thyroid gland on noncontrast-enhanced images as normal thyroid parenchyma contains iodine (high density). However, parathyroid adenomas may appear similar in attenuation to abnormal thyroid gland on plain scan in cases of chronic hypothyroidism and autoimmune conditions like Hashimoto disease when the iodine content of the gland is low and thyroid gland shows low attenuation.

Table 7 Parathyroid 4-D CT protocol¹⁵

Protocol features	Parameters
Coverage	Maxilla to carina
Iodinated contrast material administration	100 mL (370 mg iodine/mL) injected at 4 mL/s, followed by 40 mL saline flush
Phases	Noncontrast, arterial, venous
Arterial phase	30 s after start of injection
Venous phase	60 s after start of injection
Thickness	1.25 mm
Tube voltage (kVp)	140
Tube current (mA)	Minimum 180 and maximum 300
Noise index	10
Pitch	1.375
DFOV (cm)	25

Abbreviations: CT, computed tomography; DFOV, display field of view.

On contrast-enhanced images, adenomas are known to show higher attenuation in the arterial phase and demonstrate wash-out in the venous phase, consequently having lower attenuation compared with the thyroid gland. These typical imaging findings may be seen in only about one-fifth of adenomas.⁷³ Parathyroid adenomas may show cystic foci, fat deposition, or calcifications. Common understanding says that MGD is more likely when multiple parathyroid lesions are identified. On the contrary, MGD is also more likely when no lesions can be demonstrated. If the largest lesion picked up on 4D CT measures less than 7 mm, it is likely MGD (79% specificity), even when only a single lesion is identified as lesions in MGD tend to be smaller in size.⁷⁴ Significantly raised parathyroid hormone in a young patient with calcifications on imaging should raise suspicion of parathyroid carcinoma, especially in large lesions. Exophytic thyroid nodules are diagnostic mimics of parathyroid adenomas on contrast-enhanced images. This problem can however be solved by evaluating the noncontrast images, where thyroid appears of higher attenuation as compared with parathyroid lesions. Correlation of findings with US can be helpful, where parathyroid adenomas are typically hypoechoic in contrast to thyroid nodules which are either isoechoic or hyperechoic relative to the thyroid gland. Lymph nodes are other common diagnostic mimics of parathyroid adenomas on both contrast and noncontrast-enhanced images, as both are hypoattenuating relative to the thyroid gland. On contrast-enhanced images, lymph nodes exhibit progressive enhancement, whereas parathyroid adenomas show wash-out. Identification of a fatty hilum can also help in differentiation. In patients with pHPT, one or more hyperfunctioning parathyroid glands are localized by radionuclide parathyroid imaging. It can help in the detection of ectopic and supernumerary glands.^{75,76}

Principles of Management

The only definitive cure remains surgical excision of the abnormal parathyroid tissue. Since the most common presentation is a single adenoma, it is excised preserving all other glands. This approach of unilateral exploration is called focused or Minimally invasive parathyroidectomy (MIP).⁷⁷ Bilateral neck exploration (BNE) is adopted in cases with four gland hyperplasia or in cases where imaging fails to localize the diseased gland. In BNE, all parathyroid glands are examined and abnormal/diseased tissue is resected leaving behind enough remnants to maintain normal calcium homeostasis. This approach usually encompasses the excision of 3 or 3.5 glands.⁶⁷ The most normal gland determined after assessing all the parathyroids should be preserved. MEN 1 is usually associated with MGD, and hence, BNE is suggested in the management of these cases. These patients should undergo subtotal or total parathyroidectomy with reimplantation which can be in the sternocleidomastoid muscle or the forearm. These sites should be marked with nonabsorbable sutures or clips to identify in cases when resurgery should occur. On the contrary, MEN 2A is usually mild and more commonly associated with single gland adenoma; therefore,

MIP may be followed in these cases. A single small midline incision may be sufficient for this procedure. In cases of ectopic or supernumerary glands larger incision may be required; hence, their documentation in radiology reports is essential.⁶⁷ In BNE, there is risk of injury to both recurrent laryngeal nerves but morbidity caused is low in experienced hands. BNE has been known to provide excellent cure rates. MIP uses smaller incisions and, thus, provides better cosmetic results with lesser operating times, shorter hospital stays, and is less costly. MIP has been known to provide results as good as that of BNE.^{78–80} The role of radiologists of ensuring patient undergoing MIP lies in providing precise localization of a solitary parathyroid adenoma. Preoperative imaging is preferred in all patients with PHPT where a surgeon can plan MIP for well-localized solitary adenoma. The recent international guidelines make preoperative localization of parathyroid disease mandatory in patients with persistent or recurrent PHPT after prior parathyroid surgery, in view of higher risks of morbidity with repeat parathyroid surgery.⁸¹

Summary of Recommendations

- The radiologists' aim in parathyroid imaging is to provide the clinician with an illustrative picture of the neck, locating lesions with respect to landmarks.
- Imaging helps in the detection of solitary versus multiglandular disease, ectopic, and supernumerary glands with precise localization.
- On 4DCT imaging, adenomas show higher attenuation than thyroid parenchyma in the arterial phase and demonstrate wash-out on in the venous phase.
- Imaging can help to decide the plan of management by detecting solitary parathyroid adenoma which can undergo Minimally invasive parathyroidectomy (MIP) or multiglandular disease where BNE will have to be done.

Salivary Glands, Introduction, Risk Factors, and Etiopathogenesis

The etiology of the salivary gland is poorly understood; however, one of the known risk factors of salivary gland neoplasms is irradiation to the head and neck.⁸² For instance, an increased incidence was noted in the survivors from Hiroshima and Nagasaki. Male sex, obesity, human immunodeficiency virus infection, family history of cancer, industrial exposure to occupational radiation, formaldehyde, or nickel compounds are associated with an increased risk of salivary gland malignancies.^{83,84}

Epidemiology and Clinical Features

Salivary gland tumors account for approximately 0.5% of all neoplasms. The most common location is the parotid gland (70%), followed by submandibular gland, minor salivary glands, and sublingual gland, in descending order. In the parotid, approximately 80% of neoplasms are benign, while 20% are malignant. Benign pleomorphic adenomas comprise around 65% of all parotid tumors, followed by adenolymphoma

or Warthin's tumor (15–20%). Malignant epithelial salivary gland tumors encompass approximately 20% of parotid tumors, 40 to 50% of submandibular gland tumors, 50% of minor salivary gland tumors, and 90% of sublingual gland tumors. The commonest malignant neoplasms include adenoid cystic carcinoma and mucoepidermoid carcinoma.^{85,86} In 2020, 7,850 new cases of salivary gland malignancies were detected in India (0.59%), while 5,127 patients died.⁸⁷ Painless palpable mass in the parotid or submandibular gland is the commonest symptom, and enlarged lymph nodes may be seen with malignancies. Pain and facial nerve palsy may be seen with parotid tumors.⁸⁸

Clinical/ Diagnostic Work-Up Excluding Imaging

The initial step in the workup of salivary gland neoplasms (SGNs) is a thorough history and physical examination. Both Benign and malignant SGNs may typically manifest as a painless lump in the preauricular or submandibular region. However, a prior history of pain, rapid growth, or symptoms suggesting cranial nerve abnormalities should warn of possible malignancy. A physical examination demonstrating severe tenderness, cranial neuropathy including facial or oral cavity weakness or numbness, lymphadenopathy, or fixation of masses to skin or other surrounding structures is usually associated with malignancy.^{89,90} ASCO consensus guidelines suggest that FNAC should be performed to establish the tissue diagnosis and to determine the high-grade features. Core needle biopsy should be considered where the FNAC provides inadequate tissue or for deep-seated lesions.

Imaging Referral Guidelines

Appropriate selection and use of imaging studies are crucial for the proper management of patients with SGNs. As per NCCN guidelines, initial evaluation with imaging of the primary site is to be done with CT and/or MRI. MRI is generally preferred over CT in patients with suspected SGNs because of the superior soft-tissue resolution and its ability to better delineate perineural invasion. Contrast enhanced MRI (CE-MRI) is the preferred modality if there is suspected intracranial extension. Diffusion weighted imaging (DWI) offers additional information that may increase the concern for malignancy. However, CT is complementary to MRI for the evaluation of bony erosion or cartilage invasion.^{91–93}

Imaging recommendations by American Society of Clinical Oncology (ASCO) guidelines⁹⁴:

1. Imaging with neck US, CT with intravenous contrast, and/or MRI of the neck and primary site should be performed in patients with a suspicion of a salivary gland tumor.
2. US may be used for the initial evaluation of a new mass in adult patients, differentiating extra from intraglandular masses and identifying features that are suspicious for malignancy.

3. When there is a concern for malignancy such as neck adenopathy or cranial nerve dysfunction or full tumor delineation is required for operative planning, CE-MRI of the glands and neck is recommended particularly when there is a concern for skull base invasion and/or perineural tumor spread along the large named nerves.
4. In patients with suspicion of salivary gland cancer and involvement of adjacent bone, CT of the neck with IV contrast should be performed.
5. CE-MRI with a diffusion sequence of the neck and skull base is recommended for patients with suspicion of salivary gland cancer with concern for perineural invasion and/or skull base involvement.
6. PET/CT from the skull base to mid-thighs may be performed for patients with advanced-stage high-grade salivary gland cancers. Although there is no literature to support the use of 18 F-FDG PET/CT for initial evaluation as it has poor spatial resolution, it most accurately predicts the extent of nodal and distant metastasis disease and identifies locoregional recurrence.⁹⁵

Imaging Recommendations for Diagnosis, Staging, and Management of Salivary Gland Tumors

Imaging plays a pivotal role in masses of salivary gland origin by defining its location, detecting malignant features, assessing local extension and invasion, staging the tumors according to the TNM classification, and also to assess the feasibility of surgery, being the primary treatment of most salivary gland tumors. It defines the location of the salivary gland tumors, whether it is intra- or extraglandular or is superficial or deep to the facial nerve, laterality (unilateral or bilateral), focality (unifocal or multifocal), characteristics of the tumor, the presence of perineural spread (PNS), and detects nodal metastasis and distant/systemic involvement. High-resolution US is the preferred initial imaging modality for lesions involving the superficial part of the parotid, submandibular, and sublingual gland as it provides excellent resolution and characterization of lesions as well as cervical node involvement without a radiation hazard. However, for all tumors detected in the sublingual gland, an MRI should be performed as the risk of malignancy is high. It is readily combined with FNAC. On the contrary, MRI is indicated in all patients with lesions of the deep lobe of parotid gland, minor salivary gland tumors, and a malignant tumor is suspected clinically.

Imaging in Diagnosis

Ultrasound

High-resolution US using a probe of frequency of 5 to 12 MHz with the Doppler technique plays an important role in the initial diagnostic workup for superficial parotid and submandibular swelling. It should be done bilaterally in paired glands in the same session. Benign tumors of the salivary gland are more common than the malignant lesions (3%).⁹⁶ US helps in the diagnosis of benign tumors by characterizing the size, echogenicity, margins, and vascularity of the lesion.

US is also an optimal tool to guide fine-needle aspiration cytology with its easy availability and ability to provide real-time image guidance and has two salient roles namely, diagnosis of primary and staging of lymph node metastases. The pitfall of US in diagnosis is its limited visualization of the deep lobe of the parotid gland.⁹⁷ The minor salivary glands are also located in the mucosa of the oral cavity, pharynx, and tracheobronchial tree, but these areas are inaccessible for the evaluation by US. Additionally, as the first station, nodal drainage from the oral cavity and pharyngeal mucosal space is retropharyngeal nodes, it is also not accessible by conventional US. High variability of results has been reported for US studies, with sensitivity ranging from 62 to 84%, specificity from 88 to 96%, and accuracy from 57 to 96%,¹⁹ with the plausible reason being that US is an operator-dependent modality.

Magnetic Resonance Imaging

MRI remains the favored imaging modality for staging and is indicated in all patients in whom a malignant tumor is suspected clinically because of its invaluable soft tissue contrast and multiplanar representation, detecting deep tissue extension, marrow infiltration, and importantly PNS and localizing parotid portion of facial nerve using high-resolution techniques. Routine locoregional tumor mapping is based on high-resolution multiplanar turbo spin-echo (TSE) T1, T2, and postcontrast (gadolinium) images with fat saturation (FS). With the administration of contrast, depiction of subtle tumor extension is possible, however, the main function is in the assessment of invasion into adjacent structures and demonstration of abnormal nodular enhancement along the facial or trigeminal nerves suggestive of PNS.⁹⁸ Typical imaging characteristics of high-grade malignant salivary gland tumors are ill-defined borders, low T2 SI, adjacent tissue or compartment invasion, heterogeneous enhancement, central necrosis, cystic changes, and bone erosion, whereas low-grade malignant tumors may resemble benign lesions showing well-defined borders, circumscribed margins, high T2 SI, and homogenous postcontrast enhancement.⁹⁹ Lymph node metastases are a feature of malignant tumors. DWI is also used for the differentiation of malignant from benign tumors as high-grade malignant tumors show an apparent diffusion coefficient value between 0.79 and 1.10, 103 /mm²/s, which is significantly lower than that of benign tumors.¹⁰⁰ Time-intensity curves are plotted with the help of dynamic contrast-enhanced MR, showing four different patterns: type A—persistent pattern (T-peak of >120 s without washout ratio—WR) representing benign disease, type B—plateau pattern (T-peak of >120 seconds with > 30% WR) representing Warthin's tumors, type C—washout pattern (T-peak of <120 seconds with < 30% WR) representing malignant and benign neoplasms, and type D—flat pattern which is flat curve representing cysts.¹⁰¹

Contrast-Enhanced Computed Tomography

Indications of performing CECT are a contraindication to MRI (claustrophobia, cardiac pacemaker, or ferro metallic prosthesis) or as an adjunct to MRI with suspicious bone

erosion. Thin slices are acquired (0.6–1.0 mm) with both high kernel bone and soft tissue algorithms and multiplanar reconstruction.

Fluorodeoxyglucose Positron Emission Tomography Computed Tomography

The role of FDG PET/CT in the initial staging of salivary gland tumors is currently controversial; however, early detection of distant metastasis is one of its advantages. Distant metastases are common at presentation with high-grade malignant tumors as compared with low grade and also they show low avidity for FDG PET CT is not routinely recommended for the evaluation of low-grade malignant tumors.¹⁰²

Imaging During Follow-Up

Clinical examination becomes onerous after curative treatment due to altered anatomy and fibrosis. Seventy percent of recurrences of high-grade malignant tumors are within three years; hence, follow-up periods are reported from 3 to 10 years or lifelong.^{103,104} The most common sites of distant metastasis are located within the lung followed by bones, liver, and brain.

- US: It is a rapid, easily available modality to differentiate solid from cystic lesions in the superficial areas of the head and neck, look for its vascularity, and to rule out nodal recurrence. Additionally, US-guided FNAC helps in establishing the diagnosis of recurrent disease or nonmalignant complications.
- MRI: MRI with DWI and DCE-MRI helps in the recognition of early recurrent disease during follow-up. It is recommended to have a baseline study at 3 months after the completion of therapy that serves as an invaluable road map and increases the level of confidence to demonstrate or exclude recurrent disease.¹⁰⁵ As per the ASCO consensus guidelines, serial MRI should be performed at 6 to 12 months for initial 2 years in cases where the probability of locoregional recurrence is high including high-grade tumors and locally advanced tumors. Subsequent to it, imaging should be performed in accordance with the symptoms and clinical examination findings. After the completion of 5 years, chest CT may be performed to detect distant metastasis in cases with high-risk histopathology features.
- FDG PET/CT: Recent papers do not demonstrate a significant contribution during surveillance due to a lot of false-positive and false-negative results.¹⁰⁶

Principles of Management

Surgery is the mainstay of treatment and should be offered to all patients with a resectable locoregional disease without distant metastasis. The surgery for the primary thyroid disease is determined by the extent of local disease. Superficial parotidectomy is done for small lesions confined to the superficial lobe, total conservative parotidectomy for tumors reaching or involving the deep lobe, T3/4 or high-grade

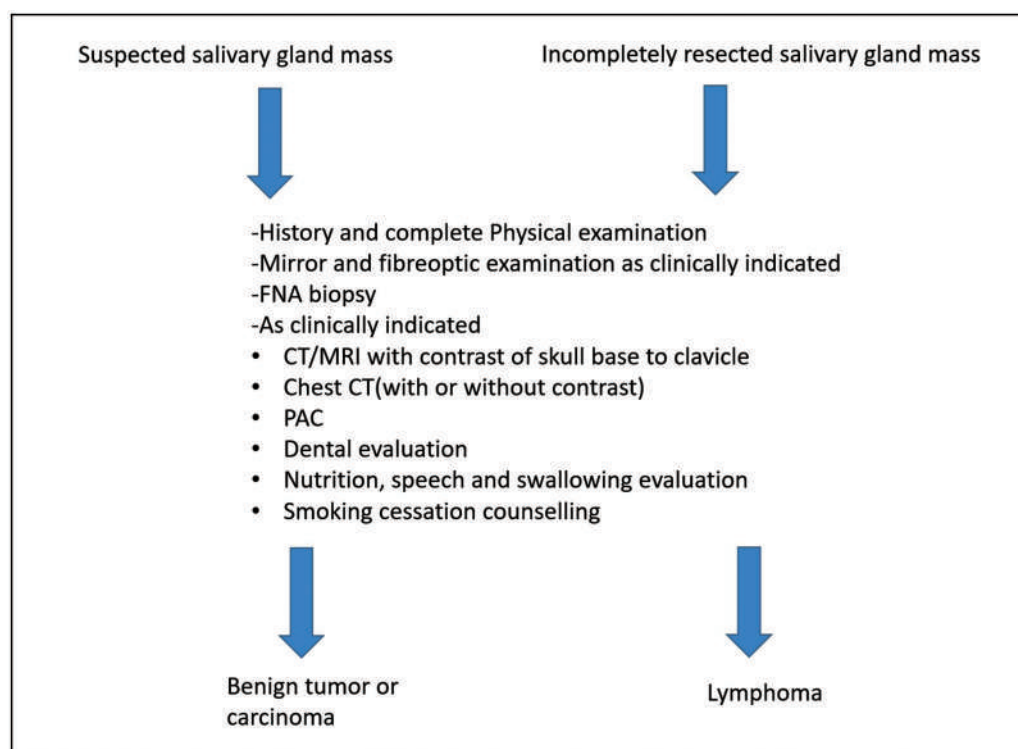


Fig. 1 Imaging recommendations by NCCN guidelines.

tumors and radical or extended radical parotidectomy for extensive disease involving the surrounding structures. Every attempt should be made to preserve the functional facial nerve which should only be sacrificed if grossly infiltrated or involved by the disease. Elective neck dissection clearing level II–IV should be performed for high-grade tumors and locally advanced T3/4 lesions. Therapeutic neck dissection clearing level I–V should be done in cases with regional metastasis. Adjuvant radiotherapy should be administered based on the high-risk features on histopathology like high grade, T3/4 disease, regional metastasis, perineural invasion, lymphovascular emboli, etc. Any locoregional recurrence if completely resectable should be excised and adjuvant radiotherapy if feasible should be offered. Even if the patients develop distant metastasis locoregional disease clearance should be considered especially in low-grade tumors if the metastasis is not rapidly progressing or endangering life. Radiotherapy should be recommended for unresectable tumors. The role of upfront or adjuvant chemotherapy is not established and hence such an approach should be considered mainly in a trial setting (ref ASCO consensus guidelines).

Conventional follow-up surveillance regimens include a detailed history and clinical examination every 1 to 3 months for the 1st year after completion of treatment, every 2 to 6 months in the second year, and every 4 to 8 months for years 3 to 5. When 5 years have elapsed after the completion of treatment without evidence of recurrence, the patient may follow up on an annual basis. Reimaging of the primary site and neck may be considered for anatomic areas difficult to visualize or palpate on clinical examination. MRI is the

modality of choice for reimaging. PET/CT has limited utility in initial staging and has little utility in routine posttreatment surveillance. Chest imaging with CT with or without contrast should be obtained for surveillance imaging in ACC, due to the propensity for delayed distant metastatic disease.

Conflict Of Interest

None declared.

References

- 1 Tufano RP, Clayman G, Heller KS, et al; American Thyroid Association Surgical Affairs Committee Writing Task Force. Management of recurrent/persistent nodal disease in patients with differentiated thyroid cancer: a critical review of the risks and benefits of surgical intervention versus active surveillance. *Thyroid* 2015;25(01):15–27
- 2 Noone AM, Cronin KA, Altekruse SF, et al. Cancer incidence and survival trends by subtype using data from the surveillance epidemiology and end results program, 1992–2013. *Cancer Epidemiol Biomarkers Prev* 2017;26(04):632–641
- 3 John AM, Jacob PM, Oommen R, Nair S, Nair A, Rajaratnam S. Our experience with papillary thyroid microcancer. *Indian J Endocrinol Metab* 2014;18(03):410–413
- 4 Liu Y, Su L, Xiao H. Review of factors related to the thyroid cancer epidemic. *Int J Endocrinol* 2017;2017:5308635
- 5 Crnčić TB, Tomaš MI, Girotto N, Ivanković SG. Risk factors for thyroid cancer: what do we know so far? *Acta Clin Croat* 2020;59 (Suppl 1):66–72
- 6 Bonnefond S, Davies TF. Thyroid cancer-risks and causes. *Oncol Hematol Rev* 2014;10(02):14451
- 7 Xing M. Molecular pathogenesis and mechanisms of thyroid cancer. *Nat Rev Cancer* 2013;13(03):184–199
- 8 Patel KN, Yip L, Lubitz CC, et al. The American Association of Endocrine Surgeons Guidelines for the definitive surgical

- management of thyroid disease in adults. *Ann Surg* 2020;271(03):e21–e93
- 9 Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71(03):209–249
- 10 O'Neill CJ, Oucharek J, Learoyd D, Sidhu SB. Standard and emerging therapies for metastatic differentiated thyroid cancer. *Oncologist* 2010;15(02):146–156
- 11 Lechner MG, Herschman JM. Thyroid Nodules and Cancer in the Elderly. In: *Endotext*. South Dartmouth, MA: MDText.com, Inc.; 2000 PMID: 25905203.
- 12 Lee JY, Baek JH, Ha EJ, et al; Korean Society of Thyroid Radiology (KSThR) and Korean Society of Radiology. 2020 imaging guidelines for thyroid nodules and differentiated thyroid cancer: Korean Society of Thyroid Radiology. *Korean J Radiol* 2021;22(05):840–860
- 13 Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 2016;26(01):1–133
- 14 Gharib H, Papini E, Paschke R, et al; AACE/AME/ETA Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: executive Summary of recommendations. *J Endocrinol Invest* 2010;33(5, Suppl):287–291
- 15 Perros P, Boelaert K, Colley S, et al; British Thyroid Association. Guidelines for the management of thyroid cancer. *Clin Endocrinol (Oxf)* 2014;81(Suppl 1):1–122
- 16 Shin JH, Baek JH, Chung J, et al; Korean Society of Thyroid Radiology (KSThR) and Korean Society of Radiology. Ultrasonography diagnosis and imaging-based management of thyroid nodules: revised Korean Society of Thyroid Radiology Consensus Statement and Recommendations. *Korean J Radiol* 2016;17(03):370–395
- 17 Yi KH, Park YJ, Koong SS, et al. Revised Korean Thyroid Association management guidelines for patients with thyroid nodules and thyroid cancer. *Endocrinol Metab (Seoul)* 2010;25(04):270–297
- 18 www.nccn.org
- 19 Wells SA Jr, Asa SL, Dralle H, et al; American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid* 2015;25(06):567–610
- 20 Bible KC, Kebebew E, Brierley J, et al. 2021 American thyroid association guidelines for management of patients with anaplastic thyroid cancer: American thyroid association anaplastic thyroid cancer guidelines task force. *Thyroid* 2021;31(03):337–386
- 21 Seib CD, Harari A, Conte FA, Duh QY, Clark OH, Gosnell JE. Utility of serum thyroglobulin measurements after prophylactic thyroidectomy in patients with hereditary medullary thyroid cancer. *Surgery* 2014;156(02):394–398
- 22 Cibas ES, Ali SZ. The 2017 Bethesda System for reporting thyroid cytopathology. *Thyroid* 2017;27(11):1341–1346
- 23 Birtwhistle R, Morissette K, Dickinson JA, et al; Canadian Task Force on Preventive Health Care. Recommendation on screening adults for asymptomatic thyroid dysfunction in primary care. *CMAJ* 2019;191(46):E1274–E1280
- 24 Morrison SA, Suh H, Hodin RA. The surgical management of thyroid cancer. *Rambam Maimonides Med J* 2014;5(02):e0008
- 25 Wong KT, Ahuja AT. Ultrasound of thyroid cancer. *Cancer Imaging* 2005;5(01):157–166
- 26 Chng CL, Tan HC, Too CW, et al. Diagnostic performance of ATA, BTA and TIRADS sonographic patterns in the prediction of malignancy in histologically proven thyroid nodules. *Singapore Med J* 2018;59(11):578–583
- 27 Gharib H, Papini E, Garber JR, et al; American association of clinical endocrinologists, American college of endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules-2016 update appendix. *Endocrine practice* 2016;22:1–60
- 28 Lee YJ, Kim DW, Shin GW, et al. Comparison of ultrasonography features and K-TIRADS for isthmus and lobar papillary thyroid carcinomas: a single-center study. *Front Endocrinol (Lausanne)* 2020;11:328
- 29 Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L. European thyroid association guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: the EU-TIRADS. *Eur Thyroid J* 2017;6(05):225–237
- 30 Tessler FN, Middleton WD, Grant EG, et al. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): white paper of the ACR TI-RADS committee. *J Am Coll Radiol* 2017;14(05):587–595
- 31 Grani G, Lamartina L, Ascoli V, et al. Reducing the number of unnecessary thyroid biopsies while improving diagnostic accuracy: toward the “right” TIRADS. *J Clin Endocrinol Metab* 2019;104(01):95–102
- 32 Tessler FN, Middleton WD, Grant EG, et al. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): white paper of the ACR TI-RADS Committee. *J Amer Coll Radiol* 2017;14(05):587–595
- 33 Hoang JK, Branstetter BF IV, Gafton AR, Lee WK, Glastonbury CM. Imaging of thyroid carcinoma with CT and MRI: approaches to common scenarios. *Cancer Imaging* 2013;13(01):128–139
- 34 Kebebew E, Clark OH. Differentiated thyroid cancer: “complete” rational approach. *World J Surg* 2000;24(08):942–951
- 35 King AD. Imaging for staging and management of thyroid cancer. *Cancer Imaging* 2008;8(01):57–69
- 36 Ahuja AT, Chow L, Chick W, King W, Metreweli C. Metastatic cervical nodes in papillary carcinoma of the thyroid: ultrasound and histological correlation. *Clin Radiol* 1995;50(04):229–231
- 37 Yeh MW, Bauer AJ, Bernet VA, et al; American Thyroid Association Surgical Affairs Committee Writing Task Force. American Thyroid Association statement on preoperative imaging for thyroid cancer surgery. *Thyroid* 2015;25(01):3–14
- 38 Kim MJ, Kim EK, Park SI, et al. US-guided fine-needle aspiration of thyroid nodules: indications, techniques, results. *Radiographics* 2008;28(07):1869–1886, discussion 1887
- 39 Bhatki AM, Brewer B, Robinson-Smith T, Nikiforov Y, Steward DL. Adequacy of surgeon-performed ultrasound-guided thyroid fine-needle aspiration biopsy. *Otolaryngol Head Neck Surg* 2008;139(01):27–31
- 40 Boi F, Baghino G, Atzeni F, Lai ML, Faa G, Mariotti S. The diagnostic value for differentiated thyroid carcinoma metastases of thyroglobulin (Tg) measurement in washout fluid from fine-needle aspiration biopsy of neck lymph nodes is maintained in the presence of circulating anti-Tg antibodies. *J Clin Endocrinol Metab* 2006;91(04):1364–1369
- 41 Snozek CL, Chambers EP, Reading CC, et al. Serum thyroglobulin, high-resolution ultrasound, and lymph node thyroglobulin in diagnosis of differentiated thyroid carcinoma nodal metastases. *J Clin Endocrinol Metab* 2007;92(11):4278–4281
- 42 Boi F, Maurelli I, Pinna G, et al. Calcitonin measurement in washout fluid from fine needle aspiration of neck masses in patients with primary and metastatic medullary thyroid carcinoma. *J Clin Endocrinol Metab* 2007;92(06):2115–2118
- 43 Tran Cao HS, Johnston LE, Chang DC, Bouvet M. A critical analysis of the American Joint Committee on Cancer (AJCC) staging system for differentiated thyroid carcinoma in young patients on the basis of the Surveillance, Epidemiology, and End Results (SEER) registry. *Surgery* 2012;152(02):145–151
- 44 Adam MA, Thomas S, Roman SA, Hyslop T, Sosa JA. Rethinking the current American Joint Committee on cancer TNM Staging

- system for medullary thyroid cancer. *JAMA Surg* 2017;152(09):869–876
- 45 Perrier ND, Brierley JD, Tuttle RM. Differentiated and anaplastic thyroid carcinoma: major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin* 2018;68(01):55–63
 - 46 Lang BH, Lo CY, Chan WF, Lam KY, Wan KY. Staging systems for papillary thyroid carcinoma: a review and comparison. *Ann Surg* 2007;245(03):366–378
 - 47 Adam MA, Pura J, Goffredo P, et al. Presence and number of lymph node metastases are associated with compromised survival for patients younger than age 45 years with papillary thyroid cancer. *J Clin Oncol* 2015;33(21):2370–2375
 - 48 Zaheer S, Tan A, Ang ES, et al. Post-thyroidectomy neck ultrasonography in patients with thyroid cancer and a review of the literature. *Singapore Med J* 2014;55(04):177–182, quiz 183
 - 49 Schlumberger M, Berg G, Cohen O, et al. Follow-up of low-risk patients with differentiated thyroid carcinoma: a European perspective. *Eur J Endocrinol* 2004;150(02):105–112
 - 50 Pacini F, Molinaro E, Castagna MG, et al. Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 2003;88(08):3668–3673
 - 51 Wang LY, Ganly I. Post-treatment surveillance of thyroid cancer. *Eur J Surg Oncol* 2018;44(03):357–366
 - 52 Ito Y, Miyauchi A. Active surveillance of low-risk papillary thyroid microcarcinomas. *Gland Surg* 2020;9(05):1663–1673
 - 53 Bunch PM, Kelly HR. Preoperative imaging techniques in primary hyperparathyroidism: a review. *JAMA Otolaryngol Head Neck Surg* 2018;144(10):929–937
 - 54 Fraser WD. Hyperparathyroidism. *Lancet* 2009;374(9684):145–158
 - 55 Ruda JM, Hollenbeak CS, Stack BC Jr. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. *Otolaryngol Head Neck Surg* 2005;132(03):359–372
 - 56 Yeh MW, Ituarte PH, Zhou HC, et al. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. *J Clin Endocrinol Metab* 2013;98(03):1122–1129
 - 57 Bilezikian JP, Bandeira L, Khan A, Cusano NE. Hyperparathyroidism. *Lancet* 2018;391(10116):168–178
 - 58 Machado NN, Wilhelm SM. Diagnosis and evaluation of primary hyperparathyroidism. *Surg Clin North Am* 2019;99(04):649–666
 - 59 Palmér M, Adami HO, Bergström R, Jakobsson S, Akerström G, Ljunghall S. Survival and renal function in untreated hypercalcaemia. Population-based cohort study with 14 years of follow-up. *Lancet* 1987;1(8524):59–62
 - 60 Palmér M, Adami HO, Bergström R, Akerström G, Ljunghall S. Mortality after surgery for primary hyperparathyroidism: a follow-up of 441 patients operated on from 1956 to 1979. *Surgery* 1987;102(01):1–7
 - 61 Hedbäck G, Tisell LE, Bengtsson BA, Hedman I, Oden A. Premature death in patients operated on for primary hyperparathyroidism. *World J Surg* 1990;14(06):829–835, discussion 836
 - 62 Leifsson BG, Ahrén B. Serum calcium and survival in a large health screening program. *J Clin Endocrinol Metab* 1996;81(06):2149–2153
 - 63 Hedbäck G, Odén A. Increased risk of death from primary hyperparathyroidism—an update. *Eur J Clin Invest* 1998;28(04):271–276
 - 64 Yu N, Donnan PT, Flynn RW, et al; The Parathyroid Epidemiology and Audit Research Study (PEARS) Increased mortality and morbidity in mild primary hyperparathyroid patients. *Clin Endocrinol (Oxf)* 2010;73(01):30–34
 - 65 Zanolco K, Angelos P, Sturgeon C. Cost-effectiveness analysis of parathyroidectomy for asymptomatic primary hyperparathyroidism. *Surgery* 2006;140(06):874–881, discussion 881–882
 - 66 Zanolco KA, Wu JX, Yeh MW. Parathyroidectomy for asymptomatic primary hyperparathyroidism: a revised cost-effectiveness analysis incorporating fracture risk reduction. *Surgery* 2017;161(01):16–24
 - 67 Bunch PM, Randolph GW, Brooks JA, George V, Cannon J, Kelly HR. Parathyroid 4D CT: what the surgeon wants to know. *RadioGraphics* 2020;40(05):1383–1394
 - 68 Rodgers SE, Hunter GJ, Hamberg LM, et al. Improved preoperative planning for directed parathyroidectomy with 4-dimensional computed tomography. *Surgery* 2006;140(06):932–940, discussion 940–941
 - 69 Suh YJ, Choi JY, Kim SJ, et al. Comparison of 4D CT, ultrasonography, and 99mTc sestamibi SPECT/CT in localizing single-gland primary hyperparathyroidism. *Otolaryngol Head Neck Surg* 2015;152(03):438–443
 - 70 Kelly HR, Hamberg LM, Hunter GJ. 4D-CT for preoperative localization of abnormal parathyroid glands in patients with hyperparathyroidism: accuracy and ability to stratify patients by unilateral versus bilateral disease in surgery-naïve and re-exploration patients. *AJNR Am J Neuroradiol* 2014;35(01):176–181
 - 71 Tian Y, Tanny ST, Einsiedel P, et al. Four-dimensional computed tomography: clinical impact for patients with primary hyperparathyroidism. *Ann Surg Oncol* 2018;25(01):117–121
 - 72 Yeh R, Tay YD, Tabacco G, et al. Diagnostic performance of 4D CT and Sestamibi SPECT/CT in localizing parathyroid adenomas in primary hyperparathyroidism. *Radiology* 2019;291(02):469–476
 - 73 Bahl M, Sepahdari AR, Sosa JA, Hoang JK. Parathyroid adenomas and hyperplasia on four-dimensional CT scans: three patterns of enhancement relative to the thyroid gland justify a three-phase protocol. *Radiology* 2015;277(02):454–462
 - 74 Sho S, Yilma M, Yeh MW, et al. Prospective validation of two 4D-CT-based scoring systems for prediction of multigland disease in primary hyperparathyroidism. *AJNR Am J Neuroradiol* 2016;37(12):2323–2327
 - 75 Raghavan P, Durst CR, Ornan DA, et al. Dynamic CT for parathyroid disease: are multiple phases necessary? *AJNR Am J Neuroradiol* 2014;35(10):1959–1964
 - 76 Griffith B, Chaudhary H, Mahmood G, et al. Accuracy of 2-phase parathyroid CT for the preoperative localization of parathyroid adenomas in primary hyperparathyroidism. *AJNR Am J Neuroradiol* 2015;36(12):2373–2379
 - 77 Jason DS, Balentine CJ. Intraoperative decision making in parathyroid surgery. *Surg Clin North Am* 2019;99(04):681–691
 - 78 Wilhelm SM, Wang TS, Ruan DT, et al. The American Association of Endocrine Surgeons guidelines for definitive management of primary hyperparathyroidism. *JAMA Surg* 2016;151(10):959–968
 - 79 Minisola S, Cipriani C, Diacinti D, et al. Imaging of the parathyroid glands in primary hyperparathyroidism. *Eur J Endocrinol* 2016;174(01):D1–D8
 - 80 Parangi S, Pandian TK, Thompson G. Minimally invasive single gland parathyroid exploration. *Surgery of the thyroid and parathyroid glands*. Amsterdam, the Netherlands: Elsevier; 2021:529–536
 - 81 Stack BC Jr, Tolley NS, Bartel TB, et al. AHNS Series: do you know your guidelines? Optimizing outcomes in reoperative parathyroid surgery: definitive multidisciplinary joint consensus guidelines of the American Head and Neck Society and the British Association of Endocrine and Thyroid Surgeons. *Head Neck* 2018;40(08):1617–1629
 - 82 Schneider AB, Lubin J, Ron E, et al. Salivary gland tumors after childhood radiation treatment for benign conditions of the head and neck: dose-response relationships. *Radiat Res* 1998;149(06):625–630
 - 83 Guzzo M, Locati LD, Prott FJ, Gatta G, McGurk M, Licitra L. Major and minor salivary gland tumors. *Crit Rev Oncol Hematol* 2010;74(02):134–148

- 84 Forrest J, Campbell P, Kreiger N, Sloan M. Salivary gland cancer: an exploratory analysis of dietary factors. *Nutr Cancer* 2008;60(04):469–473
- 85 Kessler AT, Bhatt AA. Review of the major and minor salivary glands, part 2: neoplasms and tumor-like lesions. *J Clin Imaging Sci* 2018;8:48
- 86 Freling N, Crippa F, Maroldi R. Staging and follow-up of high-grade malignant salivary gland tumours: the role of traditional versus functional imaging approaches—a review. *Oral Oncol* 2016;60:157–166
- 87 Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer; 2020
- 88 Thoeny HC. Imaging of salivary gland tumours. *Cancer Imaging* 2007;7(01):52–62
- 89 Wierzbicka M, Kopeć T, Szyfter W, Kereiakes T, Bem G. The presence of facial nerve weakness on diagnosis of a parotid gland malignant process. *Eur Arch Otorhinolaryngol* 2012;269(04):1177–1182
- 90 Mantravadi AV, Moore MG, Rassekh CH. AHNS series: do you know your guidelines? Diagnosis and management of salivary gland tumors. *Head Neck* 2019;41(02):269–280
- 91 Pfister DG, Spencer S, Adelstein D, et al. Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2020;18(07):873–898
- 92 Zheng N, Li R, Liu W, Shao S, Jiang S. The diagnostic value of combining conventional, diffusion-weighted imaging and dynamic contrast-enhanced MRI for salivary gland tumors. *Br J Radiol* 2018;91(1089):20170707
- 93 Ma G, Zhu LN, Su GY, et al. Histogram analysis of apparent diffusion coefficient maps for differentiating malignant from benign parotid gland tumors. *Eur Arch Otorhinolaryngol* 2018;275(08):2151–2157
- 94 Geiger JL, Ismaila N, Beadle B, et al. Management of salivary gland malignancy: ASCO guideline. *J Clin Oncol* 2021;39(17):1909–1941
- 95 Cermik TF, Mavi A, Acikgoz G, Houseni M, Dadparvar S, Alavi A. FDG PET in detecting primary and recurrent malignant salivary gland tumors. *Clin Nucl Med* 2007;32(04):286–291
- 96 WERING B. Neoplasms of the salivary glands. *Atlas of head and neck pathology*. 2008:582–91.
- 97 Lee YY, Wong KT, King AD, Ahuja AT. Imaging of salivary gland tumours. *Eur J Radiol* 2008;66(03):419–436
- 98 Terhaard CH, Lubsen H, Van der Tweel I, et al; Dutch Head and Neck Oncology Cooperative Group. Salivary gland carcinoma: independent prognostic factors for locoregional control, distant metastases, and overall survival: results of the Dutch head and neck oncology cooperative group. *Head Neck* 2004;26(08):681–692, discussion 692–693
- 99 Christe A, Waldherr C, Hallett R, Zbaeren P, Thoeny H. MR imaging of parotid tumors: typical lesion characteristics in MR imaging improve discrimination between benign and malignant disease. *AJNR Am J Neuroradiol* 2011;32(07):1202–1207
- 100 Habermann CR, Arndt C, Graessner J, et al. Diffusion-weighted echo-planar MR imaging of primary parotid gland tumors: is a prediction of different histologic subtypes possible? *AJNR Am J Neuroradiol* 2009;30(03):591–596
- 101 Yabuuchi H, Fukuya T, Tajima T, Hachitanda Y, Tomita K, Koga M. Salivary gland tumors: diagnostic value of gadolinium-enhanced dynamic MR imaging with histopathologic correlation. *Radiology* 2003;226(02):345–354
- 102 Kim JY, Lee SW, Kim JS, et al. Diagnostic value of neck node status using 18F-FDG PET for salivary duct carcinoma of the major salivary glands. *J Nucl Med* 2012;53(06):881–886
- 103 Dignonnet A, Hamoir M, Andry G, et al. Follow-up strategies in head and neck cancer other than upper aerodigestive tract squamous cell carcinoma. *Eur Arch Otorhinolaryngol* 2013;270(07):1981–1989
- 104 Manikantan K, Khode S, Dwivedi RC, et al. Making sense of post-treatment surveillance in head and neck cancer: when and what of follow-up. *Cancer Treat Rev* 2009;35(08):744–753
- 105 Hermans R. Posttreatment imaging in head and neck cancer. *Eur J Radiol* 2008;66(03):501–511
- 106 Razfar A, Heron DE, Branstetter BF IV, Seethala RR, Ferris RL. Positron emission tomography-computed tomography adds to the management of salivary gland malignancies. *Laryngoscope* 2010;120(04):734–738

Imaging Recommendations for Diagnosis, Staging, and Management of Nasopharynx Carcinoma

Chirag Kamal Ahuja¹ Vivek Agarwal² Chirag Jain³ Sameer Vyas¹ Jyoti Kumar⁴ Paramjeet Singh¹

¹ Division of Neuroimaging and Interventional Neuroradiology, Department of Radiodiagnosis and Imaging, Postgraduate Institute of Medical Education and Research, Chandigarh, India

² Division of Neuro and Vascular Intervention, Department of Neurology, Christian Medical College and Hospital, Ludhiana, Punjab, India

³ Department of Radiodiagnosis, VMMC and Safdarjung Hospital, New Delhi, India

⁴ Department of Radiodiagnosis, Maulana Azad Medical College, New Delhi, India

Address for correspondence Chirag Kamal Ahuja, DM, Division of Neuroimaging and Interventional Neuroradiology, Department of Radiodiagnosis and Imaging, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India (e-mail: chiragkahuja@gmail.com).

Ind J Med Paediatr Oncol 2023;44:175–180.

Abstract

Nasopharyngeal carcinoma (NPC) is an epithelial carcinoma originating from lining of the nasopharyngeal mucosa usually at the fossa of Rosenmuller (pharyngeal recess). An early detection on endoscopy can be rewarding, however, often difficult as the tumor at the pharyngeal recess is hidden from the endoscopic view. Magnetic resonance imaging and positron emission tomography–computed tomography form the backbone of detection and spread of the carcinoma into local and distant regions. These modalities help further characterize the precise locoregional infiltration and lymph nodal involvement which aids in the planning of the surgery/chemoradiotherapy. They also help in the follow-up evaluation and further management strategies. Many research and treatment groups namely American Joint Committee on Cancer, National Comprehensive Cancer Network, American Society of Clinical Oncology, American College of Radiology, Radiological Society of North America, European Society of Radiology (iGuide), Indian Radiological & Imaging Association/Indian College of Radiology and Imaging, National Cancer Grid, etc. have devised guidelines for the optimal assessment and treatment of NPC. The present document aims at providing a comprehensive review of the clinicoradiological recommendations for the diagnosis and management of NPC based on these guidelines as well as personalized experience of the contributors.

Keywords

- nasopharyngeal carcinoma
- diagnosis
- staging
- magnetic resonance imaging
- computed tomography

Introduction and Etiopathogenesis

Nasopharyngeal carcinoma (NPC) is an epithelial carcinoma originating from the mucosal lining of the nasopharynx. The tumor occurs more commonly in males than females (two- to threefold) and occurs with a bimodal incidence in second and

sixth decades of life.¹ Epidemiological trends have shown a gradual decline in incidence of the disease with reduction in mortality reflecting lifestyle and environmental changes. NPC usually originates at the fossa of Rosenmuller (pharyngeal recess) which is located posterosuperior to the Eustachian tube opening, from where it spreads to adjacent areas.²

DOI <https://doi.org/10.1055/s-0042-1760309>.
ISSN 0971-5851.

© 2023. The Author(s).
This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)
Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

NPC is multifactorial disease with strong genetic basis among first-degree relatives.³ Other major risk factors include Epstein–Barr virus (EBV) infection,⁴ smoking, and exposure to salt-cured preserved foods.⁵ Usage of certain Chinese medical herbs, smoking, and nitrosamines present in preserved foods act by causing a reactivation of EBV in nasal mucosa causing NPC. Genetic polymorphisms in CYP2A6 and certain HLA haplotypes have also been studied in detail as causations in NPC.⁶ NPC has three distinct histopathological subtypes—keratinizing squamous cell (World Health Organization [WHO] type I, sporadic form contributing to less than 20% cases globally), nonkeratinizing (WHO types II and III, contributing to more than 95% cases in endemic areas), and least commonly, the basaloid squamous cell type. The nonkeratinizing type is strongly associated with EBV infection and has more favorable prognosis than the other histological subtypes.^{7,8}

Epidemiology

NPC accounts for 0.7% of all newly diagnosed cancer cases worldwide with more than 130,000 new reported cases and 80,000 deaths in global cancer registry. More than 70% new cases are reported from Southeast China, with remainder being accounted predominantly in Southeast Asia and Northeast Africa regions. India accounts for 4% of total new NPC cases with a high-ethnic incidence in Nagas community with more than 16 per 100,000 person-years incidence.⁵

Clinical Profile and Diagnostic Workup

Patient presentation is varied and the tumor may go undetected from unawareness about the symptoms of the disease and relatively “clinically occult” site of origin of the carcinoma at nasopharynx. In the early stages of cancer, patients are asymptomatic or have mild symptoms such as nasal stuffiness. Local symptoms such as epistaxis, headache, hearing defects, otalgia, or neuropathies may occur from involvement of adjacent cranial nerves. Overall, the patients usually

directly present when there is cervical lymph node enlargement (in more than 70–90% cases at initial presentation) or from symptoms at sites where distant metastasis (bones, liver, lungs, and distant nodes) has already occurred.¹ A clinical triad of nasal obstruction with epistaxis, neck mass, and serous otitis media occurs infrequently. With high clinical suspicion and genetic/environmental history, an early detection on endoscopy can be rewarding, however, often difficult as the tumor at the pharyngeal recess is hidden from the endoscopic view. This could also be hindered by the presence of a coexisting benign hyperplasia. Endoscopic biopsy plays a significant role in definitive diagnosis of the disease. Patient’s initial diagnostic workup should also include a pretreatment EBV DNA levels which have been shown to influence survival outcomes, besides investigations such as blood counts, liver function tests, cross-sectional imaging, and chest radiographs.^{8,9} The role of EBV DNA levels is also evidenced by its incorporation in the American Joint Committee on Cancer TNM staging (→Table 1). It is important to note that incisional neck biopsies or nodal dissections should be avoided as these procedures negatively impact subsequent treatment.

Imaging Referral Guidelines

American College of Radiology¹⁰ has recommended imaging using magnetic resonance imaging (MRI) of nasopharynx, skull base, and neck for the assessment of locoregional extent of the disease. In addition, it is advocated to image the upper mediastinum if there are low neck nodal metastasis. MRI scores over CT in detecting nasopharyngeal mass lesions due to its superiority at detecting the extent of osseous, cranial nerve, and intracranial involvement. This is especially important as these lesions have the propensity for skull base invasion and intracranial spread. Additional imaging of metastasis using positron emission tomography (PET) scan may be done, and if the same is not available, combination of a bone scan and a computed tomography (CT) of the chest and abdomen may be helpful.¹¹ The National

Table 1 AJCC/UICC staging system for NPC, eighth edition⁹

Primary tumor (T) TX—Primary tumor cannot be assessed; T0—EBV-positive cervical node(s), no tumor identified; Tis—tumor in situ; T1—nasopharynx, nasal cavity, oropharynx without parapharyngeal extension; T2—parapharyngeal extension, adjacent soft tissue involvement (prevertebral muscles, medial pterygoid, lateral pterygoid); T3—Bony structures (skull base, pterygoid, cervical vertebra) with or without paranasal sinuses involvement; T4—cranial nerves, intracranial extension, orbit, hypopharynx, extensive, soft tissue involvement beyond lateral surface of lateral pterygoid
Regional lymph nodes (N) NX—regional nodes cannot be assessed; N0—no regional nodal metastasis; N1—unilateral (U/L) cervical, U/L or bilateral (B/L) retropharyngeal lymph nodes ≤ 6 cm; N2—B/L metastasis in lymph nodes, ≤ 6 cm in greatest dimension, above the caudal border of the cricoid cartilage; N3—> 6 cm and/or extension below the caudal border of the cricoid cartilage
Distant metastasis (M) M0—no distant metastasis, M1—distant metastasis
Stage group classification I—T1 N0 M0 II—T2 N0–1 M0, T0 1 N1 M0 III—T3 N0–2 M0, T0 2 N2 M0 IVA—T4 or N3 M0 IVB—Any T, any N, M1

Abbreviations: AJCC, American Joint Committee on Cancer; EBV, Epstein–Barr virus; NPC, nasopharyngeal carcinoma.

Cancer Grid guidelines advocate use of CT scan of head, neck, and chest and bone scan for staging of the disease and biopsy of mass or cervical lymph nodes. MRI of the head and neck, fluorodeoxyglucose (FDG), and pure tone audiometry are optimal recommendations. For patient follow-up, PET-CT/MRI is used for response evaluation with examination of nasopharynx and neck, cranial nerve function, and evaluation of systemic complaints.¹² For T3 and T4 tumors, PET-CT/MRI is used yearly for at least 5 years and thyroid function tests are done at 1, 2, and 5 years.

American Society of Clinical Oncology¹³ recommends intensity-modulated radiotherapy (IMRT) with daily image guidance for all NPC patients. It is important to carefully delineate the gross tumor volume. Apart from the consensus guidelines that should be followed for target delineation, advanced technical parameters such as image fusion should be explored. MRI fusion with CT for target delineation is mandatory. This aids in the appreciation of potential tumor extension at the skull base and helps evaluate the presence of cranial nerve involvement and/or intracranial extension, if present.

Imaging Guidelines

Screening

Biomarkers such as circulating cell-free EBV DNA are used to detect NPC in people at risk of developing early-stage cancer.¹⁴ Patients with positive plasma biomarkers usually undergo nasopharyngeal endoscopy with or without biopsy. Pharyngeal recess (fossa of Rosenmuller) is a hidden area for the endoscopist.¹⁵ Also, early lesions in adenoids and those beneath the nasopharyngeal mucosa can be easily missed on endoscopy.¹⁵ Lesions in these areas usually appear as minimal submucosal bulge or diffuse lymphoid hyperplasia on the endoscopic examination.¹⁶ MRI can act as an adjunct to detect these endoscopically occult lesions. Early NPC (T1 lesions) is seen as asymmetry of nasopharyngeal halves, loss of adenoid septa, discontinuity of deep mucosal line, decreased signal on T2-weighted imaging (T2WI), and heterogeneity of contrast enhancement.¹⁷

Diagnosis and Staging

Imaging is used to localize NPC, to look for the patterns of spread of the tumor and to assist in clinical staging of NPC in accordance to TNM classification. Though locoregional spread can be evaluated by both CT and MRI, contrast-enhanced MRI is the preferred modality as it has higher sensitivity to detect skull base invasion, perineural spread/denervation changes, meningeal invasion, cavernous sinus involvement, and retropharyngeal lymphadenopathy.¹⁸ Bony erosions are best studied on CT.¹⁹ TNM classification is described in ►Table 1.

Local Extension/T Staging

NPC originates in the fossa of Rosenmuller, also known as lateral pharyngeal recess (►Fig. 1), and spreads mucosally submucosally in the nearby spaces. Serous otitis media can result secondary to obstruction of Eustachian tube opening

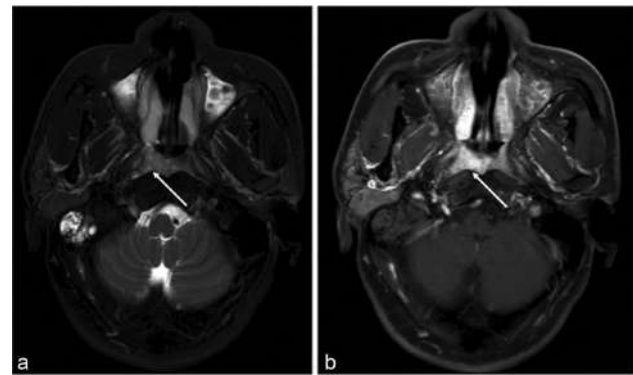


Fig. 1 (a) Axial T2W MR image showing hyperintense poorly defined mass involving the right side of nasopharynx in the fossa of Rosenmuller (white arrow) with associated fluid in the mastoid air cells. (b) Axial postgadolinium T1W MR image showing enhancement of the lesion (white arrow). MR, magnetic resonance; T2W, T2-weighted.

at torus tubarius. Anteriorly the lesion may spread to the nasal cavity and inferiorly into the adjacent oropharynx (T1 disease). The neoplasm extends posterolaterally into the parapharyngeal fat and infiltrates into pterygoid muscles (T2 disease) through the sinus of Morgagni. Loss of normal T1 hyperintense fat signal in parapharyngeal space and tumor enhancement on postcontrast images is seen in parapharyngeal extension of NPC (►Fig. 2). T3 tumor shows involvement of paranasal sinus and/or bones such as skull base, cervical vertebrae, or pterygoid plates. Loss of the normal T1 hyperintense fatty marrow signal on MRI and cortical erosion and sclerosis on CT denotes marrow invasion. Sphenoid sinus and clivus involvement are common. Further spread of the lesion on posterolateral aspect leads to carotid space invasion and spread along lower cranial nerves IX to XII. Hypoglossal nerve involvement may lead to denervation-related fatty replacement of the affected side of the tongue. Tumor may show carotid artery infiltration, which is labeled when there is more than 75% circumferential vascular

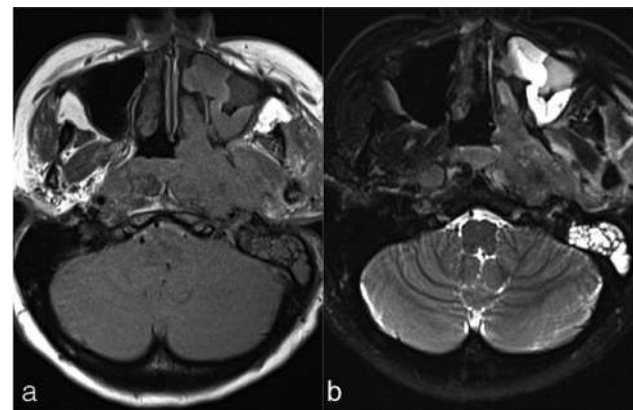


Fig. 2 Axial T1WI (a) and T2WI and (b) fat sat images showing a large mass involving the left side of nasopharynx with extension into left parapharyngeal space and involvement of pterygoid muscles. Enlarged retropharyngeal nodes and left-sided mastoiditis are also seen. T1WI, T1-weighted imaging; T2WI, T2-weighted imaging.

encasement. The patient is deemed inoperable with chances of potential carotid artery blow-out postradiotherapy (post-RT). Intracranial extension, maxillary sinus or cranial nerve involvement, hypopharyngeal and orbital invasion is seen in T4 tumors. MRI shows thickening and irregular enhancement of the involved cranial nerve either as continuous or as skip lesions. Expansion of the foramen/canal can be seen on CT. Perineural spread indicates poor prognosis and higher chances of recurrence. Perineural spread through the foramen ovale along the mandibular nerve causes denervation atrophy of the muscles of mastication. Intracranial extension is seen as nodular enhancing meningeal masses or focal deposits within the middle and/or posterior cranial fossa. Intracranial spread may extend to involve the Meckel's cave, cavernous sinus, and prepontine cistern. Extension of the mass lesion laterally into the masticator space or infratemporal fossa is also staged as T4 disease.

Nodal Involvement

Imaging can detect nodal spread of NPC in 60 to 90% of cases.²⁰ Nodal spread usually starts at retropharyngeal nodes (RPNs) followed by involvement of nodes at levels II, III, and IV.²¹ Skip metastases to lymph nodes at level VI, supraclavicular fossa, and distant spread to thoracic and abdominal nodes can be seen in about 5% cases. However, the absence of RPN involvement is seen in up to 1/3 of patients.²² Some studies have suggested that level IIb nodes may be the first echelon nodes.²² Lymphadenopathy is often bilateral in NPC. On imaging, supraclavicular nodes include levels IV and Vb nodes and are seen on the axial imaging section with a portion of the clavicle. Shortest axial diameter is used to measure the involved nodes. Normal size nodes may also harbor metastatic disease.²³ Loss of normal fatty hilum with change in the shape of the node from oval to round leading to increase in axial dimension and the longest longitudinal to axial dimension ratio <2 suggests malignant involvement.²³ Clustered nodes >3 in the drainage area of primary tumor suggests metastatic involvement.²⁴ The presence of necrosis, seen as hyperintense signal on T2WI with peripheral post-contrast enhancement, is very specific for metastatic disease. Extranodal spread beyond the capsule can be seen in up to 23% of cases.²⁵ It is seen as contour irregularity of the nodal margins with stranding in the adjacent fat.

Metastatic Spread

Distant metastases at initial diagnosis can be seen in up to 11% patients.²⁶ Most common sites are bones, chest (pulmonary lesions and mediastinal lymph nodes), liver, and distant lymph nodes other than in the mediastinum. Hypertrophic pulmonary osteoarthropathy can be rarely seen in patients with intrathoracic metastatic disease.²⁶ FDG PET/CT is preferred modality to evaluate distant metastasis, mapping/characterizing cervical/distant lymph nodes and for work up of residual and recurrent disease.²⁷

Imaging for Response Assessment and Follow-up

Follow-up assessment of patients after treatment for NPC includes evaluation of the nasopharynx and neck, cranial

nerves, and clinical work up/imaging to detect distant metastasis. A baseline scan within 6 months of completion of chemoradiotherapy in T3/4-N2/3 NPC is recommended by National Comprehensive Cancer Network. Comprehensive clinical evaluation/endoscopy guides further imaging "as indicated based on signs/symptoms."²⁸ Both MRI or PET/CT can be used for response assessment.²⁹ CT scans are considered much inferior to contrast-enhanced MRI in differentiating residual/recurrent disease from post-RT-chemotherapy changes. A baseline MRI scan is usually performed at 3 months posttreatment to detect subclinical residual lymphadenopathy.²⁹ Due to high soft tissue resolution, it may also serve as a baseline scan to detect future early recurrences. Diffusion-weighted imaging sequence with diffusion kurtosis imaging has been recently utilized to differentiate recurrent neoplasm from posttreatment changes. Increase in the apparent diffusion coefficient values after initiation of chemotherapy when compared with pretreatment scans indicates favorable response. No residual enlarged lymph nodes should be seen; otherwise, a neck dissection is necessary. On MRI, nonenhancing tissue with dark signal on T2WI represents mature fibrosis. Immature fibrosis (being cellular with fluid content) is seen as intermediate to high signal on T2WI and may sometimes enhance making it difficult to distinguish it from residual/recurrent disease.³⁰ Post-RT changes can appear as asymmetry of the nasopharynx with loss of normal contours. Also, distortion and partial effacement of the fossa of Rosenmüller (primary site) due to fibrosis can present difficulties for the radiologist to distinguish from residual/recurrent disease.

PET/CT is considered helpful in such cases and has a high negative predictive value of 95% when done after 12 weeks posttherapy.²⁹ Recurrent/residual tumor has bulging contours with enhancement that can be detected with certainty on PET/CT as an FDG avid lesion. Regression of abnormal tissue on follow-up scans may indicate post-RT changes, but unchanged or growing lesions may suggest recurrent disease. Progressing masses or the appearance of a new node suggest recurrence. Clinical assessment, endoscopy, and EBV DNA levels can be helpful guide for initial evaluation, which can be followed by either PET/CT or MRI in positive cases to detect recurrence of NPC.¹⁴ Isolated meningeal thickening in the posterior fossa at the jugular foramen or foramen magnum without any visible nasopharyngeal component can be seen in recurrent cases.³¹

Principles of Management

Management, as in any other cancer, is directed toward providing the best chance of cure/remission with good long-term outcomes and minimal adverse effects. The treatment is multidisciplinary with RT forming the mainstay for patients with early and locoregionally advanced NPC (► **Supplementary Table S1**). Concurrent chemoradiotherapy is preferred in patients beyond Stage II disease. Induction chemotherapy with cisplatin and gemcitabine has been shown to provide benefit in Stages III and IVA disease, which is followed by concurrent chemoradiation. Bilateral neck

dissection is often performed in all patients due to early involvement of lymph nodes in the disease. Patients with advanced stage disease are less responsive to therapy and also have higher chances of recurrence.

Follow-up Imaging and Management of Recurrent Disease

Follow-up MRI of the neck including the skull base and whole-body PET-CT is usually recommended after 3 to 4 months of treatment completion. An earlier imaging may create problems in distinguishing residual tumor from post-therapy changes. Posttreatment surveillance with endoscopy and a general clinical examination is recommended at 3 monthly intervals for the first 2 years followed by 6 monthly for the next 3 to 4 years. Imaging is performed in cases of clinical suspicion of recurrence.

Recurrent disease following treatment is difficult to manage. However, chemotherapy with cisplatin and gemcitabine has been shown to be of some benefit than other agents. Targeted therapy including vascular endothelial growth factor receptor and epidermal growth factor receptor inhibitors has not shown to be much useful. Reirradiation strategies using IMRT and immunotherapy are being used for treatment of a subset of recurrent NPC patients and have shown some promise; however, a lot still needs to be done for the management of this patient cohort.

Summary of Recommendations

1. Endoscopic nasopharyngeal biopsy is recommended in all clinically suspected cases of NPC, as evidenced by swelling in the nasopharynx, combined with EBV-encoded small RNAs in situ hybridization examination.
2. For assessment of the locoregional extent of the disease, imaging using MRI of nasopharynx, skull base, and neck until upper mediastinum is suggested. CT scan can be used alternatively; however, it is inferior to MRI in detecting the extent of cranial nerve, osseous, and intracranial involvement.
3. Additional imaging of metastasis using PET scan may be done, and if the same is not available, combination of a bone scan and a CT of the chest and abdomen may be helpful. Pure tone audiometry are optimal recommendations.
4. For patient follow-up, PET-CT/MRI is used for response evaluation with examination of nasopharynx and neck, cranial nerve function, and evaluation of systemic complaints. For T3 and T4 tumors, PET-CT/MRI is used yearly for at least 5 years and thyroid function tests are recommended at 1, 2, and 5 years.

Synoptic Reporting Format is given in **►Supplementary Table S2**.

Conflict of Interest
None declared.

Financial Disclosure
None.

References

- 1 Abdel Khalek Abdel Razek A, King A. MRI and CT of nasopharyngeal carcinoma. *AJR Am J Roentgenol* 2012;198(01):11–18
- 2 Chen Y-P, Chan ATC, Le QT, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. *Lancet* 2019;394(10192):64–80
- 3 Raghupathy R, Hui EP, Chan AT. Epstein-Barr virus as a paradigm in nasopharyngeal cancer: from lab to clinic. *Am Soc Clin Oncol Educ Book* 2014;34(01):149–153
- 4 Ung A, Chen CJ, Levine PH, et al. Familial and sporadic cases of nasopharyngeal carcinoma in Taiwan. *Anticancer Res* 1999;19(1B):661–665
- 5 Chua MLK, Wee JTS, Hui EP, Chan ATC. Nasopharyngeal carcinoma. *Lancet* 2016;387(10022):1012–1024
- 6 Hildesheim A, Apple RJ, Chen CJ, et al. Association of HLA class I and II alleles and extended haplotypes with nasopharyngeal carcinoma in Taiwan. *J Natl Cancer Inst* 2002;94(23):1780–1789
- 7 Barnes L, Eveson JW, Sidransky D, Reichart P, eds. *Pathology and Genetics of Head and Neck Tumours*. Geneva, Switzerland: IARC; 2005
- 8 Leung SF, Zee B, Ma BB, et al. Plasma Epstein-Barr viral deoxyribonucleic acid quantitation complements tumor-node-metastasis staging prognostication in nasopharyngeal carcinoma. *J Clin Oncol* 2006;24(34):5414–5418
- 9 Lee AWM, Lydiatt WM, Colevas AD, et al. Nasopharynx. In: Amin MB, ed. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017:103
- 10 Saba NF, Salama JK, Beitler JJ, et al; Expert Panel on Radiation Oncology-Head and Neck Cancer. ACR appropriateness criteria® for nasopharyngeal carcinoma. *Head Neck* 2016;38(07):979–986
- 11 NCG Guidelines Manual. Accessed March 20, 2022. <https://tmc.gov.in/ngc/index.php/guidelines/draft-guidelines-2020>
- 12 Colevas AD, Yom SS, Pfister DG, et al. NCCN Guidelines Insights: Head and Neck Cancers, Version 1.2018. *J Natl Compr Canc Netw* 2018;16(05):479–490
- 13 NCCN Guidelines for patients Nasopharyngeal Cancer. Accessed March 20, 2022. <https://www.nccn.org/patients/guidelines/content/PDF/hn-nasopharynx-patient.pdf>
- 14 Chan KCA, Hung ECW, Woo JKS, et al. Early detection of nasopharyngeal carcinoma by plasma Epstein-Barr virus DNA analysis in a surveillance program. *Cancer* 2013;119(10):1838–1844
- 15 Lee AWM, Ng WT, Chan LLK, et al. Evolution of treatment for nasopharyngeal cancer—success and setback in the intensity-modulated radiotherapy era. *Radiother Oncol* 2014;110(03):377–384
- 16 King AD, Vlantis AC, Bhatia KSS, et al. Primary nasopharyngeal carcinoma: diagnostic accuracy of MR imaging versus that of endoscopy and endoscopic biopsy. *Radiology* 2011;258(02):531–537
- 17 King AD, Lam WW, Leung SF, Chan YL, Teo P, Metreweli C. MRI of local disease in nasopharyngeal carcinoma: tumour extent vs tumour stage. *Br J Radiol* 1999;72(860):734–741
- 18 Chong VF, Fan YF, Khoo JB. Nasopharyngeal carcinoma with intracranial spread: CT and MR characteristics. *J Comput Assist Tomogr* 1996;20(04):563–569
- 19 King AD, Vlantis AC, Tsang RKY, et al. Magnetic resonance imaging for the detection of nasopharyngeal carcinoma. *AJNR Am J Neuroradiol* 2006;27(06):1288–1291
- 20 King AD, Ahuja AT, Leung SF, et al. Neck node metastases from nasopharyngeal carcinoma: MR imaging of patterns of disease. *Head Neck* 2000;22(03):275–281
- 21 Ng SH, Chang JT, Chan SC, et al. Nodal metastases of nasopharyngeal carcinoma: patterns of disease on MRI and FDG PET. *Eur J Nucl Med Mol Imaging* 2004;31(08):1073–1080
- 22 Chong VF, Fan YF, Khoo JB. Retropharyngeal lymphadenopathy in nasopharyngeal carcinoma. *Eur J Radiol* 1995;21(02):100–105

- 23 Som PM, Brandwein MS. Lymph nodes. In: Som PM, Curtin HD, eds. *Head and Neck Imaging*. 4th ed. Vol. 2. Missouri, USA: Mosby Inc; 2003:1910–1911
- 24 Som PM. Detection of metastasis in cervical lymph nodes: CT and MR criteria and differential diagnosis. *AJR Am J Roentgenol* 1992; 158(05):961–969
- 25 King AD, Tse GM, Ahuja AT, et al. Necrosis in metastatic neck nodes: diagnostic accuracy of CT, MR imaging, and US. *Radiology* 2004;230(03):720–726
- 26 Teo PM, Kwan WH, Lee WY, Leung SF, Johnson PJ. Prognosticators determining survival subsequent to distant metastasis from nasopharyngeal carcinoma. *Cancer* 1996;77(12):2423–2431
- 27 Chang JT, Chan SC, Yen TC, et al. Nasopharyngeal carcinoma staging by (18)F-fluorodeoxyglucose positron emission tomography. *Int J Radiat Oncol Biol Phys* 2005;62(02):501–507
- 28 Pfister DG, Spencer S, Adelstein D, et al. Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2020;18(07):873–898
- 29 Comoretto M, Balestreri L, Borsatti E, Cimitan M, Franchin G, Lise M. Detection and restaging of residual and/or recurrent nasopharyngeal carcinoma after chemotherapy and radiation therapy: comparison of MR imaging and FDG PET/CT. *Radiology* 2008;249(01):203–211
- 30 Offiah C, Hall E. Post-treatment imaging appearances in head and neck cancer patients. *Clin Radiol* 2011;66(01):13–24
- 31 Chong VF, Fan YF. Meningeal infiltration in recurrent nasopharyngeal carcinoma. *Australas Radiol* 2000;44(01):23–27

Imaging Recommendations for Diagnosis, Staging, and Management of Lung Cancer

Aparna Irodi¹ Ashu Seith Bhalla² Leena Robinson Vimala¹^{ID} Taruna Yadav³^{ID} Subathra Adithan⁴^{ID}
Harish Bhujade⁵^{ID} Parang Sanghavi⁶^{ID} Alok Kale⁸ Mandeep Garg⁵^{ID} Abhishek Mahajan⁷
Yvette Kirubha Jaykar David Livingstone⁸^{ID} Sudha Kiran Das⁹^{ID} Geethi M. H.¹⁰^{ID}
Balukrishna Sasidharan¹¹ Balamugesh Thangakunam¹²^{ID} Simon Pavamani¹³^{ID} Rajesh Isiah¹³
Anjana Joel¹⁴ Tameem Ahmad Bhat¹⁵

¹ Department of Radiology, Christian Medical College, Vellore, Tamil Nadu, India

² Department of Radiodiagnosis and Interventional Radiology, AIIMS, New Delhi, India

³ Department of Diagnostic and Interventional Radiology, All India Institute of Medical Sciences (AIIMS) Jodhpur, Rajasthan, India

⁴ Department of Radiodiagnosis, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

⁵ Department of Radiodiagnosis and Imaging, PGIMER, Chandigarh, India

⁶ Department of Radiology, Picture this by Jankharia, Mumbai, Maharashtra, India

⁷ Department of Radiodiagnosis, The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, United Kingdom

⁸ Radiology and Imaging Science Department, Apollo Main Hospital, Chennai, Tamil Nadu, India

⁹ JSS Medical College, JSSAHER, Mysore, Karnataka, India

Address for correspondence Aparna Irodi, MD, FRCR, Department of Radiology, Christian Medical College, Vellore, Tamil Nadu 632004, India (e-mail: aparnashyam@gmail.com).

¹⁰ Division of Radiation Oncology, RCC, Thiruvananthapuram, Kerala, India

¹¹ Department of Radiation Oncology, Ida B. Scudder Cancer Centre Christian Medical College, Vellore, Tamil Nadu, India

¹² Department of Pulmonary Medicine Christian Medical College, Vellore, Tamil Nadu, India

¹³ Department of Radiation Oncology, Ida B. Scudder Cancer Centre Christian Medical College, Vellore, Tamil Nadu, India

¹⁴ Department of Medical Oncology, Christian Medical College, Vellore, Tamil Nadu, India

¹⁵ Radiology, Shri Mata Vaishno Devi Narayana Superspeciality Hospital, Jammu, India

Ind J Med Paediatr Oncol 2023;44:181–193.

Abstract

Globally and in India, lung cancer is one of the leading malignancies in terms of incidence and mortality. Smoking and environmental pollution are the common risk factors for developing lung cancer. Traditionally, lung cancer is divided into small cell and nonsmall cell types, with nonsmall cell carcinomas including squamous cell carcinoma, adenocarcinoma, and large cell carcinoma.

Keywords

- cancer
- imaging
- lung
- recommendations

In this review article, we describe the imaging recommendations and findings in the diagnosis, staging, and management of lung cancer, including the imaging of treatment-related complications.

Introduction

Epidemiology

Globally, lung cancer is one of the leading malignancies in terms of incidence and mortality. It is the second most common malignancy in both the genders.¹ In India, lung cancer is one of the leading malignancies in men and fifth most common cancer in women. Its incidence varies between

numerous regions of India. The projected incidence of lung cancer in men in India in 2020 was 9.9 per 100,000 people.

Risk Factors

Smoking (80–90%) and environmental pollution are the leading risk factors for lung cancer in India.² Exposure to carcinogens in genetically susceptible individuals may cause

DOI <https://doi.org/10.1055/s-0042-1759572>.
ISSN 0971-5851.

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)
Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

activation of oncogenes and/or inactivation of tumor suppressor genes, resulting in neoplastic proliferation of cells.

Etiopathogenesis

Traditionally, lung cancer is classified into small cell lung cancer (SCLC) and nonsmall cell lung cancer (NSCLC) types, with nonsmall cell carcinomas including squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. There is an increasing incidence of NSCLC in women and non-smokers. Following the worldwide trend, some studies in India are also reporting adenocarcinoma to be the most common pathological type in recent times, unlike squamous cell carcinoma that was more common previously.² However, other studies report no such change and still consider squamous cell carcinoma as the most common histopathological type.³

Clinical Presentation

Most patients with lung cancer in India are men (up to 82.9%); this disease is more commonly observed in the age range of 46 to 70 years, with a mean age of 58 years. The most commonly reported symptoms include cough, loss of weight and appetite, dyspnea, fatigue, chest pain, and hemoptysis. Patients may also present with paraneoplastic syndromes. Examination findings include digital clubbing, lymphadenopathy, superior vena cava obstruction, and neurological deficits in metastatic disease.⁴ Although in countries which have adopted lung cancer screening could potentially be detecting lung cancers at an earlier stage, 44 to 47.6% of patients with lung cancer in India present at an advanced stage with metastatic disease.²

Imaging plays an important role not only in the initial workup of patients with lung cancer but also in their regular follow-ups. It is also important to be aware of the changing profile of imaging appearances in patients with utilization of newer cancer treatments like immunotherapy.⁵

Imaging Referral Guidelines

General practitioners and other primary healthcare providers should refer a patient for a chest radiograph (CXR) when there are symptoms and signs suggestive of lung cancer like hemoptysis, loss of weight and appetite, persistent cough or dyspnea, chest pain, and abnormal chest signs. If the CXR is abnormal or if there is high index of clinical suspicion, even if CXR is normal, patient should be referred for a computed tomographic (CT) scan and to a specialist.⁶

On CXR, lung cancer may present as a nodule, irregular mass, nonresolving consolidation, lobar collapse, effusion, hilar or mediastinal enlargement. But, usually when these are observed on CXR, the disease stage is advanced. In early stages, CXR may appear to be normal.

AJCC, NCCN Guidelines for Imaging in Lung Cancer⁷⁻⁹

The first imaging test to be performed in a suspected case of lung cancer is CXR. Contrast-enhanced CT (CECT) of chest and upper abdomen (including adrenal glands) is recommended

for further evaluation. ¹⁸F-FDG PET-CT (positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrating CT) is indicated in patients with no signs of metastatic spread on CT who are candidates for curative intent treatments.

Contrast-enhanced magnetic resonance imaging (MRI) of brain (or CECT of brain, if MRI not available) is recommended in patients with NSCLCs (stages Ib and higher) and small cell carcinomas (any stage) even if there are no relevant symptoms.

Contrast-enhanced MRI of thoracic inlet, spine, and brachial plexus is indicated to check for Pancoast tumor for the sake of local tumor extension assessment.

Indian Radiological and Imaging Association Guidelines for Imaging in Lung Cancer¹⁰

¹⁸F-FDG PET-CT scan is the most accurate investigation method for the staging of lung cancer. If a PET scan is not available, then a CECT scan of thorax, abdomen, pelvis, and whole-body bone scan needs to be done.

American College of Radiology Appropriateness Criteria for Imaging in Lung Cancer (~Table 1)¹¹

Ultrasound (US) of the abdomen may help in the evaluation of liver lesions that are observed to be ambiguous on CT scans.

According to most of the above-mentioned guidelines,⁷⁻⁹ once lung cancer is detected, a whole body ¹⁸F-FDG PET-CT scan would be the ideal modality to initially stage the disease. Gadolinium-enhanced MRI brain is recommended in all patients with SCLC or NSCLC except those with peripheral stage I (T1abc, N0). If PET-CT and MRI brain scans are not available, then CECT scan of the brain, thorax, abdomen, pelvis, and bone is recommended to be done for stage evaluation.

Clinical and Diagnostic Workup Excluding Imaging

Workup of lung carcinoma is dependent on the clinical presentation. The multipronged approach to complete diagnosis comprises three steps—histological diagnosis, staging, and functional evaluation. Additional tests are reserved for those who present with paraneoplastic syndromes.

Tests such as complete hemogram, liver function, calcium, electrolytes, blood urea nitrogen, and creatinine are performed as part of the initial assessment.

Tissue sample can be obtained via CT or endobronchoscopic-guided biopsy.^{7,9} Histology of the provided sample with light microscopy and immunohistochemical staining aids in the detection of subtypes of lung carcinoma. Molecular profiling serves as a biomarker to predict response to targeted therapies and immunotherapies.¹² Sampling of mediastinal nodes by endoscopic or endobronchial US or mediastinoscopy is recommended for histopathological analysis in all cases, with the exception of early-stage peripheral disease or if nodes are negative on PET-CT.

Table 1 ACR appropriateness criteria for imaging in lung cancer

CT thorax	CECT is preferred. NCCT can be done if contrast cannot be administered for any reason
¹⁸ F-FDG PET-CT	PET imaging from skull base to upper thigh is recommended for evaluation of extrathoracic disease
CT abdomen and pelvis	To look for extrathoracic disease if PET-CT is not available
Bone scan	To look for skeletal metastasis if PET-CT is not available
MRI brain	With gadolinium in NSCLC stage II, III, or IV even in the absence of neurological symptoms Any stage of NSCLC with neurological symptoms All small cell carcinoma (irrespective of stage)
CT head	With contrast, only if MRI brain cannot be performed
MRI thorax	For superior sulcus tumors or in equivocal findings on chest CT, to better evaluate for chest wall or mediastinal infiltration
MRI abdomen	Chemical shift imaging of adrenal gland lesions to see if they are adenomas or metastases (may not be necessary if PET-CT is performed)

Abbreviations: ACR, American College of Radiology; CECT, contrast-enhanced computed tomography; ¹⁸F-FDG PET-CT, fluorine-18 fluorodeoxyglucose positron emission tomography-computed tomography; NCCT, noncontrast computed tomography; MRI, magnetic resonance imaging; NSCLC, nonsmall cell lung cancer.

Variable sensitivity and specificity ranging from 77.4 to 81.3% and 79.4 to 90.1%, respectively, have been reported for PET-CT in mediastinal nodal staging in lung cancer.¹³

Additional diagnostic tests can be performed in patients with comorbidities or paraneoplastic symptoms; for example: a comprehensive paraneoplastic antibody panel for those with neurological syndromes, serum and urine osmolality in a suspected case of Syndrome of inappropriate antidiuretic hormone secretion, serum cortisol levels for Cushing's syndrome.⁷

If the patient has signs and symptoms suggestive of chronic obstructive pulmonary disease and has been scheduled for surgery or radiotherapy (RT), functional assessment with spirometry and 6-minute walk test and cardiac evaluation with electrocardiogram as well as echocardiogram is performed. Radionuclide lung perfusion scintigraphy can also be performed to measure the perfusion to the lung being resected during surgery and to predict postoperative lung function.¹⁴

Imaging Guidelines

Screening

It has been proven that if lung cancer is detected early, its 5-year survival rate can be significantly improved.¹⁵ National Comprehensive Cancer Network (NCCN) was the first major organization to develop lung cancer screening using low-dose CT (LDCT). It was based on the National Lung Screening Trial which showed that LDCT screening reduced the relative risk of death from lung cancer by 20%.¹⁶ The International Early Lung Cancer Action Program showed annual CT screening allows at least 80% of lung cancer cases to be diagnosed early, that is, in clinical stage I.¹⁷ The Nelson trial showed that 65 to 70% of cancers diagnosed in the screening arm were in stage IA and II, while 70% were in stage III/IV in the control arm.¹⁸

The Korean Lung Cancer Screening Project showed that lung cancer screening in a tuberculosis-endemic country may be less effective because of high incidence of false-

positive results.¹⁹ The TALENT lung cancer screening study in Taiwan showed a high detection rate of 2.6% for early lung cancer with more than 96.5% of them being operable.²⁰ A recent study by Parang and Bhavin showed high effectiveness of LDCT to detect or diagnose lung nodules and carcinoma in smokers even in a tuberculosis-endemic country like India.²¹

The American College of Radiology has developed Lung imaging Reporting and Data System to standardize the reporting and data management from LDCT examination.²²

Eligibility Criteria for Lung Cancer Screening

Various societies have proposed eligibility criteria for annual LDCT lung cancer screening that is given in ►Table 2.^{23–26}

Proposed protocol for LDCT in lung cancer screening is provided in ►Table 3.

Most societies recommend yearly LDCT for lung cancer screening in eligible individuals.

Diagnosis

As most of the cases with lung carcinoma present with advanced stages, diagnosis is usually not difficult by utilizing both modalities: CXR and CECT thorax. However, one-third of lung carcinoma cases have a solitary pulmonary nodule that may be difficult to differentiate from a benign nodule.²⁷ Some of the imaging features may help to differentiate lung malignancy from benign lung lesions that are given in ►Table 4.

The Fleischner Society has formulated the guidelines for the assessment of an incidentally detected lung nodule based on appearance, growth rate, patient age, and history of smoking.²⁸

Other features to be assessed on CT scans include invasion/ infiltration into surrounding structures like intercostal muscles and mediastinum, presence of lymphangitis (irregular nodular septal thickening adjacent to the tumor mass), adenopathy, erosion of ribs or vertebrae, and distant metastases. Central mass lesions may show either encasement and occlusion of segmental or lobar bronchus/endobronchial

Table 2 Eligibility criteria for lung cancer screening by various specialty societies

Organization	Patient age/symptoms	Smoking history (pack-years)	Other factors
ACCP, ASCO, ATS, ACS, and ALS	55–74, asymptomatic	≥ 30	Less than 15 years since smoking cessation
NCCN	55–74, asymptomatic or ≥ 50 asymptomatic	≥ 30 ≥ 20	Less than 15 years since smoking cessation or one or more additional risk factors like pulmonary disease, family history of lung cancer, personal cancer history, radon exposure
ESR	55–80 years	At least 30 pack-years	Current smoker or exsmoker who has quit smoking within the last 15 years
USPSFT	55–80 asymptomatic	≥ 30	Less than 15 years since smoking cessation

Abbreviations: ACCP, American College of Chest Physicians; ACS, American Cancer Society; ALA, American Lung Association; ASCO, American Society of Clinical Oncology; ATS, American Thoracic Society; ESR, The European Society of Radiology; NCCN, National Comprehensive Cancer Network; USPSFT - U.S. Preventive Services Task Force.

Table 3 LDCT protocol

kV	120
mAs	50
Pitch	1.2
Slice thickness	1 mm
Slice interval	0.5 mm
Scan region	Thoracic inlet to costophrenic angles
Respiration	Suspended end-inspiration
Reconstructions	Lung (e.g., B70) and soft tissue (e.g., B35) reconstructions and window setting
Effective radiation dose	< 1.2 mSv

Abbreviation: LDCT, low-dose computed tomography.

component or encasement of adjacent vessels. The imaging signs indicating invasion are tumor-mediastinal/pleural contact of more than 3 cm length, absence of the fat plane between the mass and mediastinum, thickening of the pleura, increased density of the extra-pleural fat adjacent to the tumor, angle of contact of tumor being more than 90 degrees with the aorta.

Short-axis dimension more than 10 mm is generally considered to be indicative of abnormal mediastinal or hilar lymph node. Malignant nodes can be necrotic, but infections like tuberculosis also can show necrotic nodes.

Sampling of Lung Lesions

Tissue sampling is required during these scenarios: new or growing solitary mass, multiple nodules without known malignancy, and biopsy or re-biopsy of malignancy for targeted therapy. Various methods for sampling of lung nodule are available that include fiberoptic bronchoscopy, endobronchial ultrasound (EBUS) guided sampling, transthoracic needle biopsy, and video-assisted thoracoscopic surgery.

¹⁸F-FDG PET-CT helps to locate the site of biopsy, especially in larger tumor masses, where biopsy should be done

from FDG-avid areas. For central lesions, bronchoscopic or EBUS-guided approach is preferred. Transthoracic US or CT-guided approach may be used depending upon the location and ease of access to the lung lesion. Coaxial system should be used to take multiple samples and to increase yield and safety.²⁹ As per the recent advances in molecular targeted therapy in lung cancers, larger sample volume is needed for necessary molecular testing. Therefore, core biopsy is preferred over fine needle aspirations.

Abnormalities detected by ¹⁸F-FDG PET scan have to be confirmed radiologically or pathologically. CT staging alone is not adequate for nodal involvement, as CT-based criteria of short axis dimension of more than 10 mm size of the lymph nodes has been shown to have a sensitivity of 55%, and specificity of 81%.³⁰ A higher sensitivity of 83% and specificity of 92% are reported when high FDG uptake on PET is taken as a criterion for diagnosing nodal metastasis.³¹ Invasive sampling of suspicious nodes is recommended using EUS/EBUS/mediastinoscopy/ CT guidance. If pleural or pericardial effusion is present, US-guided thoracentesis or pericardiocentesis is undertaken. Thoracoscopy can be performed when repeated pleural fluid analysis (at least 3 times) is inconclusive.

Staging

The aim of imaging with CT (► **Figs. 1** and **2**) and PET-CT (► **Fig. 3**) scans is that to assign appropriate clinical staging of lung cancer. Eighth edition American Joint Committee on Cancer Tumor, Node, and Metastasis (AJCC TNM) staging for lung cancer was implemented in 2018 (► **Tables 5** and **6**).³² All aspects towards staging should be carefully looked for in the imaging.

Combined approach using TNM and veterans administration classification of SCLCs into³³:

- Limited (where disease is confined to a single hemithorax and adjacent nodes which can be safe to include in an RT field) and
- Extensive stage (extends beyond the hemithorax including malignant pleural or pericardial effusion) is used to make treatment decisions

Table 4 CT features in favor of benign and malignant lung nodule

Imaging features	Benign	Malignant	Comments
Size ^{23,24}	Less than 1 cm	More than 3 cm	Average of two orthogonal measurements is taken Smaller lesions can also be malignant
Margins ^{23,25}	Sharp, smooth, or well-defined	Spiculated, irregular, ill-defined, "pleural tail"	20% of malignant nodules may show smooth and well-defined margins
Internal morphology			
Density ^{26,27}	Pure ground glass density nodules <5 mm in size could represent atypical adenomatous hyperplasia	- Pure ground glass density nodule 6–30 mm could represent adenocarcinoma in situ - Part-solid nodule with solid component <5 mm could represent minimally invasive adenocarcinoma - Part-solid nodule with solid component >5 mm could represent invasive adenocarcinoma - Solid nodules or consolidation could represent mucinous adenocarcinoma in situ, invasive mucinous adenocarcinoma	Based on density nodules can be solid or subsolid. Subsolid nodules can be pure ground glass density or part-solid
Calcifications	Diffuse, central, popcorn, laminated	Amorphous, punctate	
Fat ²⁸	Presence of fat (–40 to –120 HU) favors benign lesion like hamartoma	Fat is usually absent in malignancy	
Cavitation	Smooth, thin walls. Usually less than 4 mm wall thickness	Thick, irregular walls. Usually more than 16 mm wall thickness	
Growth rate ²⁹	More than 400 days or very short in infections	Doubling time 20 to 400 days (average 240)	The serial volumes instead of diameters and computer-aided doubling of volume of small nodules have been proposed to be an accurate way to evaluate growth Small and large cell cancers may show a faster growth
Contrast enhancement ³⁰	Less than 15 HU	More than 20 HU	Larger malignant lesions tend to show more heterogeneous contrast enhancement due to presence of necrosis within the lesion
Metabolism ³¹	Less than 2.5 SUV	More than 2.5 SUV	Note that infective and inflammatory conditions also can show high SUV. PET can help in guiding biopsy to the areas with increased FDG avidity

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; HU, Hounsfield unit; PET, positron emission tomography; SUV, standardized uptake value.

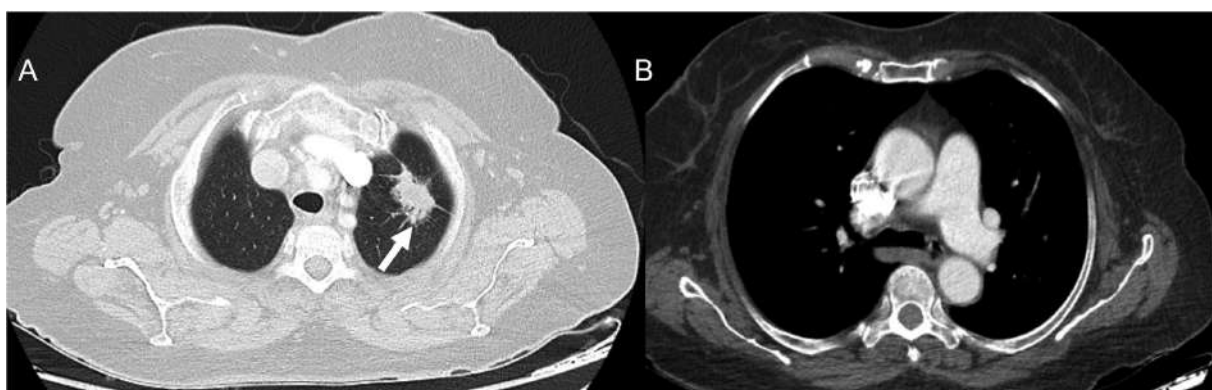


Fig. 1 (A) Axial computed tomographic (CT) thorax section in lung window shows a spiculated mass (white arrow) of longest dimension 2.8 cm in the apicoposterior segment of the left upper lobe. (B) Axial CT thorax section in mediastinal window reveals that there are no enlarged mediastinal or hilar nodes. TNM (tumor, nodes, and metastases) stage: T1cN0M0.

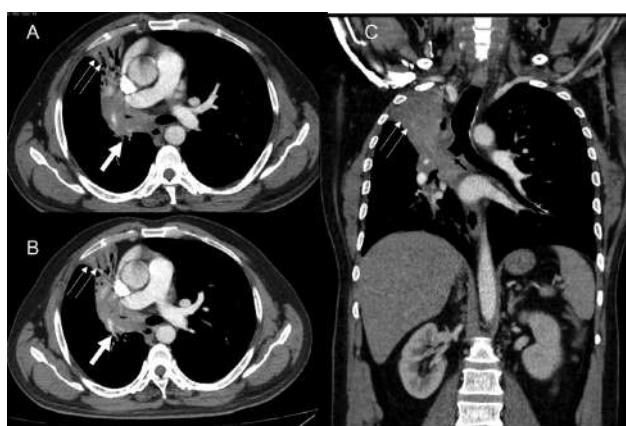


Fig. 2 (A and B) Axial computed tomographic (CT) thorax sections demonstrate central hilar mass having convex margin (white arrow) causing occlusion of right upper lobe bronchus, bronchus intermedius, right middle lobe bronchus with the resultant collapse, with mild peripheral bronchiectasis of right upper and right middle lobe having retained secretions in the peripheral bronchi (double thin white arrow). The lesion infiltrates and merges with the ipsilateral mediastinal, hilar, and subcarinal nodes. (C) The coronal CT thorax section also reveals the medial extension into the right main bronchus (black arrow). No distant metastases. TNM stage: T4N2.

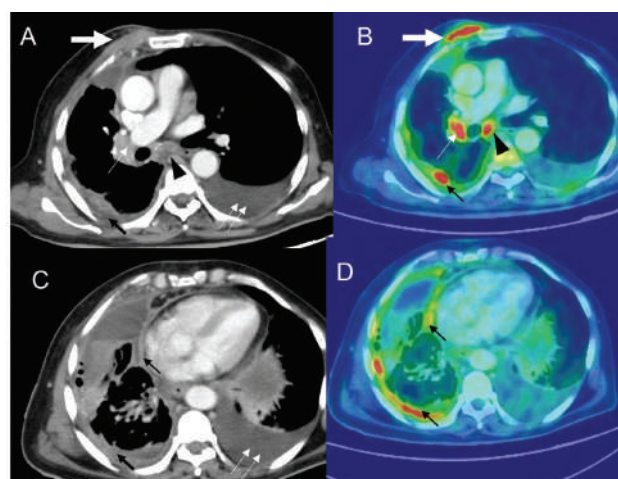


Fig. 3 Patient with adenocarcinoma of the lung with positron emission tomography-computed tomography (PET-CT) imaging. CT thorax (A and C) and corresponding fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET) images (B and D) demonstrate chest wall extension (thick white arrow), having standardized uptake value (SUV) of 9.4, enlarged right hilar (thin white arrow), and subcarinal node (black arrowhead) with SUV of 8.4 and 7.6, respectively. Pleural effusion with nodular pleural thickening (thin black arrow) with SUV of 6.6. Moderate amount of pleural effusion (double thin white arrows) on the left side.

Management (Response Assessment Imaging in Neoadjuvant, Adjuvant, and Palliative Settings)

Tumor Response Assessment

The major attribute of RECIST 1.1 that is widely used for tumor response assessment is given in **Table 7**.^{34,35}

Limitations of RECIST 1.1:

- (i) RECIST 1.1 is based on anatomical unidimensional measurement. The appropriateness of moving to three-dimensional volumetric measurement or functional measurement using PET/MRI scan was considered but not incorporated, due to insufficient standardization and evidence.
- (ii) RECIST 1.1 also does not contemplate morphological changes such as tumor cavitation.

- (iii) Interreader variability can be present in reporting new lesions and non-target lesions
- (iv) RECIST 1.1 does not consider pseudoprogression.

Immune-Related Response Criteria

Following immunotherapy, there may be an appearance of new lesions or an increase in size of existing lesions before eventual regression and partial or complete response. This may be due to infiltration by T cells and is called “pseudoprogression.” An increase in the size of lesions associated with rapid clinical decline is termed as “hyperprogression.”

The iRECIST criteria have been proposed for use in clinical trials for patients treated with immunotherapy.³⁶ (**Flowchart 1**) iRECIST has not been validated for treatment decisions. An important limitation of using iRECIST is that if the original progression was a true progression, effective salvage therapy gets delayed by several weeks.

Table 5 AJCC TNM 8th staging of lung cancer

T staging	N staging	M staging
T0—No primary tumor Tis—Carcinoma in situ T1—Tumor < 3 cm (T1mi—minimally invasive adenocarcinoma; T1a—Superficial spreading tumor in central airways) T1a—Tumor < 1 cm T1b—Tumor > 1 cm but < 2 cm T1c—Tumor > 2 cm but < 3 cm T2—Tumor > 3 cm but < 5 cm or tumor involving visceral pleura/main bronchus (not carina)/atelectasis up to hilum T2a—Tumor > 3 cm but < 4 cm T2b—Tumor > 4 cm but < 5 cm T3—Tumor > 5 cm but < 7 cm or invading chest wall, pericardium, phrenic nerve; or separate tumor nodule(s) in the same lobe T4—Tumor > 7 cm or tumor invading mediastinum/diaphragm/hear/great vessels/recurrent laryngeal nerve/carina/trachea/esophagus/spine or tumor nodule(s) in a different lobe in same lung	N0—No regional node metastasis N1—Metastasis in ipsilateral pulmonary or hilar nodes N2—Metastasis in ipsilateral mediastinal or subcarinal nodes N3—Metastasis in contralateral mediastinal, hilar, or supraclavicular nodes	M0—No distant metastasis M1a—Malignant pleural or pericardial effusion or pleural or pericardial nodules or separate tumor nodule(s) in the contralateral lung M1b—Single extrathoracic metastasis M1c—Multiple extrathoracic metastases (in 1 or >1 organ)

Abbreviation: AJCC TNM, American Joint Committee on Cancer Tumor, Node, and Metastasis.

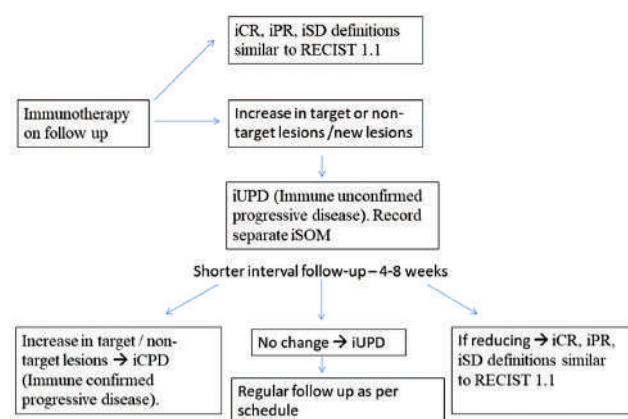
Table 6 Stage grouping according to AJCC 8th ed TNM staging of lung cancer

T/M	Subcategory	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

Abbreviation: AJCC TNM, American Joint Committee on Cancer Tumor, Node, and Metastasis.

Table 7 RECIST 1.1 criteria for tumor response assessment

Measurable and target lesions	A maximum of 5 total target lesions (a maximum of 2 per organ) are quantitatively assessed The lesion must be at least 10 mm in size The sum of the longest diameters is recorded as the sum of measurable lesions (SOM) Pathological lymph nodes with a short axis diameter of 15 mm or more can be considered as target lesions. For lymph nodes, a short axis dimension is taken for SOM
Nontarget and nonmeasurable lesions	May be recorded qualitatively Lesions less than 10 mm; nodes between 10 and 15 mm Nonmeasurable lesions like pleural or pericardial effusion or lymphangitis
Progressive disease (PD)	At least 20% increase in size over the nadir (smallest measured tumor burden during the course of the disease). The minimum increase should be at least 5 mm “Unequivocal” progression in nonmeasurable or other non-target lesions (effusions, bone lesions) is recorded as PD Any new lesions are considered as PD
Partial response (PR)	When there is more than 30% decrease in size from baseline
Complete response (CR)	When there is complete disappearance of the lesion and pathological lymph nodes are reduced to less than 10 mm
Stable disease (SD)	



Flowchart 1 iRECIST criteria for follow-up of patients who are on immunotherapy. iCR, immune complete response; iPR, immune partial response; iSD, immune stable disease.

Complications of Treatment

Complications of Radiotherapy

Conformal RT is typically used for patients with advanced stage lung cancer and the treatment course is over 6 to 7 weeks. In contrast, stereotactic body radiotherapy (SBRT) is used for early-stage lung cancer; precise high dose fractions are given over a period of 2 weeks.

Intensity-modulated RT (IMRT) is a technique in which radiation is delivered using multiple RT fields of varying influence; both conventional RT and SBRT can be delivered using this technique. Use of IMRT reduces the radiation delivered to the normal lung tissue around the tumor. Thus, treatment with IMRT can result in unusual patterns

of pneumonitis in the patient, since radiological pneumonitis changes correlates with the shape of the RT field/plan.³⁷

Acute radiation pneumonitis (**►Fig. 4**) can manifest as consolidation with air-bronchogram and straight borders and occurs 1 to 6 months after RT. Radiation fibrosis sets in at 6 to 12 months and stabilizes at 1 year period. Radiation fibrosis manifests as traction bronchiectasis, volume loss, kinking of airways, and pleural thickening/effusion.

Post RT changes in the lung can be FDG-avid for up to 2 years. In previously irradiated patients, treatment with immune checkpoint inhibitors (ICI) can cause RT recall pneumonitis (pneumonitis in the irradiated regions of the lung), years after completion of RT. Besides pneumonitis, pulmonary artery thrombosis, esophagitis, fistulas, cardiac disease have been reported as complications of RT. Unlike radiation fibrosis, if the lesion is progressively increasing in size in real time or after 1 year of treatment, when the margins are convex and bulging, there is opacification of previously seen bronchograms, or development of new adenopathy of pleural effusion, then recurrence or disease progression needs to be suspected.³⁸

Immune-Related Adverse Events^{5,39,40}

Because of their unique mechanism of action, ICI can cause toxicities in several organs in the body, which can occur earlier or later during therapy. RT recall pneumonitis, described in post RT patients on ICI, occurs in previously irradiated tissue after weeks, months, or even years of radiation therapy.

Hypophysitis, sarcoid-like granulomatosis, lymphadenopathy, pneumonitis, hepatitis, colitis, adrenalitis, and inflammation in other parts of the body have been described

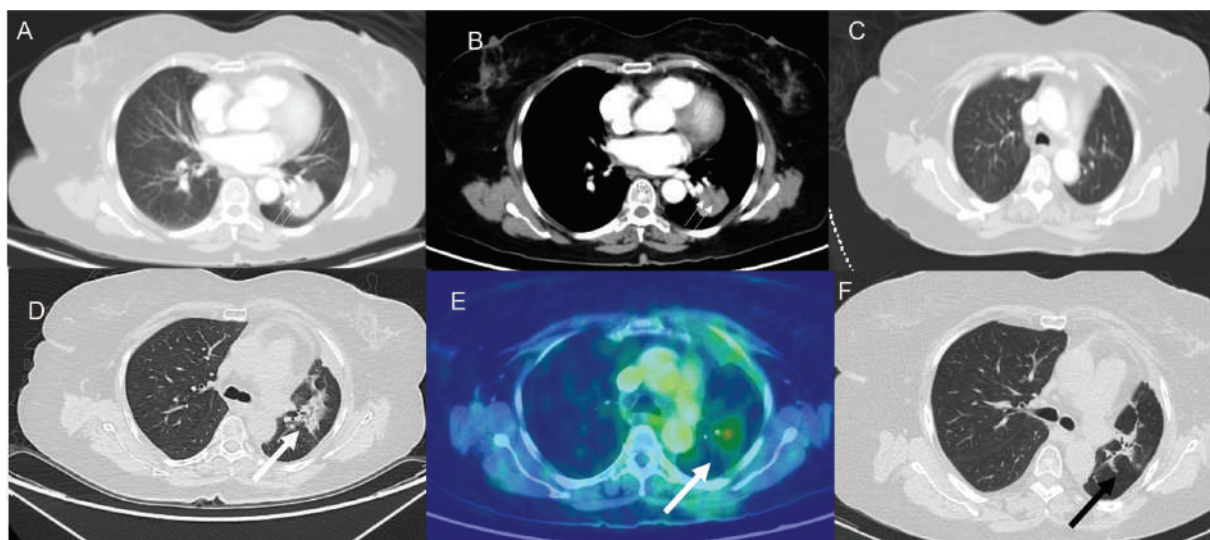


Fig. 4 (A and B) Computed tomographic (CT) thorax lung and mediastinal sections, respectively, demonstrate a lobulated mass (double thin white arrow) of 3.3 cm in the left lower lobe. No enlarged nodes. The patient underwent a left lower lobectomy. Histopathological examination revealed pleomorphic carcinoma with adenocarcinomatous component. Final stage was pT2aN2Mx. The patient had four cycles of adjuvant cisplatin and pemetrexed. (C) Post-chemotherapy and prior to radiotherapy, the CT thorax performed demonstrates no lesion in the left upper lobe. (D and E) CT thorax and corresponding fluorine-18 fluorodeoxyglucose positron emission tomography images demonstrate an irregular lesion (thick white arrow) in the left upper lobe having a standardized uptake value of 4.6. As the lesion appeared after starting radiotherapy and as there was no evidence of infection clinically, radiation pneumonitis was considered the most likely diagnosis. The patient was treated with steroids and follow-up CT thorax (F) demonstrates the replacement of the irregular parenchymal lesion with small residual fibrotic changes (black arrow).

Table 8 Radiological patterns in immune checkpoint inhibitor-related pneumonitis

Cryptogenic organizing pneumonia (COP) pattern	Peripherally distributed multifocal bilateral parenchyma consolidation and ground glass opacity (GGO)	This is the most common pattern
Diffuse alveolar damage pattern (DAD) (AIP/ARDS) (diffuse alveolar damage/acute interstitial pneumonia/acute respiratory distress syndrome)	Diffuse/multifocal; GGO/consolidation with lung volume loss and traction bronchiectasis	This is clinically the most serious type
NSIP (nonspecific interstitial pneumonitis) pattern	Peripherally distributed reticular opacities and GGO $\pm$ volume loss/traction bronchiectasis	These patients have relatively mild clinical manifestations
HP (hypersensitivity pneumonitis) pattern	Diffuse centrilobular nodules and GGO $\pm$ air trapping	

in association with ICI toxicity. They must be differentiated from metastasis, infection, or progressive disease.

ICI pneumonitis is relatively rare but clinically serious with different patterns described. (**► Table 8**).^{41,42} Treatment generally consists of corticosteroid therapy and delaying/stopping immunotherapy. After an initial response to corticosteroids, “Pneumonitis flare” can occur even without restarting immunotherapy.⁴³

Complications of Targeted Therapy

A recently published position paper by the Fleischner Society⁴⁴ recommends that radiological patterns be used to evaluate drug related pneumonitis which may be:

- Acute diffuse alveolar damage (DAD)
- Transient (simple pulmonary eosinophilia)
- Subacute—Organizing pneumonia and hypersensitivity pneumonitis (OP and HP)
- Chronic—Nonspecific interstitial pneumonitis.

A single drug may cause multiple radiological patterns. Epidermal growth factor receptor tyrosine kinase inhibitors

therapy has been associated with all the above patterns. ALK inhibitor therapy has been associated with OP and DAD patterns. The diagnosis is made based on the occurrence of new changes in the lungs, their temporal association with the drug, and exclusion of other causes. Management of these complications is by cessation of the drug course, immunosuppressive therapy, and supportive treatment.

Follow-Up Surveillance Imaging Guidelines

American Society of Clinical Oncology Guidelines⁴⁵

American Society of Clinical Oncology guidelines can be used for patients with curatively treated stage I to III NSCLC and SCLC in absence of clinical symptoms of recurrence as described in **► Table 9**. These guidelines apply for all patients treated with any modality including surgery, SBRT, and chemoradiation.

NCCN Surveillance Guidelines

NCCN guidelines are described in **► Tables 10** (NSCLC) and **11** (SCLC).^{7,9}

Table 9 ASCO guidelines for follow-up of curatively treated stage I–III NSCLC and SCLC PCI. Adapted from ASCO 2019 guidelines⁴⁵

ASCO 2019, lung cancer surveillance guidelines after definitive curative-intent therapy (stage I–III)			
	NSCLC	SCLC	Imaging modality
1. Frequency of imaging	Every 6 months for 2 years	Every 6 months for 2 years	Chest CT including adrenals $\pm$ contrast (contrast preferred)
	Annually after 2 years	Annually after 2 years	Low-dose screening chest CT
2. Role of brain MRI	No	First 2 years—every 3 months during first year and every 6 months during second year in patients with or without PCI	
3. Role of circulating biomarkers or FDG-PET-CT	No	No	
4. Any patient factors precluding surveillance?	May be omitted in clinically unsuitable patients or those unwilling to undergo further treatment. Age should not preclude surveillance imaging. Overall performance status, medical history, and patient preferences are to be considered.		

Abbreviations: ASCO, American Society of Clinical Oncology; CT, computed tomography; FDG-PET-CT, fluorodeoxyglucose positron emission tomography-computed tomography; NSCLC, nonsmall cell lung cancer; PCI, prophylactic cranial irradiation.

Table 10 NCCN surveillance guidelines: nonsmall cell lung cancer, Version 3.2020

Stage	Primary treatment	Imaging modality	Frequency of imaging
I–II	Surgery ± chemotherapy	H&P and chest CT ± contrast	Every 6 months for 2–3 years
		Low dose noncontrast chest CT	Annually after 2–3 years
I–II or III or IV (oligometastatic with all sites treated with definitive intent)	Primary treatment included RT	H&P and chest CT ¹ ± contrast	Every 3–6 months for 3 years, then
		H&P and chest CT ¹ ± contrast	Every 6 months for 2 years, then
		H&P and a low dose noncontrast CT chest	annually
		Any residual or new radiographic abnormalities	More frequent imaging may be required
Any stage	Chemotherapy ± RT—any residual or new radiographic abnormalities—more frequent imaging may be required.		
PET/CT or brain MRI	Not routinely indicated. PET-CT may be useful where CT scan shows a mass to differentiate between malignancy versus radiation fibrosis, atelectasis, or other benign conditions ²		
Smoking cessation	Smoking cessation advice, counselling, and pharmacotherapy		
Long term follow-up—cancer survivorship care	Cancer surveillance as above, immunizations, health monitoring, counselling for health promotion, and wellness		

Abbreviations: FDG, fluorodeoxyglucose; H&P, history and physical; NCCN, National Comprehensive Cancer Network; PET-CT, positron emission tomography-computed tomography; RT, radiotherapy.

1—Timing of CT scans within Guidelines parameters is a clinical decision. 2—Previous areas treated with RT may show FDG avidity till 2 years; so, histologic confirmation of apparent “recurrent” disease is mandatory. Adapted from NCCN Guideline: Non-Small Cell Lung Cancer. Version 3.2020 (2).

Table 11 NCCN surveillance guidelines: SCLC, Version 2.2022

Frequency and modality of imaging	H&P, blood work as clinically indicated. Chest CT ± abdomen/pelvis - Every 2–6 months (more frequently) for 2 years and less frequently thereafter
Brain MRI (preferred) or brain CT with contrast	Every 3–4 months during 1st year for all patients and then every 6 months during 2nd year, regardless of the PCI status
New pulmonary nodule	Workup for a potential new primary lesion should be initiated
FDG-PET-CT	Not recommended for routine follow-up
Smoking cessation intervention	For all patients with SCLC to decrease the occurrence of second primary tumors
Cancer survivorship care	Cancer surveillance as above, immunizations, health monitoring, counseling for health promotion and wellness

Abbreviations: FDG-PET-CT, fluorodeoxyglucose positron emission tomography-computed tomography; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PCI, prophylactic cranial irradiation; SCLC, small cell lung cancer.

Adapted from NCCN Guidelines: Small Cell Lung Cancer. Version 2.2022.

Principles of Management

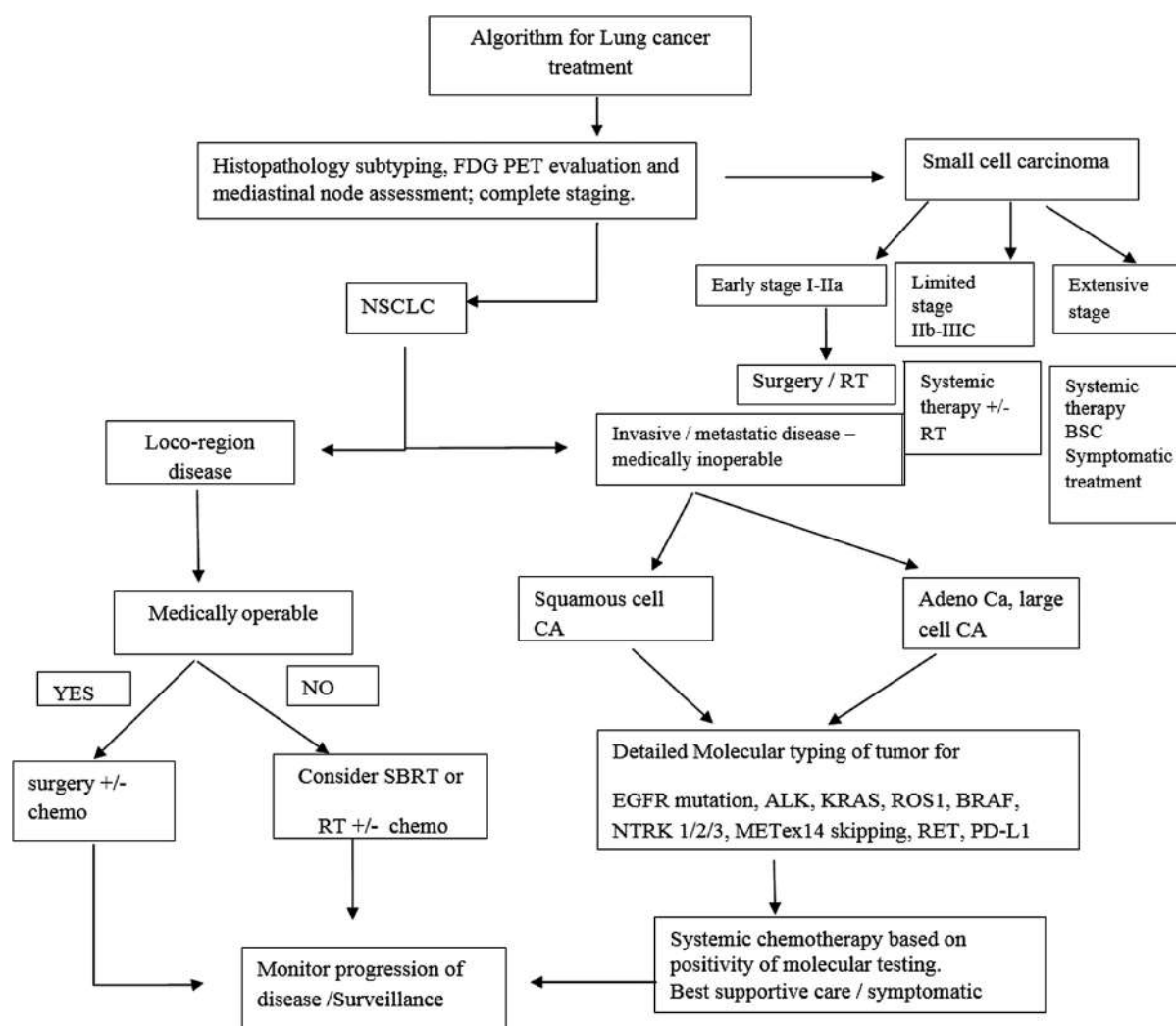
Multiple international guidelines for treatment of lung cancer exist, that is, NCCN and NICE.^{9,46} Surgery, RT, and systemic therapy are used either individually or in combination. Therapy type is determined by the histological type (NSCLC or SCLC), extent of disease, and fitness of the patient for curative surgery following multidisciplinary team assessment.⁴⁷ **Flowchart 2** highlights the main points in this complex management algorithm.

Image-guided thermal ablation treatment (IGTA) is a local ablative therapy that can be undertaken by interventional radiologist after an multidisciplinary team meeting decision is made to treat the patient with

IGTA. Most often this treatment is reserved for localized disease with tumor size less than 3 cm in size and potentially operable, but other comorbidities preclude surgery. Various electromagnetic energies like radio frequency, microwave, or cryoablation are used to thermally ablate the lesion without affecting the adjacent normal lung tissue. One of the common complications of IGTA is pneumothorax.

Follow-Up Imaging and Management of Recurrent Disease Including Specific Interventional and Palliative Measures

► **Tables 12 and 13** highlight the salient points in follow-up and management of recurrent disease.⁹



Flowchart 2 Highlights of principles of management of lung cancer. FDG PET, fluorine-18 fluorodeoxyglucose positron emission tomography; NSCLC, nonsmall cell lung cancer; SBRT, stereotactic body radiotherapy; EGFR, epidermal growth factor receptor.

Table 12 NCCN recommendations for treatment and follow-up of loco-regional recurrence found on surveillance imaging

Symptoms/site of recurrence	Treatment options	Follow-up imaging (depends on initial recurrence and any newly developing symptoms)
Hemoptysis	RT/surgery/embolization	Contrast-enhanced chest CT Contrast-enhanced MRI brain PET-CT
SVC obstruction	SVC stenting, chemoradiation	
Endobronchial obstruction	Radiotherapy/stenting/laser / photodynamic therapy	
Resectable local recurrence	Resection	
Nodal recurrence	Chemoradiation/systemic therapy	

Abbreviations: MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PET-CT, positron emission tomography-computed tomography; SVC, superior vena cava.

Summary of Recommendations (Flowchart 3)

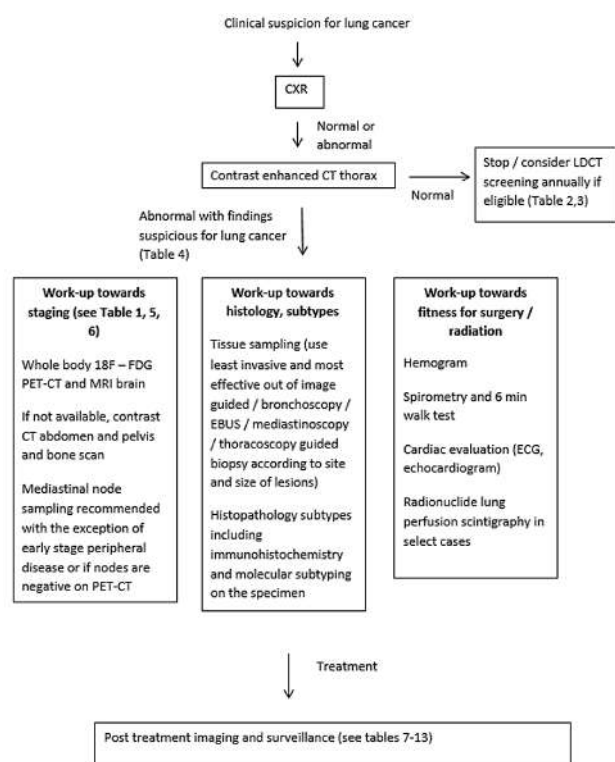
- Initial imaging in lung cancer includes CECT thorax and ^{18}F -FDG PET-CT aiming for accurate clinical staging both locoregionally and extrathoracic metastases.

- Invasive lymph node sampling is recommended for suspicious nodes detected on CT or PET scans.
- Contrast-enhanced brain MRI scan is recommended in advanced stage NSCLCs and in all stages of SCLCs.
- Different surveillance protocols are available and radiologists should be aware of pseudoprogression that can

Table 13 NCCN recommendations for the treatment of distant metastases found on surveillance imaging

Symptoms/site of recurrence	Treatment options	Follow-up imaging
Localized symptoms	Palliative RT	No specific imaging recommended
Diffuse brain metastases	Palliative RT	
Skeletal metastases	Surgical stabilization/palliative RT/bisphosphonates	
Limited metastases	Resection	
Disseminated metastases	RT/ systemic therapy	

Abbreviations: NCCN, National Comprehensive Cancer Network; RT, radiotherapy.



Flowchart 3 Summary of recommendations in workup and follow-up of patients with lung cancer. CXR, chest X-ray; LDCT, low-dose computed tomography; EBUS, endobronchial ultrasound; ECG, electrocardiogram; 18F-FDG PET-CT, fluorine-18 fluorodeoxyglucose positron emission tomography computed tomography.

occur with ICI and therapy-related toxicities in the lungs and elsewhere in the body.

Conflict of Interest

None declared.

References

- Thandra KC, Barsouk A, Saginala K, Aluru JS, Barsouk A. Epidemiology of lung cancer. *Contemp Oncol (Pozn)* 2021;25(01):45–52
- Mohan A, Garg A, Gupta A, et al. Clinical profile of lung cancer in North India: a 10-year analysis of 1862 patients from a tertiary care center. *Lung India* 2020;37(03):190–197
- Noronha V, Pinninti R, Patil VM, Joshi A, Prabhaskar K. Lung cancer in the Indian subcontinent. *South Asian J Cancer* 2016;5(03):95–103
- Mathur P, Sathishkumar K, Chaturvedi M, et al; ICMR-NCDIR-NCRP Investigator Group. Cancer statistics, 2020: report from

National Cancer Registry Programme, India. *JCO Glob Oncol* 2020;6:1063–1075

- Nishino M, Hatabu H, Hodi FS. Imaging of cancer immunotherapy: current approaches and future directions. *Radiology* 2019;290(01):9–22
- Del Giudice ME, Young SM, Vella ET, et al. Guideline for referral of patients with suspected lung cancer by family physicians and other primary care providers. *Can Fam Physician* 2014;60(08):711–716, e376–e382
- Ganti AKP, Loo BWJ, Bassetti M, et al. Small cell lung cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2021;19(12):1441–1464
- Ettinger DS, Wood DE, Aisner DL, et al. Non-small cell lung cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2022;20(05):497–530
- Ettinger DS, Wood DE, Aisner DL, et al. NCCN guidelines insights: non-small cell lung cancer, Version 2.2021. *J Natl Compr Canc Netw* 2021;19(03):254–266
- Accessed November 15, 2022, at: <https://iria.org.in/radiology-imaging-guidelines>
- de Groot PM, Chung JH, Ackman JB, et al; Expert Panel on Thoracic Imaging. ACR Appropriateness Criteria® noninvasive clinical staging of primary lung cancer. *J Am Coll Radiol* 2019;16(5S):S184–S195
- Melosky B, Blais N, Cheema P, et al. Standardizing biomarker testing for Canadian patients with advanced lung cancer. *Curr Oncol* 2018;25(01):73–82
- Schmidt-Hansen M, Baldwin DR, Hasler E, Zamora J, Abaira V, Roqué I Figuls M. PET-CT for assessing mediastinal lymph node involvement in patients with suspected resectable non-small cell lung cancer. *Cochrane Database Syst Rev* 2014;(11):CD009519. Doi: 10.1002/14651858.CD009519.pub2
- Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143(5, Suppl):e166S–e190S
- American Cancer Society. Cancer facts & figures 2020. Accessed November 15, 2022, at: <https://www.cancer.org/research/cancer-factsstatistics/all-cancer-facts-figures/cancer-facts-figures-2020.html>
- Aberle DR, Adams AM, Berg CD, et al; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365(05):395–409
- Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet* 1999;354(9173):99–105
- De Koning H, Van Der Aalst C, Ten Haaf K, et al. Effects of volume CT lung cancer screening: mortality results of the NELSON randomized-controlled population-based trial. Paper presented at: 2018 World Conference on Lung Cancer. Abstract PL02.05; 2018

- 19 Kim H, Kim HY, Goo JM, Kim Y. Lung cancer CT screening and lung-RADS in a tuberculosis-endemic country: The Korean Lung Cancer Screening Project (K-LUCAS). *Radiology* 2020;296(01):181–188
- 20 Yang P. MS16.04 National Lung Screening Program in Taiwan. *IASLC 19th World Conf. Lung Cancer* 2018;13(10, Supplement): S274–S275
- 21 Parang S, Bhavin J. LDCT screening in smokers in India-a pilot, proof-of-concept study. *Indian J Radiol Imaging* 2021;31(02): 318–322
- 22 McKee BJ, Regis SM, McKee AB, Flacke S, Wald C. Performance of ACR lung-RADS in a clinical CT lung screening program. *J Am Coll Radiol* 2016;13(2, Suppl):R25–R29
- 23 Wiener RS, Gould MK, Arenberg DA, et al; ATS/ACCP Committee on Low-Dose CT Lung Cancer Screening in Clinical Practice. An official American Thoracic Society/American College of Chest Physicians policy statement: implementation of low-dose computed tomography lung cancer screening programs in clinical practice. *Am J Respir Crit Care Med* 2015;192(07):881–891
- 24 Wood DE, Kazerooni EA, Baum SL, et al. Lung Cancer Screening, Version 3.2018, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2018;16(04):412–441
- 25 Kauczor HU, Baird AM, Blum TG, et al; European Society of Radiology (ESR) and the European Respiratory Society (ERS) ESR/ERS statement paper on lung cancer screening. *Eur Radiol* 2020;30(06):3277–3294
- 26 Nitz JA, Erkmén CP. New 2021 USPSTF lung cancer screening criteria-an opportunity to mitigate racial disparity. *JAMA Oncol* 2022;8(03):383–384
- 27 Kishi K, Homma S, Kurosaki A, et al. Small lung tumors with the size of 1cm or less in diameter: clinical, radiological, and histopathological characteristics. *Lung Cancer* 2004;44(01):43–51
- 28 Bueno J, Landers L, Chung JH. Updated Fleischner Society Guidelines for Managing Incidental Pulmonary Nodules: common questions and challenging scenarios. *Radiographics* 2018;38(05):1337–1350
- 29 Lacasse Y, Wong E, Guyatt GH, Cook DJ. Transthoracic needle aspiration biopsy for the diagnosis of localised pulmonary lesions: a meta-analysis. *Thorax* 1999;54(10):884–893
- 30 Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143(5, Suppl): e211S–e250S
- 31 Birim O, Kappetein AP, Stijnen T, Bogers AJ. Meta-analysis of positron emission tomographic and computed tomographic imaging in detecting mediastinal lymph node metastases in non-small cell lung cancer. *Ann Thorac Surg* 2005;79(01):375–382
- 32 Amin MB, Ed. *AJCC Cancer Staging Manual* 8th ed. Cham, Switzerland: Springer; 2017:431–455
- 33 Kalemkerian GP, Gadgeel SM. Modern staging of small cell lung cancer. *J Natl Compr Canc Netw* 2013;11(01):99–104
- 34 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45(02):228–247
- 35 Schwartz LH, Litière S, de Vries E, et al. RECIST 1.1-update and clarification: from the RECIST committee. *Eur J Cancer* 2016; 62:132–137
- 36 Seymour L, Bogaerts J, Perrone A, et al; RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol* 2017;18(03):e143–e152
- 37 Strange CD, Shroff GS, Truong MT, Nguyen Q-N, Vlahos I, Erasmus JJ. Imaging of the post-radiation chest in lung cancer. *Clin Radiol* 2022;77(01):19–30
- 38 Huang K, Senthil S, Palma DA, et al. High-risk CT features for detection of local recurrence after stereotactic ablative radiotherapy for lung cancer. *Radiother Oncol* 2013;109(01):51–57
- 39 Berghmans T, Dingemans AM, Hendriks LEL, Cadranet J. Immunotherapy for nonsmall cell lung cancer: a new therapeutic algorithm. *Eur Respir J* 2020;55(02):1901907. Doi: 10.1183/13993003.01907-2019
- 40 Nishino M, Tirumani SH, Ramaiya NH, Hodi FS. Cancer immunotherapy and immune-related response assessment: the role of radiologists in the new arena of cancer treatment. *Eur J Radiol* 2015;84(07):1259–1268
- 41 Nishino M, Sholl LM, Hodi FS, Hatabu H, Ramaiya NH. Anti-PD-1-related pneumonitis during cancer immunotherapy. *N Engl J Med* 2015;373(03):288–290
- 42 Nishino M. Imaging of oncologic treatment-related pneumonitis: a focused review on emerging issues of immune checkpoint inhibitor pneumonitis, from the *AJR* special series on inflammation. *AJR Am J Roentgenol* 2022;218(01):19–27
- 43 Nishino M, Ramaiya NH, Awad MM, et al. PD-1 inhibitor-related pneumonitis in advanced cancer patients: radiographic patterns and clinical course. *Clin Cancer Res* 2016;22(24):6051–6060
- 44 Johkoh T, Lee KS, Nishino M, et al. Chest CT diagnosis and clinical management of drug-related pneumonitis in patients receiving molecular targeting agents and immune checkpoint inhibitors: a position paper from the Fleischner Society. *Radiology* 2021;298(03):550–566
- 45 Schneider BJ, Ismaila N, Aerts J, et al. Lung cancer surveillance after definitive curative-intent therapy: ASCO guideline. *J Clin Oncol* 2020;38(07):753–766
- 46 Maconachie R, Mercer T, Navani N, McVeigh G. Guideline Committee. Lung cancer: diagnosis and management: summary of updated NICE guidance. *BMJ* 2019;364:l1049. Doi: 10.1136/bmj.l1049
- 47 Choi JI. Medically inoperable stage I non-small cell lung cancer: best practices and long-term outcomes. *Transl Lung Cancer Res* 2019;8(01):32–47

Imaging Recommendations for Diagnosis, Staging, and Management of Carcinoma of Unknown Origin (Lymph Node, Pulmonary, Liver, Skeletal, and Brain) with Emphasis on the Current Position of PET-CT in Carcinoma of Unknown Origin (CUP)

Sarvesh Loharkar^{1,2} Sandip Basu^{1,2} 

¹Radiation Medicine Centre, Bhabha Atomic Research Centre, Tata Memorial Hospital Annexe, Parel, Mumbai, Maharashtra, India

²Homi Bhabha National Institute, Mumbai, Maharashtra, India

Address for correspondence Sandip Basu, MBBS, DRM, DNB, MNAMS, Radiation Medicine Centre, Bhabha Atomic Research Centre, Tata Memorial Hospital Annexe, Jerbai Wadia Road, Parel, Mumbai, Maharashtra, 400 012 India (e-mail: drsanb@yahoo.com).

Ind J Med Paediatr Oncol 2023;44:194–206.

Abstract

Most of the established guidelines mention and recommend the use of FDG-PET/CT (fluorodeoxyglucose positron emission tomography/computed tomography) in carcinoma of unknown primary (CUP) especially in head–neck squamous cell carcinoma; as described in this article, this forms a powerful one-stop shop in diagnosing and staging modality and has multiple applications in difficult situations of CUPs. Although not used as a screening modality, FDG-PET/CT is recommended as the primary imaging modality in the evaluation of primary, staging, and response evaluation for CUP with histology known to demonstrate FDG avidity, especially patients presenting with lymph nodal disease. It should be remembered that many histological types do not concentrate on FDG and FDG also shows false-positive results in many other conditions like infection-inflammation; however, at the same time, it delivers high negative predictive values, an important consideration when employing FDG-PET/CT in the CUP scenario. SSTR-based PET/CT plays a pivotal role in primary diagnosis, staging, therapy planning, and response assessment in CUPs with neuroendocrine tumor or neuroendocrine neoplasm histology. The last two decades has witnessed great advancement in PET instrumentation and radiopharmaceuticals: particularly techniques like PET/magnetic resonance imaging and radiopharmaceuticals like FAPI (fibroblast-activation protein inhibitor)-based PET tracers. Hence, the role of PET/CT is expected to expand its reach in the coming years in line with accruing literature evidence, thereby upgrading its role and reliability in oncological practice strategies.

Keywords

- USG
- PET
- PET-CT
- FDG
- FNAC
- biopsy
- carcinoma of unknown primary (CUP)

DOI <https://doi.org/10.1055/s-0042-1760311>.
ISSN 0971-5851.

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)
Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Carcinoma of unknown primary (CUP) is defined as histology-proven malignancy whose organ of origin remains unidentified even after thorough investigations. This thoroughness and pre-work-up investigations are not fully defined, in fact it is a dynamic concept, expanding its scope and depth with newer developments including diagnostic studies. Newer advances in understanding molecular make-up of various malignancies, such as immunohistochemistry (IHC), and its clinical translation have revolutionized oncology practice in the last two decades. Likewise, positron emission tomography/computed tomography (PET/CT) hybrid imaging is a powerful modality that examines molecular processes/receptors in hand with an anatomical picture in a single go. Such a noninvasive single test that images the whole body with added molecular information becomes an attractive option in the CUP sitting. The role of PET/CT in the present day is based on available data and recommendations are summarized in this short review.

Risk Factors and Etiopathogenesis

Oncogenic mutations and environmental factor accepted for precipitating other known malignancies are identified as risk factors in CUP also, e.g., heavy smoking, central obesity, and alcohol consumption have been reported to have associations with CUPs.¹ Human papilloma virus subtypes are found to be associated with few forms of head-neck squamous cell carcinoma (SCC)-CUPs.² However, an association of germline mutations is not well established, and based on current literature the mutations are thought not related to genetic predisposition.³ As per the Spanish Pathology Society consensus statement, angiogenesis activation (50–89%), oncogene over-expression (10–30%), hypoxia-related proteins and epithelial-mesenchymal transition markers (16–25%), and the activation of intracellular signals (e.g., MAPK) are identified as vital drivers in the pathogenesis of CUPs.⁴

Epidemiology and Clinical Presentation: India and Global

The incidence of CUP worldwide during the last decade was 3 to 6 cases per 10,000,00 population in different series. As per National Cancer Registry Program, the figure reflects the same for Indian population also.⁵ Overall, CUPs contribute to 2 to 3% of all cancer cases.⁶ A recent analysis of population-based registries showed that the incidence rate of CUP has been decreasing over time (from its peak around the 1990s to the present era). The reasons for this decline may be related to improvements in diagnostic methods such as advanced imaging and molecular profiling.⁷

Commonly presenting clinical complaints of CUP depend on the area involved and type of primary such as squamous cell, adenocarcinoma, poorly differentiating carcinoma, etc. Adenocarcinoma is the most prevalent pathological subtype reported in the CUP setting, followed by poorly differentiated cancers, SCCs, and neuroendocrine tumors (NETs).⁸

Overview of Currently Published Imaging Referral Guidelines (NCCN/ASCO/ESMO/RCR/IRIA/NCG/EANM): Where Do CECT, MRI, and PET-CT Stand?

The most updated National Comprehensive Cancer Network (NCCN) guidelines (version 1.2022) states that PET/CT imaging has added benefits to CT or PET alone. This modality has intermediate specificity and high sensitivity in a few small studies, larger studies are warranted to determine the clinical utility and role of PET/CT compared with conventional imaging modalities in CUPs. It is not used routinely in the initial evaluation of suspected metastatic malignancy and warranted in a few special conditions like while consideration of local/regional therapy and curative intent treatment is being planned in a suspected single site. The NCCN guideline also mentions PET/magnetic resonance imaging (MRI) as an alternative to PET/CT and its added benefits like lower doses of ionizing radiations with similar or even improved accuracy.

Current ASCO (American Society of Clinical Oncology) statement (version: 2020) on “Squamous Cell Carcinoma of Unknown Primary in the Head and Neck” states that along with meticulous clinical history and examination, contrast-enhanced CT (CECT) is the first-line modality, and this will identify the majority of primary tumors. When a primary is not evident on clinical examination and CECT, PET/CT should be the next diagnostic step yet before any endoscopic biopsies if the primary remains unknown. It has added utility especially in directing biopsy, palatine tonsillectomy, or lingual tonsillectomy. This permits the dual advantage of guiding biopsies and reducing the false-positive rate.⁹

The European Society for Medical Oncology (ESMO) 2015 guidelines suggests the use of FDG-PET/CT (fluorodeoxyglucose positron emission tomography/computed tomography) for diagnosis and staging of CUP tumors and especially those with cervical adenopathies and single metastasis. But for other CUPs, the role of FDG-PET is limited and this imaging procedure is not mandatory in the systematic work-up.¹⁰ Similarly, the Royal College of Radiology (RCR) in their recommendations (2014) mentions using FDG PET/CT in locating a primary tumor in metastatic SCC of the neck, while also mentions about variable accuracy for this modality of CUP at other places.¹¹

As per the published guidelines and recommendations in oncologic imaging of Indian Radiological and Imaging Association (IRIA/ICRI) (April 2020), PET/CT and MRI of the neck should be requested (before biopsy of high-risk sites) as the first line. PET/CT is also of value in assessing the presence of recurrent disease. In patients with dysphagia having a known postcricoid or upper esophageal disease, PET/CT scan is recommended. Where there is a high clinical index of suspicion of recurrence, it would be sensible to perform MRI or CT to assess the extent of the recurrence. In cases where there is clinical doubt, or where recurrence is under evaluation, it may be more appropriate to proceed directly to PET-CT.¹²

As per the published treatment protocol of NCG (National Cancer Grid) India (April 2017), cervical nodes when

evaluated with fine needle aspiration cytology (FNAC) first turns out to be SCC of head and neck (SCCHN) or adenocarcinoma of unknown origin, and FDG-PET/CT can form one of the vital initial recommended investigations along with tumor markers and IHC. This would help guide and track the primary and also plan therapy adequately (decision making between neck dissection, adjuvant radiotherapy, concurrent chemotherapy, and so on). PET-CT is recommended as the first investigation in the clinical setting of recurrent SCCHN which is grossly defined as locoregional or distant metastatic and guides further treatment algorithm depending on disease extent and resectability. As per consensus statement of the Spanish Society of Pathology and the Spanish Society of Medical Oncology (2018), 60% of poorly differentiated malignancies eventually turn out to be lymphomas, and in such cases, when present with widespread lymphadenopathies and having liver or spleen involvement, it is advisable to analyze along with FDG-PET/CT scan and repeat biopsies to guide the use of specific therapies.⁴ The American College of Radiology appropriate use criteria statement has currently listed this entity under topics that are currently “under evaluation.” The EANM (European Association of Nuclear Medicine) procedural guidelines in tumor imaging have mentioned “searching for an unknown primary tumor when metastatic disease identified or when the patient presents with a paraneoplastic syndrome” and it forms an important indication of FDG-PET/CT.¹³ The Society of Nuclear Medicine and Molecular Imaging (SNMMI) in their appropriate use criteria statement or somatostatin receptor (SSTR) PET for NETs states that the use of PET is appropriate (and considered acceptable) in “localization of primary tumor in patients with known metastatic disease but unknown primary with NET.”¹⁴

Clinical and Diagnostic Work-Up in CUP (Excluding Imaging)

The preliminary clinical work-up consists of a detailed history with particular attention to lifestyle, addictions, environmental factors, and previous treatments received. This is followed by extensive physical examination, including oropharyngeal, genitourinary, rectal examinations, and breast examinations in females. After the clinical evaluation, the important laboratory tests like complete blood counts with peripheral smear, urine analysis, liver and renal function tests, stool examination, and tumor markers such as serum PSA, serum CEA, serum AFP, serum Ca-125, etc., histological examinations, FNACs, and biopsy, are diagnostic choice and play an important role in the classification of tumor and guide further diagnostic procedures and therapies. IHC (e.g., S-100, TTF-1, cytokeratin, chromogranin, etc.) helps to delineate tumor lineage.

Imaging Guidelines

Screening

FDG-PET/CT has a high incidence of false-positive findings (mainly benign inflammatory lesions which are amongst the

primary differentials in the CUP setting) and also false-negative findings (non-FDG-concentrating tumors such as well-differentiated NETs). Certain shortcomings of FDG-PET/CT as a screening investigation are noteworthy, viz. large amounts of image data and complex and time-consuming interpretation procedure; possibility of overlooking subtle pathological findings or over-diagnosis increasing the number of negative biopsies.¹⁵ It also exposes an individual to high radiation doses (up to 25 mSv per study). Thus, it is recommended to use nonradioactive and targeted tests such as tumor markers before posting patients for PET/CT. *In summary, FDG-PET/CT is not warranted for screening modality in suspected CUPs.*

Diagnosis of Primary Malignancy in CUP

Functional or metabolic changes on PET-CT can occur in the absence of any corresponding anatomical changes and/or not visualized by anatomical imaging. A meta-analysis investigated the diagnostic performance of FDG-PET/CT and reported a primary tumor detection rate of 37%.¹⁶ The role of FDG-PET/CT in head-neck SCCs and poorly differentiating cancers turning out to be lymphomas is well established in various guidelines as outlined above. In a subset of six reviewed studies, FDG-PET led to a change in treatment in 24.7% of cases. PET-CT had the highest accuracy for detection of primaries in the hypopharynx and larynx.^{17,18} For the extra-cervical metastases, there is lack of a thorough assessment of diagnostic performance with heterogeneous results, and the modality appears comparable to other modalities. Among the various sites, the lung, pharyngeal, and pancreatic cancers represent the most frequently detected primary tumors.

The oropharynx and the lung are the two most common locations of false-positive FDG-PET/CT results.¹⁶ Frequently, metastatic lung lesions/nodules are not FDG avid, especially primary malignancies like thyroid, hepatobiliary tree, renal, and testicular cancers, and commonly show lung metastases that have low-grade or indeterminate FDG uptake. There are also multiple physiological variants, benign tumors, and inflammatory and infective diseases known to cause increased FDG uptake and mimic malignant disease.¹⁹ At present, there is no guideline or systemic analysis/study that has demonstrated definitive clinical benefit of PET/CT over CECT in the primary diagnosis of lung and brain metastases of unknown origin.¹⁹

Similarly for skeletal lesions, common originating sites for metastases are primaries from the lung, prostate, gastric carcinoma, hepatobiliary tree, and kidney cancers, while for brain lesions, the commonly detected primaries are from the breast and lung. For these malignancies, FDG-PET/CT has lesser or comparable accuracy compared to CECT or targeted modalities like mammography. The role of FDG-PET/CT has been studied in a few retrospective studies with a reported sensitivity up to 60%, while no direct comparison with other modalities is yet available to investigate its benefit.²⁰ On failure of other imaging modalities such as CECT or MRI, the FDG-PET/CT can be considered in these situations, especially if this is expected to impact further management.

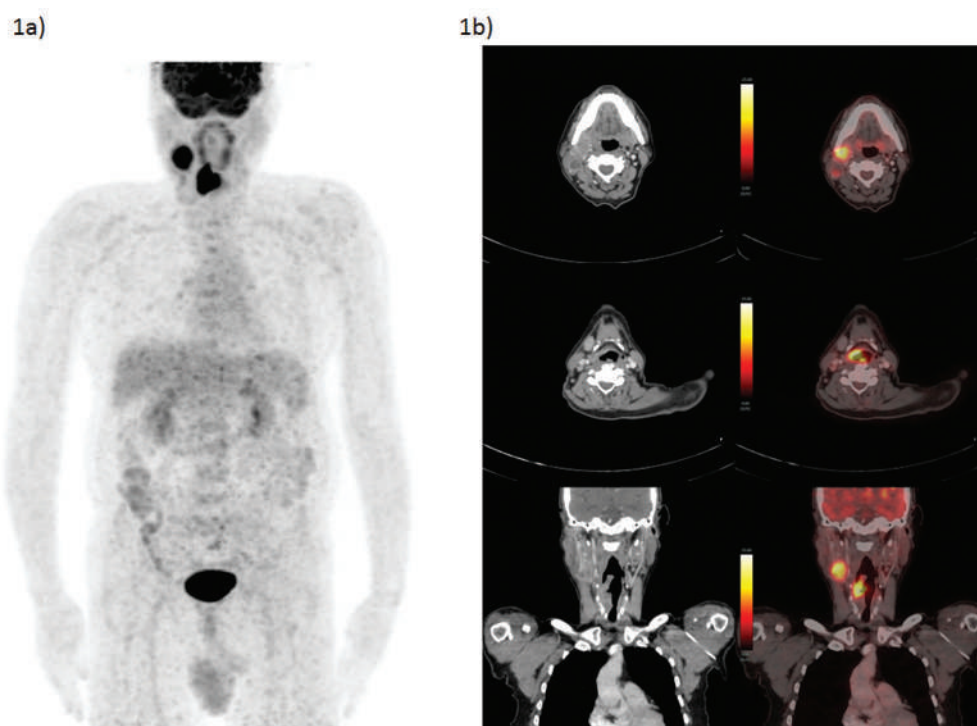


Fig. 1 A 62-year-old male presented with swelling over right-side neck over the last 1.5 months and cough of 20 days' duration. FNAC taken from neck mass turned out to be metastatic squamous cell carcinoma. He underwent FDG-PET/CT as baseline evaluation, which showed right-sided cervical lymph node, a few similar but smaller right level III nodes, and soft tissue lesion involving supraglottic larynx, arising from right-sided right PFS; no cartilage/hyoid erosion or extra-laryngeal involvement was noted. Direct laryngoscopy showed soft tissue growth involving the medial wall of right pyriform sinus. Biopsy taken from right-sided aryepiglottic fold showed squamous cell carcinoma. Considering no obvious evidence of distant metastases on present PET/CT scan, he was planned for curative surgical procedure. (a) FDG-PET/CT MIP image and (b) CECT and fused PET/CT transaxial and coronal section images showing FDG avid right-sided level II cervical node and FDG avid soft tissue lesion involving supraglottic larynx, arising from right PFS. *The present illustration demonstrates the utility of FDG-PET/CT in both identifying primary and staging of nodal disease which impacts disease management, in this case being considered for curative locoregional approach.* CECT, contrast-enhanced computed tomography; FDG-PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; FNAC, fine needle aspiration cytology; MIP, maximum intensity projection.

As mentioned earlier, thorough etiological and clinical evaluation is a must in CUP diagnosis and before targeting them for PET/CT. The usual clinical presentations are local swelling, discomfort or pain in any body part commonly the abdomen, dyspnea, cough, bone pain, weakness, fatigue, poor appetite, weight loss, unusual bleeding or discharge, pyrexia of unknown origin, change in bowel-bladder habits, drenching night sweats, etc. Depending on the organ system involved, it may also present as ascites in abdominal/pelvic malignancies like ovarian cancer. More attention is to be given to local examination where symptoms appeared first, e.g., otolaryngo-rhino and oral cavity examination for cervical nodal disease, breast examination in axillary nodal disease, adequate prostate, breast, lung, renal, or thyroid primary evaluation for bone disease, and groin, genital, and rectal areas to be examined primarily in inguinal nodal disease. Most of the times this is followed by tissue diagnosis using FNAC/biopsy. It is a consensus that the site identified above diaphragm will have primary above diaphragm only but not true every time, especially for brain and supraclavicular lymph nodal lesions. Furthermore, the PET/CT imaging protocols are to be decided depending on these pathological and clinical factors. This is to target specific areas along with the whole body for rare distant sites, e.g.,

puffed cheek view in suspected oral cavity lesions in cervical nodal disease, for mediastinal nodal masses dedicated lung protocol where even scar-like nodules are suspicious, while liver lesions are to be imaged with multiphase contrast-enhanced study in the well-distended stomach and bowel loops (using both oral and rectal contrast if needed), it is advised to screen total body (head to toe) including nodal stations in limbs for suspected melanomatous lesions.

In a primary evaluation of the CUP, dual time-point PET imaging (i.e., PET imaging at routine 1 hour and after a standard delay) is recommended in a case-based setting to enhance its sensitivity and specificity (FDG is not tumor-specific). **►Supplemental material.** Focal FDG uptake is indeterminate to differentiate malignancy versus inflammation versus physiological uptake. A gradually increasing trend of FDG uptake over time has been shown to be preponderant in malignant cells, and a decreasing or constant trend has been shown in inflammatory/infectious processes. This has proven to increase the accuracy of the FDG-PET/CT studies.²¹

Thus, FDG-PET/CECT is recommended as primary imaging investigation to identify the primary site in CUPs, particularly those presented as lymph nodal disease (►Figs. 1 and 2).

FDG-PET/CT is not recommended as the primary imaging investigation for CUPs presenting with pulmonary, bone, or

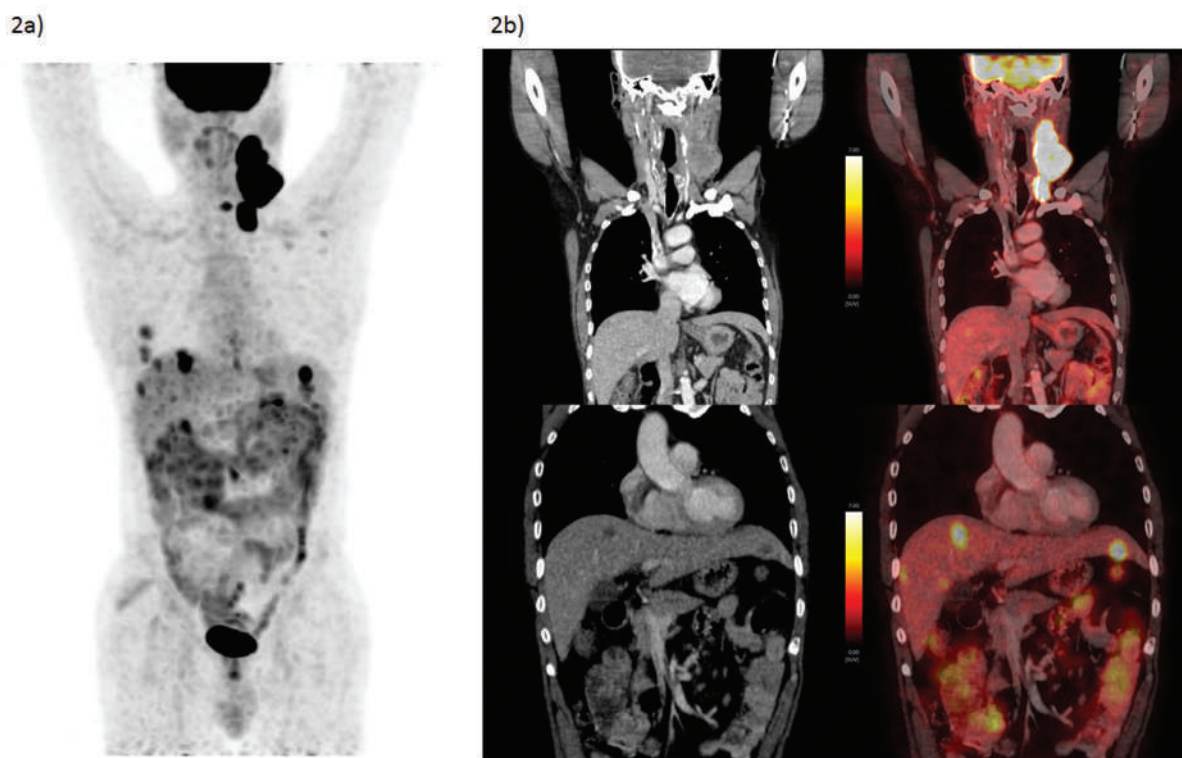


Fig. 2 A 59-year-old male presented with swelling over left-side neck over 2 months along with some dysphasia. FNAC taken from neck mass (lymph node) turned out to be metastatic squamous cell carcinoma. He also underwent direct laryngoscopy where punch biopsy from cricoid region came inconclusive. No other obvious lesion was identified. He underwent FDG-PET/CT, which showed metabolically active multiple left level II, III, IV nodes and nodal masses, left infraclavicular nodes, and liver lesions. USG-guided biopsy from the lesion was also identified as of similar histology (SCC) and a diagnosis of metastatic SCC-CUP was made. (a) FDG-PET/CT MIP image and (b) CECT and fused PET/CT coronal section images showing FDG left cervical nodal masses and metastatic FDG avid hypodense hepatic lesions. *The present illustration demonstrates the inability to identify primary lesion and diagnosis of CUP in spite of multiple diagnostic approaches as well as the utility of FDG PET/CT staging where unusually site for SCC such as liver was identified.* CECT, contrast-enhanced computed tomography; CUP, carcinoma of unknown primary; FDG-PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; FNAC, fine needle aspiration cytology; MIP, maximum intensity projection; SCC, squamous cell carcinoma; USG, ultrasonography.

brain metastases and also not the primary imaging investigation with histological subtypes with indeterminate FDG concentration (e.g., mucinous carcinoma or serous adenocarcinoma). However, it may be considered when conventional imaging modalities such as CECT and extensive clinical work-up have failed to find primary and also in treatment response monitoring scenarios (► **Figs. 3 and 4**).

FDG-PET/CT-Guided Biopsy in CUP

FDG-PET can differentiate between the metabolically active viable portions of the tumor from the nonactive part of the tumor; biopsy from the area of highest metabolic activity is expected to result in greater diagnostic yield, especially in suspected abdominal soft tissue, bone, and head-neck primaries. This approach and quantification method helped verify biopsy adequacy through a comparison of specimen activity and that expected from the PET image.²² Yet, its exact utility in CUPs and direct comparisons with a CT-guided approach are not established, thus it is recommended primarily for FDG-concentrating lesions on scan and with previously failed biopsy sampling (**Flow Chart 1**).

SSTR PET/CECT in Biopsy-Proven NEN in Unknown Primary (CUP-NEN)

CUP syndrome is common in metastatic neuroendocrine neoplasms (NENs), and in recent years SSTR-based PET-CT has emerged as a strong imaging tool with the highest accuracy. As per the above-mentioned guidelines, SSTR-based PET/CT is recommended in low-grade NETs to search primary lesions with greater accuracy. A study by Sampathirao et al used combined dual-tracer PET/CT (both ⁶⁸Ga-DOTA-TATE/NOC and FDG) correlating with MIBI-1/Ki-67 index in 51 patients of metastatic CUP-NETs and reported a sensitivity of 60.78% for the former, with an overall lesion detection sensitivity of 96.87%.²³ Small-sized pancreatic and ileum/jejunal primaries are most commonly encountered, which are missed in previous investigations. Absent SSTR expression such as in de-differentiated or high-grade tumors results in false-negative results,²³ where FDG becomes the tracer of choice. Thus, SSTR PET/CECT (⁶⁸Ga-DOTA-TATE/NOC) is recommended as a primary imaging modality in biopsy-proven NEN in unknown primary, especially for the grade 1 and 2 tumors (► **Figs. 5 and 6**).

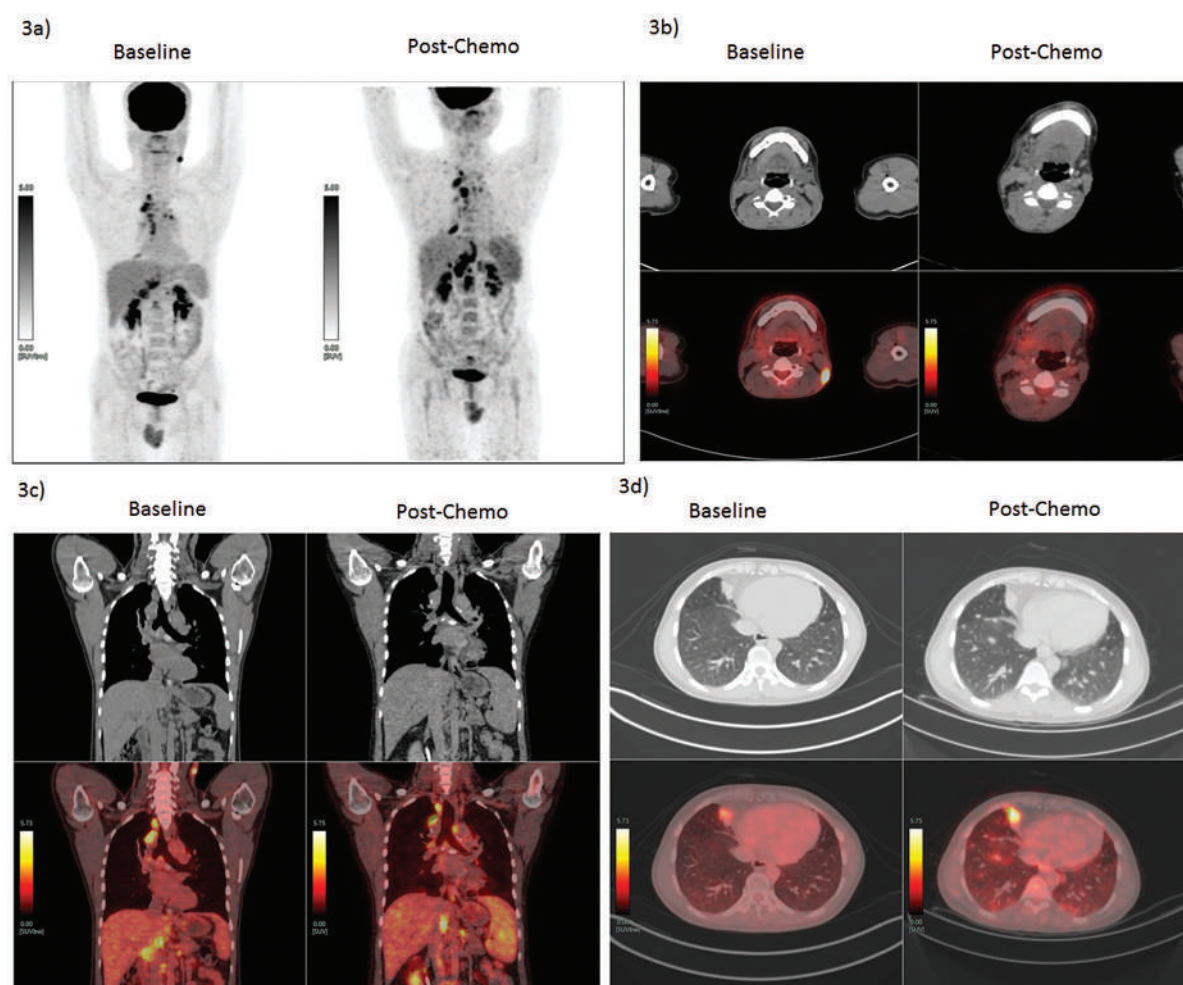


Fig. 3 A 33-year-old male, occasional smoker, presented with left-sided neck swelling. The biopsy from left level III lymph nodes turned out to be metastatic deposits of squamous carcinoma. He underwent ^{18}F -FDG PET/CT to find primary and baseline staging. The FDG-PET/CT revealed metabolically active left-sided neck node (level V), multiple mediastinal nodes, right middle lobe paracardiac lesion, and abdominal nodes. Biopsy was attempted from chest lesion and mediastinal nodules, which revealed similar histology and other infective etiologies were ruled out. A diagnosis of metastatic SCC-CUP was made. The patient further received palliative chemotherapy as per protocol (paclitaxel and carboplatin). The response evaluation using FDG PET/CT showed response to cervical lesion but there was an increase in size and metabolism of other lesions, with multiple new lung nodules noted. The present therapy was stopped and molecular analysis was underway for the patient to decide further therapeutic options. (a) PET MIP images pre- and post-chemotherapy showing disease progression, (b) CT and PET/CT fused transverse section images pre- and post-chemotherapy at level V node showing complete resolution of the lesion. (c) CT and PET/CT fused coronal section images pre- and post-chemotherapy showing disease progression in abdominal and mediastinal nodes. (d) CT and PET/CT fused transverse section images pre- and post-chemotherapy showing progression of pleural-based nodule and newly seen tiny pulmonary nodules. *The present illustration demonstrates the utility of FDG PET/CT in staging disease in CUP and response evaluation to systemic chemotherapy.* CUP, carcinoma of unknown primary; ^{18}F -FDG-PET/CT, fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography; MIP, maximum intensity projection; SCC, squamous cell carcinoma.

Staging

FDG-PET/CT, due to its high sensitivity and whole-body imaging ability, offers advantages to identify or rule out additional metastatic sites, which may have important significance for patient management. This is highlighted in multiple current practice guidelines for patients with CUP who present with only lymph node metastatic disease. Many times, these patients are being planned for radical or definitive treatments such as surgery or radiation therapy (RT) in restricted local disease. Here exact disease staging is warranted, which has important therapeutic and prognostic consequences. FDG-PET/CT performs better than most other

modalities and serves as a one-stop-shop modality mapping disease in the whole body in a single examination. It aids in the decision-making investigation, as mentioned in the above guidelines, from the viewpoint of whether to plan for definitive therapy or adjuvant palliative therapies. It is also further advised to get a pathological diagnosis when the findings change the management drastically, considering the false-positive rates.²⁴ A systematic review in cervical nodal diseases of 16 studies on 302 patients stated that FDG-PET detected previously unrecognized metastases in 27% of patients, of which 11% were distant metastases, and resulted in changes in treatment in 24.7% of cases.¹⁷ Hence,

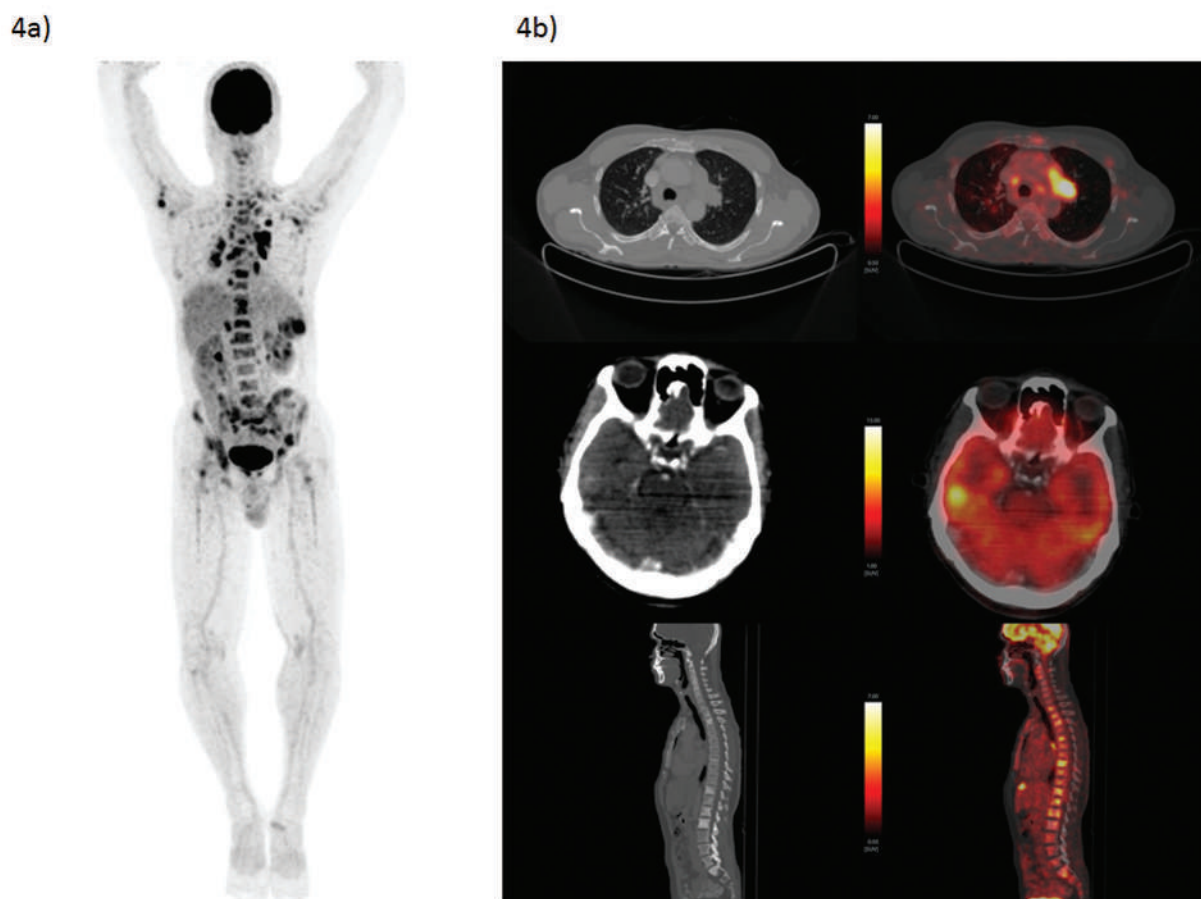


Fig. 4 A 62-year-old male presented with right hip and lower back pain for 3 months, MRI spine showed extensive marrow replacing lesion in the pelvic bones and vertebrae suggestive of metastatic deposits. FDG-PET/CT was considered to look for primary lesion and characterization of skeletal lesions, which showed FDG avid left lung mass which was suspected for primary lesion along with other tiny nodules. FDG avid metastatic appearing mediastinal, supraclavicular, and abdominal nodes were noted along with FDG avid lesions in the brain, liver, spleen, left kidney, right adrenal, and skeletal system (including multiple vertebrae, pelvis, sacrum, and bilateral femur). The USG-guided biopsy from left supra-clavicular node showed poorly differentiated non-small cell carcinoma. The disease was diagnosed as metastatic lung cancer with multiple soft tissue (including brain) and skeletal metastatic lesions. (a) FDG-PET/CT MIP images showing multiple regions of pathological skeletal and multiple other lesions scattered over the whole body. (b) CECT and PET/CT fused transverse section images, showing FDG concentrating left lung upper lobe mass and mediastinal nodes, enhancing lesion in right temporal lobe, and sagittal section image showing sclerotic lesions in multiple vertebrae and pelvic bones. The present illustration demonstrates the utility of FDG-PET/CT in guiding primary diagnosis and whole-body disease staging in evaluation of a patient presenting with metastatic skeletal disease. CECT, contrast-enhanced computed tomography; FDG-PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; MIP, maximum intensity projection; MRI, magnetic resonance imaging; USG, ultrasonography.

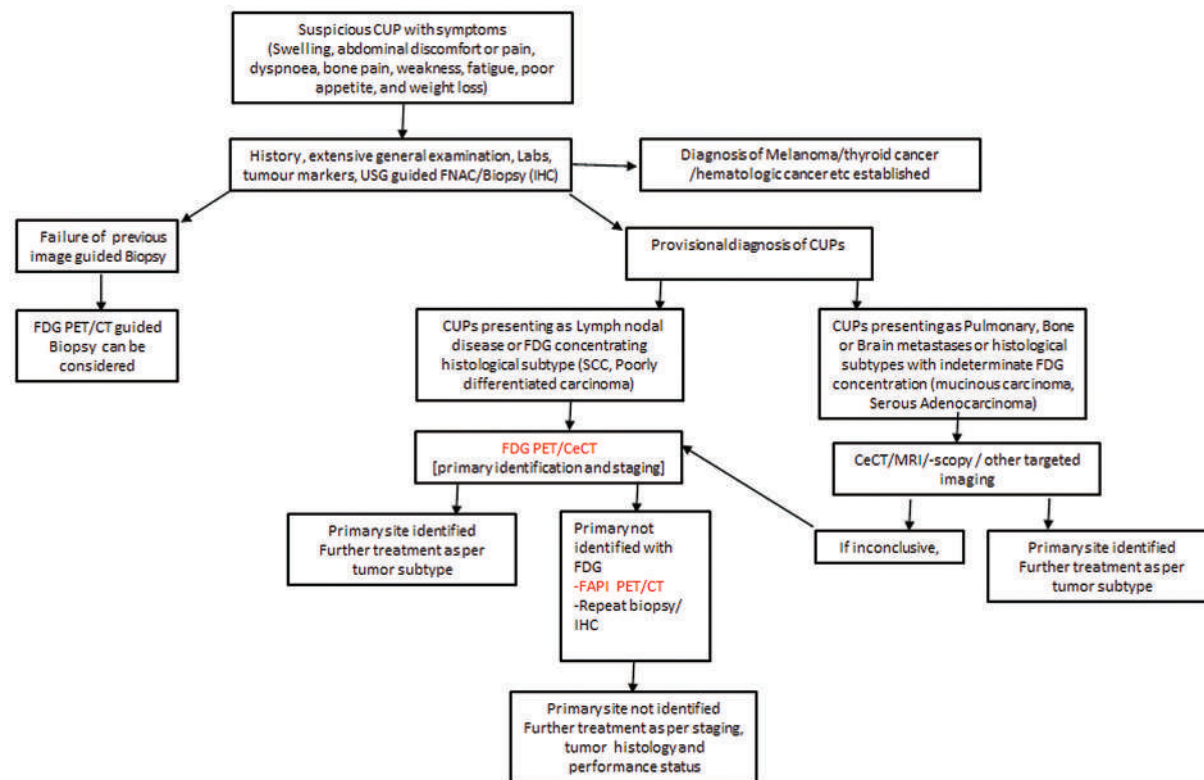
FDG-PET/CT is recommended as the primary staging modality in CUPs with histological subtype known to be FDG concentrating or avid (e.g., SCC, poorly differentiated) (–Figs. 1,2,3).

The SSTR-based PET/CT delineates the primary tumor site and frequently demonstrates additional metastatic lesions which were not previously diagnosed on ultrasonography (USG)/CT considering their indolent nature. This provides better staging that results in clinically relevant changes in management in about one-third of patients.²⁵ Although finding more lesions is not prognostically important in the NET setup, it provides a baseline scan and aids in therapy decision-making and assessment of therapeutic response like peptide receptor radionuclide therapy (PRRT) or chemotherapy. Furthermore, the concept of dual-tracer PET is now well established in NENs and fast become an important gatekeeper for therapeutic disease making amongst the different therapy options. *In summary, SSTR-based PET/CT*

is recommended as the primary staging modality in CUPs with NEN histology.

Management and Imaging Response Assessment in Neoadjuvant, Adjuvant, and Palliative Settings

Presently treatment strategies have shifted from empirical cytotoxic therapies to identifying the primary tumors and targeted therapies as per the tumor type.²⁶ Even though the source of primary is not identified, the limited disease is subjected to curative interventions such as surgical excision or RT mainly in head–neck lymph nodal disease. Conventional anatomical agents provide lower accuracy considering posttreatment dysmorphic normal anatomy and disruption of normal tissue planes. Multiple groups and studies have emphasized FDG-PET/CT as a modality of choice in response monitoring in head and neck cancers.^{27,28} Further standardized evaluation criteria have been developed in this group,



Flow Chart 1 Screening, baseline diagnosis, and staging.

such as Hopkins²⁹ and PERCIST³⁰ are based upon PET-CT and greatly influencing response evaluation in oncology. Although there is no direct comparison available in CUPs between other modalities and PET, it is imperative that PET/CT provides more confidence to clinicians for labeling patients disease-free owing to its high negative predictive value. *In conclusion, FDG-PET/CT is recommended as a first-line response evaluation modality for known FDG-concentrating histology subtype (► Fig. 3).*

Neoadjuvant systemic therapy option has been followed in clinical practice to deliver the best possible outcome in a number of malignancies and FDG-PET/CT has demonstrated its added role and higher confidence in neoadjuvant management of esophageal, rectal,³¹ and breast cancers, a similar way it is thought to aid in CUP management when baseline disease is FDG-concentrating. As per recent NCCN guideline (1.2022), when CUPs are diagnosed as disseminated disease, which is the scenario in many encountered cases, systemic therapy with cytotoxic drugs or immune-modulatory therapy even sometimes combined with RT is practiced. As per one study on head neck cancers,³² the accuracy of PET in therapy response assessment was significantly better than conventional imaging (CT/MRI) ($p < 0.001$). Early response evaluation with FDG-PET provides insights into functional characteristics before anatomical changes, which provides lead time. It is now established that anatomical response evaluation criteria based upon tumor volume cannot quantify nonmalignant or the fibrous material adequately in the tumor.³³ In addition, the guidelines also mention immuno-

modulatory therapies and trials where response patterns differ from those of chemotherapeutic and molecularly targeted agents considering the recruitment of immune cells and related changes in the tumor microenvironment. This has been highlighted in recently approved SNMMI procedure standards³⁴ and introduces new terms like pseudo-response, hyper-response, dissociated-response, and durable response. FDG-PET additionally has shown accuracy in monitoring systemic immune response and detecting immune-related adverse effects in the early stages.^{35,36} Overall, FDG-PET/CT response is better correlated with patient outcome and considered a better predictor for the effectiveness of new anticancer therapies than routine anatomical criteria (Flow Chart 2).

In summary, FDG PET/CECT is recommended as a response evaluation modality for FDG-concentrating tumor types, following systemic therapies either in neoadjuvant, adjuvant, or palliative therapy setting (cytotoxic chemotherapies, immune-modulatory therapy, other specialized approaches with or without concurrent radiation).

As per the appropriate use criteria statement by SNMMI¹⁴ for SSTR-based PET/CT in NET, a well-established practice in both pretherapy patient classification and posttherapy patient monitoring, the complete anatomical response is observed in <10% of patients in available therapy options (octreotide, PRRT, chemo-PRRT) but dual-tracer PET/CT characteristics provide vital information of tumor biology in a single examination for whole body and aid timely interventions and other therapeutic decisions (Flow Chart 3).³⁷

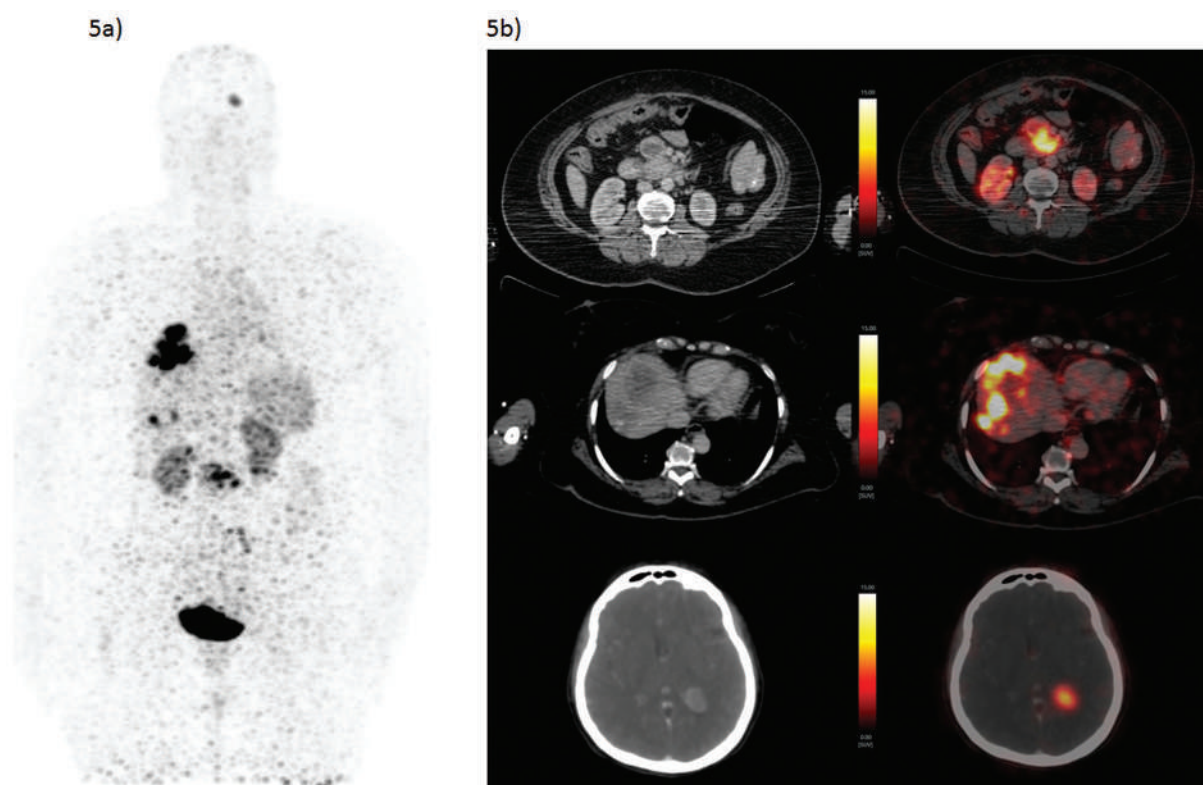


Fig. 5 A 60-year-old female presented with right upper abdomen discomfort and with USG suggestive of multiple mass lesions in the liver; patient got evaluated further with CECT scan and liver lesions were labelled not typical for HCC though they showed arterial enhancement with abdominal nodes. Her serum chromogranin A level was highly raised; thus, she was referred for ^{68}Ga -DOTATATE PET/CT scan to ascertain the primary and also evaluate disease extent. ^{68}Ga -DOTATATE PET/CT revealed SSTR-expressing mesenteric mass, abdominal nodes, liver lesions, and incidentally detected well-defined left lateral ventricular lesion in the brain, for which the patient was asymptomatic. A biopsy from the liver lesion revealed this to be grade I (Mib-1 index of 1%) neuroendocrine tumor. The disease was labelled as metastatic mesenteric NET with nodal and liver metastases and incidentally detected meningioma/? cerebral lesion. The patient was started on long-acting octreotide injections; she revealed stable and asymptomatic disease post 6 months. (a) ^{68}Ga -DOTATATE PET/CT MIP image, showing SSTR-expressing mesenteric lesion, liver lesions (Krenning score 4), and left cerebral lesion. (b) CECT and PET/CT fused transaxial section images showing SSTR-expressing mesenteric lesion, liver lesions, and left cerebral (ventricular) lesion. *The present illustration demonstrates the utility of SSTR-based PET/CT in guiding primary diagnosis, disease staging-grading, and guiding therapy in evaluation of NETs presenting with metastatic disease.* CECT, contrast-enhanced computed tomography; HCC, hepatocellular carcinoma; NET, neuroendocrine tumor; PET/CT, positron emission tomography/computed tomography; SSTR, somatostatin receptor; USG, ultrasonography.

Thus, SSTR-based PET/CT is recommended for response evaluation in CUPs with NET histology who are on systemic therapies (octreotide, PRRT, chemo-PRRT).

Follow-Up

The follow-up frequency and strategy in CUP is done differently considering the vast spectrum of diseases and outcomes. Routine follow-up especially in asymptomatic patients would not justify for unnecessary ionizing-radiation exposure in the form of FDG-PET/CT. Also, many false-positive findings in common benign conditions can lead to over-diagnosis. However, FDG PET/CT is thought to be justified in previously known FDG-concentrating disease when routine investigations like tumor markers/FNAC/USG are inconclusive in symptomatic patients (**Flow Chart 4**).

In summary, FDG-PET/CT is not recommended as a routine follow-up imaging modality in the posttreatment scenario in CUPs. The modality can be considered in the follow-up of symptomatic patients with inconclusive investigations and previously FDG-concentrating disease.

Future Directions

PET/MR

MRI brings together excellent anatomical resolution with functional information such as diffusion-weighted imaging. These parameters have been reported to differentiate benign and malignant lesions³⁸ with substantial success. This functional information in hand with PET data is perceived to aid in primary tumor detectability more efficiently and allow characterization of lesions.¹⁶ Furthermore, PET/MRI reduces radiation exposure to the patient to a great extent. In a comparative study between whole-body PET/CT and PET/MR, both modalities provided comparable diagnostic ability. In another study comparing contrast 3T multiparametric MRI with FDG-PET/CT in HN-SCC CUP patients, both modalities performed similarly, though PET/CT proved to be more sensitive while mp-MRI to be more specific, in such a way that a combined PET/MR approach is expected to deliver the greatest accuracy. Patients with pelvic lymphadenopathy or skeletal lesions suspicious for primary prostate malignancy especially with raised serum PSA levels can be imaged

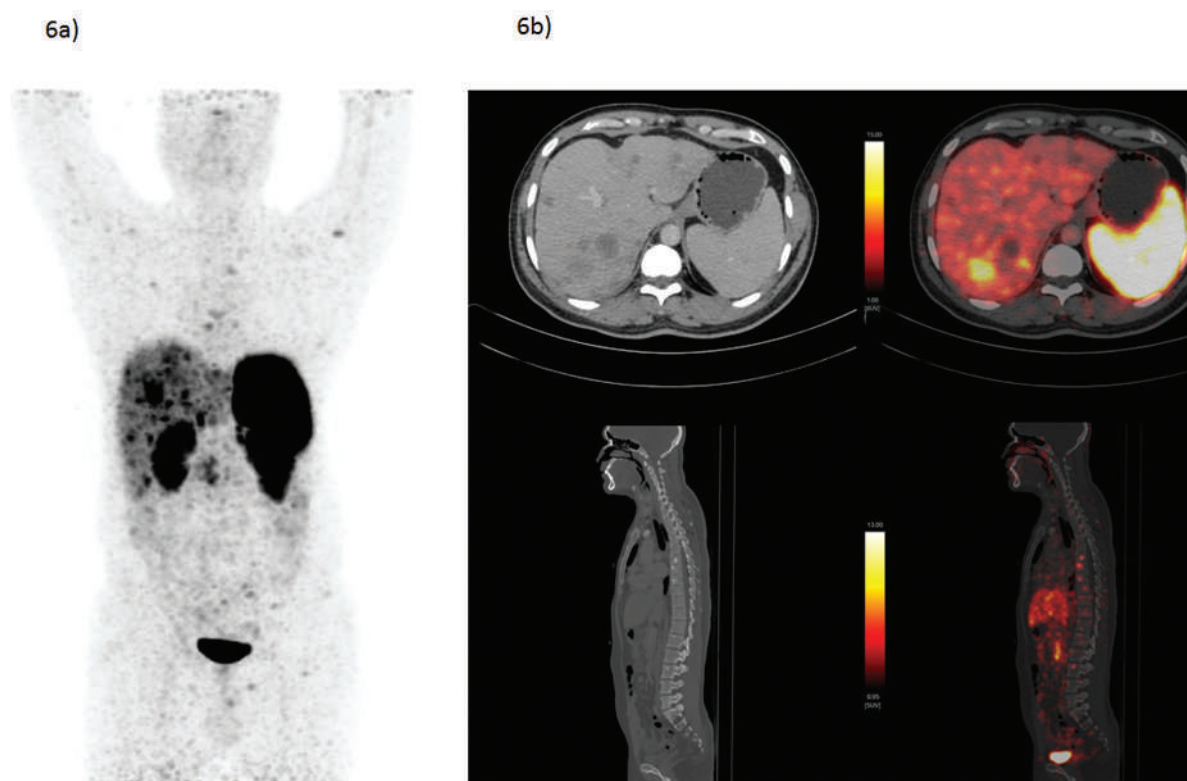
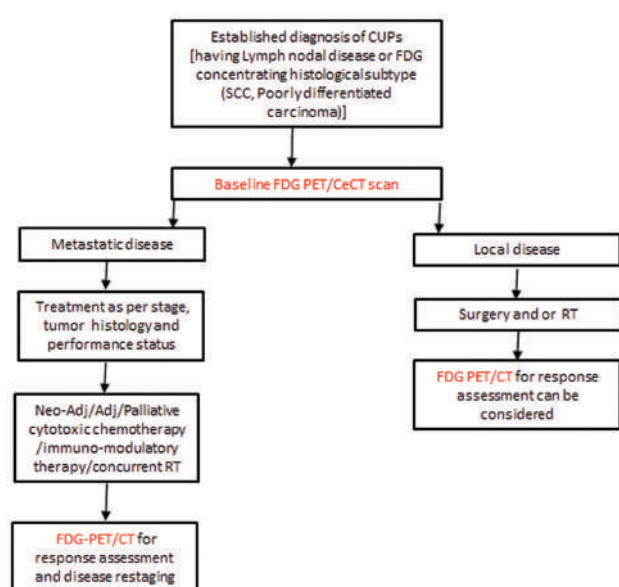


Fig. 6 A 34-year-old male presented with generalized weakness and abdominal discomfort, showed multiple liver lesions and splenomegaly on CECT. The liver biopsy revealed to be grade-II NET with Mib-1 index of 13%. He underwent baseline ^{68}Ga -DOTATATE PET/CT scan to find primary and also disease extent. ^{68}Ga -DOTATATE PET/CT revealed SSTR-expressing multiple bilobar liver lesions and sclerotic skeletal lesions; however, no obvious primary lesion could be found. The patient was diagnosed as grade II metastatic NET with unknown primary and being evaluated for Chemo-PRRT treatment protocol considering SSTR expressing (Krenning score 3) multiple liver and bone lesions. (a) ^{68}Ga -DOTATATE PET/CT MIP image showing SSTR-expressing bilobar liver lesions (Krenning score 3) and multiple skeletal lesions. (b) CECT and PET/CT fused transverse section images showing SSTR-expressing liver lesions; sagittal section showing multiple sclerotic skeletal lesions. *The present illustration demonstrates the utility of SSTR-based PET/CT in guiding diagnosis and disease staging in evaluation of CUP-NETs presenting with metastatic disease.* CECT, contrast-enhanced computed tomography; MIP, maximum intensity projection; NET, neuroendocrine tumor; PET/CT, positron emission tomography/computed tomography; SSTR, somatostatin receptor;

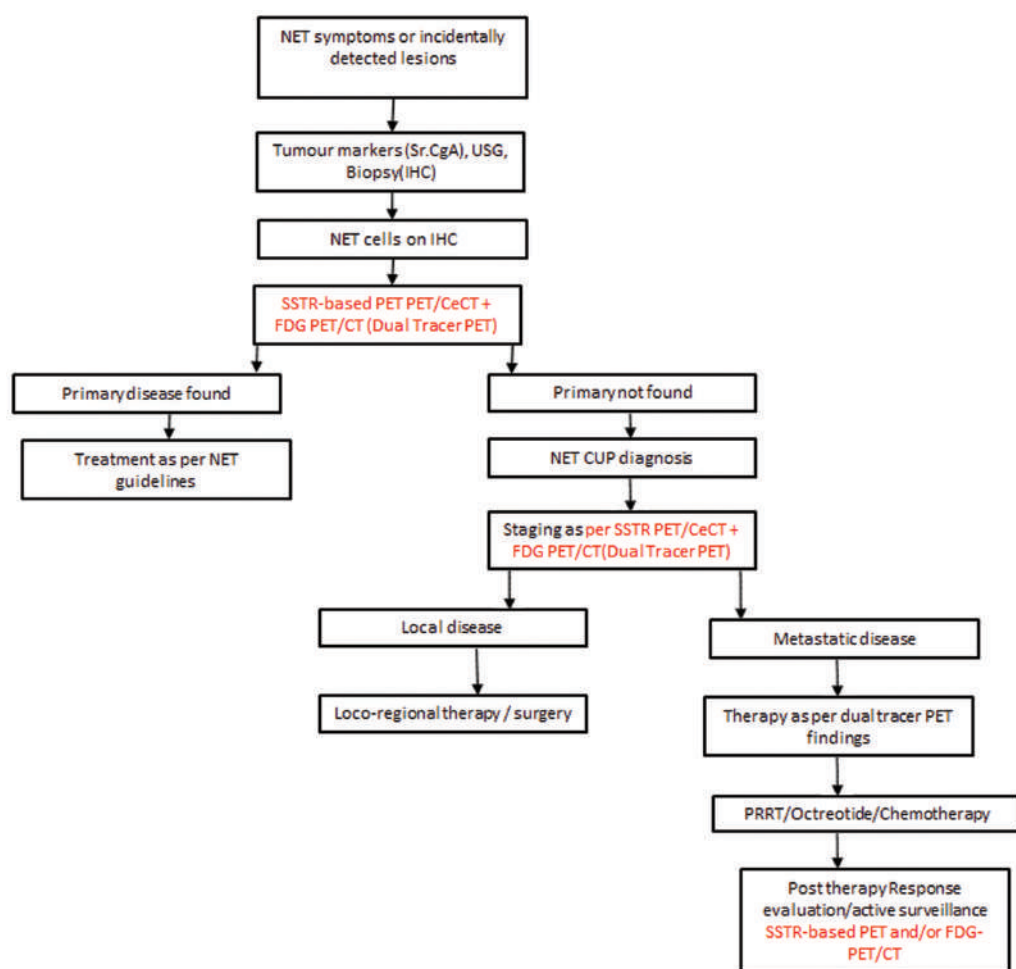


Flow Chart 2 Treatment response assessment in CUP with FDG-PET/CT.

with ^{68}Ga -PSMA-11 PET/MR with high imaging sensitivity and specificity. Such PSMA PET-assisted robotic trans-gluteal biopsy also has been reported in view of its high diagnostic yield and better safety profile, especially with prior negative results at transrectal USG-guided biopsy.³⁹ With growing experience in PET/MR techniques, this modality appears to deliver powerful output in CUP scenarios.

Newer PET Tracers: ^{68}Ga -FAPI-Based PET-CT in CUP

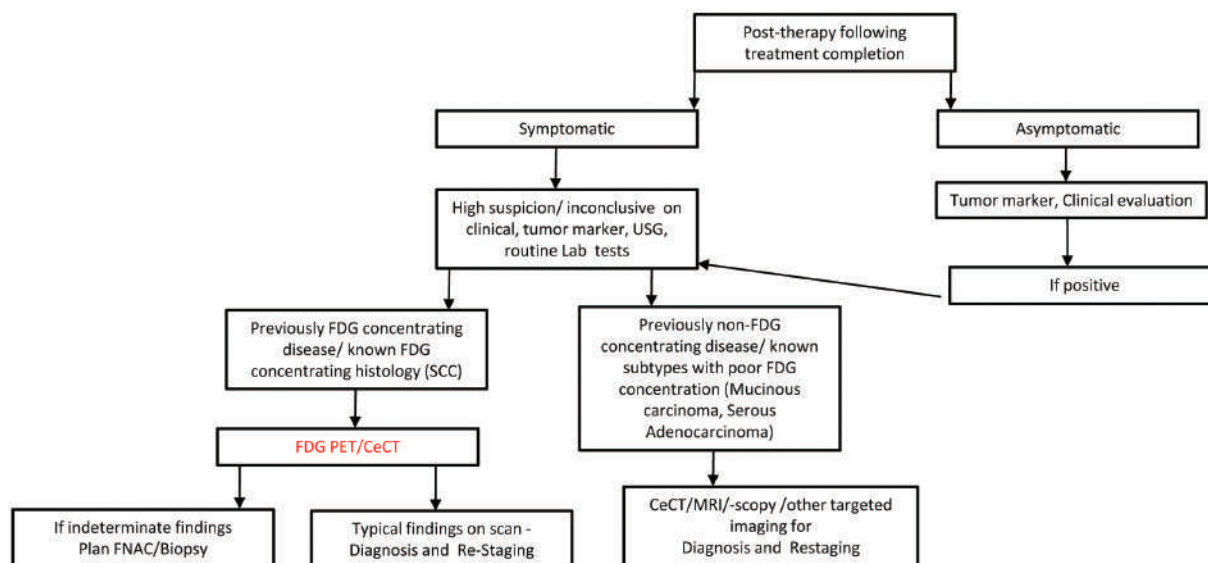
A tracer that targets the fibroblast activation protein factor (universally present in tumor stroma) has been of immense interest recently in oncology after its initial experiences in a spectrum of cancers.⁴⁰ It has shown multiple benefits over FDG, such as nonrequirement of fasting status and better physiological bio-distribution (e.g., no uptake in the brain and gastrointestinal tract as FDG). In its initial experiences in head-neck CUPs, fibroblast-activation protein inhibitor (FAPI)-PET/CT could additionally detect the primary tumor in 7 out of 18 patients (38.89%), which were negative in FDG-PET/CT.⁴¹ With gratifying results in multiple solid tumors (most gastrointestinal, genitourinary cancers) which



Flow Chart 3 An algorithmic CUP-NET management strategy.

are indeterminate on FDG, FAPI is postulated to be a potential player in CUP management. According to the present limited expertise and literature, it is not used as a direct replacement

for FDG in CUP scenarios; whenever available, FAPI-PET can be tried post-negative-FDG PET/CT results or in selective indications where histopathology is suspicious for



Flow Chart 4 Follow-up in CUP following completion of treatment.

peritoneal/gastric signet ring cell serous carcinoma and no primary lesion could be found on any previous examination.

Similarly, ^{68}Ga -Pentixafor PET/CT that targets CXCR4 (chemokine receptor-4) over-expressed in multiple hematological malignancies including multiple myeloma and solid tumors where FDG underperforms. However, its exact utility in the CUP scenario is yet to be established.

Salient Points

- FDG-PET/CT is not to be used for screening modality.
- FDG-PET/CT is recommended as the primary imaging modality in evaluation of primary, staging, and response evaluation for CUP histology known to have FDG concentration, especially CUPs presenting as lymph nodal disease.
- The exact choice of imaging protocol strongly depends on the commonly suspected sites as per symptomatology and clinical findings for every single case. Dual time-point imaging should be routinely used in the labelling of indeterminate lesions with FDG concentration.
- FDG PET/CT is not recommended as a primary imaging modality in CUPs presenting as bone/brain/lung/liver disease and histology known to have indeterminate FDG concentration. But FDG PET/CT can be considered with failure of other initial imaging and biopsies.
- SSSTR-based PET/CT is recommended as a primary imaging modality in evaluation primary, staging, therapy planning, and response evaluation of CUPs with NET histology type.
- If available, FAPI PET/CT can be tried post-negative-FDG PET/CT or other noninvasive tests results, as well as in selective indications where histopathology is suspicious for peritoneal/gastric signet ring cell serous carcinoma and no primary lesion could be found on any previous examination.

Conflict of Interest

None declared.

Acknowledgements

The authors acknowledge the help of Dr. A. Nazaar for preparing the images at places.

References

- Varghese AM, Arora A, Capanu M, et al. Clinical and molecular characterization of patients with cancer of unknown primary in the modern era. *Ann Oncol* 2017;28(12):3015–3021
- Rassy E, Nicolai P, Pavlidis N. Comprehensive management of HPV-related squamous cell carcinoma of the head and neck of unknown primary. *Head Neck* 2019;41(10):3700–3711
- Hemminki K, Chen B, Kumar A, et al. Germline genetics of cancer of unknown primary (CUP) and its specific subtypes. *Oncotarget* 2016;7(16):22140–22149
- Losa F, Iglesias L, Pané M, et al. 2018 consensus statement by the Spanish Society of Pathology and the Spanish Society of Medical Oncology on the diagnosis and treatment of cancer of unknown primary. *Clin Transl Oncol* 2018;20(11):1361–1372
- Mathur P, Sathishkumar K, Chaturvedi M, et al; ICMR-NCDIR-NCRP Investigator Group. Cancer Statistics, 2020: Report From National Cancer Registry Programme, India. *JCO Glob Oncol* 2020; 6:1063–1075
- Pavlidis N, Pentheroudakis G. Cancer of unknown primary site. *Lancet* 2012;379(9824):1428–1435
- Rassy E, Pavlidis N. The currently declining incidence of cancer of unknown primary. *Cancer Epidemiol* 2019;61:139–141
- Qaseem A, Usman N, Jayaraj JS, Janapala RN, Kashif T. Cancer of unknown primary: a review on clinical guidelines in the development and targeted management of patients with the unknown primary site. *Cureus* 2019;11(09):e5552
- Maghami E, Ismaili N, Alvarez A, et al. Diagnosis and management of squamous cell carcinoma of unknown primary in the head and neck: ASCO guideline. *J Clin Oncol* 2020;38(22):2570–2596
- Fizazi K, Greco FA, Pavlidis N, Daugaard G, Oien K, Pentheroudakis GESMO Guidelines Committee. Cancers of unknown primary site: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015;26(Suppl 5):v133–v138
- Scarbrook A. Carcinoma of unknown origin. In: Nicolson T, ed. *Recommendations of Cross Sectional Imaging in Cancer Management*. London: Royal College of Radiologists; 2014
- Anbarasu A, Joshi V, Solanki R, Kumar J, Shah D Head & Neck Imaging Sub Specialty Group Scanning Guidelines Ct Scan/Mr Imaging Version April; 2020. Accessed December 13, 2022 at: <https://icri.iria.org.in/head-and-neck-imaging-guidelines-2020>
- Boellaard R, Delgado-Bolton R, Oyen WJ, et al; European Association of Nuclear Medicine (EANM) FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. *Eur J Nucl Med Mol Imaging* 2015;42(02):328–354
- Hope TA, Bergsland EK, Bozkurt MF, et al. Appropriate use criteria for somatostatin receptor PET imaging in neuroendocrine tumors. *J Nucl Med* 2018;59(01):66–74
- Schöder H, Gönen M. Screening for cancer with PET and PET/CT: potential and limitations. *J Nucl Med* 2007;48(Suppl 1):4S–18S
- Kwee TC, Kwee RM. Combined FDG-PET/CT for the detection of unknown primary tumors: systematic review and meta-analysis. *Eur Radiol* 2009;19(03):731–744
- Rusthoven KE, Koshy M, Paulino AC. The role of fluorodeoxyglucose positron emission tomography in cervical lymph node metastases from an unknown primary tumor. *Cancer* 2004;101(11):2641–2649
- Lee JR, Kim JS, Roh JL, et al. Detection of occult primary tumors in patients with cervical metastases of unknown primary tumors: comparison of (18)F FDG PET/CT with contrast-enhanced CT or CT/MR imaging-prospective study. *Radiology* 2015;274(03):764–771
- De Wever W, Meylaerts L, De Ceuninck L, Stroobants S, Verschakelen JA. Additional value of integrated PET-CT in the detection and characterization of lung metastases: correlation with CT alone and PET alone. *Eur Radiol* 2007;17(02):467–473
- Park SB, Park JM, Moon SH, et al. Role of 18F-FDG PET/CT in patients without known primary malignancy with skeletal lesions suspicious for cancer metastasis. *PLoS One* 2018;13(05):e0196808
- Houshmand S, Salavati A, Segtnan EA, Grupe P, Høilund-Carlson PF, Alavi A. Dual-time-point imaging and delayed-time-point fluorodeoxyglucose-PET/computed tomography imaging in various clinical settings. *PET Clin* 2016;11(01):65–84
- Fei B, Schuster DM. PET molecular imaging-directed biopsy: a review. *AJR Am J Roentgenol* 2017;209(02):255–269
- Sampathirao N, Basu S. MIB-1 index-stratified assessment of dual-tracer PET/CT with ^{68}Ga -DOTATATE and ^{18}F -FDG and multimodality anatomic imaging in metastatic neuroendocrine tumors of unknown primary in a PRRT workup setting. *J Nucl Med Technol* 2017;45(01):34–41

- 24 Fletcher JW, Djulbegovic B, Soares HP, et al. Recommendations on the use of 18F-FDG PET in oncology. *J Nucl Med* 2008;49(03):480–508
- 25 Barrio M, Czernin J, Fanti S, et al. The impact of somatostatin receptor-directed PET/CT on the management of patients with neuroendocrine tumor: a systematic review and meta-analysis. *J Nucl Med* 2017;58(05):756–761
- 26 Varadhachary, Gauri, James L. Abbruzzese. “Carcinoma of unknown primary.” *Abeloff's Clinical oncology*. Elsevier; 2020:1694–1702
- 27 Gupta T, Master Z, Kannan S, et al. Diagnostic performance of post-treatment FDG PET or FDG PET/CT imaging in head and neck cancer: a systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging* 2011;38(11):2083–2095
- 28 Slevin F, Subesinghe M, Ramasamy S, Sen M, Scarsbrook AF, Prestwich RJ. Assessment of outcomes with delayed (18)F-FDG PET-CT response assessment in head and neck squamous cell carcinoma. *Br J Radiol* 2015;88(1052):20140592
- 29 Marcus C, Ciarallo A, Tahari AK, et al. Head and neck PET/CT: therapy response interpretation criteria (Hopkins Criteria)-inter-reader reliability, accuracy, and survival outcomes. *J Nucl Med* 2014;55(09):1411–1416
- 30 Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. *J Nucl Med* 2009;50(Suppl 1):122S–150S
- 31 Cliffe H, Patel C, Prestwich R, Scarsbrook A. Radiotherapy response evaluation using FDG PET-CT-established and emerging applications. *Br J Radiol* 2017;90(1071):20160764
- 32 Martin RC, Fulham M, Shannon KF, et al. Accuracy of positron emission tomography in the evaluation of patients treated with chemoradiotherapy for mucosal head and neck cancer. *Head Neck* 2009;31(02):244–250
- 33 Evilevitch V, Weber WA, Tap WD, et al. Reduction of glucose metabolic activity is more accurate than change in size at predicting histopathologic response to neoadjuvant therapy in high-grade soft-tissue sarcomas. *Clin Cancer Res* 2008;14(03):715–720
- 34 Lopci E, Hicks RJ, Dimitrakopoulou-Strauss A, et al. Joint EANM/SNMMI/ANZSNM practice guidelines/procedure standards on recommended use of [¹⁸F]FDG PET/CT imaging during immunomodulatory treatments in patients with solid tumors version 1.0. *Eur J Nucl Med Mol Imaging* 2022;49(07):2323–2341
- 35 Ayati N, Sadeghi R, Kiamanesh Z, Lee ST, Zakavi SR, Scott AM. The value of ¹⁸F-FDG PET/CT for predicting or monitoring immunotherapy response in patients with metastatic melanoma: a systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging* 2021;48(02):428–448
- 36 Wong ANM, McArthur GA, Hofman MS, Hicks RJ. The advantages and challenges of using FDG PET/CT for response assessment in melanoma in the era of targeted agents and immunotherapy. *Eur J Nucl Med Mol Imaging* 2017;44(Suppl 1):67–77
- 37 Adnan A, Basu S. Discordance between histopathologic grading and dual-tracer PET/CT findings in metastatic NETs and outcome of 177Lu-DOTATATE PRRT: does in vivo molecular PET perform better from the viewpoint of prediction of tumor biology? *J Nucl Med Technol* 2021;50(Suppl 3):248–255
- 38 Ruhlmann V, Ruhlmann M, Bellendorf A, et al. Hybrid imaging for detection of carcinoma of unknown primary: a preliminary comparison trial of whole-body PET/MRI versus PET/CT. *Eur J Radiol* 2016;85(11):1941–1947
- 39 Kumar R, Singh SK, Mittal BR, et al. Safety and diagnostic yield of ⁶⁸Ga prostate-specific membrane antigen PET/CT-guided robotic-assisted transgluteal prostatic biopsy. *Radiology* 2022;303(02):392–398
- 40 Kratochwil C, Flechsig P, Lindner T, et al. ⁶⁸Ga-FAPI PET/CT: tracer uptake in 28 different kinds of cancer. *J Nucl Med* 2019;60(06):801–805
- 41 Gu B, Xu X, Zhang J, et al. The added value of ⁶⁸Ga-FAPI PET/CT in patients with head and neck cancer of unknown primary with ¹⁸F-FDG-negative findings. *J Nucl Med* 2022;63(06):875–881
- 42 Niederkohr RD, Greenspan BS, Prior JO, et al. Reporting guidance for oncologic 18F-FDG PET/CT imaging. *J Nucl Med* 2013;54(05):756–761

Imaging Recommendations for Diagnosis, Staging, and Management of Breast Cancer

Meenakshi Thakur^{1,2} Suma Chakrabarthi³ Purvi Haria^{1,2} Smriti Hari⁴ Palak Popat^{1,2}
Aparna Katdare^{1,2} Kunal Gala^{1,2} Sonal Chouhan^{1,2} Nita Nair^{2,5} Jyoti Bajpai^{2,6} Rima Pathak^{2,7}
Tanuja Shet^{2,8} Gauravi Mishra^{2,9} Sneha Shah^{2,10} Shalaka Joshi^{2,5} Soujanya Mynalli^{1,2}
Anne Srikanth^{2,6} Suyash Kulkarni^{1,2}

¹ Department of Radiodiagnosis, Tata Memorial Centre, Mumbai, India

² Homi Bhabha National Institute, Mumbai, India

³ Department of Radiodiagnosis, Peerless Hospital and BK Roy Research Centre, Kolkata, India

⁴ Department of Radiodiagnosis, All India Institute of Medical Sciences, Delhi, India

⁵ Department of Surgical Oncology, Tata Memorial Centre, Mumbai, India

⁶ Department of Medical Oncology, Tata Memorial Centre, Mumbai, India

Address for correspondence Meenakshi Thakur, MD, Department of Radiodiagnosis, Tata Memorial Centre, Mumbai 400012, India (e-mail: thakurmh@yahoo.co.in).

⁷ Department of Radiation Oncology, Tata Memorial Centre, Mumbai, India

⁸ Department of Pathology, Tata Memorial Centre, Mumbai, India

⁹ Department of Preventive Oncology, Tata Memorial Centre, Mumbai, India

¹⁰ Department of Bio-Imaging, Tata Memorial Centre, Mumbai, India

Ind J Med Paediatr Oncol 2023;44:207–228.

Abstract

In a rapidly evolving world, with a steep rise in breast cancer incidence, there has been many advances in imaging and therapeutic options of breast cancer care. In this review article, we are trying to cover imaging guideline for cancer detection and their therapeutic options. These help in the reduction of morbidity and mortality.

Keywords

- breast cancer
- early detection
- imaging guidelines

Introduction

According to latest GLOBOCAN statistics,¹ breast cancer (BC) is the leading cause of mortality amongst all cancers. Early detection of BC improves survival. There are various societies like JCC, NCCN, ASCO, ACR, RSNA, ESR, IRIA/ICRI, National Cancer Grid (NCG) which have their guidelines for the evaluation and treatment of BC. Here in this review, we are aiming to cover imaging guidelines for the evaluation of BC.

Epidemiology, Clinical presentation in India and Globally

Globally, BC is the leading cancer among women, contributing to 2,261,419 new cases and 684,996 deaths annually.¹

There is a wide variation in incidence rates, with some countries like Netherlands and Belgium having estimated age adjusted incidence (AAI) of over 100 and others like Bhutan with AAI of 5.² Globally, both incidence and mortality of BC have increased significantly in all age groups since 1990. Mortality increased by 0.23% per year and incidence by 1.28% per year in age group of 50 to 69 and by 1.55% per year (under 50).³ BC is the most common cancer among Indian women both in terms of incidence and mortality. There are estimated 178,361 (13.5% cancers among women) cases and 90,408 (10.6%) deaths due to BC in India.³

The AAI is 25.8 in India overall, with the highest burden being observed in metropolitan cities. Around 57% of BCs are diagnosed at the locally advanced stage.⁴

DOI <https://doi.org/10.1055/s-0042-1760326>.
ISSN 0971-5851.

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)
Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

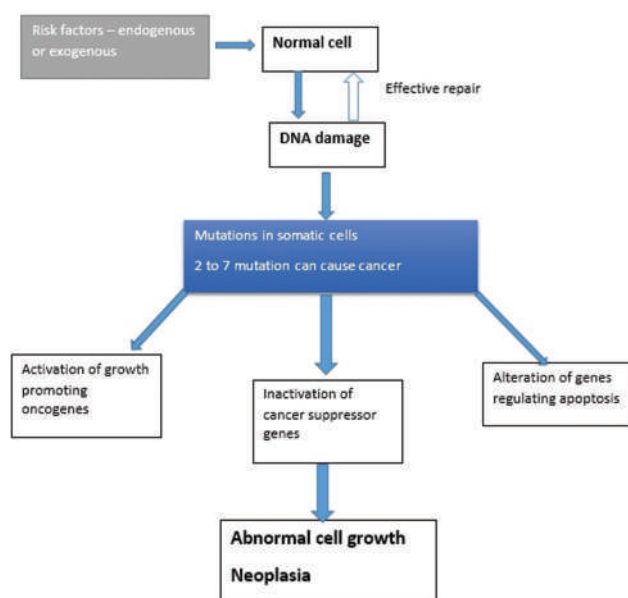


Fig. 1 Etiopathogenesis of cancer.

Risk Factors and Etiopathogenesis

Cancer, in general, is a multistep process and after decades of studies we are now aware that there are three types of risk factors: (1) exogenous modifiable risk factors like oncogenic viruses, tobacco usage, atmospheric radiation, chemical carcinogens, lack of exercise, obesity, low activity level, etc.; (2) endogenous partially modifiable risk factors like hereditary risk, hormones, inflammation, growth factors, and (3) intrinsic risk factors which are non-modifiable and created due to random errors in DNA replication.⁵ The later may be responsible for over 60% of tissue cancer burden.⁵ If a cause is known, it is much easier to know whether it can (e.g., tobacco use) or cannot (e.g., ionizing radiation in the atmosphere) be avoided easily.⁶ These factors then result in uncontrolled growth and the etiopathogenesis of cancer is summarized in ►**Fig. 1**.

Various specific risk factors for BC are as follows.

Non-modifiable risk factors are the one which cannot be changed. These are increasing age, genetic mutations (BRCA1, BRCA 2, and p53), early menarche, late menopause, dense breast, family and personal history of BC, history of radiation to chest wall, and exposure to certain drugs like diethylstilbestrol used to prevent abortion till 1970s.

Modifiable risk factors are obesity, lack of exercise, hormones in the form of HRT and contraceptive pills, late pregnancy, avoiding breastfeeding and alcohol consumption.⁷

Clinical/Diagnostic Work-Up

The triad of diagnosis of BC involves a good history taking or symptom evaluation and thorough clinical examination of both breasts, axillae and supraclavicular fossae and systemic examination, if necessary. This is followed by imaging to ascertain the risk of harboring malignancy.⁸ BC is clinically classified into operable (T1–2, N0–1, M0) (OBC), locally advanced (T3–4, N2–3, M0) (LABC), and metastatic BCs (T any N any M1).^{9,10} This clinical classification helps in decid-

ing the need of metastatic work-up versus not. Since <5% of OBC harbor occult metastases, it is not routinely recommended to do staging investigations in OBC patients unless symptomatic. However, nearly 30% of the patients of LABC may harbor foci of occult metastases and metastatic work-up with imaging is necessary to optimally stage and treat these patients. The final proof of diagnosis is always pathological evaluation—is able to discern between preinvasive and invasive malignancy and it offers prognostic and predictive information such as ER/PR and HER2 status of the tumor. A trucut biopsy is mandatory when neoadjuvant chemotherapy (NACT) is planned.

Imaging Recommendations for Diagnosis, Staging, and Management of BC

Screening mammography has resulted in the increase in the detection of early BC. Various screening guidelines are in place, which are specific to countries and societies. These guidelines vary for women with average and high risk of BC. Discussing guidelines for screening is out of scope of this article. These are discussed in depth in ►**Annexure 1**.

Screening

Mammography from the age of 40 years is recommended for women at average risk of developing BC.^{11,12} The upper age limit for screening mammography should ideally be when a woman's life expectancy exceeds 5 to 7 years so that the benefits of screening could be fully realized¹¹ and an age limit of 70 years may be deemed appropriate.^{12,13} Ultrasound can be used as an adjunct to screening mammography for women with dense breasts, but is not recommended as a standalone screening test.¹⁴ For women with a lifetime risk of BC $\geq 20\%$ according to risk assessment tools, with known BRCA1 and BRCA2 mutation or with a first degree relative to the mutation, with radiation therapy (RT) to the chest between ages of 10 and 30 years, screening can be started earlier.¹⁴ Annual mammography and contrast-enhanced magnetic resonance imaging of breasts (CEMRI) are recommended starting at 30 years of age or 10 years before the age of diagnosis of first-degree relative with BC, whichever is later. Women with RT to chest can start screening 8 years after RT. However, screening mammography is not recommended before the age of 25 years.^{11,14} Only MRI screening is advisable for women with Li-fraumeni syndrome and A-T homozygotes.¹⁵

Diagnosis

Ultrasound is the modality of choice for women less than 30 years of age as well as pregnant and lactating women.¹⁶ Symptomatic women above the age of 40 years benefit from a combination of mammography and ultrasound. Between the ages of 30 and 39 years the initial investigation of ultrasound could be followed by mammography, if required. However in the presence of strong clinical suspicion of BC, a combination of mammography and ultrasound can be performed at the outset in this group.^{12,17} All women diagnosed with BC

should have mammography irrespective of their age.¹⁷ Digital breast tomosynthesis has shown improved cancer detection rate as compared with digital mammogram alone.¹⁸ CEMRI (contrast-enhanced MRI) is indicated if there is a discrepancy in clinical and radiological findings, if breast conservation is considered with a diagnosed lobular cancer, for tumors occult on mammography, in cases of Paget's disease of the nipple if breast conservation is contemplated, if conventional imaging is suspicious for but does not confirm multifocal/multicentric disease, in cases of occult primary breast cancer such as proven metastatic axillary nodes without primary detected on mammogram and USG.^{12,17} A recognized reporting system like the American College of Radiology (ACR) Breast Imaging – Reporting and Data System (BI-RADS) should be used to report the radiological investigations. Image-guided biopsy of lesions suspicious for malignancy (BI-RADS 4) or highly suggestive of malignancy (BI-RADS 5) is advised. Probably benign (BI-RADS 3) lesions may also be biopsied if another malignant mass is detected in either breast.^{19–21}

Women presenting with breast symptoms should undergo triple assessment with clinical examination, breast imaging, and histopathology.²² Fourteen gauge core biopsy with an automated spring-loaded biopsy device under ultrasound guidance is advised for histological diagnosis in both screening and symptomatic setting.²³ Stereotactic biopsy under mammography guidance is advised for abnormalities visualized on mammography but not on ultrasound. Suspicious lesions demonstrated only on MRI should be subjected to a second-look ultrasound. If no correlating abnormality is visualized, these MRI-only lesions should be subjected to MRI-guided biopsy.^{24,25} CEMRI is not an alternative to biopsy as it does not provide tissue diagnosis. MRI-guided vacuum-assisted breast biopsy (VABB) is performed for MRI-only lesions, whereas stereotactic VABB is performed for abnormalities seen on mammography only.²⁶ VABB uses a suction system, which allows a larger tissue sample to be obtained from a single insertion. Certain imaging modalities demonstrate certain abnormalities better. For example small clusters of microcalcifications are well demonstrated on mammography whereas small intraductal masses are well seen on breast ultrasound.

Contrast-enhanced mammogram (CEM) is a relatively new imaging investigation which is fast getting popularity due to its shorter imaging time and low cost as compared with MRI. Iodinated contrast is used and images are obtained based on dual energy imaging. Evaluation of CEM is performed on subtracted post-processed images.²⁷ CEM is used to evaluate abnormality seen on mammogram such as asymmetry, architectural distortion, mass, calcification, etc. It is also used for detecting and evaluating additional abnormalities in ipsilateral or contralateral breast.²⁷

Imaging Appearance of Various Types of Cancer

BCs are broadly divided in four categories depending on IHC (immune histochemical) marker status. These are Luminal A

(ER+, PR+, Her2/Neu -), Luminal B (ER+, PR+, Her2/Neu + or ER+, PR+, any Her2/Neu with High Ki67), Her2/Neu enriched (ER-, PR-, Her2/Neu +) and TNBC (Triple Negative BC) (ER-, PR-, Her2/Neu -). This classification is for the treatment and prognostication of patient.²⁸ However, radiologically there are certain differences in imaging appearances of these common invasive cancers. Luminal cancers commonly have spiculated mass, whereas Her2/Neu-enriched tumors have mass with indistinct margin. Calcifications are more commonly associated with Her2-enriched tumors. TNBCs are more commonly associated with distinct well-defined edges.^{29,30} Details about different types of invasive and preinvasive cancer and its imaging appearance on various modalities are out of scope of this article.

In patients with reconstructed breast, imaging appearance of cancer is similar. However, additional care must be taken for imaging as well as interpretation as in cases of breast implants, additional, implant displaced views must be obtained. While evaluating cases of breast reconstruction with flaps or oncoplasty, fat necrosis is a common occurrence, and care must be taken to differentiate it from recurrence. Many times comparison with prior imaging is problem solving.

Staging

For T1 or T2, N0 or N1, M0, BCs which constitute up to T2N1M0 of stage 2B (► **Fig. 2**) of anatomical staging as per the eighth edition of AJCC Cancer Staging Manual of the American College of Surgeons,¹⁰ staging investigations to detect occult distant metastasis is not advised due to the low yield of these investigations as well as false positive studies that follow. However suspicious findings in clinical history, clinical examination, abnormal serological tests for liver or bone function may necessitate staging investigations in this cohort of patients³¹ From T3N0M0 of stage 2B of AJCC staging, including T3–4anyN and N2–3anyT cancers, the preferred tests are contrast-enhanced computed tomography (CECT) chest and abdomen and Tc99m-methylene diphosphonate bone scan (► **Fig. 3**).

Positron emission tomography-computed tomography (PET-CT) is not routinely advised for early stage BC, however, according to NCCN guidelines, it may be advised for higher stage disease if available due to its higher detection of metastatic sites and its whole body coverage.³² It may be beneficial in inflammatory BC or in oligometastatic disease to confirm absence of metastasis elsewhere in the body if radical treatment is considered for a single involved site.^{17,31,33,34}

The clinical and pathological prognostic stage groups may be different from the patient's anatomical stage group. For example, T1N0M0 tumor of anatomical stage group 1A would be pathological prognostic stage group IA if it is grade I tumor which is ER, PR, and HER2 receptor positive. However, if it is grade II ER, PR, and HER2 receptor negative it would change to pathological prognostic stage group IB.³¹

Clinical nodal (cN) category as per AJCC is based on clinical and imaging investigation of nodal basin. Axillary lymph node level depends on the location of lymph node with respect to pectoralis minor muscle. Level I lymph nodes are located lateral to the lateral margin of pectoralis minor

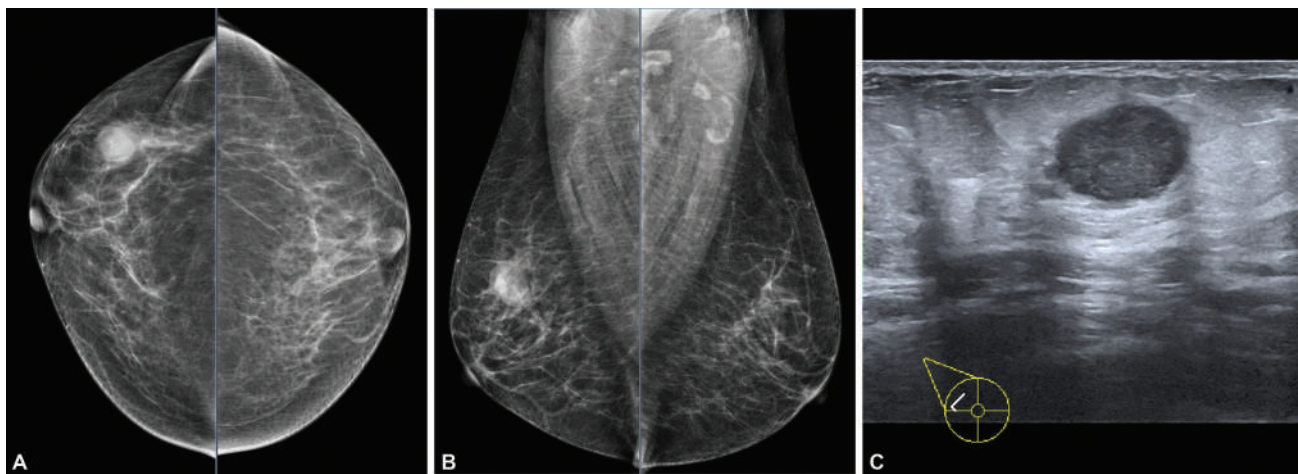


Fig. 2 A 50-year-old female with right breast lump since 1 month. No other complains. On mammogram (A and B) and USG: a well-defined high-density mass with partly obscured margins is seen in the upper outer quadrant of right breast, measuring approximately $1.9 \times 2.2 \times 2.3$ cm. No suspicious microcalcifications are seen. No other associated features are seen. On USG (C) irregular mass with microlobulated margin is seen at 10 o'clock position in right breast. The lesion is predominantly hypoechoic with posterior acoustic enhancement. The lesion is parallel in orientation. No suspicious axillary lymph nodes are seen on imaging. Histopathology of lesion is TNBC. As this lesion is early stage breast cancer without nodal involvement (stage IIA), further metastatic work-up is not needed. (TNBC, triple-negative breast cancer; USG, ultrasonography).

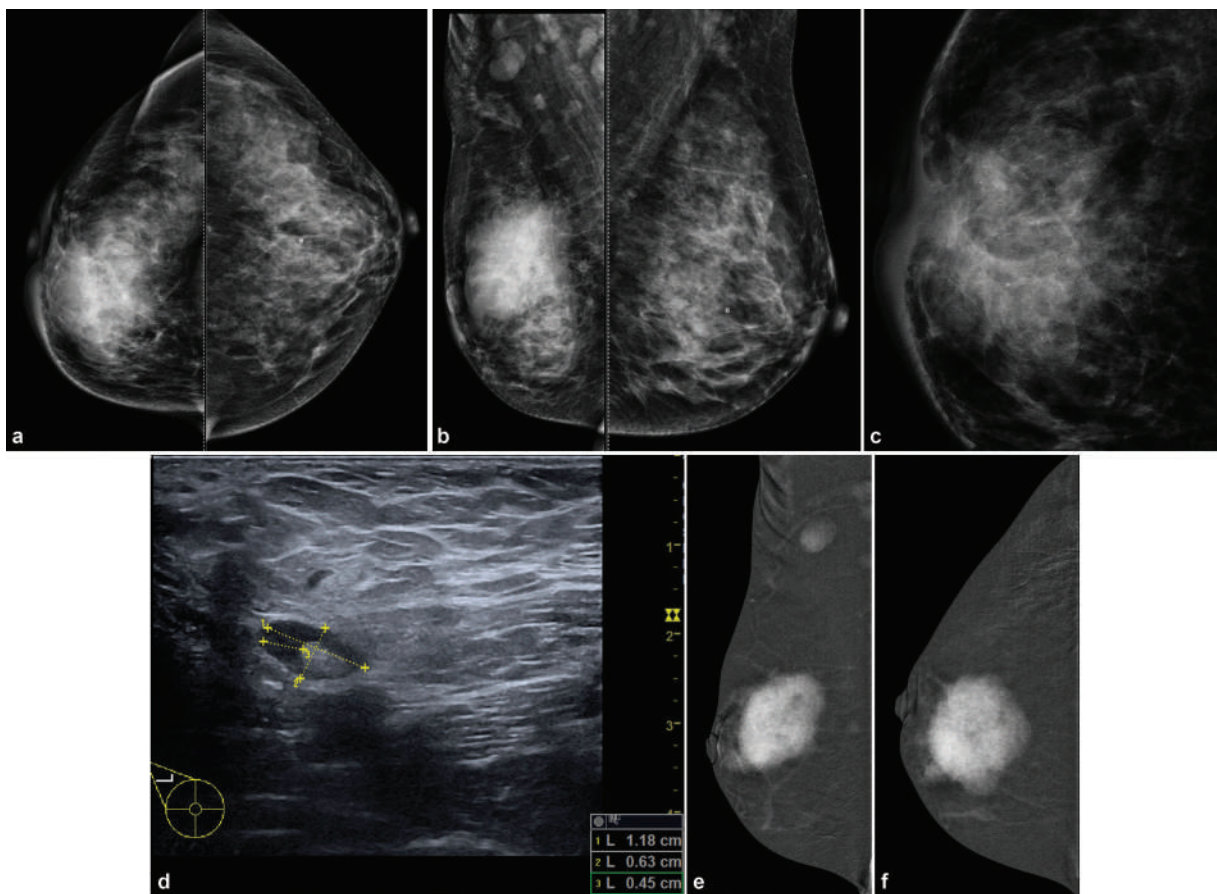


Fig. 3 A 38-year-old female with increasing right breast lump since 15 months. Mammogram (A, B): An irregular high-density mass with indistinct margins is seen in predominantly upper inner quadrant also extending in the outer quadrant measuring approximately $4.4 \times 4.4 \times 5.5$ cm. Pleomorphic microcalcifications (C) are seen within the mass, better seen on magnification view. Diffuse trabecular thickening with nipple areolar complex thickening and retraction is seen. Few suspicious right axillary nodes are seen, largest measuring 1.2×0.7 cm with 4.5-mm cortical thickness (D). In view of dense breast parenchyma, further evaluation with CEM was performed to rule out any other lesion in breast, CEM (E, F) is suggestive of large unifocal lesion. This is the case of locally advanced breast cancer (stage IIIA), further metastatic work-up was performed. On CT scan, (G, H) heterogeneously enhancing mass is seen involving right breast with involvement of overlying skin. Enlarged right axillary, right internal mammary, and right supraclavicular lymph nodes are seen. (CEM, contrast-enhanced mammogram.)

muscle; level II lymph nodes are located between lateral and medial margins of the pectoralis minor muscle. Level II also includes interpectoral lymph nodes (Rotter's node). Level III includes lymph nodes that are located medial to medial margin of pectoralis minor muscle.^{35,36}

Suspicious imaging features for axillary lymph nodes on ultrasound are focal eccentric cortical thickness, irregular margin, loss of fatty hilum, and extra nodal extension. Uniformly thin cortex with cortical thickness of less than 3 mm is considered to be normal appearance of axillary lymph node.^{37,38} Metastatic disease is most commonly seen in bones, lungs, brain, and liver.³⁵ Additional brain imaging is performed for clinical symptoms like headache, mental status alteration, nausea, or vomiting. In such situation brain MRI is preferred over CT scan.³⁹

Response Assessment Post NACT

Baseline and end of treatment mammography and ultrasound are the minimum imaging required for the assessment of response to neoadjuvant treatment. However, baseline and end of treatment CEMRI is the ideal modality to assess response.^{17,34} Recent studies have also shown comparable results with the use of CEM for response assessment.⁴⁰ Marker clip insertion is advised to mark the tumor bed for reliable identification if there is a radiologic complete response. This is especially important if the breast conservation surgery is planned. It can be placed at the time of initial biopsy or during the first few cycles of treatment if a substantial response is noted.⁴¹ A tissue marker may also be inserted into the biopsied axillary lymph node if local policy includes image-guided localization of the biopsied lymph node and targeted lymph node dissection.¹⁷ Depending on the molecular subtype, response rates of different types BC vary, for e.g., pCR (pathological complete response) is seen in approximately 30% of the patients with triple negative BC, whereas some newer targeted therapies in Her2 positive cancer are able to achieve pCR rate of up to 60%. Hormone receptor positive cancers have lowest pCR rate in range of approximately 20%. As per NCCN guidelines, response assessment should be performed on the modality on which prechemotherapy assessment is performed.⁴²

In advanced cases with metastatic or oligometastatic disease, response is to be assessed objectively using acceptable criteria of RECIST guidelines. Preferably imaging on which metastatic disease is detected, should be the modality to assess response, like abnormality seen on CT thorax, should be monitored with CT thorax³². Multiple studies have shown promising result with the use of serial PET CT in response assessment in metastatic setting.^{43,44}

In non-metastatic setting, clinical examination and imaging studies should be routinely performed during preoperative therapy.³²

Imaging Guidance for Surgery of Impalpable Malignant Lesions

Ultrasound is the modality of choice for preoperative-guided hook wire localization of nonpalpable masses.²⁴ Hook wire

localization is performed prior to the surgery on the day of surgery. If lesions are not visualized on ultrasound, mammography and MR-guided localizations can be performed for lesions seen on mammography and MR-only lesions, respectively.²⁵ Radiograph or ultrasound of the excised surgical specimen is advised to confirm total excision of the abnormality. Confirmation of enhancement seen on MRI at the time of localization and follow-up MRI is performed for MRI-only abnormality. Radioactive seeds, magnetic seeds, and electromagnetic-radiofrequency tags can be used as alternatives for hook wire localizations.^{45,46}

Imaging Follow-Up

Annual mammography is recommended after the completion of treatment.²² It is known that women with mammography detected cancers have better survival rates than clinically detected cancers.¹⁷ Comparison with previous mammograms and biopsy of any new lesion not typically benign are advised.³⁴ MRI is emerging as a valuable tool in surveillance of patients with BC and has shown clear benefit in differentiating scar tissue from tumor recurrence.^{47,48}

Post-treatment changes in the form of fat necrosis and calcification are commonly seen on mammogram. These changes are commonly seen at the site of surgical suture and need to be carefully evaluated, if suspicious biopsy can be performed. Calcification due to fat necrosis in early stage may mimic suspicious morphology.⁴⁹

If clinically asymptomatic, annual mammography screening should be initiated 6 to 12 months after the completion of radiotherapy.³²

Supplementary ultrasound may be used. However, breast ultrasound alone is not recommended for routine surveillance.¹⁷ In case of breast reconstruction, routine imaging follow-up for metastasis is not indicated.³²

In cases of reconstruction with implant, unless there is a clinical concern, routine surveillance systemic imaging to detect metastases is not recommended.³⁴ There is no significant difference in imaging appearance of locoregional or distant recurrence disease. For follow-up of known visceral metastatic disease from a primary BC, CECT of thorax, abdomen, and pelvis is usually sufficient.¹⁷ Other investigations may be helpful depending on specific clinical needs. Image-guided core biopsy and assessment of hormone receptor status of new distant metastasis are advised as receptor conversion in distant metastasis is known to occur.⁵⁰

Patients on endocrine therapy, like those on tamoxifen – routine age appropriate gynecological screening is recommended. Routine annual pelvic ultrasound is not recommended. While those on aromatase inhibitors, should have periodic bone health monitoring with bone mineral density at baseline and regularly thereafter.³²

There are no clear surveillance guidelines for patients with bilateral mastectomy and breast reconstruction with implants, however, small studies have shown, no additional benefit with MRI.⁵¹

Imaging in Pregnant and Lactating Women

Ultrasound is the modality of choice for initial assessment. Physiological changes may make interpretation difficult and hence a lower threshold for follow-up and/or biopsy is advised.¹⁷ Mammography may be safely performed in pregnant women with a negligible risk to the fetus. Wearing a lead apron reduces the radiation dose to the fetus by at least half.^{52,53}

As stochastic risks from radiation have no threshold value, mammography should be carefully used. However, this should not deter us from performing necessary mammographic studies for women suspected to have BC. Breast feeding or pumping milk prior to the examination during lactation reduces breast density.¹⁷ Gadolinium should be limited to situations where benefits clearly outweigh the risks to fetus and hence CEMRI is generally avoided in pregnancy.⁵⁴ Breast feeding does not need to be interrupted after gadolinium administration as the water soluble nature of gadolinium-based contrast agents results in a low concentration of gadolinium in the mother's milk.⁵⁴

It is best to perform CEMRI after optimum counseling.

Multidisciplinary Management of BC

Surgical Oncology

Management of BC needs a personalized multimodality approach. In the current era of de-escalation of therapy, we cannot lose sight of the spectrum theory. BC management has seen a paradigm shift from the Halstedian approach of radical local surgery to more conservative approaches based on Fishers' theory that BC is a systemic disease at inception. The current approach is personalized and straddles the spectrum of aggressive biology and genomics to more indolent cases.⁵⁵

Surgery for BC has seen a trend toward conservation of both primary and axillary lymph nodes and increased focus on cosmetic outcome and quality of life (QOL). Oncoplastic techniques have allowed for conservative surgery even in larger tumors and better cosmetic outcomes.⁵⁶

Sequencing of therapy and inclusion of various modalities of therapy (surgery, chemotherapy, targeted therapy,

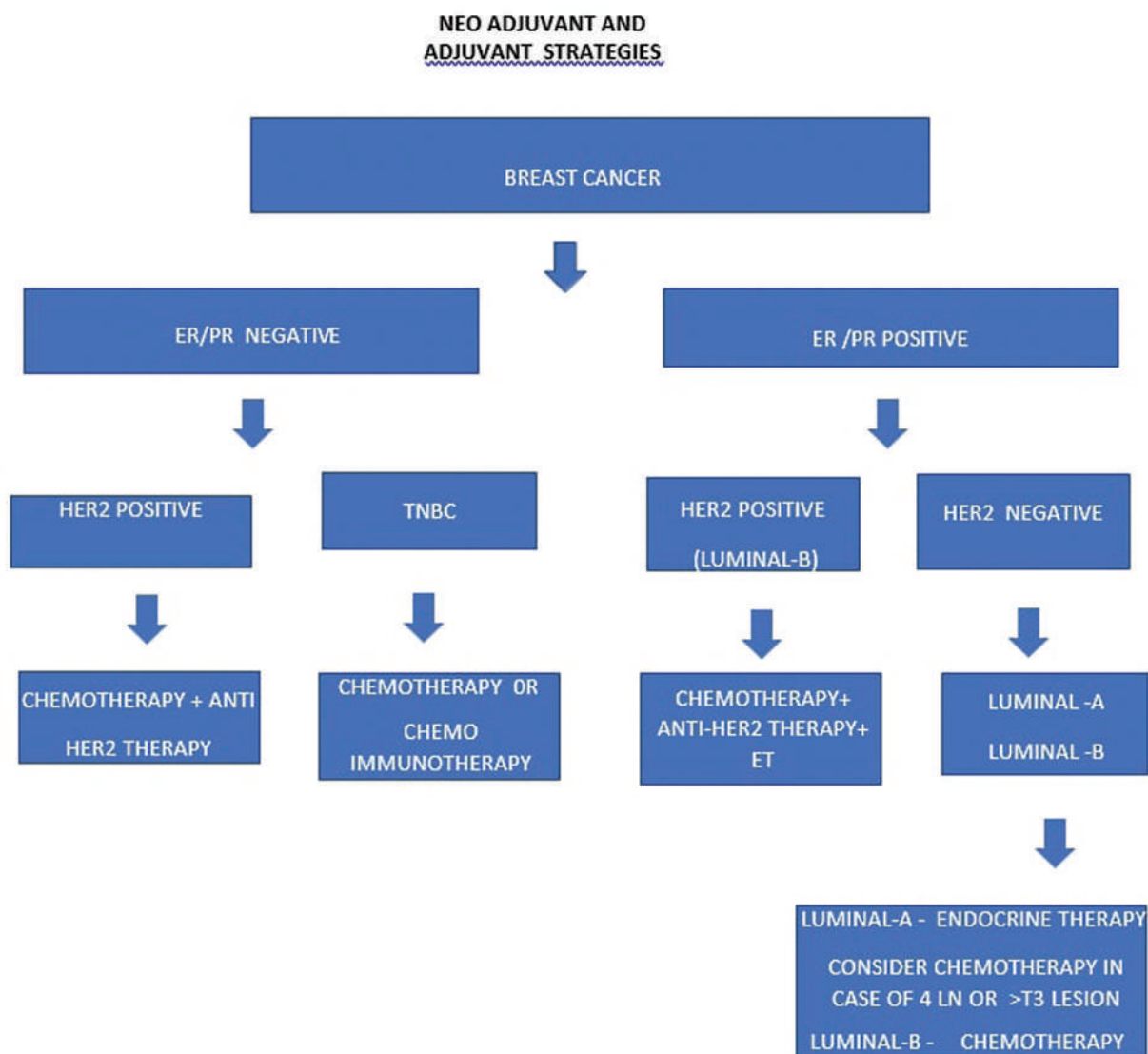


Fig. 4 Neo-adjuvant and adjuvant therapy.

hormone therapy, and radiotherapy) are dependent on patients-related factors like ECOG, co-morbidities, age and tumor-related factors like tumor size, grade, lymph node positivity, hormone and HER2 neu receptor and Ki67 status. Even the 8th AJCC staging system has included grade, receptor status, and ability to take therapy into account when staging BC.³¹

Management Schema for various stages of BC adapted from NCG guidelines 2019³³ is discussed in more details in ►Annexure 2

Medical Oncology

BC encompasses several subtypes and systemic therapy is indicated depending upon the biology and staging of the disease.

Perioperative Therapy

A multitude of regimens are used with the aim of micro-metastases control with comparable outcomes in either NACT or adjuvant chemotherapy (ACT) fashion (►Fig. 4). Sequential and dose-dense regimens are preferred (Table 1 in ►Annexure 3). pCR is a robust prognosticator in HER2-positives and triple-negative breast cancer (TNBC) groups.⁵⁷ ACT is used to reduce the risk of recurrence (RR). RR risk may be predicted using various clinicopathological factors and genomic signatures (Table 2 in ►Annexure 3).

HER2-Positive Tumors

HER2-rich patients should receive perioperative anti-Her2 therapy; 1-year trastuzumab is the current standard with/without pertuzumab (►Annexure 4).

Hormone Positive (HR +) Tumors

Neoadjuvant endocrine therapy alone is sufficient in low RR, HR+ tumors. The duration of ET varies from 5 to 10 years depending upon RR.⁵⁸ In premenopausal women, additional ovarian function suppression may be considered if RR is high.

Triple-Negative Tumors

In the NA setting, the addition of immune checkpoint inhibitors (ICIs) has shown benefit.^{59,60} Adjuvant capecitabine and PARP are options in non-pCR groups.⁶¹

Metastatic Disease

The mainstay of treatment is prolonging life and QOL. The treatment determinants are disease biology, prior therapies, ECOG – performance status, potential toxicities, and patient wishes (►Annexures 5, 6, and 7). Interestingly, outcomes of the short course ICI were found comparable to the standard course in a large real-world data.⁶²

Specific Populations

Young patients with BC (<40 years) are having unique challenges and need appropriate care including issues related to fertility and QOL.⁶³ Pregnancy-associated BC is challenging; however, stage- and biology-matched outcomes are largely comparable if appropriately managed.⁶⁴

Toxicity

Chemotherapy has various side effects including hematological and non-hematological factors (gastrointestinal, cardiac, renal, liver, body image issue, etc.). Chemo-induced alopecia is of major psychological concern; however, a scalp cooling strategy may help in mitigating this issue successfully.⁶⁵

Refer to Table 2 in ►Annexure 3 for genomic signature, which could help in decide ACT and also regimens for adjuvant setting.

Radiation Oncology

BC patients experience an improvement in locoregional control and overall survival with the addition of adjuvant RT.⁶⁶ Nearly 70% of all BC patients would require RT in their lifetime either in adjuvant or palliative setting and is well tolerated by most. In the adjuvant setting, addition of RT minimizes the microscopic tumor burden in the tumor bed (residual breast or the chest wall) and adjacent regions where the tumor cells are likely to migrate (clinically uninvolved supraclavicular region after a complete axillary clearance). Studies with long-term follow-up show that mastectomy can be avoided if adjuvant whole breast RT is delivered to the conserved breast.⁶⁷ In women <50 years, grade III tumors benefit in local control from dose escalation with a tumor bed boost.⁶⁸ Whole breast RT can produce acute and late toxicities like radiation dermatitis, induration, breast pain, shrinkage, and leads to poor cosmetic outcomes. Partial breast RT with external beam or brachytherapy delivered over shorter duration helps minimize these toxicities in early, node-negative BC patients after breast conserving surgery.^{69,70}

Palliative RT is recommended to alleviate symptoms such as pain, bleeding, prevent neurological death in brain metastasis and functional loss, and is effective in 60 to 70% of the patients with minimal side effects.

Management of Locoregional or Distant Recurrence

Locoregional or distant metastatic recurrence is managed depending on the site, however, repeat core biopsy from the first recurrence site is obtained – to look for hormone receptor status evaluation.³²

Image-Guided Interventions in Palliative Conditions

In symptomatic clinical cases having metastatic bone disease, high intensity focused ultrasound/cryoablation of symptomatic bone metastasis can be performed.^{71,72} Image-guided vertebroplasty is performed for vertebral body collapse.⁷³ RFA or microwave ablation of liver lesions can be performed by IR (interventional radiology). Chemoport insertion can be performed by IR or surgeons depending on institutional practice.

Summary

There is a rise in the incidence of BC all over the world in recent times. In this era of personalized cancer care, cross specialty knowledge of advances in cancer care is of utmost

importance in the management of cancer patients. In this document we have described diagnostic work-up for BC with an emphasis on imaging.

- Diagnostic work-up.
- Staging of BC.
- Response assessment post NACT.

This work-up is followed by philosophies of various treatment approaches (surgery, chemotherapy, or radiotherapy) for different stages and biology of BC. All these has led to decrease in cancer-specific mortality.

Synoptic reporting formats for mammogram, USG, MRI breast, CT scan, and PET CT are discussed in ► **Annexure 8**.

References

- Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71(03):209–249
- Global Cancer Observatory. Accessed March 18, 2022, at: <https://gco.iarc.fr/>
- Lima SM, Kehm RD, Terry MB. Global breast cancer incidence and mortality trends by region, age-groups, and fertility patterns. *EclinicalMedicine* 2021;38:100985
- Mathur P, Sathishkumar K, Chaturvedi M, et al; ICMR-NCDIR-NCRP Investigator Group. Cancer statistics, 2020: report from National Cancer Registry Programme, India. *JCO Glob Oncol* 2020;6(06):1063–1075
- Wu S, Zhu W, Thompson P, Hannun YA. Evaluating intrinsic and non-intrinsic cancer risk factors. *Nat Commun* 2018;9(01):3490
- Institute of Medicine (US) Committee on Cancer Control in Low- and Middle-Income Countries. Cancer Control Opportunities in Low- and Middle-Income Countries. in: Sloan FA, Gelband H, eds. Washington, DC: National Academies Press; 2007
- What Are the Risk Factors for Breast Cancer? | CDC. Accessed March 18, 2022, at: https://www.cdc.gov/cancer/breast/basic_info/risk_factors.htm
- Morris KT, Pommier RF, Morris A, et al. Usefulness of the triple test score for palpable breast masses; discussion 1012-3. *Arch Surg* 2001;136(09):1008–1012
- Hortobagyi GN, Connolly JL, D'Orsi CJ, Yang WT. Breast. In: Amin MB, Edge S, Greene F, et al., eds; American Joint Committee on Cancer. 8th ed. Springer: AJCC cancer staging manual; 2017:589–636
- AJCC 8th edition staging; 2018, Accessed on 12th Jan 2023 at: <http://www.breastsurgeonsweb.com/wp-content/uploads/downloads/2020/10/AJCC-Breast-Cancer-Staging-System.pdf>
- Mainiero MB, Moy L, Baron P, et al; Expert Panel on Breast Imaging. ACR Appropriateness Criteria® Breast Cancer Screening. *J Am Coll Radiol* 2017;14(11S):S383–S390
- Chakrabarthy S, Panwar S, Singh T, et al. Best Practice Guidelines for Breast Imaging, Breast Imaging Society, India. *Ann Natl Acad Med Sci* 2022;58(Suppl 2):060–068
- Massat NJ, Dibden A, Parmar D, Cuzick J, Sasieni PD, Duffy SW. Impact of screening on breast cancer mortality: the UK program 20 years on. *Cancer Epidemiol Biomarkers Prev* 2016;25(03):455–462
- Lee CH, Dershaw DD, Kopans D, et al. Breast cancer screening with imaging: recommendations from the Society of Breast Imaging and the ACR on the use of mammography, breast MRI, breast ultrasound, and other technologies for the detection of clinically occult breast cancer. *J Am Coll Radiol* 2010;7(01):18–27
- Protocols for surveillance of women at very high risk of developing breast cancer - GOV.UK. Accessed March 18, 2022, at: <https://www.gov.uk/government/publications/breast-screening-higher-risk-women-surveillance-protocols/protocols-for-surveillance-of-women-at-higher-risk-of-developing-breast-cancer>
- Mendelson EB. Problem-solving ultrasound. *Radiol Clin North Am* 2004;42(05):909–918, vii
- Guidance on screening and symptomatic breast imaging, Fourth edition | The Royal College of Radiologists. Accessed March 18, 2022, at: <https://www.rcr.ac.uk/publication/guidance-screening-and-symptomatic-breast-imaging-fourth-edition>
- Sharpe RE Jr, Venkataraman S, Phillips J, et al. Increased cancer detection rate and variations in the recall rate resulting from implementation of 3D digital breast tomosynthesis into a population-based screening program. *radiology*. *Radiology* 2016;278(03):698–706
- D'Orsi CJ, Sickles EA, Mendelson EB, et al. ACR BI-RADS Mammography. In: ACR BI-RADS Atlas, Breast Imaging Reporting and Data System. 5th ed. Reston, VA: American College of Radiology; 2013:134–136
- Lee S, Jung Y, Bae Y. Synchronous BI-RADS category 3 lesions on preoperative ultrasonography in patients with breast cancer: is short-term follow-up appropriate? *J Breast Cancer* 2015;18(02):181–186
- Kim SJ, Ko EY, Shin JH, et al. Application of sonographic BI-RADS to synchronous breast nodules detected in patients with breast cancer. *AJR Am J Roentgenol* 2008;191(03):653–658
- Indian Council of Medical Research, Government of India. ICMR Subcommittee on Breast Cancer. Consensus document for management of breast cancer, 2016. March 19, 2022, at: http://cancerindia.org.in/wp-content/uploads/2017/11/Breast_Cancer.pdf. - Google Search
- Canadian Association of Radiologists CAR Practice guidelines and technical standards for breast imaging and intervention. Approved on September 29, 2012; modified on September 17, 2016. Accessed September 2021, at: <https://car.ca/wp-content/uploads/Breast-Imaging-and-Intervention-2016.pdf>
- American College of Radiology ACR practice parameter for the performance of ultrasound-guided percutaneous breast interventional procedures, Revised 2021 (Resolution 31). Accessed March 19, 2022, at: <https://www.acr.org/-/media/acr/files/practice-parameters/us-guidedbreast.pdf>. - Google Search
- ACR practice parameter for the performance of magnetic resonance imaging-guided breast interventional procedures, Revised 2021 (Resolution 29). Accessed March 19, 2022, at: <https://www.acr.org/-/media/ACR/Files/Practice-Parameters/MR-Guided-Breast.pdf> - Google Search
- Chakrabarthy S. Stereotactic breast biopsy: a review & applicability in the Indian context. *Indian J Med Res* 2021;154(02):237–247
- Ghaderi KF, Phillips J, Perry H, Lotfi P, Mehta TS. Contrast-enhanced mammography: current applications and future directions. *Radiographics* 2019;39(07):1907–1920
- Harbeck N, Penault-Llorca F, Cortes J, et al. Breast cancer. *Nat Rev Dis Primers* 2019;5(01):66
- Taneja S, Evans AJ, Rakha EA, Green AR, Ball G, Ellis IO. The mammographic correlations of a new immunohistochemical classification of invasive breast cancer. *Clin Radiol* 2008;63(11):1228–1235
- Boisserie-Lacroix M, Hurtevent-Labrot G, Ferron S, Lippa N, Bonnefoi H, Mac Grogan G. Correlation between imaging and molecular classification of breast cancers. *Diagn Interv Imaging* 2013;94(11):1069–1080
- The American College of Surgeons Part IX - Breast, AJCC cancer staging manual, 8th edition, updated May 25 2018. Accessed March 19, 2022, at: <http://www.breastsurgeonsweb.com/wp-content/uploads/downloads/2020/10/AJCC-Breast-Cancer-Staging-System.pdf> - Google Search
- National Comprehensive Cancer Network Breast Cancer Version 4.2022 – June 21, 2022. Accessed November 10, 2022, at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
- National Cancer Grid India. National Cancer Grid Breast Cancer Management Guidelines, September, 2019. Accessed March 19, 2022, at: https://tmc.gov.in/ngc/docs/PDF/DraftGuidelines/Breast/NCG_guidelines_2019_Breast.pdf - Google Search
- Algorithm for Breast Imaging - Breast Imaging Society India. Accessed March 19, 2022, at: <https://www.bisi.co.in/guidelines/algorithm-for-breast-imaging/>

- 35 Kalli S, Semine A, Cohen S, Naber SP, Makim SS, Bahl M. American Joint Committee on Cancer's Staging System for breast cancer, eighth edition: what the radiologist needs to know. *Radiographics* 2018;38(07):1921–1933
- 36 Teichgraber DC, Guirguis MS, Whitman GJ. Breast cancer staging: Updates in the AJCC cancer staging manual, 8th edition, and current challenges for radiologists, from the AJR special series on cancer staging. *Am J Roentgenol* 2021;217(02):278–290
- 37 Chang JM, Leung JWT, Moy L, Ha SM, Moon WK. Axillary nodal evaluation in breast cancer: state of the art. *Radiology* 2020;295(03):500–515
- 38 van Nijnatten TJA, Jochelson MS, Lobbes MBI. Axillary lymph node characteristics in breast cancer patients versus post-COVID-19 vaccination: overview of current evidence per imaging modality. *Eur J Radiol* 2022;152:110334
- 39 Pesapane F, Downey K, Rotili A, Cassano E, Koh D-M. Imaging diagnosis of metastatic breast cancer. *Insights Imaging* 2020;11(01):79
- 40 Barra FR, Sobrinho AB, Barra RR, et al. Contrast-enhanced mammography (CEM) for detecting residual disease after neoadjuvant chemotherapy: a comparison with breast magnetic resonance imaging (MRI). *BioMed Res Int* 2018;2018:8531916
- 41 Holmes D, Colfry A, Czerniecki B, et al. Performance and practice guideline for the use of neoadjuvant systemic therapy in the management of breast cancer. *Ann Surg Oncol* 2015;22(10):3184–3190
- 42 Fowler AM, Mankoff DA, Joe BN. Imaging neoadjuvant therapy response in breast cancer. *Radiology* 2017;285(02):358–375
- 43 Riedl CC, Pinker K, Ulaner GA, et al. Comparison of FDG-PET/CT and contrast-enhanced CT for monitoring therapy response in patients with metastatic breast cancer. *Eur J Nucl Med Mol Imaging* 2017;44(09):1428–1437
- 44 Dose Schwarz J, Bader M, Jenicke L, Hemminger G, Jänicke F, Avril N. Early prediction of response to chemotherapy in metastatic breast cancer using sequential 18F-FDG PET. *J Nucl Med* 2005;46(07):1144–1150
- 45 Janssen NNY, Nijkamp J, Alderliesten T, et al. Radioactive seed localization in breast cancer treatment. *Br J Surg* 2016;103(01):70–80
- 46 Garzotto F, Comoretto RI, Michieletto S, et al. Preoperative non-palpable breast lesion localization, innovative techniques and clinical outcomes in surgical practice: a systematic review and meta-analysis. *Breast* 2021;58:93–105
- 47 Flowers CI, Mooney BP, Drukteinis JS. Clinical and imaging surveillance following breast cancer diagnosis. *Am Soc Clin Oncol Educ Book* 2012;•••:59–64
- 48 Brennan S, Liberman L, Dershaw DD, Morris E. Breast MRI screening of women with a personal history of breast cancer. *AJR Am J Roentgenol* 2010;195(02):510–516
- 49 Kerridge WD, Kryvenko ON, Thompson A, Shah BA. Fat necrosis of the breast: a pictorial review of the mammographic, ultrasound, CT, and MRI findings with histopathologic correlation. *Radiol Res Pract* 2015;2015:613139
- 50 Schrijver WAME, Suijkerbuijk KPM, van Gils CH, van der Wall E, Moelans CB, van Diest PJ. Receptor conversion in distant breast cancer metastases: a systematic review and meta-analysis. *J Natl Cancer Inst* 2018;110(06):568–580
- 51 Golan O, Amitai Y, Barnea Y, Menes TS. Yield of surveillance magnetic resonance imaging after bilateral mastectomy and reconstruction: a retrospective cohort study. *Breast Cancer Res Treat* 2019;174(02):463–468
- 52 Osei EK, Faulkner K. Fetal doses from radiological examinations. *Br J Radiol* 1999;72(860):773–780
- 53 Sechopoulos I, Suryanarayanan S, Vedantham S, D'Orsi CJ, Karellas A. Radiation dose to organs and tissues from mammography: Monte Carlo and phantom study. *Radiology* 2008;246(02):434–443
- 54 Committee Opinion No. Committee opinion no. 723: guidelines for diagnostic imaging during pregnancy and lactation. *Obstet Gynecol* 2017;130(04):e210–e216
- 55 Özmen V. Paradigm shift from Halstedian radical mastectomy to personalized medicine. *J Breast Health* 2017;13(02):50–53
- 56 Parmar V, Koppiker CB, Dixit S. Breast conservation surgery & oncoplasty in India – current scenario. *Indian J Med Res* 2021;154(02):221–228
- 57 Berruti A, Amoroso V, Gallo F, et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: a meta-regression of 29 randomized prospective studies. *J Clin Oncol* 2014;32(34):3883–3891
- 58 Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update. *J Clin Oncol* 2019;37(05):423–438
- 59 Schmid P, Cortes J, Pusztai L, et al; KEYNOTE-522 Investigators. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med* 2020;382(09):810–821
- 60 Emens LA, Adams S, Barrios CH, et al. First-line atezolizumab plus nab-paclitaxel for unresectable, locally advanced, or metastatic triple-negative breast cancer: IMpassion130 final overall survival analysis. *Ann Oncol* 2021;32(08):983–993
- 61 Masuda N, Lee S-J, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med* 2017;376:2147–2159
- 62 Abraham G, Noronha V, Rajappa S, et al. The clinical utility and safety of short-course immune checkpoint inhibitors in multiple tumours-A real-world multicentric study from India. *Int J Cancer* 2022;150(06):1045–1052
- 63 Bajpai J, Ventrapati P, Joshi S, et al. Unique challenges and outcomes of young women with breast cancers from a tertiary care cancer centre in India. *Breast* 2021;60:177–184
- 64 Bajpai J, Simha V, Shylasree TS, et al. Pregnancy associated breast cancer (PABC): Report from a gestational cancer registry from a tertiary cancer care centre, India. *Breast* 2021;56:88–95
- 65 Bajpai J, Kagwade S, Chandrasekharan A, et al. "Randomised controlled trial of scalp cooling for the prevention of chemotherapy induced alopecia". *Breast* 2020;49:187–193
- 66 Darby S, McGale P, Correa C, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378(9804):1707–1716
- 67 Clarke M, Collins R, Darby S, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;366(9503):2087–2106
- 68 Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *J Clin Oncol* 2007;25(22):3259–3265
- 69 Polgár C, Major T, Fodor J, et al. Accelerated partial-breast irradiation using high-dose-rate interstitial brachytherapy: 12-year update of a prospective clinical study. *Radiother Oncol* 2010;94(03):274–279
- 70 Meattini I, Marrazzo L, Saieva C, et al. Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: long-term results of the randomized phase III APBI-IMRT-Florence trial. *J Clin Oncol* 2020;38(35):4175–4183
- 71 Bertrand AS, Iannesi A, Natale R, et al. Focused ultrasound for the treatment of bone metastases: effectiveness and feasibility. *J Ther Ultrasound* 2018;6(01):8
- 72 Tuncali K, Morrison PR, Winalski CS, et al. MRI-guided percutaneous cryotherapy for soft-tissue and bone metastases: initial experience. *AJR Am J Roentgenol* 2007;189(01):232–239
- 73 Wallace AN, Greenwood TJ, Jennings JW. Use of imaging in the management of metastatic spine disease with percutaneous ablation and vertebral augmentation. *AJR Am J Roentgenol* 2015;205(02):434–441

Annexure 1 American Cancer Society recommends screening mammogram (MG)

American Cancer Society recommends screening mammogram (MG) as follows:

(<https://www.cancer.org/cancer/breast-cancer/screening-tests-and-early-detection/american-cancer-society-recommendations-for-the-early-detection-of-breast-cancer.html>; last revised January 14, 2022).

Age	Guideline
40–44 years	Optional – Annual MG
45–54 years	Annual MG
55 years and older	Annual/Biennial MG (to be continued till good health or expected life expectancy of at least 10 years)

American College of Radiology [ACR] and Society of Breast Imaging [SBI] recommends

Annual MG from age 40

(<https://www.acraccreditation.org/Mammography-Saves-Lives/Guidelines>)

United States Preventive Service Task Force (USPSTF) recommends Biennial screening MG for women from 50 to 74 years (B recommendation)

(<https://www.acraccreditation.org/Mammography-Saves-Lives/Guidelines>)

European Commission Breast Cancer Guidelines (ECIBC's Guideline Development Group [GDG]) recommend:

Age	Guideline
40 – 44	No screening
45 – 49	Biennial/Triennial MG
50 – 69	Biennial MG
70 – 74	Triennial MG

(<https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines/screening-ages-and-frequencies>)

Canadian Task Force recommends:

Abbreviation: MG, mammogram.

Age	Guideline
40–49	No screening, but conditional screening may be adapted by women.
50–69	Biennial/Triennial MG
70–74	Biennial/Triennial MG

(<https://canadiantaskforce.ca/guidelines/published-guidelines/breast-cancer-update>)

Breast screening program in Australia recommends:

(<https://www.cancer.org.au/cancer-information/causes-and-prevention/early-detection-and-screening/breast-cancer-screening>)

Invitation-based screening MG at biennial interval for 50 to 74 years age. Younger and older women may undergo mammography, without invitation.

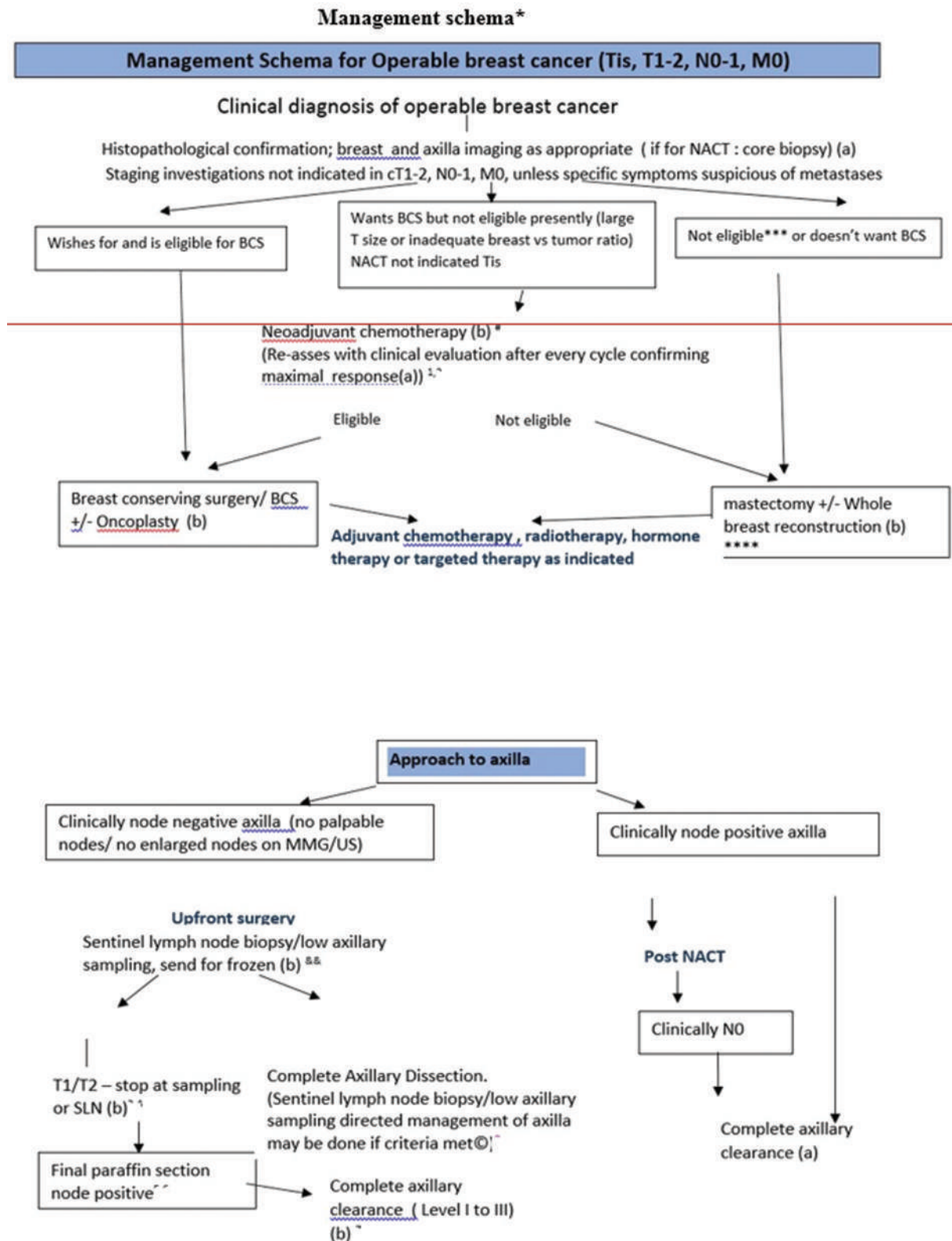
Swedish BC guidelines

(<https://www.swedish.org/services/womens-health/our-services/mammography/screening-guidelines>)

Annual screening MG for age over 40 years

Breast Imaging Society of India (BISI) recommends:

(<https://www.bisi.co.in/guidelines/mammography>)

Annexure 2 Management schema*

*Number of cycles should be based on tumor response/institutional practice.

#Tailoring treatment based on IHC, to be able to consider post NACT adjuvant therapy to non-responders can be discussed with patients ©.

***Contraindications to BCS include: diffuse microcalcification, persistent positive margins, poor patient compliance, previous chest or breast radiation, relative contraindication is multicentricity. Contraindications to radiotherapy, e.g., collagen vascular diseases.

³SNB can be performed either using *Dual Dye-Radio Colloid* and *Blue Dye* (preferred method) OR using *Blue Dye* alone. 1 to 2 mL peritumoral and/or subareolar injection/subdermal injection of patent *Blue Dye* or 2% *Methylene Blue* 10 minutes prior to the surgical incision and 40 MBq in 0.5 mL of 99m-technetium-labeled sulfur/antimony colloid peritumoral and/or subareolar injection/subdermal injection 2 to 12 hours prior to surgery.

⁵If the patient and tumor characteristics meet the ACOZOG Z-11 (T1, micro metastasis in node, low-grade tumor, ER/PR positive, BCS done, whole breast RT using tangential fields planned) and 1–2 SLN positive, no further axillary surgery may be considered. ©

****Breast reconstruction may be performed by surgeons in motivated and suitable patients following mastectomy. Implant or autologous flap reconstruction can be performed based on patient's suitability and choice of surgeon.

⁷If cN0 prior to NACT or an OBC with cN1 post chemotherapy cN0: can be considered for SLN/low axillary sampling.

⁸If FS not available: LAS and final HPR or ALND (level II if no gross enlarged nodes).

Margins in BCS: negative margin defined as no tumor on inked surface. In case of positive margins, should be revised. In case of persistent positive margins, MRM to be considered.

In patients with family history of cancer, younger than 40 years, male breast cancer or patients with synchronous and metachronous breast cancer, can be referred for genetic counselling and those who are willing may be considered for testing to rule out presence of germline pathogenic variant. ©

Screen detected low-grade DCIS undergoing lumpectomy may not require axillary assessment. ©

Management Schema for locally Advanced breast cancer (T3-4, any N, N2-3 any T)

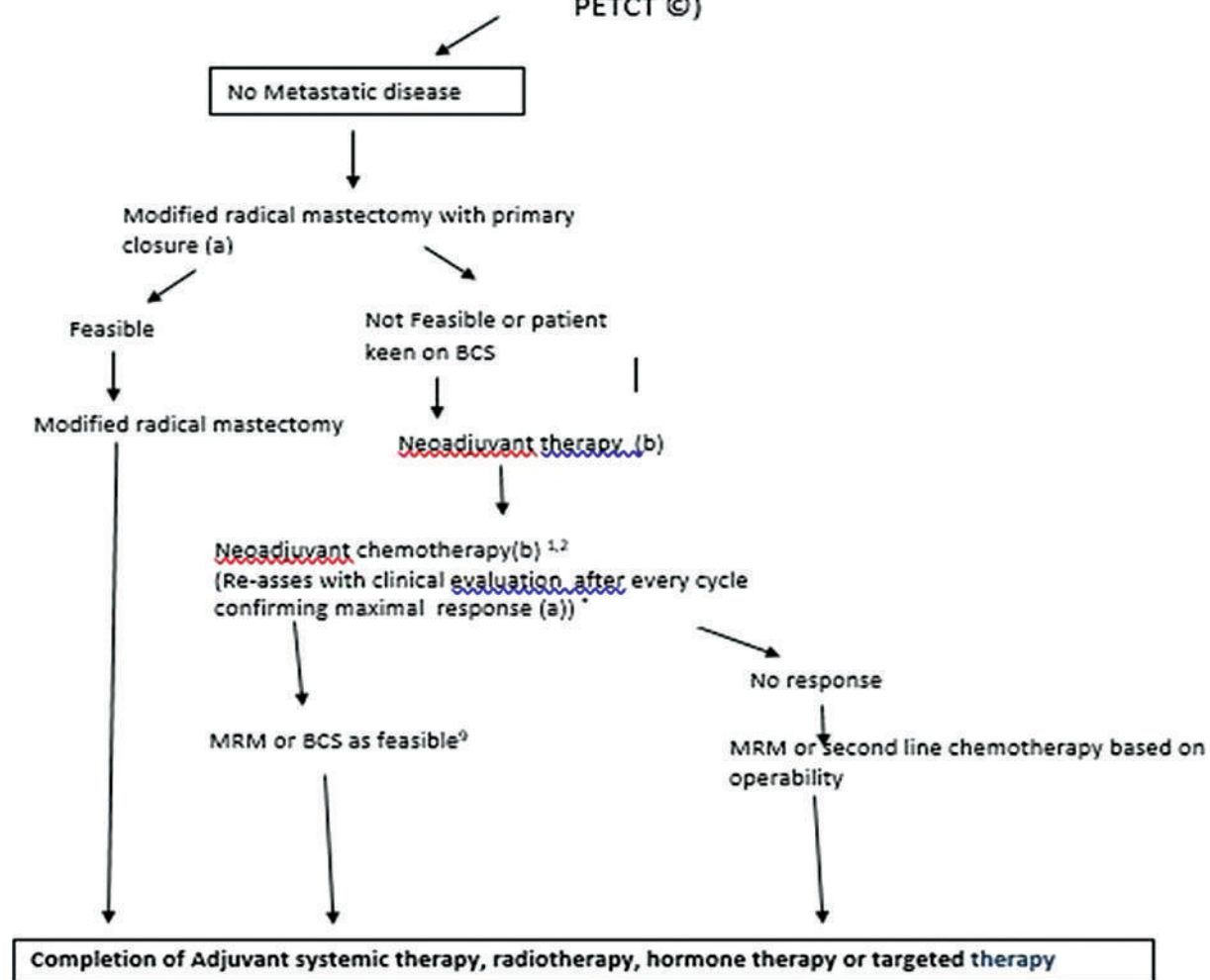
Clinical diagnosis of advanced breast cancer

Histopathological confirmation with core biopsy and breast imaging as appropriate (a)

(Clip placement (b), skin marking (a) to localize the primary tumor prior to NACT)

Metastatic work up (a)

(X-ray Chest, USG abdomen and pelvis, LFT (a)
Bone Scan, CECT CHEST /ABDO (b)
PETCT ©)



*Source: Adapted from NCCN guidelines 2019 (Accessed March 19, 2022).

Annexure 3 Chemotherapy /Targeted/Hormone Therapy Regimens (preoperative/adjvant setting)

Table 1 Chemotherapy/targeted/hormone therapy regimens (preoperative/adjvant setting)

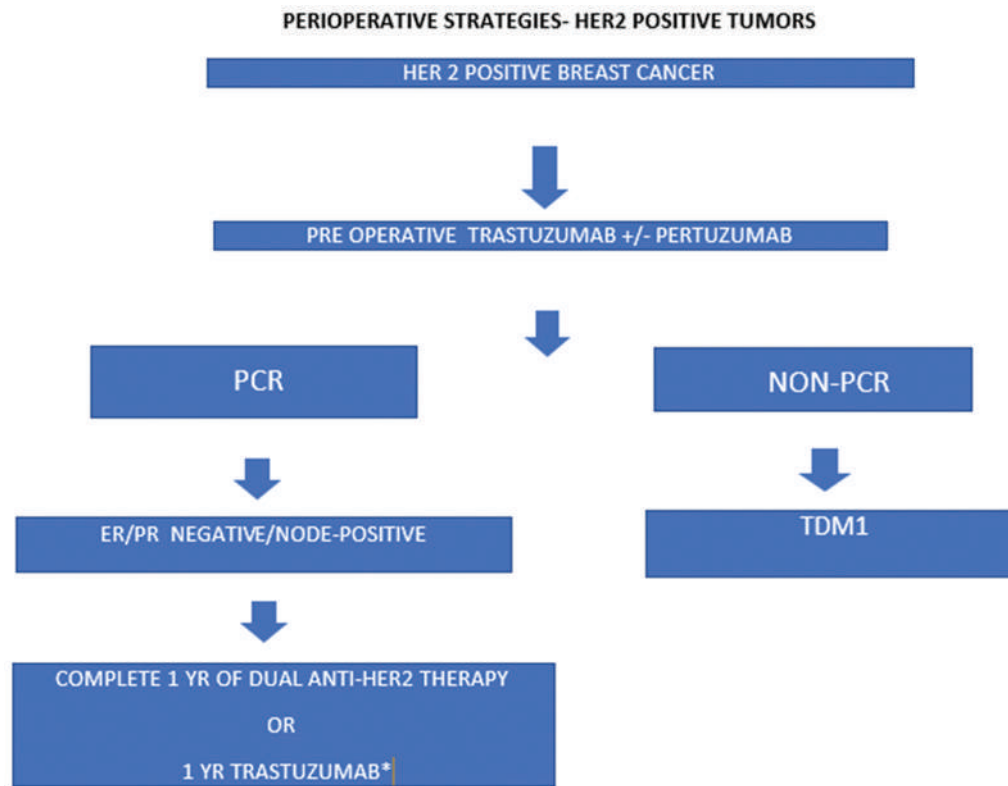
Dose-dense AC (adriamycin + cyclophosphamide) followed by paclitaxel with growth factor support
DOSE dense AC followed by weekly paclitaxel with growth factor support
CMF cyclophosphamide + methotrexate + 5 fluorouracil
TAC docetaxel + doxorubicin + cyclophosphamide
TC docetaxel + cyclophosphamide
AC followed by paclitaxel or docetaxel
EC epirubicin + cyclophosphamide
AC or dose dense ac followed by paclitaxel + trastuzumab
AC followed by paclitaxel + trastuzumab + pertuzumab
Pertuzumab + standard perioperative chemotherapy + adjuvant trastuzumab
Paclitaxel + trastuzumab
TCH (docetaxel + carboplatin + trastuzumab)
TCH + pertuzumab
Adjuvant trastuzumab for 1 y
Adjuvant trastuzumab + pertuzumab
Adjuvant tdm1 for 1 y if residual disease after complete pre-operative trastuzumab-based therapy
Weekly paclitaxel + carboplatin
Capecitabine (If TNBC and residual disease after preoperative therapy)
Immunotherapy – atezolizumab + standard chemotherapy
Pembrolizumab + chemotherapy followed by pembrolizumab maintenance
Hormonal agents
Tamoxifen
Aromatase inhibitors – letrozole/anastrozole/exemestane
Fulvestrant
CDK4/6 inhibitors
Palbociclib/ribociclib/abemaciclib

Table 2 Most of genomic signatures available could refine our choices to select patients who require adjuvant chemotherapy

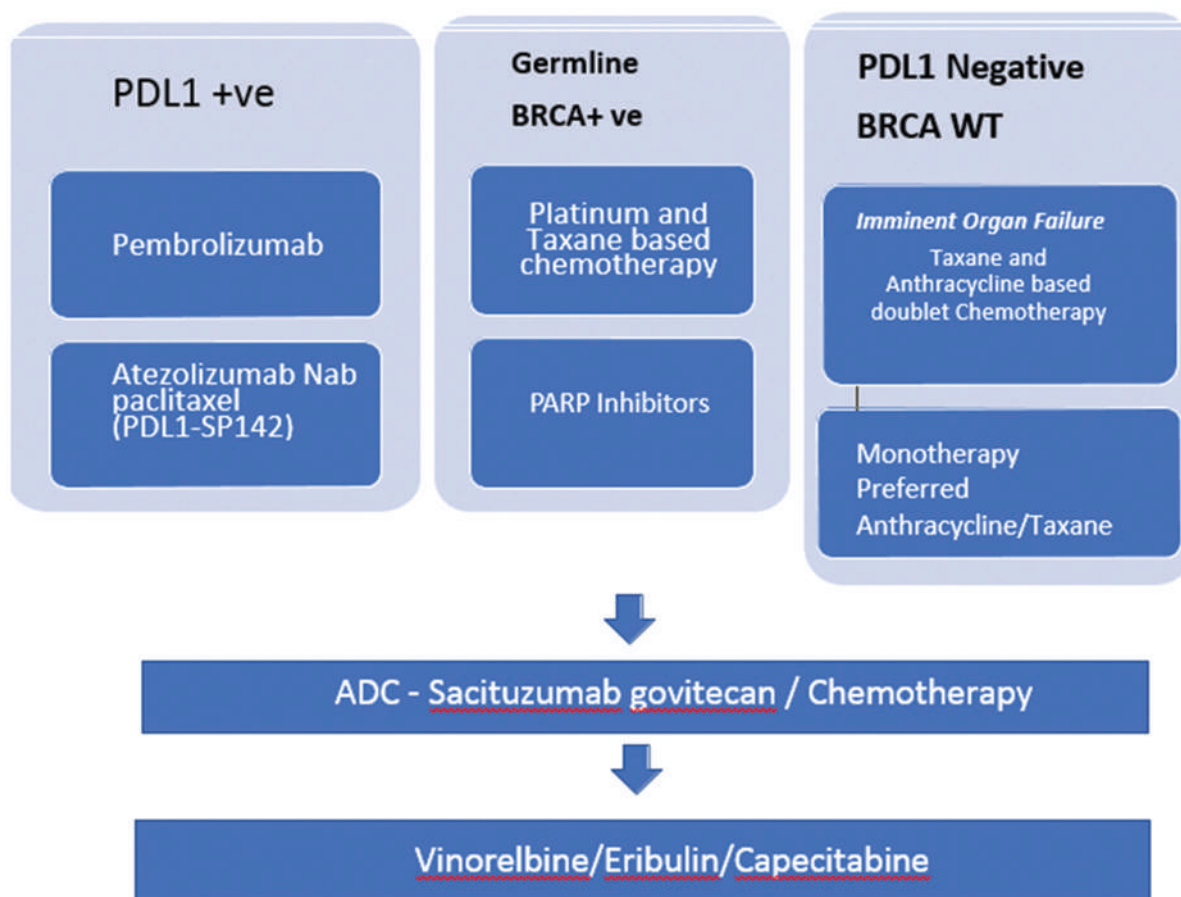
Genomic signatures Significance	
Oncotype Dx	Used in patients with ER + , node-negative breast cancer A Low recurrence score (<11) – chemotherapy does not add benefit. In intermediate recurrence score (11–26) – chemotherapy add benefit in young patients
MammaPrint (70 gene signature)	Used in both hormone positive and negative early breast cancer patients with one to three lymph nodes. Low clinical risk and low genomic risk are less likely to benefit from chemotherapy.
PAM 50 (Prosigna)	Used to predict the risk of distant recurrence for postmenopausal hormone-positive breast cancer with node-negative or with one to three lymph nodes Accurately predicts 10-y distant recurrence-free survival mainly in In negative subsets
Endopredict (RNA-based 12 gene assay)	Uses both genomic and clinicopathological parameters for predicting late distant recurrence. Low-risk groups have an excellent prognosis to endocrine therapy only.
Breast cancer index (PCR-based 11 gene assay)	Used in hormone-positive early breast cancer patients with one to three lymph nodes. Prognosticates the likelihood of recurrence at 10 y. Predicts patients who will be benefitted from the use of extended endocrine therapy.
IHC 4 + C	Used in hormone-positive postmenopausal women receiving adjuvant endocrine therapy. This score incorporates four immunohistochemical and clinicopathological features to estimate the risk of 10-y distant recurrence.

Annexure 4 HER2-positive tumors

Short course therapy may be considered in cardiac comorbidities, low recurrence risk, and/or resource-constrained setting.

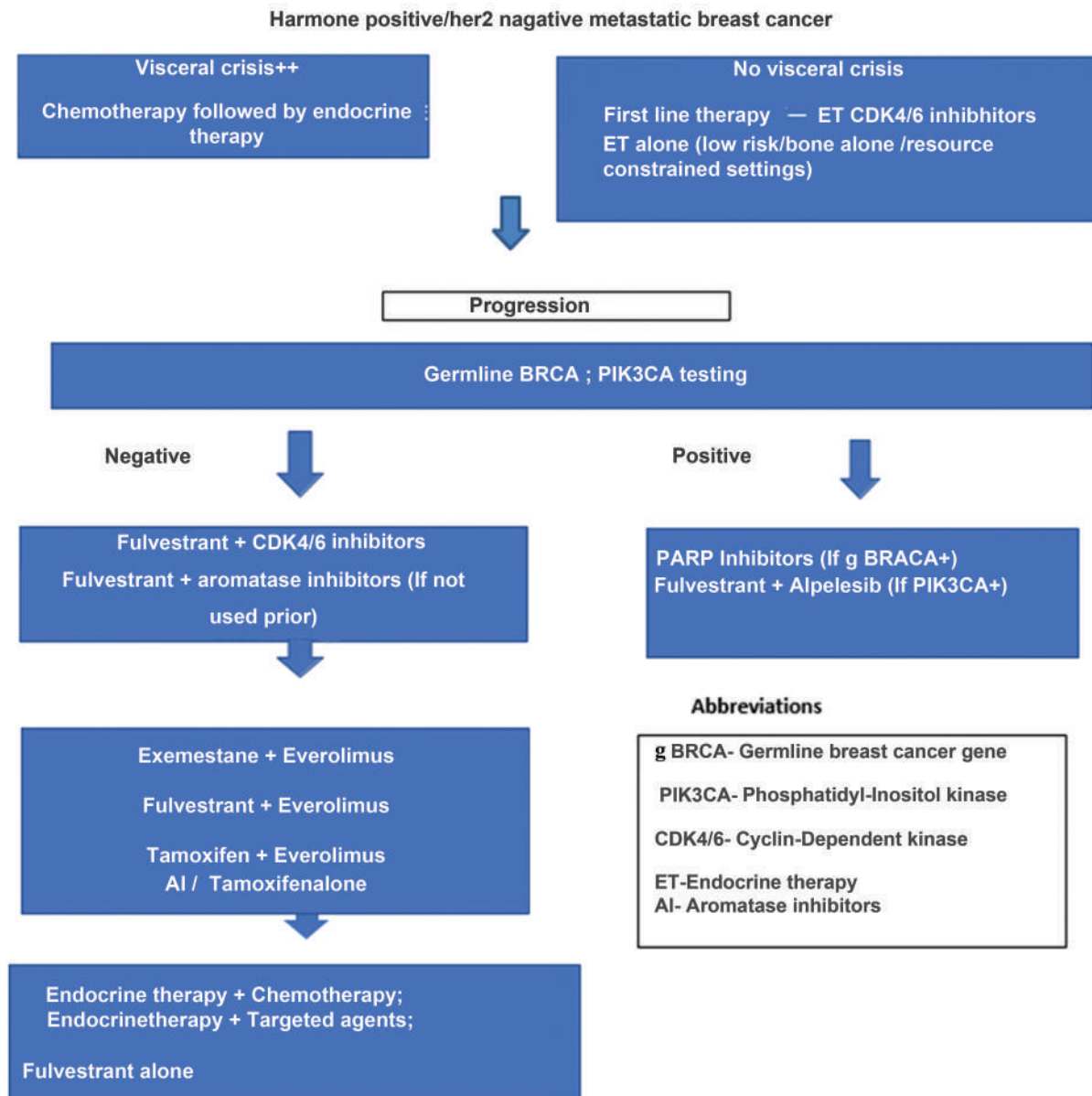


Abbreviations: HER2, human epidermal growth factor receptor; PCR, pathological complete response; TDM1, trastuzumab emtansine.

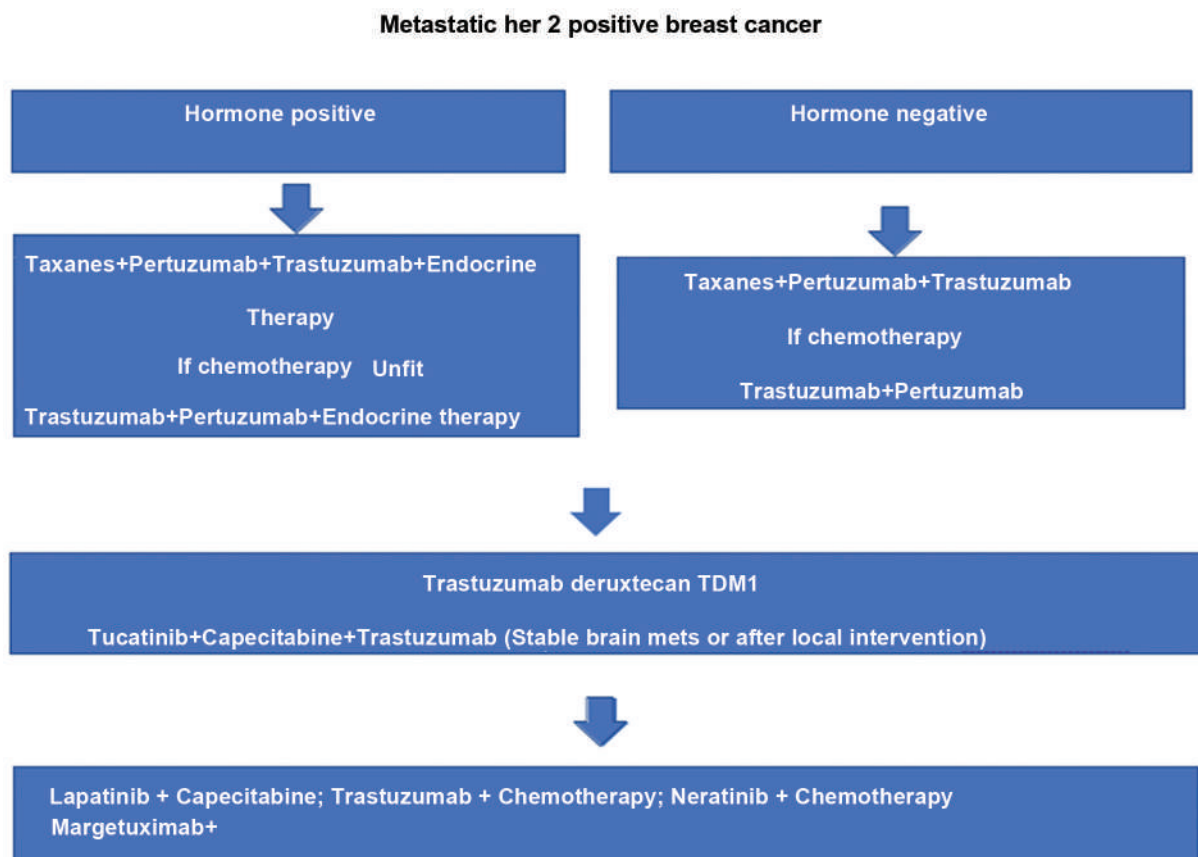
Annexure 5 Metastatic breast cancer**Metastatic Breast Cancer**

Abbreviations: ADC, antibody drug conjugate; BRCA WT, breast cancer gene wild type; PDL1, programmed death ligand receptor L1.

Annexure 6 Hormone positive and HER2-negative metastatic tumor



Annexure 7 Metastatic HER2-positive tumor



Annexure 8 Synoptic reporting formats for mammogram, USG, MRI breast, CT scan and PET CT

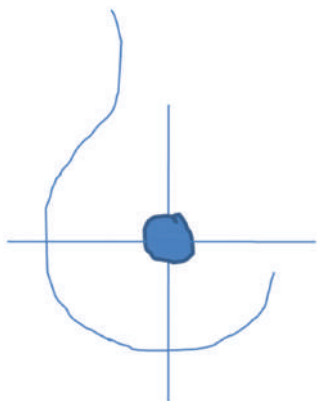
Digital mammograms: dated
Bilateral/unilateral
Indication: Screening/diagnostic
Right breast:
Breast composition:

- The breasts are almost entirely fatty.
- There are scattered areas of fibroglandular density.
- The breasts are heterogeneously dense, which may obscure small masses.
- The breasts are extremely dense, which lowers the sensitivity of mammography.

Normal/Abnormal
If abnormal

A. Mass: Absent/present

If present:
Size:
Location:



Density: iso/high/low/fat containing.
Shape: oval/round/irregular.
Margins: circumscribed/obscured/microlobulated/indistinct/spiculated.

B. Calcifications: absent/present.

If present:
Benign: Vascular/coarse/popcorn/rod-like/round/lucent centered/eggshell/milk of calcium/dystrophic/punctuate/sutural.

Suspicious morphology: Amorphous/coarse heterogeneous/fine pleomorphic/fine linear or fine-linear branching.
Distribution: diffuse/regional/grouped/linear/segmental.

C. Architectural distortion: Absent/present

D. Asymmetry: Absent/present

E. Associated findings:

Skin thickening/skin retraction/nipple retraction/trabecular thickening/abnormal axillary or intramammary nodes.

F. Additional information:

G. Comparison: No change/new lesion/regression/increase in existing lesion.

H. Assessment category:

BIRADS 0/1/2/3/4a/4b/4c/5/6

Left breast:

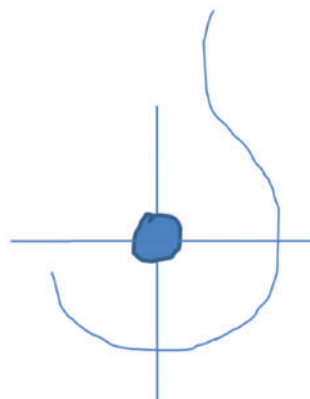
Breast composition:

- The breasts are almost entirely fatty.
- There are scattered areas of fibroglandular density.
- The breasts are heterogeneously dense, which may obscure small masses.
- The breasts are extremely dense, which lowers the sensitivity of mammography.

Normal/Abnormal
If abnormal

A. Mass: Absent/present

If present:
Size:
Location:



Density: Iso/high/low/fat containing
Shape: Oval/round/irregular
Margins: Circumscribed/obscured/microlobulated/indistinct/spiculated

B. *Calcifications:* absent/present If present:

If present:
Benign: Vascular/coarse/popcorn/rod-like/round/lucent centered/eggshell/milk of calcium/dystrophic/punctuate/sutural.

Suspicious morphology: Amorphous/coarse heterogeneous/fine pleomorphic/fine linear or fine-linear branching.
Distribution: Diffuse/regional/grouped/linear/segmental.

C. *Architectural distortion:* Absent/present.

D. *Asymmetry:* Absent/present.

E. *Associated findings:* Skin thickening/skin retraction/nipple retraction/trabecular thickening/abnormal axillary or intramammary nodes.

F. *Additional information:*

I. *Comparison: No change/new lesion/regression/increase in existing lesion.*

G. *Assessment category:*

BIRADS 0/1/2/3/4a/4b/4c/5/6

Breast ultrasound synoptic reporting

Indication

Family history of cancer: Yes/no

Parenchyma

a. Homogeneous background echotexture – fat.

b. Homogeneous background echotexture – fibroglandular.

c. Heterogeneous background echotexture.

Laterality

Right / left / both

Primary lesion evaluation

Single/multiple

Size

Quadrants involved with o'clock position

Shape

Oval/round/irregular

Margin

Circumscribed or

Non-circumscribed (indistinct/angular/microlobulated/spiculated).

Orientation

Parallel /nonparallel

Echopattern

Anechoic/hyperechoic/hypoechoic /isoechoic/complex solid cystic/heterogeneous

Posterior features

No posterior features/enhancement/shadowing/combined pattern

Vascularity

Absent/internal vascularity/vessels in rim

Elasticity assessment

Soft/intermediate/hard

Calcification: yes/no

If yes,

In Mass / Outside Mass / Intraductal

Distance from nipple

Duct

Ductal changes: Yes/No

Satellite lesions

Yes/no

Size

Quadrants

Numbers

Positions in o'clock

Distance from primary lesion and nipple

Axillary nodes

Yes/no

Size

Cortical thickening yes/no (measurement in mm)

Preserved hilum yes/no

Microcalcification in lymph node yes/no

Matted yes/no

Perinodal extension yes/no

Non-hilar blood flow yes/no

Intramammary lymph nodes

Yes/no

Size

Special cases:

Simple cyst

Clustered microcysts

Complicated cyst

Mass in or on skin

Foreign body including implants

Lymph nodes – intramammary

Lymph nodes – axillary

Vascular abnormalities AVMs (arteriovenous malformations/ pseudoaneurysms)

Mondor disease

Postsurgical fluid collection

Fat necrosis

Any other relevant finding

Assessment category

BIRADS 0/1/2/3/4a/4b/4c/5/6

Breast MRI:

Breast MRI performed in a 1.5 T/3T scanner using a dedicated breast coil. Multiplanar Plain T1, T2, STIR, DWI, post contrast dynamic T1 weighted sequence after administration of 0.1 mmol/kg body weight contrast.

Indication:

Any prior breast imaging available: Yes/no

Last menstrual period:

Amount of fibroglandular Parenchyma: Type a, b, c, d

Background parenchymal enhancement intensity: minimal, mild, moderate, severe

Symmetry: Symmetric/asymmetric

Right breast

Mass:

Location

Size

Shape: Round/oval/irregular

Margins: Circumscribed non-circumscribed: irregular/spiculated

T2 SI

DWI:

Enhancement morphology: Homogeneous/heterogeneous/rim/dark internal septations

Kinetic curve assessment:

Initial phase: Fast/medium/slow

Delayed phase: wash-out/persistent/plateau

Non-mass enhancement:

Distribution: Focal/linear/ segmental/regional/ multiple regions/diffuse

Morphology: Homogeneous/heterogeneous/ clumped/ clustered ring

Focus: Number and symmetry

Other findings: Cysts/non enhancing mass/dilated ducts/ etc.
 Skin thickening
 Nipple retraction:
 Chest wall invasion:
 Axillary nodes
 Internal mammary nodes:
 Left breast
 Mass:
 Location
 Size
Shape: round oval irregular
Margins: Circumscribed non-circumscribed: irregular/ spiculated
 T2 SI
 DWI:
Enhancement morphology: homogeneous/heterogeneous/ rim/dark internal septations
 Kinetic curve assessment:
Initial phase: fast/medium/slow
Delayed phase: Washout/persistent/plateau
 Non-mass enhancement:
Distribution: Focal/linear/segmental/regional/multiple regions/diffuse
Morphology: Homogeneous/heterogeneous/clumped/ clustered ring
Focus: Number and symmetry
 Other findings: Cysts/non enhancing mass/dilated ducts/ etc.
 Skin thickening
 Nipple retraction:
 Chest wall invasion:
 Axillary nodes
 Internal mammary nodes:
 Visualized Liver: If any abnormality seen
 Visualized bones:
 Impression:
 BIRADS: 1/2/3/4a/4b/4c/5/6
 Breast cancer CT scan

CT scan of chest, abdomen, and pelvis
 Contrast enhanced CT scan performed.

Indication:
 Base line evaluation/post-NACT evaluation. Comparison made with prior CT dated ()/other indication
 Primary lesion evaluation
Laterality: Right/left
 Tumor size
Skin thickening: present absent
Nipple retraction: present absent
Chest wall invasion: present absent
Axillary nodes: present absent
 If present, number and size of largest
 Internal mammary nodes: present absent
 If present, number and size of largest
Supraclavicular nodes: present absent
 If present, number and size of largest
Contralateral breast: unremarkable
Contralateral axilla: unremarkable
 Metastatic disease evaluation:
 Mediastinal nodes:
 Lungs:
 Pleura:
 Heart and mediastinal great vessels:
 Liver:
 Adrenals:
 Gall bladder:
 Pancreas:
 Spleen:
 Kidneys:
 Bowel:
 Peritoneum:
 Urinary bladder:
 Uterus:
 Ovaries:
 Retroperitoneal and pelvic adenopathy
 Free fluid:
 Major vessels:
 Visualized bones:
 Any other finding:
 Impression:

Synoptic reports for FDG PETCT:

Component of report	Description
Clinical history	Age of patient
	Type of cancer – histology, receptor status
	Indication – staging, restaging, treatment response
	Surgical status – preoperative staging/postoperative staging
	Histopathology (if operated) – primary, nodal status, receptor status,
	Treatment received (if restaging, treatment response)
Procedure followed	Dose of ¹⁸ F FDG injected
	Uptake time (post injection waiting before acquisition – anywhere between 45 minute–70 minute)
	Region imaged – whole body (base skull to mid-thigh, head to mid-thigh, head to toe) Only regional – liver, thorax

(Continued)

(Continued)

	Acquisition – with contrast CT or non-contrast CT, oral contrast given
	Any specific change in acquisition – prone, sideways, propped up
	Need for any medication/interventions – Anesthesia, β blockers
Findings	FDG uptake: Primary: Uptake in the region of breast – affected side • Focal uptakes in nodule (preoperative) or diffuse uptake without obvious mass lesion. • Multiplicity. • Overlying skin thickening – presence or absence. • Extension of lesion into underlying tissue – muscle, chest wall, rib. • Lateral or medial extent.
	Contra lateral breast uptake – if abnormal (describe as above)
	Nodes: Ipsilateral axilla Ipsilateral internal mammary Ipsilateral supraclavicular Cervical nodes Contra lateral internal mammary Contra lateral internal mammary Contra lateral axillary Other nodal site: Mediastinal Abdominal Pelvic
	Metastases: Lung nodules – size, well defined, multiplicity Liver – segment/lobes Bones – marrow, cortical • Lytic, sclerotic, mixed
Comparison	With previous FDG PETCT/any anatomical imaging. • Mention date • Change in size • Change in FDG uptake • New lesion
Impression	• Summarize findings to suggest presence of absence of disease if possible. • If not possible to confidentially suggest presence of disease, provide differentials. • Help direct toward additional procedure if needed to arrive at a diagnosis. • Suggestion for timings of follow up if indicated.

Imaging Recommendations for Diagnosis, Staging, and Management of Esophageal Cancer

Nivedita Chakrabarty¹ Abhishek Mahajan² Prachi Patil³ Manoranjan Chowhan⁴
Naveen Munmmudi⁵ Devayani Niyogi⁶ Deepak Dabkara⁷ Suryaveer Singh¹ Ajaykumar Singh⁸
Sanjana Devarmani¹ Varun Singh Dhull⁴ Kumar Prabhaskh⁸

¹ Department of Radiodiagnosis, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Tata Memorial Hospital, Mumbai, Maharashtra, India

² Department of Radiodiagnosis, The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, United Kingdom

³ Department of Digestive Diseases and Clinical Nutrition, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Tata Memorial Hospital, Mumbai, Maharashtra, India

⁴ Department of Nuclear Medicine and PET/CT, Aditya Birla Memorial Hospital, Pune, Maharashtra, India

⁵ Department of Radiation Oncology, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Tata Memorial Hospital, Mumbai, Maharashtra, India

⁶ Department of Surgical Oncology, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Tata Memorial Hospital, Mumbai, Maharashtra, India

⁷ Department of Oncology, CHL Hospitals, Indore, Madhya Pradesh, India

⁸ Department of Medical Oncology, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Tata Memorial Hospital, Mumbai, Maharashtra, India

Address for correspondence Abhishek Mahajan, MD, Fellowship in Cancer Imaging, MRes (KCL, London), FRCR (UK), Department of Radiodiagnosis, The Clatterbridge Cancer Centre NHS Foundation Trust, Pembroke Place Liverpool, Liverpool L7 8YA, United Kingdom (e-mail: drabhishek.mahajan@yahoo.in).

Ind J Med Paediatr Oncol 2023;44:229–240.

Abstract

Early staging and treatment initiation affect prognosis of patients with esophageal and esophagogastric junction cancer; hence, it is imperative to have knowledge of proper choice of imaging modality for staging of these patients, to effectively convey relevant imaging findings to the treating physician/surgeon. It is also essential to be aware of pertinent imaging findings that need to be conveyed to the treating physician/surgeon at staging, and after treatment, including post-therapy complications (if any), so as to provide timely management to such patients. In this article, we have provided imaging guidelines for diagnosis, staging, post-therapy response evaluation, follow-up, and assessment of post-therapy complications of esophageal and esophagogastric junction cancer in a systematic manner. Besides, risk factors and clinical workup have also been elucidated. We have also attached comprehensive staging and post-therapy contrast-enhanced computed tomography and fluorodeoxyglucose-positron emission tomography/computed tomography-based synoptic reporting formats “ECI-RADS” and “pECI-RADS,” respectively, for esophageal and esophagogastric junction cancer in the supplement, for effective communication of imaging findings between a radiologist and the treating physician/surgeon.

Keywords

- esophageal cancer
- imaging guidelines
- staging
- post-therapy
- synoptic reporting formats

DOI <https://doi.org/10.1055/s-0042-1760324>.
ISSN 0971-5851.

© 2023. The Author(s).
This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)
Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Esophageal cancer (EC) is the seventh most common cancer in the world (GLOBOCAN 2020).^{1,2} As per American Joint Committee on Cancer (AJCC), ECs have been divided into those located in the cervical, upper thoracic, middle thoracic, and lower thoracic esophagus (including the esophagogastric junction and up to 2 cm of gastric cardia).^{3,4} Squamous cell carcinoma (SCC) is the predominant EC subtype usually seen in the middle third and lower third of esophagus, while most of the adenocarcinomas (ACs) occur in the distal esophagus.^{3,5} Two to ten percent of all the cancers are located in the cervical esophagus and are of SCC subtype.^{6,7}

Risk Factors and Etiopathogenesis

Major risk factors for SCC include tobacco chewing and smoking and alcohol consumption. Achalasia and consumption of hot beverages are other predisposing factors. Main risk factors for AC include gastroesophageal reflux disease, Barrett's esophagus, obesity, and tobacco. Poor nutrition, mineral and vitamin deficiencies due to low intake of fruits and vegetables, radiotherapy for thoracic malignancies, and caustic ingestion predispose to both SCC and AC.^{8–10} Various somatic mutations implicated in the pathogenesis of EC have been identified, and most notable of them being mutations of TP53, a major tumor-suppressor gene, and PIK3CA.¹⁰

Epidemiology and Clinical Presentation

EC peaks in the seventh and eighth decades with 70% cases occurring in men.^{1,11} In the West, the incidence of SCC has declined, with AC now being the dominant subtype.¹² As per GLOBOCAN 2020 data, EC is the fifth most common cancer in terms of incidence and mortality in India, and ranks seventh and sixth, respectively, in terms of incidence and mortality worldwide.^{13,14} Patients are asymptomatic in early stages, in advanced stage, present with progressive dysphagia (solids then liquids), weight loss, hematemesis, melena, and hoarseness from recurrent laryngeal nerve involvement.¹⁵

Imaging Referral Guidelines

National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology, AJCC, National Cancer Grid, and Indian College of Radiology and Imaging (ICRI) recommend endoscopic ultrasound (EUS) and contrast-enhanced computed tomography (CECT) with oral contrast for locoregional staging and fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) for distant metastatic workup.^{4,16–19} ICRI specifically recommends the use of EUS only in early stage primary tumor evaluation of the middle third EC.¹⁹ In addition, American College of Radiology recommends the use of single water-soluble contrast esophagogram on fluoroscopy in the immediate postoperative period to detect fistula or leaks, and suggests CT scan for negative esophagogram when clinical suspicion is high.²⁰ Imaging-based clinical (cTNM) staging proposed by 8th edition AJCC is followed for esophagus and gastroesophageal junction (GEJ) epithelial cancers.⁴ ▶Fig. 1 shows the NCCN imaging algorithm and ▶Table 1 shows the 8th edition AJCC staging for EC.^{4,16}

EUS can differentiate the various layers of esophageal wall and has a sensitivity of 92 and 82%, respectively, for cT4 tumors and cT1 tumors.^{16,21} CECT best detects invasion of adjacent structures (pleura, pericardium, azygous vein, diaphragm, peritoneum, aorta, trachea, and vertebra).^{2,21,22} CT has a low accuracy for N staging showing a sensitivity of 30 to 60%, specificity of 60 to 80%, and accuracy 27 to 86% for lymph node more than 1cm.²¹ Whereas the sensitivity of PET/CT for detection of locoregional nodal involvement is also low (51%).¹⁶ EUS has a better sensitivity of 85% than either CT or PET/CT for the detection of nodal involvement.¹⁶ Metastasis that is occult on CT can be detected on FDG-PET/CT.¹⁶ PET/CT has a sensitivity and specificity of 69 and 93%, respectively, for M stage.⁴

Clinical/Diagnostic Workup (Excluding Imaging)

All patients should have a thorough history and clinical examination with particular reference to weight loss. Grade III/IV dysphagia points toward bulky primary and probably

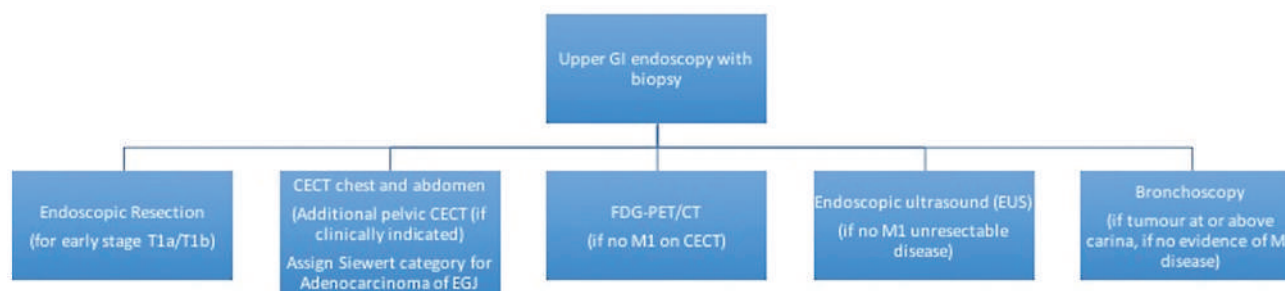


Fig. 1 Imaging guidelines for esophageal and esophagogastric junction tumors (adapted from NCCN guidelines version 2.2022).¹⁶ CECT, contrast-enhanced computed tomography; FDG-PET/CT, fluorodeoxyglucose-positron emission tomography/computed tomography; GI, gastrointestinal.

Table 1 The American Joint Committee on Cancer tumor-node-metastasis staging categories of esophagus and esophagogastric junction (8th edition)

Category	Criteria
T category	
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades the lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Tumor invades other adjacent structures, such as aorta, vertebral body, or trachea
N category	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
M category	
M0	No distant metastasis
M1	Distant metastasis

T3/T4 stage. Upper gastrointestinal (GI) endoscopy with multiple biopsies is required to have sufficient tissue for histopathological examination and biomarker testing.²³ Differentiation between squamous and AC histology has prognostic and therapeutic implication.²⁴ In case of esophageal SCC, ear nose throat (ENT) examination to evaluate oral cavity, oropharynx, and hypopharynx should be done by an ENT specialist. In case of tumors located at or above tracheal bifurcation, a tracheobronchoscopy should be done to rule out tracheal invasion and a synchronous cancer in aerodigestive tract.¹⁷

In locally advanced AC of GEJ, approximately 15% patients have peritoneal metastasis. Laparoscopy is advised in locally advanced GEJ AC to prevent futile surgeries.²⁵ For patients with metastatic disease, human epidermal growth factor receptor 2 testing by immunohistochemistry or fluorescence in situ hybridization for AC, mismatch repair deficiency/microsatellite instability, program death-ligand 1 (PD-L1) expression, and neurotrophic-tropomyosin receptor kinase fusion are advised to decide for targeted therapy/immunotherapy.²⁶

Imaging Guidelines

a) Screening: Routine screening for EC is not recommended.

b) Diagnosis: Upper GI endoscopy-guided biopsy is used for the diagnosis of primary tumor.²³ There are two types

of echoendoscopes available: radial and linear array. EUS using linear array echoendoscopes have a limited field but have the important ability to visualize a needle in real time and hence are used for tissue sampling. Endoscopy also helps in guiding nasogastric tube insertion for feeding when needed. In patients having clinically palpable and significant appearing supraclavicular node or liver metastasis, tissue diagnosis can be obtained from node or liver metastasis, when planned for palliative therapy.

c) Staging

Role of EUS

On EUS, five layers of the esophageal wall described are layer 1 (hyperechoic) superficial mucosa, layer 2 (hypoechoic) deep mucosa, layer 3 (hyperechoic) submucosa, layer 4 (hypoechoic) muscularis propria, and layer 5 (hyperechoic) adventitia. Tumors appear as hypoechoic lesions involving the wall layers, and malignant lymph nodes are typically seen in the vicinity of the tumor, appearing hypoechoic and round with smooth borders, and may be more than 10 mm in size.²⁷ The standard 7.5 to 12 MHz frequency transducers do not have adequate resolution to accurately “T” stage very early stage disease with mucosal involvement or superficial submucosal involvement, and a 20 MHz radial mini-probe may be needed for scanning in such cases. The accuracy of EUS

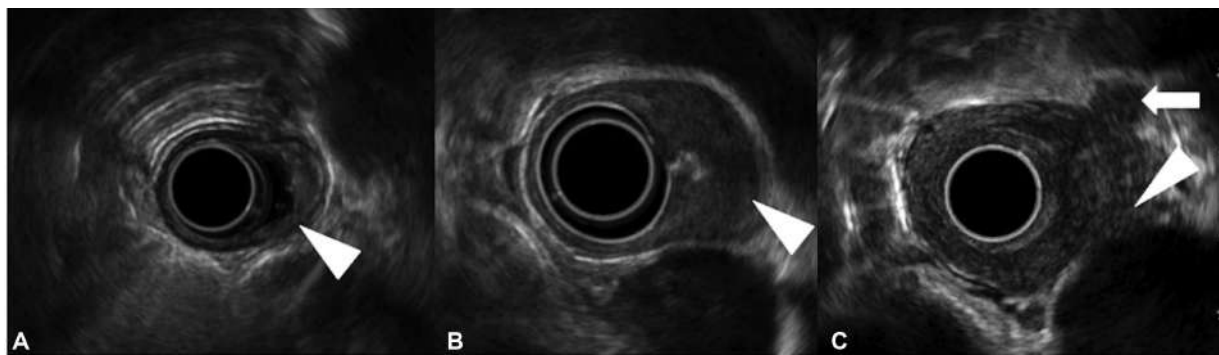


Fig. 2 Staging of esophageal cancer on endoscopic ultrasonography. (A) T1 tumor invading the submucosa (arrowhead). (B) T2 tumor invading the muscularis propria (arrowhead). (C) T4 tumor involving the aorta (arrowhead). A malignant regional lymph node is also seen (arrow).

increases with increasing T stage. EUS can be performed in patients with early-stage EC prior to endoscopic resection (ER) or in patients planned for upfront surgery, mainly to rule out lymph-node metastases in selected high-risk cases. Although EUS is the only modality for distinguishing different layers of esophageal wall, ER is more accurate than EUS for the staging of T1a/T1b EC and may also be therapeutic in some cases.¹⁶ When high-definition white-light or image-enhanced endoscopy is suggestive of a small nodular lesion with high grade dysplasia or early-stage EC, a staging ER is encouraged.^{16,28} An EUS-guided fine-needle aspiration can be performed for suspicious lymph nodes if they can be sampled without traversing the tumor or major blood vessels and if the result will change management.¹⁶ Most patients with stenotic tumors are likely to have locally advanced disease where an EUS may be unnecessary.²⁹ If at all an EUS is indicated in stenotic tumors, a smaller caliber wire-guided probe or mini-probe can be used; however, availability and cost may be an issue. ► **Fig. 2(A–C)** shows EC staging on EUS with malignant regional node.

Role of CT

CECT thorax and abdomen with oral contrast is recommended for EC staging. CT of the pelvic region should be included for esophagogastric junction tumors or if clinically indicated. Upper third EC including cervical EC requires additional evaluation with CECT neck. CT thorax protocol for EC is shown in ► **Table 2**.¹⁹

On CECT, differentiation of T1 and T2 is not possible.^{21,22} T3 stage on CT presents as mural thickening (> 3mm) and periesophageal fat infiltration without any loss of fat plane/invasion of adjacent structures.² CT

most accurately provides the craniocaudal length of the tumor (along with the corresponding vertebral level) that is essential for deciding upon the surgical resection margins.^{2,3} CT plays a significant role in T4 staging of tumor. Involvement of pleura, pericardium, azygous vein, diaphragm, or peritoneum (for esophagogastric junction EC) is considered as T4a stage, whereas, aorta, vertebral body, or tracheal involvement upgrades the lesion to T4b stage.^{2,4} Specific signs of tracheobronchial involvement by EC on CT are fistula formation with the airway, intraluminal extension of tumor within the airway, and tracheobronchial mural thickening.^{3,22} Focal loss of fat plane of the EC with the airway with preserved fat planes proximal and distal to it also likely suggests tracheobronchial involvement.²² More than 90-degree contact of EC with aorta, loss of triangular fat between esophagus, aorta, and spine, suggests aortic involvement on CECT.^{2,3,22} Pericardial involvement may be suggested by pericardial thickening/effusion.^{3,22} CECT helps in assigning Siewert category to esophagogastric junction AC tumors that have management and prognostic implications.¹⁶ Besides, CECT is important for the detection of metastasis to liver and lungs.²² ► **Fig. 3 (A–E)** shows EC staging on CECT.

Role of FDG-PET/CT

Following intravenous injection of 18F-FDG-PET-CT images are acquired from skull base to mid-thigh. Both oral and intravenous contrast is used for the acquisition of CT images. The predominant role of FDG-PET/CT is to detect distant metastases including metastasis to bones and distant nodal metastasis when no metastasis is detected on CECT scan.¹⁶ PET-CT is the modality of choice

Table 2 CT thorax protocol for EC

Modality	Typical protocol
CT thorax	-Noncontrast and CECT are performed -On table positive oral contrast (500 mL water + 30 mL nonionic contrast), or plain water, to distend the esophagus. -For CECT, 100 cc of intravenous nonionic contrast (300 mg iodine per mL) at 2.5–3 mL/sec

Abbreviations: CECT, contrast-enhanced computed tomography; EC, esophageal cancer.

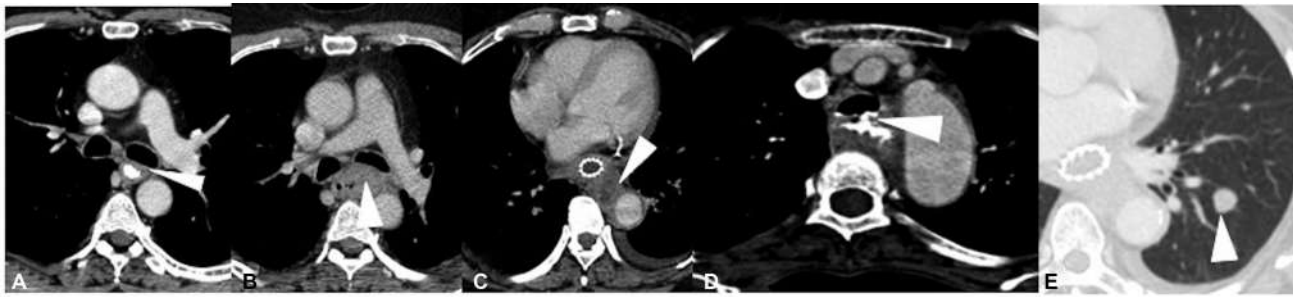


Fig. 3 Esophageal carcinoma staging on axial contrast-enhanced computed tomography. (A) Mild asymmetric mid-esophageal wall thickening (arrowhead), with no peri-adventitial infiltration and maintained fat planes with the adjacent structures (T2). (B) Mid-esophageal growth with periadventitial fat infiltration (T3) without any tracheobronchial or aortic invasion. The mass is seen to indent upon posterior wall of left mainstem bronchus (arrowhead); however, invasion was ruled out by bronchoscopy. (C) More than 90-degree arc of contact between the esophageal mass and aorta with involvement of aortic wall (arrowhead), along with soft tissue extension into the triangular fat pad indicating aortic invasion (T4b). (D) Irregular circumferential thickening involving the upper thoracic esophagus with frank fistulous communication with the tracheal lumen (arrowhead), and passage of oral positive contrast into the trachea (T4b). (E) Well defined left lower lobe nodule (arrowhead) on lung window, in a case of esophageal cancer, suggestive of lung metastasis (M1).

to diagnose occult metastasis to various organs that thus help in avoiding futile surgeries.^{30–32} Besides, PET-CT is also useful to detect second primary tumor and studies have indicated that FDG-PET/CT is superior to conventional anatomical imaging to evaluate synchronous tumors (especially head and neck cancers and colon neoplasm) during primary staging of esophageal SCC.³³ PET/CT also plays an important role in radiation therapy treatment planning of EC.^{34,35} PET-CT-based intensity-modulated radiation therapy offers several advantages that includes (1) dose escalation to target (tumor), (2) minimizes dose delivery to normal tissue, (3) decrease acute toxicity, (4) lessens long-term toxicity by optimizing treatment delivery to target tissue, thereby achieving better therapy outcome. ►**Fig. 4 (A and B)** shows EC staging on FDG-PET/CT.

Role of Other Modalities

Magnetic resonance imaging (MRI) plays a pertinent role in detecting the status of spinal cord, when there is

intraspinal extension of the tumor with involvement of vertebrae. Also, when there is doubt on CT regarding pericardial and aortic wall involvement, MRI can come to the rescue. One of the studies has shown that PET-MR has comparable sensitivity with EUS in staging primary esophageal involvement, and offers higher diagnostic accuracy compared with EUS and PET/CT.³⁶ However, due to limited availability and cost factor, PET-MR is not routinely used.

►**Table 3** enlists the role of each modality in staging of EC.^{2–4,16,22,30–32}

d) Response Assessment

A retrospective multicenter study demonstrated that use of short axis diameter (instead of the usual longest diameter) in the Response Evaluation Criteria in Solid Tumors (RECIST) for EC after neoadjuvant chemotherapy correlates well with pathological response and is significantly associated with survival.³⁷ On comparison with

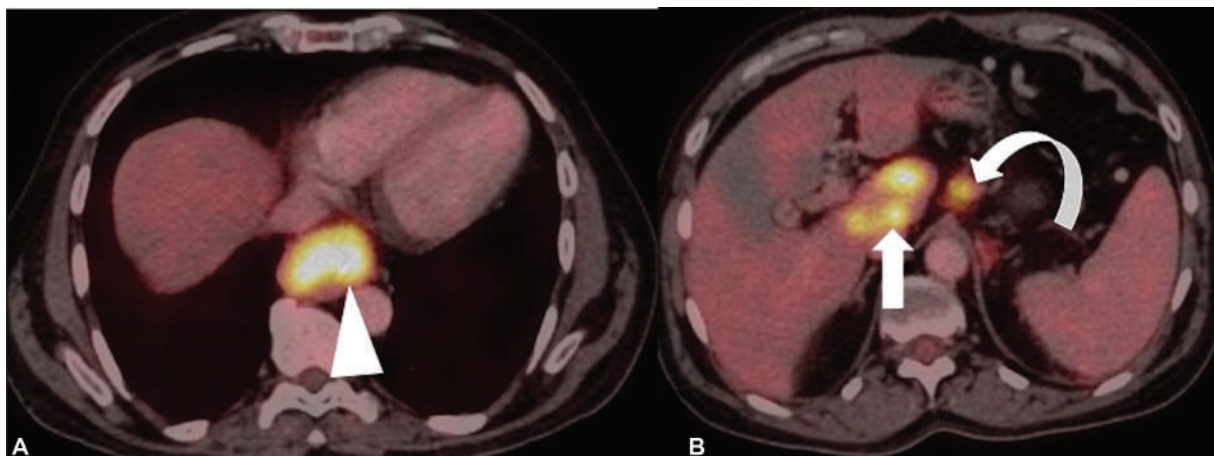


Fig. 4 (A and B) Staging of esophageal cancer on fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) images reveals moderately FDG-avid primary esophageal mass lesion (arrowhead) with extensive FDG-avid metastatic abdominal nodes (curved arrow) and multifocal hypermetabolic hepatic (metastatic) lesions (arrow) implying M1 stage.

Table 3 Role of various modalities in staging of EC^{2-4,16,22,30-32}

Modality	Role in staging
Endoscopic resection	-Differentiating T1a from T1b -Biopsy from lesion
EUS	-T staging -N staging -EUS-guided FNA of regional nodes
CECT thorax and abdomen with oral contrast -Additional CECT neck if upper third (including cervical) EC -Additional CECT pelvis (if pelvic symptoms or EGJ tumors)	-T3 stage -T4a and T4b stages -Craniocaudal dimension of the tumor -Helps to assign Siewert category for adenocarcinoma of EGJ as follows: a. Siewert type I: tumor epicenter within 1 to 5 cm above EGJ b. Siewert type II: tumor epicenter within 1 cm above and 2 cm below EGJ c. Siewert type III: tumor epicenter between 2 and 5 cm below EGJ (included under gastric carcinoma) -Metastasis to liver and lungs
FDG-PET/CT	-Distant metastasis (including bone and distant nodal metastasis) when CECT is negative for metastasis -Occult metastasis to various organs -Synchronous tumors
MRI	-Status of spinal cord in case of intraspinal extension of the tumor with involvement of vertebrae. -Pericardial involvement when doubtful on CT -Aortic involvement when doubtful on CT

Abbreviations: CECT, contrast-enhanced computed tomography; EC, esophageal cancer; EGJ, esophagogastric junction; EUS, endoscopic ultrasound; FDG-PET/CT, fluorodeoxyglucose-positron emission tomography/computed tomography; MRI, magnetic resonance imaging.

pre-therapy CECT, new onset enhancing mural thickening anywhere in esophagus, significant increase in lymph nodal size as per RECIST or new onset metastatic lesions, all are suggestive of disease progression on CECT. FDG-PET/CT parameters like maximum standard uptake value (SUVmax) or metabolic tumor volume (MTV), aid in predicting prognosis and response assessment of patients treated after concurrent chemoradiation therapy.³⁸ Im-

mune-modified Response Evaluation Criteria in Solid Tumors (iRECIST) is used for assessing response in advanced EC receiving immunotherapy to take into account the phenomenon of pseudoprogression.^{39,40}

► **Fig. 5 (A and B)** shows pre-treatment and post-radiotherapy response on PET/CT. ► **Table 4** shows post-therapy response evaluation for EC.^{37,38}

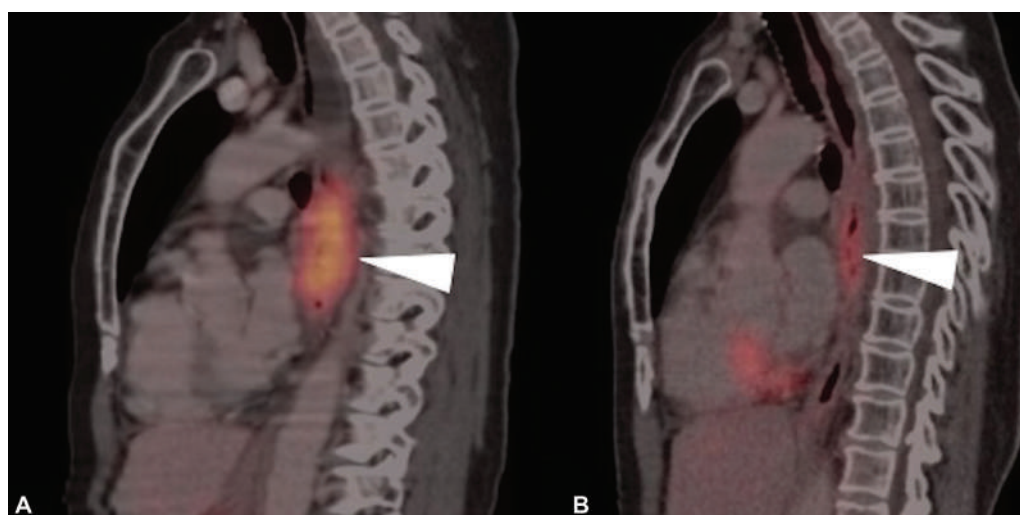


Fig. 5 (A and B) Fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) images of a 50-year-old patient diagnosed as metastatic carcinoma esophagus treated with radiotherapy (RT). (A) Sagittal pretreatment PET/CT image depicts the metabolically active primary neoplastic mass lesion (arrowhead). (B) Sagittal post therapy PET/CT image after 3 months of RT reveals significant reduction in metabolic activity of primary lesion, suggestive of significant metabolic remission.

Table 4 Post-therapy response assessment for EC

Modality	Response assessment after therapy
CECT	$\geq 30\%$ decrease in esophageal mural thickening (short axis) or the lymph node (short axis), post-therapy suggests partial response $\geq 20\%$ increase in esophageal mural thickening (short axis) or the lymph node (short axis), post-therapy suggests disease progression
FDG-PET/CT	SUVmax and MTV after concurrent chemoradiation therapy help in assessing response as well as prognosis. No definite cutoff value has been mentioned

Abbreviations: CECT, contrast-enhanced computed tomography; EC, esophageal cancer; FDG-PET/CT, fluorodeoxyglucose-positron emission tomography/computed tomography; MTV, metabolic tumor volume; SUVmax, maximum standard uptake value.

Table 5 Guidelines on follow-up of EC patients

Follow-up method	Frequency
CECT thorax and abdomen	- First 2 years: Every 6 months 2–5 years: Annual - After 5 years: Only if indicated
Upper GI endoscopy	- At 3 months 1 year - Then 3 yearly
Clinical (history and physical examination)	- First 2 years: 3 monthly 2–5 years: 6 monthly - After 5 years: Annual

Abbreviations: CECT, contrast-enhanced computed tomography; EC, esophageal cancer; GI, gastrointestinal.

bimodality therapy (definitive chemoradiotherapy) and first 3 years after trimodality therapy (chemoradiotherapy and surgery).⁴¹ There are no well-established guidelines for follow-up; however, CT scan of chest and abdomen with contrast is recommended every 6 months for first 2 years at least.¹⁶ Along with this, 3 monthly follow-up with history and physical examination, upper GI tract endoscopy at 3 months, followed by at 1 year, and then every 3 yearly are recommended. From 2 to 5 years, follow-up can be 6 monthly (clinical) with annual imaging, and after 5 years annual clinical follow-up with imaging only if indicated clinically.¹⁷ ▶Table 5 shows the follow-up guidelines for EC.^{16,17}

e) Follow-Up

In the post-treatment setting, most of the recurrences (95%) are known to occur within the first 2 years after

Principles of Management

For mucosal tumors, treatment options include ER and/or ablation (high-grade dysplasia, AC limited to mucosa, small

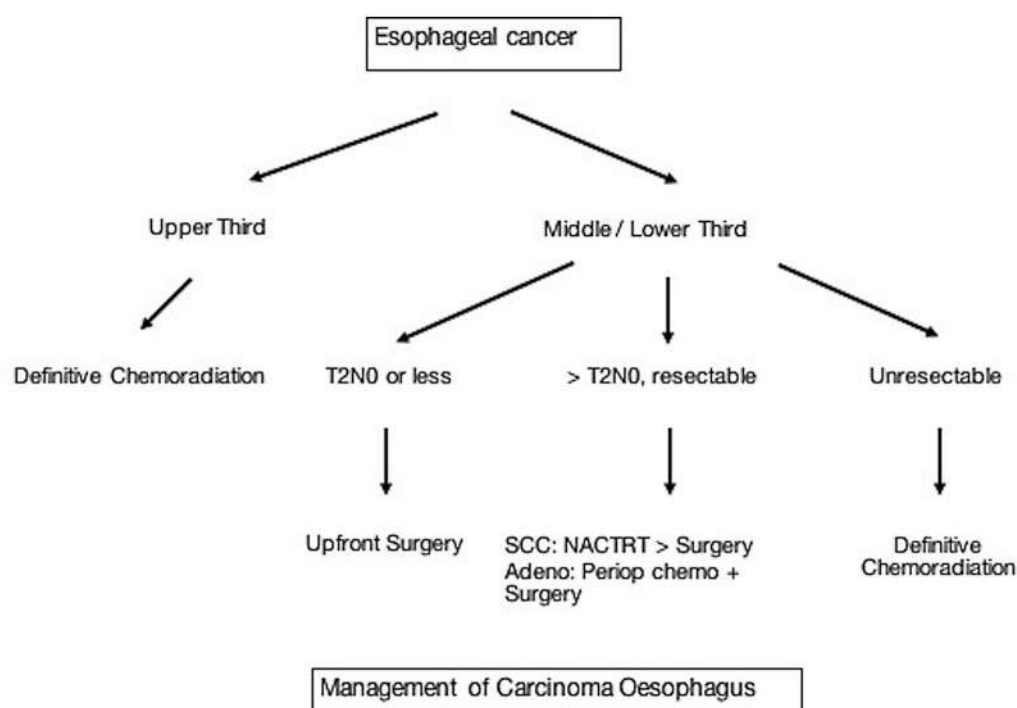


Fig. 6 Algorithm for the management of esophageal carcinoma. NACTRT, neoadjuvant chemoradiotherapy; Periop, perioperative; SCC: Squamous cell carcinoma.

Table 6 Location/stage-wise treatment of esophageal cancer

Location/stage of EC	Treatment
Upper third EC (including cervical)	Definitive chemoradiation
Tis, T1a	Endoscopic mucosal resection
Middle and lower third T1b, T2N0 or less	Upfront surgery
Middle and lower third localized disease greater than T3N0	NACTRT with CROSS protocol for SCC and perioperative chemotherapy with FLOT regimen for AC
T4b stage	Definitive chemoradiation
Involvement of trachea, great vessels, vertebra or heart	Palliative chemotherapy
Metastatic disease	Systemic therapy (chemotherapy and/or immunotherapy)

Abbreviations: EC: Esophageal cancer, NACTRT: neoadjuvant chemoradiotherapy, SCC: Squamous cell carcinoma, FLOT: Fluorouracil, Leucovorin, Oxaliplatin, Docetaxel, AC: Adenocarcinoma

Synoptic reporting format 1

Staging (pre-treatment) Esophageal and esophagogastric junction Cancer Imaging - Reporting and Data System (ECI-RADS) based on CECT or FDG-PET/CT

Demographics (Information provided by RIS and DICOM headers)

Name of the facility where examination was provided

- Name of the patient
 - Patient's gender
 - Patient's date of birth and age
 - Name(s) of referring physician(s) or other health care provider(s)
 - Name of type of examination
 - Date and time of the examination
 - Date and time of dictation and final transcription
- Relevant clinical information
- Clinical symptoms
 - Addictions – Smoking/Alcohol/ Chewing tobacco
 - Co-existing health morbidities – Gastroesophageal reflux disease (GERD)/achalasia/ H. pylori status/COPD/ Diabetes Mellitus/ Immunocompromised status
 - Occupational history for any relevant occupational exposures
 - Previous cancer
 - Previous surgery
 - Previous chemotherapy or radiation
 - Endoscopy findings (if done): distance of tumor from incisors, proximal and distal tumor extent, luminal obstruction, Barrett's esophagus
 - Endoscopic ultrasound findings (if done): T staging, regional nodal status
 - Current working diagnoses (if any)
 - Recent most relevant laboratory tests including biomarkers (if available):

Body of the report:

- Type of study and the technical protocol
- Quality of examination

T Category

Esophagus

Location/epicenter: Cervical/upper third thoracic/middle third thoracic/lower third thoracic including esophagogastric junction

Size: Thickness* and craniocaudal dimension (including vertebral levels)

SUVmax (FDG-PET/CT):

Luminal obstruction: Present/Absent

Local invasion: Present/absent

Local invasion (for cervical esophageal cancer): Larynx, hypopharynx, thyroid gland, vertebrae

Local invasion (T4a) (for thoracic esophagus and esophagogastric junction cancer)

Pleura: Involved/indeterminate/uninvolved

Pericardium[§]: Involved/indeterminate/uninvolved

Azygous vein: Involved/indeterminate/uninvolved

Peritoneum (for esophagogastric junction): Involved/indeterminate/uninvolved

Diaphragm: Involved/indeterminate/uninvolved

Local invasion (T4b)

Aorta[§]:

Loss of fat plane: Yes/no

Angle of contact: $\leq 90^\circ$ / $> 90^\circ$ degree

Involved/indeterminate/uninvolved

Vertebra[§]:

Involved/indeterminate/uninvolved

Trachea/bronchus:

Abutment/mass within airway lumen/fistula formation with airway

Involved/indeterminate/uninvolved

Siewert type (for esophagogastric junction tumors): I/II/III

N Category

Nodes:

Number of regional nodes (if involved): 1–2/ 3–6/ 7 or more

Size and station of node (if involved):

SUVmax (FDG-PET/CT):

Involved/indeterminate/uninvolved #

M Category

Distant metastasis:

Site:

SUVmax (FDG-PET/CT):

Other findings

Synchronous tumor: Yes/ No

Any other finding:

*Needs additional imaging: EUS

\$ Needs additional imaging: MRI

Needs FNAC correlation

Synoptic reporting format 2

Post-therapy Esophageal and esophagogastric junction Cancer Imaging - Reporting and Data System (pECI-RADS) based on CECT or FDG-PET/CT

Demographics (information provided by RIS and DICOM headers)

Name of the facility where examination was provided

a. Name of the patient

b. Patient's gender

c. Patient's date of birth and age

d. Name(s) of referring physician(s) or other health care provider(s)

e. Name of type of examination

f. Date and time of the examination

g. Date and time of dictation and final transcription

Relevant clinical information

a. Clinical symptoms

d. Recent most relevant laboratory tests and/or imaging findings

Indication: [Post surgery/ post neoadjuvant chemotherapy/chemoradiotherapy/post definitive radiotherapy]

Body of the report:

a. Type of study and the technical protocol

b. Quality of examination

c. Comparison to previous study and date

Findings:

1. No evidence of residual disease/recurrence

2. No evidence of residual pathological lymph nodes/no new pathological lymph nodes.

3. Post-treatment changes are noted including:

[a] Post-surgery anastomotic stricture/leak: Yes/no

[b] Post-RT mucosal edema/stricture/pneumonitis: Yes/no

4. There are no findings to suggest a second primary in the oropharynx/head and neck/lungs

5. Evaluation of the visualized portions of liver, adrenals, lungs and bones show no aggressive lesions suspicious for metastatic involvement.

IMPRESSION:

1. Expected post treatment changes

2. Category of disease*.

***CECT or FDG-PET/CT Surveillance Legend:**

Category 1: No evidence of residual disease/recurrence.

Category 2: Low volume residual disease/low suspicion of recurrence.

SUVmax on FDG-PET/CT:

Category 3: High volume residual disease/ high suspicion of recurrence

SUVmax on FDG-PET/CT:

Category 4: No change in tumor volume/definitive recurrence

SUVmax on FDG-PET/CT:

Synoptic reporting format 3

Endoscopic ultrasound reporting format for esophageal cancer

- Tumor—T stage, maximal tumor thickness (mm)
- Nodes—Size, echogenicity, shape, borders, location, N stage, whether FNAC done
- Metastases (if seen)
- Incomplete staging due to stenotic tumors (when present)

Abbreviations: CECT, contrast enhanced computed tomography; COPD, chronic obstructive pulmonary disease; DICOM, digital imaging and communications in medicine; EUS, endoscopic ultrasonography; FDG-PET/CT, fluorodeoxyglucose positron emission tomography computed tomography; FNAC, fine-needle aspiration cytology; MRI, magnetic resonance imaging; RIS, radiology information system; SUVmax, maximum standardized uptake value.

tumor [$<2\text{cm}$] that are asymptomatic and non-circumferential).⁴² Upper third EC are best treated with definitive chemoradiation (CTRT). In middle and lower third, patients with T2N0 or less may be operated upfront without any neoadjuvant therapy.¹⁶ Any localized disease greater than T3N0 mandates neoadjuvant therapy despite being upfront resectable. As of today, the best evidence is for neoadjuvant chemoradiotherapy (NACTRT) with CROSS protocol for SCC and perioperative chemotherapy with Fluorouracil, Leucovorin, Oxaliplatin, Docetaxel (FLOT) regimen for AC.⁴³

For early-stage resectable tumors, either transhiatal or transthoracic (Ivor-Lewis) total esophagectomy or extended-3 field lymphadenectomy is performed depending upon the location or extent of tumor.⁴⁴ CTRT is given for T4b stage, except when trachea, great vessels, vertebra or heart, are involved, in which case, palliative chemotherapy is the only option. Depending on HER 2 overexpression and PD-L1 expression, targeted therapy or immunotherapy respectively, are given.¹⁶

Overall EC is very aggressive disease with poor prognosis. Five-year overall survival for localized disease is 39 and 4% for metastatic disease. SCC histology has poor outcome as opposed to AC histology.⁴⁵ Nutritional rehabilitation and cardiopulmonary evaluation are vital components in the overall management of EC patients.

►Fig. 6 depicts an algorithm for the management of EC. Location/stage-wise treatment of EC is presented in ►Table 6.^{16,43}

Follow-Up Imaging and Management of Recurrent Disease

Anastomotic leak is suspected in presence of fever, tachycardia, tachypnea, or arrhythmia in immediate postoperative period. Also, a close watch needs to be kept on the neck wound (for erythema /swelling) and nature of drain output (bilious/

purulent) in the postoperative period. CECT detects immediate post-surgical complications like fistulization of neoesophagus with airway and anastomotic leaks, and is also useful for the detection of esophageal edema after definitive concurrent chemoradiotherapy.^{2,46} CECT thorax assists in diagnosis by showing oral contrast extravasation and or air fluid level in pleural/mediastinum. CECT thorax also helps in draining out the collection by guiding pigtail.

Esophagogram on fluoroscopy can also be used in the immediate postoperative period to detect fistula or leaks, and a negative test warrants CECT, if clinical suspicion is high.²⁰ Delayed post-therapy imaging includes detection of recurrence and post-surgery/RT stricture. ►Fig. 7 (A and B) CECT images show post-NACTRT stricture formation in mid-esophagus (in supplement). Mantziari et al found FDG-PET/CT parameters (SUVmax, total lesion glycolysis and MTV) to be quite useful in predicting tumor recurrence and disease-free survival in patients with EC.⁴⁷ CECT may show new onset enhancing esophageal mural thickening suggestive of recurrence. Post-RT esophageal stricture occurs 3 to 8 months later and can be seen as esophageal luminal narrowing with proximal dilatation and air-fluid levels.^{2,48}

Localized recurrences after surgery are best treated with CTRT. Residual or recurrent disease after CTRT is considered for salvage surgery. Various systemic therapy options exist for both histologies. For palliation of dysphagia, local radiation (external beam or brachytherapy), feeding procedures (nasojunal/gastric tube), or esophageal or airway stenting (for tracheobronchial infiltration) are feasible options.

Summary of Recommendations

1. Differentiation of T1a and T1b is best achieved by ER.¹⁶
2. EUS is the modality of choice for T staging of EC and for regional lymph node assessment.¹⁶

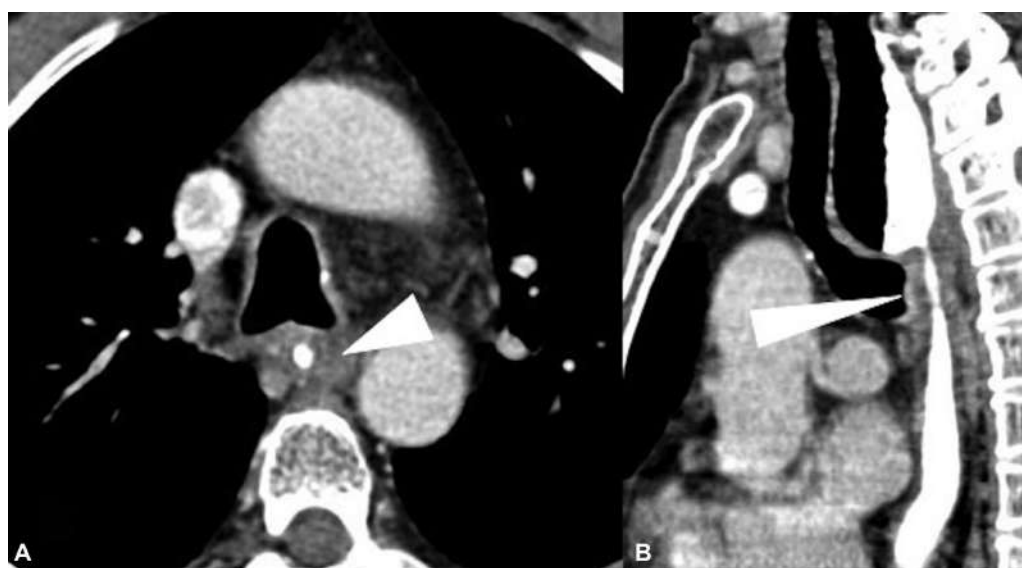


Fig. 7 (A and B) Case of squamous cell carcinoma of the middle third of the esophagus, postneoadjuvant chemoradiotherapy, presented with increasing dysphagia. Brush cytology was negative for malignancy. Axial (A) and sagittal (B) computed tomographic images show a short segment smooth circumferential wall thickening (arrowhead), with proximal esophageal dilatation.

3. Invasion of surrounding structures (T4 stage) is best depicted on CECT scan. Metastasis to liver and lungs and post-therapy complications are well visualized on CECT scan.^{2–4,22,46}
4. FDG-PET/CT is the modality of choice for detecting distant metastasis, occult metastasis, and synchronous tumors. Besides, detection of post-therapy recurrence and response evaluation is best achieved with FDG-PET/CT.^{16,30–33}

Synoptic reporting formats for pre-treatment (ECI-RADS) and post-therapy assessment (pECI-RADS),⁴⁹ along with EUS staging reporting format, are provided in the supplement.

The manuscript has been read and approved by all the authors and the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

Author's Contributions

Nivedita Chakrabarty was involved in conceptualization, designing, definition of intellectual content, literature search, manuscript preparation, manuscript editing, Abhishek Mahajan was involved in manuscript editing and review.. Kumar Prabhash, Prachi Patil, Manoranjan Chowhan, Naveen Munmmudi, Devayani Niyogi, Deepak Dabkara, Suryaveer Singh, Ajaykumar Singh, Sanjana Devarmani, and Varun Singh Dhull contributed to manuscript preparation.

Ethical Committee Clearance

Not required as patient data not revealed.

Conflicts of Interest

None declared.

References

- 1 Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71(03): 209–249
- 2 Jayaprakasam VS, Yeh R, Ku GY, et al. Role of imaging in esophageal cancer management in 2020: update for radiologists. *AJR Am J Roentgenol* 2020;215(05):1072–1084
- 3 Kim TJ, Kim HY, Lee KW, Kim MS. Multimodality assessment of esophageal cancer: preoperative staging and monitoring of response to therapy. *Radiographics* 2009;29(02):403–421
- 4 Rice TW, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. *Ann Cardiothorac Surg* 2017;6(02): 119–130
- 5 Daly JM, Fry WA, Little AG, et al. Esophageal cancer: results of an American College of Surgeons patient care evaluation study. *J Am Coll Surg* 2000;190(05):562–572, discussion 572–573
- 6 Hoebe A, Polak J, Van De Voorde L, Hoebers F, Grabsch HI, de Vos-Geelen J. Cervical esophageal cancer: a gap in cancer knowledge. *Ann Oncol* 2016;27(09):1664–1674
- 7 Lee DJ, Harris A, Gillette A, Munoz L, Kashima H. Carcinoma of the cervical esophagus: diagnosis, management, and results. *South Med J* 1984;77(11):1365–1367
- 8 Domper Arnal MJ, Ferrández Arenas Á, Lanás Arbeloa Á. Esophageal cancer: Risk factors, screening and endoscopic treatment in Western and Eastern countries. *World J Gastroenterol* 2015;21(26):7933–7943
- 9 Huang FL, Yu SJ. Esophageal cancer: Risk factors, genetic association, and treatment. *Asian J Surg* 2018;41(03):210–215
- 10 Watanabe M. Risk factors and molecular mechanisms of esophageal cancer: differences between the histologic subtypes. *J Cancer Metastasis Treat* 2015;1:1–7
- 11 Choksi D, Kolhe KM, Ingle M, et al. Esophageal carcinoma: an epidemiological analysis and study of the time trends over the last 20 years from a single center in India. *J Family Med Prim Care* 2020;9(03):1695–1699
- 12 Sekar A, Rajendra A, Noronha V, et al. The epidemiological trend of esophageal cancer in Mumbai, India over the past two decades. *Journal of Clinical Oncology* 2021;39(15_suppl):e16095–e16095
- 13 Accessed December 10, 2022, at: <https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf>
- 14 Accessed December 10, 2022, at: <https://gco.iarc.fr/today/data/factsheets/cancers/6-Oesophagus-fact-sheet.pdf>
- 15 Accessed December 10, 2022, at: <https://www.msmanuals.com/en-in/professional/gastrointestinal-disorders/tumors-of-the-gastrointestinal-tract/esophageal-cancer>
- 16 Accessed December 10, 2022, at: https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf
- 17 Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold DESMO Guidelines Committee. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016;27(suppl 5):v50–v57
- 18 Accessed December 10, 2022, at: https://tmc.gov.in/ngc/docs/PDF/DraftGuidelines/ThoacicGuidelinesAndResearch/NCG_Esophageal_Cancer_Guidelines.pdf
- 19 Accessed December 10, 2022, at: <https://iria.org.in/oncologic-imaging-protocols-and-reporting-checklist/>
- 20 Accessed December 10, 2022, at: <https://acsearch.acr.org/docs/69471/narrative/>
- 21 Elsherif SB, Andreou S, Virarkar M, et al. Role of precision imaging in esophageal cancer. *J Thorac Dis* 2020;12(09):5159–5176
- 22 Iyer R, Dubrow R. Imaging of esophageal cancer. *Cancer Imaging* 2004;4(02):125–132
- 23 Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003;349(23):2241–2252
- 24 Shah MA, Kennedy EB, Catenacci DV, et al. Treatment of locally advanced esophageal carcinoma: ASCO guideline. *J Clin Oncol* 2020;38(23):2677–2694
- 25 Convie L, Thompson RJ, Kennedy R, Clements WD, Carey PD, Kennedy JA. The current role of staging laparoscopy in oesophagogastric cancer. *Ann R Coll Surg Engl* 2015;97(02):146–150
- 26 Dhakras P, Uboha N, Horner V, Reinig E, Matkowskyj KA. Gastrointestinal cancers: current biomarkers in esophageal and gastric adenocarcinoma. *Transl Gastroenterol Hepatol* 2020;5:55
- 27 DaVee T, Ajani JA, Lee JH. Is endoscopic ultrasound examination necessary in the management of esophageal cancer? *World J Gastroenterol* 2017;23(05):751–762
- 28 Mannath J, Ragunath K. Role of endoscopy in early oesophageal cancer. *Nat Rev Gastroenterol Hepatol* 2016;13(12):720–730
- 29 Bang JY, Ramesh J, Hasan M, et al. Endoscopic ultrasonography is not required for staging malignant esophageal strictures that preclude the passage of a diagnostic gastroscope. *Dig Endosc* 2016;28(06):650–656
- 30 Erasmus JJ, Munden RF. The role of integrated computed tomography positron-emission tomography in esophageal cancer: staging and assessment of therapeutic response. *Semin Radiat Oncol* 2007;17(01):29–37 s.
- 31 Mamede M, Abreu-E-Lima P, Oliva MR, Nosé V, Mamon H, Gerbaudo VH. FDG-PET/CT tumor segmentation-derived indices of metabolic activity to assess response to neoadjuvant therapy and progression-free survival in esophageal cancer: correlation with histopathology results. *Am J Clin Oncol* 2007;30(04): 377–388

- 32 Rustgi AK, El-Serag HB. Esophageal Carcinoma. *New England Journal of Medicine* 2014;371(26):2499–2509
- 33 Chen SH, Chan SC, Chao YK, et al. Detection of synchronous cancer by flurodeoxy glucose positron emission tomography/CT during primary staging work up for esophageal squamous cell carcinoma in Taiwan. *PLoS One* 2013;8(11):e82812
- 34 Metzger JC, Wollschläger D, Miederer M, et al. Inclusion of PET-CT into planning of primary or neoadjuvant chemoradiotherapy of esophageal cancer improves prognosis. *Strahlenther Onkol* 2017;193(10):791–799
- 35 Zhong X, Yu J, Zhang B, et al. Using 18F-fluorodeoxyglucose positron emission tomography to estimate the length of gross tumor in patients with squamous cell carcinoma of the esophagus. *Int J Radiat Oncol Biol Phys* 2009;73(01):136–141
- 36 Lee G, Hoseok I, Seong-Jung K, et al. Clinical implication of PET-CT, MR in preoperative esophageal carcinoma staging compared with PETCT, EUS and CT. *JNM* 2014;55(08):1242–1247
- 37 Taniyama Y, Murakami K, Yoshida N, et al. Evaluating the effect of Neoadjuvant chemotherapy for esophageal cancer using the RECIST system with shorter-axis measurements: a retrospective multicenter study. *BMC Cancer* 2021;21(01):1008. Doi: 10.1186/s12885-021-08747-y
- 38 Lee S, Choi Y, Park G, et al. ¹⁸F-FDG PET/CT parameters for predicting prognosis in esophageal cancer patients treated with concurrent chemoradiotherapy. *Technol Cancer Res Treat* 2021Jan-Dec;20–15330338211024655
- 39 Hodi FS, Ballinger M, Lyons B, et al. Immune-modified response evaluation criteria in solid tumors (imRECIST): refining guidelines to assess the clinical benefit of cancer immunotherapy. *J Clin Oncol* 2018;36(09):850–858
- 40 Chakrabarty N, Mahajan A, Baheti AD, et al. A radiologist's perspective on treatment-related pseudo progression: clues and hues. *Indian J Med Paediatr Oncol* 2022;43(01):52–59
- 41 Sudo K, Xiao L, Wadhwa R, et al. Importance of surveillance and success of salvage strategies after definitive chemoradiation in patients with esophageal cancer. *J Clin Oncol* 2014;32(30):3400–3405
- 42 Malik S, Sharma G, Sanaka MR, Thota PN. Role of endoscopic therapy in early esophageal cancer. *World J Gastroenterol* 2018;24(35):3965–3973 cited 2022Mar2 [Internet]
- 43 Al-Batran SE, Homann N, Pauligk C, et al; FLOT4-AIO Investigators. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet* 2019;393(10184):1948–1957 cited 2022Feb11 [Internet]
- 44 Allum WH, Bonavina L, Cassivi SD, et al. Surgical treatments for esophageal cancers. *Ann N Y Acad Sci* 2014;1325(01):242–268 cited 2022Mar2 [Internet]
- 45 Cancer E. Statistics | Cancer.Net [Internet]. [cited 2022 Mar 2]. Accessed December 10, 2022, at: Available from: <https://www.cancer.net/cancer-types/esophageal-cancer/statistics>
- 46 Zeng C, Zhai T, Chen J, et al. Imaging biomarkers of contrast-enhanced computed tomography predict survival in oesophageal cancer after definitive concurrent chemoradiotherapy. *Radiat Oncol* 2021;16(01):8
- 47 Mantziari S, Pomoni A, Prior JO, et al. ¹⁸F- FDG PET/CT-derived parameters predict clinical stage and prognosis of esophageal cancer. *BMC Med Imaging* 2020;20(01):7
- 48 Park J-H, Kim KY, Song H-Y, et al. Radiation-induced esophageal strictures treated with fluoroscopic balloon dilation: clinical outcomes and factors influencing recurrence in 62 patients. *Acta Radiol* 2018;59(03):313–321
- 49 Chakrabarty N, Mahajan A. Esophageal cancer imaging - reporting and data system (ECI-RADS) and post-therapy ECI-RADS (pECI-RADS): Comprehensive synoptic reporting formats for esophageal cancer imaging: A narrative review. *Cancer Research, Statistics, and Treatment* 2022;5(03)

Imaging Recommendations for Diagnosis, Staging, and Management of Hepatic and Biliary Tract Cancer

Argha Chatterjee¹ Sumit Mukhopadhyay¹ Priya Ghosh¹ Diva Shah² Anisha Gehani¹
Akshay Baheti³ Bharat Gupta¹ Aditi Chandra¹ Arvind K. Chaturvedi⁴ Jeevitesh Khoda⁵
Anurima Patra¹ Dayananda Lingegowda¹ Saugata Sen¹

¹ Department of Radiology and Imaging Sciences, Tata Medical Center, Kolkata, West Bengal, India

² Department of Radiology, HCG Cancer Centre, Ahmedabad, Gujarat, India

³ Department of Radiodiagnosis, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, Maharashtra, India

⁴ Department of Radiology and Interventional Oncology, Rajiv Gandhi Cancer Institute and Research Center, New Delhi, India

⁵ Department of Radiology, Rajiv Gandhi Cancer Institute and Research Center, New Delhi, India

Address for correspondence Argha Chatterjee, MD, Department of Radiology and Imaging Sciences, Tata Medical Center, Kolkata, West Bengal, India (e-mail: arghachat84@gmail.com).

Ind J Med Paediatr Oncol 2023;44:241–250.

Abstract

Keywords

- cholangiocarcinoma
- computed tomography
- gallbladder carcinoma
- hepatocellular carcinoma
- magnetic resonance imaging

Major hepatobiliary cancers include hepatocellular carcinoma, gallbladder carcinoma, and cholangiocarcinoma. There are multiple guidelines and recommendations for the imaging evaluation of these cancers. This article reviews and summarizes principles and recommendations of imaging in hepatobiliary cancers. The cross-sectional imaging protocol is similar among these lesions and is discussed at first followed by the separate discussion of each cancer.

Introduction

Major hepatobiliary cancers include hepatocellular carcinoma (HCC), gallbladder carcinoma, and cholangiocarcinoma (CCA). There are multiple guidelines and recommendations for the imaging evaluation of these cancers. This article reviews and summarizes principles and recommendations of imaging in hepatobiliary cancers. The cross-sectional imaging protocol is similar among these lesions and is discussed at first followed by the separate discussion of each cancer. Authors have reviewed existing international and Indian guidelines includ-

ing but not limited to National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), American College of Radiology (ACR), Indian Council for Medical Research (ICMR), and Indian College of Radiology and Imaging (ICRI). Imaging recommendations that are unequivocally mentioned in the majority of guidelines are included in this article. In the presence of conflicting or absent recommendations, authors have reviewed the existing literature, achieved a consensus regarding the issue in question, and, based on current evidence and their experience, provided recommendations following a short discussion.

DOI <https://doi.org/10.1055/s-0042-1760320>.
ISSN 0971-5851.

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)
Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Imaging Protocol in Hepatobiliary Cancer

Ultrasound of Whole Abdomen

Ultrasound of the upper abdomen is the modality of choice for screening of at-risk patients for liver cancer. Ultrasound does not have any role in diagnosis of liver lesions except as a guide to biopsy and other interventional procedures.

Computed Tomography Scan of the Whole Abdomen with Contrast

1. Noncontrast phase: For identification of fat, iron, calcification, blood products, and iodized oil (after chemoembolization). Necessary for generation of subtraction images.
2. Early arterial phase (15–20 seconds, for all cases): Identified by complete enhancement of aorta and hepatic arteries and no or minimal enhancement of portal vein. This is important for arterial anatomy that is essential for surgical planning.
3. Late arterial phase (35–40 seconds, for suspected hepatocellular cancers): Identified by complete enhancement of hepatic arteries and streaky partial enhancement of portal vein. Early arterial enhancement of HCC is best visualized in this phase.
4. Portal venous phase (75–90 seconds): Identified by complete enhancement of portal vein and partial enhancement of hepatic veins. Some enhancement of hepatic veins is essential for surgical planning and volumetry.
5. Delayed phase (120–300 seconds): Only necessary for hepatic venous anatomy and to rule out suspected hemangioma.
6. Contrast dose: A total of 1.8 to 2 mL/kg of 300 to 350 mg iodine/mL contrast through antecubital vein with a flow rate of at least 3 mL/s (Optimal contrast flow rate is crucial for arterial phase images. One may consider lower flow rate if the disease is already metastatic and information regarding vascular anatomy and vascular involvement is not critical).
7. Coverage of the whole abdomen from diaphragm to symphysis pubis is recommended to screen for peritoneal metastasis.
8. Slice thickness: 2/3 mm, slice interval: 0 mm.
9. Neutral oral contrast with 350 to 500 mL of water immediately to 15 minutes before computed tomography (CT) (optional). Positive oral contrast is discouraged.
10. Multiplanar reformat in coronal and sagittal is critical (thickness: 2 mm, interval: 0 mm).

Multiphasic Magnetic Resonance Imaging with Contrast

It is used as a problem solving tool in biliary tract cancers and can be used as a primary diagnostic modality in suspected HCC or intrahepatic cholangiocarcinoma (IHCC).

1. Minimum required sequences:
 - a. Axial and coronal T2-weighted.
 - b. Axial diffusion-weighted imaging.
 - c. Axial T1-weighted in and opposed phase images: for intralesional fat.

- d. Axial and coronal T1-weighted (VIBE/LAVA) precontrast, multiphasic arterial, portal venous, and delayed phase. In magnetic resonance imaging (MRI), multiple arterial phases are acquired in tandem. The timing of the rest of the phases is similar to that of CT. It is very important to generate subtraction images from post-contrast images to look for residual enhancement in treated liver nodules.
- e. Thin-slab and thick-slab magnetic resonance cholangiography (MRCP) (HASTE/SSFSE/RARE) and three-dimensional MRCP (for biliary tract tumors).
- f. If gadobenate dimeglumine is used as an intravenous contrast, then a hepatobiliary phase taken at 45 to 90 minutes is useful.
- g. Technical requirements:
 - i. High field strength magnet (> 1.5 Tesla).
 - ii. Phased array multichannel torso coil.
 - iii. Contrast: Both extracellular contrast agent (e.g., gadovist, gadobutrol, gadoterate, etc.) or hepatobiliary contrast agent (gadobenate dimeglumine) are acceptable. Contrast dose 0.1 mmol/kg.

Hepatocellular Carcinoma

Risk Factors and Etiopathogenesis

Cirrhosis of the liver is the single most important risk factor for HCC. In India, 70 to 97% of patients with HCC at the time of diagnosis had underlying cirrhosis of the liver.¹ Other important risk factors are chronic hepatitis B and C infection, alcoholic liver disease, and nonalcoholic fatty liver disease.² In India, hepatitis B virus (HBV), particularly genotype D is most commonly implicated in chronic hepatitis-related HCC.³

Epidemiology, Clinical Presentation in India and Global

Worldwide, HCC accounts for 90% of cancers of the liver. It is the third leading cause of cancer-related death annually and constitutes the fifth most common cancer globally.⁴ In India, age-adjusted incidence rate of liver cancer 0.7 to 7.5 in men and 0.2 to 2.2 in women per 100,000 population per year.¹ Based on a prospective observational study from North India, the annual incidence rate of HCC in cirrhotic patients is 1.6%.⁵ The incidence of liver cancer in India is increasing.⁶ The age standardized mortality rate is reported to be 6.8/100,000 population in men and 5.1/100,000 population in women.⁷ The incidence of liver cancer increased with increasing age, with a median age at presentation of 40 to 70 years. It is four times more common in men.

Imaging Referral Guidelines

The imaging referral algorithm for HCC in at-risk patients is demonstrated in ►Fig. 1.

Clinical/Diagnostic Workup Excluding Imaging

Along with estimation of functional status of the patient and staging of the tumor, the following workup is recommended:

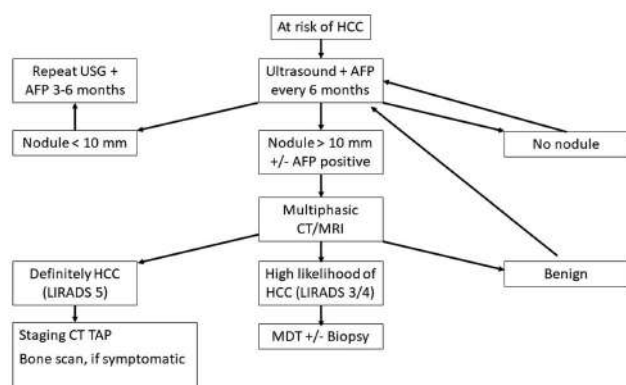


Fig. 1 Imaging referral algorithm in hepatocellular carcinoma (HCC) in at-risk patients. Modified from National Comprehensive Cancer Network (NCCN) guidelines.

- Serology for HBV and hepatitis C virus (HCV) (hepatitis B surface antigen [HBsAg], immunoglobulin G [IgG]/total-HBc, anti-HBs, anti-HCV). If HBsAg is positive, then hepatitis B e-antigen, anti-HBe antibody, and HBV-deoxyribonucleic acid levels are estimated. If anti-HCV is positive, then HCV genotype and HCV-ribonucleic acid levels are estimated.
- Liver function test (LFT), for assessment liver functional reserve (Child–Pugh score or Model for End-Stage Liver Disease score) and surgical planning.
- Assessment of portal hypertension (upper gastrointestinal endoscopy for varices and hepatic venous pressure gradient measurement).
- Chest CT, with or without contrast.
- Bone scan in presence of bone symptoms.
- Positron emission tomography (PET)-CT is not recommended.

Imaging Guidelines

Screening

ICMR has recommended surveillance with a 6-monthly ultrasound examination of the liver by an experienced radiologist. Doppler ultrasound may be added for better detection of new thrombus in hepatic or portal vein. Candidates for surveillance include those with Child A and B cirrhosis of any etiology and Child C patients on the waiting list for a liver transplantation. Non-cirrhotic patients with chronic hepatitis B (males > 40 years and females > 50 years), chronic HBV infection of any age with family history of HCC, or chronic HCV with advanced fibrosis are candidates for surveillance⁸ (ICMR 2019). Although

Chart 2 US-LIRADS category

Category	Description	Recommendation
US-LIRADS 1, negative	No or benign observation	Routine follow-up
US-LIRADS 2, subthreshold	Observation < 10 mm	Ultrasound at 3 mo
US-LIRADS 3, positive	Observation > 10 mm or new thrombus in a vein	Multiphasic CT or MRI

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; US-LIRADS, Ultrasound Liver Reporting and Data System.

ICMR does not recommend serum alpha-fetoprotein (AFP) as a screening method, addition of serum AFP has been shown to increase sensitivity of HCC detection in at-risk patients and NCCN has recently recommended addition of AFP in their 2021 guidelines.^{9,10} ACR recommends use of a standard Ultrasound Liver Reporting and Data System (US-LIRADS) for the reporting of surveillance ultrasound examination. Quality or adequacy of the diagnostic ultrasound examination can be reported with a visualization score (**Chart 1**). If an observation of size > 10 mm is visualized on ultrasound, further evaluation with multiphasic CT or MRI is warranted. Final ultrasound can be reported with an US-LIRADS score (**Chart 2**).¹¹

Diagnosis (Including Interventions)

Noninvasive characterization of a liver nodule can lead to a definitive diagnosis of HCC if the patient is considered to have high risk of HCC, that is, cirrhosis, chronic hepatitis B infection, and current/prior HCC. For nodules < 1 cm in size, further characterization by imaging or biopsy is of limited value and follow-up at 3 to 6 monthly intervals for 2 years is recommended.

For nodules > 1 cm, multiphase CT (with iodinated contrast) or multiphase MRI with gadolinium-based contrast are investigations of choice. Use of hepatocyte-specific gadolinium-based agents (gadobenate dimeglumine) is not mandatory but may have additional value. Liver Imaging Reporting and Data System and American Association for the Study of Liver Diseases have adopted imaging criteria for diagnosis of HCC. In a nodule that shows non-rim arterial phase hyperenhancement, presence of at least one major feature in nodules > 2 cm and presence of two or more major features in nodules measuring 1 to 1.9 cm is diagnostic of HCC in a

Chart 1 Ultrasound visualization score—US-LIRADS

Score	Description	Explanation
A	No or minimal limitation. No limitation to sensitivity of detecting small nodules.	Nearly the entire liver is visible with homogeneous echotexture
B	Moderately limited sensitivity to detect small nodules	Moderately echogenic liver when a part of liver or diaphragm is not visible
C	Severely limited sensitivity to detect liver nodules	Severely heterogeneous liver with ultrasound attenuation and > 50% liver or diaphragm is not visible

Abbreviation: US-LIRADS, Ultrasound Liver Reporting and Data System.

patient with high risk of HCC. Major features include wash-out in delayed phase, presence of enhancing capsule, and threshold growth.^{12,13} Specific criteria is described for major venous invasion by the tumor.

Calculation of liver remnant by CT volumetry is necessary in surgically resectable cases.

Tissue diagnosis is reserved for following situations:

- High suspicion of malignancy but the lesions does not meet imaging criteria for HCC.
- Lesion meets criteria for HCC but the patient is not considered high risk for HCC.
- Lesion meets criteria for HCC but the patient has cardiac cirrhosis, congenital hepatic fibrosis, or cirrhosis due to vascular disorders such as Budd–Chiari syndrome.
- Elevated CA19–9 or carcinoembryonic antigen (CEA) raising suspicion of IHCC.

Tissue diagnosis should be obtained by ultrasonography (USG) or CT-guided needle core biopsy. Multidisciplinary discussion is recommended before biopsy in patients who are candidates for hepatic resection, liver transplant (LT), or curative ablative therapy.¹⁰

Staging

The Barcelona Clinic Liver Cancer (BCLC) staging system is most widely used. It takes into account tumor number, size, liver function, and patients' performance status. BCLC also recommends a treatment strategy (► Fig. 2).

Management—Role of Interventional Radiology

Role of interventional radiology (IR) is increased in the 2022 update of the BCLC recommendations. In BCLC 0, ablation is the treatment of choice. Resection should be considered only when ablation is not feasible. Transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) can also be considered. TARE is to be used in single lesions that are less than 8 cm.¹⁴ In BCLC-A with single lesions, resection is favored in tumors up to 2 cm in size. For larger lesions, TARE can be considered in case the remnant liver is small. In multiple lesions with increased portal pressure or high bilirubin, ablation is recommended. For patients with > 3 lesions, TACE and TARE may be indicated. In LT candidates with > 6 months waiting time, ablation, TACE, or TARE can be used for bridging. BCLC-B patients with preserved portal flow and well-defined lesions TACE is recommended. Some cases of BCLC-B can still be considered for LT if they meet local practice guidelines. Some advanced cases of stage B may be downstaged to become eligible for LT through TACE or TARE and systemic therapies.¹⁵

Response Assessment

For follow-up of locoregional and systemic therapy in HCC, modified Response Evaluation Criteria in Solid Tumors (mRECIST) is recommended over RECIST 1.1 guidelines in early and intermediate cases. In advanced cases, both methods can be used.¹⁶ mRECIST takes into account the concept of “viable” tumor. After locoregional and systemic therapy in HCC,

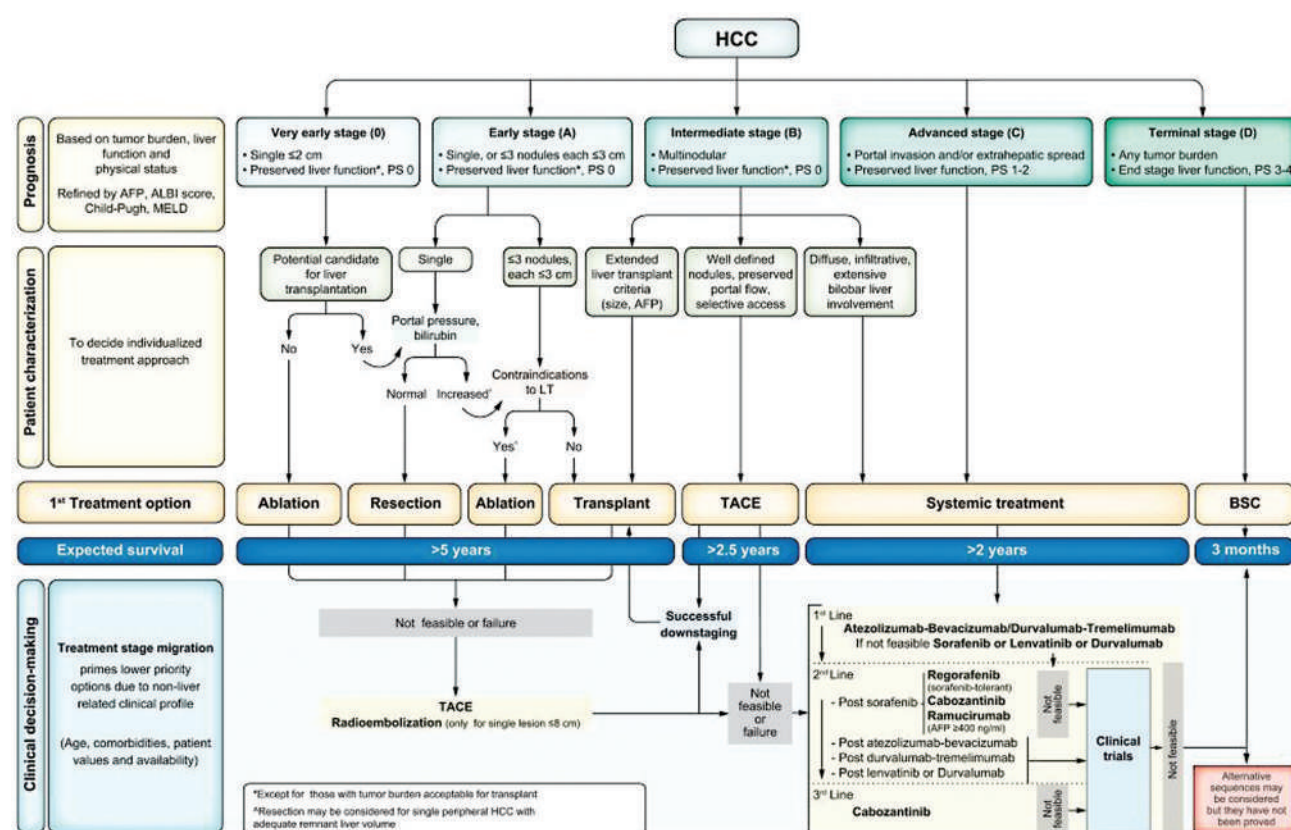


Fig. 2 Barcelona Clinic Liver Cancer (BCLC) staging system and treatment strategy.

many lesions do not show tumor shrinkage but show necrosis which is defined by loss of enhancement. mRECIST advocates measurement of enhancing or “viable” tumors only. Furthermore, enlargement of portal nodes and ascites/pleural effusion can also be a part of the chronic liver disease process and adjustments are made in this criteria to prevent overdiagnosis of disease progression.

mRECIST:

- Selection and measurement of target lesions:
 - Typical intrahepatic target lesion: ≥ 1 cm, intratumoral arterial phase enhancement.
 - Atypical intrahepatic target lesion: ≥ 1 cm, no arterial phase enhancement.
 - Extrahepatic target lesion, non-nodal: ≥ 1 cm longest axis.
 - Extrahepatic target lesion, nodal: ≥ 2 cm short axis if portal node, 1.5 cm short axis for nodes elsewhere.
 - Target lesions should be suitable for accurate and repeat measurement. Total number of target lesions should not exceed five with no more than two lesions per organ.
 - For hepatic targets, the longest diameter of the viable (arterially enhancing) tumor is measured. For extrahepatic non-nodal targets, the longest diameter is measured and for nodal lesions, the short axis diameter is measured.
- For baseline assessment sum of diameters of all target lesions are measured. The disease status on follow-up images is assessed using criteria similar to RECIST 1.1 (► **Table 1**). Follow-up is usually done at 6 to 8 weeks intervals.
- For immunotherapy, mRECIST criteria can be applied with a longer follow-up interval of 8 to 12 weeks since immunomodulating agents take longer to show tumor response.

Follow-Up

Resected lesions or post-LT cases should undergo multiphasic CT/MRI of upper abdomen, chest CT, and complete abdominopelvic CT/MRI every 3 to 6 months for 2 years and every 6 to 12 months thereafter along with serum AFP measurement.

Principles of Management

Imaging not only helps in local and metastatic staging of HCC, it also provides crucial information regarding the status of underlying liver disease. Presence of bland thrombus in the portal or superior mesenteric vein significantly alters surgical or local treatment decision. Presence of ascites and large

portosystemic shunt indicate hepatic decompensation and potentially high portal venous pressure. IR helps in direct measurement of portal venous pressure as well.

LT is indicated in BCLC 0, A, and some cases of B stage provided transplant is feasible. In stage B with multiple lesions TACE can be considered. For other cases of stage B and all cases of stage C are considered for systemic chemotherapy. ASCO recommends atezolizumab and bevacizumab combination as a first-line therapy after esophageal varices are managed.¹⁷ Sorafenib and lenvatinib is recommended as a second-line therapy. Stereotactic body radiotherapy is a treatment option in liver-limited disease with one to three lesions in cases with Child A or B cirrhosis that are unresectable. It can be used as an alternative to local ablative therapies or when these treatments have failed.¹⁸

Gallbladder Carcinoma

The most common histopathology of gallbladder cancer (GBC) is adenocarcinoma. The following discusses adenocarcinoma of gallbladder.

Risk Factors and Etiopathogenesis

Risk factors of GBC include gallstone, chronic inflammation, gallbladder polyp, primary sclerosing cholangitis, and obesity.¹⁹

Epidemiology, Clinical Presentation in India and Global

GBC is the only digestive cancer with a higher incidence in women. Women have two to six times higher risk of developing GBC than men.²⁰ It is more common in South American countries such as Chile and Bolivia and Asian countries such as Nepal and Bangladesh. In India, GBC is most common in North and Eastern India in the Gangetic plains and relatively less common in Western and Southern states. Incidence of GBC can be as high as 8.8 to 17.1/million population in Northern India. Age of presentation in Indian patients is earlier than that of Western population and it is usually in the 5th to 6th decade.²¹

Twenty-seven to 41% of patients of all GBC are incidentally detected during or after routine cholecystectomy (postop biopsy) for gallstone-related or benign gallbladder disease.²² This category is named *incidental GBC* (IGBC). Rest of the cancers can present with nonspecific abdominal symptoms such as dyspepsia and abdominal pain and a mass is detected at initial imaging. Advanced diseases can present with obstructive jaundice or ascites.

Table 1 mRECIST criteria

Complete response	No intraluminal arterial enhancement in all hepatic typical target and disappearance of atypical hepatic target and all extrahepatic target lesions
Partial response	$\geq 30\%$ reduction in sum of diameters of all viable (arterially enhancing) target lesions
Stable disease	Not classifiable as partial response or progressive disease
Progressive disease	$\geq 20\%$ increase in sum of diameters of all viable (arterially enhancing) target lesions

Abbreviation: mRECIST, modified Response Evaluation Criteria in Solid Tumors.

Imaging Referral Guidelines

Diagnosis of GBC is initially made by ultrasound as a gallbladder fossa mass or biliary obstruction. For assessment of operability and follow-up, CT or MRI or both are performed. Multiphasic contrast imaging is essential. For staging contrast-enhanced CT thorax is necessary. PET-CT has limited sensitivity in the detection of occult metastatic local or peritoneal metastatic disease when compared with surgical or laparoscopy findings.²³ PET-CT may have some role in detecting occult metastases in retroperitoneal nodes and liver in locally advanced GBC; however, data on predictive value in comparison to diagnostic laparoscopy is limited. In IGCB, PET-CT has similar positive predictive value compared with CT in the determination of resectability (HPB 2008;10:439). Therefore, the ICRI and NCCN do not recommend PET-CT for the staging of GBC and current authors concur.

Image-guided biopsy or fine-needle aspiration cytology (FNAC) are not performed in operable lesions to avoid tract dissemination. However, image-guided FNAC/biopsy is usually needed before any chemotherapy radiation in unresectable tumors.

Clinical/Diagnostic Workup Excluding Imaging

- LFT.
- Consider serum CEA, CA 19–9.
- Staging laparoscopy in operable lesions to rule out peritoneal metastases.

Imaging Guidelines

- USG is the initial modality of choice to image a suspected case of GBC. Once there is a mass detected, multiphasic CT is needed for initial staging and operability assessment.
- Multiphasic CT abdomen is the principal modality in the initial staging, preoperative planning, and follow-up of GBC.

- MRI with contrast and MRCP sequence is performed when knowledge of detailed biliary anatomy and nature and level of biliary obstruction is important in the management.
- Preoperative staging of GCB (→ **Table 2**) needs delineation of local mass, nodal involvement, and distant metastases (see reporting format).
- Nodal disease: Nodes larger than 1 cm in short-axis dimension are considered abnormal. Round shape, heterogeneous enhancement, and irregular margin of nodes are also suspicious features.
- Regional nodes (definitely regional; N1/N2 as per the American Joint Committee on Cancer [AJCC]/TNM guideline): Cystic duct, pericholedochal, retroportal (posterior to portal vein up to uncinate process of pancreas), liver hilar, and common hepatic artery nodes.
- Watershed nodes (controversially regional as per the Japanese Society of Biliary Surgery): Posterior-superior pancreaticoduodenal (located in the posterior and superior portion of pancreatoduodenal groove) and right side of celiac artery nodes.
- Metastatic nodes (definitely nonregional): Left side of celiac or superior mesenteric artery, para-aortic, interoaortocaval, and retrocaval nodes.

Detection of involved nonregional and watershed nodes is critical in imaging as they are missed in routine cancer surgery or staging laparoscopy.

Principles of Management

After initial staging in patients who are incidentally diagnosed with GBC at surgery and found to have resectable disease with no metastases, a completion cholecystectomy with en bloc liver resection, lymphadenectomy with/without bile duct resection is recommended. Unfortunately, 40 to 76% of patients of IGBC are found to have residual disease on surgical reexploration. Most symptomatic patients present

Table 2 TNM staging of gallbladder carcinoma—AJCC 8th edition

Category	Subcategory	Description
T	Tis	Carcinoma in situ
	T1	T1a Limited to lamina propria
		T1b Invasion of muscular layer
	T2	T2a Invasion of perimuscular connective tissue on peritoneal side
		T2b Invasion of perimuscular connective tissue on liver side
	T3	Perforates serosa and/or invades liver and/or one other adjacent [stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts]
	T4	Invades main portal vein or hepatic artery or two or more extrahepatic organs
N	N0	No regional node metastases
	N1	Metastasis in 1–3 regional nodes
	N2	Metastasis in ≥ 4 regional nodes
M	M0	No distant metastases
	M1	Distant metastases

Abbreviation: AJCC, American Joint Committee on Cancer.

with inoperable and/or metastatic disease, principally in the liver. In such situations, palliative chemotherapy is the only option. In other cases, imaging helps to demarcate GBC into resectable and nonresectable cancers, which decides further treatment such as upfront surgery or neoadjuvant chemotherapy followed by surgery. In case of borderline resectable lesions, neoadjuvant chemotherapy followed by surgery is offered. In operable candidates, the surgery may vary from radical cholecystectomy to right or extended right hepatectomy. Prior to hepatectomy percutaneous transhepatic biliary drainage (PTBD) and portal vein embolization may be required.

Cholangiocarcinoma

Introduction

CCAs are usually adenocarcinomas arising from biliary epithelium. CCAs are characterized by slow growth, local invasion, and intense desmoplastic reaction. Metastases are not common. *Combined hepatocellular-CCA* (also called *biphenotypic primary liver cancer*) is a distinct type of CCA with histologic features of both cancers.²⁴

Based on its location it is classified into IHCC and extrahepatic CCA (ECCA). ECCA is much more common, accounting for approximately 90% of the CCA.²⁵

1. Intrahepatic: Tumors that arise peripheral to the secondary bifurcation of the left or right hepatic duct are considered IHCC.
2. Extrahepatic:
 - a. *Perihilar CCA* (pCCA): Tumors that arise anywhere from the bifurcation of right and left common hepatic duct (CHD) up to the insertion of the cystic duct are called pCCA. When the tumor involves the CHD bifurcation, they are called *Klatskin tumors*.
 - b. *Distal CCA* (dCCA): Cancers arising between cystic duct insertion and the ampulla, but not including the ampulla.

Risk factors and Etiopathogenesis

About 90% patients diagnosed with CCA do not have any identifiable risk factors, but commonly recognized risk factors are primary sclerosing cholangitis, hepatolithiasis, liver fluke infestation, choledochal cyst, and abnormal pancreaticobiliary junction.²⁶

There are two precursors to CCA: intraductal papillary mucinous neoplasm of the bile duct (IPN-B) and biliary intraepithelial neoplasia (BilIN).²⁷ BilIN is not visible on imaging.²⁸ IPN-B appears as solitary or multiple papillary lesions within the bile duct lumen and produces a variable degree of mucin.

Epidemiology, Clinical Presentation in India and Global

CCA is the second most common cancer of the hepatobiliary system worldwide after HCC. It is slightly more common in men, usually diagnosed within 50 to 70 years of age. Patients with ECCA present with painless progressive jaun-

dice, which may be associated with abdominal pain and weight loss. IHCC presents with a liver mass and jaundice is uncommon.

Imaging Referral Guidelines

1. Multiphasic CT or MRI is recommended for evaluation of local disease. CT or MR is especially critical in the evaluation of vascular invasion.
2. MRCP is preferred over endoscopic or percutaneous cholangiography for evaluation of biliary anatomy and level of obstruction.
3. CT thorax with or without contrast is necessary for evaluation of lung metastases.
4. 18-Fluorodeoxyglucose-PET may be considered in the evaluation of nodal staging, distant metastases, and cases with suspected relapse.²⁹ It has no role in the diagnosis of the primary tumor.
5. Biopsy: In case of suspected IHCC, percutaneous biopsy is indicated. In case of ECCA and some cases of IHCC in non-cirrhotic patients, who are candidates for surgery, biopsy may be not necessary if the index of suspicion is high. Biopsy is indicated in all other cases of ECCA. Biopsy and biliary drainage should be performed after all imaging necessary for staging are done as these can interfere with imaging appearance of the tumor.

Clinical/Diagnostic Workup Excluding Imaging

- CEA and CA 19–9.
- AFP, in case of IHCC if HCC is considered in differentials.
- LFT.
- Viral serology.
- Serum IgG4, to rule out possible autoimmune cholangitis.¹⁰
- Endoscopic ultrasound, in cases of ECCA.

Imaging guidelines

Screening

Patients with primary sclerosing cholangitis are recommended to undergo CCA surveillance with MRI/MRCP or ultrasound and serum CA 19–9 level every 6 to 12 months.³⁰ Screening recommendation for IHCC is the same as that of HCC.

Diagnosis

Intrahepatic Cholangiocarcinoma

Mass-forming IHCC appears as an irregular but well-defined mass, often associated with upstream peripheral biliary dilatation. It can invade the portal vein and adjacent liver forming satellite nodules. The typical multiphasic CT/MRI finding of IHCC is a well-defined mass that shows irregular continuous rim-like enhancement in the hepatic arterial phase with gradual centripetal enhancement on portal venous and delayed phases.³¹ Additionally, MRI with gadobenate agent shows peripheral hypointensity with contrast retention at the center in the hepatobiliary phase. Other characteristic findings include rim-like diffusion restriction and overlying liver capsular retraction.³²

Table 3 TNM staging of intrahepatic cholangiocarcinoma—AJCC 8th edition

Category	Subcategory	Description
T	Tis	Carcinoma in situ
	T1	T1a
		Solitary tumor without vascular invasion, size < 5 cm
	T1b	T1b
		Solitary tumor without vascular invasion, size > 5 cm
	T2	Solitary tumor with vascular invasion or multiple tumors
N	T3	Tumor perforating visceral peritoneum
	T4	Tumor invading local extrahepatic structures
	N0	No regional node metastases
	N1	Regional node metastases
M	M0	No distant metastases
	M1	Distant metastases

Abbreviation: AJCC, American Joint Committee on Cancer.

Extrahepatic Cholangiocarcinoma

ECCA are often not seen on ultrasound but can be identified by presence of biliary dilatation. Klatskin tumor presents as focal hypoechoic mass at liver hilum with nonunion of right and left hepatic ducts. Distal cancers present as dilatation of common bile ducts (CBDs). CT shows the extent of ductal obstruction and vascular involvement by the tumor. CT has moderate diagnostic value in nodal staging. MRCP is preferred for demonstration of the bile duct anatomy. Both CT and MRI show an ill-defined mass and/or long segment asymmetric irregular wall thickening of bile duct. Progressive enhancement in delayed phases is characteristic.

Staging

The AJCC 8th edition recommended different staging strategies for ICCA, pCCA, and dCCA. The staging for ICCA and dCCA is given in ►Tables 3 and 4, respectively. The Memorial Sloan-Kettering Cancer Center classification for pCCA is discussed in ►Table 5 as it takes into consideration vascular invasion, extension of biliary involvement, and degree of liver lobar atrophy which are surgically relevant information.

After resectability of pCCA is established liver volumetry is sometimes necessary to calculate the functional liver residue (FLR) after resection.

Management

Role of IR in biliary malignancy:

Biliary Procedures

Therapeutic access to the biliary system is mainly limited to endoscopic or percutaneous biliary procedures. Many percutaneous transhepatic biliary interventions are applicable for the diagnosis and treatment of biliary system pathologies. The fundamental procedures are:

- Percutaneous transhepatic cholangiography.
- Internal/external biliary drainage.
- Biliary stenting.
- Endobiliary biopsy techniques.
- Intraluminal brachytherapy.

PTBD is an image-guided therapeutic procedure where bile duct is cannulated followed by external or internal/external catheter drainage of bile. PTBD is usually reserved

Table 4 TNM staging of distal cholangiocarcinoma—AJCC 8th edition

Category	Subcategory	Description
T	Tis	Carcinoma in situ/high-grade dysplasia
	T1	Tumor invades bile duct wall with a depth of < 5 mm
	T2	Tumor invades bile duct wall with a depth of 5–12 mm
	T3	Tumor invades bile duct wall with a depth of > 12 mm
	T4	Tumor involves celiac axis, superior mesenteric or common hepatic artery
N	N0	No regional node metastases
	N1	Metastasis in 1–3 regional nodes
	N2	Metastasis in ≥ 4 regional nodes
M	M0	No distant metastases
	M1	Distant metastases

Abbreviation: AJCC, American Joint Committee on Cancer.

Table 5 MSKCC classification of perihilar cholangiocarcinoma

Classification	Biliary involvement	Portal vein invasion	Liver lobe atrophy
T1	Hilum $\pm$ unilateral second order bile ducts	No	No
T2	Hilum $\pm$ unilateral second order bile ducts	Ipsilateral	Ipsilateral
T3	Hilum $\pm$ bilateral second order bile ducts	Any	Any
	Hilum $\pm$ unilateral second order bile ducts	Contralateral	Any
	Hilum $\pm$ unilateral second order bile ducts	Any	Contralateral
	Hilum $\pm$ unilateral second order bile ducts	Bilateral	Any

Abbreviation: MSKCC, Memorial Sloan-Kettering Cancer Center.

for when endoscopic intervention fails or if there is high intrahepatic obstruction.³³

Biliary stenting usually follows percutaneous transhepatic biliary drainage. Plastic stents and self-expandable metal stents are available options, but selection varies on reintervention risk and life expectancy. Self-expanding metal stents are more commonly used malignant strictures.

Percutaneous transhepatic endobiliary biopsy can be performed with varying techniques that include exfoliative cytology of bile aspirates, intraluminal brush biopsy, and intraluminal forceps biopsy. They are generally reserved when endoscopic access is failed or unsuccessful. Endobiliary biopsy techniques are more successful in establishing a diagnosis of malignancy in small biliary tumors limited to CBD or periductal infiltrating CCA which are difficult for percutaneous access. Forceps biopsy has the highest sensitivity among all sampling techniques.^{34–36}

Intraluminal brachytherapy is a percutaneous palliative intervention that involves catheter-mediated delivery of radiation to malignant biliary strictures. Intraluminal brachytherapy can improve obstructive jaundice, stent patency, and increase patient survival.³⁷

Portal Vein Embolization

Portal vein embolization (PVE) of the segments to be resected may benefit patients who undergo aggressive liver resection so that the residual liver may hypertrophy before surgery.³⁸

Follow-Up

For patients undergoing chemotherapy or in postoperative period, surveillance imaging with multiphasic CT/MRI is recommended after treatment for every 3 to 6 months for the first 2 years and every 6 to 12 months for 5 years.

Follow-up imaging after biliary procedures is necessary for evaluation of stent function. A functioning stent usually shows reduction or resolution of biliary dilatation and pneumobilia of the drained portion of the liver. Common causes of stent blockage are tumor ingrowth and sludge.

Following PVE, a repeat volumetry is necessary to document hypertrophy of the contralateral liver and calculate FLR.

Summary of Recommendations

1. Ultrasound is a screening tool in hepatobiliary malignancy which includes screening for hepatocellular cancer in high-risk patients.
2. Multiphasic CT is the primary imaging modality for initial staging and preoperative evaluation of hepatobiliary malignancy.
3. MRI is used for problem solving; especially in the diagnosis of liver nodules and delineation of biliary anatomy.
4. Bone scan is recommended in suspected/diagnosed cases of HCC with bone symptoms. PET-CT scan has limited application in CCA.
5. For follow-up of treated hepatocellular cancer, measurement of viable lesions as per mRECIST criteria is recommended.
6. Volumetry is essential before liver resection in HCC and CCA.

References

- 1 Acharya SK. Epidemiology of hepatocellular carcinoma in India. *J Clin Exp Hepatol* 2014;4(Suppl 3):S27–S33
- 2 Herbst DA, Reddy KR. Risk factors for hepatocellular carcinoma. *Clin Liver Dis (Hoboken)* 2013;1(06):180–182
- 3 Asim M, Sarma MP, Kar P. Etiological and molecular profile of hepatocellular cancer from India. *Int J Cancer* 2013;133(02):437–445
- 4 European Association For The Study Of The Liver European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012;56(04):908–943
- 5 Paul SB, Sreenivas V, Gulati MS, et al. Incidence of hepatocellular carcinoma among Indian patients with cirrhosis of liver: an experience from a tertiary care center in northern India. *Indian J Gastroenterol* 2007;26(06):274–278
- 6 Yeole BB. Trends in cancer incidence in esophagus, stomach, colon, rectum and liver in males in India. *Asian Pac J Cancer Prev* 2008;9(01):97–100
- 7 Dikshit R, Gupta PC, Ramasundarahettige C, et al; Million Death Study Collaborators. Cancer mortality in India: a nationally representative survey. *Lancet* 2012;379(9828):1807–1816
- 8 Singal AG, Zhang E, Narasimman M, et al. HCC surveillance improves early detection, curative treatment receipt, and survival in patients with cirrhosis: a systematic review and meta-analysis. *J Hepatol* 2022;77(01):128–139
- 9 Tzartzeva K, Obi J, Rich NE, et al. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis. *Gastroenterology* 2018;154(06):1706–1718.e1

- 10 Benson AB, D'Angelica MI, Abbott DE, et al. Hepatobiliary Cancers, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2021;19(05):541–565
- 11 American College of Radiology. Ultrasound LI-RADS v2017. Accessed December 23, 2022. <https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS/LI-RADS-UI-trasound-v2017>
- 12 Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 Practice Guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2018;68(02):723–750
- 13 American College of Radiology. Liver imaging reporting and data system. American College of Radiology website. Accessed December 23, 2022 <https://www.acr.org/Quality-Safety/Resources/LIRADS>
- 14 Salem R, Johnson GE, Kim E, et al. Yttrium-90 radioembolization for the treatment of solitary, unresectable HCC: the LEGACY study. *Hepatology* 2021;74(05):2342–2352
- 15 Mazzaferro V, Citterio D, Bhoori S, et al. Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial. *Lancet Oncol* 2020;21(07):947–956
- 16 Llovet JM, Lencioni R. mRECIST for HCC: performance and novel refinements. *J Hepatol* 2020;72(02):288–306
- 17 Gordan JD, Kennedy EB, Abou-Alfa GK, et al. Systemic therapy for advanced hepatocellular carcinoma: ASCO guideline. *J Clin Oncol* 2020;38(36):4317–4345
- 18 Akinyemiju T, Abera S, Ahmed M, et al; Global Burden of Disease Liver Cancer Collaboration. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the Global Burden of Disease Study 2015. *JAMA Oncol* 2017;3(12):1683–1691
- 19 Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. *Gut Liver* 2012;6(02):172–187
- 20 Rawla P, Sunkara T, Thandra KC, Barsouk A. Epidemiology of gallbladder cancer. *Clin Exp Hepatol* 2019;5(02):93–102
- 21 Dutta U, Bush N, Kalsi D, Popli P, Kapoor VK. Epidemiology of gallbladder cancer in India. *Linchuang Zhongliuxue Zazhi* 2019;8(04):33
- 22 Rathanaswamy S, Misra S, Kumar V, et al. Incidentally detected gallbladder cancer- the controversies and algorithmic approach to management. *Indian J Surg* 2012;74(03):248–254
- 23 Rodríguez-Fernández A, Gómez-Río M, Medina-Benítez A, et al. Application of modern imaging methods in diagnosis of gallbladder cancer. *J Surg Oncol* 2006;93(08):650–664
- 24 Akiba J, Nakashima O, Hattori S, et al. Clinicopathologic analysis of combined hepatocellular-cholangiocarcinoma according to the latest WHO classification. *Am J Surg Pathol* 2013;37(04):496–505
- 25 DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007;245(05):755–762
- 26 Ben-Menachem T. Risk factors for cholangiocarcinoma. *Eur J Gastroenterol Hepatol* 2007;19(08):615–617
- 27 Chatterjee A, Lopes Vendrami C, Nikolaidis P, et al. Uncommon intraluminal tumors of the gallbladder and biliary tract: spectrum of imaging appearances. *Radiographics* 2019;39(02):388–412
- 28 Ainechi S, Lee H. Updates on precancerous lesions of the biliary tract: biliary precancerous lesion. *Arch Pathol Lab Med* 2016;140(11):1285–1289
- 29 Lamarca A, Barriuso J, Chander A, et al. ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸FDG-PET) for patients with biliary tract cancer: systematic review and meta-analysis. *J Hepatol* 2019;71(01):115–129
- 30 Ahn JC, Yang JD. Screening indications and treatments for cholangiocarcinoma. *Curr Hepatol Rep* 2019;18:408–416
- 31 Lim JH. Cholangiocarcinoma: morphologic classification according to growth pattern and imaging findings. *AJR Am J Roentgenol* 2003;181(03):819–827
- 32 Kang Y, Lee JM, Kim SH, Han JK, Choi BI. Intrahepatic mass-forming cholangiocarcinoma: enhancement patterns on gadoteric acid-enhanced MR images. *Radiology* 2012;264(03):751–760
- 33 Watkinson AF, Adam A. *Interventional Radiology: A Practical Guide*. New York, USA: Radcliffe Publishing; 1996
- 34 Jung G-S, Huh J-D, Lee SU, Han BH, Chang H-K, Cho YD. Bile duct: analysis of percutaneous transluminal forceps biopsy in 130 patients suspected of having malignant biliary obstruction. *Radiology* 2002;224(03):725–730
- 35 Ahrar K, Gupta S. *Percutaneous Image-Guided Biopsy*. Springer Science & Business Media; 2013
- 36 Brugge WR, De Witt J, Klapman JB, et al. Techniques for cytologic sampling of pancreatic and bile duct lesions: the Papanicolaou Society of Cytopathology guidelines. *Cytojournal* 2014;11(Suppl 1):2
- 37 Madhusudhan KS, Gamanagatti S, Gupta AK. Imaging and interventions in hilar cholangiocarcinoma: a review. *World J Radiol* 2015;7(02):28–44
- 38 Nimura Y, Kamiya J, Kondo S, et al. Aggressive preoperative management and extended surgery for hilar cholangiocarcinoma: Nagoya experience. *J Hepatobiliary Pancreat Surg* 2000;7(02):155–162

Imaging Recommendations for Diagnosis, Staging, and Management of Peritoneal Malignancies

Amit Kumar Choudhari¹ Anuradha Chandramohan³ Nitin Shetty¹ Suyash Kulkarni¹
 Shailesh Shrikhande^{2,4} Avanish Saklani⁴ Rohin Mittal⁵ Kedar Deodhar^{2,6} Subhash Yadav^{2,6}
 Reena Engineer^{2,7} Vikas Ostwal^{2,8} Prachi Patil^{2,9}

¹ Department of Radiodiagnosis, Tata Memorial Center, Mumbai, India

² Homi Bhabha National Institute, Mumbai, India

³ Dept. of Radiodiagnosis, Christian Medical College, Vellore, India

⁴ Gastrointestinal and Hepato-Pancreato-Biliary Service, Tata Memorial Center, Mumbai, India

⁵ Dept. of Surgery, Christian Medical College, Vellore, India

⁶ Dept. of Pathology, Tata Memorial Center, Mumbai, India

⁷ Dept. of Radiation Oncology, Tata Memorial Center, Mumbai, India

⁸ Dept. of Medical Oncology, Tata Memorial Center, Mumbai, India

⁹ Dept. of Digestive Diseases & Clinical Nutrition, Tata Memorial Center, Mumbai, India

Address for correspondence Amit Kumar J. Choudhari, DNB (Radiodiagnosis), Department of Radiodiagnosis, Tata Memorial Center, E. Borges Road, Parel, Mumbai 400012, India (e-mail: amikumarchoudhari@tmc.nationalcancergrid.org).

Ind J Med Paediatr Oncol 2023;44:251–256.

Abstract

Keywords

- CRS
- guidelines
- peritoneal surface malignancies
- recommendations

Peritoneum is a serosal membrane lining the solid viscera and the hollow viscus of the abdomen and is made of a single layer of mesothelial cells. The most common primaries that spread to the peritoneum include gastrointestinal, ovarian, colorectal, and peritoneal metastases can be seen at some point during the disease course in 15 to 43%, 60 to 70% and 15 to 20% of patients, respectively. Other malignancies involving the peritoneum such as primary peritoneal carcinoma, peritoneal mesothelioma, peritoneal lymphomatosis, pseudomyxoma peritonei from low-grade appendiceal mucinous neoplasm, are far less common. The review strives to provide a framework for diagnosis and management of the disease.

Introduction

Peritoneum is a serosal membrane lining the solid viscera and the hollow viscus of the abdomen and is made of a single layer of mesothelial cells. Due to low sensitivity of imaging modalities to detected small peritoneal metastasis, the incidence of peritoneal malignancies remains unclear. Peritoneal carcinomatosis is the most common peritoneal surface malignancy and its incidence among the Czech population was 99 per 1,000,000. Primary peritoneal surface malignancies are very uncommon with an incidence of 4.36 per 1,000,000.¹ The most common primaries that spread to the peritoneum include gastrointestinal, ovarian, colorectal, and peritoneal metastases

can be seen at some point during the disease course in 15–43%, 60–70%, and 15–20% of patients, respectively.² Other malignancies involving the peritoneum such as primary peritoneal carcinoma, peritoneal mesothelioma, peritoneal lymphomatosis, pseudomyxoma peritonei from low grade appendiceal mucinous neoplasm are far less common.

Advanced stage of the primary tumor predisposes to peritoneal carcinomatosis. Apart from T- and N-stage, positive peritoneal fluid cytology and histological subtype of the primary are risk factors for peritoneal metastases. The most common symptoms of peritoneal surface malignancies include abdominal pain, abdominal distension from ascites or bowel obstruction. Non-specific symptoms include nausea,

DOI <https://doi.org/10.1055/s-0043-1761165>.
 ISSN 0971-5851.

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)
 Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

vomiting, fatigue, weight loss, and constipation. Tumor markers are used for diagnosis, prognosis, and for assessing treatment response. Carcinoembryonic antigen (CEA) and CA-19-9 are used in gastrointestinal malignancies. CA-125 is used for ovarian cancer and mesothelioma. CA-125 and CA72-4 are used for gastric cancer.

Risk Factors and Etiopathogenesis²

Advanced stage of the primary tumor, regional lymph node involvement, histological subtype and positive peritoneal cytology, are the usual risk factors for the development of peritoneal metastases from underlying primary neoplasm.

Loss of E-cadherin, a cell-cell adhesion molecule, is responsible for the detachment of cancer cells from the primary tumor. Rapid cellular proliferation, defective lymphatic drainage, fibrosis, and contraction of the interstitial matrix, and increased osmotic pressure generated by anaerobic glycolysis and leakage of plasma proteins, result in the shading of cells, due to elevated interstitial fluid pressure. Cutting of tumor or sectioning of the vascular, lymphatic, or biliary drainage is also responsible for peritoneal seeding.

The peritoneal deposits tend to gravitate in the cul-de-sac and the right paracolic gutters. Other locations include the subdiaphragmatic area and the mesentery, owing to diaphragmatic excursions.

Clinical/Diagnostic Workup

Clinically, the patient can present with signs and symptoms of primary malignancy.

Clinical features of peritoneal involvement are abdominal distention and pain. Patient can also have non-specific presentations such as fatigue, nausea, anorexia, weight loss, and constipation.

Serum tumor markers can be used for diagnosis, prognosis, and response assessment of peritoneal malignancy. The common tumor markers are CA 19-9 for pancreatobiliary system, CEA for GI tract, and CA 125 for ovarian primaries and mesothelioma. Cell block preparation, immunohistochemistry with appropriate markers indicate the possible primary, if not evident at presentation.

Surgical exploration using laparoscopy is the most sensitive modality for evaluation of the extent of the disease and assessment of its potential surgical resectability. Diagnostic laparoscopy is essential for the assessment of peritoneal cancer index (PCI).

Imaging Referral Guidelines:

- Ultrasound findings might raise the suspicion of an underlying peritoneal malignancy and act as a trigger for cross-sectional imaging. However, ultrasound is not recommended as a sole imaging modality for staging peritoneal surface malignancy.
- Ultrasound is useful for image-guided biopsy of peritoneal or omental disease.

- CECT of the thorax, abdomen, and pelvis is the recommended imaging modality for initial assessment of patients with peritoneal malignancy.
- Administration of both intravenous and positive oral contrast are recommended as a part of an optimal CT protocol.
- MRI is not recommended for all patients with peritoneal surface malignancy. Contrast-enhanced MRI with diffusion-weighted imaging may have a role in select patients with low-volume peritoneal disease on CECT and incomplete diagnostic laparoscopy due to adhesions.³
- PET-CT is not recommended for initial assessment of peritoneal malignancy.

Imaging Guidelines

a) Screening and diagnosis

Peritoneal surface malignancy is often suspected based on incidentally detected ultrasound findings such as ascites, omental, or peritoneal thickening. However, confirmation of diagnosis is with histopathology either using ultrasound-guided biopsy or by diagnostic laparoscopy and biopsy.

b) Staging

CECT of the thorax, abdomen, and pelvis is the imaging modality of choice for staging peritoneal surface malignancy. Studies done on new-generation CT scanners with thin section imaging and multiplanar reconstructions have improved sensitivity of 88 to 93% for detecting peritoneal disease. However, sensitivity to detect disease smaller than 1 cm and for detecting small bowel and mesenteric disease remain poor. Staging system used for primary peritoneal surface malignancy is the same as ovarian cancer and fallopian tube malignancies. Peritoneal cancer index (PCI) provides a comprehensive estimate of tumor volume within the peritoneal cavity. Imaging underestimates PCI. Despite these limitations, CECT is an effective modality for obtaining a general overview of the disease extent and exclude those who may not benefit from cytoreductive surgery and HIPEC.⁴

Radiology reports must mention the following⁵:

P – radiological estimation of PCI (rPCI), local extent of the primary malignancy in patients with peritoneal carcinomatosis.

A – presence or absence of ascites and abdominal wall disease

U – presence of disease in unfavorable sites, which make complete cytoreduction unlikely or difficult.

S – small bowel and mesenteric disease

E – presence of extraperitoneal metastases or lymph nodes.

Peritoneal Cancer Index

Peritoneal cancer index (PCI) is a measure of the peritoneal disease burden and distribution, introduced by Jacquet and Sugarbaker.⁶ The abdomen is divided into 13 regions (► **Table 1**)⁷ and a score is assigned depending on the disease burden in each region, resulting in minimal score of 0 to

Table 1 Peritoneal Cancer Index

	Region	Score	Scoring	Size
0	Central		LS0	No visible tumor
1	Right upper			
2	Epigastrium			
3	Left upper		LS1	< 0.5 cm
4	Left flank			
5	Left lower			
6	Pelvis		LS2	0.5 cm–5.0 cm
7	Right lower			
8	Right flank			
9	Upper jejunum		LS3	> 5cm or caking
10	Lower jejunum			
11	Upper ileum			
12	Lower ileum			
Total				

maximum score of 39. PCI is best assessed at laparoscopy and/or laparotomy. Preoperative assessment of PCI by MDCT can arm the surgeon with surgical roadmap and act as an arbitrator for decision regarding cytoreductive surgery⁸

c) Re-staging and follow-up

- CECT is again the preferred modality for re-staging peritoneal surface malignancy following neo-adjuvant chemotherapy. Images are reassessed for similar findings as described above.
- In this setting, there is a role for PET-CT in select patients with peritoneal malignancy who are being considered for cytoreductive surgery to exclude extraperitoneal metastases.

d) Follow-up

Follow-up evaluation is with a combination of clinical examination, tumor markers, and CECT of the thorax, abdomen, and pelvis at 6 monthly intervals for 2 years, followed by annual evaluation for at least 5 years.

Principles of Management

Common treatment modalities for peritoneal surface malignancies (PSM) are systemic chemotherapy, cytoreductive surgery, and intraperitoneal chemotherapy, with curative or palliative intent.

Systemic chemotherapy can be used either as neoadjuvant or adjuvant measure in either curative or palliative setting. Anti-angiogenic agents are being explored for their roles in the management of PSM to target neo-angiogenesis associated with tumor growth and peritoneal dissemination. Targeted therapy and immunotherapy also hold promise in the management of PSM. Endocrine therapy can be an option in the management of PSM, from hormone-dependent primaries.

Cytoreductive surgery (CRS) is a vital curative treatment for PSM with the objective of resecting all possible peritoneal

deposits. It can be combined with HIPEC to increase efficacy of therapy in patients with CC > 0.

Disease specific managements are summarized in ►Table 2.²

Palliative Measures

Palliative measures and best supportive care are required in patients not amenable to curative treatment and patients developing complications such as malignant bowel obstruction (MBO), ascites, and malnutrition.

Patients with MBO present with pain, nausea, vomiting, and aspiration. Recommended measures for alleviating the symptoms include decompression using an NG tube, gastric anti-secretory therapies such as histamine-2 receptor blockers and proton pump inhibitors. Steroids, due to their anti-inflammatory can reduce pain by decreasing bowel wall and mesenteric edema. Octreotide, a somatostatin analog, and gastric anti-secretory and ant motility agent, in combination with steroids has been shown to reduce gastrointestinal secretions and vomiting, as well as morbidity associated with MBO. In the event of failure of medical management, decompressive gastrostomy tube placement is recommended.

Surgery may be required for patients with acute perforation. Resection-anastomosis can be an option in patients unresponsive to conservative management of MBO. Complete cytoreductive surgery with or without intraperitoneal chemotherapy can also be considered. However, surgery in the setting of disseminated disease is associated with high morbidity and mortality.

Malnutrition is associated with longer hospital stays, post-operative complications, and a reduction in overall survival. Patients failing to achieve adequate oral or enteral caloric intake are recommended parenteral nutrition (PN) support.

Ascites is commonly caused by ovarian, esophageal, gastric, colorectal, hepatobiliary, and primary peritoneal

Table 2 Principles of management

Pathologies	Neoadjuvant treatments	Surgery	HIPEC	Targeted therapies	Intraperitoneal treatments	Systemic chemotherapy
Pseudomyxoma peritonei and PM from appendiceal cancers						
Curative	No	Upfront CC-0 or CC-1 CRS	recommended	No	Option of EPIC	Adjuvant if poor prognostic factors
Palliative	-	Upfront CC-2 or 3 CRS	recommended	Antiangiogenic* Bromelain and Acetylcysteine (BroMac) in early clinical development	PIPAC under evaluation	Palliative according to right-sided colorectal cancer*
Malignant peritoneal mesothelioma						
Curative	Intraperitoneal chemotherapy, NIPS and PIPAC under evaluation	Upfront CC-0 CC-1 CRS	recommended	No standard recommendation*	Option of EPIC	Adjuvant if poor prognostic factors to be considered*
Palliative		No	No	Immunotherapy, PARP-inhibition and other targeted agents under evaluation*	Option of long- term intraperitoneal chemotherapy or PIPAC	Palliative Platinum- /Pemetrexed-based regimens
PM from Ovarian Cancer						
1st line	Systemic chemotherapy if CC-0 CRS not possible	Upfront or interval CC-0 CRS	Option in interval surgery	Antiangiogenic or PARP-inhibition	No	Adjuvant Platinum- /Taxane-based
Platin sensitive Recurrence	Systemic chemotherapy if CC-0 CRS not possible	Upfront or delayed CC-0 CRS	Under evaluation into RCT	Antiangiogenic or PARP-inhibition	PIPAC under evaluation	Palliative Platinum- based
Platin resistant recurrence	Systemic chemotherapy if CC-0 CRS not possible	Option if CC-0 CRS	Option if CC-0 CRS	Antiangiogenic	PIPAC under evaluation	Palliative Topotecan or Anthracyclines
PM from colorectal cancer						
Curative	Option of systemic chemotherapy Intraperitoneal chemotherapy, NIPS and PIPAC under evaluation	CC-0 CRS	Option into specialized centers	No standard recommendation*	PIPAC under evaluation	Adjuvant if poor prognostic factors*
Palliative	-	No	No	Antiangiogenic and anti-EGFR according to mutational status and sidedness of primary tumor Immunotherapy in MSI patients	PIPAC under evaluation	Palliative oxaliplatin/fluoro pyrimidine- based or irinotecan/fluoro pyrimidine or trifluridine- tipiracil (3rd-line)

Table 2 (Continued)

Pathologies	Neoadjuvant treatments	Surgery	HIPEC	Targeted therapies	Intraperitoneal treatments	Systemic chemotherapy
PM from gastric cancer						
Curative	Option of systemic chemotherapy Intraperitoneal chemotherapy and NIPS, PIPAC under evaluation	CC-0 CRS in patients with low PCI	Option in combination with CC-0 CRS	No standard recommendation*	PIPAC under evaluation	Adjuvant
Palliative	PIPAC under evaluation	No	Under evaluation	Trastuzumab in Her 2 positive patients Immunotherapy in MSI and under further evaluation in MSS	PIPAC under evaluation	Palliative Platinum/ Fluoropyrimidine based 1st-line, Taxane (2nd-line) or irinotecan or trifluridine-tipiracil (3rd-line)
PM from others malignancies						
Curative	To select adequate candidate	Only in case of CC-0 CRS	Option in combination with CC-0 CRS	-		Optional
Palliative	-	No	Option in malignant ascites	-	Optional	Registered and established disease specific regimens

Abbreviations: CC, Completeness of cytoreduction surgery; CC0, no residual nodule; CC1, <2.5 mm; CC2, <25 mm; and CC3, >25 mm; CRS, cytoreductive surgery; EPIC, early postoperative intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy; MSI, microsatellite instability; MSS, microsatellite stable; NIPS, n intraperitoneal and systemic chemotherapy; PARP, poly (ADP-ribose) polymerase; PCI, Peritoneal Cancer Index; PIPAC, pressurized intraperitoneal aerosol chemotherapy; PM, peritoneal metastasis.

*No definitive evidence from controlled trials available.

carcinomatosis. Lung, pancreatic, endometrial, breast primaries are less likely to be associated with ascites. Malignancy related ascites should be confirmed with diagnostic paracentesis and cytology, esophagogastroduodenoscopy, colonoscopy, contrast-enhanced CT/magnetic resonance imaging of the abdomen and pelvis, and pelvic ultrasound (in female patients). These investigations can also help in establishing the diagnosis of primary malignancy. In the event of negative results, diagnostic laparoscopy and biopsy with PCI scoring is recommended, in addition to ruling out other causes of ascites such as cirrhosis or infectious diseases such as peritoneal tuberculosis. Supportive paracentesis can be effective for relieving ascites related symptoms.

Summary of Recommendations: 100 Words

- i) Contrast-enhanced CT of the abdomen and pelvis is the imaging modality of choice for peritoneal disease.
- ii) Review of thin sections (1–2 mm) in both axial and coronal planes is recommended for assessing the extent of peritoneal disease.
- iii) Use of positive oral contrast is recommended to improve the detection of disease in the small bowel mesentery and serosa.
- iv) PET-CT is recommended to exclude extraperitoneal disease before considering major surgical management such as cytoreductive surgery and HIPEC.
- v) Radiology reports must include a succinct description of the volume of peritoneal disease in terms of PCI and address specific sites of disease that might hinder completeness of cytoreduction.

Synoptic Reporting CT, MRI, and PET-CECT

Synoptic reporting of peritoneal surface malignancy must address the following

Is there an obvious primary? Gastrointestinal/ovarian/-colorectal/appendix/pancreaticobiliary/urachal

Fluid: ascites (yes/no), mild/moderate/severe

Peritoneal or omental thickening: (yes/no)

Is ultrasound-guided biopsy possible? (yes/no)

Bowel, mesentery:

- Bowel wall thickening/dilatation/obstruction (yes/no)

- Mesenteric fold thickening (yes/no)

- Mesenteric tethering (yes/no)

- Root of mesenteric disease (yes/no)

Upper abdomen: subphrenic spaces, lesser omentum, gastro-splenic ligament, porta, portocaval space (yes/no)

Liver and biliary system: Focal lesions in the liver (-yes/no); biliary dilatation (yes/no)

Spleen: focal lesions in the spleen, splenic hilar disease

KUB:

Hydronephrosis (yes/no)

Pelvis:

- Plane between pelvic masses and recto-sigmoid colon (lost/maintained)

- Iliac vessel encasement (yes/no)

- Ureteric encasement (yes/no)

- Presacral space or pelvic side wall infiltration (yes/no)

Abdominal wall: surgical scars/port site metastases

Nodes:

Metastases: liver, lungs, bones, spleen, adrenals, etc.

Impression:

P – Radiological PCI

A – Ascites/abdominal wall disease

U – Unfavorable sites of disease

S – Small bowel and mesenteric disease

E – Extraperitoneal disease

Authors' Contributions

The manuscript has been read and approved by all the authors, that the requirements for authorship have been met, and that each author believes that the manuscript represents honest work. All authors have contributed equally towards concept, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, manuscript preparation, manuscript editing and manuscript review.

Funding

None.

Conflict of Interest

None declared.

References

- Klos D, Riško J, Loveček M, et al. Trends in peritoneal surface malignancies: evidence from a Czech nationwide population-based study. *World J Surg Oncol* 2019;17(01):182. Doi: 10.1186/S12957-019-1731-4
- Cortés-Guiral D, Hübner M, Alyami M, et al. Primary and metastatic peritoneal surface malignancies. *Nat Rev Dis Primers* 2021; 7(01):91https://doi.org/10.1038/s41572-021-00326-6
- Chandramohan A, Shah N, Thrower A, et al. Communicating imaging findings in peritoneal mesothelioma: the impact of 'PAUSE' on surgical decision-making. *Insights Imaging* 2021;12(01):174. Doi: 10.1186/S13244-021-01118-Y
- Chandramohan A, Thrower A. A practical guide to peritoneal malignancy. In: Cecil T, Bunni J, Mehta A, eds. *The PMI Manual*. CRC Press; 2019
- Chandramohan A, Thrower A, Smith SA, Shah N, Moran B. "PAUSE": a method for communicating radiological extent of peritoneal malignancy. *Clin Radiol* 2017;72(11):972–980. Doi: 10.1016/J.CRAD.2017.07.005
- Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res* 1996;82:359–374. Doi: 10.1007/978-1-4613-1247-5_23
- Aherne EA, Fenlon HM, Shields CJ, Mulsow JJ, Cronin CG. What the radiologist should know about treatment of peritoneal malignancy. *Am J Roentgenol* 2017;208(03):531–543https://doi.org/10.2214/AJR.16.16646
- Panagiotopoulou PB, Courcousakis N, Tentes A, Prassopoulos P. CT imaging of peritoneal carcinomatosis with surgical correlation: a pictorial review. *Insights Imaging* 2021;12(01):168. Doi: 10.1186/S13244-021-01110-6/FIGURES/16

Imaging Recommendations for Diagnosis, Staging, and Management of Bone Tumors

Amit Janu^{1,2} Anurima Patra³ Mahesh Kumar^{1,2} Ashish Gulia^{2,4} Suyash Kulkarni^{1,2}
Nitin Sudhakar Shetty^{1,2} Ajay Puri^{2,4} Prakash Nayak^{2,4} Manish Pruthi^{2,4}

¹ Department of Radio-Diagnosis, Tata Memorial Hospital, Tata Memorial Centre, Mumbai, Maharashtra, India

² Homi Bhabha National University (HBNI), Mumbai, Maharashtra, India

³ Department of Radiodiagnosis, Tata Medical Center, Kolkata, West Bengal, India

⁴ Department of Surgical Oncology, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National University (HBNI), Mumbai, Maharashtra, India

Address for correspondence Amit Janu, DNB Radiodiagnosis, Room no. 128, Main Building, Tata Memorial Hospital, Parel, Mumbai, Maharashtra, India (e-mail: amiteasy10@gmail.com).

Ind J Med Paediatr Oncol 2023;44:257–260.

Abstract

Keywords

- bone tumor
- imaging
- management
- MRI
- radiograph
- radiology
- staging

Primary bone sarcomas account for less than 1% of diagnosed cancers each year. In this era of multiplanar and functional imaging, the approach to the radiographic diagnosis of bone cancers goes much beyond traditional radiography. Radiographs are still the most pertinent part of the initial diagnosis of bone tumors. Multimodal imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI), can help with issues such as complex anatomy, marrow assessment, soft assessment, and better local staging. The emerging imaging modality such as positron emission tomography (PET)-CT/PET-MRI has further transformed the imaging of bone malignancies. Radiologist plays an important role in the workup, staging, and management of bone tumors. The purpose of this article is to review imaging recommendations for better diagnosis, staging, and management of bone tumors.

Introduction

The diagnosis, staging, and management of bone tumors involve a holistic approach including meticulous history taking and clinical examination by experienced orthopaedic onco-surgeon and imaging interpretation. Teamwork in multidisciplinary meetings between expert radiologists, orthopaedic onco-surgeon, and pathologists help in deciding a road map for diagnosing and treatment of bone tumors. Radiographs remain the most pertinent part of initial evaluation of bone tumors. Next best modality is magnetic reso-

nance imaging (MRI) which is usually indicated for confirmation, better characterization of the lesion, and local staging. Computed tomography (CT) scan is usually advised to assess bone erosion, to see nidus in osteoid osteoma and matrix evaluation. Positron emission tomography (PET)-CT provides critical information regarding occult metastasis to lung and distant bone. PET-CT and MRI have additional use in assessment of response to therapy. We provide an overview of the multidisciplinary approach to the imaging, diagnosis, treatment, and surveillance of bone tumors from the perspective of an onco-radiologist.

Risk Factors and Etiopathogenesis

Bone cancers are not linked with known risk factors. But there are few factors that can raise the risk of bone cancers.¹

The article is not under consideration for publication elsewhere. Each author participated sufficiently for the work to be submitted. The publication is approved by all authors.

DOI <https://doi.org/10.1055/s-0042-1760313>.
ISSN 0971-5851.

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)
Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Risk of osteosarcoma and Ewing sarcoma is highest for those between the ages of 10 and 30 years, whereas risk for chondrosarcoma increases in older age group above 40 years. Osteosarcoma, Ewing sarcoma, and chondrosarcoma show slightly male predominance over females.² Prior radiotherapy and Paget's disease are known risk factors for secondary osteosarcoma.³ Multiple enchondromatosis can show degeneration into chondrosarcoma. Hereditary retinoblastoma and Li-Fraumeni syndrome have increased risk of osteosarcoma. EWS and ETS family of genes rearrangements have been implicated in the pathogenesis of Ewing sarcoma.⁴

Epidemiology, Clinical Presentation in India and Global

Primary bone sarcomas account for less than 1% of diagnosed cancers each year. Global incidence ranges from 3 to 7 per 100,000 individuals affected yearly. Osteosarcoma (35%) and Ewing sarcoma (16%) have high incidence in children and young adults in the second decade of life, while chondrosarcoma (30%) is most common in older age groups.⁵ In Indian data, bone tumors from approximating 0.2% of all cancers, with osteosarcoma, chondrosarcoma, and Ewing sarcoma being the most common cancers in this subset.⁶ Pain is the most common presenting symptom of primary bone cancers and is usually associated with local swelling.⁷ These symptoms may mimic common musculoskeletal injuries, and pain often begins after minor physical trauma. Pathologic fracture may be the first presentation of a primary bone tumor. Systemic symptoms are rare but are more common in Ewing sarcoma and include unexplained relapsing fever.

Imaging Referral Guidelines

The National Comprehensive Cancer Network (NCCN) provides interdisciplinary evidence-based recommendations for the assessment and management of primary bone cancers. They focus on chordoma, chondrosarcoma, Ewing sarcoma, and osteosarcoma. The guidelines also provide recommendations for treating giant cell tumors of bone which is benign, but locally aggressive and can lead to significant bone destruction. NCCN suggests that workup of an abnormal radiograph is decided by the age of the patient. If the patient is more than 40 years of age, metastatic workup should be performed with chest/abdomen/pelvis CT, chest radiograph, bone scan, mammogram, and prostate-specific antigen. If no other lesions are detected elsewhere, the patient should be referred to orthopaedic oncologists for evaluation of possible bone primary. If the patient's age is less than 40 years, the patient should be directly referred to an orthopaedic oncologist for biopsy.

Clinical/Diagnostic Workup

Persistent bone pain lasting more than a few weeks should raise concern and lead to further immediate evaluation.

Swelling will be present only when the tumor has breached the cortex and periosteum.⁷ Before 5 years of age, a destructive bone lesion is most commonly metastatic neuroblastoma or eosinophilic granuloma; above 5 years, it is often a primary bone sarcoma; after 40 years of age, it tends to be metastasis, myeloma or lymphoma.⁸

Patients with suspected bone tumors should be referred immediately to a cancer center with an experienced orthopaedic oncologist for further workup. The clinical history should focus on symptoms such as duration, intensity, and timing of complaints, family history, and previous radiotherapy. A recent injury must not prevent appropriate diagnostic procedures. Physical examination should focus on the size, consistency of the swelling, tenderness, location and mobility, relation of swelling to the underlying bone, and the presence of local lymph nodes.

There is not much role of laboratory investigations in the workup of bone tumors. However, some tests are of prognostic value in the follow-up in Ewing sarcoma and osteosarcoma, such as alkaline phosphatase and lactate dehydrogenase.⁹ Blood workup such as serum electrophoresis with immunofixation helps in diagnosing multiple myeloma.¹⁰ For suspected Ewing sarcoma, cytogenetic and/or molecular studies of the biopsy specimen can be performed to evaluate the t (11;22) translocation, and a bone marrow biopsy should be considered to complete the workup.¹¹ Histopathology is the gold standard for diagnosis of bone tumors but should be ordered after imaging is performed.

Imaging Guidelines—Diagnosis

Radiography remains the mainstay for initial diagnosis. CT, MRI, an PET CT are useful in evaluating the extent of lesion and its local and distant staging for the appropriate treatment and in assessing therapeutic response.¹² Biopsy should be performed after imaging to confirm the diagnosis and decide further management. Imaging is also crucial to decide the need and target site for biopsy. All cases of suspected bone tumors should be discussed by orthopaedic oncologist at a multidisciplinary meeting that includes the expert radiologist who has interpreted the imaging and the pathologist who has reviewed the biopsy material and the surgeon and oncologist undertaking treatment. This will minimize the risk of errors in diagnosis, avoid unnecessary biopsies, staging, risk assessment, and treatment.

As per the European Society for Medical Oncology (ESMO) guidelines, whenever a bone tumor is suspected, a conventional radiograph is ordered first to confirm the bone origin of the pathology. It is the most indispensable, inexpensive, and readily available investigation. It should be ordered in two orthogonal planes and should include the proximal and distal joints as well. Not only it helps in primary assessment of benign or aggressive nature of the tumor, it provides important diagnostic information that can be correlated with MRI later. The most important determinators in the analysis of a potential bone tumor are morphology and location of the lesion and age of the patient. The morphology

indicators are lytic/sclerotic, matrix mineralization (osseous, calcified, fibrous), zone of transition, cortical erosion, periosteal reaction, soft tissue component, location (epi/meta/diaphysis or eccentric/central/juxtacortical), and multiplicity.¹³ The age of the patient is crucial to note before deciding the possible differentials. For example, benign tumors and primary bone sarcomas are more common in early decades of life, while the top differentials for a bone lesion in patients older than 50 years are lymphoma, myeloma, and metastasis.

Following radiographs, further evaluation requires MRI of the entire compartment with adjacent joints. MRI is the best modality for local staging and surgical planning, that is, assessment of proximity of mass to neurovascular structures, intertumoral extension, and skip lesions, which are important for planning the length of surgical resection and deciding limb salvage surgery.¹⁴

CT should be performed only in case of diagnostic problems or doubt or to provide additional information, such as better visualization of calcifications, periosteal bone formation, and cortical breach. All imaging should be completed before biopsy to avoid confounding of intrinsic tumor characteristics by post-biopsy inflammation or altered tissue planes.

Biopsy is required for diagnosis confirmation and establishing tumor grade. It should be performed by a trained intervention radiologist or orthopaedic oncologist. The aim is to carefully plan the biopsy in the expected plane of surgery and avoid injury to neurovascular structures and development of hematoma. Image-guided needle biopsy should be preferred over open true cut biopsy because of lower complications and decreased risk of development of post-biopsy hematoma which has increased risk for local recurrence.¹⁵ Image guidance can also help avoid targeting the necrotic/cystic/nonenhancing areas that may be nonavid on PET CT that can otherwise lead to a nondiagnostic yield. Improperly performed biopsies can also lead to misdiagnosis, local recurrence, amputation, and decreased survival. If there is a definite soft tissue component, ultrasound-guided biopsy is preferred while CT guidance is preferred in case of purely intraosseous lesions. While ordering biopsy, the referring orthopaedic oncologist should mention the potential site of surgical incision for limb salvage surgery so that the radiologist can insert the biopsy needle through the same site and avoid contaminating the surgical compartments requiring unnecessary amputation or additional soft tissue reconstructions. The pathologist reading the sample should receive information regarding the clinical/radiological context in which the tumor has arisen, relevant observations made at the time of biopsy, and whether the patient has received preoperative chemotherapy.

There are multiple staging systems for bone tumors in the literature. However, none of them are universally accepted. Malignant bone neoplasms are staged based on the size, regional lymph node involvement, and distant organ metastasis.¹⁶ CT, bone scintigraphy, and fluorodeoxyglucose (FDG) PET-CT play a key role in staging. PET-CT is commonly performed to evaluate the distant metastatic disease spread

and also treatment response. Noncontrast CT thorax is preferred over PET-CT to detect lung nodules that can deem a patient as metastatic.¹⁷ Certain bone tumors have typical morphological features on CT such as calcified lung nodules in osteosarcoma metastasis. Counting the number of nodules and their location on CT also helps in metastasectomy planning.

Post chemotherapy treatment response is monitored primarily by MRI. Decrease in size of soft tissue component, decrease in marrow edema, decreased enhancement, and facilitated diffusion on diffusion-weighted imaging are indicators for positive response on MRI.¹⁸ Increased sclerosis in bone metastasis following chemotherapy seen on CT also suggests response. PET-CT can also be used in tumor surveillance to assess tumor response to chemotherapy and radiation treatment, and for detection of recurrent tumors in follow up cases.

Principles of Management

Bone tumors are managed by a specialist group with experience in treating bone cancer, usually done through multidisciplinary team (MDT). MDT includes an orthopaedic onco-surgeon, a medical oncologist, and radiation oncologist.¹⁹ Recommended treatment plan is usually a combination of surgery which includes wide local excision, limb-sparing surgery, amputation, and rehabilitation. Chemotherapy is usually provided in four ways, neoadjuvant chemotherapy prior to surgery, concurrent chemoradiotherapy, adjuvant chemotherapy, and palliative chemotherapy.²⁰ Radiotherapy is usually provided in radiosensitive tumors.

Follow-Up Imaging and Management of Recurrent Disease

Limited published evidence is available to support specific policies for surgically treated patient's follow-up. Lung relapses are the most common type of relapse. The ESMO guidelines (2021) for follow-up of high-grade bone sarcoma include physical examination, cross-sectional imaging, and plain radiograph of the primary site together with chest X-ray (CXR)/CT scan, at intervals of approximately every 3 months for the first 2 years; every 6 months for years 3 to 5; every 6 to 12 months for years 5 to 10; and thereafter every 6 months to 1 to 2 years. For low-grade bone sarcoma, the frequency of follow-up visits may be lower (e.g., 6 months for 2 years and then annually).²¹ NCCN recommends separate regimes for the most common tumors. For osteosarcoma, MRI, contrast CT, local radiograph for local recurrence, and chest imaging (CT preferred over chest CXR) at following intervals—3 monthly $\times$ 2 years, 4 monthly $\times$ 3 years, 6 monthly $\times$ 4 to 5 years, and annually thereafter. PET-CT/bone scan can also be considered. For Ewing's sarcoma imaging recommendation is same as osteosarcoma at intervals 2 to 3 monthly for 2 years, followed by increasing intervals up to 5 years. In high-grade chondrosarcoma, MRI, local radiograph, and chest imaging (CT is preferred over CXR) at the following intervals: 3 to 6 monthly $\times$ 5 years and yearly after that till a minimum of 10 years.²² Indian

randomized trial TOSS study showed an overall survival of patients who are treated for sarcoma of the limb is not inferior when followed up with a less intensive regimen than a more intensive protocol, in terms of frequency of visits and mode of imaging. CXR at 6-monthly intervals and patient education about the examination of the local site of the surgery will detect most recurrences without affecting the eventual outcome.²³

Conflict of Interest

None declared.

References

- American Cancer Society. (cancer.org): Bone Cancer Causes, Risk Factors, and Prevention. <https://www.cancer.org/cancer/bone-cancer/causes-risks-prevention/risk-factors.html>
- Savage SA, Mirabello L. Using epidemiology and genomics to understand osteosarcoma etiology. *Sarcoma* 2011;2011:548151
- Hansen MF, Seton M, Merchant A. Osteosarcoma in Paget's disease of bone. *J Bone Miner Res* 2006;21(Suppl 2):58–63
- Letson GD, Muro-Cacho CA. Genetic and molecular abnormalities in tumors of the bone and soft tissues. *Cancer Contr* 2001;8(03):239–251
- Franchi A. Epidemiology and classification of bone tumors. *Clin Cases Miner Bone Metab* 2012;9(02):92–95
- Ramaswamy A, Rekhi B, Bakhshi S, Hingmire S, Agarwal M. Indian data on bone and soft tissue sarcomas: a summary of published study results. *South Asian J Cancer* 2016;5(03):138–145
- George A, Grimer R. Early symptoms of bone and soft tissue sarcomas: could they be diagnosed earlier? *Ann R Coll Surg Engl* 2012;94(04):261–266
- Salom M, Chiari C, Alessandri JMG, Willegger M, Windhager R, Sanpera I. Diagnosis and staging of malignant bone tumours in children: what is due and what is new? *J Child Orthop* 2021;15(04):312–321
- Baptista AM, Zumárraga JP, Dos Santos RP, Haubert GO, de Camargo OP. Serum values of alkaline phosphatase and lactate dehydrogenase in EWING'S SARCOMA. *Acta Ortop Bras* 2016;24(04):196–199
- Rajkumar SV, Kumar S. Multiple myeloma: diagnosis and treatment. In: *Mayo Clinic Proceedings*. Vol. 91. Elsevier; 2016 January 1:101–119
- Zucman J, Delattre O, Desmaze C, et al. Cloning and characterization of the Ewing's sarcoma and peripheral neuroepithelioma t (11;22) translocation breakpoints. *Genes Chromosomes Cancer* 1992;5(04):271–277
- Goyal N, Kalra M, Soni A, Baweja P, Ghonghe NP. Multi-modality imaging approach to bone tumors - state-of-the art. *J Clin Orthop Trauma* 2019;10(04):687–701
- Costelloe CM, Madewell JE. Radiography in the initial diagnosis of primary bone tumors. *AJR Am J Roentgenol* 2013;200(01):3–7
- Golfieri R, Baddeley H, Pringle JS, Leung AW, Greco A, Souhami R. MRI in primary bone tumors: therapeutic implications. *Eur J Radiol* 1991;12(03):201–207
- Jelinek JS, Murphey MD, Welker JA, et al. Diagnosis of primary bone tumors with image-guided percutaneous biopsy: experience with 110 tumors. *Radiology* 2002;223(03):731–737
- Stacy GS, Mahal RS, Peabody TD. Staging of bone tumors: a review with illustrative examples. *AJR Am J Roentgenol* 2006;186(04):967–976
- Costelloe CM, Chuang HH, Madewell JE. FDG PET/CT of primary bone tumors. *AJR Am J Roentgenol* 2014;202(06):W521–31
- Hayashida Y, Yakushiji T, Awai K, et al. Monitoring therapeutic responses of primary bone tumors by diffusion-weighted image: initial results. *Eur Radiol* 2006;16(12):2637–2643
- Bestic JM, Wessell DE, Beaman FD, et al; Expert Panel on Musculoskeletal Imaging. ACR Appropriateness Criteria® primary bone tumors. *J Am Coll Radiol* 2020;17(5S):S226–S238
- Jaffe N. Chemotherapy for malignant bone tumors. *Orthop Clin North Am* 1989;20(03):487–503
- Strauss SJ, Frezza AM, Abecassis N, et al; ESMO Guidelines Committee, EURACAN, GENTURIS and ERN PaedCan. Electronic address: clinicalguidelines@esmo.org. Bone sarcomas: ESMO-EURACAN-GENTURIS-ERN PaedCan Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2021;32(12):1520–1536
- National Comprehensive Cancer Network. 2021 Bone cancer (version.2.2022). Accessed December 13, 2022, at: https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf
- Puri A, Ranganathan P, Gulia A, Crasto S, Hawaldar R, Badwe RA. Does a less intensive surveillance protocol affect the survival of patients after treatment of a sarcoma of the limb? Updated results of the randomized TOSS study. *Bone Joint J* 2018;100-B(02):262–268

Imaging Recommendations for Diagnosis, Staging, and Management of Soft Tissue Sarcomas

Kenneth Lupton¹ Manjusha Salins² Bill Pass³ Raj Negi⁴ Harun Gupta¹

¹Leeds Teaching Hospitals, Leeds, United Kingdom

²Department of Radiology, Leeds Teaching Hospitals, Leeds, United Kingdom

³Department of Musculoskeletal Radiology, Leeds Teaching Hospitals, Leeds, United Kingdom

⁴Department of Radiology and Imaging, University Hospital Lewisham, London, United Kingdom

Address for correspondence Harun Gupta, MBBS, MD, DNB, MRCP, FRCR, Leeds Teaching Hospitals, Leeds, LS1 3EX, United Kingdom (e-mail: harun.gupta@nhs.net).

Ind J Med Paediatr Oncol 2023;44:261–267.

Abstract

Keywords

- human gammaherpesvirus 8
- human immunodeficiency virus
- MFS
- soft tissue sarcoma

Soft tissue lesions are a wide range of tumors of mesenchymal cell origin, occurring anywhere in the body with a vast number of histological subtypes both benign and malignant. These are common in clinical practice and vast majority are benign. This article focuses on soft tissue sarcoma of the trunk and extremities and discusses their imaging guidelines.

Introduction

Soft tissue sarcoma (STS) refers to a wide range of tumors of mesenchymal cell origin, occurring anywhere in the body with a vast number of histological subtypes both benign and malignant.¹ ► **Table 1** summarizes the main subtypes sarcoma that are comprehensively described by Bansal et al.² The study of STS is a constantly evolving field and regularly updated guidelines exist to summate the most up to date evidence providing a framework against which STS can be managed. This article will focus on imaging STS of the trunk and extremities and will not specifically address retroperitoneal sarcoma, aggressive fibromatosis, or neurofibromatosis.

Risk Factors and Etiopathogenesis

As with most malignancies, there is no single causative factor for STS. Instead, the etiology is multifactorial with both genetic

and environmental factors known to increase the risk of disease. These factors include viral infections (human gamma-herpesvirus 8 and human immunodeficiency virus), previous radiation therapy, chronic lymphoedema, and environmental carcinogens. Several genetic conditions including but not limited to Li-Fraumeni syndrome, neurofibromatosis-1, and Gardner syndrome are also known to increase the risk.^{3–5}

Epidemiology and Clinical Presentation

The disease is rare making up approximately 1% of adult and 15% of childhood malignancies and in 75% of cases occurs in the extremities.^{3,4} The clinical presentation is variable but is typically of a growing soft tissue lump that in some cases may have been present for many years. Constitutional symptoms (weight loss, fever, etc.) are rare but can occur and the disease will often present late.⁶

DOI <https://doi.org/10.1055/s-0042-1760404>.
ISSN 0971-5851.

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)
Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Table 1 Selected sarcoma subtypes excluding peripheral nerve sheath tumors, gastrointestinal stromal tumors, and chondro-osseous tumors. Adapted from article by Bansal et al²

Sarcoma subtype	Benign	Malignant
Adipocytic	Lipoma Lipoma variant	Liposarcoma
Fibroblastic and myofibroblastic	Nodular fasciitis Elastofibroma	Solitary fibrous tumor Myxofibrosarcoma Fibrosarcoma
Fibrohistiocytic tumors	Tenosynovial giant cell tumor	Malignant tenosynovial giant cell tumor
Vascular	Hemangioma Epithelioid hemangioma	Angiosarcoma Epithelioid hemangioendothelioma
Pericytic	Glomus tumor Angioleiomyoma	Malignant glomus tumor
Smooth muscle	Leiomyoma	Leiomyosarcoma
Skeletal muscle	Rhabdomyoma	Rhabdomyosarcoma
Tumors of uncertain differentiation	Myxoma Angiomyolipoma	Synovial sarcoma Alveolar soft part sarcoma Clear cell sarcoma Undifferentiated pleomorphic Sarcoma Undifferentiated spindle cell sarcoma
Neural	Schwannoma Neurofibroma	Malignant peripheral nerve sheath tumor

Imaging Referral Guidelines

The referral for investigation of STS is of paramount importance to ensure that the correct diagnosis can be obtained and appropriate treatment initiated as soon as possible. Patients (both children and adults) should be urgently referred for further investigation in all suspicious soft tissue lumps.⁷ The referral pathway utilised at the authors institution is summarized in ►Fig. 1.

Imaging plays a central role in the workup of STS in terms of early diagnosis, through assessment of treatment response and monitoring for disease recurrence. The choice of initial investigation will depend on clinical factors including site of concern and examination findings. In general, investigation of the head, neck, mediastinum, and retroperitoneum is best served by computed tomography (CT), while ultrasound is considered the optimum initial investigation for clinically palpable lesions. This is reflected in several guidelines that recommended ultrasound as the initial investigation.^{1,2,8} Plain radiographs also have a role in the workup particularly in lesions affecting the extremities. Magnetic resonance imaging (MRI) is considered the gold standard investigation; however, its role as an initial investigation is not supported and instead it is used to further and more accurately characterize lesions.^{2,9}

Clinical/ Diagnostic work-up Excluding Imaging

The variable presentation of sarcoma coupled with its rarity and heterogeneity as a disease entity poses a diagnostic challenge for the clinician at the time of patient presentation. While almost all cases will require imaging to further investi-

gate, it is important to remember that the vast majority will be benign.^{1,10,11} A detailed clinical history and thorough clinical examination should therefore be performed to triage those cases in which there is a higher suspicion of malignancy. This will enable appropriate onward referral.⁷ The clinical history should detail the site, pain symptoms, duration of lump, and any history of malignancy or previous surgery. Further information on the rate of growth and any associated symptoms should also be elucidated. Examination should confirm the size, depth, consistency, mobility, skin alterations, and presence of lesions elsewhere as well as confirm the presence or absence of tenderness. Clinical findings that raise the concern of malignancy include but are not limited to a size of more than 5cm, pain/tenderness, and lesion growth.^{10,11}

Imaging Guidelines

Screening

There is no specific screening program for STS. While in some conditions known to increase the risk—such as Li-Fraumeni syndrome—there may be specific individualized guidance in relation to the detection of malignancy; the broad aim is to encourage early presentation at the development of concerning symptoms.^{4,12}

Diagnosis

As already discussed, imaging is a fundamental component of patient workup for STS and essentially all patients will undergo some form of radiological investigation. The full range of modalities can be utilized, ranging from traditional plain film radiography to newer and less well-established techniques such as positron emission tomography/

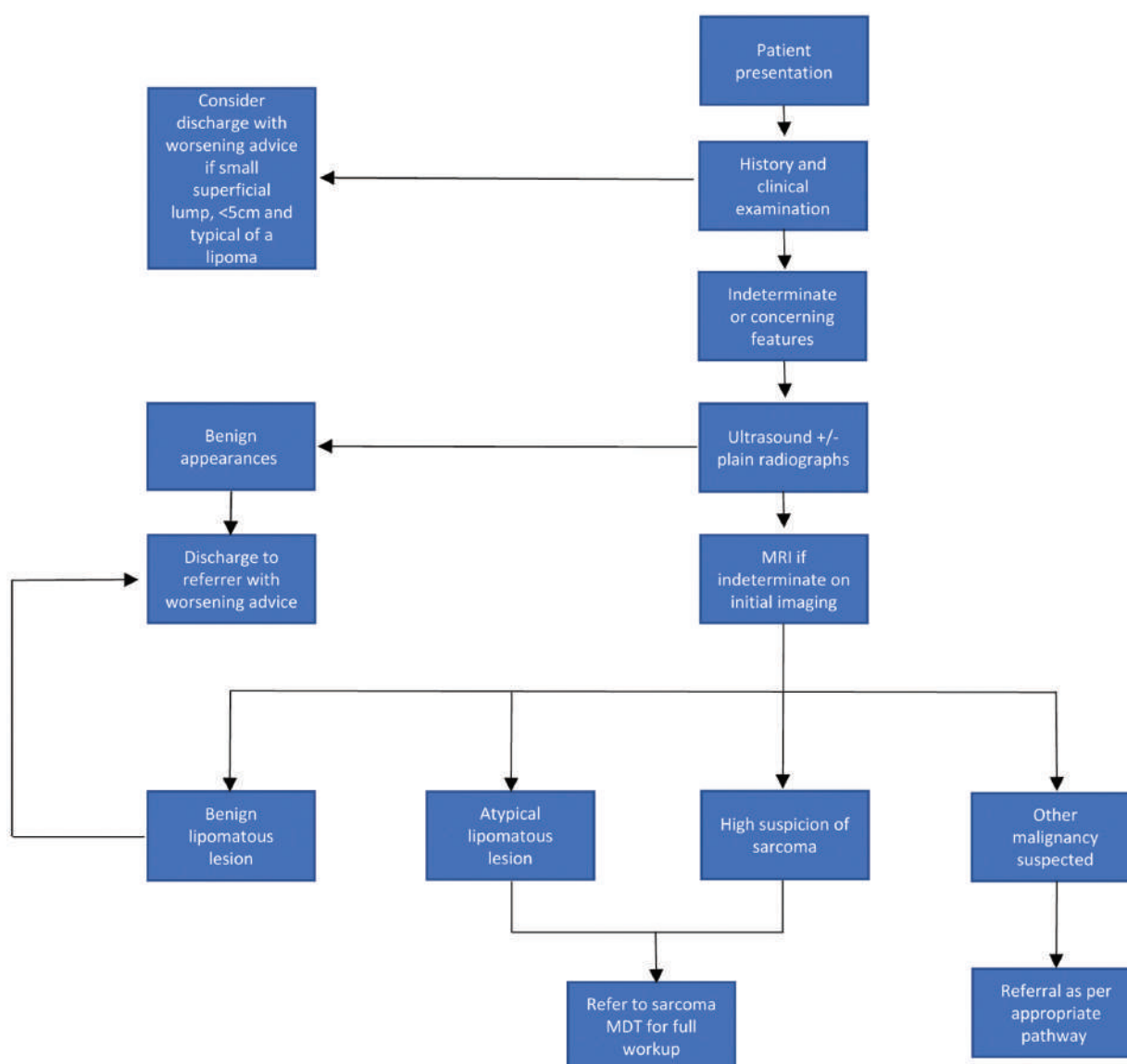


Fig. 1 A simplified referral pathway utilized by the authors institution in combination with relevant recommendations in the literature.

magnetic resonance imaging (PET/MRI). Imaging can be considered in terms of the advantages and disadvantages of the specific modality in question, the clinical presentation, and also the histological subtype of sarcoma that will determine the disease course.^{2,9,13} Detailed below is a summary of the commonly used modalities and their role in the investigation of STS.

Plain radiographs are a cheap and widely available test that can be of use in the initial workup of a soft tissue lump—indeed the American College of Radiologists recommend them as part of the initial evaluation of a superficial lesion.⁹ They are, however, limited by poor soft tissue contrast. For this reason, use is limited to the assessment of any relevant bony or mineralization changes at the site of concern (e.g., periosteal reaction, bony destruction). In certain situations, they may provide a diagnosis or significantly narrow the differential such as a lump corresponding to normal bony

anatomy or reveal the presence of phleboliths indicating a hemangiomatous lesion.^{14,15}

Ultrasound has been shown to be an effective investigation for the initial evaluation of a soft tissue lump.^{16,17} In contrast to plain radiographs, ultrasound provides good soft tissue resolution and is a useful triage test to differentiate benign pathology such as simple lipomas, ganglion cysts, muscle hernias, and uncomplicated vascular malformations from more sinister lesions.^{11,17} The easy access of ultrasound to most primary care physicians has the advantage of providing patients reassurance and reducing the referral burden on local tertiary referral centers.¹⁰ It is, however, limited by several factors, including but not limited to operator experience and patient body habitus. Location is also an important factor to consider as deeper lesions tend not to be easily amenable to assessment, particularly when a large geographical body area is required to be assessed.

Table 2 MRI findings associated with specific sarcoma subtypes. Adapted from article by Scalas et al^{13,20,21,24}

Sign	Sarcoma subtype	Significance
Tail sign	Undifferentiated pleomorphic sarcoma, myxofibrosarcoma	Higher risk of local recurrence and distant metastases at diagnosis
Water like appearance	Myxofibrosarcoma	Increased likelihood of local recurrence with increasing percentage of water like signal within lesion
Triple sign	Synovial sarcoma	Reduced disease-free survival
Absence of calcifications	Synovial sarcoma	Reduced disease-free survival
Signal heterogeneity	Myxoid liposarcoma	High-grade lesions and poorer prognosis

Similarly, bony lesions/bony involvement is not easily assessed.^{17,18}

MRI provides high spatial resolution, optimum soft tissue contrast, and allows accurate assessment of not just lesion size and morphology but also the relationship of the lesion to other structures (including local neurovasculature anatomy) enabling accurate local staging.^{9,13} Studies have assessed the utility of MRI in predicting the eventual grade of lesion and clinical outcome.^{19–23} Crombé et al found that MRI features of tumor necrosis, heterogeneity, and peritumoral enhancement were associated with higher grade lesions. They also found that two or more of these features in combination were associated with a worse metastasis-free survival (MFS) as well as overall survival (OS). Interestingly, when the same principle of the presence of two or more of these features was applied to lower grade lesions (1 and 2), the MFS and OS were the same as for grade 3 lesions with the authors surmising that these MRI features could be used to predict prognosis on the baseline scan.¹⁹ Other features that have been found to correlate with poor outcomes include lesion heterogeneity and size more than 10cm (in all STS subtypes) as well as features specific to individual sarcoma subtypes of which there are several. Scalas et al comprehensively describe several of these features which include the tail sign adjacent to the lesion in undifferentiated pleomorphic sarcoma and myxofibrosarcoma and the so-called triple sign in synovial sarcoma. This reflects the presence of low, intermediate, and high signal within the lesion. These features and others are summarized in ►Table 2 along with their significance.^{13,20,21,24}

CT can be useful in patients unable to undergo MRI assessment (e.g., incompatible pacemakers and severe claustrophobia) or in cases where plain radiographs are unlikely to provide sufficient information on bony anatomy, bony involvement, or matrix mineralization.^{9,14} Indeed, a historic study by Panicek et al acknowledged the superior soft tissue contrast of MRI over CT; however, it did not show an advantage of MRI over CT for local staging translating into improved clinical outcomes.²⁵ It is worth considering that this study was performed over two decades ago and it is at least theoretically possible that with improved imaging techniques, the results could be different were a similar more up to date study performed. It is, therefore, the author's view that every effort should be made to perform an MRI where possible.

FDG-PET-CT is a well-established investigation for the workup of many malignancies. However, its role in the assessment of STS is less so. Several studies have assessed its utility in the workup of STS specifically in terms of the ability to predict tumor behavior and prognosis.^{26–30} Generally, higher maximum standardized uptake value values have tended to correlate with higher grade disease/malignant disease.^{26–28} Caution is, however, advised as there are several limitations, including the low uptake of fluorodeoxyglucose (FDG) in certain tumor subtypes including myxoid liposarcoma and synovial sarcoma that inherently limit the application of PET in these specific subtypes.²⁶ Conversely, there is also a considerable issue of false positives that may arise as the result of inflammatory pathology and benign soft tissue lesions that are FDG avid.^{27,28} Irrespective of these limitations, FDG-PET-CT has been shown to lead to a change in management in a not insignificant number of patients as demonstrated by Lee et al, although this was not necessarily in direct relation to the known diagnosis of STS.²⁹

Percutaneous biopsy is the standard/preferred method by which to obtain a definitive diagnosis. Although this is now a well-established technique, there are pitfalls that the clinician must be aware of including the potential for undergrading the lesion. It is recognized that lesions may harbor areas of higher-grade tumor or dedifferentiation that the biopsy can miss.²⁴ For obvious reasons this may have significant treatment repercussions and may only come to light on subsequent analysis of a surgically excised lesion at which point the tumor is upgraded. To gain as representative sample as possible, it is, therefore, recommended that the biopsy be undertaken by a clinician experienced in sarcoma imaging, usually a radiologist. In addition, guidelines suggest planning the biopsy in conjunction with the operative surgeon such that the biopsy tract can be excised to reduce the likelihood of tumor seeding. While this is common practice, there seems to be relatively little evidence base for this in the literature.³¹ In cases where a percutaneous biopsy is either not possible (e.g., due to anatomical constraints) or has failed, open biopsy can be performed. Small (typically <3cm) lesions can be considered for excisional biopsy.^{1,4,8,32}

Staging

The staging of STS typically follows the American Joint Committee on Cancer (8th edition) guidelines. This provides

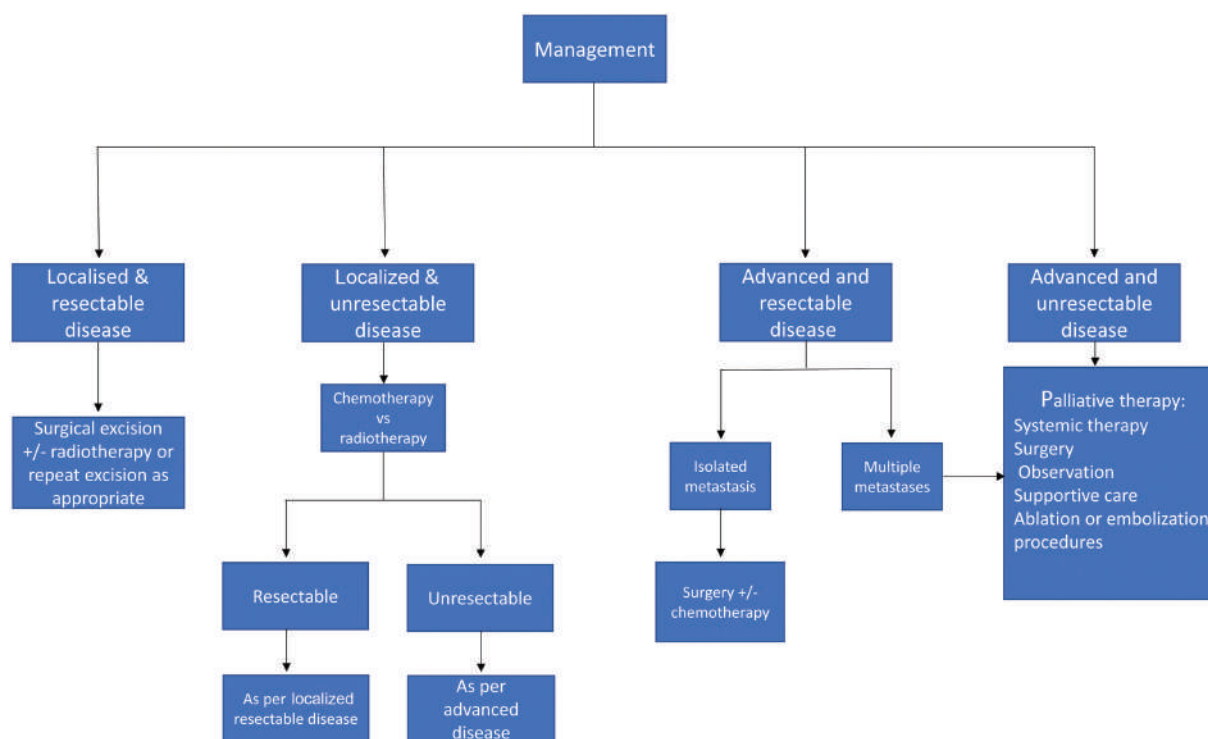


Fig. 2 Summarized flow chart showing the broad principles of management as per the UK, EU and US guidelines.

a tumor, node, and metastasis (TNM) classification, according to lesion size, nodal involvement and distant metastases. The Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC) criteria take into account tumor differentiation, mitotic activity, and extent of necrosis to provide a tumor grade. The TNM score and the tumor grade are used in combination to assign disease stage (I–IV).³³ The approach to staging in terms of imaging will vary somewhat depending on the histology of the tumor. Typical staging consists of CT chest for STS and others include CT abdomen and pelvis for myxoid liposarcoma, and central nervous system imaging is usually performed in cases of alveolar soft part and also clear cell sarcoma as a result of a higher likelihood of metastatic disease to these regions, respectively.^{1,8} Whole body MRI is recommended as part of staging for myxoid liposarcomas due to the possibility of bone metastasis.

Follow-Up

The follow-up of STS is important given the risk of local recurrence (LR) and of distant metastases. While there is no universally agreed regimen, in practice this usually combines clinical examination, imaging to assess the site of primary tumor, and a chest X-ray (CXR) or CT chest to exclude metastatic disease (the lungs being the most common site). It is also important to consider the original grade of tumor as local recurrence is more likely with the higher-grade lesions. It is, therefore, reasonable to follow up such groups more aggressively and this is reflected in various guidelines. Typically, lower grade lesions can be followed up with yearly clinical exam ± MRI, while higher grade lesions are followed up more regularly—intervals ranging from 3 to 6 months initially and gradually tapered down if no recurrent

disease is discovered. Particular attention is paid to the first 2 to 3 years, where the risk of recurrence is at its highest with the risk of recurrence after 10 years considered small.^{1,4,8} It is worth noting that there is dubiety as to the value of imaging follow-up versus clinical examination. Rothermundt et al demonstrated that most local recurrences were picked up clinically, either by the patient or physician on follow-up.³⁴ However, more recent studies have shown improved detection of LR with the use of MRI versus clinical examination alone.^{35,36} The role of CT over CXR has also been questioned in the detection of pulmonary metastases with a study by Puri et al showing that the use of CT neither conferred a survival advantage nor an improvement in the detection of pulmonary metastatic disease.³⁷

Principles of Management

As emphasized in all major guidelines, the cornerstone of good sarcoma care is management through a dedicated and formalized multidisciplinary team meeting. This enables a team of professionals including but not limited to surgeons, oncologists, radiologists, and specialist nurse practitioners to gain sufficient exposure to this rare disease to be in a position to offer the latest evidence-based care to patients. A detailed discussion on the treatment of STS is beyond the scope of this article, but the standard treatment is surgical excision for localized disease. Supplementary therapies are often given and in particular pre/postoperative radiotherapy. Chemotherapy has a role in certain chemosensitive subtypes but in general its use is limited in STS. The specific therapy offered to patients depends on a vast array of factors including histological subtype, amenability to resection, grade of

tumor, co-morbid status/goals of therapy, lesion size, and anatomical location. The management of recurrent disease depends of whether this is localized or metastatic with palliative care often appropriate in the latter. This may take the form of best supportive care, or in specific scenarios ablation/embolization procedures or metastasectomy as appropriate.^{1,4,8} ► **Fig. 2** summarizes the main points in relation to the management of STS according to the UK, US, and European guidelines for illustrative purposes only.^{1,4,8} The reader is advised to refer directly to local guidance according to their area of practice.

Summary of Recommendations

- STS encompasses a heterogenous group of tumors making investigation and management a challenge.
- All patients with a soft tissue lump more than 5cm, rapidly enlarging, or in any way suspicious of sarcoma should be referred for further investigation.
- Ultrasound and plain radiographs are usual baseline tests often able to identify benign pathology and reassure patients.
- MRI is the gold standard investigation and is best able to characterize the lesion with other investigations such as PET-CT utilized on a problem-solving basis.
- The core theme of good sarcoma care is management through a dedicated multidisciplinary team meeting.

Conflict of Interest

None declared.

References

- Dangoor A, Seddon B, Gerrand C, Grimer R, Whelan J, Judson I. UK guidelines for the management of soft tissue sarcomas. *Clin Sarcoma Res* 2016;6(01):20
- Bansal A, Goyal S, Goyal A, Jana M. WHO classification of soft tissue tumours 2020: An update and simplified approach for radiologists. *Eur J Radiol* 2021;143:109937. Doi: 10.1016/j.ejrad.2021.109937
- van Vliet M, Kliffen M, Krestin GP, van Dijke CF. Soft tissue sarcomas at a glance: clinical, histological, and MR imaging features of malignant extremity soft tissue tumors. *Eur Radiol* 2009;19(06):1499–1511
- von Mehren M, Kane JM, Agulnik M, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines®). Soft Tissue Sarcoma. Version 2.2022 - 17/05/2022. NCCN.org. Accessed 23/05/2022. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf
- PDQ Adult Treatment Editorial Board. PDQ Soft Tissue Sarcoma Treatment. Bethesda MD. National Cancer Institute. Updated 19/01/2022. Accessed December 23, 2022, at: <http://www.cancer.gov/types/soft-tissue-sarcoma/hp/adult-soft-tissue-treatment-pdq>
- Ilaslan H, Schils J, Nageotte W, Lietman SA, Sundaram M. Clinical presentation and imaging of bone and soft-tissue sarcomas. *Cleve Clin J Med* 2010;77(1, Suppl 1):S2–S7
- NICE has updated NICE Guideline 12, Suspected cancer: recognition and referral. Guidelines in Practice [Internet]. 2020 Oct [cited 2022 Jun 6];23(10):8. Accessed December 23, 2022, at: <https://search.ebscohost.com/login.aspx?direct=true&AuthType=sso&db=edo&AN=146957423&site=eds-live>
- Gronchi A, Miah AB, Dei Tos AP, et al; ESMO Guidelines Committee, EURACAN and GENTURIS. Electronic address: clinicalguidelines@esmo.org. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up*. *Ann Oncol* 2021;32(11):1348–1365
- Krandsdorf MJ, Murphey MD, Wessell DE, et al; Expert Panel on Musculoskeletal Imaging. ACR Appropriateness Criteria® Soft-Tissue Masses. *J Am Coll Radiol* 2018;15(5S):S189–S197
- Bradley M, Robinson P, Gerrand C, Hayes A, et al. Ultrasound screening of soft tissue masses in the trunk and extremity. A British sarcoma group guide for ultrasonographers and primary care British Sarcoma Group. January 2019. Accessed Dec 2022. <https://britishsarcomagroup.org.uk/news/ultrasound-screening-of-soft-tissue-masses-in-the-trunk-and-extremity/>
- Noebauer-Huhmann IM, Weber MA, Lalam RK, et al. Soft tissue tumors in adults: ESSR-approved guidelines for diagnostic imaging. *Semin Musculoskelet Radiol* 2015;19(05):475–482
- American Cancer Society. Soft Tissue Sarcoma Early Detection, Diagnosis, and Staging [Internet]. Revised 06/04/2018. Cited 06/06/2022. Accessed December 23, 2022, at: <https://www.cancer.org/cancer/soft-tissue-sarcoma/detection-diagnosis-staging/detection.html>
- Scalas G, Parmeggiani A, Martella C, et al. Magnetic resonance imaging of soft tissue sarcoma: features related to prognosis. *Eur J Orthop Surg Traumatol* 2021;31(08):1567–1575
- Aga P, Singh R, Parihar A, Parashari U. Imaging spectrum in soft tissue sarcomas. *Indian J Surg Oncol* 2011;2(04):271–279
- Gartner L, Pearce CJ, Saifuddin A. The role of the plain radiograph in the characterisation of soft tissue tumours. *Skeletal Radiol* 2009;38(06):549–558 cited 2022Jun6 [Internet]
- Rowbotham E, Bhuva S, Gupta H, Robinson P. Assessment of referrals into the soft tissue sarcoma service: evaluation of imaging early in the pathway process. *Sarcoma* 2012;2012:781723
- Lakkaraju A, Sinha R, Garikipati R, Edward S, Robinson P. Ultrasound for initial evaluation and triage of clinically suspicious soft-tissue masses. *Clin Radiol* 2009;64(06):615–621
- Singer AD, Wong P, Umpierrez M, et al. The accuracy of a novel sonographic scanning and reporting protocol to survey for soft tissue sarcoma local recurrence. *Skeletal Radiol* 2020;49(12):2039–2049
- Cromb  A, Marcellin PJ, Buy X, et al. Soft-tissue sarcomas: assessment of MRI features correlating with histologic grade and patient outcome. *Radiology* 2019;291(03):710–721
- Spinnato P, Clinca R, Vara G, et al. MRI features as prognostic factors in myxofibrosarcoma: proposal of MRI grading system. *Acad Radiol* 2021;28(11):1524–1529
- Yoo HJ, Hong SH, Kang Y, et al. MR imaging of myxofibrosarcoma and undifferentiated sarcoma with emphasis on tail sign: diagnostic and prognostic value. *Eur Radiol* 2014;24(08):1749–1757
- Sambri A, Spinnato P, Bazzocchi A, Tuzzato GM, Donati D, Bianchi G. Does pre-operative MRI predict the risk of local recurrence in primary myxofibrosarcoma of the extremities? *Asia Pac J Clin Oncol* 2019;15(05):e181–e186
- Tateishi U, Hasegawa T, Beppu Y, Satake M, Moriyama N. Synovial sarcoma of the soft tissues: prognostic significance of imaging features. *J Comput Assist Tomogr* 2004;28(01):140–148
- Kimber LH, Montgomery EA, Morris CD, Krupinski EA, Fayad LM. MRI characteristics associated with high-grade myxoid liposarcoma. *Clin Radiol* 2017;72(07):613.e1–613.e6
- Panicek DM, Gatsonis C, Rosenthal DI, et al. CT and MR imaging in the local staging of primary malignant musculoskeletal neoplasms: report of the Radiology Diagnostic Oncology Group. *Radiology* 1997;202(01):237–246
- Sambri A, Bianchi G, Longhi A, et al. The role of 18F-FDG PET/CT in soft tissue sarcoma. *Nucl Med Commun* 2019;40(06):626–631
- Bischoff M, Bischoff G, Buck A, et al. Integrated FDG-PET-CT: its role in the assessment of bone and soft tissue tumors. *Arch Orthop Trauma Surg* 2010;130(07):819–827
- Shin DS, Shon OJ, Han DS, Choi JH, Chun KA, Cho IH. The clinical efficacy of (18)F-FDG-PET/CT in benign and malignant musculoskeletal tumors. *Ann Nucl Med* 2008;22(07):603–609

- 29 Lee L, Kazmer A, Colman MW, Gitelis S, Batus M, Blank AT. What is the clinical impact of staging and surveillance PET-CT scan findings in patients with bone and soft tissue sarcoma? *J Surg Oncol* 2022;125(05):901–906
- 30 Kassem TW, Abdelaziz O, Emad-Eldin S. Diagnostic value of ¹⁸F-FDG-PET/CT for the follow-up and restaging of soft tissue sarcomas in adults. *Diagn Interv Imaging* 2017;98(10):693–698
- 31 Seeger LL. Revisiting Tract Seeding and Compartmental Anatomy for Percutaneous Image-Guided Musculoskeletal Biopsies. Vol. 48, *Skeletal Radiology*. Springer Verlag; 2019:499–501
- 32 Veltri A, Bargellini I, Giorgi L, Almeida PAMS, Akhan O. CIRSE guidelines on percutaneous needle biopsy (PNB). *Cardiovasc Intervent Radiol* 2017;40(10):1501–1513
- 33 Cates JMM. The AJCC 8th edition staging system for soft tissue sarcoma of the extremities or trunk: a cohort study of the SEER database. *J Natl Compr Canc Netw* 2018;16(02):144–152 cited 2022Jun7 [Internet]
- 34 Rothermundt C, Whelan JS, Dileo P, et al. What is the role of routine follow-up for localised limb soft tissue sarcomas? A retrospective analysis of 174 patients. *Br J Cancer* 2014;110(10):2420–2426
- 35 Hovgaard TB, Nymark T, Skov O, Petersen MM. Follow-up after initial surgical treatment of soft tissue sarcomas in the extremities and trunk wall. *Acta Oncol* 2017;56(07):1004–1012
- 36 Park JW, Yoo HJ, Kim HS, et al. MRI surveillance for local recurrence in extremity soft tissue sarcoma. *Eur J Surg Oncol* 2019;45(02):268–274
- 37 Puri A, Gulia A, Hawaldar R, Ranganathan P, Badwe RA. Does intensity of surveillance affect survival after surgery for sarcomas? Results of a randomized noninferiority trial. *Clin Orthop Relat Res* 2014;472(05):1568–1575

Imaging Recommendations for Diagnosis, Staging, and Management of Bladder and Urethral Malignancies

Jinita Majithia¹ Gagan Prakash² MH Thakur¹ Palak Popat¹ Nilesh Sable¹ Aparna Katdare¹
Suyash Kulkarni³ Daksh Chandra⁴

¹ Department of Radiodiagnosis, Tata Memorial Hospital, Mumbai, Maharashtra, India

² Department of Uro-Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India

³ Department of Radiology, Tata Memorial Hospital, Mumbai, Maharashtra, India

⁴ Intervention Radiology, Tata Memorial Hospital, Mumbai, Maharashtra, India

Address for correspondence Jinita Majithia, MBBS, DNB, Consultant, Department of Radiodiagnosis, Tata Memorial Hospital, Mumbai, Maharashtra 400012, India (e-mail: jinita_10@hotmail.com).

Ind J Med Paediatr Oncol 2023;44:268–274.

Abstract

Bladder cancer (BCa) is a leading cause of cancer worldwide with high incidence and mortality across all ages. Early diagnosis and treatment can lead to significantly improved survival rate and overall prognosis. Smoking is the biggest contributing factor for the development of BCa. Urothelial carcinoma is the most common histological subtype. Commonly implemented imaging techniques include computed tomography urography (CTU) and multiparametric magnetic resonance imaging (mpMRI). CTU is the investigation of choice for muscle invasive bladder cancer (MIBC) and is best utilized for local assessment and staging of larger and higher staged tumors, that is, T3b and T4. mpMRI encompasses T2-weighted imaging, diffusion-weighted imaging, and dynamic contrast-enhanced imaging. It can differentiate $\leq T1$ and $\geq T2$ tumors based on the Vesicle Imaging-Reporting and Data System (VI-RADS) assessment as well as differentiate Ta from T1 tumors, and is useful in post-therapy response assessment of BCa. Positron emission tomography/computed tomography is used in selected patients of MIBC for metastatic evaluation, particularly those with deranged renal function. A synoptic reporting template should be used to have standardization of data. Primary urethral cancer (UCa) is a rare and aggressive malignancy, accounting for less than 1% of all malignancies. MRI is the investigation of choice for UCa.

Keywords

- bladder cancer
- radiology
- staging
- urethral cancer
- urology

Introduction and Epidemiology

As per GLOBOCAN 2020, there were 573,278 new cases with a total of 212,536 number of deaths associated with bladder cancer (BCa) across all ages and both sexes in the year 2020.¹ BCa was ranked 10th in incidence and 13th in mortality among all cancers, and is estimated to be the 6th most commonly diagnosed cancer in men worldwide.¹ In India,

it is ranked 17th in incidence and 19th in mortality, having varying incidence rates across different regions and populations.²

As per the SEER statistics (Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, US), the 5-year survival rate is as high as 90% for carcinoma in situ and 70% for localized disease, with a significant drop to 36% for regional and 5% for metastatic disease.³ This

DOI <https://doi.org/10.1055/s-0042-1760315>.
ISSN 0971-5851.

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)
Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

indirectly reflects the success of early diagnosis and poor prognosis of metastatic disease. Improved understanding of the disease, superior imaging techniques for diagnosis, and advances in treatment have contributed to a significant decrease in the BCa-related mortality rates worldwide.⁴

A four times higher incidence rate has been observed in men than women.⁵ The worldwide age-standardized incidence rate (per 100,000 person/years) is 9.5 for men and 2.4 for women.⁵ Almost 90% of the newly diagnosed cases of BCa are seen in individuals of age 55 years or older with an average age of diagnosis of 73 years.⁶ BCa is not typically hereditary; however, some cancer syndromes can predispose an individual to BCa, like Cowden syndrome and Lynch syndrome.^{7,8}

Risk Factors and Etiopathogenesis

Active and passive tobacco smoking has a strong relationship with BCa and is one of the greatest risk factors that is quantity and duration dependent. The relative risk for cancer-mortality from smoking is second only to lung cancer.⁹ The attributable risk to smoking is similar between men and women.^{5,9} Exposure to aromatic amines, polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons from dyes, paint, metal, rubber, or petroleum industries is another common preventable risk factor for BCa. Occupational exposures are responsible for approximately 18% of all BCa cases.¹⁰ An environmental factor most commonly implicated in BCa is arsenic consumption, typically through ingestion of contaminated water.¹¹ Increased rates of secondary BCa have also been reported following use of external-beam radiotherapy (EBRT) for gynecological malignancies; however, lower rates have been observed with use of intensity-modulated radiotherapy for prostate cancer.^{12,13} A tropical protozoan schistosomiasis, through generation of N-nitroso carcinogenic compound,¹⁴ and chronic bladder irritation from indwelling catheters or vesicle stones are responsible for squamous cell carcinoma (SCC) of the bladder.

Urothelial carcinoma (UC), also known as transitional cell carcinoma, is the most common subtype of BCa, seen in 90% of cases.¹⁵ At presentation, approximately 2% cases with urothelial BCa will have a synchronous upper urinary tract tumor and approximately 6% will develop a metachronous lesion.¹⁶ SCC is the second most common subtype of BCa, representing 6 to 8% of all cases. The incidence rate of SCC is disproportionately higher, up to 50%, in endemic areas of schistosomiasis.¹⁴ Adenocarcinomas are rare, accounting for less than 2% cases. They may be urachal (one-third) or nonurachal (two-third). Other histologic types of BCa, such as lymphoma, carcinosarcoma, small cell carcinoma, pheochromocytoma and sarcoma, are also extremely rare.¹⁷ The presence of some of these variant histology subtypes increases the chances of distant metastases even in nonmuscle invasive bladder cancer (NMIBC), suggesting the need for cross sectional imaging.

Clinical Features

The most common presentation of BCa is painless hematuria, either gross or microscopic. Other symptoms like urgency,

dysuria, increased frequency, pelvic pain, and symptoms related to urinary tract obstruction may also be observed. Urinary tract infection is a less common presenting symptom. Urine cytology for voided exfoliated cancer cells has good sensitivity and is a useful indicator of high-grade malignancy; however, it lacks specificity as it is unable to localize the origin of the UC in the entire urinary tract. A negative cytology does not exclude malignancy. Urine cytology is not routinely performed for initial evaluation of hematuria but can be considered when there is suspicion of BCa, as per NCCN (National Comprehensive Cancer Network) guidelines.¹⁸ The United States Food and Drug Administration (FDA) has currently approved six urinary assays to use alongside cystoscopy for diagnosis and surveillance; these include nuclear matrix proteins 22 and bladder tumor antigen assays.

Role of Imaging

Imaging plays a key role in the diagnosis, locoregional, and distant staging, for deciding management protocols and for follow-up. Various techniques are available for imaging the urinary tract, commonly used are computed tomography urography (CTU), magnetic resonance imaging (MRI) pelvis, and whole body [¹⁸F]Fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG-PET/CT) and historically intravenous urography. According to NCCN, no single follow-up plan is suitable or appropriate for all patients and the follow-up intervals should be individualized. Routine screening for BCa beyond the high-risk population is currently not recommended.¹⁹ The gold standard for confirmation of BCa is direct visualization of the tumor on cystoscopy (flexible or rigid) and transurethral resection of bladder tumor (TURBT). TURBT is performed for pathological confirmation with the goal to resect all of the visible tumor up to muscle depth.

Ultrasonography

According to the American College of Radiology "Appropriateness Criteria," ultrasound is recommended as the initial diagnostic evaluation for microscopic hematuria.²⁰ The specificities of ultrasonography and CTU are found to be similar; however, CTU has a higher sensitivity.

Computed Tomography

CTU is the most common and preferred imaging modality for patients in whom intravenous iodinated contrast can be safely injected without contraindications and has successfully replaced the historical fluoroscopy-guided intravenous pyelography. It has high diagnostic accuracy (91%), sensitivity (79–93%), and specificity (83–99%).^{21,22} The high specificity of CTU allows the treating physician to eliminate the use of a diagnostic flexible cystoscopy in the outpatient department and directly do a rigid cystoscopy, often at the same time as TURBT. CTU can be performed by the "single-bolus technique" with administration of a full bolus and acquisition of three phases, that is, noncontrast, urothelial, and delayed excretory or by the "split-bolus technique" with a

noncontrast phase and a single urothelial and excretory phase following administration of a partial bolus. Split-bolus technique has the advantage of reduced radiation exposure but comes at the potential cost of missing smaller lesions.

According to the NCCN guidelines, CTU is the investigation of choice for patients with high suspicion for BCa, for primary evaluation of diagnosed cases, for staging and restaging, and for surgical planning.¹⁸ It is also the investigation of choice for metastatic assessment in MIBC.²³ It allows macroscopic characterization (site, size, and number) and extent of lesion; **T** Stage, evaluation of spread to primary/regional (perivesicle, internal iliac, external iliac, obturator, and presacral) and secondary/distant (common iliac, para-aortic, aortocaval, and paracaval) lymph nodes; **N** Stage, aides in assessing the involvement of upper urinary tract and distant organs; **M** Stage, involvement of lymph nodes above the iliac chain is considered metastatic disease. Metastasis to the lung and liver is common and to the bone and brain is rare.

On CT, BCa appears as intraluminal papillary masses with frond-like appearance or as nodular masses or as focal or diffuse wall thickening. Early enhancement is observed. Calcification can be seen in approximately 5% cases, typically encrusting the surface of the tumor and may be nodular or arched.²⁴ CTU is suboptimal, as compared with MRI, in the differentiation of NMIBC from muscle invasive bladder cancer (MIBC) and in the local staging of smaller tumors and cancers less than T3a stage. However, it is best utilized for local assessment and staging of larger and higher staged tumors, that is, T3b and T4.²⁵ CT is also used for restaging high-risk NMIBC and MIBC following treatment. CT is useful for nodal staging of BCa, as it identifies regional and distant nodal metastasis. Morphological abnormalities, such as enlarged size, round shape, irregular borders, central necrosis, and loss of fatty hilum, are the major criteria for categorizing lymph nodes. The accepted measurement cutoff for suspicious lymph nodes is 10 mm for abdominal adenopathy and 8 mm for pelvic adenopathy in the short axis²⁶ however, the accuracy varies widely based on the cutoff used.

Magnetic Resonance Imaging

Growing interest in the application of multiparametric MRI (mpMRI) for imaging in BCa is a result of its superior soft tissue resolution. mpMRI has proven to be successful in differentiating MIBC from NMIBC with a high diagnostic accuracy; thus, it is the investigation of choice for T-Staging of BCa. Recent systemic reviews and meta-analysis have shown a better sensitivity and specificity of mpMRI for differentiating $\leq T1$ and $\geq T2$ tumors.^{27,28}

MRI should be performed before endoscopic management or at least 2 weeks after cystoscopic procedures and intravesicle treatments and a gap of 2 days should be maintained after removal of indwelling catheters to minimize artifacts from intravesicle air. Optimal bladder distention and administration of antispasmodic agents are methods to reduce motion artifacts from peristalsis. mpMRI consists of anatomical T2-weighted images (T2WI), functional diffusion-weighted images (DWI), and dynamic contrast-enhanced (DCE). Ideally, large field-of-view (FOV) T1W spin echo

sequence, from the aortic bifurcation to the pubic symphysis, should also be performed before contrast administration for the evaluation of metastatic retroperitoneal adenopathy. mpMRI has limitations in assessment of metastatic disease because of the smaller FOV; however, there is a paradigm shift to MRI for metastatic evaluation with the introduction of PET/MR and whole-body MRI.²³

T2WI without fat saturation performed in at least two planes (axial, coronal and / or sagittal) is primarily used for anatomic characterization of the tumor, like lesion size, growth pattern, morphology, location, and the degree of interruption of muscle, all of which are essential for local staging.^{22,29} Isotropic three-dimensional T2W images can serve as an adjunct.²⁹ DWI provides qualitative and quantitative data regarding cellularity of the tumor. High cellularity tumors reveal bright signal intensity on DWI. The apparent-diffusion coefficient (ADC) map is a quantitative representation of restricted diffusion showing decreased signal intensity corresponding to the high cellularity and aggressiveness of the tumor, thus identifying the possible histological grade of the tumor. The muscularis propria layer of the bladder wall is identified on T2WI and DWI, showing low-signal intensity on T2WI and intermediate signal on DWI. The tumor can be easily distinguished by its intermediate signal intensity on T2WI and high-signal intensity on DWI. Muscle invasion can be inferred if interruption in the low signal intensity is seen on T2WI and intermediate signal intensity on DWI can be demonstrated, thus making these two sequences the most useful sequences for identifying MIBC and consequently for local staging of BCa.²⁹ The infiltration of extravescicle tissue is also best demonstrated on T2WI as hypo- to intermediate intensity infiltrative streaks in contrast to the hyperintense extravescicle fat. Higher b-value sequences improve the detection of nodal disease and marginally improve the sensitivity and specificity³⁰; thus, DWI should be generated with at least two b-value sequences.

DCE images are multiple, rapidly acquired fat suppressed gradient echo sequence T1WIs obtained before, during and after intravenous administration of gadolinium contrast. The highly vascular inner layer, that is, the urothelium and lamina propria, which is not well visualized on T2WI and DWI, can be very well demonstrated on early sequences of DCE images as an avidly enhancing inner most layer. The muscularis layer enhances later, slowly, and progressively. Thus, DCE imaging is best suited for demonstration of the early enhancing BCa. There is a statistically significant improvement in the specificity and accuracy of mpMRI in differentiating T1 stage BCa from lower-grade tumors T2 stage BCa when DCE imaging supplements DWI and T2WI.³¹

Patients in whom TURBT reveals muscle invasion, surgery becomes only of diagnostic value. There is concern that this could delay the definitive management of MIBC, which entails chemotherapy and cystectomy or radiation therapy. Further, there are also concerns of micro-perforations during TURBT of large tumors which might potentially upstage the disease. Based on this apprehension, the BladderPath trial was designed which is trying to assess if MRI could obviate the need for TURBT in patients who are likely to be harboring a muscle invasive disease.³²

Differentiation of Ta from T1 tumors is also possible with mpMRI. These tumors present as sessile or pedunculated masses and the imaging features of the center or stalk of the tumor can correspond to the stage of the lesion. The phase of enhancement of the submucosal tissue is usually earlier than that of the cancer component in Ta cancer; however, the cancer component usually enhances as strongly as the submucosal tissue in T1 cancer on DCE imaging.³³ Additionally, difference in the Ta to T1 tumors can also be related to the size of the tumor in contact with the bladder wall.³³

T2WI has limited application in post-therapy evaluation of BCa due to presence of inflammation and fibrosis. DWI has higher specificity and sensitivity compared with T2WI and DCE for accurately predicting histopathological response.²⁹ Changes in the ADC value after administration of neoadjuvant chemotherapy or following chemoradiation is an early indicator of pathologic response.³⁴ A recent study (PURE-01) evaluated the potential use of mpMRI as a tool for assessing complete tumor response to pembrolizumab, which is an FDA approved immune checkpoint inhibitor (programmed cell death protein 1 [PD-1] inhibitor).^{34,35}

Positron Emission Tomography

As per the American College of Radiology (ACR) Appropriateness Criteria for pre-treatment staging of MIBC, the use of PET/CT in BCa is considered as “may be appropriate.”³⁶ European Association of Urology and the European Society for Medical Oncology recently issued a consensus statement, stating that FDG-PET/CT should be used for staging of oligo-metastatic BCa when radical treatment is considered to minimize the risk of overtreatment.³⁷ The NCCN guidelines suggest that PET/CT may be useful for selected patients $\geq$ T2 tumors of MIBC and can significantly alter the treatment approach in $\geq$ T3 tumors. PET/CT has a pooled sensitivity and specificity for detection of lymph node metastases of 57 and 95%, respectively.³⁸ PET/CT is most often utilized in MIBC where the incidence of metastasis is much higher compared with NMIBC, where routine use of PET/CT is not justified.

PET/CT can be utilized for metastatic staging of BCa (not local staging) and for response assessment and restaging after neoadjuvant chemotherapy. The greatest strength of PET/CT is its ability to detect metastasis in lymph nodes that are not pathologically enlarged. An integrated approach, with information on the standardized uptake values and the size criterion of lymph nodes, can improve the accuracy of PET/CT.³⁹ FDG-PET/CT also serves as a noninvasive indicator of PD-1/PD-L1 expression that is extremely beneficial especially with introduction of newer targeted immunotherapy, like pembrolizumab.⁴⁰ FDG-PET/CT is accurate in distinguishing primary tumor downstaging from nonresponse in BCa.⁴¹ For the detection of recurrent BCa, the sensitivity and specificity of PET/CT are 94 and 76%, respectively.⁴²

PET/MR is a novel hybrid imaging modality that combines the advantage of superior soft tissue resolution of mpMRI with the metabolic and functional information of PET, providing greater accuracy for detecting tumors, pelvic lymph node metastasis, and nonnodal pelvic malignancy.⁴³ It is also useful for evaluating response to neoadjuvant chemotherapy.

Two new, alternative, experimental radiotracer agents being evaluated for use in imaging of BCa are [¹¹C] choline and [¹¹C] acetate. Their diagnostic accuracy for lymph node staging showed a pooled sensitivity and specificity of 66 and 89%, respectively.⁴⁴

A significant proportion of patients with MIBC present with obstructive uropathy and deranged parameters. While some of them may be eligible for contrast studies following urinary diversion, an early assessment of the disease burden in these patients can best be done using FDG-PET-CT.

Image-Guided Interventions

Intractable hematuria in patients with lower urinary tract malignancies has been successfully treated with selected transcatheter arterial embolization. Cross-sectional imaging may depict intravesicle clots; however, CTU and DCE MRI both can be unsuccessful in accurately locating the site of bleed. When radical surgery is not feasible or contraindicated, angiography with embolization, as a palliative approach, provides a minimally invasive means to control bladder hemorrhage.⁴⁵

Percutaneous cryoablation is being explored as a minimally-invasive technique, which can be used as an adjuvant therapy with TURBT to eliminate the possibility of residual tumor in MIBC and high-risk NMIBC to the maximum possible extent.⁴⁶ It is also considered in few cases to eliminate the of systemic chemotherapy and decrease the degree of complications.⁴⁷ Very few studies have used CT guidance for cryoablation; transurethral approach is generally preferred. Although still under exploration, it shows a promise in the future as an alternative to the current first-line of treatment, that is, TURBT.

VI-RADS

Vesicle Imaging-Reporting and Data System (VI-RADS), developed in 2018, is a standardized mpMRI-based scoring system, incorporating tumor appearances on T2WI, DWI, and DCE imaging for assessing the overall risk of muscle invasion. It provides a systemic reporting template for preoperative staging of BCa. It also provides information on the management approach, assessment of therapeutic response, and prognosis. Multiple retrospective and prospective studies have investigated the validity and reproducibility of VI-RADS upon confirmation with TURBT, and demonstrated good diagnostic accuracy and reliability.^{48–50}

VI-RADS score incorporates three categories; structural category (SC) that is assessed on T2WI, contrast-enhanced category (CE) assessed on DCE imaging and the diffusion-weighted category (DW) assessed on DWI which have been tabulated in Tables 1, 2 and 3, in an attempt to simplify the different assessment categories.²⁹

The final score is firstly based on T2WI based on morphology, because of its high spatial resolution in evaluating the integrity of muscularis propria. However, the presence of definitive muscle invasion is decided by DWI and DCE imaging, which are the dominant sequences for risk assessment. In case of discordance between T2WI and DCE images,

DWI improves the accuracy.^{51,52} An algorithm for approach to final VI-RADS category of BCa is provided in Table 4. A schematic diagram of mpMRI appearances of VI-RADS categories has been presented in Figure 1.

Approach to Reporting

The American Joint Committee on Cancer (AJCC) Staging Manual, 8th edition, provides structured guidelines for the staging of BCa (Table 5.1 and 5.2). A TNM Stage; **T** (tumor), **N** (node) and **M** (metastasis); of the tumor is provided which stratifies patients into different stages of cancer allowing prognostication and guiding patient management.

A synoptic template for reporting is also proposed, elaborating primary tumor characteristics and nodal and metastatic disease, making it simpler for a radiologist and the treating physician and surgeon to follow a checklist which includes all relevant clinical and radiological information that can potentially influence patient management (Figure 2).

Urethral Cancer

Primary urethral cancer (UCa) is a rare and aggressive malignancy. Secondary UCa is a recurrent carcinoma, following a treated primary in the urinary tract, usually reported after radical cystectomy in a case of BCa.⁵³ Primary UCa accounts for less than 1% of all malignancies⁵⁴ and as per the SEER analysis, the incidence is highest above the age of 75 years (0.76/lakh) and almost negligible in less than 55 years (0.02/lakh),⁵⁵ with a male preponderance. The common predisposing risk factors for UCa include urethral strictures, chronic irritation after intermittent catheterization/urethroplasty, external-beam radiation therapy (EBRT) to the pelvis, radioactive seed implantation, and chronic urethral inflammation or urethritis following sexually transmitted diseases (like HPV16) in men and urethral diverticula and recurrent urinary tract infections in women. UC is the predominant histologic subtype, followed by SCC and adenocarcinoma. Clear cell adenocarcinoma has a congenital cause.

The most common location for UCa in men is the bulbomembranous urethra, whereas in women the anterior urethra, comprising of the distal one-third, is the most common location. Conventional imaging techniques, like voiding cystourethrography and retrograde urethrography, are helpful for urethral imaging in men, however, and are invasive and unable to evaluate extraluminal spread or periurethral conditions.⁵⁶ High-resolution, transvaginal, transperineal, and transurethral ultrasound have also been explored; however, MRI is the mainstay for urethral imaging in both sexes.

MRI is useful for diagnosis and characterization of tumor and local staging of UCa. The commonly performed sequences include T1WI, T2WI, and post-contrast T1WI in small FOV. Larger FOV is used for imaging the pelvic and inguinal lymph nodes that constitute the route for metastatic spread of UCa. Relative to the normal corporal tissue, UCa appears hypointense on T1WI, hypointense on T2WI, and progressively enhances on post-contrast T1WI. In men, invasion of the corpus spongiosum, prostate and periurethral muscle,

upstages UCa with further upstaging following invasion of corpus cavernosa. Anterior urethral lesions can metastasize to the inguinal group of lymph nodes and eventually external iliac group, whereas posterior UCa extends to the deep pelvic lymph nodes.

The differential diagnosis for UCa includes complex cystic periurethral lesions like inflamed urethral diverticulum, amyloidosis, and rarely hematogenous metastasis to corpus spongiosum in men with melanoma, prostate, bladder, colon, testicular, and renal cancers.⁵⁷

The extent of surgical clearance of disease may vary from only urethrectomy to total penectomy to cysto-prostato-urethrectomy and MRI is the cornerstone imaging for surgical planning.

References

- 1 Accessed December 12, 2022, at: <https://gco.iarc.fr/today/data/factsheets/cancers/30-Bladder-fact-sheet.pdf>
- 2 Three-Year Report of Population Based Cancer Registries 2012–2014. 2016. Incidence, Distribution, Trends in Incidence Rates and Projections of Burden of Cancer (Report of 27 PBCRs in India). Accessed December 12, 2022, at: http://www.ncdirindia.org/NCRP/all_ncrp_reports/pbcr_report_2012_2014/all_content/pdf_printed_version/preliminary_pages_printed.pdf
- 3 SEER*Explorer. [(accessed on 13 January 2020)]; Accessed December 12, 2022, at: <https://seer.cancer.gov/explorer/>
- 4 Al-Husseini MJ, Kunbaz A, Saad AM, et al. Trends in the incidence and mortality of transitional cell carcinoma of the bladder for the last four decades in the USA: a SEER-based analysis. *BMC Cancer* 2019;19(01):46
- 5 Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of bladder cancer. *Med Sci (Basel)* 2020;8(01):15
- 6 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019;69(01):7–34
- 7 Riegert-Johnson DL, Gleeson FC, Roberts M, et al. Cancer and Lhermitte-Duclos disease are common in Cowden syndrome patients. *Hered Cancer Clin Pract* 2010;8(01):6. Doi: 10.1186/1897-4287-8-6
- 8 van der Post RS, Kiemeny LA, Ligtenberg MJL, et al. Risk of urothelial bladder cancer in Lynch syndrome is increased, in particular among MSH2 mutation carriers. *J Med Genet* 2010; 47(07):464–470
- 9 Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. *JAMA* 2011;306(07):737–745
- 10 Chen HI, Liou SH, Loh CH, Uang SN, Yu YC, Shih TS. Bladder cancer screening and monitoring of 4,4'-methylenebis(2-chloroaniline) exposure among workers in Taiwan. *Urology* 2005;66(02): 305–310
- 11 Marshall G, Ferreccio C, Yuan Y, et al. Fifty-year study of lung and bladder cancer mortality in Chile related to arsenic in drinking water. *J Natl Cancer Inst* 2007;99(12):920–928
- 12 Chrouser K, Leibovich B, Bergstralh E, Zincke H, Blute M. Bladder cancer risk following primary and adjuvant external beam radiation for prostate cancer. *J Urol* 2005;174(01):107–110, discussion 110–111
- 13 Zelefsky MJ, Housman DM, Pei X, et al. Incidence of secondary cancer development after high-dose intensity-modulated radiotherapy and image-guided brachytherapy for the treatment of localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;83(03):953–959
- 14 Verma S, Rajesh A, Prasad SR, et al. Urinary bladder cancer: role of MR imaging. *Radiographics* 2012;32(02):371–387
- 15 Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO Classification of tumors of the urinary system and

- male genital organs—part B. Prostate and Bladder Tumors. *Eur. Urol.* 2016;70:106–119
- 16 Lee CH, Tan CH, Faria SC, Kundra V. Role of imaging in the local staging of urothelial carcinoma of the bladder. *AJR Am J Roentgenol* 2017;208(06):1193–1205
 - 17 Chalasani V, Chin JL, Izawa JL. Histologic variants of urothelial bladder cancer and nonurothelial histology in bladder cancer. *Can Urol Assoc J* 2009;3(6, Suppl 4):S193–S198
 - 18 Flaig TW, Spiess PE, Agarwal N, et al. Bladder cancer, Version 3.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2020;18(03):329–354
 - 19 Sun M, Trinh Q-D. Diagnosis and staging of bladder cancer. *Hematol Oncol Clin North Am* 2015;29(02):205–218, vii
 - 20 Wolfman DJ, Marko J, Nikolaidis P, et al. Expert panel on urological imaging. ACR Appropriateness Criteria® Hematuria. *J Am Coll Radiol* 2020;17(5S):S138–S147
 - 21 Trinh TW, Glazer DI, Sadow CA, Sahni VA, Geller NL, Silverman SG. Bladder cancer diagnosis with CT urography: test characteristics and reasons for false-positive and false-negative results. *Abdom Radiol (NY)* 2018;43(03):663–671
 - 22 Mirmomen SM, Shinagare AB, Williams KE, Silverman SG, Malayeri AA. Preoperative imaging for locoregional staging of bladder cancer. *Abdom Radiol (NY)* 2019;44(12):3843–3857
 - 23 Galgano SJ, Porter KK, Burgan C, Rais-Bahrami S. The role of imaging in bladder cancer diagnosis and staging. *Diagnostics (Basel)* 2020;10(09):703
 - 24 Moon WK, Kim SH, Cho JM, Han MC. Calcified bladder tumors. CT features. *Acta Radiol* 1992;33(05):440–443
 - 25 Mossanen M, Chang SL, Kimm S, Sonpavde GP, Kibel AS. Current staging strategies for muscle-invasive bladder cancer and upper tract urothelial cell carcinoma. *Urol Clin North Am* 2018;45(02):143–154
 - 26 Pichler R, De Zordo T, Fritz J, et al. Pelvic lymph node staging by combined ¹⁸F-FDG-PET/CT imaging in bladder cancer prior to radical cystectomy. *Clin Genitourin Cancer* 2017;15(03):e387–e395
 - 27 Cornelissen SWE, Veenboer PW, Wessels FJ, Meijer RP. Diagnostic accuracy of multiparametric MRI for local staging of bladder cancer: a systematic review and meta-analysis. *Urology* 2020;145:22–29
 - 28 Gandhi N, Krishna S, Booth CM, et al. Diagnostic accuracy of magnetic resonance imaging for tumour staging of bladder cancer: systematic review and meta-analysis. *BJU Int* 2018;122(05):744–753
 - 29 Panebianco V, Narumi Y, Altun E, et al. Multiparametric magnetic resonance imaging for bladder cancer: development of VI-RADS (vesical imaging-reporting and data system). *Eur Urol* 2018;74(03):294–306
 - 30 Caglic I, Panebianco V, Vargas HA, et al. MRI of bladder cancer: local and nodal staging. *J Magn Reson Imaging* 2020;52(03):649–667
 - 31 Takeuchi M, Sasaki S, Ito M, et al. Urinary bladder cancer: diffusion-weighted MR imaging—accuracy for diagnosing T stage and estimating histologic grade. *Radiology* 2009;251(01):112–121
 - 32 Bryan RT, Liu W, Pirrie SJ, et al. Comparing an imaging-guided pathway with the standard pathway for staging muscle-invasive bladder cancer: preliminary data from the BladderPath Study. *Eur Urol* 2021;80(01):12–15
 - 33 Yuan L, Li D, Mu D, et al. Combined T2 SPAIR, dynamic enhancement and DW imaging reliably detect T staging and grading of bladder cancer with 3.0T MRI. *Front Oncol* 2020;10:582532
 - 34 Necchi A, Bandini M, Calareso G, et al. Multiparametric magnetic resonance imaging as a noninvasive assessment of tumor response to neoadjuvant pembrolizumab in muscle-invasive bladder cancer: preliminary findings from the PURE-01 study. *Eur Urol* 2020;77(05):636–643
 - 35 Bidnur S, Savdie R, Black PC. Inhibiting immune checkpoints for the treatment of bladder cancer. *Bladder Cancer* 2016;2(01):15–25
 - 36 van der Pol CB, Sahni VA, Eberhardt SC, et al; Expert Panel on Urologic Imaging. ACR appropriateness criteria® pretreatment staging of muscle-invasive bladder cancer. *J Am Coll Radiol* 2018;15(5S):S150–S159
 - 37 Witjes JA, Babjuk M, Bellmunt J, et al. EAU-ESMO consensus statements on the management of advanced and variant bladder cancer—An International Collaborative Multistakeholder Effort†: Under the Auspices of the EAU-ESMO Guidelines Committees. *Eur Urol* 2020;77(02):223–250
 - 38 Soubra A, Hayward D, Dahm P, et al. The diagnostic accuracy of ¹⁸F-fluorodeoxyglucose positron emission tomography and computed tomography in staging bladder cancer: a single-institution study and a systematic review with meta-analysis. *World J Urol* 2016;34(09):1229–1237
 - 39 Girard A, Rouanne M, Taconet S, et al. Integrated analysis of ¹⁸F-FDG PET/CT improves preoperative lymph node staging for patients with invasive bladder cancer. *Eur Radiol* 2019;29(08):4286–4293
 - 40 Chen R, Zhou X, Liu J, Huang G. Relationship between the expression of PD-1/PD-L1 and ¹⁸F-FDG uptake in bladder cancer. *Eur J Nucl Med Mol Imaging* 2019;46(04):848–854
 - 41 van de Putte EEF, Vegt E, Mertens LS, et al. FDG-PET/CT for response evaluation of invasive bladder cancer following neo-adjuvant chemotherapy. *Int Urol Nephrol* 2017;49(09):1585–1591
 - 42 Zattoni F, Incerti E, Colicchia M, et al. Comparison between the diagnostic accuracies of ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography and conventional imaging in recurrent urothelial carcinomas: a retrospective, multicenter study. *Abdom Radiol (NY)* 2018;43(09):2391–2399
 - 43 Rosenkrantz AB, Friedman KP, Ponzo F, et al. Prospective pilot study to evaluate the incremental value of PET information in patients with bladder cancer undergoing ¹⁸F-FDG simultaneous PET/MRI. *Clin Nucl Med* 2017;42(01):e8–e15
 - 44 Kim S-J, Koo PJ, Pak K, Kim I-J, Kim K. Diagnostic accuracy of C-11 choline and C-11 acetate for lymph node staging in patients with bladder cancer: a systematic review and meta-analysis. *World J Urol* 2018;36(03):331–340
 - 45 Loffroy R, Pottecher P, Cherblanc V, et al. Current role of transcatheter arterial embolization for bladder and prostate hemorrhage. *Diagn Interv Imaging* 2014;95(11):1027–1034
 - 46 Liu S, Zhang L, Zou L, Wen H, Ding Q, Jiang H. The feasibility and safety of cryoablation as an adjuvant therapy with transurethral resection of bladder tumor: a pilot study. *Cryobiology* 2016;73(02):257–260
 - 47 Liang Z, Fei Y, Lizhi N, et al. Percutaneous cryotherapy for metastatic bladder cancer: experience with 23 patients. *Cryobiology* 2014;68(01):79–83
 - 48 Barchetti G, Simone G, Ceravolo I, et al. Multiparametric MRI of the bladder: inter-observer agreement and accuracy with the Vesical Imaging-Reporting and Data System (VI-RADS) at a single reference center. *Eur Radiol* 2019;29(10):5498–5506
 - 49 Ueno Y, Takeuchi M, Tamada T, et al. Diagnostic accuracy and interobserver agreement for the Vesical Imaging-Reporting and Data System for muscle-invasive bladder cancer: a multireader validation study. *Eur Urol* 2019;76(01):54–56
 - 50 Del Giudice F, Barchetti G, De Berardinis E, et al. Prospective Assessment of Vesical Imaging Reporting and Data System (VI-RADS) and Its Clinical Impact on the Management of High-risk Non-muscle-invasive Bladder Cancer Patients Candidate for Repeated Transurethral Resection. *Eur Urol* 2020;77(01):101–109
 - 51 Panebianco V, De Berardinis E, Barchetti G, et al. An evaluation of morphological and functional multi-parametric MRI sequences in classifying non-muscle and muscle invasive bladder cancer. *Eur Radiol* 2017;27(09):3759–3766

- 52 Woo S, Suh CH, Kim SY, Cho JY, Kim SH. Diagnostic performance of MRI for prediction of muscle-invasiveness of bladder cancer: a systematic review and meta-analysis. *Eur J Radiol* 2017;95:46–55
- 53 Boorjian SA, Kim SP, Weight CJ, Cheville JC, Thapa P, Frank I. Risk factors and outcomes of urethral recurrence following radical cystectomy. *Eur Urol* 2011;60(06):1266–1272
- 54 Gatta G, van der Zwan JM, Casali PG, et al; RARECARE working group. Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer* 2011;47(17):2493–2511
- 55 Swartz MA, Porter MP, Lin DW, Weiss NS. Incidence of primary urethral carcinoma in the United States. *Urology* 2006;68(06):1164–1168
- 56 Chaudhari VV, Patel MK, Douek M, Raman SS. MR imaging and US of female urethral and periurethral disease. *Radiographics* 2010;30(07):1857–1874
- 57 Kawashima A, Sandler CM, Wasserman NF, LeRoy AJ, King BF Jr, Goldman SM. Imaging of urethral disease: a pictorial review. *Radiographics* 2004;24(Suppl 1):S195–S216

Imaging Recommendations for Diagnosis, Staging, and Management of Testicular Cancer

Aparna Katdare^{1,2} Palak Popat^{1,2} Rachel Sequeira³ Nilesh Sable^{1,2} Kunal Gala^{1,2}
Daksh Chandra^{1,2} Archi Agrawal^{1,2} Gagan Prakash^{1,2} Vedang Murthy^{1,2} Santosh Menon^{1,2}
Amit Joshi^{1,2} Ajaykumar Singh^{1,2} Suyash Kulkarni^{1,2}

¹ Department of Radiodiagnosis, Tata Memorial Centre, Mumbai, Maharashtra, India

² Homi Bhabha National Institute, Mumbai, Maharashtra, India

³ Department of Radiodiagnosis, Mangalore Institute of Oncology, Mangalore, Karnataka, India

Address for correspondence Aparna Katdare, MBBS, DMRD, DNB, Department of Radiodiagnosis, Tata Memorial Centre, Mumbai, Maharashtra 400012, India (e-mail: aparnaringe@yahoo.com).

Ind J Med Paediatr Oncol 2023;44:275–280.

Abstract

Keywords

- guidelines
- imaging
- recommendations
- testicular cancer

The common testicular tumors affect young males in the third and fourth decades and germ cell tumors especially have excellent post-treatment outcomes. Hence, guidelines for clinical, radiological, and tumor marker assessment for diagnosis, response assessment, and surveillance of these tumors have critical impact on the management of these tumors. This article aims to discuss the current recommendations and guidelines regarding the clinical and radiological assessment and treatment pathways of testicular tumors.

Introduction

Testicular malignancies constitute approximately 0.8% of newly diagnosed cases of malignancies in the male population.¹ While the incidence has been on the rise in the recent years, the mortality due to testicular malignancies has been on the decline.²

Classification

The World Health Organization (WHO) classification of testicular tumors is given in ►Table 1.³

Testicular malignancies are classified into germ cell tumors (GCTs) and nongerm cell tumors. GCTs can further be divided into seminomatous and nonseminomatous (NSGCTs). A vast majority of nearly 98% of testicular cancers are GCTs.

Other testicular neoplasms include lymphoma, sarcoma, fibroma, leiomyoma, vascular tumors, and metastases.⁴

Risk Factors and Etiopathogenesis

The etiology of testicular GCTs is still poorly understood, but certain pre-existing medical conditions associated with tes-

ticular GCTs include cryptorchidism, radiation, impaired fertility, testicular dysgenesis, and family history or previous history of testicular cancer.⁵

Malignant postpubertal GCTs (type II GCTs) commonly originate from the germ cell neoplasia “in situ” (GCNIS) and are subdivided into seminomas and NSGCTs. The rarer non-related GCNIS tumors comprise pre-pubertal type teratoma and yolk sac tumors (Type I GCT) and spermatocytic tumors (Type III GCT) seen in the elderly.⁶

Epidemiology and Clinical Presentation

The highest incidence of testicular malignancy is in the twenties for NSGCT and in the thirties for seminomas.⁷ The less common pre-pubertal type teratomas and yolk sac tumors, and the spermatocytic tumors are diagnosed in pre-puberty and elderly age group respectively. About 68% of these malignancies have organ-limited disease while 32% have nodal or distant metastases.⁸

Testicular swelling or pain, scrotal heaviness or lump, dull abdominal, flank or back pain and gynecomastia are common symptoms depending on testicular descent status, hormonal status and nodal or other metastatic disease.

DOI <https://doi.org/10.1055/s-0042-1760328>.
ISSN 0971-5851.

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)
Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Table 1 The World Health Organization (WHO) 2016 classification of testicular tumors³

Germ cell tumors
Germ cell neoplasia in situ (GCNIS)
Derived from GCNIS
Seminoma
Embryonal carcinoma
Yolk sac tumor, postpubertal type
Trophoblastic tumors
Teratoma, postpubertal type
Teratoma with somatic malignant components
Mixed germ cell tumors
Germ cell tumors unrelated to GCNIS
Spermatocytic tumor
Yolk sac tumor, prepubertal type
Mixed germ cell tumor, prepubertal type
Sex cord/stromal tumors
Leydig cell tumor
Malignant Leydig cell tumor
Sertoli cell tumor
Malignant Sertoli cell tumor
Large cell calcifying Sertoli cell tumor
Intratubular large cell hyalinizing Sertoli cell neoplasia
Granulosa cell tumor
Adult type
Juvenile type
Thecoma/fibroma group of tumors
Other sex cord/gonadal stromal tumors
Mixed
Unclassified
Tumors containing both germ cell and sex cord/gonadal stromal—gonadoblastoma
Miscellaneous non-specific stromal tumors
Ovarian epithelial tumors
Tumors of the collecting ducts and rete testis
Adenoma
Carcinoma
Tumors of paratesticular structures
Adenomatoid tumor
Mesothelioma (epithelioid, biphasic)
Epididymal tumors
Cystadenoma of the epididymis
Papillary cystadenoma
Adenocarcinoma of the epididymis
Mesenchymal tumors of the spermatic cord and testicular adnexae

Staging

The American Joint Commission on Cancer staging of testicular malignancy—TNM based on tumor (T), node (N) and metastases (M)—is given in ►Table 2⁹.

In addition, a unique marker for testicular malignancies is the tumor marker level (α fetoprotein [AFP], β human chorionic gonadotrophin [β -hCG] and lactate dehydrogenase [LDH]), which is included into the International Germ Cell Cancer Collaborative Group (IGCCCG) system of classification of testicular tumors given in ►Table 3; this system classifies patients into good, intermediate, and poor risk, taking into account location of tumor and metastases as well as post-orchidectomy tumor markers.^{9,10}

Clinical Workup

Clinical History

This should include present symptoms and any history of previous testicular cancer and treatment.

Physical Examination

This includes local site examination and chest, abdominal, and supraclavicular examination.¹¹

Hormonal Levels

AFP, β -hCG, and LDH levels are assessed post-orchidectomy. Maintained or rising levels can point to presence of metastases. Normalizing levels post-orchidectomy, although a favorable indicator, do not definitively exclude metastases. Tumor markers are also used for surveillance as indicators of recurrence.¹¹ Micro-RNAs are promising new biomarkers for diagnosis and monitoring and also for differentiating GCTs from non-GCTs, but not yet included in routine practice and are awaiting standardisation.¹²

Imaging Guidelines

Imaging in testicular malignancies plays an important role in diagnosis, staging, post-treatment disease response assessment, and surveillance.

Diagnosis and Staging

Ultrasound (US)

Ultrasound (US) of testis is done by a high frequency linear transducer (>10 MHz). The objective of US is to localize the scrotal mass (whether testicular or extratesticular), characterize the mass based on morphology, estimate size and volume, look for testicular lesions in known metastatic disease as well as for screening the contralateral testis. US has greater than 90% sensitivity and specificity in diagnosing testicular lesions.¹³ Testicular microlithiasis, defined as 5 or more hyperechoic microliths in one US image, is currently not included as an independent risk factor for testicular cancer.^{14,15} Contrast-enhanced US is not used routinely, while elastography that reveals increased stiffness in

Table 2 TNM Classification for testicular cancer²⁸

pT—Primary tumor
pTX—Primary tumor cannot be assessed
pT0—No evidence of primary tumor
pTis—Intratubular germ cell neoplasia (carcinoma in situ)
pT1—Tumor limited to testis and epididymis without vascular/lymphatic invasion; tumor may invade tunica albuginea but not tunica vaginalis
pT2—Tumor limited to testis and epididymis without vascular/lymphatic invasion, or tumor extending through tunica albuginea with involvement of tunica vaginalis
pT3—Tumor invades spermatic cord with or without vascular/lymphatic invasion
pT4—Tumor invades scrotum with or without vascular/lymphatic invasion
N—Regional Lymph Nodes: Clinical
Nx—Regional lymph nodes cannot be assessed
N0—No regional lymph node metastasis
N1—Metastasis with a lymph node mass 2cm or less in greatest dimension or multiple lymph nodes, none more than 2cm in greatest dimension
N2—Metastasis with a lymph node mass more than 2 cm but not more than 5cm in greatest dimension; or more than 5 nodes positive, none more than 5cm; or evidence of extranodal extension of tumor
N3—Metastasis with a lymph node mass more than 5 cm in greatest dimension
Pn—Regional Lymph Nodes: Pathological
pNx—Regional lymph nodes cannot be assessed
pN0—No regional lymph node metastasis
pN1—Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2cm in greatest dimension
pN2—Metastasis with a lymph node mass more than 2cm but not more than 5cm in greatest dimension; or more than 5 nodes positive, none more than 5cm; or evidence of extranodal extension of tumor
pN3—Metastasis with a lymph node mass more than 5cm in greatest dimension
M—Distant metastases
Mx—Distant metastasis cannot be assessed
M0—No distant metastasis
M1—Distant metastasis cannot be assessed
M1a Nonregional lymph node(s) or lung metastasis
M1b Distant metastasis other than nonregional lymph nodes or lung

testicular tumors as compared with benign lesions cannot yet be used as a substitute for histopathological evidence in suspicious lesions.^{16,17}

Computed Tomography (CT)

CT is recommended for staging retroperitoneal nodal metastases and for diagnosing pulmonary metastases and mediastinal lymphadenopathy. For retroperitoneal nodal metastases, the left-sided malignancies have propensity for paraaortic nodal involvement and right-sided malignancies for aortocaval nodal involvement due to the drainage of the left-sided and right-sided gonadal veins into the left renal vein and inferior vena cava, respectively.⁸ Contrast-enhanced CT study is helpful in better delineation of the nodal size, morphology, and vascular relations. N-staging employs the greatest dimension of the node and the short axis dimension is used for distinguishing between benign and metastatic nodes. While there is no clear consensus for the cutoff value for the short axis diameter, 8 mm

or larger can be considered suspicious.⁸ In masses up to 2 cm in the retroperitoneum or thorax and negative tumor markers, restaging scan after 6 to 8 weeks is advisable instead of starting treatment immediately.¹¹ CT brain is a recommendation in patients with NSGCT having pulmonary metastases and poor prognosis IGCCCG risk group (beta hCG values > 5,000 UI/L), or in the presence of clinical symptoms,¹⁸ but magnetic resonance imaging (MRI) can be preferred.

Magnetic Resonance Imaging (MRI)

MRI can help in scenarios where US cannot definitively characterize testicular lesions,⁴ but is not universally used. Its use is limited to defining location of scrotal lesions (if intra- or extra- testicular), for planning of testis-sparing surgery, and to characterize intratesticular masses when US is inconclusive. Retroperitoneal nodes can also be assessed by MRI if patient is allergic to iodinated contrast of CT. Brain MRI is particularly useful in aggressive tumors such as choriocarcinomas that

Table 3 Prognostic-based staging system for metastatic germ cell cancer (IGCCCG)¹⁰

Good prognosis group	
Nonseminoma 5-year PFS 90% 5-year survival 96%	All of the following criteria: • Testis/retroperitoneal primary • No nonpulmonary visceral metastases • AFP < 1,000 ng/mL • β-hCG < 5,000 IU/L (1000 ng/mL) • LDH < 1.5 x ULN
Seminoma 5-year PFS 89% 5-year survival 95%	All of the following criteria: • Any primary site • No nonpulmonary visceral metastases • Normal AFP • Any β-hCG • Any LDH
Intermediate prognosis group	
Nonseminoma 5-year PFS 78% 5-year survival 89%	Any of the following criteria: • Testis/retroperitoneal primary • No nonpulmonary visceral metastases • AFP 1,000–10,000 ng/mL • β-hCG 5,000–50,000 IU/L (1,000 ng/mL) • LDH 1.5–10 x ULN
Seminoma 5-year PFS 79% 5-year survival 88%	All of the following criteria: • Any primary site • Nonpulmonary visceral metastases • Normal AFP • Any β-hCG • Any LDH
Poor prognosis group	
Nonseminoma 5-year PFS 54% 5-year survival 67%	Any of the following criteria: • Mediastinal primary • Nonpulmonary visceral metastases • AFP > 10,000 ng/mL • β-hCG > 50,000 IU/L (10,000 ng/mL) • LDH > 10 x ULN
Seminoma	No patients classified as “poor-prognosis”

Abbreviations: AFP, α fetoprotein; β -hCG, β -human chorionic gonadotropin; IGCCCG, International Germ Cell Cancer Collaborative Group; LDH, lactate dehydrogenase; PFS, progression-free survival; ULN, upper limit of normal.

have propensity for brain metastases. The National Comprehensive Cancer Network (NCCN) recommends brain MRI in seminoma patients with pulmonary metastasis or β -hCG more than 5,000 IU/L. In NSGCTs, brain MRI is recommended when serum AFP is more than 10,000 ng/mL, β -hCG is more than 5,000 IU/L, and in the presence of visceral or extra-pulmonary metastases or neurological symptoms.¹⁹

Bone Scan and Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography /CT (18F-FDG-PET/CT)

These are not recommended in initial staging studies.

Response Assessment and Surveillance

Computed Tomography

CT is the modality of choice to evaluate treatment response and diagnose disease recurrence. The standardized Response Evaluation Criteria in Solid Tumors (RECIST 1.1) is used to label response as complete response, partial response, stable disease, and progressive disease. The National Comprehensive Cancer Network (NCCN) guidelines recommend surveillance by CT for 3 to 5 years or beyond after treatment, the frequency of scan depending on tumor histology, stage, treatment, and risk factors.¹⁹

Magnetic Resonance Imaging

In patients with allergy to iodinated contrast, MRI can be used for restaging instead of CT.

18F-FDG-PET/CT study

PET/CT study is not a part of guidelines for initial staging, but in the restaging scenario, especially in seminomas, 18F-FDG-PET/CT study is of value to differentiate between viable and nonviable residual lesions based on FDG avidity and CT morphology characteristics; indeed, it has shown decrease in overtreatment of seminomas.^{20,21} Various studies have shown positive predictive values ranging from 30 to 69%.^{22–24} Current recommendations include using 18F-FDG-PET/CT study in post-treatment seminomas with residual mass more than 3 cm. It should be delayed until at least 2 months post last chemotherapy cycle, to prevent false positive findings as a result of inflammation and desmoplastic reaction induced by chemotherapy.²⁵ 18F-FDG PET/CT in the surveillance setting can be used in certain patients with advanced stage seminoma. 18F-FDG-PET/CT is not recommended in response assessment or surveillance in other testicular tumor subtypes.¹⁹

Screening

There is no evidence of screening of asymptomatic patients having any utility in detecting testicular carcinoma at a more curable stage.²⁶

Management Principles

Orchidectomy, by dividing the spermatic cord at the internal inguinal ring, is the initial diagnostic and partially therapeutic step in patients with testicular cancer. Prosthesis may be offered at the time of surgery or later. Contralateral testicular biopsy is not done routinely but can be considered in patients with high risk for contralateral tumor, such as volume of testis less than 12 mL with or without cryptorchidism.¹¹ All patients should be offered semen preservation and fertility assessment prior to treatment by estimation of testosterone, follicle-stimulating hormone, and luteinizing hormone levels.²⁷ Histopathological evaluation of testicular cancer can be supplemented with specific immunohistochemical markers with comment on the presence of lymphovascular infiltration, rete testis involvement, tumor size, and proportion of each histological component in mixed NSGCTs.¹¹

The European Association of Urology (EAU) recommends tailoring of treatment according to patient risk profile in testicular tumors post-orchidectomy after discussing all options. Some broad principles of the recommendations are described below.¹¹

Local radiotherapy can be considered for GCNIS. Seminomas clinical stage 1 can have subclinical retroperitoneal metastases in up to 15% patients; hence treatment options including surveillance, adjuvant chemotherapy, and adjuvant radiotherapy have to be tailored to each patient. In NSGCT clinical stage 1, options comprise surveillance, adjuvant chemotherapy, or retroperitoneal lymph node dissection (RPLND).

For stage IIA/B seminomas, radiotherapy or alternatively chemotherapy is considered standard of care. In stage II NSGCTs, with elevated tumor marker levels and retroperitoneal nodal disease with elevated tumor levels, primary chemotherapy is the initial treatment of choice, while in retroperitoneal nodal disease without tumor marker elevation, RPLND can be the first-line treatment. For stage IIC/III seminomas as well as NSGCTs, chemotherapy is the initial line of treatment.

Post-treatment residual seminomas are monitored by tumor marker levels and imaging. If residual lesion is less than 3 cm, then observation and follow-up can be considered. If residual lesion is more than 3 cm, a PET/CT is recommended that is usually done 10 to 12 weeks after treatment completion. In patients with residual NSGCTs, if size of residual lesion is more than 1 cm, then it should be resected and if less than 1 cm, then it can be observed on follow-up with imaging and tumor marker levels.

Follow-Up Timelines

The EAU recommends follow-up protocols for different patient subsets as described below.¹¹

For seminoma stage 1 on active surveillance or after adjuvant treatment, abdominopelvic CT is recommended at 6 months interval for the initial 2 years, once in the 3rd year and once at 5 years. Tumor markers are assessed at 6 monthly intervals for the initial 3 years and once at 5 years.

For NSGCT stage 1 on active surveillance, abdominopelvic CT is recommended at 6 monthly intervals in the 1st year, annually for the next 2 years, and once at 5 years. Chest radiograph is recommended at 6 monthly intervals in the first 2 years for all patients and once after 3rd and 5th year in case of lymphovascular infiltration. Tumor markers are assessed four times a year in the first 2 years and two times a year for the next 3 years.

For advanced disease after adjuvant treatment or complete remission, thoracoabdominopelvic CT is recommended at 6 monthly intervals in the 1st year, annually in the second and 3rd year and once at 5 years. Chest radiograph is recommended at 6 monthly intervals in the 1st year, annually in the next 2 years and once at 5 years. Tumor markers are assessed four times a year in the first 2 years and twice a year for the next 3 years.

Summary of Recommendations

- US is used for evaluation of scrotal/testicular masses including screening of contralateral testis.
- CT is the primary modality for staging for metastatic disease and for post-treatment restaging and surveillance.
- MRI can be done in patients with iodinated contrast allergy. Brain MRI is used in advanced disease to look for metastases.
- PET/CT study is not recommended for initial staging, but can be useful in restaging of seminomas to distinguish between viable and nonviable residual lesions.
- Tumor markers are useful in conjunction with imaging for initial risk stratification and in follow-up and surveillance.

Conclusion

Management of testicular malignancies needs multidisciplinary approach by radiologists, pathologists, and treating physicians. Imaging along with tumor marker levels is crucial in staging, risk stratification, assessing treatment response, and for surveillance. Decision-making regarding treatment algorithms and surgical planning is aided by imaging. Since these are potentially curable malignancies in young males, all efforts must be invested by the treating physician team for optimum treatment planning in these patients.

Conflict of Interest

None declared.

References

- 1 [World Cancer Research Fund. Worldwide Cancer Data: Global cancer statistics for the most common cancers. Accessed December 9, 2022, at: <https://www.wcrf.org/dietandcancer/cancer-trends/worldwide-cancer-data>].
- 2 Znaor A, Lortet-Tieulent J, Jemal A, Bray F. International variations and trends in testicular cancer incidence and mortality. *Eur Urol* 2014;65(06):1095–1106
- 3 Williamson SR, Delahunt B, Magi-Galluzzi C, et al; Members of the ISUP Testicular Tumour Panel. The World Health Organization 2016 classification of testicular germ cell tumours: a review and update from the International Society of Urological Pathology Testis Consultation Panel. *Histopathology* 2017;70(03):335–346
- 4 Mittal PK, Abdalla AS, Chatterjee A, et al. Spectrum of extratesticular and testicular pathologic conditions at scrotal MR imaging. *Radiographics* 2018;38(03):806–830
- 5 Makovník M, Rejleková K, Uhrin I, Mego M, Chovanec M. Intricacies of radiographic assessment in testicular germ cell tumors. *Front Oncol* 2021;10:587523 <https://www.frontiersin.org/article/10.3389/fonc.2020.587523>
- 6 Looijenga LHJ, Van der Kwast TH, Grignon D, et al. Report From the International Society of Urological Pathology (ISUP) Consultation Conference on Molecular Pathology of Urogenital Cancers: IV: current and future utilization of molecular-genetic tests for testicular germ cell tumors. *Am J Surg Pathol* 2020;44(07):e66–e79
- 7 Oosterhuis JW, Looijenga LHJ. Testicular germ-cell tumours in a broader perspective. *Nat Rev Cancer* 2005;5(03):210–222
- 8 Hale GR, Teplitsky S, Truong H, Gold SA, Bloom JB, Agarwal PK. Lymph node imaging in testicular cancer. *Transl Androl Urol* 2018;7(05):864–874
- 9 Magers MJ, Idrees MT. Updates in staging and reporting of testicular cancer. *Surg Pathol Clin* 2018;11(04):813–824

- 10 International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. *J Clin Oncol* 1997; 15(02):594–603
- 11 Laguna M, et al. EAU guidelines on testicular cancer 2022. Accessed December 9, 2022, at: <http://www.uroweb.org/guideline/testicularcancer/>
- 12 Lobo J, Leão R, Gillis AJM, et al. Utility of Serum miR-371a-3p in predicting relapse on surveillance in patients with clinical stage I testicular germ cell cancer. *Eur Urol Oncol* 2021;4(03):483–491
- 13 Wilson SR, Greenbaum LD, Goldberg BB. Contrast-enhanced ultrasound: what is the evidence and what are the obstacles? *AJR Am J Roentgenol* 2009;193(01):55–60
- 14 Coursey Moreno C, Small WC, Camacho JC, et al. Testicular tumors: what radiologists need to know—differential diagnosis, staging, and management. *Radiographics* 2015;35(02):400–415
- 15 Winter TC, Kim B, Lowrance WT, Middleton WD. Testicular microlithiasis: what should you recommend? *AJR Am J Roentgenol* 2016;206(06):1164–1169
- 16 Lock G, Schmidt C, Helmich F, Stolle E, Dieckmann KP. Early experience with contrast-enhanced ultrasound in the diagnosis of testicular masses: a feasibility study. *Urology* 2011;77(05):1049–1053
- 17 Aigner F, De Zordo T, Pallwein-Prettner L, et al. Real-time sonoe-lastography for the evaluation of testicular lesions. *Radiology* 2012;263(02):584–589
- 18 Feldman DR, Lorch A, Kramar A, et al. Brain metastases in patients with germ cell tumors: Prognostic factors and treatment options - an analysis from the Global Germ Cell Cancer Group. *J Clin Oncol* 2016;34(04):345–351
- 19 National Comprehensive Cancer Network NCCN Clinical Practice Guidelines in Oncology. Testicular Cancer. Version 1.2019. October 22, 2018. Accessed December 9, 2022, at: https://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf
- 20 Necchi A, Nicolai N, Alessi A, et al. Interim 18F-Fluorodeoxyglucose Positron Emission Tomography for Early Metabolic Assessment of Response to Cisplatin, Etoposide, and Bleomycin Chemotherapy for Metastatic Seminoma: Clinical Value and Future Directions. In: *Clinical Genitourinary Cancer*. Vol 14.; 2016 Doi: 10.1016/j.clgc.2015.08.010
- 21 Honecker F, Aparicio J, Berney D, et al. ESMO consensus conference on testicular germ cell cancer: diagnosis, treatment and follow-up. In: *Annals of Oncology*. Vol 29.; 2018 Doi: 10.1093/annonc/mdy217
- 22 Bachner M, Lorient Y, Gross-Goupil M, et al. 2-¹⁸fluoro-deoxy-D-glucose positron emission tomography (FDG-PET) for postchemotherapy seminoma residual lesions: a retrospective validation of the SEMPET trial. *Ann Oncol* 2012;23(01):59–64
- 23 Cathomas R, Klingbiel D, Bernard B, et al. Questioning the value of fluorodeoxyglucose positron emission tomography for residual lesions after chemotherapy for metastatic seminoma: results of an International Global Germ Cell Cancer Group Registry. *J Clin Oncol* 2018;36(34):JCO1800210. Doi: 10.1200/JCO.18.00210
- 24 Murthy V, Karmakar S, Carlton J, et al. Radiotherapy for postchemotherapy residual mass in advanced seminoma: a fluorodeoxyglucose positron emission tomography-computed tomography-based risk-adapted approach. *Clin Oncol (R Coll Radiol)* 2021;33(07):e315–e321
- 25 Oechsle K, Hartmann M, Brenner W, et al; German Multicenter Positron Emission Tomography Study Group. [18F]Fluorodeoxyglucose positron emission tomography in nonseminomatous germ cell tumors after chemotherapy: the German multicenter positron emission tomography study group. *J Clin Oncol* 2008;26(36):5930–5935
- 26 Ilic D, Misso ML. Screening for testicular cancer. *Cochrane Database Syst Rev* 2011;(02):CD007853
- 27 Gilbert K, Nangia AK, Dupree JM, Smith JF, Mehta A. Fertility preservation for men with testicular cancer: is sperm cryopreservation cost effective in the era of assisted reproductive technology? *Urol Oncol* 2018;36(03):92.e1–92.e9
- 28 Brierley JE, et al. The TNM Classification of Malignant Tumours 8th edition. 2016. Accessed December 9, 2022, at: <https://www.uicc.org/resources/tnm-classification-malignant-tumours-8th-edition>

Imaging Recommendations for Diagnosis, Staging, and Management of Penile Cancer

Rachel Sequeira¹ Aparna Katdare^{2,3} Palak Popat^{2,3} Nilesh Sable^{2,3} Kunal Gala^{2,3}
Daksh Chandra^{2,3} Archi Agrawal^{2,3} Gagan Prakash^{2,3} Vedang Murthy^{2,3} Santosh Menon^{2,3}
Amit Joshi^{2,3} Ajaykumar Singh^{2,3} Suyash Kulkarni^{2,3}

¹ Department of Radiodiagnosis, Mangalore Institute of Oncology, Mangalore, Karnataka, India

² Department of Radiodiagnosis, Tata Memorial Centre, Mumbai, Maharashtra, India

³ Homi Bhabha National Institute, Mumbai, Maharashtra, India

Address for correspondence Aparna Katdare, MBBS, DMRD, DNB, Department of Radiodiagnosis, Tata Memorial Centre, Mumbai, Maharashtra 400012, India (e-mail: aparnaringe@yahoo.com).

Ind J Med Paediatr Oncol 2023;44:281–286.

Abstract

Keywords

- ▶ guidelines
- ▶ imaging
- ▶ penile cancer
- ▶ recommendations

Penile cancer is more common in developing countries and presents unique challenges in treatment, given the psychological impact of surgical treatment options on patients. While clinical assessment of the lesions and nodal disease is critical, imaging does play a role in initial staging, response assessment, and surveillance. This article aims to delineate the guidelines for clinical and radiological evaluation of penile cancers and the approach to disease management.

Introduction

Malignancy of the penis is a rare occurrence, more frequently afflicting men in the age group of 50 to 70 years.¹ Developing countries, such as those in South America, the Indian sub-continent and Africa, have the highest burden of cases as compared with the developed world, with high rates of occurrence of up to 6% of malignant neoplasms. These may correspond to lower rates of circumcision in these countries.² In penile malignancies, in addition to the diagnostic challenges, it is a unique battle to handle the psychological devastation to the patient, which must be dealt with at each phase, right from clinical and radiological diagnosis to curative or palliative treatment.^{2,3}

Risk Factors and Etiopathogenesis

Majority of penile malignancies occur in the glans. Other sites of occurrence, in decreasing order of frequency, include the prepuce, coronal sulcus, and the shaft.⁴ The aggressive nature of this malignancy can be attributed to invasive growth and the predisposition to early metastatic spread to lymph nodes.

There are multiple risk factors that contribute to the increased incidence of developing invasive disease,⁴ which include phimosis, human papilloma virus (HPV), erythroplasia of Queyrat or Bowen's disease, immunocompromised status, obesity, smoking, poor genital hygiene, and ultraviolet-A phototherapy. Neonatal circumcision and HPV vaccination are known to be protective factors against malignancy.

Almost 95% of lesions in penile carcinoma arise from the glans epithelium that is nonkeratinized, or from the preputial inner layer⁴; the most common histology is squamous cell carcinoma. Extremely rare types of malignancies in the penis include melanoma, sarcoma, or metastases.

Various histologic subtypes of penile carcinoma are differentiated on the basis of the classification provided by the World Health Organization⁵ (►Table 1). These differ with respect to their pathogenesis, histologic and molecular characteristics, and prognosis.⁶

Clinical Presentation

Penile malignancy may manifest as pain, bleeding, and discharge occurring from a visible or palpable mass. If these lesions remain below the phimotic foreskin, diagnosis may

DOI <https://doi.org/10.1055/s-0042-1760307>.
ISSN 0971-5851.

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)
Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Table 1 The WHO classification of penile carcinomas, their relative frequency, and mean cancer-specific mortality^{5,9}

Squamous-cell carcinomas	Relative frequency	Tumor-specific mortality
Non-HPV associated		
Squamous cell carcinoma, common type	70–75%	30%
Pseudohyperplastic carcinoma	<1%	0%
Pseudoglandular carcinoma	<1%	>50%
Verrucous carcinoma	2–3%	Low
Carcinoma cuniculatum	<1%	Low
Papillary carcinoma, NOS	5–8%	Low
Adenosquamous carcinoma	Rare	Low
Sarcomatoid carcinoma	1–4%	75%
HPV-associated		
Basaloid carcinoma	5–10%	>50%
Papillary basaloid carcinoma	Rare	
Warty carcinoma	5–10%	Low
Warty basaloid carcinoma	9–14%	30%
Clear-cell carcinoma	1–2%	20%

Abbreviations: HPV, human papilloma virus; NOS, not otherwise specified; WHO, World Health Organization.

be missed; this can be avoided by viewing discharge or bleeding from a nonretractile foreskin with a high index of suspicion.

Biopsy confirms the diagnosis of penile malignancy. Preferably an excisional biopsy is performed for gauging the T-stage of the disease. A negative surgical margin after an excision biopsy, with tumor free margin of 5 mm obtained in the intraoperative fresh frozen section, is considered oncologically adequate.⁷

Staging and Prognosis

Two systems of assessment are used in penile malignancy: the standard TNM system based on Tumor (T), Node (N), and Metastasis (M) given in ►Table 2⁸ and the less frequently used Jackson classification system.

Probability of nodal infiltration depends on the T-stage of the penile lesion, histological subtype and grade, depth of the tumor, and presence of lymphovascular invasion. The extent of involvement of lymph node is a defining prognostic indicator.⁹

Imaging Considerations

Staging

Clinical examination is complemented by imaging for a comprehensive assessment of the T-stage of primary lesion, locoregional lymphadenopathy status, and distant organ metastases.

Imaging of the Primary Tumor

Infiltration of the corpora can be assessed by ultrasound (USG). Penile Doppler USG appears to have a higher staging accuracy than magnetic resonance imaging (MRI) for corpo-

ral infiltration. Penile Doppler may prove to be of higher value in organ preserving surgery.¹⁰

However, MRI is a more preferred modality for T-staging. Proper positioning by elevation of the scrotum and penis is a prerequisite for MRI of the penis. Present guidelines issued by the European Association of Urology (EAU) state that injection of the corpora with prostaglandin E1 causing penile erection prior to MRI study may improve local staging; however, due to the disadvantage of priapism which is sometimes associated with this method, prostaglandin E1 is not commonly used.^{9,11,12}

For local staging, T2-weighted and gadolinium-enhanced postcontrast T1-weighted sequences are essential. Postcontrast T1-weighted images can confirm early onset recurrence and presence of small masses and can serve as problem-solving sequences when noncontrast MRI findings are equivocal. If multifocal lesions are seen in the corpora cavernosa and corpus spongiosum on T1- and T2-weighted sequences, penile metastases may be suspected. Adjacent organ involvement such as prostate invasion by the penile mass can be evaluated.¹¹

Imaging of Lymph Nodes

Management of penile malignancies differs depending on the size of the nodes, which are primarily assessed by palpation. However, there can be over-staging as palpable inguinal lymph nodes may be reactive.

The characterization of lymph nodes on imaging is best done with USG. The superficial USG transducer (7.5 MHz) can detect enlarged nodes which are abnormal. Highly specific findings for metastases include the loss of the lymph node hilum and decreased longitudinal/transverse diameter ratio.¹³ A longitudinal/transverse diameter ratio of more than 2 is considered normal for inguinal lymph nodes. Inguinal

Table 2 TNM classification of tumors of the penis (primary carcinomas)⁸

T	Primary tumor
Tx	Tumor cannot be assessed
T0	Absence of tumor
Tis	Carcinoma in situ
Ta	Superficial verrucous cancer
T1	Tumor invades subepithelial connective tissue
T2	Invasion of the corpus spongiosum or cavernosum
T3	Invasion of the urethra or prostate
T4	Invasion of other adjacent structures
N	Regional lymph nodes
Nx	Cannot be assessed
N0	Absence of regional lymph node metastases
N1	Single superficial inguinal lymph node metastasis
N2	Bilateral or multiple superficial inguinal lymph node metastases
N3	Unilateral or bilateral deep inguinal or pelvic metastasis or metastases
M	Distant metastases
Mx	Cannot be assessed
M0	Absence of metastases
M1	Distant metastasis or metastases

lymph nodes with short-axis diameter greater than 20 mm or eccentric cortical hypertrophy of 2mm may be considered as indeterminate.¹⁴ Indeterminate nodes can be targeted for fine-needle aspiration cytology (FNAC) or biopsy under USG guidance for confirmation of metastases.

MRI enables both local tumor staging and lymph node assessment. Lymphotropic nanoparticle-enhanced MRI is a novel imaging technique that has been shown to accurately differentiate benign from metastatic lymph nodes and rule out metastatic disease, with significant sensitivity and specificity rates of 100 and 97% respectively, according to a study by Tabatabaei et al.¹⁵ Provided that similar specificity and sensitivity rates are obtained with larger sample studies, usage of lymphotropic nanoparticles in MRI has the potential to be an all-inclusive staging technique obviating the need for multiple modalities for staging.^{9,11,15,16}

Nonpalpable Inguinal Lymphadenopathy

Even if the lymph nodes are not clinically palpable, the chance of micrometastatic disease is still approximately 25%.^{9,16} In this scenario, there is no utility of imaging studies in staging clinically normal inguinal regions. Definite detection of micrometastases with computed tomography (CT) or MRI is not possible.¹⁶ Positron emission tomography/CT (PET/CT) also cannot detect metastatic inguinal nodes, when short-axis diameter of a node is less than

10 mm.^{17,18} Imaging is useful in obese patients where palpation of the nodes may not be reliable.

Pathological risk factors dictate further course of treatment of patients with nonpalpable inguinal lymphadenopathy. Grade and local staging with lymphovascular invasion can predict lymphatic metastasis.^{17,19}

Palpable Inguinal Lymphadenopathy

Palpable inguinal lymph nodes can suggest lymph node metastases. Additional imaging does not change management. Patients having an intermediate to high risk (pT1b, T2-T4) of lymphatic spread are required to undergo invasive lymph node staging in this case.^{9,11,20,21}

Pelvic lymph nodes can be assessed by CT or imaging by PET/CT with fluorine-18-fluorodeoxy-D-glucose, which shows significant sensitivity (88–100%) and specificity (98–100%) for confirming metastases in palpable inguinal lymphadenopathy.^{17,19,22}

Imaging of Distant Metastases

Lung, liver, and retroperitoneum are frequent sites of metastases in penile malignancy. Distant metastases occur infrequently (less than 3% of cases) and herald poor prognosis. Current EAU guidelines recommend that patients with metastatic inguinal lymphadenopathy undergo evaluation for systemic metastases.^{9,20}

CT has a miniscule role in primary tumor local invasion assessment, but it is the mainstay of evaluation of distant spread.

In accordance with the National Comprehensive Cancer Network (NCCN) guidelines, in patients with T1a and nonpalpable inguinal lymphadenopathy, evaluation of the chest, abdomen, and pelvis for distant metastases with CT is not recommended. Patients with T1b or greater invasion levels or with palpable inguinal lymphadenopathy warrant CT of the chest, abdomen, and pelvis. Pelvic CT can detect nodes not amenable to palpation such as retroperitoneal and pelvic nodes. PET/CT can also be performed, though results may be ambiguous when there are micrometastases to inguinal lymph nodes.^{9,11,20,23}

The use of CT is not only confined to staging and treatment response but also finds use in the early postoperative phase, especially during occurrence of complications like collections and abscesses. These complications can also be addressed by CT-guided drainage procedures.

Follow-Up Imaging

The objective of surveillance is to diagnose recurrence. Long-term survival is not significantly reduced by local recurrence, if detected early and appropriately treated.

Once the inguinal lymph nodes are affected, it signifies worse prognosis and negatively impacts long-term survival. Most regional or local nodal recurrences are known to occur within 2 years of primary treatment.^{9,24}

An additional benefit of regular follow-up is detection and management of treatment-related complications.

Regular follow-up visits are recommended by EAU as well as NCCN guidelines. The timeline is once in 3 months

for the first 2 years, every 6 months during years 3 to 5, and annually thereafter.^{9,23} Disease stage and grade, though, have not been strictly considered while putting forth these recommendations. As recurrence may occur even after 5 years, indefinite follow-up may be the recommendation.^{23,25}

In case of suspicion of recurrence in local or inguinal postoperative bed, according to NCCN guidelines, image-guided biopsy may be performed.²³

A chest CT is suggested at 6 months interval during the first 2 years after diagnosis. In addition, an abdominopelvic CT is recommended once in 3 months during the first year and then, once in 6 months for a period of 2 years for N2 or N3 disease. This is done to detect early recurrence, so that local therapies, including lymphadenectomy, chemotherapy and radiation therapy can be administered. Patients with metastatic disease will require regular follow-up for treatment response assessment.

In cases where initial treatment was organ sparing or in obese patients, MRI can be done to detect local recurrence, necessitating a partial or total penectomy.^{23,26}

CT or MRI for the purpose of detection of regional recurrence is not routinely used. In suspicious cases, USG and guided FNAC may be used for detection of regional recurrence.²⁷

Treatment

The most important principle of penile cancer surgery is organ preservation while pursuing an essential degree of radicality.

Radical circumcision is done for lesions confined to the preputial inner layer. Glans sparing techniques in pTis, pTa tumors of the glans include local chemotherapy, immunotherapy, laser ablation, radiation therapy, or surgery. Chemotherapy and topical immunotherapy (imiquimod, 5-fluorouracil) are treatment modalities for carcinoma in situ (pTis). Laser (CO₂, neodymium-doped yttrium aluminum garnet) ablation, glans resurfacing, and radiation therapy are other treatment options, especially considered for recurrent or persistent lesions.

Localized treatment is followed up with posttreatment biopsy from primary tumor site to rule out residual disease. Local excision or partial or complete amputation of the glans is the mainstay for treatment of pT1 and pT2 tumors of the glans.

Measures such as glans amputation with plastic reconstruction are employed for tumors invading the corpus spongiosum or the corpora cavernosa.

Partial amputation of the penis or radical penectomy is performed in large tumors (pT4).

In T2 and higher stages, superficial and deep inguinal lymph node dissection is also indicated.

As squamous cell carcinomas are sensitive to radiation, lesions up to 4 cm in size can be subjected to local radiation therapy.

After radical lymphadenectomy, four to six cycles of adjuvant chemotherapy improve tumor-specific survival.

For the management of patients who are not candidates for curative intent, palliative radiotherapy or chemotherapy is considered.^{3,28,29}

Summary of Recommendations

1. Early detection of penile cancer is mainly by clinical examination. Imaging plays a role in staging that should be performed accurately.
2. Inguinal lymph node assessment is a very important factor for prognostication, disease management, and surveillance.
3. Newer imaging techniques that can detect micrometastases in inguinal nodes can be promising additions for comprehensive staging of penile cancer.

Conclusion

Penile carcinoma can be easily staged with present-day imaging modalities, and suitably treated with good outcomes in early cases. With better imaging techniques, there is scope for increasing focus on organ-preserving techniques. This will help in reducing the psychological implications associated with the diagnosis and contribute to quality of life. Patient education on follow-up self-examination will go a long way in the early treatment of recurrences and prolonged survival.

Conflict of Interest

None declared.

References

- 1 Pow-Sang MR, Ferreira U, Pow-Sang JM, Nardi AC, Destefano V. Epidemiology and natural history of penile cancer. *Urology* 2010; 76(2, Suppl 1):S2–S6
- 2 Misra S, Chaturvedi A, Misra NC. Penile carcinoma: a challenge for the developing world. *Lancet Oncol* 2004;5(04):240–247
- 3 Hakenberg OW, Dräger DL, Erbersdobler A, Naumann CM, Jünnemann KP, Protzel C. The diagnosis and treatment of penile cancer. *Dtsch Arztebl Int* 2018;115(39):646–652
- 4 Douglawi A, Masterson TA. Updates on the epidemiology and risk factors for penile cancer. *Transl Androl Urol* 2017;6(05):785–790
- 5 Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO classification of tumours of the urinary system and male genital organs-part a: renal, penile, and testicular tumours. *Eur Urol* 2016;70(01):93–105
- 6 Erbersdobler A. [Pathology and histopathological evaluation of penile cancer]. *Urologe A* 2018;57(04):391–397
- 7 Clark PE, Spiess PE, Agarwal N, et al; National Comprehensive Cancer Network. Penile cancer. *J Natl Compr Canc Netw* 2013;11(05):594–615
- 8 Brierley JE, et al. The TNM Classification of Malignant Tumours, 8th edition. 2016 Accessed December 8, 2022, at: <https://www.uicc.org/resources/tnm-classification-malignant-tumours-8th-edition>
- 9 Hakenberg OW, et al. EAU Guidelines on Penile Cancer 2022. Accessed December 8, 2022, at: <https://uroweb.org/guidelines/penile-cancer>
- 10 Bozzini G, Provenzano M, Romero Otero J, et al. Role of penile Doppler US in the preoperative assessment of penile squamous cell carcinoma patients: results from a large prospective multicenter European study. *Urology* 2016;90:131–135

- 11 Suh CH, Baheti AD, Tirumani SH, et al. Multimodality imaging of penile cancer: what radiologists need to know. *Abdom Imaging* 2015;40(02):424–435
- 12 Scardino E, Villa G, Bonomo G, et al. Magnetic resonance imaging combined with artificial erection for local staging of penile cancer. *Urology* 2004;63(06):1158–1162
- 13 Krishna RP, Sistla SC, Smile R, Krishnan R. Sonography: an underutilized diagnostic tool in the assessment of metastatic groin nodes. *J Clin Ultrasound* 2008;36(04):212–217
- 14 Solivetti FM, Elia F, Graceffa D, Di Carlo A. Ultrasound morphology of inguinal lymph nodes may not herald an associated pathology. *J Exp Clin Cancer Res* 2012;31(01):88. Doi: 10.1186/1756-9966-31-88
- 15 Tabatabaei S, Harisinghani M, McDougal WS. Regional lymph node staging using lymphotropic nanoparticle enhanced magnetic resonance imaging with ferumoxtran-10 in patients with penile cancer. *J Urol* 2005;174(03):923–927, discussion 927
- 16 Mueller-Lisse UG, Scher B, Scherr MK, Seitz M. Functional imaging in penile cancer: PET/computed tomography, MRI, and sentinel lymph node biopsy. *Curr Opin Urol* 2008;18(01):105–110
- 17 Schlenker B, Scher B, Tiling R, et al. Detection of inguinal lymph node involvement in penile squamous cell carcinoma by 18F-fluorodeoxyglucose PET/CT: a prospective single-center study. *Urol Oncol* 2012;30(01):55–59
- 18 Leijte JAP, Graafland NM, Valdés Olmos RA, van Boven HH, Hoefnagel CA, Horenblas S. Prospective evaluation of hybrid 18F-fluorodeoxyglucose positron emission tomography/computed tomography in staging clinically node-negative patients with penile carcinoma. *BJU Int* 2009;104(05):640–644
- 19 Alkatout I, Naumann CM, Hedderich J, et al. Squamous cell carcinoma of the penis: predicting nodal metastases by histologic grade, pattern of invasion and clinical examination. *Urol Oncol* 2011;29(06):774–781
- 20 Ottenhof SR, Vegt E. The role of PET/CT imaging in penile cancer. *Transl Androl Urol* 2017;6(05):833–838
- 21 Zhang W, Gao P, Gao J, Wu X, Liu G, Zhang X. A clinical nomogram for predicting lymph node metastasis in penile cancer: a SEER-based study. *Front Oncol* 2021;11:640036. Doi: 10.3389/fonc.2021.640036
- 22 Leijte JAP, Horenblas S. Shortcomings of the current TNM classification for penile carcinoma: time for a change? *World J Urol* 2009;27(02):151–154
- 23 National Comprehensive Cancer Network Penile Cancer (Version 1.2022). Accessed December 8, 2022, at: https://www.nccn.org/professionals/physician_gls/pdf/penile.pdf
- 24 Leijte JAP, Kirrander P, Antonini N, Windahl T, Horenblas S. Recurrence patterns of squamous cell carcinoma of the penis: recommendations for follow-up based on a two-centre analysis of 700 patients. *Eur Urol* 2008;54(01):161–168
- 25 Salami SS, Montgomery JS. Surveillance strategies in the management of penile cancer. *Transl Androl Urol* 2017;6(05):868–873
- 26 Galgano S, et al. Imaging for the initial staging and post-treatment surveillance of penile squamous cell carcinoma. *Diagnostics (Basel)* 2022;12(01):170
- 27 Djajadiningrat RS, Teertstra HJ, van Werkhoven E, van Boven HH, Horenblas S. Ultrasound examination and fine needle aspiration cytology-useful for followup of the regional nodes in penile cancer? *J Urol* 2014;191(03):652–655
- 28 Manjunath A, Brenton T, Wylie S, Corbishley CM, Watkin NA. Topical Therapy for non-invasive penile cancer (Tis)-updated results and toxicity. *Transl Androl Urol* 2017;6(05):803–808
- 29 Imamura M, MacLennan S, Lam TBL, et al. Surgical management for localised penile cancer. *Cochrane Database Syst Rev* 2015;3: CD011533



1st ISMPO Preceptorship Programme

Eklavya-Let's Learn Together

In Collaboration with Amrita Hospital, Faridabad, Haryana



The recent ISMPO Preceptorship Programme on **LYMPHOMA** held on 25th & 26th March 2023, was a **HUGE SUCCESS**, with great reviews from preceptees and faculties alike!



Dr. Padmaj Kulkarni
Program Director



Dr. Prashant Mehta
Chief Organizer



Dr. Kumar Prabhash
Hon. Secretary, ISMPO



Dr. Pravas Mishra
Co-Organizer



Dr. Saphalta Baghmar
Co-Organizer



Stay Tuned

More Preceptorships **Coming Soon**

Eligibility Criteria

1. Member of ISMPO
2. Should be the citizen of India
3. Age <40 years as on 31st Dec 2023. A GOI-approved ID should be provided to identify oneself and as proof of birth.
4. DM/DNB/DrNB in Medical Oncology / Pediatric oncology/Hematology OR in-training in these specialties.
5. Brief Curriculum Vitae- 2 pages maximum (signed & dated)
6. Letter of Intent from the applicant - 500 words describing why and how you plan to benefit from this course.
7. Institute letter of recommendation - By HOD in case of a student, by HOD of the hospital where working or HOD of the institute where trained in the case of YMO.
8. A case presentation in PPT format (6 slides) that relates to the course's topic, in the format provided.

For any queries and to receive the application form along with the PPT slide template, please contact

Mr. Yogesh Kembhavi
yogeshkembhavi1@gmail.com | +91 99675 94597