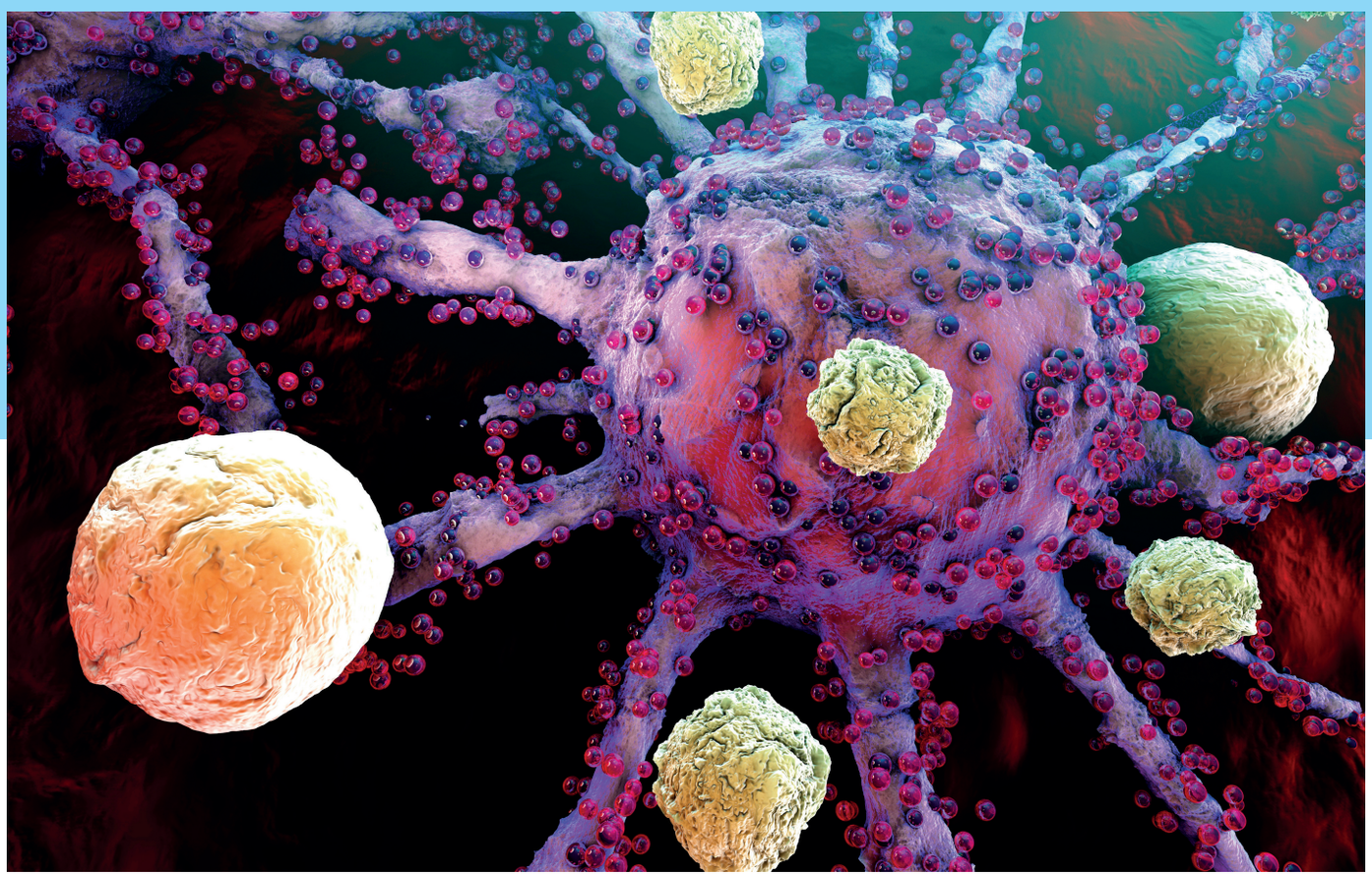
ISSN 0971-5851
eISSN 0975-2129

Indian Journal of Medical and Paediatric Oncology

Number 1 • Volume 45 • Pages 1–94 • February 2024

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



INDIAN SOCIETY OF MEDICAL & PAEDIATRIC ONCOLOGY
OPEN ACCESS
CASPA
Scopus®
CLARIVATE ANALYTICS EMERGING SOURCES CITATION INDEX INDEXED
Thieme

Indian Journal of Medical and Paediatric Oncology

Volume 45 • Number 1 • Pages 1–94 • February 2024

STAY TUNED

IJMPO

is coming up with
a special issue in **2024**

Current Status of Psycho-Oncology in India

ISSN 0971-5851
eISSN 0975-2129

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. Karthik Bommannan B.K., DM
Department of Oncopathology,
Cancer Institute (WIA), Adyar,
Chennai, Tamil Nadu, India

Joint Editors

Amol Akhade, DM (Medical Oncology) MD (Medicine)
Department of Medical Oncology,
Nair Hospital, Mumbai,
Bethany Hospital, Thane,
Suyog Cancer Clinic, Thane,
Maharashtra, India

Tarini Prasad Sahoo, MD, DM, (Medical Oncology)
Department of Medical Oncology,
Silverline Hospital,
Bhopal, Madhya Pradesh, India

Editorial Advisor

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

Section Editors

Viraj Lavingia, DNB
Director-GI Medical Oncology,
Department of Medical Oncology,
HCG Cancer Center,
Ahmedabad, Gujarat, India

Avinash Bonda, MD, DM
Department of Medical Oncology,
and Hematology,
AIG Hospitals Gachibowli,
Hyderabad, Telangana, India

Sujay Srinivas, MD, DM
Department of Medical Oncology,
Bharath Hospital, Kottayam,
Kerla, India

Reshma Puranik, MBBS, MD Medicine, DNB Medicine, DM, DNB Medical Oncology, ECMO, MRCP UK, PGDGM
Ruby Hall Clinic, Jupiter hospital,
Jehangir hospital, Assistant professor at
Dy Patil medical college,
Pune, India

Sachin Khurana, MD, DM, Fellowship-Phase 1 trials
Department of Medical Oncology,
AIIMS, New Delhi, India

Maya Prasad, MD, Fellowship in Pediatric Oncology
Department of Paediatric Oncology,
Tata Memorial Centre, Mumbai, India

Lingraj Nayak, MD, DM
Department of Medical Oncology,
Tata Memorial Centre, Mumbai,
Maharashtra, India

Nita Nair, DNB, MRCS, MCh
Department of Surgical Oncology,
Apollo Hospital, Mumbai,
Maharashtra, India

Vamshi Krishna, MD
Department of Medical Oncology and
Hematology AIG Hospital, Gachibowli,
Hyderabad, Telangana, India

Amol Akhade, DM (Medical Oncology) MD (Medicine)
Department of Medical Oncology,
Nair Hospital, Mumbai, Bethany Hospital,
Thane, Suyog Cancer Clinic, Thane,
Maharashtra, India

Section Advisors

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

ISSN 0971-5851
eISSN 0975-2129

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 Medical
College & Hospital,
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, MCh
Department of Surgical Oncology,
Apollo Hospital, 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

Bhavesh 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

ISSN 0971-5851
eISSN 0975-2129

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 Chittem, 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 Kembhavi, MBA, CHR, CTM, DHA, PMP, DCR
Department of Administration,
Tata Memorial Centre,
Mumbai, Maharashtra, India

Editorial Assistant

Namarata Saluja, MSc (Microbiology)
Pune, Maharashtra, India

Ryan Varghese, Bpharm
Chennai, Tamil Nadu, 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 Warrier, 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. Maka, 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,
Basavatarakam 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,
Deenananth 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,
Cytecare 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

ISSN 0971-5851
eISSN 0975-2129

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

Ghassan 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

© 2024. The Author(s). This journal is published by Thieme under the Creative Commons license CC BY (Attribution), permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (https://creativecommons.org/licenses/by/4.0/).

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.

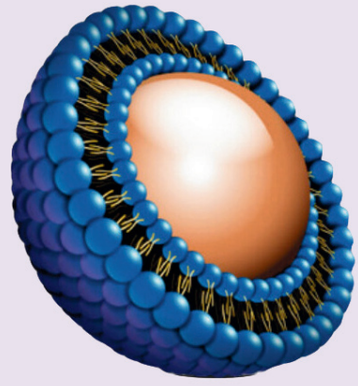
Indian Journal of Medical and Paediatric Oncology is indexed in *Emerging Sources Citation Index* and SCOPUS. Thieme Medical Publishers is a member of the CrossRef initiative.

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

INTAS
ONCOLOGY

Improving
Quality of Life
with
Novel Formulations of Taxanes



DoceAqualip 20mg / 80mg

Nanosomal Docetaxel Lipid Suspension

PacliAqualip 30 mg / 100 mg

Nanosomal Paclitaxel Lipid Suspension

Sign up for new article alerts!

Thieme's Alert Service makes it easy for you to stay on top of the latest articles. As soon as new content becomes available, an alert is sent directly to your inbox ensuring you are always among the first to know about new articles.

Follow the simple steps below to sign up today on
www.thieme-connect.com/products

1 Visit **www.thieme-connect.com/products** and go to Login. Login or click Register now if you haven't registered yet.

2 If you register for a new account, you will receive an email with an activation link. Once you have activated your registration, login.

3 Browse to your journal on **www.thieme-connect.com/products** and click the Alert Service icon

4 Edit your alerts in My Journal Alerts

www.thieme-connect.com/products

Thieme

Volume 45, Number 1/2024

Indian Journal of Medical and Paediatric Oncology

Editorial

1 Local Clinical Trials: The Need of the Hour to Improve Global Cancer Care
Apar Kishor Ganti

Review Articles

3 Breast Cancer in Transgenders: Narrative Review
Pankaj Goyal, Praveen Jain, Chaturbhuj Agrawal, Sneha Bothra Jain, Vineet Talwar, Ullas Batra, Sumit Goyal, Udip Maheshwari, Krushna Chaudhari, Varun Goel, Amrith BP, Dinesh Chandra Doval

9 Soft Tissue Sarcomas with Special Reference to Molecular Aberration, Chemotherapy, and Recent Advances: A Review Article
Linu Abraham Jacob, Sreevalli A., Shwetha Ninutha, Lokanatha Dasappa, Suresh Babu MC, Lokesh KN, Rudresha AH, Rajeev LK, Smitha Saldanha

Original Articles

22 Treatment Outcome of Burkitt's Lymphoma in Adolescents and Adults: A Retrospective Study
Sugeeth MT, Geetha Narayanan, Anoop TM, Sreejith G. Nair, Prakash NP, Jagathnath Krishna KM, Rekha A. Nair

28 Assessment of Knowledge and Attitude of Breast and Ovarian Cancer Patients Regarding Hereditary Breast-Ovarian Cancer Syndrome at a Tertiary Cancer Institute: A Cross-Sectional Observational Study
Raja Pramanik, Shubhra Vats, Sanchita Mitra, SVS Deo, Lalit Kumar, Ajay Gogia, Sachin Khurana, Atul Batra

35 Clinicodemographic Profile of Childhood Cancer in a Mining State, Odisha: A Retrospective Analysis
Dipti Rani Samanta, Ajitesh Avinash, Surendra Nath Senapati, Suchitra Samal, Tapas Kumar Dash, Abhisekh Kumar Sarangi

44 Unveiling the Molecular Mechanisms Behind the Devastating Impact of the ALK Protein on Pediatric Cancers: Insights into Deleterious SNPs through In Silico Predictions, Molecular Docking, and Dynamics Studies
Abdulhadi Almazroea

52 Multiple Primary Malignancies: A Clinicopathological Profile of Patients at a Tertiary Center of North India—A Retrospective Hospital-Based Observational Study
Abdul W. Mir, Shaheena Parveen, Ifrah Ahmad, Shah Naveed, Syed N. Ahmad, Mir M. Hussain, Nazir A. Dar

Oncology Beyond Science

61 Surviving Colorectal Cancer: More Than Treatment
Belsiyal C. Xavier

Thieme
Delhi • Stuttgart • New York • Rio de Janeiro
Copyright © 2024 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

Images in Oncology

64 Clinical Syndrome of Seizures, Headache, and Visual Blurring in Metastatic Carcinoma Colon
Lakshmi Raj, T.M. Anoop, Rakesh CA

Report on International Publication

66 To Augment or Not to Augment Consolidation Therapy for High-Risk Childhood Acute Lymphoblastic Leukemia
Shyam Srinivasan

How I Treat

68 How I Treat Alveolar Soft Part Sarcoma? The Therapeutic Journey from Nihilism to Cautious Optimism...
Deepa Susan Joy Philip, Jyoti Bajpai

Brief Communication

74 TP53 Mutations R175H and R249S Are Rare in Indian Head and Neck Cancer Patients
Arjita Ghosh, Anbalagan Moorthy

Case Report with Review of Literature

80 A Case Report and Literature Review of Primary Central Nervous System Lymphoma in a Patient with Crigler–Najjar Syndrome: How We Managed
Udip Maheshwari, Disha Morzaria, Seema Jagiasi, Vashishth Maniar, Ashish Joshi, Sameer Soneji

83 Complete Remission of Cutaneous Metastasis from Invasive Breast Cancer with Abemaciclib plus Letrozole
Shaunak N. Valame, Dhruti D. Manek

87 Bleeding Diathesis Secondary to a Heparin-Like Anticoagulant in a Patient with Multiple Myeloma—A Case Report and Review of Literature
Nihar Desai, Seema Biswas, Dinesh Chandra, Ruchi Gupta, Anshul Gupta, Rajesh Kashyap

Letter to the Editor

92 SETBP1 in Myeloid Malignancies—Putting Breadcrumbs Together in Rare, Uncommon, and Common Pediatric Cases
Aroonima Misra, Bhavika Rishi, Srilatha Bajaj, Sumita Saluja, Amitabh Singh

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 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.

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.

www.thieme.com/news

Sign up to get notified about free contents, the latest product releases, and news right here!

New email subscribers get 15% off their next order.

Go to **thieme.com/news** or scan this code:

@thiemepublishers @ThiemeNY @thieme-group @thieme.ny

Thieme

Use social media to increase the impact of your published article

Why social media matters?

Reach a larger audience: In addition to traditional indexing services, social media can help your work to be found by other researchers and cited accordingly.

Networking: More and more authors connect to fellow researchers via social media creating a new avenue for career development.

Contribute to safe and factual information: Social media is here to stay. Fake news can only be remediated by disseminating facts and thoroughly researched information.

How to use social media?

- Pick your favorite channel such as Twitter, Facebook, Instagram, LinkedIn, Weibo etc
- Create an account
- Search for fellow researchers to connect with
- Share your own work
- Use channel specific tools such as #hashtags or @handles to disseminating information

Other ways to promote your article:

- Encourage your institution to promote your article via website, newsletter, or press release
- Present your work at medical gatherings
- Include information about your article in your email signature

© denisismagilov/stock.adobe.com

Connect with us on social media

@thiemepublishers @thieme-group @ThiemeNY @thieme.ny @Thieme_Group

Thieme

Editorial

Local Clinical Trials: The Need of the Hour to Improve Global Cancer Care

Apar Kishor Ganti[1]

[1] VA Nebraska Western Iowa Health Care System, University of Nebraska Medical Center, Omaha, Nebraska, United States

Ind J Med Paediatr Oncol 2024;45:1–2.

Advances in the care of cancer patients are almost always due to clinical trials that demonstrate improved patient outcomes in terms of better survival or improved quality of life. Pharmaceutical companies invest a large amount of time, effort, and money in developing novel agents, but only a few of these end up actually changing patient care. Agents such as imatinib, osimertinib, trastuzumab, rituximab, and pembrolizumab, among others, are prime examples of this approach. A recent analysis found that the median cost of development of an anticancer drug was $648.0 million.[1]

Research is key to the long-term improvement of cancer control. In fact, the National Comprehensive Cancer Network states that the best treatment of any cancer patient is administered in the context of a clinical trial (www.nccn.org). Unfortunately, even in advanced countries, the proportion of cancer patients enrolled on to clinical trials is very low (<10%).[2] Global studies tend to accrue patients from countries that have robust clinical trial infrastructure that allow for increased efficiency. Another possible reason for this could be the regulatory atmosphere in countries where pharmaceutical companies are interested in selling their product. On the other hand, patients in countries that did not participate in these trials may be treated based on data that may not necessarily be applicable to them.

Recently the U.S. Food and Drug Administration (FDA) refused approval to an immune checkpoint inhibitor, sintilimab, which was studied in China.[3] The ORIENT-11 trial was a randomized, double-blind, phase 2 study of 397 patients administered a platinum-pemetrexed doublet with or without sintilimab as first-line treatment of metastatic nonsquamous nonsmall cell lung cancer.[4] The addition of sintilimab was associated with a significant improvement in progression-free survival (8.9 vs. 5.0 months; $p < 0.00001$). Despite the clinical efficacy, there was concern regarding the applicability of the results of a trial conducted in subjects who are ethnically different from the U.S. population.

This concern is not unwarranted, as there are significant differences in the tolerability and efficacy of anticancer drugs between different populations. For example, irinotecan was shown to be significantly superior to etoposide, when combined with cisplatin in patients with extensive stage small cell lung cancer in a Japanese population.[5] However, a similar study in the United States failed to show difference between the two drugs, and the pharmacogenetic differences between the two populations were thought to be the cause of the differential results between the two trials[6]

While cancer is often thought to be a disease of the affluent, there has been an increased incidence of cancer in lower- and middle-income countries (LMICs). Currently, although LMICs have a lower incidence of most malignancies than developed countries, almost two-thirds of cancer cases and >70% of cancer deaths worldwide in 2020 occurred in LMICs.[7] While cancer death rates seem to be declining in the United States and other developed countries, this is not the case elsewhere.[8] Another aspect that needs to be remembered is that the incidence of individual malignancies is different in different parts of the world. For example, invasive cervical cancer is a major problem worldwide, but over 75% of the cases occur in Asia and Africa, probably due to a robust implementation of cancer screening in Europe and North America.[9] Similarly, the common causes of cancer morbidity and mortality are not the same worldwide. Lung, colorectal, pancreatic, and central nervous system cancers have a higher mortality in high and middle sociodemographic regions, while the most common causes of high morbidity and mortality in the lower sociodemographic regions were cervical and oral cancer.[10] Hence, studies to improve outcomes need to be done in the countries where these cancers are more prevalent and aggressive, as tumor biology may not be the same worldwide.

It is obvious that the benefits of research in the developed world are not reaching the countries with the highest burden of cancer. A major reason for this may be the limited

Address for correspondence
Apar Kishor Ganti, MD, MS, FACP, Division of Oncology-Hematology, Department of Internal Medicine, University of Nebraska Medical Center, 987680 Nebraska Medical Center, Omaha, NE 68198-7680, United States
(e-mail: aganti@unmc.edu).

DOI https://doi.org/10.1055/s-0043-1768568.
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

ability of individual countries to deliver optimal cancer care to their population based on research conducted elsewhere. Hence to ensure that patients are treated with treatments that are most likely to be relevant to them, local research is mandatory.

This is, however, not without its own challenges. Conducting clinical trials requires formal training in the research methodologies and unfortunately a lot of clinicians in LMICs lack the necessary training to conduct research.[11] Another aspect that needs to be considered is the lack of time available to devote to research activity given the overwhelming clinical volume for oncologists practicing in these settings.[12] The clinical burden often lead to a deprioritization of research and consequently a lack of adequate research infrastructure. Educating the population regarding the benefits of participating in the research is another aspect that needs to be considered. Studies have shown that among certain ethnic groups, individuals with a less than high school education were less likely to participate in research studies.[13]

Given the novel challenges with logistics and resources in each part of the world, individual governments should consider facilitation of clinical trials. This should include, among others, establishment of adequate infrastructure staffed by trained research personnel, development of training programs geared toward busy clinicians and decreasing the barriers that currently exist while conducting research. This will not only allow the conduct of trials pertinent to the local population but also facilitate increased efficiency and quality of care. The development of research infrastructure can foster regional collaborations and thereby enable individual centers to incorporate best practices from partnering institutions, thereby improving the quality of care overall. This is an important factor that can potentially reduce disparities in cancer care and alleviate the cancer burden worldwide.

Conflict of Interest

No relevant conflicts of interest related to this work. Other unrelated conflicts include Consultant: AstraZeneca, Jazz Pharmaceuticals, Flagship Biosciences, Sanofi, Regeneron Pharmaceuticals, Cardinal Health DSMC chair: Y-mAbs Therapeutics, outside the submitted work.

References

1 Prasad V, Mailankody S. Research and development spending to bring a single cancer drug to market and revenues after approval. JAMA Intern Med 2017;177(11):1569–1575

2 Unger JM, Vaidya R, Hershman DL, Minasian LM, Fleury ME. Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. J Natl Cancer Inst 2019;111(03):245–255

3 Oncologic Drugs Advisory Committee (ODAC) Meeting. FDA website. Accessed February 10, 2022 at: https://www.fda.gov/media/157576/download

4 Yang Y, Wang Z, Fang J, et al. Efficacy and safety of sintilimab plus pemetrexed and platinum as first-line treatment for locally advanced or metastatic nonsquamous NSCLC: a randomized, double-blind, phase 3 study (Oncology pRogram by InnovENT anti-PD-1–11). J Thorac Oncol 2020;15(10):1636–1646

5 Noda K, Nishiwaki Y, Kawahara M, et al; Japan Clinical Oncology Group. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 2002;346(02):85–91

6 Lara PN Jr, Natale R, Crowley J, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol 2009;27(15):2530–2535

7 Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023;73(01):17–48

8 National Cancer Institute.Global Cancer Research. Accessed April 10, 2023 at: https://www.cancer.gov/research/areas/global-health

9 International Agency for Research on Cancer.Estimated number of new cases in 2020, World, both sexes, all ages (excl. NMSC). Accessed April 10, 2023 at: https://gco.iarc.fr/today/online-analysis-table?v=2020&mode=cancer&mode_population=continents&population=900&populations=900&key=asr&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&group_cancer=1&include_nmsc=0&include_nmsc_other=1

10 Lin L, Li Z, Yan L, Liu Y, Yang H, Li H. Global, regional, and national cancer incidence and death for 29 cancer groups in 2019 and trends analysis of the global cancer burden, 1990-2019. J Hematol Oncol 2021;14(01):197

11 Pramesh CS, Badwe RA, Bhoo-Pathy N, et al. Priorities for cancer research in low- and middle-income countries: a global perspective. Nat Med 2022;28(04):649–657

12 Rubagumya F, Hopman WM, Gyawali B, et al. Participation of lower and upper middle–income countries in oncology clinical trials led by high-income countries. JAMA Netw Open 2022;5(08):e2227252

13 Palmer NR, Borno HT, Gregorich SE, Livaudais-Toman J, Kaplan CP. Prostate cancer patients' self-reported participation in research: an examination of racial/ethnic disparities. Cancer Causes Control 2021;32(10):1161–1172

Breast Cancer in Transgenders: Narrative Review

Pankaj Goyal[1] Praveen Jain[1] Chaturbhuj Agrawal[1] Sneha Bothra Jain[2] Vineet Talwar[1] Ullas Batra[1] Sumit Goyal[1] Udip Maheshwari[3] Krushna Chaudhari[1] Varun Goel[1] Amrith BP[1] Dinesh Chandra Doval[1]

[1] Department of Medical Oncology, Rajiv Gandhi Cancer Institute and Research Center, Delhi, India
[2] Department of medical oncology, Action cancer hospital, New Delhi, India
[3] Department of Medical Oncology, Mumbai Oncocare Center, Mumbai, Maharashtra, India

Address for correspondence Chaturbhuj Agarwal, MBBS, MD, DNB (Medicine), DNB Med Oncology, MRCP Oncology, ESMO, MNAMS, Department of Medical Oncology, Rajiv Gandhi Cancer Institute and Research Center, Sir Chotu Ram Marg, Sector – 5, Rohini Institutional Area, Rohini, New Delhi, Delhi 110085, India (e-mail: chaturbhujagarwal06@rediffmail.com).

Ind J Med Paediatr Oncol 2024;45:3–8.

Abstract

The molecular pathogenesis of breast cancer (BC), the second most common cancer, varies significantly between sexes, with minimal data in the transgender population. The overall prevalence of BC in transgenders is estimated to be 0.02%. Besides experiencing social disparities, transgenders have to face a lot of discrimination in the healthcare system. Adversities faced, along with the urge to identify with physical attributes to the gender felt by them, forces transgenders to use non-prescribed hormones. Gender affirming hormone therapy (GAHT) is a key feature of transition-related care, rehabbing mental health, and the quality of life of transgenders, but at the expense of their health. Studies have reported that GAHT is associated with severe health conditions such as cancer in transgenders. Estrogens and testosterone are associated with a moderate risk of developing BC. The types of BC diagnosed in transgenders after cross-sex hormone therapy include invasive ductal and neuroendocrine carcinoma, in addition to tubular adenocarcinoma. Although diagnosed at an age earlier compared with ciswomen, BC screening recommendations for transgenders are the same as for ciswomen. This review studies in detail the types of transgenders, their characteristics, different types of breast cancers associated, issues faced while treatment, and their best possible solutions. We also hope to have well-designed research in the future, which will fill the existing gaps in knowledge and provide scientific insight into the transgender population and issues related to their health. There are no international guidelines on screening and management of transgender patients but it appears that breast screening before cosmetic mastectomy, exposure to hormonal therapy for more than 5 years, and as per natal women screening guidelines should be offered to the patient with detailed discussion on the harms and benefits of the same.

Keywords
- transgenders
- breast cancer
- transwomen
- transmen
- gender-affirming hormone therapy

article published online
July 28, 2022

DOI https://doi.org/10.1055/s-0041-1740140.
ISSN 0971-5851.

© 2022. 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

Transgenders are the ones who have a gender individuality that is different from the sex at the time of birth.[1] It is estimated that from 8 to 25 million individuals worldwide now identify as transgenders.[2] The census of 2011 in India revealed the total population of transgenders to be around 4.88 lakh.[3] These people experience unique disparities in terms of social, hormonal, or surgical transition and are the subject of limited focused health research.[4,5] As a consequence, little is known regarding the medical and mental health of transgender individuals.[6] Transgender people face psychological stress due to the uncomfortable feeling of living in a discordant gender role.[4] To reduce this distress, these people opt for various measures such as cross-sex hormone therapy (CSH) or gender-affirming hormone therapy (GAHT) apart from surgical transitions, which are reported to be associated with serious conditions such as breast and prostate cancers.[7,8]

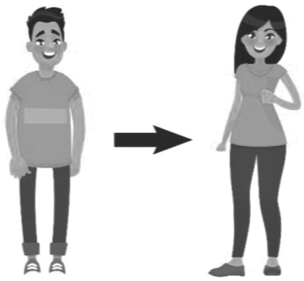
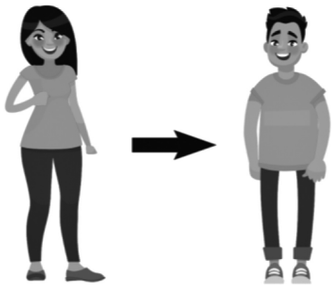
Breast cancer (BC) is the second most common cancer overall and the most common cancer in females with a lifetime risk of 12% and 0.1% in males.[2,9,10] The molecular pathogenesis of BC differs between sexes.[2] The proportion of transgender affected with BC is not known accurately although one study reported the overall prevalence of BC in transgenders to be 200 per 1,00,000 patients after years of CSH treatment in a cohort study.[10] In transgenders, the first two cases were reported in 1968 in two male to female (MtF) patients.[11] Among transgenders, transwomen (male to female) are at a higher risk of BC, as reported by de Block et al in a retrospective study.[10] In this report, we try to gain more insights into types of transgenders, GAHT, the risk associated with GAHT, patient presentation, and the dilemmas faced by this population in our society. We would also discuss the paucity of standard international guidelines on the screening and management of transgender individuals and possible solutions. Relevant clinical articles (published in the English language) included in this narrative review are selected from PubMed, Google Scholar, and appropriate websites (keywords: transgender, breast cancer, transwomen, transmen, female to male, male to female, hormone therapy). Also, transgender is a heterogeneous entity and consists of transmen and transwomen with different clinical characteristics and hormonal profiles. Below is a brief description of the types of transgenders and ►**Table 1** shows the differences between them.

Types of Transgenders

Male To Female Patients

Male to female (MtF) or transwomen are persons assigned male sex at birth but have a longing to live as a female.[5,10,12] The important physical features of a female body are breast growth, wider hips, less fat in the abdominal region, decreased hair growth on the body, and softer skin.[7,8] To develop these characteristics, transwomen require surgical transitions including breast augmentation and orchiectomy or vaginoplasty[10,13] and exogenous hormones or GAHT including estrogens and anti-androgens.[5–7] Also, therapy should be able to reduce the number of spontaneous erections and sperm production, which are characteristics of a male body.[7,8] The surgical interventions such as breast

Table 1 Difference between MtF and FtM transgenders

Male to Female (MtF)	Female to Male (FtM)
	
Transwoman	Transman
Assigned male sex at birth	Assigned female sex at birth
They require predominant hormone manipulation with estrogen and progesterone	They require predominant hormone manipulation with testosterone
To develop female characteristics, they usually undergo orchiectomy, vaginoplasty, breast augmentation	Surgical intervention required is hysterectomy, oophorectomy, and phalloplasty, and subcutaneous mastectomy
Estrogens given exogenous increase the risk of prolactinoma and breast cancer	Exogenous testosterone increases the risk of breast and endometrial cancer

augmentation and placements of implants may give rise to rare type of lymphomas of the breast such as implant-associated anaplastic large cell lymphoma.

Female to Male Patients

Female to male (FtM) or transmen are persons born as female at the time of birth but associate themselves to male sex.[2,6,12] Transmen require testosterone preparations in their GAHT regimens to stimulate virilization, to emulate male-like body hair growth and contours, along with surcease of menstruation, diminished glandular tissue, and increased fibrous connective tissue.[2,13] Progestational agents are administered when transdermal or oral testosterone is used as they are unable to cease menstruation and to prevent endometrial hyperplasia.[2,14] Surgical transition in transmen includes subcutaneous mastectomy, which is primarily done to achieve aesthetic masculine thorax and uterus extirpation and/or oophorectomy, and phalloplasty.[10,18]

Dilemmas Faced by Transgenders in the Healthcare System and Transgender Care

Apart from society, transgenders have to face a lot of discrimination in the healthcare system.[5] Although the standard treatments for transgenders are available, they still face many barriers.[15] According to the Virginia Transgender Health Initiative Study, the social stigma of being transgender is the basis of poor health status, resulting in alienation that accumulates throughout their life.[15] Various studies reported that transgenders were either denied medical care or have faced some form of harassment in the healthcare system.[15,16,18] The doctors refuse to provide treatment to them either because they feel insufficient to care for them[5] or due to their low financial status.[7,14,17,18] As a consequence, to avoid harassment, these people either hide their gender identity from doctors, which is important for getting correct advice regarding their breast health or avoid seeking medical attention.[5,15] These difficulties and a serious urge of confirming their physical attributes to the gender felt by them incite them to use alternatives to the standard treatments such as non-prescribed hormones (NPH).[5,18]

Transgender Care

Prevalent inequity and neglect threaten the health and well-being of the transgender population, making them one of the most marginalized populations in medicine.[18] Therefore, as per the Endocrine Society's updated clinical practice guidelines 2017, the medical team dealing with transgenders should involve a psychiatrist having the knowledge to diagnose gender dysphoria, and GAHT should be trained and experienced in assessing psychopathology and should be willing to participate in ongoing care.[19] The involvement of a psychiatrist helps by supporting access to care to the transgender population that may benefit from treatment.[18] For optimum care, pretreatment education and assessment, customized dosing, continuous monitoring, and standard screening for BC and prostate cancer are important.[20]

For children and adolescents who qualify for gender dysphoria, standards of care have been developed that involve puberty suppression, appropriate mental health support, and hormonal interventions, which may make future affirmation easier and safer.[20,21] The development of undesired secondary sexual characteristics in transgender adolescents can be prevented by drugs that either suppress the sex hormone production or block its action.[21] Drugs such as GnRH agonists for pubertal suppression, progestins for the reduction in biologic hormone production, and androgen receptor antagonists are useful.[21] The best treatment regimen for adolescents is the use of a GnRH agonist for complete suppression of puberty starting at tanner stage 2, followed by the introduction of cross-sex hormones in later adolescence.[21]

Gender Affirming Hormone Therapy

Gender affirming hormone therapy is the standard treatment used along with surgical transitions in transgenders to develop secondary sexual characteristics that align with their felt gender.[8] Transgenders have been receiving GAHT since the early 1960s.[6] GAHT is a key feature of transition-related care, rehabbing mental health, and the quality of life of transgenders.[5] The treatment regimens of GAHT are different for MtF patients and FtM patients.[2,6,10,13]

GAHT for Transwomen

The GAHT regimen for transwomen includes estrogen and anti-androgen drugs such as spironolactone.[5–7] Cyproterone is given as adjunctive therapy for lowering testosterone concentrations in the body and adds to curb testosterone production or to deter the androgen receptor.[7] This therapy helps in developing female secondary sex characteristics (breast development, redistribution of fat, reduction in body hair) and minimizing male characteristics (reduced number of spontaneous erections, reduced sperm production, slowing of scalp alopecia).[7,8,18] The use of progestin along with these drugs is controversial. According to a study, adding progestin to estrogen does not alter breast size,[2,22] rather it increases the risk of BC.[15]

In guidelines, estrogen also has caveats to its use as serum concentrations of conjugated equine estrogens cannot be accurately measured, conferring dose adjustments difficult.[5] Additionally, two studies reported that estrogens use in MTF individuals might put them at risk of BC due to high levels of circulating androgens and increased estrogen exposure.[1,2] The length and dosage of estrogen treatment also play a role in the propagation of neoplastic breast epithelium.[11] Oral ethinylestradiol, an estrogen preparation, is not advised owing to the associated increased risks of blood clots and cardiovascular (CV) morbidity and mortality. However, transdermal estradiol patches or gel are safer to use as the risk of blood clotting is low. The use of transdermal estradiol has been suggested and employed predominantly in older TW.[5]

After the administration of GAHT, breast development is modest in transwomen.[8] Mean breast-chest difference increase ranged from 3.7 cm (95% CI: 3.3–4.2) to 4.16 ± 2.9 cm at baseline to 7.9 ± 3.1 cm after 1 year of CHT.[8] Additionally, anatomical differences in the thoracic bone structure

compared with ciswomen may result in breast size appearing smaller than the objectively measured volume.[5]

GAHT for Transmen

Testosterone preparations are the standard treatment to stimulate virilization, emulate male-like body hair growth and contours, along with surcease in menstruation, diminished glandular tissue, and increased fibrous connective tissue.[2,13] Testosterone is administered in the form of injectable, gels, and transdermal patches.[14] Androgens are usually administered 6 months prior to reassignment surgery and continued thereafter.[13] Progestational agents are administered when transdermal or oral testosterone is used as they are unable to cease menstruation and prevent endometrial hyperplasia.[2,14] In transmen, serum testosterone levels are in the mid to normal range.[2] The removal of breasts in sex reassignment surgery (SRS) reduces the risk of BC in transmen by around 90%.[15] However, a few studies have reported BC in transmen. One study reported BC in the residual mammary cells of transmen after 10 years of mastectomy.[14] Another study reported a total of four cases of BC in transmen, three of which were diagnosed several years after subcutaneous mastectomy and the other at the time of mastectomy.[10] A large retrospective study conducted at the U.S. Veterans Affairs medical health system identified seven cases of BC in transmen.[22] Various studies reported that the aromatization of the circulating testosterone into estradiol by the aromatase enzyme was the reason for BC in transmen.[2,14,23]

Self-Use of Hormone Therapy

The widespread use of NPH has been documented in several studies.[17,18] In Washington, DC, 58% of transgenders reported the use of NPH once in their lives.[17] A report in Virginia suggested that around 60% of MTFs and 22% of FTMs patients were using NPH.[5] Similar reports were obtained from Chicago, California (San Francisco),[26]and Europe.[27,5] The majority of patients taking NPH were transwomen.[17] The major sources to obtain NPH were friends and online purchasing.[18,27] In rare cases, people have performed surgeries on themselves as they were unable to afford SRS.[17] Opting for such dangerous measures indicates pre-existing mental conditions such as depression, psychiatric comorbidity, social distress, and body dissatisfaction.[17]

Risks associated with GAHT

Gender affirming hormone therapy certainly improves the QOL of transgenders, but at the expense of their health. Various studies have reported that GAHT use is associated with severe health conditions such as cancer in transgenders.[10,28–30] Many benign and malignant tumors are known to be associated with CSH therapy as different organ-specific malignancies express sex hormone receptors.[31] It is seen that breast tumors develop rapidly in transgenders after short-term exposure to hormone therapy (median duration: 18 years).[10]

International guidelines published by the World Professional Association for Transgender Health in 2012 and the Endocrine Society in 2017 suggest estrogens presents a moderate risk of prolactinoma and BC development[31] and testosterone therapy is associated with a moderate risk of breast and endometrial cancer.[22] The proposed mechanism of BC development in transwomen is the binding of exogenous estrogen to the estrogen receptor (ER) in the breast tissue and stimulating carcinogenesis via increased cell proliferation, decreased apoptosis, and elevated production of oxidative metabolites that result in DNA damage.[32] For transmen, the aromatization of testosterone to estrogens in peripheral tissues, and the activation of androgen receptors leads to cellular growth and proliferation, particularly in mammary tissues leads to BC development.[33] Other risks associated with estrogens use in transwomen are myocardial infarction, thrombosis,[25]and ischemic stroke.[34] Conversely, transmen receiving testosterone did not suggest the increased probability of cardiovascular or cerebrovascular disease.[34]

Patient Presentation

The most common clinical feature of BC is a lump in the breast, which may be painful or painless.[33,35] Other symptoms of BC are bloody nipple discharge,[11] enlarged lymph nodes in one of the axilla,[6] dense breast tissues, or subareolar masses[11] on mammographic screening. In a systemic review by Fledderus et al, 7 out of 23 FtM transgenders were diagnosed to have breast cancer incidentally on routine histological examination after they underwent a cosmetic mastectomy. Genetic testing in transgenders has shown that the use of CSH therapy is also associated with the upregulation of various oncogenes.[10,35] Studies have reported that these symptoms are noticed after long-term use of CSH therapy.[6,37] The types of BC diagnosed in transgenders after CSH therapy were variable, including invasive ductal carcinoma, neuroendocrine carcinoma, and tubular adenocarcinoma.[35] Most of these tumors are hormone receptor-positive. The development of BC affects the GAHT regimen in transgenders. Most patients were put on low doses of exogenous hormones or even their CSH therapy was discontinued.[35,38]

Screening Recommendations for Transgenders

Breast cancer in transgenders is diagnosed at an early age as compared with ciswomen.[39] The median age of diagnosis of BC in transwomen is 51 years and for transmen, it is 47 years.[6,10] There are no guidelines defined especially for transgenders. However, BC screening recommendations for the cis population have been extrapolated for them.[39] The annual mammography screening is advised in transwomen older than 50 years of age and continuously undergoing GAHT, having greater than 5 years use of estrogen and progestin, a body mass index >35, or a positive family history.[6,10,15] For transwomen with implants, ultrasound serves as the first-line imaging technique because mammographic screening becomes less sensitive in the presence of implants.[5] Magnetic resonance imaging (MRI) should be performed, if there is concern about intracapsular rupture not visible by ultrasound.[5,40] Because the SRS does not

include removal of the prostate, prostate cancer screening should also be performed annually in transwomen after the age of 40 years.[6]

The current guidelines suggest the regular monitoring of the hormone profile of transwomen under estrogen therapy to minimize the risk of thromboembolism, hypertension, and cholestasis.[6,22] For transmen, who have undergone chest reconstruction surgery, annual examinations of the sub- and peri-areolar breast by MRI or ultrasound, together with chest wall and axillary examination remain the key screening tool.[10,15] Transmen who retain their physical characteristics should opt for routine annual screening using mammography starting at the age of 40 years.[10,15,41]

Treatment Recommendations: Differences?

There is a scarcity of data regarding the plan of management of BC in transgenders and so is the lack of data regarding the survival of these patients. The review of literature also suggests management from a case-to-case basis with the management in line with breast cancer in women. The plan of management involves surgical resection, hormone status, and further management as per the stage of the patient. Most of the patients reported were hormone positive thus receiving hormone therapies as a part of their BC treatment. Individual hormonal profiles of the patient including serum estradiol, luteinizing hormone, follicle-stimulating hormone, and testosterone levels should be tested before deciding about the choice of hormonal therapy and whether LHRH analogs are required in addition to aromatase inhibitors.

The basic difference comes in the treatment outcome as there are a lot of social reasons for the delay in reaching the healthcare systems and further bias after reaching hospitals. Special clinics may be needed in the major cancer centers where their medical needs may be met and these patients visit at the earliest after detecting a lump in the breast.

Conclusion

This review article highlights that transgenders are at the margins of the healthcare system. This is attributed to their low financial status and the negligence of the clinicians. These factors are responsible for NPH use, which is assuredly deleterious for them. Therefore, a need to develop the skills essential for the safe management of transgenders has been felt. This will improve patient interaction and will ensure the rational use of exogenous hormones and appropriate screening. Rational usage of GAHT is necessary as it is reported to be associated with reproductive organ cancer risks. Contradictory to this, a study by Hambree et al did not report any increased risk of BC.[22] The duration after which these symptoms appear in a person on GAHT is also contrasting in different studies. A few authors have suggested that the BC develops rapidly after short-term exposure to hormone therapy, while some studies have indicated that these symptoms are noticed after long-term use of CSH therapy. Because many of these cancers are diagnosed incidentally after cosmetic mastectomy, preoperative breast cancer screening should be advocated to decide about the type of surgery. Epidemiology of transgenders in low-to-middle income group countries such as India will be different from the developed countries as not many transgender individuals take hormonal therapy or undergo advanced surgeries and access to tertiary care centers is lesser thereby more advanced disease on presentation. Follow-up of patients after cosmetic mastectomy is also important as few of these histopathology specimen are positive for malignancy and can be missed if not followed. Also, over time we need better screening guidelines and treatment recommendations. For a concrete opinion on this, further research is required, until then it is recommended to follow the screening recommendations designed for the normal population strictly as early detection can increase the chances of survival.

Conflict of Interest
None declared.

References

1 Kiran T, Davie S, Singh D, et al. Cancer screening rates among transgender adults: Cross-sectional analysis of primary care data. Can Fam Physician 2019;65(01):e30–e37
2 Sonnenblick EB, Shah AD, Goldstein Z, Reisman T. Breast imaging of transgender individuals: a review. Curr Radiol Rep 2018;6(01):1
3 Sawant NS. Transgender: status in India. Ann of Indian Psychiatry [serial online] 2017[cited 2022 Jun 9]1:59–61Available from: https://www.anip.co.in/text.asp?2017/1/2/59/220257
4 Feldman J, Brown GR, Deutsch MB, et al. Priorities for transgender medical and healthcare research. Curr Opin Endocrinol Diabetes Obes 2016;23(02):180–187
5 Iwamoto SJ, Defreyne J, Rothman MS, et al. Health considerations for transgender women and remaining unknowns: a narrative review. Ther Adv Endocrinol Metab 2019;10:2042018819871166
6 Eismann J, Heng YJ, Fleischmann-Rose K, et al. Interdisciplinary management of transgender individuals at risk for breast cancer: case reports and review of the literature. Clin Breast Cancer 2019;19(01):e12–e19
7 Tangpricha V, den Heijer M. Oestrogen and anti-androgen therapy for transgender women. Lancet Diabetes Endocrinol 2017;5(04):291–300
8 de Blok CJM, Klaver M, Wiepjes CM, et al. Breast development in transwomen after 1 year of cross-sex hormone therapy: results of a prospective multicenter study. J Clin Endocrinol Metab 2018;103(02):532–538
9 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(06):394–424
10 de Blok CJM, Wiepjes CM, Nota NM, et al. Breast cancer risk in transgender people receiving hormone treatment: nationwide cohort study in the Netherlands. BMJ 2019;365:l1652
11 Hartley RL, Stone JP, Temple-Oberle C. Breast cancer in transgender patients: a systematic review. part 1: male to female. Eur J Surg Oncol 2018;44(10):1455–1462
12 Deutsch MB, Bhakri V, Kubicek K. Effects of cross-sex hormone treatment on transgender women and men. Obstet Gynecol 2015;125(03):605–610
13 Grynberg M, Fanchin R, Dubost G, et al. Histology of genital tract and breast tissue after long-term testosterone administration in a female-to-male transsexual population. Reprod Biomed Online 2010;20(04):553–558

14 Gooren LJ, Giltay EJ, Bunck MC. Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. J Clin Endocrinol Metab 2008;93(01):19–25
15 Phillips J, Fein-Zachary VJ, Mehta TS, Littlehale N, Venkataraman S, Slanetz PJ. Breast imaging in the transgender patient. AJR Am J Roentgenol 2014;202(05):1149–1156
16 Bradford J, Reisner SL, Honnold JA, Xavier J. Experiences of transgender-related discrimination and implications for health: results from the Virginia Transgender Health Initiative Study. Am J Public Health 2013;103(10):1820–1829
17 Rotondi NK, Bauer GR, Scanlon K, Kaay M, Travers R, Travers A. Nonprescribed hormone use and self-performed surgeries: "do-it-yourself" transitions in transgender communities in Ontario, Canada. Am J Public Health 2013;103(10):1830–1836
18 Tollinche LE, Walters CB, Radix A, et al. The Perioperative Care of the Transgender Patient. Anesth Analg 2018;127(02):359–366
19 Libman H, Safer JD, Siegel JR, Reynolds EE. Caring for the transgender patient: Grand Rounds Discussion From Beth Israel Deaconess Medical Center. Ann Intern Med 2020;172(03):202–209
20 Klein DA, Paradise SL, Goodwin ET. Caring for transgender and gender-diverse persons: what clinicians should know. Am Fam Physician 2018;98(11):645–653
21 Shumer DE, Nokoff NJ, Spack NP. Advances in the care of transgender children and adolescents. Adv Pediatr 2016;63(01): 79–102
22 Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, et al. ENDOCRINE TREATMENT OF GENDER-DYSPHORIC/GENDER-INCONGRUENT PERSONS: AN ENDOCRINE SOCIETY CLINICAL PRACTICE GUIDELINE. Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol 2017Dec23(12):1437
23 Shao T, Grossbard ML, Klein P. Breast cancer in female-to-male transsexuals: two cases with a review of physiology and management. Clin Breast Cancer 2011;11(06):417–419
24 Sanchez NF, Sanchez JP, Danoff A. Health care utilization, barriers to care, and hormone usage among male-to-female transgender persons in New York City. Am J Public Health 2009;99(04): 713–719
25 Randolph JF Jr. Gender-affirming hormone therapy for transgender females. Clin Obstet Gynecol 2018;61(04):705–721
26 Transgender Care UCSFDepartment of Family and Community Medicine, University of California San Francisco. Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People. In: Deutsch MB, ed. 2nd ed. 2016. Available at transcare.ucsf.edu/guidelines
27 Dekker MJ, Wierckx K, Van Caenegem E, et al. A European network for the investigation of gender incongruence: endocrine part. J Sex Med 2016;13(06):994–999
28 Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288(03):321–333
29 Beral VMillion Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. [abstract]. Lancet 2003;362(9382):419–427
30 Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. [abstract]N Engl J Med 1995;332(24):1589–1593
31 McFarlane T, Zajac JD, Cheung AS. Gender-affirming hormone therapy and the risk of sex hormone-dependent tumours in transgender individuals-a systematic review. Clin Endocrinol (Oxf) 2018;89(06):700–711
32 Braun H, Nash R, Tangpricha V, Brockman J, Ward K, Goodman M. Cancer in transgender people: evidence and methodological considerations. Epidemiol Rev 2017;39(01):93–107
33 Tongson K, Konovalova V, Dhawan N, Sharma S, Bahl J, Masri M. Breast cancer suspicion in a transgender male-to-female patient on hormone replacement therapy presenting with right breast mass: breast cancer risk assessment and presentation of a rare lesion. Case Rep Oncol Med 2017;2017:5172072. Doi: 10.1155/2017/5172072
34 Connelly PJ, Marie Freel E, Perry C, et al. Gender-affirming hormone therapy, vascular health and cardiovascular disease in transgender adults. Hypertension 2019;74(06):1266–1274
35 Barghouthi N, Turner J, Perini J. Breast cancer development in a transgender male receiving testosterone therapy. Case Rep Endocrinol 2018;2018:3652602. Doi: 10.1155/2018/3652602
36 Fledderus AC, Gout HA, Ogilvie AC, van Loenen DKG. Breast malignancy in female-to-male transsexuals: systematic review, case report, and recommendations for screening. Breast 2020; 53:92–100
37 Mattingly AE, Kiluk JV, Lee MC. Clinical considerations of risk, incidence, and outcomes of breast cancer in sexual minorities. Cancer Contr 2016;23(04):373–382
38 Joint R, Chen ZE, Cameron S. Breast and reproductive cancers in the transgender population: a systematic review. BJOG 2018;125 (12):1505–1512
39 Teoh ZH, Archampong D, Gate T. Breast cancer in male-to-female (MtF) transgender patients: is hormone receptor negativity a feature? BMJ Case Rep 2015;2015:bcr2015209396. Doi: 10.1136/bcr-2015-209396
40 Evans A, Trimboli RM, Athanasiou A, et al; European Society of Breast Imaging (EUSOBI), with language review by Europa Donna–The European Breast Cancer Coalition. Breast ultrasound: recommendations for information to women and referring physicians by the European Society of Breast Imaging. Insights Imaging 2018;9(04):449–461
41 Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2018: a review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin 2018;68(04):297–316

Soft Tissue Sarcomas with Special Reference to Molecular Aberration, Chemotherapy, and Recent Advances: A Review Article

Linu Abraham Jacob[1] Sreevalli A.[1] Shwetha Ninutha[1] Lokanatha Dasappa[1] Suresh Babu MC[1] Lokesh KN[1] Rudresha AH[1] Rajeev LK[1] Smitha Saldanha[1]

[1] Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bengaluru, India

Address for correspondence A. Sreevalli, MD, Senior Resident, Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Dr M H, Marigowda Road, Hombegowda Nagar, Bengaluru, Karnataka- 560029, India (e-mail: svalli88@gmail.com).

Ind J Med Paediatr Oncol 2024;45:9–21.

Abstract

Soft tissue sarcomas (STS) are a diverse group of rare solid tumors of mesenchymal cell origin with distinct clinical and pathological features. They account for less than 1% of all adult malignancies and 15% of pediatric neoplasms. They include over hundreds of different histological subtypes. Many of these subtypes can occur at any age and are not confined to a specific site. Each subtype displays variable clinical behavior. Low incidence, variable presentation, behavior, and long-term outcomes further make it challenging to treat. There are multiple ongoing trials that focus on the anatomic site and histologic subtype to tailor the treatment. Further rarity of each histotype is a major barrier to recruit patients to randomized controlled trials. A multidisciplinary approach is mandatory in all cases of soft tissue sarcomas.

The purpose of this review is to thoroughly understand the existing literature on history, incidence, epidemiology, etiology, histology, pathogenesis, diagnostic modalities, prognosis, management, and post treatment surveillance of STS. Uterine sarcomas, gastrointestinal stromal tumors (GIST), and pediatric sarcomas are not included here. It briefly highlights various molecular aberrations, changes in staging as per the American Joint Committee on Cancer (AJCC) 8, drugs that are used off-label in specific subtypes of sarcoma along with the recent advances. The classification of STS is undergoing continuous evolution. A wide variety of subtypes can only be diagnosed accurately with sophisticated molecular diagnostic tests and with the involvement of expert geneticists and pathologists to interpret it.

There is no clarity on tailoring the treatment of STS to date. There is always a question on how best we can incorporate chemotherapy and radiotherapy along with surgery as a part of multimodality treatment. The heterogeneity of STS has hindered the development of robust, evidence-based treatment strategies, and our therapeutic approach is neither histology-specific nor widely standardized. Increased knowledge about sarcoma biology could help to discover new and more effective treatment strategies and help overcome the therapeutic challenge imposed by this deadly

Keywords

- soft tissue sarcoma
- heterogenous
- mesenchyme
- molecular aberration

article published online
February 16, 2022

DOI https://doi.org/10.1055/s-0041-1740324.
ISSN 0971-5851.

© 2022. 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

disease. Continued collaboration among various sarcoma centers globally will be of prime importance to optimize STS management. This will allow studies to be both sufficiently large and reasonably focused to generate evidence that is clinically meaningful in specific STS patient populations.

Introduction

Soft tissue sarcomas (STS) are rare and heterogenous group of malignant tumors that originate from embryonic stem cells. Rudolf Virchow, Samuel Gross, and Samuel Wilks laid the foundation of our current understanding of soft tissue sarcomas.[1,2] They represent a diverse family of malignancies comprising over hundred histological subtypes and many molecular aberrations.[3] The delay in diagnosis and presentation with advanced disease or metastasis account for poor prognosis. The rarity of the disease along with a wide variety of subtypes has made sarcomas a challenging topic to understand.

Incidence and Epidemiology

STS comprise less than 1% of all adult malignancies and 15% of pediatric malignancies.[4] As per National Cancer Institute Surveillance Epidemiology End Results (NCI SEER) cancer database, STS accounts for 0.7% of all new cancer cases with estimated new STS cases in 2020 being 13,130. The life time risk of developing STS is 0.4%. It is most commonly diagnosed in the age group of 65 to 74 years. It represents 0.9% of all cancer deaths.

The death rate was 1.3 per 100,000 men and women per year.[5]

As per SEER cancer database 60% of STS are localized at diagnosis, 19% spread to the regional lymph nodes, 15% have distant metastasis, and 6% are of unknown stage. The 5-year overall relative survival is 64.7%.[5] Patients with high-grade tumors are at a significant risk for distant recurrence, and as many as 50% of these patients die of their disease.[6] On the contrary, low-grade STS have an excellent prognosis with 5-year survival rates of 85% or more.[7]

Histologic Subtypes

The World Health Organization (WHO) 2020 (5th edition) classifies STS based on presumptive tissue of origin, architectural pattern if of uncertain histogenesis, and genetics as shown in ►**Table 1**. As per the WHO, there are more than 100 different histologic subtypes.[3] The most common STS in adults are liposarcoma, followed by leiomyosarcoma, undifferentiated pleomorphic sarcoma, gastrointestinal stromal tumors (GIST), and many others as shown in ►**Fig. 1**.[8] The Network for Sarcomas (NETSARC) is a large database that enables the exploration of rare clinical and histological subtypes.[9]

Etiology

The various etiological factors are discussed as below:

1. Genetic Predisposition

Genetic syndromes associated with STS are Li-Fraumeni syndrome (LFS), Gardner syndrome (familial adenomatous polyposis), and neurofibromatosis type 1 (NF 1). Mutations in *TP53* are the most common germline mutations that predispose to sarcomas such as osteosarcoma, Ewing, and rhabdomyosarcoma.[10] Sarcomas account for 25 to 33% of tumors seen in genetic cancer syndromes.[11]

2. Radiation Therapy and Chemotherapy

Radiation exposure and risk of STS at 15 to 20 years is almost 0.5%.[12] The risk is the highest in childhood cancer survivors following RT and chemotherapy with regimens containing anthracyclines and alkylating agents. The most common histopathologic type of radiation-associated sarcoma is undifferentiated pleomorphic sarcoma, previously termed malignant fibrous histiocytoma (MFH).[12] Undifferentiated pleomorphic sarcoma (UPS) was seen in 26%, angiosarcoma in 21%, fibrosarcoma in 12%, leiomyosarcoma (LMS) in 12%, and malignant peripheral nerve sheath tumor (MPNST) in 9% of patients.[13]

3. Chemicals

Exposure to various chemical agents such as vinyl chloride and arsenic was found to be associated with hepatic angiosarcoma. Other chemicals, exposure to which are at an increased risk of soft tissue sarcoma are thorotrast, dioxin, phenoxy herbicides, and chlorophenol.[14]

4. Chronic Edema, Chronic Irritation Trauma

Chronic lymphedema is known to be associated with angiosarcoma. Chronic irritation secondary to foreign bodies and trauma may be responsible for abdominal desmoid.[15]

5. Viral Infections

Viral infections such as human immunodeficiency virus (HIV), human herpesvirus-8 (HHV 8), and Epstein–Barr virus (EBV) have also been implicated in the pathogenesis of STS.[16]

Genetics and Molecular Pathogenesis

The genetics of STS can be divided into those with simple and highly complex karyotypes. Simple karyotype includes fusion genes due to reciprocal translocations or specific point

Table 1 WHO histologic classification of soft tissue sarcomas

A) Fibroblastic/ myofibroblastic tumors a) Benign 1. Angiomyofibroblastoma 2. Desmoplastic fibroblastoma 3. Myositis ossificans 4. Nodular fasciitis 5. Elastofibroma 6. Fibromatosis colli 7. Angiofibroma NOS b) Intermediate locally aggressive 1. Solitary fibrous tumor, benign 2. Desmoid - type fibromatoses 3. Palmar/plantar type fibromatoses c) Intermediate rarely metastasising 1. DFSP - Dermatofibrosarcoma protuberans NOS 2. Inflammatory myofibroblastic tumor 3. Solitary fibrous tumor NOS 4. Infantile fibrosarcoma 5. Superficial CD34-positive fibroblastic tumor 6. Myofibroblastic sarcoma d) Malignant 1. Solitary fibrous tumor, malignant 2. Fibrosarcoma NOS 3. Myxofibrosarcoma
B) Fibrohistiocytic a) Benign 1. Tenosynovial giant cell tumor NOS 2. Deep benign fibrous histiocytoma b) Intermediate (Rarely Metastasizing) Tumors 1. Giant cell tumor of soft part NOS 2. Plexiform fibrohistiocytic tumor c) Malignant 1. Malignant tenosynovial giant cell tumor
C) Adipocytic a) Benign 1. Lipoma NOS 2. Lipomatosis 3. Angiomyolipoma NOS 4. Hibernoma intermediate b) Intermediate 1. Atypical lipomatous tumor /well differentiated liposarcoma c) Malignant 1. Liposarcoma well differentiated NOS 2. Dedifferentiated liposarcoma 3. Myxoid liposarcoma 4. Pleomorphic liposarcoma
D) Smooth muscle a) Benign 1. Leiomyoma NOS b) Malignant 1. Leiomyosarcoma NOS
E) Skeletal muscle a) Benign 1. Rhabdomyoma NOS b) Malignant 1. Embryonal rhabdomyosarcoma NOS 2. Alveolar RMS 3. Pleomorphic RMS NOS 4. MYOD1 mutant spindle cell/sclerosing RMS 5. Ectomesenchymoma
F) Vascular a) Benign

(*Continued*)

Table 1 (*Continued*)

1. Hemangioma NOS 2. Lymphangioma NOS 3. Epitheloid hemangioma b) Intermediate Locally Aggressive 1. Kaposiform hemangioendothelioma c) Intermediate Rarely Metastasising 1. Kaposi sarcoma 2. Composite hemangioendothelioma 3. Pseudomyogenic hemangioendothelioma d) Malignant 1. Angiosarcoma 2. Epitheloid hemangioendothelioma NOS with WWTR1-CAMTA1 fusion 3. Epitheloid hemangioendothelioma with YAP1-TFE3 fusion
G) Perivascular a) Benign 1. Glomus tumor NOS 2. Angioleiomyoma 3. Myopericytoma b) Malignant 1. Malignant glomus tumor
H) Neural a) Benign 1. Neurofibroma NOS 2. Schwannoma NOS 3. Perineuroma NOS 4. Granular cell tumor NOS 5. Benign triton tumor b) Malignant 1. Malignant peripheral nerve sheath tumor 2. Malignant triton tumor
I) Extraskeletal chondro-osseous tumor a) Benign 1. Chondroma NOS 2. Chondroblastoma-like soft tissue chondroma b) Malignant 1. Extraskeletal osteosarcoma
J) Tumors of uncertain differentiation a) Benign 1. Myxoma NOS 2. Angiomyolipoma b) Intermediate locally aggressive 1. Hemosiderotic fibrolipomatous tumor c) Intermediate rarely metastasising 1. Atypical fibroxanthoma 2. Myoepithelioma NOS d) Malignant 1. Alveolar soft part sarcoma 2. Synovial sarcoma NOS (biphasic, spindle cell, poorly differentiated) 3. Desmoplastic small round cell tumor 4. Epithelioid sarcoma 5. NTRK-rearranged spindle cell neoplasm 6. Clear cell sarcoma NOS 7. Extraskeletal myxoid chondrosarcoma 8. Perivascular epithelioid tumor, malignant 9. Rhabdoid tumor NOS
K) Undifferentiated/ unclassified tumor a) Malignant 1. Undifferentiated pleomorphic sarcoma 2. Undifferentiated round cell sarcoma 3. Undifferentiated epithelioid sarcoma 4. Undifferentiated sarcoma, not otherwise specified

Abbreviations: NOS, not otherwise Specified; RMS, rhabdomyosarcoma.

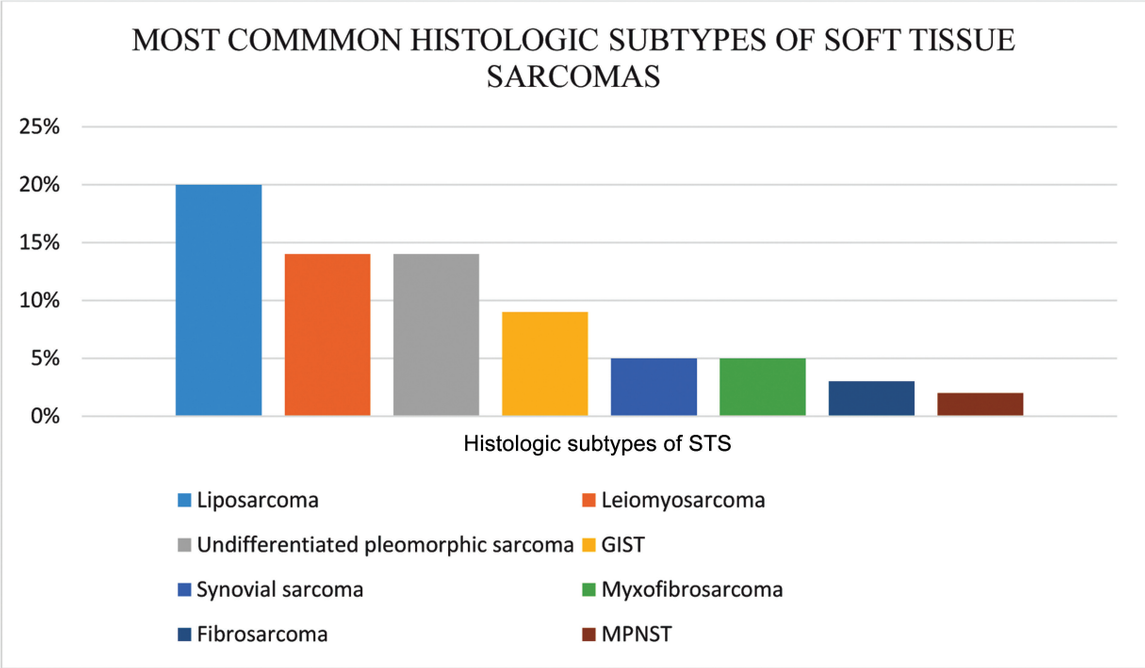


Fig. 1 Histologic subtypes of soft tissue sarcomas with decreasing order of frequency.[3]

Table 2(a) Sarcoma subtypes with associated translocation and genes

Sarcoma Subtype	Translocation	Genes
Myxoid/ round cell liposarcoma	t(12;16)(q13;p11) t(12;22)(q13;q12)	FUS-DDIT3 (>90%) EWSR1-DDIT3 (<5%)
Ewing sarcoma	t(11;22)(q24;q12) t(21;22)(q22;q12)	EWSR1-FLI1 (>80%) EWSR1-ERG (10-15%)
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	EWSR1-WT1 (>75%)
Synovial sarcoma	t(x;18)(p11;q11)(>90%)	SYT-SSX1 (66%) SYT-SSX2 (33%) SYT-SSX4 (<1%)
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14) t(1;13)(p36;q14)	PAX3-FOXO1 (<80%) PAX7-FOXO1 (<20%) PAX3-NCOA1 (<1%) PAX3-NCOA2 (<1%)
Alveolar soft part sarcoma	t(X;17)(p11;q25)	ASPSCR1-TFE3(>90%)
Dermatofibrosarcoma Protuberans	t(17;22) (>75%) t(17;22)(q22;q13.1)(10%)	COL1A1-PDGFB
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12) t(9;17)(q22;q11) t(9;15)(q22;q21) t(3;9)(q12;q22)	EWSR1-NR4A3 (75%) TAF15-NR4A3 (<10%) TCF12-NR4A3 (<10%) TFG–NR4A3 (<5%)
Endometrial stromal tumor	t(7;17)(p15;q21)	JAZF1-SUZ12 (30%)
Clear cell sarcoma	t(12;22)(q13;q12) t(2;22)(q34;q12)	EWSR1-ATF1 (>75%) EWSR1-CREB1 (<5%)
Infantile fibrosarcoma	t(12;15)(p13;q25)	ETV6-NTRK3 (>75%)
Inflammatory myofibroblastic Tumor	t(1;2)(q25;p23) t(2;19)(p23;p13) t(2;17)(p23;q23)	ALK-TPM34 ALK-TPM ALK-CLTC
Undifferentiated round cell sarcoma	t(X;X)(p11;p11) t(4;19)(q35;q13) t(10;19)(q26;q13)	BCOR-CCNB3 CIC-DUX4

Table 2(b) Sarcoma subtypes with associated mutations

Sarcoma subtype	Mutations	Genes
Desmoid fibromatosis	Trisomies 8 and 20 (30%)	APC inactivation by mutation/deletion (10%) CTNNB1 (β-catenin) mutations (85%)
Embryonal rhabdomyosarcoma	Trisomies 2q, 8, and 20 (>75%)	LOH at 11p15 (>75%)
Solitary fibrous tumor	12q13 inversion	NAB2-STAT6 (>95%)
Gastrointestinal stromal tumor	Monosomies 14 and 22 (>75%) Deletion of 1p (>25)	KIT or PDGFRA mutation (>90%)

Abbreviations: APC, adenomatous polyposis coli; LOH, loss of heterozygosity; PDGFRA, platelet-derived growth factor receptor A.

Table 2(c) Sarcoma subtypes with associated complex karyotype

Sarcoma subtype	Complex karyotype	Genes
Well differentiated/ dedifferentiated liposarcoma	12q13-15 rings(amplification) and giant markers	MDM2 CDK4
Pleomorphic liposarcoma	13q14, 17q11	Rb NF1
Myxofibrosarcoma and undifferentiated pleomorphic sarcoma	5p amplification	
Leiomyosarcoma	del1p, 10q	p53, PTEN, Rb1
Malignant peripheral nerve sheath tumor	17q11	NF1, p53
Angiosarcoma	8q24,	MYC (50%)
	10p12	KDR (VEGFR2)

Abbreviations: VEGFR2, vascular endothelial growth factor receptor 2.

mutations/inversions. Translocation-associated sarcomas account for one-third of sarcomas and is more common in young adults 30 to 40 years of age.[17] Complex karyotype in the form of numerous genetic losses and gains is more common in the 50 to 60 years of age group. The detection of these cytogenetic abnormalities by fluorescence in situ hybridization (FISH) and reverse transcriptase polymerase chain reaction (RT-PCR) can assist in the diagnosis of specific STS as illustrated in ►**Tables 2(a)**, **2(b)**, **2(c)**.[18]

Clinical Features

The most common clinical presentation is a gradually enlarging painless mass. The most common site of STS is extremities of which the thighs, buttocks, and groin constitute 46%, upper extremity 13%, torso 18%, retroperitoneum 13%, and head and neck 9%.[19] Particular histologic subtypes have proclivity to certain anatomic sites, for example liposarcomas (LPS) are more common in the thighs, desmoplastic small round cell tumors mainly involve the abdominal cavity and pelvis. The most common retroperitoneal sarcomas (RPS) are LPS and leiomyosarcomas followed by undifferentiated/unclassified STS. Well-differentiated LPS are the most common followed by dedifferentiated LPS.[20]

Mode of Spread

The most common mode of spread is hematogenous and mainly to the lungs. According to Christie-Large et al, the incidence of distant metastases at the time of diagnosis of STS was 10%, of which 83% were located in the lungs.[21] Other rare sites include the liver, bone, brain, skin, and soft tissues. Extrapulmonary site metastases to retroperitoneum, spine, paraspinous tissues is seen with myxoid/round cell liposarcomas. Overall, 25% of patients will develop distant metastases after the treatment of primary disease. The chance of distant metastases is almost 40 to 50% if the tumor size is more than 5 cm, deep to fascia, and intermediate or high grade.[22]

Lymph node spread in STS is very rare and associated with poor prognosis. It is seen more commonly in subtypes such as rhabdomyosarcoma, synovial sarcoma, epithelioid sarcoma, clear cell sarcoma, and angiosarcoma.[23]

Investigations

Radiological diagnosis is essential to determine the extent of primary, rule out metastases, and plan surgery. Magnetic resonance imaging (MRI) is the investigation of choice for primary extremity lesion and also for detecting local recurrence.[24] Computerized tomography(CT) is preferred for

Table 3 FNLCC histologic grading of STS

	Tumor differentiation
1	Sarcomas closely resembling normal adult mesenchymal tissue (e.g., low-grade leiomyosarcoma)
2	Sarcomas of which histologic typing is certain (e.g., myxoid/round cell liposarcoma)
3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcoma, soft tissue osteosarcoma, Ewing sarcoma/PNET of soft tissue
	Mitotic count: In most mitotically active area of the sarcoma, 10 successive HPFs are assessed using a 40x objective
1	0–9 mitoses per 10 HPF
2	10–19 mitosis per 10 HPF
3	$\geq$20 mitoses per 10 HPF
	Tumor necrosis: evaluated on gross examination
0	No necrosis
1	$<$ 50% tumor necrosis
2	$\geq$50% tumor necrosis
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6,7 or 8

Abbreviations: HPF, high-power field; PNET, primitive neuroectodermal tumor.

primary abdominal, visceral, or retroperitoneal lesion. CT chest is required as a part of staging workup to rule out pulmonary metastases.[25] CT abdomen and pelvis need to be done in round cell/myxoid liposarcoma due to a high risk of metastasis to the abdomen and retroperitoneum, brain imaging in angiosarcoma and alveolar soft part sarcoma as high chances of brain metastases, bone scan for round cell/myxoid liposarcomas. Positron emission tomography computed tomography (PET CT) is not a part of initial staging workup of STS, including retroperitoneal sarcomas, due to its restricted ability to differentiate benign from low to intermediate grade sarcomas.[26] As per the National Comprehensive Cancer Network (NCCN), PET scan in STS may be useful for prognostication, grading, and determining the response to neoadjuvant chemotherapy.

Percutaneous core needle biopsy is indicated only if diagnosis is in doubt or if neoadjuvant therapy is planned.[27] It is rarely performed if initial surgery is planned based on radiographic diagnosis as there is a high chance of tumor seeding. IHC, FISH, RT-PCR, and NGS are the various molecular methods to arrive at final diagnosis. Common IHC markers include NKX2.2 for Ewing sarcoma, CDK4 and MDM2 for well-differentiated/dedifferentiated LPS, TLE-1 for synovial sarcoma, H3K27me3 for MPNST, STAT6 for SFT, EBER-ISH and Pan-NTRK.

Histologic Grading

The grading of sarcoma includes features such as mitotic index, necrosis, cellularity, pleomorphism, and histologic subtype or differentiation. Among them, the two most important are mitotic index and the extent of necrosis.[28] Half of retroperitoneal tumors are high grade although this varies according to histology. There are several grading systems of which the two most commonly used are the National Cancer Institute (NCI) system and the FNCLCC system-Federation Nationale des Centres de Lutte Contre le Cancer. The prediction of distant metastasis and tumor mortality was slightly better with the FNCLCC system than the NCI system.[29] Hence, FNLCC is more commonly used. FNLCC histologic grading is determined by three parameters, i.e., differentiation, mitotic activity, and the extent of necrosis. Each parameter is scored as in ►**Table 3**. The scores are added to determine the grade.

Staging

The most commonly used staging system for STS is tumor, node, and metastasis (TNM) system, which was developed in collaboration with the Union for International Cancer Control (UICC) with American Joint Committee on cancer (AJCC). The AJCC TNM system uses tumor size (T), lymph node involvement (N), presence or absence of distant metastases (M) along with histologic grading (G) to determine the stage grouping. The recent AJCC 8 determines separate T staging and prognostic stage groups for STS of extremity/trunk and retroperitoneum unlike AJCC 7 as given below in ►**Table 4(a)**. It also describes a separate T staging for STS of the abdomen and thorax but no separate N and M and prognostic stage groupings (►**Table 4(b)**). TNM staging for retroperitoneal sarcomas is same as for the trunk and extremities, except that any T, N1 M0 of any grade is stage IIIB and not stage IV.

Table 4(a) AJCC 8 TNM staging/prognostic grouping for soft tissue sarcoma of trunk and extremities

T	Primary tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 5cm or less in greatest dimension
T2	Tumor more than 5cm and less than or equal to 10cm in greatest dimension
T3	Tumor more than 10cm and less than or equal to 15cm in greatest dimension
T4	Tumor more than 15cm in greatest dimension
N	**Regional lymph nodes**
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis
M	**Distant metastases**
M0	No distant metastasis
M1	Distant metastasis

Table 4(b) AJCC 8 T staging of abdominal and thoracic visceral organs

T	Primary tumor
TX	Primary tumor cannot be assessed
T1	Organ confined
T2a	Tumor invades serosa or visceral peritoneum
T2b	Tumor extends beyond serosa (mesentery)
T3	Invades another organ
T4a T4b T4c	Multifocal involvement (2 sites) multifocal (3–5 sites) Multifocal (>5 sites)

	T	N	M	G
Stage IA	T1	N0	M0	G1, GX
Stage IB	T2	N0	M0	G1, GX
	T3	N0	M0	G1, GX
	T4	N0	M0	G1, GX
Stage II	T1	N0	M0	G2, G3
Stage IIIA	T2	N0	M0	G2, G3
Stage IIIB	T3 T4	N0	M0	G2, G3 G2, G3
Stage IV	Any T Any T	N1 Any N	M0 M1	Any G Any G

Prognostic Factors

The most important prognostic factors include histologic grading, tumor size, and pathologic stage at diagnosis.[8] Others include histologic subtype, anatomic site, depth, patient age, positive margin, recurrent disease at presentation.[30] Patients with extremity and superficial trunk lesions have better prognosis compared to retroperitoneal and visceral sarcomas.

Grade is an independent predictor of early distant metastases and death. The initial tumor size determines the chances of local recurrence and distant metastases. In a review by Suit et al from Massachusetts General Hospital (MGH), the frequency of distant metastasis increased with an increase in the tumor size, accounting for 38% of tumors 5–10 cm, 49% of tumors 10.1–15 cm, 58% for tumors 15.1–20 cm, and 83% for tumors > 20 cm. Bone and neurovascular invasion are associated with bad prognosis.

Grade, completeness of resection, presence or absence of metastatic disease are independent prognostic factors for disease-specific survival in case of retroperitoneal sarcomas.[31] Patients with MPNST, LMS, high-grade liposarcoma had worse survival compared to solitary fibrous tumor (SFT), low-grade liposarcoma. A nomogram developed by the Memorial Sloan-Kettering Cancer Centre (MSKCC) aids in predicting survival and treatment decision-making for individual patients. It includes patients' age, tumor size, FNLCC grade, histologic subtype, multifocality, and the extent of resection.[32]

Treatment

■ Soft Tissue Sarcoma of Extremities

The main aim of treating STS of extremities is to improve survival, prevent local and distant recurrences, improve limb function, and minimize morbidity and mortality. The only curative approach is surgical resection. Radiotherapy is indicated for more than 5 cm tumor to improve local control. The role of chemotherapy in adjuvant and neoadjuvant setting is still controversial.

Adjuvant Chemotherapy

Despite 20 randomized controlled trials (RCTs) and two meta-analyses, data on adjuvant chemotherapy are still irreconcilable. As per NCCN and ESMO, adjuvant chemotherapy is an option for high-risk patients–deep-seated STS, high-grade, large primary $\geq$ 5 cm, locally recurrent extremity sarcoma. Present approach is to individualize treatment based on performance status (PS), age, comorbidity, site of the disease, histology such as synovial sarcoma, leiomyosarcoma, and myxoid round cell liposarcoma, which are chemosensitive.

Sarcoma meta-analysis collaboration (SMAC) in 1997 included 14 RCTs of doxorubicin-based adjuvant chemotherapy (less than 5% received ifosfamide-containing regimen) after local treatment of 1,568 adults with localized resectable STS. The median follow-up was 9.4 years. It was observed that doxorubicin-based adjuvant chemotherapy significantly improved the time to local recurrence with hazard ratio (HR) of 0.73 (95% confidence interval [CI]: 0.56–0.94) and distant recurrence with HR of 0.70 (95%CI: 0.57–0.85), and overall recurrence-free survival (RFS) in adults with HR of 0.75 (95%CI: 0.64–0.87) and an absolute 6 to 10% improvement in RFS at 10 years. There was a trend toward OS although not statistically significant. There was no difference in the outcome in relation to various parameters such as age, sex, stage, site, grade, histology, extent of resection, tumor size, or exposure to radiotherapy. However, on subset analysis those with extremity and truncal sarcomas had significant OS benefit. There was almost 7% absolute benefit in OS at 10 years in those receiving doxorubicin-based regimens, which was statistically significant.[33,34]

However, the main drawback of this meta-analysis was it included only one negative trial of the two European organizations for research and treatment of cancer (EORTC) negative trials.

Petrioli et al in an Italian trial included 88 patients with high-risk extremity sarcoma were randomized to surgery with or without RT and surgery with or without RT with chemotherapy (epirubicin or IE regimen). The 5-year disease-free survival (DFS) and OS were higher in chemotherapy arm, which was statistically significant accounting for 69% versus 44% and 72% versus 47%, respectively.[35] This study highlights the advantage of epirubicin-based adjuvant chemotherapy in high-risk STS.

EORTC and an Austrian trial could not demonstrate the survival benefit from adjuvant doxorubicin- and ifosfamide-containing regimens.[36,37] EORTC included 351 patients with completely resected STS, of which 67% were extremity tumors, 60% were high grade, and 40% were $\geq$10 cm in size. There was no difference in RFS and OS in chemotherapy (five cycles of ifosfamide 5 gm/m^2 cycle and adriamycin 75 mg/m^2-IA) and observation arm.[36] The limitations of these studies were small number of patients, admittance of non-extremity, small and low/intermediate-grade primaries, and the use of relatively low ifosfamide dose.

Pervaiz et al in 2008 demonstrated the benefit of chemotherapy in an updated systematic meta-analysis (SMAC) of 18 RCTs. It included negative trials such as Austrian and two Italian trials but not the EORTC trial. A total of 1,953 patients with localized surgically amenable STS were included between 1973 and 2002 (five trials used IA regimen, while others used either doxorubicin alone or a combination regimen). The odds ratio (OR) for local and distant recurrence favored chemotherapy similar to the SMAC meta-analysis. When compared to the SMAC meta-analysis, doxorubicin and ifosfamide were associated with statistically significant OS benefit (HR for death: 0.56, 95% CI: 0.36–0.85) with an absolute risk reduction accounting to 11% (30 vs. 41% risk of death). However, the benefit could not be shown for doxorubicin alone. Thus, ifosfamide is of utmost importance in adjuvant setting of sarcomas.

■ **Role of tumor histology, grade, and size in adjuvant therapy**

There are no prospective trials to prove the same. Three retrospective studies have showed benefit of adjuvant chemotherapy in chemosensitive subtypes such as myxoid round cell liposarcoma and synovial sarcoma. In a single center Italian trial of 251 patients with localized synovial sarcoma, 61 patients who had undergone macroscopically complete resection, received adjuvant chemotherapy. The 5-year metastasis-free survival (MFS) in chemotherapy arm was 60% as against 48% in surgery only arm. The benefit was more for those older than 17 years and $\geq$ 5 cm tumor size (MFS: 47 vs. 27%, respectively).[38] However, as per both MSKCC and MD Anderson retrospective data between 1984 and 1999, patients undergoing adjuvant chemotherapy for high-grade, $\geq$ 5 cm extremity STS did not show any benefit.[39]

The optimal regimen is unspecified- the AIM regimen consisting of adriamycin 75 mg/m^2, ifosfamide 9–10 gm/m^2 D1-D3 with mesna every three weekly for a total of six cycles is used commonly.

Neoadjuvant Chemotherapy

The role of neoadjuvant therapy is in large, recurrent, and high-grade tumors where limb salvage is an issue. The correct sequencing of chemotherapy (CT), RT, and surgery is unknown. The main purpose of neoadjuvant therapy is the treatment of micro metastases, need for less radical surgery, and more effectiveness of preop RT or chemotherapy. There are no randomized phase III trials to support neoadjuvant chemotherapy. A randomized phase II EORTC study of 150 patients randomizing them to three cycles of neoadjuvant ifosfamide and adriamycin versus surgery alone was negative.

■ **Role of histology in neoadjuvant therapy**

In a phase III multicentric randomized trial, as compared to histology-based treatment with high-dose ifosfamide alone for synovial sarcoma, gemcitabine plus dacarbazine for LMS, gemcitabine plus docetaxel for undifferentiated pleomorphic sarcoma, trabectedin for high-grade myxoid liposarcoma, etoposide plus ifosfamide for MPNST, anthracycline-based regimen (IE regimen) showed DFS benefit among all histologies including LMS and MPNST. Data are still not convincing as to how epirubicin influenced the trial

results as doxorubicin is more commonly used in all other trials.

■ **Retroperitoneal Sarcomas**

The only curative treatment for RPS has been surgery. The ability to achieve R0/R1 resection at the time of initial presentation is the most important prognostic factor for survival. Debulking surgery (R2 resection) should be preferred only in large unresectable well-differentiated retroperitoneal liposarcomas, which aids in symptom improvement and prolongs survival.

Intra-op radiotherapy (IORT) of 10 to 15 Gy can be administered to the areas of residual microscopic or gross disease as it improves local control, RFS, and OS. However, no RCTs are available to support the same.[40] Reresection is advised for gross residual disease (R2 resection), if technically feasible.

Adjuvant Therapy

Evidence for adjuvant therapy for RPS, may it be RT and/or chemotherapy, is lacking. Adjuvant RT is indicated for intermediate- to high-grade tumors and incompletely resected tumors at high risk for recurrence. Survival benefit has been demonstrated in retrospective and case–control studies.[41] Postoperative RT enhances local tumor control and has shown a trend toward long-term RFS. However, the management of radiation-associated morbidity is challenging. Hence, safe delivery of RT is feasible preoperatively than postop. Anthracycline/ifosfamide-containing regimen significantly improved the survival as per an updated meta-analysis but it did not include two negative trials.[42,43]

Neoadjuvant Therapy

Data on neoadjuvant chemotherapy for RPS are very limited. As per the ESMO guidelines tailoring treatment is based on histology and grade. In case of large well-differentiated liposarcoma (WD LPS), intermediate-and high-grade tumors that are not chemosensitive or patient not suitable for chemotherapy neoadjuvant RT, followed by a surgery is preferred. Pre-op RT permits safe delivery of higher doses than in post-op setting and is biologically more effective; however, no RCTs are available as yet to support the same in RPS. Results of STRASS I, a randomized EORTC phase III trial is awaited.[44] Intensity modulated radiotherapy (IMRT) has the ability to improve the therapeutic index; however, longer follow-up is needed.[45] There are no randomized control trials on concurrent chemoradiation. Smaller studies have been done in cases of leiomyosarcoma, undifferentiated pleomorphic sarcoma but long-term outcomes are not reported.

Neoadjuvant CT with or without perioperative RT would be an option for intermediate- and high-grade tumors with chemosensitive histology such as synovial sarcoma, myxoid/round cell, LPS and those with high risk of distant metastases such as LMS, large undifferentiated LPS (STRASS-2 trial).[46] Data on optimal regimen to be chosen for RPS are lacking. Histotype-driven treatment when compared to ifosfamide and adriamycin regimen in high-risk STS did not show any significant benefit. Patients with high-risk tumors may benefit from regional hyperthermia along with systemic chemotherapy (EORTC study 62961).[47] However, data on whether this approach is superior to surgery, with or without RT are lacking.

■ **Metastatic STS**

Once distant metastases develop, the median survival is 12 to 19 months. Surgical resection of isolated pulmonary metastatic disease results in long-term RFS with 5-year survival of 25 to 40%.[48] In patients with unresectable disease, around 20 to 25% are still alive at 2 to 3 years.[49] However, the survival is dependent on disease biology, histology, and treatment received.

For asymptomatic, low-grade, unresectable tumors such as low-grade intra-abdominal LMS, intra-abdominal WDLPS, follow-up may be reasonable. Patients with good performance status (PS), minimal comorbidity with anthracycline sensitive high-grade histologies (►**Table 5**), chemotherapy with doxorubicin with or without ifosfamide is preferable.

Combination chemotherapy with doxorubicin ifosfamide instead of single agent doxorubicin is chosen for symptomatic patients who require rapid tumor response. Gemcitabine-based chemotherapy is preferred for those with contraindication to anthracyclines such as cardiac failure, who have received doxorubicin cumulative dose of $\geq$ 375 mg/m^2.[50] Paclitaxel is an advisable alternative to anthracyclines for initial treatment of angiosarcoma. Various combination regimens available are doxorubicin plus ifosfamide with mesna (AIM), or AIM with dacarbazine (MAID), gemcitabine plus either docetaxel, vinorelbine, or dacarbazine, doxorubicin plus dacarbazine. Combination regimens are associated with higher response rates (18–46%) when compared to single-agent doxorubicin (12–18%).[51–53]

Table 5 Tumor sensitivity to anthracycline

Anthracycline-sensitive histology	Anthracycline-resistant histology
Leiomyosarcoma Myxoid/round cell liposarcoma Dedifferentiated and pleomorphic liposarcoma Synovial sarcoma Epithelioid sarcoma (ES) Angiosarcoma Undifferentiated pleomorphic sarcoma Malignant pleomorphic sarcoma	Alveolar soft part sarcoma Extraskeletal myxoid chondrosacroma Solitary fibrous tumor Hemangiopericytoma PEComas: angiomyolipoma/lymphangioleiomyomatosis Tenosynovial giant cell tumor (TGCT) Clear cell sarcoma Dermatofibrosarcoma protruberans (DFSP)

Abbreviations: DFSP, dermatofibrosarcoma protruberans; ES, epithelioid sarcoma; PEComas, perivascular epithelioid cell tumor; TGCT, tenosynovial giant cell tumor.

Patients with poor PS, multiple comorbidities single-agent gemcitabine, pegylated liposomal doxorubicin are the options. Single-agent doxorubicin, epirubicin, and ifosfamide provide response rates (RR) of more than 20% in metastatic STS.[17] Other single agents such as vinorelbine, dacarbazine, temozolomide particularly for leiomyosarcomas have a RR less than 20%.[54]

For patients with metastatic or advanced STS with anthracycline-resistant histologies, the following are the options:

- Pazopanib or sunitinib can be used for alveolar soft part sarcoma or extraskeletal myxoid chondrosarcoma with symptomatic or progressive disease. Phase II elderly patients with metastatic or advanced soft tissue sarcoma (EPAZ), a trial showed that pazopanib was noninferior to doxorubicin in terms of PFS (median PFS 4.4 vs. 5.3 months, HR: 1.00, 95%CI: 0.65–1.53) with similar OS.[55]
- Dacarbazine with or without doxorubicin, temozolomide plus bevacizumab, pazopanib or sunitinib are the options for SFT/hemangiopericytoma.[55]
- Imatinib is an alternative for locally advanced, metastatic, or recurrent dermatofibrosarcoma protruberans (DFSP) as per a systematic review (complete response [CR] in 5.2% and partial response [PR] in 55.2%).[56]
- Sirolimus can be chosen for symptomatic progressive, recurrent perivascular epithelioid cell differentiation PEComas including angiomyolipoma/lymphangioleiomyomatosis.[57]
- Pexidartanib colony-stimulating factor 1 receptor (CSF1R) inhibitor is an option for unresectable, recurrent, or relapsed tenosynovial giant cell tumor (TGCT) based on positive results from phase III ENLIVEN trial.[58]
- Cediranib has substantial single-agent activity in metastatic alveolar soft part sarcoma (ASPS) with an ORR of 35% and a disease control rate of 84% at 24 weeks.[59]

■ Options for Second Line

For patients with good PS who progress on doxorubicin-based first line, later therapies are based on histology, which may include

- Gemcitabine docetaxel combination regimen for LMS, MFH.[60] PLD, gemcitabine alone or combination regimens, ifosfamide alone or with doxorubicin are the other chemotherapy options.[61]
- Trabectadine is an option for advanced LMS, myxoid/round cell liposarcoma and translocation-related sarcomas based on phase III, T-SAR trial with OS and PFS benefit in those previously treated with anthracycline-based chemotherapy when compared to dacarbazine.[62] Three-weekly regimen was superior to weekly dosing.
- Eribulin can be preferred over trabectadine for pleomorphic and dedifferentiated liposarcomas due to better OS and PFS and similar PFS and OS in LMS when compared to dacarbazine.[63]
- Pazopanib is an alternative for non-adipocytic advanced sarcomas-mainly LMS, synovial sarcoma, angiosarcoma, SFT. Phase III PALETTE trial showed a significant PFS benefit (median PFS 4.6 vs. 1.6 m) when compared to placebo.[64]
- Among patients with progressive, refractory, or symptomatic desmoid tumors, sorafenib significantly prolonged PFS and induced durable responses in a phase III trial.[65]
- Larotrectinib or entrectinib could be an option for tumors with gene fusions involving one of neurotrophic tyrosine receptor kinase (*NTRK*) genes. ALKA, STARTRK-1, and STARTRK-2 trials demonstrated an ORR of 46% with entrectinib and 75% with larotrectinib.[66,67]
- Pembrolizumab is an alternative for microsatellite instability (MSI) high/mismatch repair-deficient STS.[68]

Recent Advances

- Doxorubicin with olaratumab in phase III ANNOUNCE trial showed an inferior PFS and hence olaratumab has been withdrawn from the market[68].
- In a phase III trial evofosfamide in combination with doxorubicin compared to doxorubicin alone in previously untreated patients with locally advanced, unresectable, or metastatic STS showed no significant difference in median OS and PFS.[69]
- Aldoxorubicin, a tumor-targeted doxorubicin conjugate, in a phase III study, showed significant PFS (5.3 vs. 2.9 months) and disease control rate (41.7 vs. 27%) in a subcohort of L-sarcomas.[70]
- Tazemostat, first and only Enhancer of zeste homolog (EZH2) inhibitor—an epigenetic regulator—was approved by the Food and Drug Administration (FDA) for advanced, recurrent metastatic epithelioid sarcoma (ES) not amenable for resection on Jan 23, 2020, based on a phase II trial.[69]
- Pazopanib can be used as an initial therapy in anthracycline-sensitive advanced STS histologies for elderly who may not tolerate doxorubicin (October 2020, phase II study).[55]
- Crizotinib in phase I/II trial, demonstrated CR and PR in 36% and 50% of inflammatory myofibroblastic tumor (IMT) with ALK translocation. More recently, ceritinib was thought to improve disease-free interval in those with acquired resistance to crizotinib.[71]
- Anlotinib in a phase II study showed a statistically significant PFS benefit when compared to placebo in metastatic STS who had failed standard chemotherapy (China FDA in 2019).[72]
- Maintenance ridaforolimus for advanced STS in a phase III study showed 28% reduction in PFS after four cycles of chemotherapy (SUCCEED).[70]
- Palbociclib and abemaciclib in several phase I/II trials was associated with a favorable PFS of 66% in patients with cyclin-dependent kinase 4 (CDK4)-amplified WDLS/DDLS who had progressive disease despite systemic therapy.[73]

- Selinexor, an oral selective inhibitor of nuclear exportin protein in phase II/III trial (SEAL) for patients with DDLS showed improved PFS. Currently, recruitment of patients for phase III portion is ongoing.[74]

Follow-Up

As per NCCN and ESMO, follow-up is recommended every three to six monthly with history and physical examination for 2 to 3 years, then every 6 months for next 2 years, and then annually for 10 years. Periodic imaging of the primary site and CT chest for histologies with high chance of pulmonary metastases is recommended on follow-up.[75]

Conclusion

Heterogeneity of STS makes it a challenging rare malignancy to treat. The disease has got diverse outcomes determined by numerous factors. Prognostic factors and molecular aberrations should be taken into account while tailoring the treatment plan. A multidisciplinary approach is warranted. Many randomized prospective trials including patients with a single histological subtype of STS are needed due to heterogeneity across the histological subtypes and also in terms of chemosensitivity to formulate uniform guidelines for management of the same.

Authors' Contributions

L.A.J., S.A., S.N., and L.D. contributed to the conception of the study. S.A., L.A.J., L.D., and S.S. were responsible for the acquisition. S.A., L.A.J., S.B.M.C., L.K.N., A.H.R., and L.K.R. drafted the manuscript. L.D., L.A.J., and L.K.R. substantively revised it. All authors have read and approved the manuscript.

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

We would like to thank the residents and faculty of the Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bangalore.

References

1 Gross SD. (Samuel D). A System of Surgery: Pathological, Diagnostic, Therapeutic, and Operative. Philadelphia: H.C. Lea; 1866
2 VIRCHOW. Rudolf (1821–1902). Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre. Berlin: August Hirschwald; 1858
3 Fletcher CDM BJ, Hogendoorn PCW, Mertens F. WHO Classification of Tumours of Soft Tissue and Bone. 4th ed. Lyon: IARC Press; 2013
4 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69(01):7–34
5 Cancer of soft tissue including heart - Cancer Stat Facts. SEER. Accessed September 18, 2020 at: https://seer.cancer.gov/statfacts/html/soft.html
6 Kattan MW, Leung DHY, Brennan MF. Postoperative nomogram for 12-year sarcoma-specific death. J Clin Oncol 2002;20(03):791–796
7 Marcus SG, Merino MJ, Glatstein E, et al. Long-term outcome in 87 patients with low-grade soft-tissue sarcoma. Arch Surg 1993;128(12):1336–1343
8 Zagars GK, Ballo MT, Pisters PWT, et al. Prognostic factors for patients with localized soft-tissue sarcoma treated with conservation surgery and radiation therapy: an analysis of 1225 patients. Cancer 2003;97(10):2530–2543
9 Blay J-Y, Toulmonde M, Penel N, et al. Natural history of sarcomas and impact of reference centers in the nationwide NETSARC study on 35,784 patients (pts) from 2010 to 2017. Ann Oncol 2018;29(08):viii576–viii595. 10.1093/annonc/mdy299
10 Carnevale A, Lieberman E, Cárdenas R. Li-Fraumeni syndrome in pediatric patients with soft tissue sarcoma or osteosarcoma. Arch Med Res 1997;28(03):383–386
11 Mai PL, Best AF, Peters JA, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. Cancer 2016;122(23):3673–3681
12 Brady MS, Gaynor JJ, Brennan MF. Radiation-associated sarcoma of bone and soft tissue. Arch Surg 1992;127(12):1379–1385
13 Torres KE, Ravi V, Kin K, et al. Long-term outcomes in patients with radiation-associated angiosarcomas of the breast following surgery and radiotherapy for breast cancer. Ann Surg Oncol 2013;20(04):1267–1274
14 Kogevinas M, Becher H, Benn T, et al. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. An expanded and updated international cohort study. Am J Epidemiol 1997;145(12):1061–1075
15 Stewart FW, Treves N. Classics in oncology: lymphangiosarcoma in postmastectomy lymphedema: a report of six cases in elephantiasis chirurgica. CA Cancer J Clin 1981;31(05):284–299
16 Purgina B, Rao UNM, Miettinen M, Pantanowitz L. AIDS-related EBV-associated smooth muscle tumors: a review of 64 published cases. Patholog Res Int. 2011. Doi: 10.4061/2011/561548
17 Borden EC, Baker LH, Bell RS, et al. Soft tissue sarcomas of adults: state of the translational science. Clin Cancer Res 2003;9(06):1941–1956
18 Italiano A, Di Mauro I, Rapp J, et al. Clinical effect of molecular methods in sarcoma diagnosis (GENSARC): a prospective, multicentre, observational study. Lancet Oncol 2016;17(04):532–538
19 Lawrence W Jr, Donegan WL, Natarajan N, Mettlin C, Beart R, Winchester D. Adult soft tissue sarcomas. A pattern of care survey of the American College of Surgeons. Ann Surg 1987;205(04):349–359
20 Pham TH, Iqbal CW, Zarroug AE, Donohue JH, Moir C. Retroperitoneal sarcomas in children: outcomes from an institution. J Pediatr Surg 2007;42(05):829–833
21 Christie-Large M, James SLJ, Tiessen L, Davies AM, Grimer RJ. Imaging strategy for detecting lung metastases at presentation in patients with soft tissue sarcomas. Eur J Cancer 2008;44(13):1841–1845
22 Weitz J, Antonescu CR, Brennan MF. Localized extremity soft tissue sarcoma: improved knowledge with unchanged survival over time. J Clin Oncol 2003;21(14):2719–2725
23 Fong Y, Coit DG, Woodruff JM, Brennan MF. Lymph node metastasis from soft tissue sarcoma in adults. Analysis of data from a prospective database of 1772 sarcoma patients. Ann Surg 1993;217(01):72–77
24 Aisen AM, Martel W, Braunstein EM, McMillin KI, Phillips WA, Kling TF. MRI and CT evaluation of primary bone and soft-tissue tumors. Am J Roentgenol 1986;146(04):749–756
25 Casali PG, Abecassis N, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO– EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol 2018;29:iv51–iv67.6

26 Folpe AL, Lyles RH, Sprouse JT, Conrad EU III, Eary JF. (F-18) fluorodeoxyglucose positron emission tomography as a predictor of pathologic grade and other prognostic variables in bone and soft tissue sarcoma. Clin Cancer Res 2000;6(04):1279–1287
27 Strauss DC, Qureshi YA, Hayes AJ, Thway K, Fisher C, Thomas JM. The role of core needle biopsy in the diagnosis of suspected soft tissue tumours. J Surg Oncol 2010;102(05):523–529
28 World Health Organization. Classification of tumours. In: Fletcher CDM, Unni KK, Mertens F, eds. Pathology and Genetics of Tumors of Soft Tissue. Lyon: IARC Press; 2002:12–224
29 Guillou L, Coindre JM, Bonichon F, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. J Clin Oncol 1997;15(01): 350–362
30 Pisters PW, Leung DH, Woodruff J, Shi W, Brennan MF. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol 1996;14(05):1679–1689
31 Tan MCB, Brennan MF, Kuk D, et al. Histology-based classification predicts pattern of recurrence and improves risk stratification in primary retroperitoneal sarcoma. Ann Surg 2016;263(03):593–600
32 Gronchi A, Miceli R, Shurell E, et al. Outcome prediction in primary resected retroperitoneal soft tissue sarcoma: histology-specific overall survival and disease-free survival nomograms built on major sarcoma center data sets. J Clin Oncol 2013;31(13): 1649–1655
33 Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Lancet 1997;350(9092):1647–1654
34 Sarcoma Meta-analysis Collaboration (SMAC) Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults. Cochrane Database Syst Rev 2000;(02):CD001419
35 Petrioli R, Coratti A, Correale P, et al. Adjuvant epirubicin with or without Ifosfamide for adult soft-tissue sarcoma. Am J Clin Oncol 2002;25(05):468–473
36 Woll PJ, Reichardt P, Le Cesne A, et al; EORTC Soft Tissue and Bone Sarcoma Group and the NCIC Clinical Trials Group Sarcoma Disease Site Committee. Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial. Lancet Oncol 2012;13(10):1045–1054
37 Brodowicz T, Schwameis E, Widder J, et al. Intensified adjuvant IFADIC chemotherapy for adult soft tissue sarcoma: a prospective randomized feasibility trial. Sarcoma 2000;4(04):151–160
38 Ferrari A, Gronchi A, Casanova M, et al. Synovial sarcoma: a retrospective analysis of 271 patients of all ages treated at a single institution. Cancer 2004;101(03):627–634
39 Cormier JN, Huang X, Xing Y, et al. Cohort analysis of patients with localized, high-risk, extremity soft tissue sarcoma treated at two cancer centers: chemotherapy-associated outcomes. J Clin Oncol 2004;22(22):4567–4574
40 Petersen IA, Haddock MG, Donohue JH, et al. Use of intraoperative electron beam radiotherapy in the management of retroperitoneal soft tissue sarcomas. Int J Radiat Oncol Biol Phys 2002;52 (02):469–475
41 Nussbaum DP, Rushing CN, Lane WO, et al. Preoperative or postoperative radiotherapy versus surgery alone for retroperitoneal sarcoma: a case-control, propensity score-matched analysis of a nationwide clinical oncology database. Lancet Oncol 2016;17 (07):966–975
42 Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer 2008;113(03):573–581
43 Le Cesne A, Ouali M, Leahy MG, et al. Doxorubicin-based adjuvant chemotherapy in soft tissue sarcoma: pooled analysis of two STBSG-EORTC phase III clinical trials. Ann Oncol 2014;25(12): 2425–2432
44 Bonvalot S, Gronchi A, Le Pechoux C, et al. STRASS (EORTC 62092): a phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with retroperitoneal sarcoma. J Clin Oncol 2019;37(15, suppl):11001–11001
45 Bossi A, De Wever I, Van Limbergen E, Vanstraelen B. Intensity modulated radiation-therapy for preoperative posterior abdominal wall irradiation of retroperitoneal liposarcomas. Int J Radiat Oncol Biol Phys 2007;67(01):164–170
46 van Houdt WJ, Raut CP, Bonvalot S, Swallow CJ, Haas R, Gronchi A. New research strategies in retroperitoneal sarcoma. The case of TARPSWG, STRASS and RESAR: making progress through collaboration. Curr Opin Oncol 2019;31(04):310–316
47 Issels RD, Lindner LH, Verweij J, et al; European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) European Society for Hyperthermic Oncology (ESHO) Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. Lancet Oncol 2010;11(06): 561–570
48 Choong PF, Pritchard DJ, Rock MG, Sim FH, Frassica FJ. Survival after pulmonary metastasectomy in soft tissue sarcoma. Prognostic factors in 214 patients. Acta Orthop Scand 1995;66(06): 561–568
49 Billingsley KG, Burt ME, Jara E, et al. Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival. Ann Surg 1999;229(05):602–610, discussion 610–612
50 Merimsky O, Meller I, Flusser G, et al. Gemcitabine in soft tissue or bone sarcoma resistant to standard chemotherapy: a phase II study. Cancer Chemother Pharmacol 2000;45(02):177–181
51 Santoro A, Tursz T, Mouridsen H, et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol 1995;13(07): 1537–1545
52 Antman K, Crowley J, Balcerzak SP, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. J Clin Oncol 1993;11(07):1276–1285
53 Hensley ML, Maki R, Venkatraman E, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. J Clin Oncol 2002;20(12):2824–2831
54 Borden EC, Amato DA, Rosenbaum C, et al. Randomized comparison of three adriamycin regimens for metastatic soft tissue sarcomas. J Clin Oncol 1987;5(06):840–850
55 Grünwald V, Karch A, Schuler M, et al. Randomized comparison of pazopanib and doxorubicin as first-line treatment in patients with metastatic soft tissue sarcoma age 60 years or older: results of a German Intergroup Study. J Clin Oncol 2020;38(30):3555–3564
56 Navarrete-Dechent C, Mori S, Barker CA, Dickson MA, Nehal KS. Imatinib treatment for locally advanced or metastatic dermatofibrosarcoma protuberans: a systematic review. JAMA Dermatol 2019;155(03):361–369
57 Folpe AL, Mentzel T, Lehr H-A, Fisher C, Balzer BL, Weiss SW. Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. Am J Surg Pathol 2005;29(12):1558–1575
58 Lamb YN. Pexidartinib: First Approval. Drugs 2019;79(16): 1805–1812
59 Kummar S, Allen D, Monks A, et al. Cediranib for metastatic alveolar soft part sarcoma. J Clin Oncol 2013;31(18):2296–2302
60 Leu KM, Ostruszka LJ, Shewach D, et al. Laboratory and clinical evidence of synergistic cytotoxicity of sequential treatment with gemcitabine followed by docetaxel in the treatment of sarcoma. J Clin Oncol 2004;22(09):1706–1712
61 Grenader T, Goldberg A, Hadas-Halperin I, Gabizon A. Long-term response to pegylated liposomal doxorubicin in patients with

metastatic soft tissue sarcomas. Anticancer Drugs 2009;20(01): 15–20
62 Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. J Clin Oncol 2016;34(08):786–793
63 Schöffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet 2016;387(10028):1629–1637
64 van der Graaf WTA, Blay J-Y, Chawla SP, et al; EORTC Soft Tissue and Bone Sarcoma Group PALETTE study group. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012;379(9829): 1879–1886
65 Gounder MM, Mahoney MR, Van Tine BA, et al. Sorafenib for advanced and refractory desmoid tumors. N Engl J Med 2018;379 (25):2417–2428
66 Doebele RC, Drilon A, Paz-Ares L, et al; trial investigators. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21(02):271–282
67 Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378(08):731–739
68 Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol 2017;18(11):1493–1501
69 Epizyme. Investors & Media. Epizyme Announces U.S. FDA accelerated approval of TAZVERIKTM (tazemetostat) for the treatment of patients with epithelioid sarcoma. 2020. Accessed October 13, 2021 at: https://epizyme.gcs-web.com/news-releases/news-release-details/epizyme-announces-us-fda-accelerated-approval-tazveriktm-0
70 Blay J-Y, Chawla SP, Ray-Coquard I, et al. Phase III, placebo-controlled trial (SUCCEED) evaluating ridaforolimus as maintenance therapy in advanced sarcoma patients following clinical benefit from prior standard cytotoxic chemotherapy: long-term ($\geq$ 24 months) overall survival results. J Clin Oncol 2012;30(15, suppl):10010–10010
71 Mansfield AS, Murphy SJ, Harris FR, et al. Chromoplectic TPM3-ALK rearrangement in a patient with inflammatory myofibroblastic tumor who responded to ceritinib after progression on crizotinib. Ann Oncol 2016;27(11):2111–2117
72 Chi Y, Yao Y, Wang S, et al. Anlotinib for metastasis soft tissue sarcoma: a randomized, double-blind, placebo-controlled and multi-centered clinical trial. J Clin Oncol 2018;36(15, suppl): 11503–11503
73 Dickson MA, Schwartz GK, Keohan ML, et al. Progression-Free Survival Among Patients With Well-Differentiated or Dedifferentiated Liposarcoma Treated With CDK4 Inhibitor Palbociclib: A Phase 2 Clinical Trial. JAMA Oncol 2016 Jul 1;2(07):937–940
74 Gounder MM, Somaiah N, Attia S, et al. Phase 2 results of selinexor in advanced de- differentiated (DDLS) liposarcoma (SEAL) study: a phase 2/3, randomized, double blind, placebo controlled cross-over study. J Clin Oncol 2018;36(15, suppl):11512–11512
75 Patel SR, Zagars GK, Pisters PWT. The follow-up of adult soft-tissue sarcomas. Semin Oncol 2003;30(03):413–416

Treatment Outcome of Burkitt's Lymphoma in Adolescents and Adults: A Retrospective Study

Sugeeth MT[1] Geetha Narayanan[1] Anoop TM[1] Sreejith G. Nair[1] Prakash NP[1] Jagathnath Krishna KM[2] Rekha A. Nair[3]

[1] Department of Medical Oncology, Regional Cancer Centre, Trivandrum, Kerala, India
[2] Department of Epidemiology & Biostatistics, Regional Cancer Centre, Trivandrum, Kerala, India
[3] Department of Pathology, Regional Cancer Centre, Trivandrum, Kerala, India

Address for correspondence Geetha Narayanan, MD, DNB, DM, Professor & Head, Department of Medical Oncology, Regional Cancer Centre, Trivandrum 695011, Kerala, India (e-mail: geenarayanan@yahoo.com).

Ind J Med Paediatr Oncol 2024;45:22–27.

Abstract

Introduction Burkitt's lymphoma (BL) is a highly aggressive B cell non-Hodgkin lymphoma (NHL) having three distinct subtypes: endemic, sporadic, and immunodeficiency-associated BL. Sporadic BL accounts for only 1 to 2% of adult NHL.

Objectives The objective of this article was to study the clinical profile and treatment outcome of patients with BL.

Materials and Methods This was a retrospective study of 60 patients with BL conducted in the department of medical oncology at a tertiary cancer center in India during a 10-year period. Patients with BL/leukemia above 14 years of age diagnosed during the study period were included and their clinical presentation, treatment details, and outcome were studied.

Results Among 60 cases with BL, there were 41 males and 19 females. The median age at presentation was 42 years (range: 14–81 years). The main symptoms were lymphadenopathy, abdominal pain, and abdominal distension. Two patients each had paraparesis, breast lump, and jaw swelling and one patient had involvement of the cervix. Thirteen patients had features of tumor lysis at presentation. The Ann Arbor stage was I in 17, II in 16, III in 5, and IV in 22. Fifty-five patients received combination chemotherapy that included hyper-cyclophosphamide, vincristine, adriamycin, dexamethasone ± rituximab (hyper-CVAD ± R; 35), cyclophosphamide, adriamycin, vincristine, prednisolone/ cyclophosphamide, vincristine, prednisolone ± rituximab CHOP ± R (13), Berlin-Frankfurt-Munich protocol (4), and others (3). Thirty-four patients attained remission, 13 patients had progressive disease, and 8 patients died during chemotherapy. At a median follow-up of 113 months, 58% patients were alive.

Conclusions BL accounts for 1.57% of NHL above the age of 14 years with male preponderance. Intensive, short-duration chemotherapy is the standard treatment. Treatment with hyper-CVAD ± R gives 8-year progression-free survival and overall survival (OS) of 60%. Treatment with CHOP ± R is an alternative option in elderly frail patients with an 8-year OS of 46%.

Keywords
- Burkitt's lymphoma
- non-Hodgkin lymphoma
- clinical characteristics
- treatment outcome

article published online
April 24, 2023

DOI https://doi.org/10.1055/s-0043-1768177.
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

Burkitt's lymphoma (BL) is an aggressive B-cell lymphoma characterized by a high degree of proliferation of the malignant cells and deregulation of the proto-oncogene c-myc.[1] BL is predominantly a disease of childhood, but it is also seen in the adult population. The World Health Organization (WHO) classification of BL describes three clinical variants: endemic, sporadic, and immunodeficiency-related.[2] These types are similar in morphology, immunophenotype, and genetic features. Endemic BL is the most common childhood cancer in equatorial Africa associated with Epstein–Barr virus (EBV) and plasmodium falciparum malaria. The sporadic type predominates in the rest of the world with no special climatic or geographical links, and is rarely associated with EBV infection. Sporadic BL (sBL), accounts for 1 to 2% of all adult lymphomas in Western Europe and the United States.[3] The diagnostic and therapeutic principles of BL in adults are the same as those in the pediatric population. A recent study of the Swedish Lymphoma Registry confirmed advanced age, poor WHO performance status, and elevated serum lactate dehydrogenase (LDH) as significant prognostic factors for adult BL.[4]

The present retrospective analysis provides information on clinical presentation, histology patterns, and outcome of adolescents, adults, and elderly patients with BL treated at a tertiary cancer center in India.

Objectives

The objectives of this article were to study the clinical characteristics, treatment response, and survival of BL in adolescent and adult patients. The primary outcome measures were treatment response and progression-free survival (PFS). The secondary outcome measure was overall survival (OS) at 8 years.

Materials and Methods

Study Setting: This was a retrospective study conducted in the department of medical oncology at a tertiary cancer center in India during a 10-year period (January 2005 to December 2014). Patients with BL/leukemia above 14 years of age treated during the study period were included. We analyzed 60 patients with BL.

Inclusion/ Exclusion Criteria: Eligibility criteria included all patients aged above 14 years with a histological diagnosis of BL/leukemia. Patients with relapsed BL and who received some prior treatments were excluded from the study.

Methodology: Medical records of patients were studied with respect to the demographic details, clinical history, physical examination, baseline investigations like complete hemogram, serum chemistry, and serum LDH. Staging work-up including histopathology report, bone marrow study, cerebrospinal fluid analysis, and imaging studies were noted. The disease was staged according to the Ann Arbor staging system. The treatment response at the end of induction and on completion of treatment was obtained. Clinical response was classified as complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease based on modified Cheson lymphoma response evaluation criteria.[5] OS was assessed from the initiation of definitive chemotherapy to the last follow-up or death and PFS was calculated from the initiation of chemotherapy till disease progression.

Statistical Analysis: The baseline patient characteristics, treatment details, and response assessment were analyzed using descriptive statistics. OS and PFS were obtained by Kaplan–Meier method, using SPSS v. 11. The risk analysis for OS and PFS was done using Cox regression analysis. Statistical significance was defined as a *p*-value less than 0.05.

Ethics: The study was approved by the Institutional Review Board (IRB No. 09/2016/03, dated September 1, 2016). Informed consent was waived off due to retrospective nature of the study. All procedures performed in study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Baseline Patient Characteristics (shown in ►Table 1)
During the period 2005 to 2014, 3,811 cases of non-Hodgkin lymphoma (NHL) above 14 years of age were treated in our

Table 1 Baseline patient characteristics

Baseline patient characteristics ($n = 60$)	Frequency, *n* (%)
Median age (years)	42 (range: 14–81)
M: F ratio	2.16: 1
B symptoms	39 (65)
Hb < 10 g/ dL	15 (25)
Platelet count $< 1{,}00{,}000/mm^3$	06 (10)
Elevated LDH	44 (73)
Biochemical TLS (S.UA$\geq$8mg/dL, S. K$\geq$6mEq/L, S. Ph$\geq$4.6mg/dL, S. Ca $\leq$ 7mg/dL)	13 (22)
Hypoalbuminemia (S. albumin $<$ 3.5 g/dL)	13 (22)
Renal impairment (S. Cr $>$ 1.5 of ULN)	06 (10)
Hepatic impairment (S. Bil $>$ 2 times of ULN)	7 (12)
Stage I II III IV	17 (28) 16 (27) 05 (8) 22(37)
Burkitt's leukemia (bone marrow blast $>$ 20%)	11(18)

Abbreviations: Hb, hemoglobin; LDH, lactate dehydrogenase; M: F, male: female ratio; S. Bil, serum bilirubin; S. Ca, serum calcium; S. Cr, serum creatinine; S. K, serum potassium; S. Ph, serum phosphorus; S. UA, serum uric acid; TLS, tumor lysis syndrome; ULN, upper limit of normal.

Table 2 Treatment summary

Treatment outcome	HCVAD ± R	CHOP/CVP ± R	BFM	R CODOX M-IVAC	Murphy's protocol
Total no.	35	13	4	1	2
Complete remission	22 (63%)	6 (47%)	3 (75%)	1 (100%)	2 (100%)
Progressive disease	9 (26%)	3 (23%)	1 (25%)	Nil	Nil
Death	4 (11%)	4 (30%)	Nil	Nil	Nil
Relapse	2 (6%)	NIL	1 (25%)	Nil	1 (50%)
8-year OS	60%	46.2%	50%	100%	50%

Abbreviations: BFM; standard Berlin-Frankfurt-Munich protocol; CHOP/ CVP ± R; cyclophosphamide, adriamycin, vincristine, prednisolone/ cyclophosphamide, vincristine, prednisolone ± rituximab; HCVAD ± R; cyclophosphamide, vincristine, adriamycin, dexamethasone ± rituximab; OS, overall survival; R CODOX M- IVAC, rituximab ± cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide and cytarabine.

department, of which 60 were BL (1.57%). The median age at presentation was 42 years (range: 14–81 years). There were 41 males and 19 females, with the male to female ratio of 2.16: 1. Twenty-five patients (42%) were less than 40 years of age and elderly patients above more than 65 years constituted 10% of our study population. The most common presenting symptoms were lymphadenopathy, abdominal pain and abdominal distension. Two patients each presented with paraparesis, breast lump, jaw swelling and one patient presented with vaginal mass. (►**Supplementary Material Table A**, available in the online version). Three patients presented to us following surgery for acute intestinal obstruction and diagnosis of BL was confirmed on histopathological examination of the surgically resected specimen. B symptoms were present in 39 patients (65%). The median duration of symptoms was 4 weeks (range: 1–16 weeks). Eleven patients had BL at presentation (18%) and 13 patients had features of tumor lysis syndrome (22%). Laboratory tumor lysis syndrome was present in all 13 patients and clinical tumor lysis syndrome in 6 patients (10%). Patient had a mean hemoglobin of 11.6 g/dL, mean total leucocyte count of 8,586/mm^3, and a mean platelet count of 2.8 lakhs/mm^3. In our study population, only one patient tested positive for human immunodeficiency virus (HIV) infection. Cerebrospinal fluid was positive for malignant cells in two patients (3%). Twenty-nine patients had extra nodal disease with bone marrow being the most common site (48%). The Ann Arbor stage was I in 17 (28%), II in 16 (27%), III in 5 (8%), and IV in 22 (37%).

All patients had a histopathological diagnosis either from lymph node biopsy or biopsy from the involved organ. Morphologically the tumor cells were seen in sheets having scanty cytoplasm with clumped chromatin, surrounded by normal phagocytic cells having "starry sky pattern." Immunohistochemically (IHC) the tumor cells were positive for CD 10, CD 19, CD20, BCL6 and Surface immunoglobulin M and negative for terminal deoxynucleotidyl transferase. Complete IHC marker panel was done in 40 patients. Out of 11 patients with BL, four patients were diagnosed as acute lymphoblastic leukemia L3 on flow cytometry (►**Supplementary Material Table B**, available in the online version). Thirty-nine patients had a MIB labeling index of 100% and the lowest MIB labeling index was 80%.

Treatment Characteristics (►Table 2)

Among the 60 patients, 55 (92%) received treatment and five refused to get treated. All received combination chemotherapy that included hyper-CVAD ± rituximab (HCVAD ± R) in 35 (63%), CHOP/ CVP ± rituximab (CHOP/CVP ± R) in 13 (24%), Berlin-Frankfurt-Munich protocol (BFM) in 4 (7%), Murphy's protocol in 2(4%), and rituximab ± cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide and cytarabine (R CODOX M-IVAC) in 1 (2%) patient depending on the time period when the diagnosis was made. Patients with poor performance status (ECOG - Eastern Co-operative Oncology Group performance status 3 or 4) and advanced age (age > 65 years) received CHOP/ CVP ± R (median age 69) and young and fit patients received intensive chemotherapy (median age 32). Thirty-four patients attained CR, 33 after chemotherapy, and 1 patient following radiation (RT) after chemotherapy. Thirteen patients had progressive disease and eight patients died during chemotherapy. Among the 34 (62%) patients who attained CR, 22 received HCVAD ± R, 6 had CHOP/ CVP ± R, 3 had BFM, 1 had R CODOX M-IVAC, and 2 patients received Murphy's protocol.

Thirty-five patients received HCVAD ± R among them, 22 (63%) attained complete remission, 9 (26%) had progressive disease, 2 (6%) relapsed, and 4 (11%) patients died during the treatment. The median cycles of HCVAD regimen were 8 (4 cycles of A and 4 cycles of B). Twenty-two out of thirty-five patients (63%) were able to complete all planned cycles of chemotherapy with a median duration of 7 months (range: 6–10 months). Out of thirteen patients who received CHOP/ CVP ± R chemotherapy, only six (46%) patients attained complete remission, three (23%) had disease progression, and four patients (31%) died during chemotherapy. All patients on R CODOX-M/IVAC, Murphy's protocol and three of four patients on BFM protocol attained complete remission.

Among the 34 patients who achieved remission, four patients (12%) relapsed and received palliative chemotherapy later. Two patients with central nervous system (CNS) disease at diagnosis, two with extra nodal primary and one patient with residual disease after chemotherapy received RT after completion of the chemotherapy.

Table 3 Survival data

Variables	8-year PFS (%)			8-year OS (%)		
	%	SE	*p*-Value	%	SE %	*p*-Value
Age (years) < 40 40–65 > 65	80.0 41.2 16.7	8.0 10.1 15.2	0.001	80.0 45.8 16.7	8.0 10.2 15.2	0.001
Sex Male Female	52.5 66.0	7.9 12.4	0.301	55.0 66.7	7.9 12.2	0.299
LDH < 2000 ≥ 2000	58.3 69.2	8.2 12.8	0.573	61.1 69.2	8.1 12.8	0.558
Burkitt's lymphoma Burkitt's leukemia	56.8 54.5	7.5 15.0	0.885	59.1 54.5	7.4 15.0	0.87
Stage 1 2 3 4	56.3 42.9 100 58.7	12.4 13.2 - 10.6	0.425	62.5 42.9 100 59.1	12.1 13.2 - 10.5	0.430
Chemo CHOP ± R HCVAD ± R	36.9 60.0	13.8 8.3	0.123	46.2 60.0	13.8 8.3	0.125

Abbreviations: CHOP/ CVP ± R; cyclophosphamide, adriamycin, vincristine, prednisolone/ cyclophosphamide, vincristine, prednisolone ± rituximab; HCVAD ± R; cyclophosphamide, vincristine, adriamycin, dexamethasone ± rituximab; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; SE, standard error.

Survival (►Table 3)

The PFS was 58.3 at 2 years and 56.2 at 5 and 8 years. The 2-year OS was 61.6% and 58.2% at 5 and 8 years (►**Fig. 1**). The 8-year OS for patients with age group less than 40 years, 40 to 65 years, and more than 65 years were 80, 41.2, and 16.7%, respectively. Both OS and PFS were significantly high in adolescents and young adults compared to patients above 40 years of age (*p*-value of 0.001). There was no significant survival difference with respect to sex, stage of disease, serum LDH, and site of involvement. Patients who received HCVAD-based chemotherapy had better survival compared with CHOP/CVP chemotherapy even though it was not statistically significant (8 years OS of 60.0% ± 8.3% vs. 36.9% ± 13.8% with a *p*-value of 0.123). Rituximab arm had a trend toward better survival compared with no rituximab arm, but it was not statistically significant (66.7 vs. 55.8%) with a *p*-value of 0.584. Univariate Cox regression analysis showed significance only for age with a *p*-value of 0. 001 with a hazard ratio of 10.3. (►**Supplementary Material Table C**, available in the online version) Twenty-four patients out of 55 did not receive rituximab.

Discussion

BL is one of the most aggressive types of cancer and yet one of the most curable. Mostly, BL originates from B cells in the

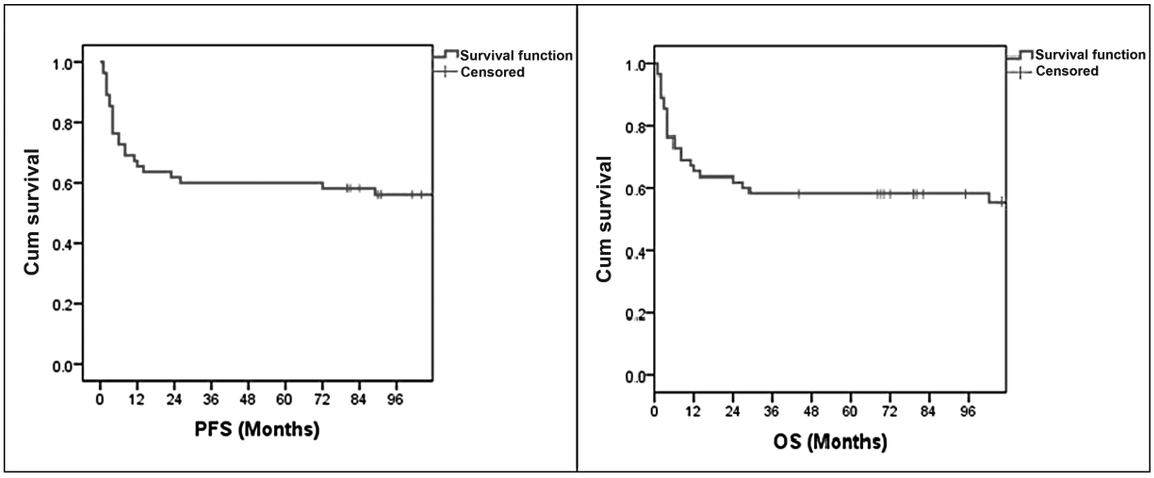


Fig. 1 Survival Chart Showing Progression Free Survival (PFS) and Overall Survival (OS) at 8 years.

follicular germinal center. BL is the first lymphoma reported to be associated with HIV infection.[6] sBL in North America and Europe makes up 30 to 40% of childhood NHL and 1 to 5% of adult NHL.[7] sBL attacks regions outside Africa, with an incidence of about 4 per million in the United States.[8] In India, BL constitutes 1.8 to 3.4% of all adult NHL.[9] BL is a classic example of a human malignancy whose pathogenesis involves a specific cellular genetic change characterized by a chromosomal translocation deregulating expression of the c-myc oncogene, complemented in many cases by the action the EBV.[10]

This is the largest case series from India describing the treatment outcome of adolescent and adult patients with BL. In our series, the median age at presentation was 42 years (range: 14–81 years) with 11% patients above 65 years of age. These findings are consistent with other case series.[3,11,12] In an Indian study including pediatric patients, BL constituted 3.5% of all NHL and the median age at presentation was 22 years.[13] In this study, patients have a higher frequency of B-symptoms (65%) and advanced disease compared to European studies.[14] In our study, bone marrow involvement was the most common extranodal site (30%) followed by gastrointestinal tract (22%). CNS involvement in our study was 3% compared to 15% in a study by Saleh et al.[14] Eleven patients (18%) had BL at presentation that was comparable with another study by Mbulaiteye et al.[7]

Treatment success of BL resulted from the introduction of dose-intense multidrug chemotherapy, prophylaxis of CNS disease, and improvements in supportive care. The management of this aggressive lymphoma is a challenge in our resource-limited setting and the published data from the Indian population is scarce. The frequently used regimens in adolescent and adults based on pediatric protocols are CODOX-M/IVAC, the German BFM, and the French Lymphome Malins B regimens. Other regimens used for adult BL include the HCVAD, the Cancer and Leukemia Group B regimen, and the dose-adjusted EPOCH.[15–17] In our study, most of the young and fit patients received HCVAD ± R (63.5%) and elderly patients with poor performance status received CHOP/CVP ± R (22%). The complete response rate in the entire population was 62%, 2-year PFS of 58.3%, and a 2-year OS of 61.6%. A study from India showed similar results with a complete response rate of 63% with 2-year PFS of 56%.[18] Patients above 65 years of age and frail patient who received less intense therapy, the 8-year OS was 46% that makes it an alternate option in elderly and frail patients. Similar studies in BL in adult patients receiving CHOP-based chemotherapy had a 2-year OS of 33 to 39%.[19,20] Patients who received HCVAD ± R chemotherapy had a complete response rate of 63%, 8-year PFS and OS of 60%. Review on treatment outcome in BL is given in ►**Table 4**.[12,17,21–25] In this study, only a few patients received other chemotherapy regimens like CODOX-M/IVAC, BFM, and Murphy's protocol to compare on survival. ►**Table 4** shows review of treatment outcome in BL.

Limitations

The study period was January 2005 to December 2014, during this period molecular study for BL was not available at our center. This is a retrospective data analysis. Patients were not treated with uniform protocol as they received different protocols depending on the time period the diagnosis was made.

Future Research Directions

Risk-adapted treatment that limits early and late drug toxicity ensuring optimal outcome should be adopted for BL. In elderly patients, R DA EPOCH is the preferred choice with better outcomes. Randomized control trials in Indian population are required to better define the treatment for elderly patients with BL.

Conclusions

BL accounts for 1.57% of NHL above the age of 14 years with male preponderance. Intensive, short-duration chemotherapy is the standard treatment. Treatment with HCVAD ± R gives 8-year PFS of 60% at 8 years. Treatment with R CHOP is an alternative option in elderly frail populations with an 8-year OS of 46%.

Table 4 Review of treatment outcome in Burkitt's lymphoma

Reference	Regimen	*n*	Median age (years)	EFS/PFS	OS
Thomas et al[21]	Hyper-CVAD	26	58	3-year CCR 61%	3-year OS 49%
Thomas et al[17]	R-hyper CVAD	31	46	3-year EFS 80%	3-year OS 89%
Mead et al[12]	CODOX-M/IVAC	53	37	2-year EFS 64%	2-year OS 67%
Magrath et al[22]	CODOX-M/IVAC	41	25	2-year PFS 92%	NA
Lacasce et al[23]	CODOX-M/IVAC	14	47	2-year PFS 92%	NA
Patekar et al[24]	CODOX-M/IVAC	18	38	1-year PFS 76%	1-year OS 81.1%
Rizzieri et al[25]	CALGB regimen	105	44	2-year EFS 74%	3-year OS 58%
Present study	Hyper-CVAD ± R	35	43	8-year PFS 56.3%	8-year OS 60%

Abbreviations: CALGB, Cancer and Leukemia Group B; CCR, continuous complete remission; CODOX-M/IVAC, cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide and cytarabine; EFS, event-free survival; hyper-CVAD, hyper-cyclophosphamide, adriamycin, vincristine, prednisolone/ cyclophosphamide; OS, overall survival; PFS, progression-free survival.

Authors' Contributions

S.M.T. was involved in design, literature search, data acquisition, data analysis, statistical analysis, and manuscript preparation. G.N. contributed to conceptualization, designing, data acquisition, data analysis, manuscript preparation, manuscript editing, and manuscript review. A.T.M. helped in data acquisition and manuscript editing. S.G.N., P.N.P., and R.A.N. contributed to data acquisition. Jagathnath Krishna did statistical analysis.

Funding

None.

Conflict of Interest

None declared.

References

1 Jaffe ES, Harris NL, Stein H, Vardiman JW. Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2001
2 Jaffe ES. The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. Hematology (Am Soc Hematol Educ Program) 2009;1:523–531
3 Boerma EG, van Imhoff GW, Appel IM, Veeger NJ, Kluin PM, Kluin-Nelemans JC. Gender and age-related differences in Burkitt lymphoma–epidemiological and clinical data from The Netherlands. Eur J Cancer 2004;40(18):2781–2787
4 Wästerlid T, Jonsson B, Hagberg H, Jerkeman M. Population based study of prognostic factors and treatment in adult Burkitt lymphoma: a Swedish Lymphoma Registry study. Leuk Lymphoma 2011;52(11):2090–2096
5 Cheson BD, Pfistner B, Juweid ME, et al; International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25(05):579–586
6 Schulz TF, Boshoff CH, Weiss RA. HIV infection and neoplasia. Lancet 1996;348(9027):587–591
7 Mbulaiteye SM, Biggar RJ, Bhatia K, Linet MS, Devesa SS. Sporadic childhood Burkitt lymphoma incidence in the United States during 1992-2005. Pediatr Blood Cancer 2009;53(03):366–370
8 Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin 2016;66(06):443–459
9 Nair R, Arora N, Mallath MK. Epidemiology of non-Hodgkin's lymphoma in India. Oncology 2016;91(1, Suppl 1):18–25
10 Kelly GL, Rickinson AB. Burkitt lymphoma: revisiting the pathogenesis of a virus-associated malignancy. Hematology (Am Soc Hematol Educ Program) 2007;1:277–284 PubMed
11 Mead GM, Sydes MR, Walewski J, et al; UKLG LY06 collaborators. An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study. Ann Oncol 2002;13(08):1264–1274
12 Mead GM, Barrans SL, Qian W, et al; UK National Cancer Research Institute Lymphoma Clinical Studies Group; Australasian Leukaemia and Lymphoma Group. A prospective clinicopathologic study of dose-modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY10 trial). Blood 2008;112(06):2248–2260
13 Arora N, Manipadam MT, Nair S. Frequency and distribution of lymphoma types in a tertiary care hospital in South India: analysis of 5115 cases using the World Health Organization 2008 classification and comparison with world literature. Leuk Lymphoma 2013;54(05):1004–1011
14 Saleh K, Michot JM, Camara-Clayette V, Vassetsky Y, Ribrag V. Burkitt and Burkitt-Like lymphomas: a systematic review. Curr Oncol Rep 2020;22(04):33
15 Lee EJ, Petroni GR, Schiffer CA, et al. Brief-duration high-intensity chemotherapy for patients with small noncleaved-cell lymphoma or FAB L3 acute lymphocytic leukemia: results of cancer and leukemia group B study 9251. J Clin Oncol 2001;19(20):4014–4022
16 Wilson WH, Grossbard ML, Pittaluga S, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. Blood 2002;99(08):2685–2693
17 Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 2006;106(07):1569–1580
18 Sengar M, Akhade A, Nair R, et al. A retrospective audit of clinicopathological attributes and treatment outcomes of adolescent and young adult non-Hodgkin lymphomas from a tertiary care center. Indian J Med Paediatr Oncol 2011;32(04):197–203
19 Wästerlid T, Brown PN, Hagberg O, et al. Impact of chemotherapy regimen and rituximab in adult Burkitt lymphoma: a retrospective population-based study from the Nordic Lymphoma Group. Ann Oncol 2013;24(07):1879–1886
20 Longo DL, Duffey PL, Jaffe ES, et al. Diffuse small noncleaved-cell, non-Burkitt's lymphoma in adults: a high-grade lymphoma responsive to ProMACE-based combination chemotherapy. J Clin Oncol 1994;12(10):2153–2159
21 Thomas DA, Cortes J, O'Brien S, et al. Hyper-CVAD program in Burkitt's-type adult acute lymphoblastic leukemia. J Clin Oncol 1999;17(08):2461–2470
22 Magrath I, Adde M, Shad A, et al. Adults and children with small non-cleaved-cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen. J Clin Oncol 1996;14(03):925–934
23 Lacasce A, Howard O, Lib S, et al. Modified Magrath regimens for adults with Burkitt and Burkitt-like lymphomas: preserved efficacy with decreased toxicity. Leuk Lymphoma 2004;45(04):761–767
24 Patekar M, Gogia A, Tiwari A, et al. Adult Burkitt lymphoma: an institutional experience with a uniform chemotherapy protocol. South Asian J Cancer 2018;7(03):195–199
25 Rizzieri DA, Johnson JL, Byrd JC, et al; Alliance for Clinical Trials In Oncology (ACTION) Improved efficacy using rituximab and brief duration, high intensity chemotherapy with filgrastim support for Burkitt or aggressive lymphomas: cancer and Leukemia Group B study 10 002. Br J Haematol 2014;165(01):102–111

Assessment of Knowledge and Attitude of Breast and Ovarian Cancer Patients Regarding Hereditary Breast-Ovarian Cancer Syndrome at a Tertiary Cancer Institute: A Cross-Sectional Observational Study

Raja Pramanik[1] Shubhra Vats[2] Sanchita Mitra[3] SVS Deo[4] Lalit Kumar[1] Ajay Gogia[1] Sachin Khurana[1] Atul Batra[1]

[1] Department of Medical Oncology, All India Institute of Medical Sciences, New Delhi, India
[2] Department of Biotechnology, University of Allahabad, Prayagraj, Uttar Pradesh, India
[3] Department of Biotechnology, Manav Rachna International Institute of Research and Studies, Faridabad, Haryana, India
[4] Department of Surgical Oncology, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence Raja Pramanik, MD, Department of Medical Oncology, Dr. B. R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi-110 029, India (e-mail: drrajapramanik@gmail.com).

Ind J Med Paediatr Oncol 2024;45:28–34.

Abstract

Introduction Hereditary breast and ovarian cancer (HBOC) syndrome affects a significant proportion of our breast and ovarian cancer patients. Mutations in genes, for example, BRCA1 and 2, confer a high risk of acquiring certain malignancies, including breast cancer in both men and women, and ovarian cancer in women. Mutation carriers provide a unique opportunity for healthcare professionals to intensively screen and detect malignancy at an early and curable stage. But, patient awareness and acceptance are the keys to the success of these strategies.

Objective There is a need to assess the awareness of the patients in this field as the patients come from varied backgrounds, and differ in their socioeconomic profiles, educational backdrop, and cultures. In this study, done prior to establishing our cancer genetics clinic, we evaluated the knowledge and attitude toward HBOC in patients with breast cancer and ovarian cancer.

Materials and Methods This cross-sectional observational study was conducted on patients registered in IRCH-AIIMS, who has a diagnosis of breast cancer or ovarian cancer using a self-administered questionnaire based on knowledge and attitude. The sample population included 84 women aged between 25 and 80 years. A binary response was given to knowledge questions, whereas a categorical response was given to attitude questions. The overall data was computed using STATA v13 software.

Results According to the findings of the study, 39.3% (5.11/13) of the patients were aware of hereditary cancer. Knowledge among the targeted population was poor, but 72.1% (37.5/52) of the population had a neutral attitude toward learning more about

Keywords
- hereditary breast and ovarian cancer
- mutation
- genetic counseling

article published online
May 12, 2023

DOI https://doi.org/10.1055/s-0043-1768178.
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

hereditary cancer tests. Only 23/84 (27%) people had heard of genetic counseling. Seventy of eighty-four (83%) patients agreed that they would opt for a genetic test if indicated. While 60/84 (72%) of the population wanted to interact with a counselor over a telephonic call, only 41/84 (49%) wanted to interact in person.

Conclusion We concluded from the study that breast and ovarian cancer patients in our clinic have little understanding of HBOC syndrome but have a neutral attitude toward learning more about it.

Introduction

Breast and ovarian cancers are among the most common cancers in women across the world.[1] In the Indian population, the healthcare burden of breast and ovarian cancers has been steadily rising, thus stressing the need for early detection, surveillance, and disease management measures. In Delhi, breast and ovarian cancers rank first and fourth among the most common malignancies in females with an age-standardized incidence rate of 32.25 and 8.8 per 100,000 population.[2] A family history of cancer is one of the most important risk factors for developing breast cancer and ovarian cancer. Hereditary breast and ovarian cancer (HBOC) syndrome is characterized by an early age of onset, overrepresentation of bilateral breast cancers, and familial congregation of ovarian and breast cancers. HBOC constitutes 21 to 30.5% of ovarian cancers[3,4] and 8 to 18% of breast cancers in India.[2,5] Mittal et al's, in contrast, studies from the Western population have shown a prevalence of 5 to 9% of germline BRCA1 and 2 mutations among patients with breast and ovarian cancers.[6–8] Pathogenic mutations in the *BRCA1* and *BRCA2* genes, which operate as tumor suppressors, appear to account for the majority of these cases. Carriers of germline mutations in BRCA1 are believed to have a 57 to 85% lifetime risk of developing breast cancer, while those with the BRCA2 mutation have 49 to 85% by the age of 70 years.[2] The average risk of ovarian cancer in women with a BRCA1 and 2 mutation is 40 and 18%, respectively.[2,5,9,10] Identification of these germline mutations has profound implications in the management of these patients as well as their first-degree relatives who then qualify for single site-specific mutation testing. For the patient, it opens a cafeteria choice for prophylactic risk-reducing surgeries like RRSO (risk-reducing salpingo-oophorectomy), RRM (risk-reducing mastectomies) as well as newer therapeutic agents like PARP inhibitors like olaparib, niraparib. Prophylactic surgeries (like oophorectomy and mastectomy) substantially reduce the risk of otherwise inevitable cancer and mortality.[11] The previvors with these mutations are yet another cohort who will benefit from prophylactic surgeries like RRM and RRSO.[12,13] The National Comprehensive Cancer Network guidelines have elaborately given recommendations for managing these patients according to the specific mutation detected.

But the core of success for all these interventions lies in the awareness of the patients and their acceptance of these interventions. This highlights the importance of the availability of cancer genetic counseling services in the different oncology centers in the country. Cancer genetic counseling should be incorporated in all the centers providing breast oncology and gynecology oncology services. In order to successfully start any "High risk familial /cancer genetic clinic," it is essential to understand the ground realities of the targeted population, their understanding of the subject, what it means to them, and the attitude they have in their minds toward these tests. The Indian population is diverse with multiple levels of ethnic, cultural, linguistic, and religious groups that contribute to this diversity. These factors along with the level of education make the Indian population very heterogeneous. Patients visiting the breast cancer clinic and gynecology oncology clinic comes from diverse backgrounds, rural and urban, with varying levels of education and a variety of religious and cultural backgrounds from different parts of northern India.[14]

This study was planned as a survey to assess the knowledge of our patients with breast and ovarian cancers about HBOC, and their attitude and acceptance of genetic tests and possible interventions.

Objectives

The main aim of this study was to assess the knowledge and attitude of breast and ovarian cancer patients about HBOC.

Materials and Methods

In this cross-sectional observational study conducted in our breast cancer and gynecological cancer clinics of Dr. BRA-IRCH, All India Institute of Medical Sciences (AIIMS), New Delhi, from January 2018 to December 2018, patients with a diagnosis of breast or ovarian cancer attending clinics for treatment or follow-up were invited to participate with a patient information sheet and informed consent form. This was done during a personal meeting in the outpatient department (OPD). We included patients aged 18 years and above with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 3 and who gave informed consent. Acutely sick patients and ECOG PS4 were excluded. Those consenting were asked to fill up the questionnaire using tick marks that took 5 to 7 minutes. Data collection variables included demographic details, diagnosis, family history of cancer, and responses to short questions assessing the knowledge about hereditary

cancers and attitudes toward genetic counseling and testing. Illiterate patients were interviewed by translating and reading out each question and their response was recorded in the proforma (see supplementary file). The primary outcome of the study was to determine the average knowledge score and average attitude score of these patients using an in-house validated questionnaire. No formal sample size calculation was done. We intended to do the study as a pilot survey as there is no data available in the literature. We included as many patients as available during this time period.

An in-house expert-validated questionnaire was developed for the study. This questionnaire consisted of two parts: knowledge assessment and attitude assessment. The KAP survey was interviewer-administered and quantitative. The 27 questions covered knowledge and attitude aspects. The knowledge section consisted of 13 questions. (minimum possible score 0 and maximum possible score 13). Based on the score, the knowledge assessment was evaluated as follows: excellent knowledge more than 75%; good knowledge 45 to 75%; poor knowledge less than 45%. The attitude section consisted of 14 questions, with each question formatted to have five possible choices (strongly agree, agree, not sure, disagree, strongly disagree). The total marks for the attitude assessment were 60 (maximum possible score = 60, minimum possible score = 0). Based on the score, the attitude assessment was evaluated as follows: favorable attitude-attitude score more than 75%; neutral attitude-attitude score between 50 and 75%; unfavorable attitude-attitude score less than 50%.

Preliminary Work on Quality Control

To optimize the scientific rigor of this research, the following processes were done: *Translation and back translation:* Questionnaire questions were developed first in English with a panel of medical experts. These questions were then translated into Hindi by specialist medical translators and then back into English again by a separate, nonmedical translator before they were finally checked for consistency by the research team.

Peer and expert review: A panel of medical and research experts was formed to review the research design and questionnaire development.

Pretesting using cognitive interviewing: A process of cognitive interviewing was used to study the interpretation of the questionnaire questions on lay volunteers. This involves verbalizing the thought processes occurring while reading the questions.

Statistical Analysis

Demographic characteristics were analyzed using mean and median (range). Each knowledge question has a binary response, and each attitude question has a categorical response. The total score was also calculated for knowledge and attitude separately. The association of these scores with demographic and disease factors was determined using Student's *t*-test. STATA v13 software was used for analysis and *p*-value less than 0.05 was considered significant.

Ethics

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964, as revised in 2013. Ethical Approval was obtained from the Institutional Ethics Committee vide letter no. IEC- 186/3/2018 dated 19.03.18 (see supplementary material). Informed consent was taken from all the participants.

Results

A total of 84 women patients participated in the study aged between 25 and 75 years among which 69/84 (82%) had breast cancer and 15/84 (18%) had ovarian cancer (see ►**Table 1**). Among the sample population, 77/84 (92%) did not recall having any relatives with cancer. Twenty-six of eighty-four (31%) patients reported that they feared that cancer may run in their family (►**Supplementary Fig. S1**, available in the online version).

The knowledge part of the questionnaire had 13 questions, and the binary responses to which have been tabulated in ►**Table 2**. Briefly, 55/84 (65%) of the sample population were unaware that some cancers run in families. Only around 13/84 (15%) of respondents were aware that specific genes are responsible for cancer. *BRCA* genes were unknown to 78/84 (93%) of the population. Fifty-four of eighty-four (64%) patients were unaware that breast and ovarian cancer can coexist in certain cases. Only 23/84 (27%) of patients had heard of genetic counseling. Around 54/84 (64%) had the notion that genetic counseling was required prior to genetic testing (►**Fig. 1**). About 19/84 (23%) of the participant had the idea that genetic test reports are kept confidential and not disclosed to anyone else. The mean knowledge score of the patients was 5.11 ± 2.54. With a maximum possible score of 13, this amounted to $39.3 \pm 19.5\%$. This correlated with poor knowledge about HBOC in this patient's cohort.

Table 1 Baseline characteristics of patients who participated in the survey

Baseline characteristics		
	Females	**Males**
1. Sex of patients	84 (100%)	0
	Breast cancer	Ovarian cancer
2. Diagnosis of patients	69 (82%)	15 (18%)
	Yes	No
3. Do you have any other relatives with cancer?	7 (8%)	77 (92%)
	Yes	No
4. Are they related to you by blood?	6 (7%)	78(93%)
	Yes	No
5. Do you fear that cancer may run in your family?	58 (69%)	26 (31%)

Table 2 Question-wise responses to the knowledge part of the questionnaire

Knowledge questionnaires	Yes	No
KQ1: Do you know certain cancers run in the family?	29 (35%)	55 (65%)
KQ2: Do you know that breast, ovary, or colorectal cancer may run in certain families?	18 (21%)	66 (79%)
KQ3: Do you know that certain genes may be responsible for cancer?	13 (15%)	71 (85%)
KQ4: Have you heard of BRCA genes?	6 (7%)	78 (93%)
KQ5: Do you think some cancers are preventable?	64 (76%)	20 (24%)
KQ6: Do you think breast cancer and ovary cancer can occur together in certain cases?	30 (36%)	54 (64%)
KQ7: Have you heard of preventive surgery to prevent familial ovarian cancer/ breast cancer?	71 (85%)	13 (15%)
KQ8: Do you know preventive ovarian surgery is done after completion of the family generally after 40 years of age?	35 (42%)	49 (58%)
KQ9: Have you heard of genetic counseling?	23 (27%)	61 (73%)
KQ10: Do you know blood tests are available to detect whether cancer runs in your family or not?	62 (74%)	22 (26%)
KQ11: Do you know both blood and saliva samples are taken for cancer tests?	6 (7%)	78 (93%)
KQ12: Do you know that the result of this test will be disclosed only to you and no one else?	19 (23%)	65 (77%)
KQ13: Do you think genetic counseling is essential before genetic testing?	54 (64%)	30 (36%)

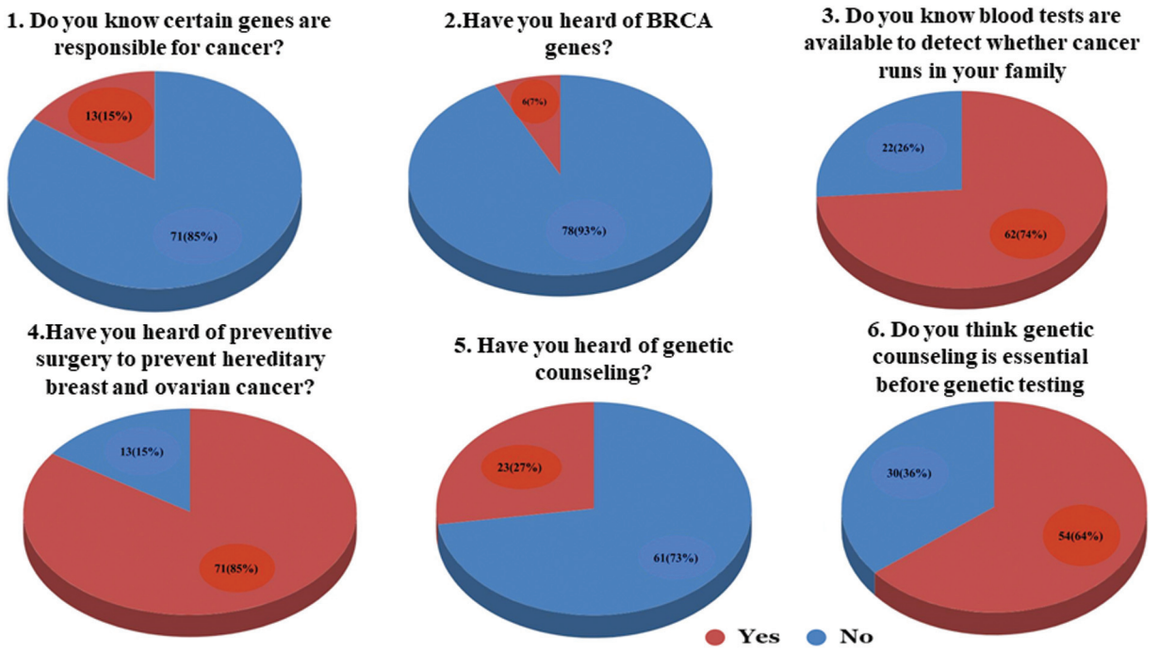


Fig. 1 Pie charts showing binary responses to selected knowledge questions.

Following that, we evaluated the attitudes of the respondents toward genetic testing. In this domain, there were 14 questions, and the responses are tabulated in ►**Supplementary Table S1** (available in the online version).

Briefly, 70/84 (83%) of patients agreed that they would opt for a genetic test if available, and 54/84 (64%) mentioned that they would opt for it even if they had to pay the expenses. A total of 62/84 (74%) of patients believed that these sorts of tests would impact their future decision-making. Around 79/84 (94%) of respondents stated that they would recommend it to their relatives. Given an opportunity, 76/84 (90%) of the participant wanted to interact with a genetic counselor. While 60/84 (72%) of the population wanted to interact with a counselor over a telephonic call, only 41/84 (49%) wanted to interact in person. Approximately 75/84 (89%) of participants were interested in learning more about medical or surgical options for cancer prevention (►**Fig. 2**). The average attitude score of the patients was 40.78 ± 8.05. With a maximum possible score of 52, this amounted to $78.42 \pm 15.48\%$. This meant that the sample population had a neutral attitude toward learning more about genetic testing.

We compared the mean total knowledge marks and mean total attitude marks of our patients dividing them into binary groups according to age ($>/<50$ years), primary diagnosis

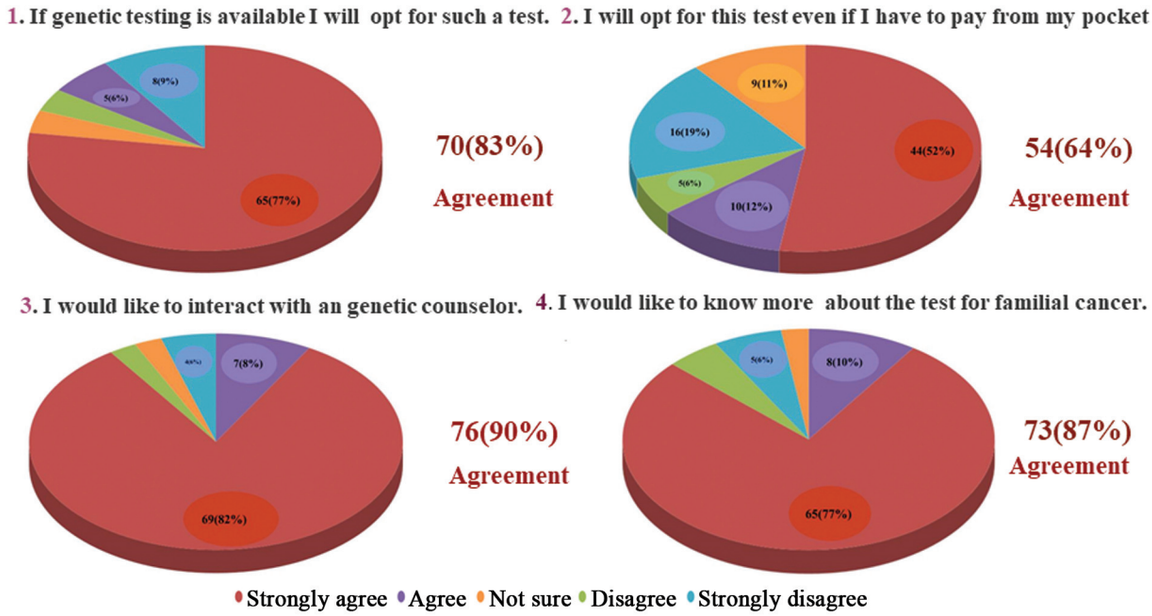


Fig. 2 Pie charts showing categorical responses to questions in the attitude part of the questionnaire.

Table 3 Comparison of knowledge and attitude scores with baseline demographic characteristics

		Knowledge marks			Attitude marks		
Age			*p*-Value			*p*-Value	
≤50	$n=49$	5.08 ± 2.47	0.87	Not significant	40.69 ± 8.07	0.90	Not significant
≥50	$n=35$	5.17 ± 2.68			40.91 ± 8.14		
Diagnosis							
Breast cancer	$n=69$	4.95 ± 2.55	0.21	Not significant	41.44 ± 7.54	0.10	Not significant
Ovarian cancer	$n=15$	5.86 ± 2.47			37.73 ± 9.81		
Relative with cancer							
Yes	$n=7$	4.42 ± 1.18	0.45	Not significant	40.78 ± 7.83	0.98	Not significant
No	$n=77$	5.18 ± 2.60			40.78 ± 11.01		

(breast versus ovary) and whether they had a relative with cancer or not. There were no significant differences between these groups (see ►**Table 3**).

Discussion

We found some interesting results during this study. A large proportion of patients were unaware of hereditary cancers. Most of them were unaware that particular genes are responsible for cancer. Only a small proportion of the participant had heard of genetic counseling. These findings illustrate that public awareness of HBOC is quite low. Interestingly, the study showed that the participants had a neutral attitude toward learning more about genetic testing. More than half agreed to genetic testing, even if they had to pay out of their own pockets. This study was conducted prior to the coronavirus disease 2019 (COVID-19) pandemic, yet it was observed that most individuals preferred to communicate with a genetic counselor over the telephone instead of an in-person visit. A large proportion of those surveyed was interested in learning more about the test for hereditary cancers, as well as the medical or surgical methods for cancer prevention.

Individuals at high risk of getting breast or ovarian cancer in most developed nations receive genetic counseling before undergoing BRCA mutation testing. By precisely building their family lineage and acquiring pertinent medical histories, genetic counseling plays a crucial role in choosing individuals suited for genetic testing. However, in many countries, like America, Africa, and Asia, genetic counseling, and genetic testing are still not widely used in cancer management programs.[15] In a systematic review by Hann et al ethnic minority groups, including African Americans, Asian Americans, and Hispanics, had low awareness and understanding of genetic counseling/testing for cancer risk.[16] In a recent study published by our institution, where

we tested 246 consecutive breast cancer patients irrespective of guidelines, and we reported 18.6% pathogenic/likely pathogenic mutations.[2,5] This is almost double what is reported in Western literature.[17] Therefore, there is a high unmet need for genetic counseling and testing in India. In view of the severe scarcity of cancer genetic counseling services, Indian oncologists and breast surgeons have already embarked on the idea of "mainstreaming."[18,19]

But the million-dollar questions that remain unanswered are "How much do the Indian patients know about hereditary cancers, how much are they eager to know about HBOC, what would be their attitude towards these genetic tests, and how would they like to participate in genetic counseling sessions." Unfortunately, to the best of our knowledge, such a survey has not been reported from India. So, the present attempt is a novel step to unearth and bring forward the perspective of Indian patients suffering from breast and ovarian cancers.

India is a multilingual country, and most patients prefer to communicate in their own language. Face-to-face therapy is the conventional counseling style in India. Telephone, video, Skype, and WhatsApp counseling sessions are being increasingly adopted by genetic clinics and counselors to expand their access. This trend has received an impetus during the recent COVID-19 pandemic.[20] It was surprising to know that even in pre-COVID-19 times more patients preferred telegenetic consultation over an in-person visit. Although the reasons remain unclear, we speculate that it might be emotionally less overwhelming for cancer patients to receive the counseling session over the telephone without any visual contact with the counselor, at least for the initial visit. Also navigating busy OPDs and hospital environments for counseling sessions may be challenging. Thus, telegenetic counseling appears acceptable and promising for Indian society.

Another important takeaway from this study may be that the knowledge and information regarding HBOC should be imparted as awareness programs in colleges, workplaces, and primary healthcare centers. It is quite evident that Indian women are receptive and inquisitive to current scientific knowledge about healthcare.

We used a questionnaire evaluated by a panel of experts at AIIMS. This population's general understanding of HBOC was relatively low. Patients, on the other hand, had a neutral attitude toward learning more about genetic testing.

There are some limitations to our study as well. Despite the fact that the questionnaire used in the study was pretested, it may restrict the comparability of our findings to other investigations. Furthermore, because this study was confined to only 84 females, the sample size is quite small hence, additional surveys with larger samples are required. Nevertheless, this study is novel and unique, for it voices the perspective of Indian patients.

Conclusion

This study shows that there is limited knowledge about HBOC among our patients with breast and ovarian cancer. Yet, they have a neutral attitude to learn more about HBOC, medical and surgical risk reduction, and genetic counseling. The report, thus, emphasizes the importance of educational programs to raise knowledge about genetic testing. An increasing number of oncologists in India are projected to utilize genetic counseling and testing. Such studies are intended to improve clinical practices for better patient care.

Ethical Approval

The study was approved by the Institute Ethical Committee vide Letter No. IEC-186/06.04.2018, RP-47/2018.

Availability of Data and Material

Data regarding this study will be available from the corresponding author (R.P.) at reasonable request.

Authors' Contributions

R.P., S.D., L.K. conceptualized the study, S.V. collected data, S.M., R.P., S.K., A.G., and A.B. analyzed data, and R.P. and S. M. drafted the manuscript. The final manuscript was reviewed and edited by all authors.

Funding

None.

Conflict of Interest

None declared.

References

1 Momenimovahed Z, Tiznobaik A, Taheri S, Salehiniya H. Ovarian cancer in the world: epidemiology and risk factors. Int J Womens Health 2019;11:287–299
2 Malhotra H, Kowtal P, Mehra N, et al. Genetic counseling, testing, and management of HBOC in India: an expert consensus document from Indian Society of Medical and Pediatric Oncology. JCO Glob Oncol 2020;6:991–1008
3 Kadri MSN, Patel KM, Bhargava PA, et al. Mutational landscape for Indian hereditary breast and ovarian cancer cohort suggests need for identifying population specific genes and biomarkers for screening. Front Oncol 2021;10:568786
4 Gupta S, Rajappa S, Advani S, et al. Prevalence of *BRCA1* and *BRCA2* mutations among patients with ovarian, primary peritoneal, and fallopian tube cancer in India: a multicenter cross-sectional study. JCO Glob Oncol 2021;7:849–861
5 Singh J, Thota N, Singh S, et al. Screening of over 1000 Indian patients with breast and/or ovarian cancer with a multi-gene panel: prevalence of BRCA1/2 and non-BRCA mutations. Breast Cancer Res Treat 2018;170(01):189–196
6 Mittal A, Deo SVS, Gogia A, et al. Spectrum and management of breast cancer patients with variant of uncertain significance mutations at a tertiary care centre in North India. Ecancermedicalscience 2022;16:1434
7 Paradiso AV, Digennaro M, Patruno M, De Summa S, Tommasi S, Berindan-Neagoe I. BRCA germline mutation test for all woman with ovarian cancer? BMC Cancer 2019;19(01):641
8 Yadav S, Hu C, Hart SN, et al. Evaluation of germline genetic testing criteria in a hospital-based series of women with breast cancer. J Clin Oncol 2020;38(13):1409–1418
9 Mannan AU, Singh J, Lakshmikeshava R, et al. Detection of high frequency of mutations in a breast and/or ovarian cancer cohort:

implications of embracing a multi-gene panel in molecular diagnosis in India. J Hum Genet 2016;61(06):515–522
10 Petrova D, Cruz M, Sánchez MJ. BRCA1/2 testing for genetic susceptibility to cancer after 25 years: A scoping review and a primer on ethical implications. Breast 2022;61:66–76
11 Carbine NE, Lostumbo L, Wallace J, Ko H. Risk-reducing mastectomy for the prevention of primary breast cancer. Cochrane Database Syst Rev 2018;4(04):CD002748
12 Puski A, Hovick S, Senter L, Toland AE. Involvement and influence of healthcare providers, family members, and other mutation carriers in the cancer risk management decision-making process of BRCA1 and BRCA2 mutation carriers. J Genet Couns 2018;27 (05):1291–1301
13 Yamauchi H, Takei J. Management of hereditary breast and ovarian cancer. Int J Clin Oncol 2018;23(01):45–51
14 Singh S, Shrivastava JP, Dwivedi A. Breast cancer screening existence in India: a nonexisting reality. Indian J Med Paediatr Oncol 2015;36(04):207–209
15 Ormond KE, Laurino MY, Barlow-Stewart K, et al. Genetic counseling globally: where are we now? Am J Med Genet C Semin Med Genet 2018;178(01):98–107
16 Hann KEJ, Freeman M, Fraser L, et al; PROMISE study team. Awareness, knowledge, perceptions, and attitudes towards genetic testing for cancer risk among ethnic minority groups: a systematic review. BMC Public Health 2017;17(01):503
17 Kwong A, Shin VY, Ho JC, et al. Comprehensive spectrum of BRCA1 and BRCA2 deleterious mutations in breast cancer in Asian countries. J Med Genet 2016;53(01):15–23
18 Khatak S, Wadhwa N, Pandey AK, et al. Public perception of genetic counseling in India: opening mind eyes. Shodh Sarita 2020;7:104–111
19 Singh M, Prasad CP, Singh TD, Kumar L. Cancer research in India: challenges & opportunities. Indian J Med Res 2018;148(04):362–365
20 Monaghesh E, Hajizadeh A. The role of telehealth during COVID-19 outbreak: a systematic review based on current evidence. BMC Public Health 2020;20(01):1193

Clinicodemographic Profile of Childhood Cancer in a Mining State, Odisha: A Retrospective Analysis

Dipti Rani Samanta[1] Ajitesh Avinash[2] Surendra Nath Senapati[2] Suchitra Samal[2]
Tapas Kumar Dash[2] Abhisekh Kumar Sarangi[2]

[1] Department of Medical Oncology, Acharya Harihar Post Graduate Institute of Cancer, Mangalabag, Cuttack, Odisha, India
[2] Department of Radiation Oncology, Acharya Harihar Post Graduate Institute of Cancer, Mangalabag, Cuttack, Odisha, India

Address for correspondence Dipti Rani Samanta, MD, Professor & Head, Department of Medical Oncology, Acharya Harihar Post Graduate Institute of Cancer, Mangalabag, Cuttack, Odisha 753007, India (e-mail: e-mail-diptiranisamanta@rediff.com).

Ind J Med Paediatr Oncol 2024;45:35–43.

Abstract

Introduction Pediatric malignancy represents 5% of total cancer diagnosed in India. Due to delayed diagnosis and inaccessibility to healthcare system, the overall outcome is poor in our country. The clinicodemographic profile of childhood malignancy is well described in the Western world and in certain parts of India. The incidence of pediatric malignancy in Eastern India, especially Odisha, has not yet been reported that has motivated us to conduct such a study.

Objective This study aims to evaluate the clinicodemographic profile and pattern of childhood malignancy among pediatric patients who received the treatment at a tertiary cancer institute of Odisha.

Materials and Methods It was a retrospective observational study, carried out for a period of 8 years, from January 1, 2013 to December 31, 2020 at a tertiary cancer center in Eastern India. A total of 759 eligible childhood malignancy patients were recruited in the study. IBM SPSS v23 was used for descriptive statistical analysis, that is, number and percentage of various clinicodemographic parameters of the above patients.

Result Childhood malignancy accounted for 1.6% of all cancers reported during the above study period. The male to female ratio was 1.8:1. Out of 759 eligible childhood cancer patients, majority of patients were suffering from leukemia (173; 22.8%) followed by malignant bone tumors (137; 18.0%), and lymphoma (122; 16%). Leukemia was predominant in the age group of 0 to 14 years; lymphoma, central nervous system neoplasms, germ cell tumors malignant bone tumors, and soft tissue sarcoma (STS) were common in the age group of 10 to 18 years; neuroblastoma, retinoblastoma, and renal and hepatic tumors were seen commonly in the age group of 0 to 9 years. The most common presentation in leukemia was fever, while lymphadenopathy was the chief complaint in lymphoma. Local swelling and pain were the presenting symptoms in malignant bone tumors, while STS patients had painless swelling.

Conclusion This study provides an overview of the burden and pattern of childhood malignancy for the state of Odisha and acts as a roadmap for the clinicians to conduct further research in the field of pediatric oncology.

Keywords
- pediatric malignancy
- Eastern India
- childhood leukemia

article published online
May 4, 2023

DOI https://doi.org/10.1055/s-0043-1768180.
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

According to the World Health Organisation, childhood cancer is defined as any cancer arising in children aged between 0 and 19 years. Nearly 4 lakh children are diagnosed with cancer every year globally.[1] The cure rate in childhood malignancy has improved from less than 10% in 1950s to about 80% in present day due to better understanding of biology and proper implementation of multidisciplinary treatment approach.[2]

In India, approximately 45,000 new cases of childhood malignancy are detected each year that accounts for 5% of total cancer burden.[3] The cure rate of childhood malignancies in India ranges from 10 to 30% that is quite low as compared to 80% in developed countries.[4] Last few decades have witnessed strengthening of healthcare services for treatment of childhood cancers in India, but these services are mostly confined to tertiary cancer centers. Due to absence of nation-wide population-based cancer registry (PBCR), there is lack of data about the exact burden of childhood cancer in India. Further, the existing PBCRs mostly cater data about prevalence of malignancies in the urban population.[5] Hence, there is a need to accurately define the burden of childhood cancers in India.

Childhood malignancies include a spectrum of diseases whose clinical and demographic picture varies from country to country and also inter-regionally within the same country. In India, children with cancer are detected at an older age with advanced stage, likely due to poor awareness and delay in diagnosis that further leads to delay in treatment. In addition, lack of appropriate supportive care, treatment refusal, and abandonment are the main hurdles to such low cure rate in the country.[5]

Publications on childhood cancer are few from India and scarce from the eastern zone. The lack of clinicodemographic data of childhood malignancy from the state of Odisha has driven us to conduct such a study that will highlight the cancer burden in children in the state of Odisha and also act as a stimulus for all the oncologists and pediatrician for further health-related research in the field of pediatric malignancies.

Materials and Methods

Study design: This was a retrospective observational study was conducted in the month of July 2021 by the department of medical oncology in conjunction with the department of radiation oncology at a tertiary cancer center of Odisha. All childhood cancer patients who received treatment during the period January 1, 2013 to December 31, 2020 were included for screening.

Inclusion criteria: Residents of Odisha with histopathology or flow cytometry proved malignancy were included in this study.

Exclusion criteria: Patients aged more than 18 years were excluded from the study.

Data: The complete demographic and clinical data of the eligible patients such as age, sex, year of admission to our institute, clinical histories, presenting symptoms, and duration of symptoms were collected from clinical case sheets from medical record section of our institute. The final study population of pediatric malignancy after screening of data during this period was 759 as shown in flow diagram in ►**Fig. 1**. The primary outcome measure was to find out the pattern of distribution of childhood malignancies in a mining state, Odisha. The secondary outcome measure was to correlate any difference in distribution of childhood malignancies with that of national and international level.

Statistical Analysis

The number and percentage of male, female, and district-wise distribution of childhood cancers were calculated for this study period. The distribution of childhood cancers was further done into four major age groups—0 to 4 years, 5 to 9 years, 10 to 14 years, and 15 to 18 years according to the third edition of the International Classification of Childhood Cancers (ICCC-3). The number and percentage of common presenting symptoms and the median duration of symptoms of various malignancy were studied. International Business Machine (IBM) Statistical Package for the Social Sciences (SPSS) version 23 was used for the above descriptive study of data.

Ethics approval: Permission from the Institutional Ethics Committee was received on June 3, 2021 via letter no. 05-IEC-AHPGIC. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

During the study period from January 2013 to December 2020, 47,678 patients of our state were admitted to the tertiary cancer center out of which 759 belonged to the pediatric age (0–18 years). Highest number of pediatric cancer patients were admitted in the year 2016 (141), while lowest was in the year 2020 (57) as shown in ►**Table 1**. The prevalence of malignancy was more among males than females with an overall male: female ratio of 1.8:1 (95% confidence interval: 1.3–2.3).

On analysis of the district-wise distribution of childhood cancers as depicted in ►**Table 2**, highest frequency of childhood cancer was from the district of Mayurbhanj (79, 10.41%), followed by Ganjam (60, 7.91%), Cuttack (50, 6.59%), Jajpur (47, 6.20%), Balasore (40, 5.27%), Balangir (39, 5.14%) Puri (38, 5.01%), and Khordha (37, 4.87%), while only two (0.26%) cases of childhood malignancy were admitted to our center from the district of Deogarh during the study period.

In this study, on analysis of the type of malignancy in ►**Table 3**, it was observed that childhood leukemia was the commonest type of childhood malignancy constituting 173 (22.8%) patients followed by malignant bone tumors 137 (18.0%) and lymphoma 122 (16.1%). The least common malignancy was retinoblastoma constituting only 11 (1.4%)

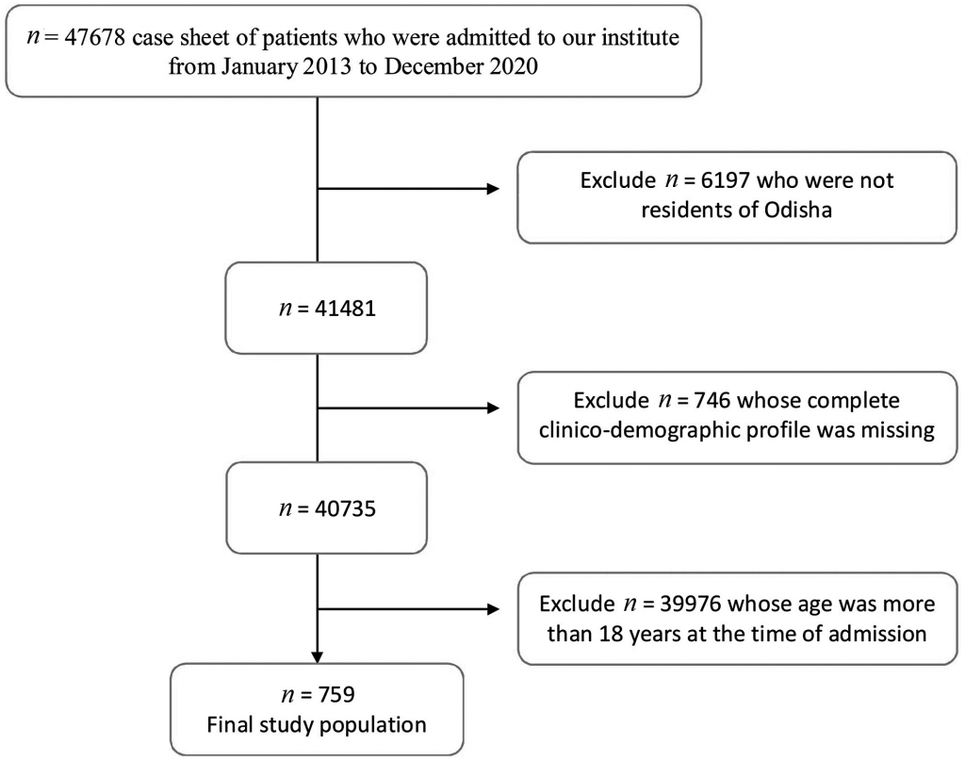


Fig. 1 The flowchart depicting screening process of the final study population.

Table 1 The year and gender distribution and frequency of childhood cancers from 2013 to 2020

Year	Total no. of cases	No. of childhood cancers	Frequency (%)	Male	Female	Male:female ratio
2013	4,968	94	1.9	73	21	3.47
2014	5,981	102	1.7	66	36	1.83
2015	5,769	131	2.3	78	53	1.47
2016	6,032	141	2.3	97	44	2.20
2017	6,647	92	1.4	60	32	1.87
2018	7,072	83	1.2	46	37	1.24
2019	6,519	59	0.9	35	24	1.46
2020	4,690	57	1.2	33	24	1.37
Total	47,678	759	1.6	488	271	1.80

patients. On analysis, it was observed that in the age group of 0 to 4 years, childhood leukemia was the most common malignancy 45 (5.9%) followed by renal tumors 36 (4.7%), central nervous system (CNS) neoplasms 15 (1.9%), and lymphoma 13 (1.7%). In this age group, the incidence of malignant bone tumors was the least with only four (0.5%) patients. In the age group 5 to 9 years, childhood leukemia also was the commonest malignancy 43 (5.6%) followed by CNS neoplasm 29 (3.8%) and lymphoma 26 (3.4%), while hepatic tumors was the lowest with only three (0.4%) patients. In the age group 10 to 14 years, again the predominance of childhood leukemia was noted among all malignancy with 52 patients (6.8%), followed by lymphoma 47 (6.2%) and malignant bone tumors with 43 (5.6%) patients. Malignant bone tumor was the most frequent malignancy 70 (9.2%) in the adolescent age group of 15 to 18 years, followed by lymphoma in 36 patients (4.7%) and leukemia in 33 patients (4.3%) and germ cell tumors in 20 patients (2.6%).

Among childhood leukemia, acute lymphoblastic leukemia (ALL) was the most common malignancy 132 (76.3%) in all the groups, followed by acute myelogenous leukemia (AML) 33 (19.0%) and chronic myelocytic leukemia 8 (4.7%). There was a predominance of non-Hodgkin lymphoma (HL; 68 patients) over HL (54 patients). Medulloblastoma was the most common CNS neoplasms (30 patients). Ewing sarcoma (ES) had the highest frequency among malignant

Table 2 The district-wise distribution of childhood cancers from 2013 to 2020

District	Total childhood cancers	Frequency (%)
Anugul	12	1.58
Balangir	39	5.14
Balasore	40	5.27
Bargarh	30	3.95
Bhadrak	34	4.48
Boudh	15	1.98
Cuttack	50	6.59
Deogarh	2	0.26
Dhenkanal	22	2.90
Gajapati	8	1.05
Ganjam	60	7.91
Jagatsinghpur	20	2.64
Jajpur	47	6.20
Jharsuguda	6	0.79
Kalahandi	21	2.77
Kandhamal	16	2.11
Kendrapara	35	4.61
Keonjhar	31	4.08
Khordha	37	4.87
Koraput	14	1.84
Malkangiri	8	1.05
Mayurbhanj	79	10.41
Nabarangpur	7	0.92
Nayagarh	19	2.50
Nuapada	5	0.66
Puri	38	5.01
Rayagada	7	0.92
Sambalpur	18	2.37
Sonepur	21	2.77
Sundargarh	18	2.37

bone tumor (67 patients) followed by osteosarcoma (66 patients). Among soft tissue sarcoma (STS), maximum cases reported were of rhabdomyosarcoma (RMS; 32 patients). Other epithelial tumors reported in this study include carcinoma nasopharynx (10 patients), carcinoma recto-sigmoid region (4 patients), Langerhans cell histiocytosis (4 patients), carcinoma stomach, ovary, and melanoma (1 patient each).

In this study, fever was the most common presenting symptom seen in 129 patients (74.6%) out of total 173 patients of childhood leukemia, followed by generalized weakness in 47 patients (27.2%), bleeding manifestation in 22 patients (12.7%), and joint pain in 3 patients (1.7%) as depicted in ►**Table 4**. Lymphadenopathy was the commonest presentation of lymphoma (82 patients, 67.2%) followed by fever (36, 29.5%) and pain abdomen (19, 15.6%). Majority of the CNS neoplasms presented with vomiting (86, 94.5%) and headache (49, 53.8%). Other presentation included fever and seizure. Patients of neuroblastoma presented with abdominal lump (9; 52.9%) followed by pain abdomen (3; 17.6%), fever (3; 17.6%), and seizure (1; 5.9%). Maximum children (10, 90.9%) with retinoblastoma had swelling of unilateral eye as the most common presentation, while only one (9.1%) child presented as bilateral retinoblastoma. Out of 56 renal tumors (Wilms tumor [WT]) detected during the study period, maximum (51, 91.1%) patients had abdominal swelling as their common presentation. Abdominal lump was also the most common presentation of the hepatic tumors seen in eleven patients (73.3%) followed by pain abdomen seen in seven patients (46.7%), fever in two patients (13.3%), and vomiting in one patient (6.7%) only. Among 137 cases of malignant bone tumors included in the study, maximum (125 patients; 91.2%) presented with local swelling followed by pain at local site seen in 20 patients (14.6%). Soft tissue tumors in children (total 42 patients) presented with local swelling as their most common presentation in 31 patients (73.8%), pain at local site in 6 patients (14.3%), and blood in urine in 4 patients (9.5%). Also, in 45 childhood germ cell tumors, majority of patients 22 (48.9%) presented with abdominal swelling followed by pain abdomen (18 patients; 40%) and scrotal swelling (8 patients; 17.7%).

The median duration of symptoms was 1 month for childhood leukemia, CNS tumors, neuroblastoma, retinoblastoma, and germ cell tumors, while it was 2 months for lymphoma, renal tumors, hepatic tumors, bone and soft tissue tumors, and other malignant epithelial tumors.

Discussion

In India, the pivotal role in cancer registration is mostly accomplished by PBCR and hospital-based cancer registries (HBCRs). Currently, there are 33 PBCRs and 101 HBCRs in India. The latest data on the burden of cancer in India was reported by 27 PBCRs for the years 2012 to 2014 that covered only 10% of the population.[6] Therefore, the exact burden of cancer in India is lacking due to nonavailability of nation-wide PBCR. Behera et al have highlighted the lacunae of the existing PBCRs that include dominance of urban cases being reported over rural, lack of quality assurance for data, loss to follow-up, and absence of survival data. Further the cost of registration in PBCR is high and there is no link between one PBCR with the others.[7] All these loopholes need to be addressed in order to increase the cancer case registration that will help in predicting the burden of cancer in Indian children.

Steliarova-Foucher et al evaluated 153 population-based registries from 62 countries during the period 2001 to 2010 and reported that the global incidence of malignancy in children aged between 0 and 19 years was 3,85,509 that accounted for 2.64 billion person-years.[8] According to 3 years (2012–2014) report of 27 PBCRs of India, the proportion of childhood cancer for the age group of 0 to 14 years ranged from 0.7 to 4.4% as compared to cancers in all groups.[9] In this study from 2013 to 2020, the proportion of childhood cancer

Table 3 The distribution of childhood cancers according to four major age groups

Types of cancer	Age group (in years)				Total
	0–4	5–9	10–14	15–18	
Leukemia	45	43	52	33	173
ALL	39	36	34	23	132
AML	6	6	15	6	33
CML	0	1	3	4	8
Lymphoma	13	26	47	36	122
Hodgkin lymphoma	3	15	22	14	54
Non-Hodgkin lymphoma	10	11	25	22	68
CNS neoplasms	15	29	29	18	91
Medulloblastoma	6	14	7	3	30
High-grade gliomas	3	3	6	5	17
Low-grade gliomas	2	4	6	3	15
Craniopharyngioma	1	3	6	3	13
Meningioma	0	0	0	2	2
Ependymoma	2	4	1	1	8
Gliosarcoma	0	0	1	0	1
Intracranial embryonal tumor	0	1	1	1	3
Germinoma	0	0	1	0	1
Pinealoblastoma	1	0	0	0	1
Neuroblastoma	8	7	1	1	17
Retinoblastoma	7	4	0	0	11
Renal tumors (Wilms' tumor)	36	15	3	2	56
Hepatic tumors (hepatoblastoma)	8	3	3	1	15
Malignant bone tumors	4	20	43	70	137
Osteosarcoma	0	6	18	42	66
Ewing sarcoma	4	14	23	26	67
Chondrosarcoma	0	0	1	0	1
Giant cell tumor	0	0	1	2	3
Soft tissue sarcomas	10	5	11	16	42
Rhabdomyosarcoma	8	5	10	9	32
Fibrosarcoma	1	0	0	1	2
Epithelioid sarcoma	1	0	0	1	2
Synovial sarcoma	0	0	1	3	4
Peripheral nerve sheath tumor	0	0	0	2	2
Germ cell tumors	9	9	7	20	45
Other malignant epithelial neoplasms	10	6	11	23	50
Carcinoma nasopharynx	0	0	3	7	10
Carcinoma ovary	0	0	0	1	1
Carcinoma rectosigmoid	0	0	0	4	4
Carcinoma stomach	0	0	0	1	1
Malignant melanoma	0	0	0	1	1
Langerhans cell histiocytosis	3	0	1	0	4
Others unspecified carcinoma	7	6	7	9	29
Total	165	167	207	220	759

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myelocytic leukemia; CNS, central nervous system.

for the age group of 0 to 18 years was 1.6% as compared to malignancy of all age groups that is in concordance with that of the Indian data. The childhood cancer patients reporting for treatment to our institute were maximum (141) in year 2016 and minimum (57) during the year 2020. The probable reason being less patients seeking healthcare due to nation-wide lockdown in India due to the coronavirus disease 2019 pandemic.

Globally, the male to female ratio of pediatric malignancy in the age group of 0 to 19 years was 1.14:1, while 1.17:1 in the age group of 0 to 14 years, which suggests the male predominance.[8] The data on overall male to female ratio is lacking in PBCR report of 2012 to 2014. However, the proportion of pediatric malignancy among the male child was highest (5.4%) in PBCR of Delhi, while it was lowest (0.7%) in PBCR of Nagaland. Similarly, among the female child, the

Table 4 The common clinical presentation and median duration of symptoms of childhood malignancies

Type of malignancy	Symptoms	Number of patients (%)	Median duration of symptoms (in months)
Leukemia	Fever Generalized weakness Facial swelling Pain abdomen Bleeding manifestation Abdomen swelling Jaundice Joint pain Breathlessness, cough Vomiting	173 129 (74.6%) 47 (27.2%) 25 (14.4%) 17 (9.8%) 22 (12.7%) 12 (6.9%) 2 (1.2%) 3 (1.7%) 7 (4.0%) 7 (4.0%)	1
Lymphoma	Lymphadenopathy Fever Pain abdomen Breathlessness, cough, chest pain	122 82 (67.2%) 36 (29.5%) 19 (15.6%) 16 (13.1%)	2
CNS tumors	Vomiting Headache Fever Seizure	91 86 (94.5%) 49 (53.8%) 2 (2.2%) 2 (2.2%)	1
Neuroblastoma	Abdomen swelling Pain abdomen Swelling over scalp Swelling over eye Fever Seizure	17 9 (52.9%) 3 (17.6%) 1 (5.9%) 2 (11.7%) 3 (17.6%) 1 (5.9%)	1
Retinoblastoma	Swelling of unilateral eye Swelling of bilateral eye Fever	11 10 (90.9%) 1 (9.1%) 1 (9.1%)	1
Renal tumors	Abdominal mass Pain abdomen Fever Blood in urine Vomiting	56 51 (91.1%) 7 (12.5%) 4 (7.1%) 1 (1.8%) 1 (1.8%)	2
Hepatic tumors	Abdomen mass Pain abdomen Fever Vomiting	15 11 (73.3%) 7 (46.7%) 2 (13.3%) 1 (6.7%)	2
Malignant bone tumors	Local swelling Pain at local site Fever Breathlessness, cough Vomiting, headache	137 125 (91.2%) 20 (14.6%) 3 (2.2%) 4 (2.9%) 1 (0.7%)	2
Soft tissue tumors	Local swelling Pain at local site Blood in urine Breathlessness, cough	42 31 (73.8%) 6 (14.3%) 4 (9.5%) 2 (4.7%)	2
Germ cell tumors	Abdomen swelling Pain abdomen Scrotal swelling Breathlessness, cough Vomiting	45 22 (48.9%) 18 (40%) 8 (17.7%) 4 (8.9%) 2 (4.4%)	1
Other epithelial tumors		50	2

Abbreviation: CNS, central nervous system.

proportion of pediatric malignancy was highest (3.5%) in PBCR of Naharlagun (excluding the district of Papumpare) and was lowest (0.5%) in PBCR of Meghalaya (in East Khasi Hills District).[9] In this study, the male:female ratio was 1.80:1 highlighting the male predominance of pediatric malignancy.

During the above study period, maximum number of childhood cancer patients were from the district of Mayurbhanj, Ganjam, Cuttack, Jajpur, Balasore, Balangir, Puri, and Khordha. Availability of developed tertiary care hospitals in the above districts of Odisha that leads to increased detection may be the reason for higher cases of pediatric malignancy being detected in above districts as compared to others.

Based on tumor site and morphology, theICCC-3 has grouped childhood cancers into 11 main categories of childhood malignancy, that is, (i) leukemia, myeloproliferative diseases and myelodysplastic diseases; (ii) lymphoma and reticuloendothelial neoplasms; (iii) CNS and miscellaneous intracranial and intraspinal neoplasms; (iv) neuroblastoma and other peripheral nervous cell tumors; (v) retinoblastoma; (vi) renal tumors; (vii) hepatic tumors; (viii) malignant bone tumors; (ix) soft tissue and other extraosseous sarcomas; (x) germ cell tumors, trophoblastic tumors and neoplasms of gonads; (xi) other malignant epithelial neoplasms and malignant melanomas.[10]

Globally, the commonest malignancy in the age group of 1 to 14 years is childhood leukemia followed by CNS neoplasm and lymphoma, whereas in the age group of 15 to 19 years, the most common neoplasm is lymphoma followed by epithelial tumor and melanoma.[8] Childhood leukemia is also the most common childhood malignancy in India.[4] In this study, childhood leukemia was the most common childhood malignancy that was consistent with global and Indian data. In the developed countries, CNS tumor exceeds lymphoma cases, but in India and in our study lymphoma cases were more as compared to childhood CNS neoplasms.[11]

In India, childhood leukemia represents 40 to 50% of pediatric malignancy and the most common subtype was ALL followed by AML.[8,11] In this study, leukemia was the most common childhood malignancy constituting 22.8% of all patients. Out of all leukemia patients, ALL was the most predominant childhood leukemia reporting 76.3% of cases. The median age at diagnosis ranged from 6 to 10 years in Indian scenario, while maximum number of patients were seen in the age group of 3 to 14 years in this study.[5] Childhood leukemia usually present clinically with nonspecific symptoms such as fever that mimics other childhood infectious and parasitic infestations. This lack of recognition of symptoms as any other childhood ailment usually leads to delayed diagnosis of leukemia.[12] The common symptoms of leukemia noted in this study were fever, weakness, bleeding manifestation, and joint pain that were similar to those reported by Prajapati et al.[13]

The incidence of childhood lymphoma in India is quite identical with Western world.[8] In this study, lymphoma was the third most common malignancy with a total of 122 (16.1%) patients, and was seen in the age groups from 2 to 18 years. The most common type of lymphoma in India was HL, whereas the non-Hodgkin lymphoma (NHL) was predominant in this study.[5] Most patients of HL usually present with B symptoms (fever, drenching night sweats and loss of more than 10% of weight in the last 6 months), while NHL patients present commonly with abdominal swelling followed by lymphadenopathy.[14,15] In this study, lymphadenopathy was the most common presentation in both HL and NHL patients. These patients are often misdiagnosed as tuberculosis that leads to advanced stage at diagnosis.[5]

Jain et al have studied 3,936 pediatric CNS neoplasms patients from seven tertiary cancer hospitals in India and have highlighted astrocytoma histology was the most common primary childhood brain tumor. Others histologies, that is, medulloblastoma, supratentorial primitive neuroectodermal tumors, craniopharyngiomas, and ependymal tumors, were reported in decreasing order of frequency.[16] In our study, out of 91 patients of CNS neoplasms medulloblastoma was the most common CNS malignancy constituting 30 (32.9%) followed by pediatric glioma 17 (18.7%) and astrocytoma 15 (16.5%). The median duration of diagnosis was 1 month. Patients of brain tumors in our study mostly presented in the age group of 2 to 9 years with vomiting, headache, fever, and seizures as the presenting symptoms that correlated with the findings reported by Madhavan et al.[17]

Neuroblastoma was considered as the commonest childhood extracranial solid tumor.[18] Neuroblastoma in Indian children ranged from 2.4 to 7.5% as stated in the consolidated report of seven HBCRs 2012 to 2014.[19] In this study, only 17 (2.2%) patients of neuroblastoma were seen out of which two patients (11.8%) had age less than 547 days, while maximum (15 cases; 88.2%) patients had age more than 547 days. Majority (88.2%) of patients of neuroblastoma in our study had age more than 547 days suggestive of poor prognosis.[18] Patients of neuroblastoma usually presented with abdominal swelling, pain abdomen, swelling over scalp, swelling of eye, fever, and seizure as seen in our study.

Retinoblastoma being the commonest primary intraocular tumor has a global incidence of 3 to 5 million children per year. In the developed countries, retinoblastoma represented 2.5 to 4% of all childhood cancers, while it ranged from 6 to 10% of all pediatric malignancies in Indian children.[8] These patients are diagnosed at median age of 29 months and commonly presented with leukocoria and/or proptosis.[20] Only 11 (1.4%) retinoblastoma patients out of the total 759 pediatric patients presented to our institute during the above study period. Patients in the age group of 0 to 4 years were seven, while only four patients were in the age group of 5 to 9 years. Proptosis was the most common presentation with unilateral proptosis seen in 10 patients and bilateral proptosis in only 1 patient.

In pediatric age, the most common renal malignant tumor was WT that accounted for 5.9% of all childhood malignancies. The incidence of WT in Asian population was half of that of the Western population. The median age at diagnosis was 3 years, and the most common presentation was abdominal mass followed by pain abdomen, fever and blood in urine.[21] In our study out of a total of 56 patients of WT, 36 patients

(64.3%) presented in age group of 1 to 4 years with abdominal mass as the most frequent clinical presentation.

Hepatoblastoma, the most common primary hepatic childhood malignancy, with a global incidence of 1.5 per million children mostly presented at the median age of 11 months. Abdominal mass followed by pain abdomen, fever, jaundice, and vomiting was the clinical presentation at the time of diagnosis.[22] During our study period, 15 patients with hepatoblastoma were reported. Majority of patients (8; 53.3%) were in the age group of 0 to 4 years and presented with abdominal mass as their initial presentation that also correlated with the western literature.

ES was the most common primary malignant bone tumor followed by osteosarcoma. Osteosarcoma in pediatric patients was mostly seen during the period of rapid bone growth, that is, second decade. ES was common among Asians as compared to Western population. Local swelling and pain were the most common presenting complaints in all malignant bone tumors.[18] Majority of malignant bone tumors in our study presented in the adolescent age group of 15 to 18 years and ES outnumbered the osteosarcoma in this age group. The common complaints were local swelling and pain at local site and the median duration of symptoms was 2 months.

RMS was the most common STS in children that represented one half of childhood STS, while the other half was collectively called as non-RMS that included fibrosarcoma, dermatofibrosarcoma protuberance, synovial sarcoma, liposarcoma, epithelioid sarcoma, and malignant peripheral nerve sheath tumor. RMS was predominant in age group of 0 to 5 years. Among non-RMS, fibrosarcoma was more frequent in infants, while other non-RMS were seen in adolescent age.[18] In this study, RMS was the most common STS constituting 76.1% of all the STS patients. With respect to the age of presentation, majority (64.3%) of patients in this study were in the age group of 10 to 18 years that differs from that of the Western literature. STS usually presented with painless local swelling and was found in majority (73.8%) of STS patients included in our study.[18]

Childhood malignant germ cell tumors (MGCT) was a group of heterogenous tumors that represented 3% of all childhood cancers.[23] These tumors clinically presented with abdominal swelling, pain abdomen, or as a scrotal swelling and are more prevalent in adolescent age group. MGCT in this study was seen in 45 patients that represented 5.9% of total pediatric malignancy. Maximum number of patients (20; 44.4%) were in the adolescent age group of 15 to 18 years.

In this study of pediatric malignancy, the incidence, age of presentation, and clinical symptoms were similar to that of the Western literature except the clinical presentation of HL and age at presentation of RMS.

Limitation

This study does not provide data regarding the outcome and survival of pediatric malignancy patients who received treatment during the study period due to discontinuation of treatment and lack of follow-up by patient's family.

Conclusion

This study gives an insight to the clinicodemographic pattern of pediatric malignancies of the state of Odisha for 8 years (2013–2020). The most common malignancy in this study was childhood leukemia followed by malignant bone tumors and lymphoma, while retinoblastoma was the least common. Childhood leukemia followed by CNS neoplasm was predominant in the age group of 0 to 9 years; leukemia and lymphoma were seen in all the age group 10-14 years, while malignant bone tumors were seen commonly in adolescent age group of 15 to 18 years. Males outnumbered females and the frequency of detection of childhood malignancy were more in the districts that had access to tertiary care hospitals.

Authors' Contributions

All authors contributed to the study conception and design. Data collection and analysis were performed by A.A., S.S., T.K.D., and A.K.S. The statistical analysis and manuscript preparation were done by D.R.S., S.N.S., and A.A., All authors edited and reviewed the manuscript.

Ethical Conduct of Research

The study was approved by the Institutional Ethics Committee of Acharya Harihar Post Graduate Institute of Cancer, Letter No: 05-IEC-AHPGIC.

Funding

None.

Conflict of Interest

None declared.

References

1 Childhood Cancer WHO. Accessed March 27, 2023 at: https://www.who.int/news-room/fact-sheets/detail/cancer-in-children
2 Arora RS, Bakshi S. Indian Pediatric Oncology Group (InPOG) – collaborative research in India comes of age. Pediatric Hematology Oncology Journal 2016;1:13–17
3 Arora B, Kanwar V. Childhood cancers in India: burden, barriers, and breakthroughs. Indian J Cancer 2009;46(04): 257–259
4 Suhag V, Sunita BS, Vats P, Sarin A, Singh AK, Jain M. Clinical profile of pediatric oncology patients treated by external beam radiotherapy: an institutional experience. Indian J Med Paediatr Oncol 2017;38(01):28–32
5 Ganguly S, Kinsey S, Bakhshi S. Childhood cancer in India. Cancer Epidemiol 2021;71(Pt B):101679
6 Cancer samiksha. Accessed March 27, 2023 at: https://ncdirindia.org/cancersamiksha/
7 Behera P, Patro BK. Population based cancer registry of india – the challenges and opportunities. Asian Pac J Cancer Prev 2018;19 (10):2885–2889
8 Steliarova-Foucher E, Colombet M, Ries LAG, et al; IICC-3 contributors. International incidence of childhood cancer, 2001-10: a population-based registry study. Lancet Oncol 2017;18(06): 719–731
9 Cancer in childhood: three year report of PBCR 2012–2014. Accessed March 27, 2023 at: https://ncdirindia.org/ncrp/

ALL_NCRP_REPORTS/PBCR_REPORT_2012_2014/ALL_CONTENT/PDF_Printed_Version/Chapter4_Printed.pdf
10 International Incidence of Childhood Cancer. Volume III (electronic version) Lyon, FranceInternational Agency for Research on Cancer. Accessed March 27, 2023 at: https://iicc.iarc.fr/results/
11 Arora RS, Eden TO, Kapoor G. Epidemiology of childhood cancer in India. Indian J Cancer 2009;46(04):264–273
12 Johnston WT, Erdmann F, Newton R, Steliarova-Foucher E, Schüz J, Roman E. Childhood cancer: estimating regional and global incidence. Cancer Epidemiol 2021;71(Pt B):101662
13 Prajapati Z, Kokani MJ, Gonsai RN. Clinicoepidemiological profile of hematological malignancies in pediatric age group in Ahmedabad. Asian J Oncol 2017;3:54–58
14 Arya LS, Dinand V, Thavaraj V, et al. Hodgkin's disease in Indian children: outcome with chemotherapy alone. Pediatr Blood Cancer 2006;46(01):26–34
15 Meena JP, Gupta AK, Parihar M, Seth R. Clinical profile and outcomes of Non-Hodgkin's lymphoma in children: a report from a tertiary care hospital from India. Indian J Med Paediatr Oncol 2019;40:41–47
16 Jain A, Sharma MC, Suri V, et al. Spectrum of pediatric brain tumors in India: a multi-institutional study. Neurol India 2011;59(02):208–211
17 Madhavan R, Kannabiran BP, Nithya AM, Kani J, Balasubramaniam P, Shanmugakumar S. Pediatric brain tumors: an analysis of 5 years of data from a tertiary cancer care center, India. Indian J Cancer 2016;53(04):562–565
18 Pizzo PA, Poplack DG, Adamson PC, Blaney SM, Helman LJ. Principles and Practice of Pediatric Oncology. 7th ed. Philadelphia, PA: Wolters Kluwer | Lippincott Williams and Wilkins; 2015
19 Consolidated Report of Hospital Based Cancer Registries: 2012–2014. Accessed March 27, 2023 at: https://www.ncdirindia.org/All_Reports/HBCR_REPORT_2012_2014/index.htm
20 Kaliki S, Patel A, Iram S, Ramappa G, Mohamed A, Palkonda VAR. Retinoblastoma in India: clinical presentation and outcome in 1,457 patients (2,074 eyes). Retina 2019;39(02):379–391
21 Varan A. Wilms' tumor in children: an overview. Nephron Clin Pract 2008;108(02):c83–c90
22 Archana B, Thanka J, Sneha LM, Xavier Scott JJ, Arunan M, Agarwal P. Clinicopathological profile of hepatoblastoma: an experience from a tertiary care center in India. Indian J Pathol Microbiol 2019;62(04):556–560
23 Agarwala S, Mitra A, Bansal D, et al. Management of pediatric malignant germ cell tumors: ICMR consensus document. Indian J Pediatr 2017;84(06):465–472

Unveiling the Molecular Mechanisms Behind the Devastating Impact of the ALK Protein on Pediatric Cancers: Insights into Deleterious SNPs through In Silico Predictions, Molecular Docking, and Dynamics Studies

Abdulhadi Almazroea[1]

[1] Associate Professor of General Pediatrics, Medical College, Taibah University, Saudi Arabia

Address for correspondence Dr. Abdulhadi Almazroea, MD, Associate Professor of General Pediatrics, Medical College, Taibah University, Saudi Arabia (e-mail: amazroea@taibahu.edu.sa).

Ind J Med Paediatr Oncol 2024;45:44–51.

Abstract

Introduction Pediatric cancers present significant challenges in terms of diagnosis and treatment, and the anaplastic lymphoma kinase (ALK) protein has emerged as a crucial molecular target in these malignancies. ALK, a receptor tyrosine kinase, plays a vital role in normal cellular processes, but genetic alterations and aberrant activation of the ALK gene have been implicated in various pediatric cancer types. While genetic alterations have been well studied, the precise molecular mechanisms underlying the pathogenicity of the ALK protein in pediatric cancers remain poorly understood.

Objective In this study, the primary objective is to uncover the molecular mechanisms associated with the effects of deleterious single-nucleotide polymorphisms (SNPs) on the structure and functionality of the ALK protein.

Material and Methods Several known point mutations of the ALK protein were taken for the in silico predictions such as PolyPhen-2, SIFT, PANTHER, PredictSNP, etc., residue conservation analysis using Consurf server, molecular docking (AutoDock), and molecular dynamics simulation studies (GROMACS).

Results The computation predictions found that the studied variants are deleterious in different tools. The residue conservation analysis reveals all the variants are located in highly conserved regions. The molecular docking study of wild-type and mutant structures with the crizotinib drug molecule found the variants were modulating the binding cavity and had a strong impact on the binding affinity. The binding energy of the wild-type is –5.896 kcal/mol, whereas the mutants have –9.988 kcal/mol. The specific amino acid Ala1200 of wild-type was found to interact with crizotinib, and Asp1203 residue was found to interact predominantly in the mutant structures.

Conclusion The simulation study differentiates the variants in terms of structural stability and residue fluctuation. Among the studied variants, R1275Q, F1245V, and F1174L had strong deleterious effects, structural changes, and pathogenicity based on the in silico predictions. By elucidating the functional consequences of deleterious mutations within the ALK gene, this research may uncover novel therapeutic targets

Keywords
- ALK
- pediatric cancer
- SNP
- molecular docking
- molecular dynamics simulation

article published online
September 23, 2023

DOI https://doi.org/10.1055/s-0043-1771403.
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

and personalized medicine approaches for the management of pediatric cancers. Ultimately, gaining insights into the molecular mechanisms of the ALK protein's role in driving response and resistance will contribute to improving patient outcomes and advancing our understanding of this complex disease.

Introduction

Pediatric cancers continue to pose significant challenges in terms of diagnosis and treatment. Among the various molecular targets implicated in pediatric cancers, the anaplastic lymphoma kinase (ALK) protein has gained considerable attention due to its devastating impact on tumor development and progression.[1,2] ALK is a receptor tyrosine kinase that plays a crucial role in normal cellular processes, including neuronal development.[1] However, aberrant activation or genetic alterations in the ALK gene have been associated with the onset and progression of several pediatric cancer types, including neuroblastoma and anaplastic large cell lymphoma.[3,4]

While genetic alterations, such as chromosomal rearrangements and gene fusions, have been well documented as key events in ALK-driven pediatric cancers, the precise molecular mechanisms underlying the pathogenicity of ALK protein remain largely unexplored. Recent advancements in genomic research have revealed the presence of single-nucleotide polymorphisms (SNPs) within the ALK gene, some of which are predicted to have deleterious effects on the protein structure and function.[1] These deleterious SNPs hold the potential to contribute to the susceptibility and progression of pediatric cancers, but their specific roles and impact on ALK signaling pathways remain elusive.

Since 2011, crizotinib drug molecule approved by the Food and Drug Administration has been used as a first-line treatment for ALK fusion positives and anaplastic large cell lymphomas.[5,6] Crizotinib resistance was found in the patients with L1196M, I1171N, and F1174L/V/C mutations. From the detailed review analysis, it was found R1275Q/L has 45% of frequency in ALK-mutant tumors, 30 and 12% for the F1174C/V/L and F1245V/C, respectively.[4] These observations suggest that specific molecular contexts play a role in determining varying sensitivity to direct ALK kinase inhibition. This implies that the effectiveness of ALK inhibition and the mechanisms of resistance may be influenced by the specific context in which it is applied, highlighting the context-dependent nature of ALK's role in driving response and resistance.[7,8]

Pediatric cancers pose a significant public health concern, and understanding the molecular mechanisms driving their development is crucial for the development of effective treatment strategies. The ALK protein has emerged as a key player in various pediatric cancers, making it a promising target for further investigation. Deleterious SNPs in the ALK gene have been associated with an increased risk of pediatric cancers. Therefore, studying these SNPs and their impact on ALK protein function can offer valuable insights into the underlying molecular mechanisms that drive disease progression.

In silico studies provide a powerful approach for exploring the structural and functional aspects of proteins. By utilizing computational techniques such as molecular docking and dynamics simulations, we can investigate the interactions between the ALK protein and its ligands or potential therapeutic agents. These computational methods yield detailed insights into the molecular mechanisms and potential therapeutic targets. Molecular docking allows for the prediction of protein–ligand interactions, aiding in the identification of potential inhibitors or modulators of ALK protein activity. This information can guide the development of novel therapeutic interventions tailored to combat pediatric cancers associated with ALK dysregulation. On the other hand, molecular dynamics (MD) simulations enable the examination of the dynamic behavior of the ALK protein, providing valuable information about its conformational changes, stability, and interactions over time. These simulations shed light on how deleterious SNPs may affect the structure and function of the ALK protein, thus aiding in the identification of key functional regions and potential molecular targets.

Overall, the aim of this study is to unravel the intricate molecular mechanisms underlying the devastating impact of the ALK protein on pediatric cancers by investigating deleterious SNPs. The integration of in silico studies, molecular docking, and dynamics simulations will provide crucial insights that can ultimately contribute to the development of targeted therapies for pediatric cancer patients.

Therefore, in this study, the aim is to unveil the molecular mechanisms behind the ALK protein's devastating impact on pediatric cancers by focusing on the insights provided by deleterious SNPs.[9,10] By elucidating the functional consequences of deleterious SNPs within the ALK gene, this research holds the potential to uncover novel therapeutic targets and strategies for the management of pediatric cancers. Moreover, it may pave the way for personalized medicine approaches that take individual genetic variations and their impact on the ALK signaling pathways.[11] Ultimately, gaining insights into the molecular mechanisms of the ALK protein's devastating impact on pediatric cancers will contribute to improving patient outcomes and advancing our understanding of this complex disease.

Methodology

Data Collection

Genomic and protein data relevant to pediatric cancer patients with ALK gene alterations were obtained from publicly available databases and repositories, including PubMed, RCSB-PDB, Ensembl genome browser, and UniProt. The focus was on identifying SNPs associated with the ALK

Table 1 Complete genetic data of the SNPs included in this study

Missense SNP	dbSNP ID	Chr.bp position/alleles	Evidence	Clinical significance	Transcript ID
I1171N	rs1057519698	rs1057519698-A/G/**T**	Cited, disease phenotype	Pathogenic	ENST00000389048.8
F1174L	rs863225281	2:29220829-G/C/**T**	Cited, disease phenotype	Pathogenic	ENST00000389048.8
F1174V	rs281864719	2:29220831-A/G/**C**/T	Cited, disease phenotype	Pathogenic	ENST00000389048.8
F1174C	rs1057519697	2:29220830-A/C	Cited, disease phenotype	Pathogenic	ENST00000389048.8
L1196M	rs1057519784	2:29220765-G/T	Cited, disease phenotype	Likely pathogenic	ENST00000389048.8
F1245V	rs281864720	2:29213994-A/**C**/G/T	Cited, disease phenotype	Pathogenic	ENST00000389048.8
F1245C	rs863225283	2:29213993-A/C	Cited, disease phenotype	Pathogenic	ENST00000389048.8
R1275Q	rs113994087	2:29209798-C/A/**T**	Cited, disease phenotype	Pathogenic	ENST00000389048.8
R1275L	rs113994087	2:29209798-C/**A**/T	Cited, disease phenotype	Pathogenic	ENST00000389048.8

Abbreviations: dbSNP, Single Nucleotide Polymorphism Database; SNP, single-nucleotide polymorphism.
Note: Bold values indicate the allele entries in dbSNP and ensembl genome browser.

protein that have been reported to be deleterious. The selection of these SNPs was based on the article by Mossé[4] and served as input for subsequent computational predictions. ►**Table 1** provides detailed information about the identified SNPs within the ALK gene, including variant position, transcript identity (ID), chromosome position, and variant information.

In Silico Analysis

A comprehensive bioinformatics analysis was conducted to evaluate the potential deleterious effects of the identified SNPs on the structure and function of the ALK protein. This analysis involved the use of various noncommercial prediction tools and software, including PolyPhen-2, SIFT, PredictSNP, PANTHER, MetaLR, SNAP (screening for nonacceptable polymorphisms), and PhD-SNP.[12] These tools were employed to assess the functional implications of nonsynonymous SNPs (nsSNPs) within the coding region of the ALK gene.[13]

PolyPhen-2 utilizes principles of physical and evolutionary comparisons to assess the impact of amino acid changes on protein structure and function. It calculates the difference in position-specific independent count scores between variants, assigning probabilistic scores ranging from 0 (neutral) to 1 (deleterious), categorizing functional significance as benign, possibly damaging, or probably damaging. SIFT predicts the impact of amino acid substitutions on protein function by assigning tolerance index scores ranging from 0 (deleterious) to 1 (neutral) based on sequence alignments.[14] PhD-SNP is an support vector machine-based method that analyzes the local sequence environment of mutations to distinguish disease related from neutral mutations. PANTHER is a widely used bioinformatics tool for predicting and evaluating genetic changes in gene and protein sequences, employing the position-specific evolutionary preservation metric to quantify the evolutionary preservation of positions within proteins.[15] PredictSNP is a Web server housing multiple SNP prediction tools for identifying deleterious SNPs, while MetaLR employs a logistic regression-based ensemble method to predict the pathogenicity of single-nucleotide variants. SNAP, a neural network-based screening tool, integrates various sequence information to predict the functional impact of nsSNPs and provides reliability information for the predictions.[16]

Amino Acid Conservation Analysis

To assess the conservation and evolutionary importance of the SNPs across various species, multiple sequence alignments were conducted. The Consurf server was employed for this purpose, utilizing the Multiple Alignment using Fast Fourier Transform (MAFFT) algorithm to perform the alignments by searching for homologous sequences in the UNIREF90 database using the HMMER search algorithm.[17,18] The server utilized a Bayesian method to predict conservation scores for each amino acid and determined the most suitable amino acid substitution based on the alignment. The resulting alignment was then presented with a color-coded scheme, distinguishing conserved and variable amino acids, providing insights into the conservation patterns within the protein sequence across different species.[19]

Structural Modeling and Molecular Docking

A three-dimensional (3D) structural model of the ALK protein (wild-type) and its variants was generated based on the crystal structure (PDB ID: 2ZP2). To assess the binding affinity changes associated with the studied mutations, molecular docking studies were conducted between the ALK protein and the drug molecule crizotinib (►**Fig. 1**). ►**Fig. 1** represents the 3D cartoon structure of the protein molecule (green) and ligand molecule (blue) docked in the active site. Each structure, including the wild-type and mutant variants, was generated using the PyMol software by introducing one amino acid mutation at a time. AutoDock Tools version 4.2.6 was employed to prepare the protein and ligand structures, assigning polar hydrogens, united atom Kollman charges, solvation parameters, and fragmental volumes to the protein.[20,21] The prepared structures were saved in PDBQT format. AutoGrid was utilized to create a grid map,

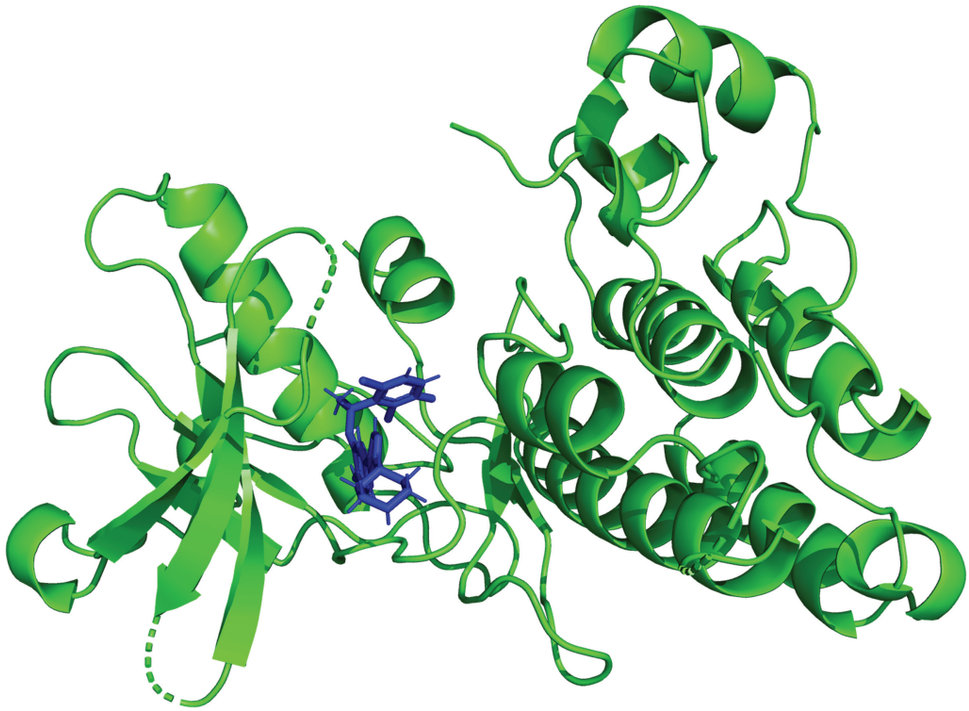


Fig. 1 Three-dimensional structure of anaplastic lymphoma kinase (ALK) protein with crizotinib drug molecule at the active site of the protein.

specifying a grid box size of $60 \times 60 \times 60$ *xyz* points, 0.375 Å of grid spacing, and a designated grid center at coordinates (*x*, *y*, *z*): 27.468, 46.380, and 7.560. To reduce computation time, a scoring grid was calculated from the ligand structure. Docking was performed using AutoDock/Vina, employing an iterated local search global optimizer and treating both the protein and ligands as rigid entities during the docking process. Docked results with a positional root-mean-square deviation (RMSD) below 1.0 Å were clustered, and the cluster representative with the most favorable free energy of binding was selected. The docking pose with the lowest energy of binding or highest binding affinity was extracted and aligned with the protein receptor structure for further analysis. Each mutant and wild-type structure underwent individual docking, and the predicted binding energies were correlated.[22] The docked structures were visualized and analyzed using PyMol and Maestro, Schrödinger workspace,[23] for detailed examination of the binding poses and interactions.

Molecular Dynamics Simulation (MDS)

In this study, a MD simulation was conducted to analyze the structural stability and changes caused by the impact of SNPs. The simulation included one wild-type structure and four mutant structures (I1171N, R1275Q, F1174L, and F1245V), while excluding other structures due to minimal changes observed during docking studies and computational efficiency. The flexibility and conformational stability of the ALK protein and mutant complexes were determined by the GROMACS v5.0.6 (Groningen Machine for Chemical Simulations) software. The energy-minimized ligand topologies were generated using the PRODRG server (http://davapc1.bioch.dundee.ac.uk/cgi-bin/prodrg). The ligands were merged into the protein structure and the cubic systems were generated with 1.0 nm distance from the protein–ligand complexes.[24,25] Furthermore, the systems were added by water molecules. The entire systems were neutralized by adding the appropriate Na^+ and Cl^- counterions. The GROMOS96 43a1 force field was used to minimize the structure energy and the electrostatic interaction was utilized by the particle-mesh Ewald and the steepest algorithm methods. In the energy minimization process, the steepest descent (50,000 steps) algorithm was utilized to maintain the solvating system. The system maintained a constant temperature and pressure despite being solvated. In the NVT ensemble, the temperature was maintained using the Berendsen thermostat (0.1 ps). The NPT ensemble was maintained at constant pressure (1 bar).[26] The well-equilibrated complexes were further used for the MDS production run for 500 nanoseconds time period. Finally, the obtained simulation data were analyzed and plotted using Origin Pro, 2018 for further structural analysis.

Inclusion & Exclusion Criteria

NA.

Primary & Secondary Outcome

NA.

Statistical Analysis

NA.

Results

Computational Prediction on nsSNPs

Based on the online tools used to predict the functional and structural effects of the studied nsSNPs, it was observed that all the mutations listed in this study had deleterious effects on the protein structure. These mutations played a substantial role in impacting protein function and reducing the overall structural stability.[27] However, it is noteworthy that the mutations I1171N, L1196M, and F1174L were predicted to be neutral according to the PredictSNP, SNAP, and PhD-SNP tools, as indicated in ►**Suppl. Table. 1** On the other hand, the remaining variants were determined to have deleterious effects with higher confidence scores by these prediction tools.

Residue Conservation Analysis

The Consurf server was utilized for residue conservation analysis of the ALK protein, using the UniProt database entry (ID: Q9UM73) as the input source. The analysis revealed that all the mutated positions were found to be highly conserved, and a majority of the amino acids were exposed, as depicted in ►**Fig. 2**. The region spanning from position 1171 to 1275 exhibited complete conservation in the ALK protein, and these mutations within this region are likely the primary cause for the deleterious effects and negative impact on protein function. ►**Fig. 2** provided a visualization of the conservation pattern across the entire protein structure, indicating that the helix regions were highly conserved, and interestingly, all the studied mutations were located within these helices.

Molecular Docking

The molecular docking analysis of ALK wild-type and mutant structures was done using AutoDock software. The results revealed that all the mutant structures exhibited better scores compared with the wild-type structure. This indicates that the mutations had an impact on the ligand-binding site. The mutant structures demonstrated increased binding energy and favorable interaction patterns, as observed in ►**Suppl. Table 2**. Specifically, the amino acids Ala1200, Asp1203, Glu1197, and Met1199 were frequently identified in the docking results for both the wild-type and mutant structures when docked with the crizotinib drug molecule. Notably, the L1196M and I1171N mutants did not exhibit significantly higher binding energy compared with the wild-type, and their binding poses and patterns were similar (►**Suppl. Fig. 1**). Intriguingly, both the wild-type and the I1171N and L1196M mutants displayed identical binding poses with similar interaction patterns, suggesting that these mutations did not significantly impact the binding affinity of the docked compound. On the other hand, the

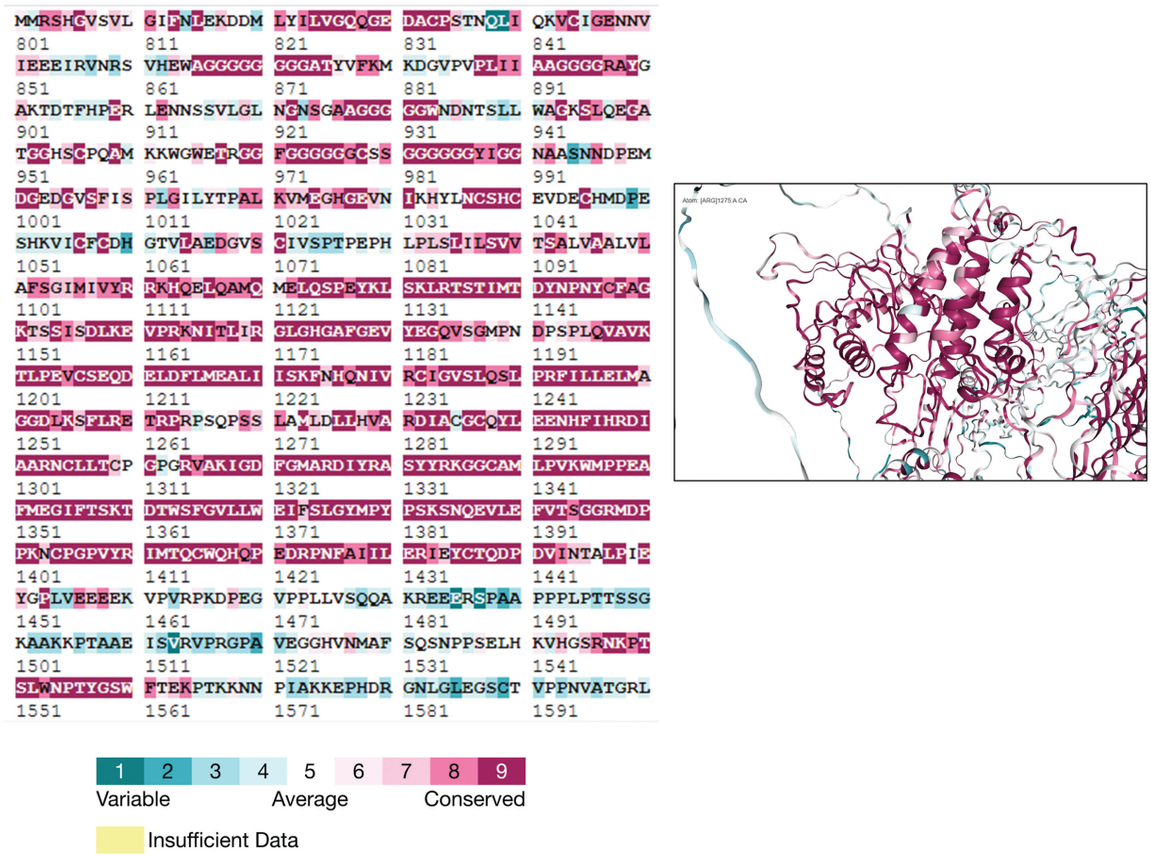


Fig. 2 Amino acid conservation analyzed using Consurf server and tertiary structure of anaplastic lymphoma kinase (ALK) protein representing the conserved region shown in dark purple color.

variants R1275Q/L, F1174L/V/C, and F1245V/C exhibited binding energies greater than –9.458 to –9.988 kcal/mol and displayed strong hydrogen bond interactions with the ALK protein (►**Suppl. Table 2**). This indicates that the mutant structures have a higher affinity for binding the drug molecule within the active site of the ALK protein, thereby increasing the overall binding affinity.[28]

Molecular Dynamics

A MD simulation was executed to evaluate the stability and dynamics of the wild-type and mutant ALK protein structures. Molecular docking results revealed no significant changes in the docking score or interactions for the mutants F1174L/V/C and F1245V/C complexes. Consequently, one mutant was selected for each position and subjected to further MD studies. The study included four mutant structures (I1171N, R1275Q, F1174L, and F1245V) along with the wild-type structure. Analysis of the RMSD of the studied complexes indicated that the wild-type structure remained stable throughout the simulation period. However, the mutant structures displayed notable instability and substantial fluctuations, indicating structural alterations compared with the wild-type. During the simulation, the variants F1174L and I1171N demonstrated stable RMSD values throughout the entire duration, as shown in ►**Fig. 3**. Initial deviations observed were attributed to the stabilization of the protein's equilibrium state. Conversely, the variants R1275Q and F1245V exhibited unstable RMSD values when compared with the wild-type, as depicted in ►**Fig. 4**. Even after 300 nanoseconds of simulation, these mutant structures remained unstable, with a difference of 2 Å in deviation. Analyzing the root mean square fluctuation of ALK protein residues revealed a significant fluctuation in the plot for amino acids 1150 to 1160, which are in proximity to the mutant positions 1171 and 1174 (►**Suppl. Fig. 2**). While other variants showed substantial fluctuations, the I1171N and F1174L mutants displayed lesser fluctuations due to the structural changes they introduce. The remaining residues

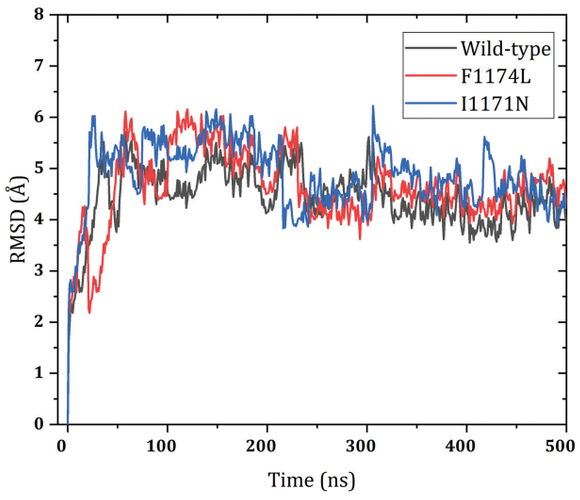


Fig. 3 Root-mean-square deviation (RMSD) plot of the least deviated protein mutant complex with wild-type obtained from molecular dynamics (MD) simulation study.

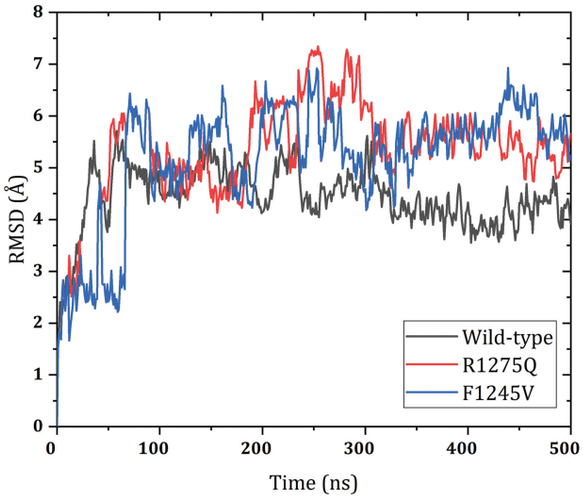


Fig. 4 Root-mean-square deviation (RMSD) plot of the most deviated protein mutant complex with wild type obtained from molecular dynamics (MD) simulation study.

exhibited stability with an average deviation of 3 Å, with similar changes observed in the loop region of the protein.

Discussion

The computational prediction in this study provides valuable insights into the functional and structural effects of the identified mutations in the ALK protein. The analysis revealed that all the studied mutations had deleterious or damaging effects on the protein structure, resulting in reduced stability and potentially affecting protein function. Interestingly, certain prediction tools predicted a few of the studied mutations, namely I1171N, L1196M, and F1174L, to be neutral or benign, in contrast to the deleterious effects predicted by other tools and software. Residue conservation analysis indicated that the mutated positions in the protein sequence were highly conserved, with a Consurf score of 9, suggesting their importance for protein function. Mutations in these positions directly impact function through structural and functional changes. Molecular docking results demonstrated that the mutant structures exhibited better binding scores (∼ –9.80 kcal/mol) compared with the wild-type (–5.89 kcal/mol), indicating potential alterations in ligand binding sites. The interacting amino acid residues, specifically Glu197 and Met1199, were found to be commonly present in all structures. However, Ala200 was observed only in the wild-type and L1196M mutant structures. Interestingly, the mutant structures with higher docking scores exhibited interactions with the Asp1203 residue. This clearly demonstrates that the interaction with Asp1203 residue enhances the binding affinity. The mutations in and around the active site of the protein disrupt the cavity and create a favorable region for drug binding. Furthermore, MD simulations revealed that the mutant structures displayed instability and substantial fluctuations, suggesting structural alterations. Hence, the promising binding affinity observed in the mutant complexes during the

docking studies may not be sustained, as their considerable structural fluctuations observed in the dynamics simulation suggest potential instability (> 3Å) and alterations that could affect their binding interactions. Based on the observations, the mutant structures R1275Q and F1245V exhibited good docking scores. However, during the simulation, the stability of the complex was found to be consistently unstable. In contrast, both the wild-type and mutant structures I1171N and F1174L, despite having low docking scores, demonstrated high stability during the simulation. This suggests that the binding affinity of the drug molecule in the mutant structure may be compromised in a dynamic environment. Overall, these findings underscore the significance of the studied nsSNPs in the ALK protein's function and stability, providing a basis for further exploration and understanding of their role in pediatric cancers and potential implications for targeted therapies. Moreover, as a prospective study, it would be beneficial to generate clinical correlation and genetic data through clinical trials or pharmacogenomic studies. This additional information would contribute to a better understanding and management of this condition, enabling more personalized and effective approaches to treatment.

Conclusion

Computational prediction and screening of deleterious SNPs consistently offer significant contributions to disease diagnosis and treatment. The variants studied in the ALK protein were predicted to be deleterious and had a significant impact on modulating protein function, according to a series of computational analyses. The pathogenic nature of these variants was further supported by their location in highly conserved regions of the protein. Comparisons with wild-type variants showed changes in binding affinity during molecular docking studies. Additionally, MD simulations revealed destabilization of protein structure and higher fluctuation in variant structures compared with wild-type. Further pharmacogenomics studies can help correlate these findings with experimental data to better understand the molecular mechanisms underlying the devastating impact of ALK protein in pediatric cancers. These results, along with patient clinical data, can be used to draw conclusions regarding the role of specific SNPs in pediatric cancer susceptibility, progression, and potential therapeutic implications.

Financial Support
None.

Conflict of Interest
None declared.

References

1 Bresler SC, Weiser DA, Huwe PJ, et al. ALK mutations confer differential oncogenic activation and sensitivity to ALK inhibition therapy in neuroblastoma. Cancer Cell 2014;26(05):682–694
2 Roskoski R Jr. Anaplastic lymphoma kinase (ALK): structure, oncogenic activation, and pharmacological inhibition. Pharmacol Res 2013;68(01):68–94
3 Gridelli C, Peters S, Sgambato A, Casaluce F, Adjei AA, Ciardiello F. ALK inhibitors in the treatment of advanced NSCLC. Cancer Treat Rev 2014;40(02):300–306
4 Mossé YP. Anaplastic lymphoma kinase as a cancer target in pediatric malignancies. Clin Cancer Res 2016;22(03):546–552
5 Roskoski R Jr. The preclinical profile of crizotinib for the treatment of non-small-cell lung cancer and other neoplastic disorders. Expert Opin Drug Discov 2013;8(09):1165–1179
6 Schönherr C, Ruuth K, Yamazaki Y, et al. Activating ALK mutations found in neuroblastoma are inhibited by Crizotinib and NVP-TAE684. Biochem J 2011;440(03):405–413
7 Infarinato NR, Park JH, Krytska K, et al. The ALK/ROS1 inhibitor PF-06463922 overcomes primary resistance to crizotinib in ALK-driven neuroblastoma. Cancer Discov 2016;6(01):96–107
8 Desai A, Lovly CM. Strategies to overcome resistance to ALK inhibitors in non-small cell lung cancer: a narrative review. Transl Lung Cancer Res 2023;12(03):615–628
9 Ando K, Manabe R, Kishino Y, et al. Comparative efficacy of ALK inhibitors for treatment-naïve ALK-positive advanced non-small cell lung cancer with central nervous system metastasis: a network meta-analysis. Int J Mol Sci 2023;24(03):2242
10 Karachaliou N, Santarpia M, Gonzalez Cao M, et al. Anaplastic lymphoma kinase inhibitors in phase I and phase II clinical trials for non-small cell lung cancer. Expert Opin Investig Drugs 2017;26(06):713–722
11 Katayama R, Lovly CM, Shaw AT. Therapeutic targeting of anaplastic lymphoma kinase in lung cancer: a paradigm for precision cancer medicine. Clin Cancer Res 2015;21(10):2227–2235
12 Loganathan L, Kuriakose BB, Mushfiq S, Muthusamy K. Mechanistic insights on nsSNPs on binding site of renin and cytochrome P450 proteins: a computational perceptual study for pharmacogenomics evaluation. J Cell Biochem 2021;122(10):1460–1474
13 George Priya Doss C, Nagasundaram N, Chakraborty C, Chen L, Zhu H. Extrapolating the effect of deleterious nsSNPs in the binding adaptability of flavopiridol with CDK7 protein: a molecular dynamics approach. Hum Genomics 2013;7(01):10
14 Rajasekaran R, Sudandiradoss C, Doss CGP, Sethumadhavan R. Identification and in silico analysis of functional SNPs of the BRCA1 gene. Genomics 2007;90(04):447–452
15 Mi H, Muruganujan A, Thomas PD. PANTHER in 2013: modeling the evolution of gene function, and other gene attributes, in the context of phylogenetic trees. Nucleic Acids Res 2013;41(Database issue, D1):D377–D386
16 Johnson AD, Handsaker RE, Pulit SL, Nizzari MM, O'Donnell CJ, de Bakker PI. SNAP: a web-based tool for identification and annotation of proxy SNPs using HapMap. Bioinformatics 2008;24(24):2938–2939
17 Landau M, Mayrose I, Rosenberg Y, et al. ConSurf 2005: the projection of evolutionary conservation scores of residues on protein structures. Nucleic Acids Res 2005;33(Web Server issue):W299-302
18 Ashkenazy H, Abadi S, Martz E, et al. ConSurf 2016: an improved methodology to estimate and visualize evolutionary conservation in macromolecules. Nucleic Acids Res 2016;44(W1):W344-50
19 Carlus SJ, Almuzaini IS, Karthikeyan M, et al. Next-generation sequencing identifies a homozygous mutation in ACADVL associated with pediatric familial dilated cardiomyopathy. Eur Rev Med Pharmacol Sci 2019;23(04):1710–1721
20 Ogrizek M, Turk S, Lešnik S, et al. Molecular dynamics to enhance structure-based virtual screening on cathepsin B. J Comput Aided Mol Des 2015;29(08):707–712
21 Choudhry H, Alzahrani FA, Hassan MA, et al. Zika virus targeting by screening inhibitors against NS2B/NS3 protease. BioMed Res Int 2019;2019:3947245

22 Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem 2010;31(02):455–461
23 Release S. 2023–2: Maestro. New York, NY: Schrödinger, LLC; 2023
24 Loganathan L, Muthusamy K. Investigation of drug interaction potentials and binding modes on direct renin inhibitors. A computational modeling studies. Lett Drug Des Discov 2019;16(08):919–938
25 Loganathan L, Natarajan K, Muthusamy K. Computational study on cross-talking cancer signalling mechanism of ring finger protein 146, AXIN and Tankyrase protein complex. J Biomol Struct Dyn 2020;38(17):5173–5185
26 Jayaraman M, Loganathan L, Muthusamy K, et al. Virtual screening assisted discovery of novel natural products to inhibit the catalytic mechanism of Mycobacterium tuberculosis InhA. J Mol Liq 2021;335:116204
27 Loganathan L, Gopinath K, Sankaranarayanan VM, et al. Computational and pharmacogenomic insights on hypertension treatment: rational drug design and optimization strategies. Curr Drug Targets 2020;21(01):18–33
28 Loganathan L, Al-Haidose A, Ganesh Kumar A, et al. An in silico analysis of the impact of POLE mutations on cladribine docking. Eur Rev Med Pharmacol Sci 2022;26(20):7580–7593

Multiple Primary Malignancies: A Clinicopathological Profile of Patients at a Tertiary Center of North India—A Retrospective Hospital-Based Observational Study

Abdul W. Mir[1] Shaheena Parveen[2] Ifrah Ahmad[1] Shah Naveed[1] Syed N. Ahmad[3] Mir M. Hussain[3] Nazir A. Dar[4]

[1] Department of Surgical Oncology, Sheri Kashmir Institute of Medical Sciences, Srinagar, Kashmir, India
[2] Department of Gastroenterology, Sheri Kashmir Institute of Medical Sciences, Srinagar, Kashmir, India
[3] Department of Medical Oncology, Sheri Kashmir Institute of Medical Sciences, Srinagar, Kashmir, India
[4] Department of Radiation Oncology, Sheri Kashmir Institute of Medical Sciences, Srinagar, Kashmir, India

Address for correspondence Syed Nisar Ahmad, MD, DM, Department of Medical Oncology, Sheri Kashmir Institute of Medical Sciences, Soura, Srinagar 190011, India (e-mail: syednisar76@yahoo.co.in).

Ind J Med Paediatr Oncol 2024;45:52–60.

Abstract

Introduction The incidence, prevalence, as well as survival of cancer patients, is increasing day by day due to the use of screening and improved diagnostic modalities. Simultaneously, the development of multiple primary malignancies (MPMs) in cancer survivors is not uncommon in recent years, because of an improved understanding of biology and effective management of cancer in the form of local (i.e., surgery/radiotherapy) and systemic (chemotherapy/targeted therapy) treatment, leading to improved survival and subsequent development of more malignancies. The study was conducted to describe the clinicopathological profile of patients diagnosed with MPMs.

Objective To study the clinicopathological profile of MPMs and to look for treatment patterns of these patients.

Materials and Methods This was a retrospective hospital-based observational study. Medical records of 73 patients with MPMs, who were registered in the department of medical and surgical oncology between January 2016 and December 2018, were enrolled in the study. The statistical analysis was done by using IBM SPSS Statistics for Windows from IBM Corp. Categorical data were expressed in the form of frequencies and percentages.

Results Out of the total 73 patients, 2 patients were diagnosed to have triple malignancies and were excluded from the study for discussion purposes. Among 71 patients with double malignancies, 19 patients had synchronous and 52 had metachronous malignancies with synchronous to metachronous ratio of 1:2.73. The study included 39 men and 32 women with a male to female ratio of 1.21:1. Gastrointestinal system was the most common system involved in first primary as well as in second primary malignancy. Squamous cell carcinoma and adenocarcinoma equally were the

Keywords
- malignancy
- synchronous
- metachronous

article published online
May 12, 2023

DOI https://doi.org/10.1055/s-0043-1768051.
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

most common histologies seen in primary, whereas adenocarcinoma was the most common histology seen in second primary malignancy.

Conclusions The phenomenon of MPMs is not an uncommon presentation due to longer survival and side effects of treatment (radiotherapy/chemotherapy). It should always be kept in consideration in any cancer survivor during surveillance in order to detect it and treat at the earliest.

Background

Multiple primary malignancies (MPMs) in cancer patients are not very rare because of prolonged survival due to advances made in the treatment of cancer patients. The probability of recurrence or a secondary from the initial malignancy may delay treatment and impact the overall prognosis and survival, making the diagnosis of MPMs complicated. The most common presentation of MPMs is double malignancies.[1,2] MPMs were first described by Billroth[3] in 1889 and reported in a detailed study by Warren and Gates[4] in 1932. The criteria for diagnoses of MPM, as proposed by Warren and Gates, include: (1) histological confirmation of malignancy in both the index and second primary tumors; (2) there should be at least 2 cm of normal mucosa between the tumors; if the tumors are in the same location, then they should be separated in time by at least 5 years; (3) probability of one being the metastasis of the other must be excluded.

Double primary malignancies could be divided into two categories, depending upon the interval between tumor diagnoses. Synchronous malignancies are defined where second tumor develops simultaneously or within 6 months after the diagnosis of first malignancy, whereas in metachronous malignancies, second tumor develops after 6 months or more after the diagnosis of the first malignancy.[5]

The aim of our study was to assess the clinical and pathological profile of patients diagnosed with MPMs in our region.

Material and Methods

This was a retrospective hospital-based observational study. Medical records of 73 patients with MPMs who were registered in the department of medical and surgical oncology between January 2016 to December 2018 were enrolled in the study. The patient's details were entered in a set proforma, which include age, sex, family history, smoking and drinking history, histology of synchronous and metachronous lesions, and treatment received.

Inclusion Criteria

Patients with two or more lesions at different sites with different histology or those with two lesions at different sites with similar histology but with different immunohistochemistry markers were included in the study. The tumors were divided into synchronous and metachronous lesions depending upon the time interval between the occurrence of two lesions. Synchronous tumors developed simultaneously or within 6 months of each other, whereas metachronous lesion occurred more than 6 months apart from each other.

Exclusion Criteria

Patients with malignancy at different sites but with same immunohistochemistry or disease at same site within 5 years of first malignancy were excluded from the study.

Sample Size

Sample size was calculated by using the Cochran's formula $n = (1.96)^2 p(1\text{-}P)/d^2$, $p = 0.73\%$, $d = 0.10\%$, and thus, the calculated sample size is 76. Case records of three patients were incomplete and were excluded from the study, so the final sample size of our study was 73 patients having 85% power of study.

Primary Outcome

To study the clinicopathological profile of MPMs.

Secondary Outcome

To study the treatment patterns of MPM patients.

Statistical Analysis

The data analysis was done on a computer running Microsoft Windows. The data were initially entered into a Microsoft Excel spreadsheet to be checked for mistakes. The IBM Corp.'s IBM SPSS Statistics for Windows was used for the statistical analysis (released 2020, Version 27.0. Armonk, New York, USA). The frequency and percentage representations of categorical variables were displayed.

Results

Out of 13,852 newly diagnosed cancer cases, 73 patients were diagnosed to have MPMs comprising of 0.51% of the total cases enrolled during the study. Two patients had triple malignancies, whereas 71 patients had double malignancies. In the two patients with triple malignancy, one had non-Hodgkin's lymphoma and developed metachronous squamous cell carcinoma of esophagus and adenocarcinoma of sigmoid colon. In another patient with index squamous cell carcinoma of skin (thigh), developed two metachronous malignancies, i.e., renal cell carcinoma and adenocarcinoma stomach. For rest of discussion purposes, we will exclude triple malignancies. Of the 71 cases of double malignancy, 39

(54.92%) were men and 32 (45.07%) were women with a male to female ratio of 1.21:1. Median age of our patients was 55 (30–80) with median time to diagnosis of second cancer of 36 months (12–228).

Among the 71 patients with MPMs, 52 patients harbored metachronous double malignancies, whereas 19 patients harbored synchronous double malignancies with metachronous to synchronous malignancy ratio of 2.73:1. The most common systems involved in primary cancer were gastrointestinal system (GI; 22; 30.99%), breast (8; 11.27%), reproductive (8; 11.27%), urinary tract (8; 11.27%), and head and neck (7; 9.86%), whereas in second primary cancer most common systems involved were GI (28; 39.43%), lung (12; 16.9%), reproductive (8; 11.27%), head and neck (8; 11.27%), and breast (4; 5.63%), with esophagus (8; 11.26%), stomach (7; 9.85%), and breast (7; 9.85%) being the most common organs involved in primary cancers, whereas lung (12; 16.90%), colorectal (9; 12.67%), and stomach (8; 11.26%) being the most common organs involved in second primary cancers (►**Table 1**, ►**Fig. 1**). Squamous and adenocarcinoma were equally distributed (16 cases each; 22.53%), the most common histologies involved in primary cancers, whereas adenocarcinoma (22; 30.99%) followed by squamous cell carcinoma (18; 25.35%) were as the most common histologies in second primary cancers (►**Supplementary Fig. S1**, available in the online version). Of the 71 patients with MPMs, 20 (28.17%) were treated with surgery, 14 (19.71%) with surgery + chemotherapy, 10 (14.08%) with chemotherapy + radiotherapy, whereas in second primary malignancy, 15 (21.12%) underwent surgery; 13 (18.30%) chemotherapy + radiotherapy, and 10 (14.08%) patients received surgery + chemotherapy (►**Tables 2** and **3**, ►**Supplementary Fig. S2** [available in the online version])

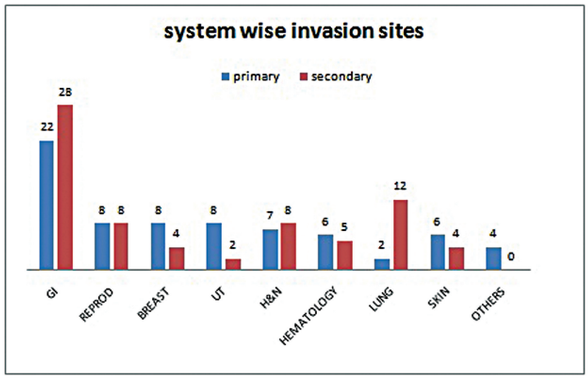


Fig. 1 System wise invasion sites.

Discussion

Recently, there has been a sharp increase in the prevalence of MPMs, ranging from 0.7 to 11.7% among various populations.[6] This can be due to multitude of reasons including the improved survival of cancer patients due to improved treatment modalities, better diagnostic modalities, and more stringent surveillance of cancer survivors.[7] The prevalence of MPMs in the studied group was 0.51%.

MPMs are a special phenomenon in the tumorigenesis. A number of studies have been conducted worldwide leading to better understanding of this phenomenon. The etiopathogenesis of MPMs can be attributed to genetic events or the common environmental risk factors.[8] Various other mechanisms like aging, an unhealthy lifestyle, cancer treatments, or interactions between any of these factors are also believed to contribute to the development of MPMs.[9] The increased risk of MPMs can be attributed to field carcinogenesis due to exposure to tobacco, smoking, and alcohol consumption.[10] In our study population, 32% patients had smoking history, and none had history of alcohol consumption.

The treatment of primary malignancy by chemotherapy and/or radiotherapy may contribute to increased risk of second malignancy as both ionizing radiation and cytotoxic agents (etoposide, cyclophosphamide, and Adriamycin etc.) can cause DNA damage leading to carcinogenesis. The harmful effects of these treatments as well as of the tumor microenvironment on the patient's immune system may be an important contributing factor allowing future renegade mutant cancer cells from

Table 1 System wise invasion sites

Site	Primary	%	95% CI		Second primary	%	95% CI	
			Lower	Upper			Lower	Upper
Gastrointestinal	22	30.99	20.00	43.00	28	39.44	28.00	51.00
Reproductive	8	11.27	4.00	21.00	8	11.27	4.00	21.00
Breast	8	11.27	4.00	21.00	4	5.63	1.00	13.00
Urinary tract	8	11.27	4.00	21.00	2	2.82	0.30	9.00
Head and neck	7	9.86	4.00	19.00	8	11.27	4.00	21.00
Hematology	6	8.45	3.00	17.00	5	7.04	2.00	15.00
Lung	2	2.82	0.30	9.00	12	16.90	9.00	27.00
Skin	6	8.45	3.00	17.00	4	5.63	1.00	13.00
Others	4	5.63	1.00	13.00	0	0.00	–	–

Abbreviation: CI, confidence interval.

Table 2 Summary of synchronous primary malignancies

S No.	Age	Sex	Primary site	Histopathology	Treatment	Second primary	Histopathology	Treatment
1	48	F	Esophagus (20 cm)	SCC	CT-RT	Esophagus (34-37 cm)	SCC	CT-RT
2	80	M	Prostate	Adenoca	GnRH analogues	Thyroid	Papillary carcinoma	Total thyroidectomy
3	36	M	Prostate	Adenoca	Local R/T	Bladder	Malignant paraganglioma	Radiotherapy
4	40	F	Ovary	Endometriod carcinoma	TAH + BSO (OCR) +Chemo	Uterus	Endometrial carcinoma	TAH/BSO done as part of ca ovarian staging
5	41	F	Breast	IDC	BCS + ALND + radiotherapy + chemo	Thyroid	Papillary carcinoma	Total Thyroidectomy
6	60	M	Tongue	SCC	WLE + radiotherapy	Gall bladder	Adenoca	Radical cholecystectomy
7	60	M	Esophagus	SCC	CT-RT	Lung	Adenoca	CT-RT
8	60	M	Urinary Bladder	TCC	TURBT	Lung	Adenoca	CT-RT
9	65	M	Oral cavity	SCC	WLE	Thyroid	PTC	Total thyroidectomy
10	55	M	Stomach	Adenoca	Palliative care	Liver	Hepatocellular carcinoma	Palliative care
11	75	M	Cervical node	NHL	CT + RT	Esophagus	SCC	CT-RT
12	67	M	Esophagus	SCC	CT-RT	Lung	SCC	CT-RT
13	65	M	Stomach	Adenoca	NACT + surgery + adjuvant chemo	Colon	Adenoca	Left hemicolectomy
14	60	M	Esophagus	SCC	CT-RT	Lung	SCC	CT-RT
15	30	F	Ovary	HGS Ca	Surgery/optimal cytoreduction + chemo	Endometrium (1b)	Endometrial Ca	EBRT
16	46	F	Endometriod Ca of ovary	TAH + BSO (OCR)	Observation	Endometrium	Endometrial Adenoca (1A)	Observation (sx already done)
17	50	M	GE junction	Adenoca	Palliative chemo	Larynx	SCC	Palliation
18	50	M	RCC	Clear cell	Immunotherapy	Lung	Adeno	Immuno + chemo
19	55	F	Breast	IDC	Chemo	Ovary	HGS Ca	Chemo

Abbreviations: Adeno, adenocarcinoma; ALND, axillary lymph node dissection; BCS, breast conservative surgery; Chemo, chemotherapy; CLL, chronic lymphocytic leukemia; CT-RT, chemoradiation; DLBCL, diffuse large B cell lymphoma; HGS, Ca-high-grade serous carcinoma; IDC, infiltrating duct ca; NACT, neoadjuvant chemotherapy; NHL, non-Hodgkin's lymphoma; OCR, optimal cytoreduction; PSC, papillary serous adenocarcinoma; PTC, papillary thyroid carcinoma; RAIA, radioactive iodine ablation; RT, radiation therapy; SCC, squamous cell ca; Sx., surgery; TAH, total abdominal hysterectomy with salpingo-oopherectomy; TCC, transitional cell carcinoma; TURBT, transurethral resection of bladder tumor; WLE, wide local excion.

escaping the body's defense mechanisms. Children and young adults may be especially prone to such iatrogenically induced cancers.[11] This was also seen in our patient population, as around 40% of the patients in total and 51.71% patient in metachronous group had received either chemotherapy/radiotherapy or both as treatment for their primary cancers.

In the present study, the incidence of multiple primaries was more common in men as compared with women with a male to female ratio of 1.21:1. Although MPMs can occur at any age, there are several studies that show that incidence is more in older patient population.[12–16] The median age in our study was 55 years (range 30–80 years). Etiz et al in their study had male to female ratio of 1.19:1 with a median age of 59 years (range 29–80 years),[17] consistent with our study. The interval between index primary and second primary in our study was 12 to 228 months (median 36 months), which is consistent with other studies[9,18] (comparison between different studies given in ►**Table 4**).

The ratio of synchronous to metachronous malignancies varies in different studies.[19–22] In a study by Aydiner et al,[14] synchronous malignancies constituted 34%, whereas metachronous malignancies constituted 66%, consistent with our study with synchronous and metachronous malignancy of 27 and 73%, respectively. The most common system involved in first primary as well as second primary malignancy in our study was GI (30.99 and 39.44%) with lung being the most

Table 3 Summary of metachronous double malignancies

S.no	Age	Sex	Primary site	Histopathology	Treatment	Second primary	Histopathology	Treatment	Time interval (mo)
1	51	F	Thyroid	Follicular carcinoma	Total thyroidectomy + RAIA	Blood	CLL	Chemotherapy + targeted therapy	84
2	60	F	Kidney	Clear cell carcinoma	Right radical nephrectomy	Left kidney	Clear cell carcinoma	Sunitinib	24
3	40	F	Skin	Mycosis fungoids	Phototherapy	Ovary	PSCa	Surgery (OCR) + chemotherapy	60
4	70	M	Lymph node	NHL(DLBCL)	Chemotherapy + targeted	Esophagus	SCC	Chemoradiation	24
5	55	M	Lymph node	NHL (small cell type)	Chemotherapy	Blood	CLL	Chemotherapy	12
6	50	F	Colon	Malignant carcinoid	Right hemicolectomy + chemotherapy	Cheek (skin)	Basal cell carcinoma	WLE	12
7	55	F	Cervix	SCC	CT-RT	Labia majora (skin)	SCC	WLE	48
8	41	F	Lung	Adenoca	CT-RT	Choroid	Melanoma	Enucleation of eyeball	24
9	55	M	Urinary bladder	Papillary carcinoma	TURBT + chemotherapy	Colon	Adenoca	Hemicolectomy + chemotherapy	60
10	55	F	Uterus	Adenoca	TAH + BSO	Rectum	Adenoca	Chemoradiation	12
11	35	M	Right kidney	Chromo-phobe carcinoma	Radical nephrectomy	Thyroid	PTC	Total thyroidectomy	12
12	58	F	Skin	SCC	WLE	Stomach	Adenoca	Supportive care	60
13	50	F	Colon	Adenoca	Left hemicolectomy	Uterus	Endometrial carcinoma	TAH + BSO	72
14	67	F	Ovary	Papillary carcinoma	NACT + surgery	Breast	IDC	MRM	24
15	55	F	Uterus	Adenoca	TAH + BSO	Gall bladder	Adenoca	Chemotherapy	24
16	65	M	Skin	SCC	WLE	Esophagus	SCC	CT-RT	12
17	51	F	Thyroid	Follicular ca	Total thyroidectomy	Blood	CLL	Chemotherapy + targeted	84
18	40	F	Rectum	Adenoca	Anterior resection + CT-RT	Uterus	Adenoca	TAH + BSO + radiotherapy	192
19	52	M	Esophagus	SCC	CT-RT	Lung	SCC	Chemotherapy	36
20	55	F	Eyelid	Merkel cell carcinoma	WLE	Breast	IDC	MRM + chemotherapy	12

 © 2023. The Author(s).

Table 3 (*Continued*)

S.no	Age	Sex	Primary site	Histopathology	Treatment	Second primary	Histopathology	Treatment	Time interval (mo)
21	48	F	Breast	IDC	MRM + chemotherapy	Colon	Adenoca	Hemicolectomy + chemotherapy + radiotherapy	48
22	70	M	Colon	Adenoca	Hemicolectomy + chemotherapy	Lung	SCC	Chemotherapy	36
23	60	M	Lung	SCC	CT-RT	Skin	SCC	WLE	36
24	50	F	Gall bladder	Adenoca	Radical cholecystectomy	Stomach	Adenoca	Distal gastrectomy + chemotherapy	24
25	68	M	Esophagus	SCC	Surgery + chemotherapy	Lung	SCC	CT-RT	192
26	55	M	Bladder	TCC	TURBT	Stomach	Adenoca	Distal gastrectomy + CT-RT	36
27	76	M	Bladder	TCC	TURBT + intravesical BCG	GE junction	SCC	Chemotherapy	180
28	40	F	Breast	IDC	MRM + Chemo + RT	Ovary	HGS Ca	Surgery (OCR) + Chemo	84
29	50	M	Esophagus	SCC	Surgery + radiotherapy	Stomach	Neuroendocrine tumor (G1)	Distal gastrectomy	96
30	75	M	Lymph node	NHL	Chemotherapy	Stomach	Adenoca	Defaulted	36
31	56	M	Blood	CLL	Chemotherapy	Lip	Merkel cell carcinoma	WLE + radiotherapy	228
32	60	M	Skin	SCC	WLE + chemotherapy	Lung	SCC	CT-RT	12
33	65	F	Lymph node	NHL	Chemotherapy	Rectum	Adenoca	CT-RT	48
34	50	M	Stomach	Adenoca	NACT with distal gastrectomy + adjuvant chemotherapy	Blood	DLBCL	Supportive care	36
35	70	M	Skin	SCC	WLE	Esophagus	SCC	Radiotherapy	36
36	65	M	Skin	Basal cell carcinoma	WLE	Lung	SCC	Radiotherapy	36
37	55	M	Colon	Adenoca	Hemicolectomy with chemotherapy	Esophagus	Adenoca	Chemotherapy	36
38	40	F	Breast	IDC	MRM	Brain	Meningioma	Observation	12
39	62	M	Spinal cord	Ependymoma	Laminectomy with excision	Blood	CML	Imatinib	60

(*Continued*)

Table 3 (*Continued*)

S.no	Age	Sex	Primary site	Histopathology	Treatment	Second primary	Histopathology	Treatment	Time interval (mo)
40	70	M	Stomach	Adenoca	NACT + total gastrectomy + adjuvant chemotherapy	Rectum	Adenoca	Palliative care	36
41	51	F	Breast	IDC	MRM + chemo + RT	Esophagus	SCC	CT-RT	96
42	55	F	Esophagus	SCC	CT-RT	Stomach	SCC	Palliative care	24
43	55	M	Stomach	Adenoca	Chemo + surgery	Colon	Adenoca	Sx + chemo	20
44	60	F	Breast	IDC	Sx + chemo + RT + hormones	Gallbladder	adeno	Surgery	60
45	65	M	Gastric	GIST	Sx + imatinib	Stomach	Adeno	Sx + chemo	12
46	75	M	Bone marrow	Multiple myeloma	Chemo + immuno	Colon	Adeno	Sx + chemo	36
47	80	M	Colon	Adenocarcinoma	Sx + chemo	Lung	Adeno	Chemo	96
48	56	F	Breast (right)	IDC	Sx + chemo + hormones	Breast (Left)	IDC	Sx + chemo + hormones	108
49	75	F	Thyroid	Papillary carcinoma	Sx + RAIA	Breast	IDC	Sx + chemo + radiotherapy	204
50	45	F	Uterus	Endometrial ca	Surgery (1A)	Periampullary ca	Adenoca	Surgery	48
51	53	M	Kidney	Clear cell ca	Surgery (1B)	Lung	Squamous cell	Chemo	84
52	47	F	Thyroid	Papillary carcinoma	Surgery	Lung	Adeno	TKI	96

Abbreviations: Adeno, adenocarcinoma; ALND, axillary lymph node dissection; BCS, breast conservative surgery; Chemo, chemotherapy; CLL, chronic lymphocytic leukemia; CT-RT, chemoradiation; DLBCL, diffuse large B cell lymphoma; HGS, Ca-high-grade serous carcinoma; IDC, infiltrating duct ca; NACT, neoadjuvant chemotherapy; NHL, non-Hodgkin's lymphoma; OCR, optimal cytoreduction; PSC, papillary serous adenocarcinoma; PTC, papillary thyroid carcinoma; RAIA, radioactive iodine ablation; RT, radiation therapy; SCC, squamous cell ca; Sx., surgery; TAH, total abdominal hysterectomy with salpingo-oopherectomy; TCC, transitional cell carcinoma; TURBT, transurethral resection of bladder tumor; WLE, wide local excion.

Table 4 Multiple primary malignancies: comparison of different studies

Study (ref. No)	Total no. of patients	No. of patients with multiple primary malignancies		Synchronous/ metachronous	Male/ female	Median age (metachronous group)		Common site		Median interval between index and second primary (mo)
		No.	%			Index primary	Second primary	Index primary	Second primary	
Vadgaonkar et al[18]	16,461	44	0.26	7/37	13/31	48	56	Gynecological	Gynecological	38
								Breast	Gastrointestinal	
								Head and neck	–	
Etiz et al[17]	9,772	122	1.2	36/86	67/55	56	62	Lung	Lung	–
								Gastrointestinal	Gastrointestinal	
								Genitourinary	Genitourinary	
Zhai et al[9]	15,321	167	1.09	98/69	117/50	62	64	Gastrointestinal	Gastrointestinal	31.15
								lung	lung	
								Head and neck	Head and neck	
Bisht et al[7]	3,879	29	0.74	8/21	10//19	54	56	Breast	Gastrointestinal	–
								Head and neck	Head and neck	
								Lung	Lung	
Irimie et al[8]	–	63	–	24/41	34/29	58.2 y in entire group		Genital	Breast	–
								Breast	Gastrointestinal	
								Gastrointestinal	Lung	
Present study	13,852	71	0.51	19/52	39/32	55 y in entire group		Gastrointestinal	Gastrointestinal	36
								Breast	Lung	
								Reproductive	Reproductive	

common second primary malignancy after GI (16.9%). In a retrospective study, Zhai et al[9] found that the most common pairs were digestive–digestive (25.75%) followed by digestive–lung pairs (19.16%), which coincides with our findings. In another study conducted by Etiz et al, the most common second primary malignancies were GI (22%) and lung (19%), similar to present study.[17] There is high prevalence of GI malignancies in this region of country, which is presumed due to geographic, dietary, and cultural reasons. In a study from the region by Khan et al,[23] which included 22,180 patients, cancer of esophagus, stomach, and colon were second, third, and sixth most common causes of cancer incidence. This could explain the reason for GI tract being the most common site in both synchronous and metachronous groups.

The possibility of existence of MPMs must always be considered during pretreatment evaluation. There is some evidence that screening will improve outcomes among patients who may develop second malignancies, although the data are limited. The optimal screening modalities and strategies to reduce mortality from second malignancies remain to be defined for most tumor sites.[21] With careful monitoring, second primary tumors can be detected early, and with appropriate intervention might be better managed, without compromising survival.

A sizable prospective study needs to be conducted to better understand the profile and outcome of MPMs in order to better develop the various strategies for screening and early identification of second primary malignancies and to enhance outcomes.

Limitations

The small sample size and retrospective nature of our study are its primary limitations.

Conclusion

In conclusion, second primary malignancies are not rare. They can be synchronous or metachronous. Improvements in diagnostic and staging modalities and improved survival after management of primary cancers have increased the detection of second primary malignancies. A strong clinical suspicion and thorough evaluation would be beneficial in the management of these tumors. A regular follow-up in a patient diagnosed and treated for primary malignancy would help not only to detect recurrence but also could detect most of the metachronous second primary malignancies at an early stage.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the guidelines of the Institutional Ethics Committee (IEC) and approved on January 31, 2022 vide IEC SKIMS No: 2022-34 of the Sheri Kashmir Institute of Medical Sciences (SKIMS), Srinagar. This

study was conducted in accordance with the Declaration of Helsinki. As this was a retrospective audit of the hospital records, the full consent of the patients was waived by Institutional Ethics Committee, SKIMS, Srinagar.

Consent for Publication
Not Applicable.

Authors' Contributions
A.W.M., S.P., and S.N. designed the study and oversaw the research. A.W.M., S.N., I.A., S.N., and N.A.D. developed the concept and drafted the manuscript. S.N. and N.A.D. prepared the tables and figures. A.W.M., S.N., I.A., N.S., S.P., M.H., and N.A. check data for accuracy, contributed to data preparation and analysis. A.W.M., S.N., I.A., N.S., S.P., M.M.H., and N.A. reviewed the results. A.W.M., S.N., I.A., N.S., S.P., M.M.H., and N.A.D. reviewed all versions of the manuscript. A.W.M., S.N., I.A., N.S., S.P., M.M.H., and N.A.D. finalized the manuscript. All authors reviewed the finalized manuscript. The author(s) read and approved the final manuscript.

Funding
None.

Conflict of Interest
None declared.

Acknowledgments
The authors would like to sincerely thank the Department of Medical Records for their support for data collection.

References
1 Noh SK, Yoon JY, Ryoo UN, et al. A case report of quadruple cancer in a single patient including the breast, rectum, ovary, and endometrium. J Gynecol Oncol 2008;19(04): 265–269
2 Lee JS, Moon W, Park SJ, et al. Triple synchronous primary cancers of rectum, thyroid, and uterine cervix detected during the workup for hematochezia. Intern Med 2010;49(16):1745–1747
3 Billroth T. General Surgical Pathology and Therapy in 51 Lectures: A Handbook for Students and Physicians. 14th ed. Berlin, Germany: Reimer; 1889:908
4 Warren S. Multiple malignant tumors. A survey of the literatures and statistical study. Am J Cancer 1932;16:1358–1414
5 Suzuki T, Takahashi H, Yao K, et al. Multiple primary malignancies in the head and neck: a clinical review of 121 patients. Acta Otolaryngol Suppl 2002;(547):88–92
6 Amer MH. Multiple neoplasms, single primaries, and patient survival. Cancer Manag Res 2014;6:119–134
7 Bisht N, Singh S, Sarin A, et al. The conundrum of dual primary malignancies: four years' experience of a single tertiary care institute in India. Indian J Med Paediatr Oncol 2019; 40:521–530
8 Irimie A, Achimas-Cadariu P, Burz C, Puscas E. Multiple primary malignancies–epidemiological analysis at a single tertiary institution. J Gastrointestin Liver Dis 2010;19(01):69–73
9 Zhai C, Cai Y, Lou F, et al. Multiple primary malignant tumors - a clinical analysis of 15,321 patients with malignancies at a single center in China. J Cancer 2018;9(16):2795–2801
10 Cheng HY, Chu CH, Chang WH, et al. Clinical analysis of multiple primary malignancies in the digestive system: a hospital-based study. World J Gastroenterol 2005;11(27):4215–4219
11 Curtis RE, Freedman DM, Ron E, et al. New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973-2000. Bethesda, MD: National Cancer Institute; 2006:9–14
12 Hajdu SI, Hajdu EO. Multiple primary malignant tumors. J Am Geriatr Soc 1968;16(01):16–26
13 Berge T, Cederqvist L, Schönebeck J. Multiple primary malignant tumours. an autopsy study of a circumscribed population. Acta Pathol Microbiol Scand 1969;76(02):171–183
14 Aydiner A, Karadeniz A, Uygun K, et al. Multiple primary neoplasms at a single institution: differences between synchronous and metachronous neoplasms. Am J Clin Oncol 2000;23(04): 364–370
15 Lee TK, Barringer M, Myers RT, Sterchi JM. Multiple primary carcinomas of the colon and associated extracolonic primary malignant tumors. Ann Surg 1982;195(04):501–507
16 Vyas JJ, Deshpande RK, Sharma S, Desai PB. Multiple primary cancers in Indian population: metachronous and synchronous lesions. J Surg Oncol 1983;23(04):239–249
17 Etiz D, Metcalfe E, Akcay M. Multiple primary malignant neoplasms: a 10-year experience at a single institution from Turkey. J Cancer Res Ther 2017;13(01):16–20
18 Vadgaonkar RA, Nayak SS, Doni S, Digumarti L, Mullapally SK, Digumarti R. Distinct patterns of occurrence, common associations, and survival of patients with second primary malignancies: a 5-year single institute experience with review of literature. Indian J Pathol Microbiol 2021;64(04):725–731
19 Jena A, Patnayak R, Lakshmi AY, Manilal B, Reddy MK. Multiple primary cancers: an enigma. South Asian J Cancer 2016;5(01): 29–32
20 Lv M, Zhang X, Shen Y, et al. Clinical analysis and prognosis of synchronous and metachronous multiple primary malignant tumors. Medicine (Baltimore) 2017;96(17):e6799
21 Mehdi I, Shah AH, Moona MS, et al. Synchronous and metachronous malignant tumours expect the unexpected. J Pak Med Assoc 2010;60(11):905–909
22 Vogel VG. Identifying and screening patients at risk of second cancers. Cancer Epidemiol Biomarkers Prev 2006;15(11): 2027–2032
23 Khan NA, Ahmad Syed N, Dar NA, Masoodi SR, Lone MM. Changing pattern of common cancers in the last five years in Kashmir, India: a retrospective observational study. Int J Med Paediatr Oncol 2021;42:439–443

Surviving Colorectal Cancer: More Than Treatment

Belsiyal C. Xavier[1]

[1] College of Nursing, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India

Address for correspondence Belsiyal C. Xavier, PhD, Associate Professor, AIIMS, Rishikesh 249203, India (e-mail: jinbelsi@gmail.com).

Ind J Med Paediatr Oncol 2024;45:61–63.

Abstract

The main aim of this article is to contribute to a complete patient perspective on the psychosocial impact of colorectal cancer. The details included patient personal experience of being a colorectal cancer survivor and perception regarding psychosocial support during management of the illness. Health professionals should assume that patients may have difficulty in illness management and should encourage a discussion of patients' concerns.

Keywords

- colorectal cancer
- emotional distress
- personal experience
- psychosocial support

Introduction

I began to experience significant fatigue around the start of this year 2022, as well as weight loss that was not alarmingly rapid. I also observed that I was leaner than usual. I assumed that it was due to administrative responsibilities I took at my workplace. But soon after, I decided to get blood tests, and I started seeing a drop in my hemoglobin level (7.7 gm/dL). This alarming change made me realize that I should get blood tests, and it gave me a bad feeling. My physician suggested going for the fecal occult blood test, as there were no other bleeding issues. Out of three samples, one test was found to be positive. I was referred to a gastroenterologist who suggested I go for upper and lower endoscopies.

As there was no history of cancer in my family, I did undergo mammography a few months back for a routine screening; I was confident that there is no possibility of having a cancer diagnosis. Shockingly, after my colonoscopy, everything changed. I awoke from the anesthesia and got to know that I need to go for a computed tomography (CT) scan. While I was getting ready without knowing the exact diagnosis (though the gastroenterologist informed my husband about my diagnosis and they withheld the information from me), another doctor who assumed I was informed about my diagnosis came to meet me to discuss the treatment options and revealed the bad news. "We have discovered a mass, and you will need surgery. Do you intend to have surgery here or in South India?." I can still hear those frightening words. I felt like my blood was draining from my body and remember thinking, "This is cancer, and I could die, I am a mother of two young boys, how come this happened to me?." I was praying in my heart while I was prepared to go for a CT scan to look for metastasis. Thank God. There was no metastasis but there was the involvement of lymph nodes. The diagnosis was stage III colorectal cancer (CRC), and at that moment, I felt that was a dead end.

Four weeks after the colonoscopy, I went for an exploratory laparotomy. Though the postoperative period was uneventful, I was still going through a tough time as my biopsy report of resected colon mentioned that there were some abnormal genetic mutations. The oncologist I met with suggested that the mass in my colon is removed yet, I need to go for an adjuvant chemotherapy regimen of capecitabine and oxaliplatin for 6 months as I come under the high-risk group.

The emotional and physical struggles that I have gone through during my chemotherapy made me realize that psycho-oncological counseling in India is not much addressed as it is supposed to be. I began to realize the pain of having a cancer diagnosis. When you are uncertain about whether the rest of your life will be measured in months, years, or decades, you tend to concentrate more on what's happening right now and what matters in your life. I was aware that I wanted to repay the oncology community

article published online
April 24, 2023

DOI https://doi.org/10.1055/s-0043-1768242.
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

for everything that it had done for me. My personal experience with cancer has inspired me to seek out strategies for increasing public awareness of CRC, particularly in younger persons.

At first, I believed that "my close relatives and friends from the church community have been the key support." Support from the medical personnel that was deemed appropriate and sensitive was extremely helpful, but I frequently preferred support from friends.

Cancer changes everything; "the longer the treatment goes, obviously, the more people sort of move on and don't make contact anymore, so that sort of made me feel a little bit alone."

Our lives were significantly impacted by the social isolation brought on by the disease. Social isolation and several treatments had a direct correlation, "I hardly ever go outside. It's challenging when my life has been consumed by cancer. I was hesitant to ask for help because I didn't want to burden others or because I didn't want to seem weak."

Though it seemed to be supportive in and of itself, seeing someone else going through a similar experience gave me the impression that I am not going through this alone. "Well, I always knew that other cancer survivors were having the same experience.... I knew they were going through the same as me," "We can discuss topics that we probably won't discuss with anyone else." Even though it only lasted a short while, this shared experience opened the door to helpful relationships. I occasionally went out of my way to find people who had received the same diagnosis or therapy.

Much more crucial is the emotional support of our loved ones. In this way, "I had one [friend]...who was there the entire time, and I was in communication with him and, you know, he just listened and kept me updated and dropped in and, you know, that was a great support" (My husband's). When talking about emotional support, it is more important to focus on the quality of your relationships than the quantity of sources you have. Here, I give some insight into my experiences receiving psychosocial care as a CRC patient, an area that has not yet been thoroughly studied.

Emotional Distress during the Breaking of Bad News

The most common initial responses when receiving a diagnosis of cancer were disbelief and shock. Likewise, many reported breaking down upon receiving the news of their cancer diagnoses.[1] I thought I have temporary mental incapacity in which I felt blank and lost upon knowing that I have cancer. I was unable to comprehend any information that was given to me. I was extremely distressed because of worries about my young children's future in the event of my death.

Previous studies also reported having severe emotional distress experienced by people who had younger children. Yet, older participants coped better when informed of their cancer diagnoses because their children were independent and they were no longer the breadwinners of the family. Evidence revealed that persons with a family history of cancer were also relatively less shocked by the news of a cancer diagnosis.[2,3]

Psychosocial Support from Healthcare Workers

Patients and caregivers could benefit from support from having a good working relationship with the healthcare workers. In particular, it seems that the presence of this therapeutic relationship made the staff more approachable to patients and carers, promoting interaction and information-seeking. A noteworthy finding was the significance of both formal and informal communication with the treatment team. Notably, the findings showed how positive and respectful communication seems to affect patients' and carers' opinions of support.[4]

Existing literature proves that the use of active listening and empathy are the major elements of patient and provider communication in clinical settings.[5] Besides, negative experiences included negative interactions (not communicating in a compassionate and caring manner), being treated disrespectfully, feeling pressured by time constraints, and helplessness due to physical infirmity, based on the results of a recent systematic study of patient and healthcare provider communication.[4,6]

Due to the devastating nature of cancer, the stigma attached to it, and the sizeable psychosocial burden that can be brought on by the disease, positive communication may be even more important in the context of CRC oncology. It seems that in this situation, the healthcare professional-patient-caregiver interaction necessitates a high degree of compassion and trust, and as a result, effective communication is crucial.[4,6]

Peer Support/Shared Experience

Peer support can be particularly beneficial for patients with cancer. The majority of participants talked about becoming friends with cancer survivors they had met, and half said that getting treatment at a cancer center opened up opportunities for casual and social engagement with other patients.[1,7]

Emotional Support

It is widely documented in the literature that emotional support is important for both patients and carers; those who actively sought help had most of their needs met. Furthermore, it appears that the quality of support was crucial because even those who received less support indicated that it was worthwhile when they felt it was "appropriate."[1,7]

Overall, I was satisfied with the treatment, including the quality and timeliness of the information I received, the quality of their healthcare, and the level of involvement in decision-making. However, I was looking for psychological support for counseling to focus on a positive outlook on my illness experience. Despite the focus on positive change, I still have difficulty coping with the side effects of treatment.

In my opinion, I am still working on the ambiguity of my health, the need to accept the new normal, losing control and taking back control, experiencing positive and negative life changes, and the need to continually reframe my perspectives to focus on the positives.

Managing one's health after CRC may have specific challenges given long-term impacts on biopsychosocial functioning. Understanding experiences of managing one's health post-treatment is important to informing patient-centered supportive care.

Conflict of Interest
None declared.

Acknowledgement
The author would also like to thank the Almighty God, family members, friends, and treating team for enabling me to fight this battle.

References

1 Law E, Levesque JV, Lambert S, Girgis A. The "sphere of care": a qualitative study of colorectal cancer patient and caregiver experiences of support within the cancer treatment setting. PLoS One 2018;13(12):e0209436. Doi: 10.1371/Journal.Pone.0209436
2 Wong LP, Kong YC, Bhoo-Pathy NT, et al. Breaking news of cancer diagnosis: a qualitative study on the experiences and emotional needs of patients with cancer in a multiethnic Asian setting. JCO Oncol Pract 2021;17(04):e548–e555
3 Sahay TB, Gray RE, Fitch M. A qualitative study of patient perspectives on colorectal cancer. Cancer Pract 2000;8(01):38–44
4 Rocque R, Leanza Y. A systematic review of patients' experiences in communicating with primary care physicians: intercultural encounters and a balance between vulnerability and integrity. PLoS One 2015;10(10):e0139577. Doi: 10.1371/Journal.Pone.0139577
5 Kvrgic Z, Asiedu GB, Crowson CS, Ridgeway JL, Davis JM III. "Like No One Is Listening to Me": a qualitative study of patient-provider discordance between global assessments of disease activity in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2018;70(10):1439–1447
6 Shen MJ, Peterson EB, Costas-Muñiz R, et al. The effects of race and racial concordance on patient-physician communication: a systematic review of the literature. J Racial Ethn Health Disparities 2018;5(01):117–140
7 Cuthbert CA, Farragher JF, Farrer CL, Cheung WY. Living with paradox: a qualitative study of colorectal cancer patients' experiences in managing their health after cancer treatment. Eur J Cancer Care (Engl) 2021;30(03):e13416. Doi: 10.1111/ECC.13416

Clinical Syndrome of Seizures, Headache, and Visual Blurring in Metastatic Carcinoma Colon

Lakshmi Raj[1] T.M. Anoop[1] Rakesh CA[2]

[1] Department of Medical Oncology, Regional Cancer Centre, Thiruvananthapuram, Kerala, India
[2] Department of Radiodiagnosis, Regional Cancer Centre, Thiruvananthapuram, Kerala, India

Address for correspondence T.M. Anoop, MD, DM, DNB, FRCP (Edin), Associate Professor, Department of Medical Oncology, Regional Cancer Centre, Thiruvananthapuram, Kerala, 596011, India (e-mail: dranooptm@yahoo.co.in).

Ind J Med Paediatr Oncol 2024;45:64–65.

Abstract

A 51-year-old lady diagnosed as a case of metastatic carcinoma colon stage IV involving lung and left adrenal metastasis was initiated with palliative chemotherapy with FOLFOX-6 chemotherapy infusion regimen that consisted of 5-flurouracil, calcium leucovorin, and oxaliplatin and injection bevacizumab was added to cycle seven of FOLFOX-6 chemotherapy. After 2 months of initiating bevacizumab, she was presented with one episode of generalized tonic clonic seizure, headache, and visual blurring of 2 days duration and magnetic resonance imaging brain T2 fluid-attenuated inversion recovery image revealed subcortical white matter edema in bilateral frontoparietal, occipital, left temporal lobes (Fig. 1A and B), and hyperintense edema with effacement of folia in both cerebellum with nodular areas of contrast enhancement suggestive of posterior reversible encephalopathy syndrome.

Keywords

- bevacizumab
- medical oncology
- posterior reversible encephalopathy syndrome (PRES)
- magnetic resonance imaging

The clinical syndrome of posterior reversible encephalopathy syndrome (PRES) is characterized by varied clinical symptomatology like headache, altered consciousness, visual disturbances, and seizures. Sometimes neurological features such as aphasia and sensory changes are also seen.[1] Pathophysiology of PRES is attributed to autoregulatory failure and hypertension. This results in brain hyperperfusion, especially in arterial border zones that may lead to breakdown of the blood–brain barrier allowing extravasation of fluid and blood products into brain parenchyma. The incidence of chemotherapy-associated PRES is increasing nowadays. The platinum-containing regimens, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP) regimen and gemcitabine, have been implicated in the causation of PRES.

A 51-year-old lady diagnosed as a case of carcinoma colon stage IV involving lung and left adrenal metastasis was initiated with palliative chemotherapy with FOLFOX-6 chemotherapy infusion regimen that consisted of 5-flurouracil, calcium leucovorin, and oxaliplatin. Response assessment using computed tomographic chest abdomen and pelvis, following six cycles of chemotherapy, showed stable residual ascending colonic eccentric wall thickening up to 2.1 cm for a length of 3 cm and stable three pulmonary nodule in right lower, middle lobe, and lingular segment. She completed 12 cycles of FOLFOX-6 chemotherapy. Injection bevacizumab was added to cycle seven of FOLFOX-6 chemotherapy. The reason for adding bevacizumab toward 7th cycle was due to financial difficulty at the time of initiation of treatment. There was no prior history of hypertension, underlying kidney disease, and autoimmune disease. Her blood pressure was 130/80 mm Hg at presentation, before initiation of bevacizumab and during the course of bevacizumab. After 2 months of initiating bevacizumab, she was presented with one episode of generalized tonic–clonic seizure, headache, and visual blurring of 2 days duration. She had no history of new medications, trauma to head, or infection prodrome. On examination, patient was drowsy, vitals were stable, and central nervous system (CNS) examination showed no focal neurological deficits or no neck stiffness.

article published online
September 22, 2023

DOI https://doi.org/10.1055/s-0043-1772710.
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

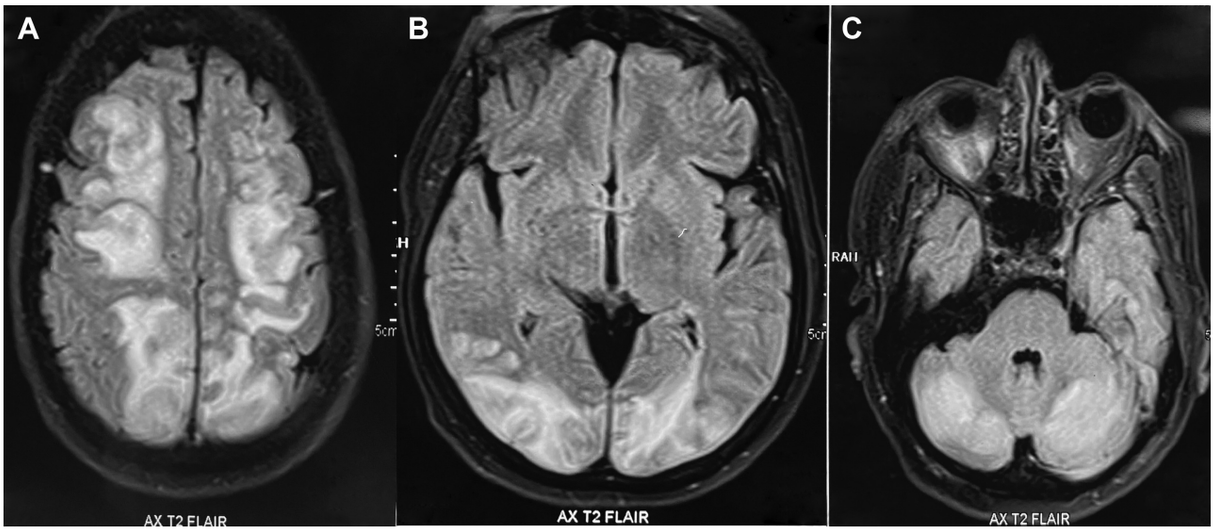


Fig. 1 MRI Brain T2 FLAIR image showing subcortical white matter oedema in bilateral frontoparietal, occipital, left temporal lobes (**A-B**) and hyper-intense edema with effacement of folia in both cerebellum with nodular areas of contrast enhancement (**C**) suggestive of Posterior reversible encephalopathy syndrome (PRES).

Cardiovascular, respiratory, and abdominal examination was unremarkable. There was documented hypertension of blood pressure of 140/90 mm Hg but no evidence of proteinuria. Magnetic resonance imaging (MRI) brain T2 fluid-attenuated inversion recovery (FLAIR) image revealed subcortical white matter edema in bilateral frontoparietal, occipital, and left temporal lobes (►**Fig. 1A** and **B**) and hyperintense edema with effacement of folia in both cerebellum with nodular areas of contrast enhancement suggestive of PRES (►**Fig. 1C**). During her admission, she was given antihypertensives and antiepileptics. She was discharged on fifth day post-admission after clinical resolution of her symptoms. She was reviewed 1 week post-discharge and she had no further episodes of seizures or other CNS symptoms. In our patient, bevacizumab is most likely the causative agent for PRES. The mechanism by which bevacizumab causes PRES is hypothesized that it disrupts the blood–brain barrier through endothelial dysregulation resulting in hyperperfusion and vasogenic edema leading to failure of autoregulation.[2] Bevacizumab-induced hypertension might also have contributed to PRES. The time between starting a medicine and the onset of PRES has not been well described. Typically, PRES occurs within the half-life of bevacizumab that is 20 days, but it can occur from 16 hours to 1 year.

There are various conditions that would be mistaken for PRES that could lead to diagnostic confusion. They include viral and autoimmune encephalitis, demyelinating disease, CNS vasculitis, central/extrapontine myelinolysis, and cerebral venous thrombosis. The typical MRI features include almost symmetrical hemispheric vasogenic edema affecting subcortical white matter and often extending to the overlying cortex, with FLAIR sequences. There are three patterns of postcontrast enhancement like a leptomeningeal pattern, a cortical pattern, or a combined pattern. Patients typically show symptomatic improvement within 2 weeks of symptom onset. Prompt recognition of syndrome is critical since it is reversible with appropriate management.[3]

Authors' Contributions

L.R., R.C.A., and T.M.A. were involved in data collection, literature review, manuscript preparation, and final approval

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given their consent for her images and other clinical information to be reported in the journal. The patient understands that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Funding

None.

Conflict of Interest

None declared.

References

1 Allen JA, Adlakha A, Bergethon PR. Reversible posterior leukoencephalopathy syndrome after bevacizumab/FOLFIRI regimen for metastatic colon cancer. Arch Neurol 2006;63(10): 1475–1478

2 Glusker P, Recht L, Lane B. Reversible posterior leukoencephalopathy syndrome and bevacizumab. N Engl J Med 2006;354(09): 980–982, discussion 980–982

3 Hamid M, Ghani A, Micaily I, Sarwar U, Lashari B, Malik F. Posterior reversible encephalopathy syndrome (PRES) after bevacizumab therapy for metastatic colorectal cancer. J Community Hosp Intern Med Perspect 2018;8(03):130–133

To Augment or Not to Augment Consolidation Therapy for High-Risk Childhood Acute Lymphoblastic Leukemia

Shyam Srinivasan[1]

[1] Department of Pediatric Oncology, ACTREC/Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

Address for correspondence Shyam Srinivasan, DM, Department of Pediatric Oncology, Tata Memorial Hospital, Parel, Mumbai, Maharashtra 400 012, India (e-mail: srinivas.shyam@gmail.com).

Ind J Med Paediatr Oncol 2024;45:66–67.

Nachman et al in the year 1998 published the results of the Children's Cancer Group (CCG)-1882 study in which they explored the role of augmented intensive postinduction therapy among children with high-risk acute lymphoblastic leukemia (ALL).[1] Following this study, the augmented Berlin-Frankfurt-Munster (BFM) consolidation which consists of additional vincristine and asparaginase during periods of myelosuppression of the standard IB phase became the preferred postinduction therapy for high-risk ALL across several cooperative groups. Nearly 25 years later, the intercontinental BFM group have published results of the BFM-2009 study, which aimed to address a similar question.[2] In the BFM-2009 study, patients belonging to the intermediate-/high-risk group were randomized following induction therapy to either the standard IB phase or the augmented IB phase. The results of this study showed no difference in relapse incidence (19.1% vs. 20.5%; $p = 0.55$) or overall survival (OS) (81.9% vs. 80.3%; $p = 0.46$) between the standard IB and augmented IB phases, respectively. Further, a subgroup analysis failed to demonstrate an impact of the augmented regimen on either risk group (intermediate-risk or high-risk) or immunophenotype (B-ALL or T-ALL). In addition, the incidence of allergic reactions to asparaginase, infections, and pancreatitis were higher in the augmented IB arm. In contrast to the results of the BFM-2009 study, the CCG-1882 randomized study showed a significant improvement in survival following postinduction augmentation of therapy.[1] So, what accounted for the disparity between the two studies? First, the CCG-1882 study included National Cancer Institute (NCI) high-risk (age $\geq$ 10 years or total leukocyte count [TLC] $\geq 50 \times 10^9$ /L) patients with poor early response defined as $>$ 25% marrow blasts on day 7, whereas the BFM-2009 study employed a different age (6 years) and TLC cutoff ($\geq 20 \times 10^9$/L) in addition to day 15 measurable residual disease (MRD) and adverse cytogenetics to define risk groups eligible for randomization. Moreover, the CCG-1882 study extended intensification not only to the IB phase but also to the interim maintenance and delayed intensification phases, while the BFM-2009 study limited augmentation to the IB phase. A significant difference was also observed in the central nervous system (CNS) prophylaxis between the two studies. The BFM-2009 study restricted cranial radiotherapy (CRT) exclusively for CNS-3 disease and offered high-dose methotrexate (HDMTX) to all patients, whereas the CCG-1882 offered Capizzi I escalating intravenous MTX without leucovorin rescue plus asparaginase and prophylactic CRT for all patients. The promising results of the CCG-1882 study led to a similar randomized study (CCG-1961) but among NCI high-risk patients with rapid early response ($<$ 25% marrow blasts on day 7), which again concluded in favor of the augmented regimen.[3] More recently, the Medical Research Council group in their UKALL-2003 trial also studied the role of postinduction augmentation in a randomized manner among high-risk ALL patients.[4] In this study, standard intermediate-risk patients, defined based on NCI risk and day 8 response, were randomized to receive augmented postinduction therapy or risk-specific standard therapy if they had a MRD of more than 0.01% on day 29 of induction. Augmented therapy in this context consisted of an additional eight doses of pegylated asparaginase and extra 18 doses of vincristine during consolidation and delayed intensification phase along with Capizzi I escalating MTX. The study's findings indicated superior event-free survival (89.6% vs. 82.8%, $p = 0.04$) and OS (92.9% vs. 88%, $p = 0.16$) among patients receiving the augmented therapy. While this study highlights the importance of augmenting therapy among

article published online
September 18, 2023

DOI https://doi.org/10.1055/s-0043-1774778.
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

patients with persistent disease at the end of induction, it does not definitely establish the benefit of augmented BFM consolidation.[4] Several previous studies have shown the importance of achieving clearance of MRD by day 78 (end of consolidation), in both B- and T-cell ALL.[5–8] In the COG AALL0232 study, all high-risk B-ALL patients received four-drug induction followed by augmented IB consolidation.[6] Among the 2,473 patients evaluated for MRD in this study, 685 patients had a positive ($\geq$ 0.01%) MRD at the end of induction while only a small proportion of patients ($n = 45$) remained MRD positive at the end of consolidation.[6] This suggests that employing augmented IB consolidation might be justified for a subset of high-risk ALL patients defined based on day 29 MRD, as it has the potential for a more effective clearance of MRD. A limitation of the BFM-2009 study was the lack of day 29 MRD details, which could have shed light on the benefit of the augmented IB consolidation for patients with MRD positive disease receiving a BFM backbone chemotherapy. It is also important to note that patients in the COG AALL0232 study were randomized to receive either Capizzi I MTX or HDMTX during interim maintenance and the effect of HDTMX (compared to Capizzi I MTX) was more pronounced among patients who were MRD positive. Based on the data from the COG ALL0232 study and more recent findings from the UKALL-2011 study, HDMTX may have an important role in mitigating bone marrow disease and its benefit may not be limited to only sanctuary sites.[9]

Needless to say, such cross-comparisons across trials for childhood ALL are fraught with limitations, including differences in risk stratification among cooperative groups, variations in MRD detection methods and time points, and even disparities in the number of chemotherapy cycles administered. Nevertheless, following the two successive randomized CCG studies, augmented BFM consolidation IB regimen became the standard of care for pediatric and young adult with high-risk ALL across several cooperative groups. However, the results of the BFM-2009 study challenge the necessity of augmenting the standard BFM consolidation, particularly with the inclusion of HDMTX, a notable absence in both the CCG studies and the UKALL-2003 trial. Given the higher incidence of toxicities and the lack of survival benefits in the BFM-2009 study, routine use of the augmented IB regimen during consolidation phase for intermediate- or high-risk ALL patients, especially when treated with BFM chemotherapy, would be inappropriate. Nonetheless, the augmented IB regimen could still hold value for certain high-risk ALL defined based on end of induction MRD, and contribute to the eradication of residual disease.

Conflict of Interest
None declared.

References

1 Nachman JB, Sather HN, Sensel MG, et al. Augmented post-induction therapy for children with high-risk acute lymphoblastic leukemia and a slow response to initial therapy. N Engl J Med 1998;338(23):1663–1671
2 Campbell M, Kiss C, Zimmermann M, et al. Childhood acute lymphoblastic leukemia: results of the randomized acute lymphoblastic leukemia intercontinental-Berlin-Frankfurt-Münster 2009 trial. J Clin Oncol 2023;41(19):3499–3511
3 Seibel NL, Steinherz PG, Sather HN, et al. Early postinduction intensification therapy improves survival for children and adolescents with high-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. Blood 2008;111(05):2548–2555
4 Vora A, Goulden N, Mitchell C, et al. Augmented post-remission therapy for a minimal residual disease-defined high-risk subgroup of children and young people with clinical standard-risk and intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial. Lancet Oncol 2014;15 (08):809–818
5 Conter V, Bartram CR, Valsecchi MG, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood 2010;115(16):3206–3214
6 Borowitz MJ, Wood BL, Devidas M, et al. Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. Blood 2015;126(08): 964–971
7 Schrappe M, Valsecchi MG, Bartram CR, et al. Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study. Blood 2011;118 (08):2077–2084
8 Parekh C, Gaynon PS, Abdel-Azim H. End of induction minimal residual disease alone is not a useful determinant for risk stratified therapy in pediatric T-cell acute lymphoblastic leukemia. Pediatr Blood Cancer 2015;62(11):2040–2043
9 Kirwood AA, Goulden N, Moppett J, et al. High dose methotrexate does not reduce the risk of CNS relapse in children and young adults with acute lymphoblastic leukemia and lymphoblastic lymphoma. Results of the randomised phase III study UKALL 2011. Blood 2022;140(Suppl 1):516–518

How I Treat Alveolar Soft Part Sarcoma? The Therapeutic Journey from Nihilism to Cautious Optimism...

Deepa Susan Joy Philip[1] Jyoti Bajpai[2]

[1] Department of Medical Oncology, Regional Cancer Centre, Trivandrum, Kerala, India
[2] Department of Medical Oncology, Tata Memorial Centre, Mumbai, Maharashtra, India

Address for correspondence Jyoti Bajpai, MD, DM, Department of Medical Oncology, Tata Memorial Centre, Mumbai 400012, Maharashtra, India (e-mail: drjyotibajpai25@gmail.com).

Ind J Med Paediatr Oncol 2024;45:68–73.

Introduction

Alveolar soft part sarcoma (ASPS) is a very rare subtype, constituting less than 0.5% of malignant Soft tissue sarcoma.[1] It is an orphan disease affecting adolescents and young adults, predominantly females.[2] The rarity of the disease, with its indolent but relentless natural history and enigmatic line of differentiation, makes its diagnosis a challenge. Despite being a chemoresistant disease, it is known for prolonged survival even in a few metastatic patients with spontaneous disease stabilization and indolent disease behavior. Targeted therapy with antiangiogenic agents and immunotherapy is the way forward for this rare disease. In this review, we aim to give an overview of the approach to diagnosis and management of this orphan disease in 2022 in the Indian setting, which is widely applicable in other low-middle income countries (LMIC) as well.

Case history

A 25-years-old lady, a housewife, presented to our outpatient department (OPD) with a 2-year history of discomfort in her right thigh. Six months after the onset of symptoms, she felt a vague mass in the lateral aspect of the proximal right thigh with a doubtful gradual increase in the size of the swelling. There was no associated pain, fever, or weight loss. In view of the COVID pandemic, she reassured herself and had delayed any evaluation of this symptom. Now in view of increased anxiety and insistence of family, she has come to our OPD for evaluation.

How do I Evaluate her to Reach a Diagnosis?

The diagnostic evaluation will be **C.R.P**

- **C**linical evaluation: history and physical examination
- **R**adiological evaluation
- **P**athological evaluation

Clinical Evaluation

History and examination reveal an indolent, slow-growing, painless soft tissue mass of 3×3 cm in the lateral aspect of right thigh, with no constitutional symptoms and no local compressive symptoms. In view of the above clinical presentation, one may misinterpret it to be a benign disease such as hemangioma.

Radiological evaluation

X-ray of the right thigh [antero-posterior/lateral views]: soft tissue mass in the right thigh, with no bony erosion and no calcification.

MRI: Radiological evaluation is to be completed before planning a biopsy.[3–5]

- Flow voids due to intra and peri-tumoral vessels.
- Hyperintense to muscle in T1 images
- Moderate to intense contrast enhancement.

Pathological Evaluation

Core needle biopsy of the lesion classically shows[2]:

- Pseudo-alveolar pattern [which gives it the name]
- Intracytoplasmic rod-shaped crystals [PAS/diastase resistant]
- Intravascular extension
- Immunohistochemistry: TFE-3 and Cathepsin-K are highly sensitive, though not specific for ASPS. It is consistently negative for cytokeratin, epithelial membrane antigen (EMA), human melanoma black (HMB-45), synaptophysin, and chromogranin.

[*When the clinicopathological features of ASPS were initially described in 1952,*[1] *Christopherson noted that "the most striking feature of the alveolar soft-part sarcoma is the basic uniformity throughout a given tumor and the similarity of one tumor to another.*"]

article published online
December 3, 2022

DOI https://doi.org/10.1055/s-0042-1758540.
ISSN 0971-5851.

© 2022. 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

The highly characteristic histopathology leads us to the diagnosis of ASPS.

Molecular studies

ASTS is a translocation-associated STS, with unbalanced non-reciprocal t(X,17) leading to ASPSCR1-TFE3 fusion gene on der (17) and ASPSCR1-TFE3 chimeric transcript, which is seen in almost all cases. In pathologically challenging cases, RT-PCR for the fusion transcript or FISH for TFE3 rearrangement will be helpful in making a definitive diagnosis.[6,7]

Learning Point

The low incidence, lack of unique clinical features, indolent behavior with the small primary in metastatic disease and atypical sites [adults most common in thigh/gluteal region and in children in head and neck] may lead to misdiagnosis.

A systematic clinical + radiological + pathological evaluation leads us to a definite diagnosis of ASPS.

Now the Definitive Diagnosis of ASPS is Made. How do we Stage the Patient?

The natural history of ASPS is unique with an extremely indolent behavior with late metastasis becoming symptomatic months to years after diagnosis. The most common sites of metastasis are lungs, bone, and brain. Brain metastasis in ASPS is more than in other soft tissue sarcomas.[8]

a) NCCT chest: multiple bilateral lung metastases.
b) MRI Brain: normal.
c) PET-CT: not recommended as initial staging in NCCN/ESMO guidelines.

We have reached a final diagnosis of metastatic ASPS.

Learning Point

ASPS is unique among STS, to have a small primary with an indolent behavior with late metastasis in the lungs. It is one of the few STS, with a high risk of brain metastasis.

How do we Treat Patients with ASPS?

Goals of Treatment

- Minimize local recurrence.
- Minimize perioperative morbidity and mortality.
- Maximize functionality and QOL.
- Maximize overall survival.

The overview of the management plan of ASPS is depicted in the ►**Fig. 1**.

Localized Disease

Localized disease is treated with wide local excision followed by adjuvant radiotherapy if there is evidence of microscopic or macroscopic residual disease or if the margin status is questionable.[9]

Metastatic Disease

Is there a role for surgical excision of primary in metastatic disease with resectable primary?

In the pre-targeted-therapy era, if complete resection was feasible, with limited postoperative morbidity then surgery of the primary, followed by systematic treatment was adopted, the rationale being the indolent disease biology. SEER retrospective data of 25 patients with 58% having a metastatic disease with primary resections, showed an improvement in the overall survival. The role remains questionable and controversial in the present targeted therapy era.[9]

- **Metastatic Disease, Limited Disease Burden:**

Patients with the limited disease who are asymptomatic may be observed with close follow-up, considering the indolent behavior. Brain metastasis [symptomatic/asymptomatic] should be treated with CNS-directed therapy.

- **Metastatic Disease with Heavy disease burden/ Symptomatic/Rapidly progressive Disease:**

ASPS is a relatively chemo-resistant disease. Hence, in both adjuvant and metastatic settings, chemotherapy is not offered.[2,10]

First-line therapy includes targeted therapy with anti-angiogenic [VEGF] agents pazopanib and sunitinib and immunotherapy with immune checkpoint inhibitors and combinations of both.

In view of the rarity of the disease, evidence for treatment options comes from small retrospective case series and recent prospective studies. So, it is difficult to draw definite conclusions. The best treatment happens to be a lot of educated guesses.

Recommended Treatment Agents for Metastatic Disease

NCCN recommendation 2021 [Evidence blocks of therapy is shown in ►**Table 1**].

1. Pazopanib
2. Sunitinib
3. Pembrolizumab

Targeted Antiangiogenic Agents against VEGF

Rationale

ASPS is a translocation associated STS, with the ASPSCR1-TFE3 fusion as a hallmark. This fusion transcript leads to MET overexpression and increased angiogenesis in this highly vascular tumor. Hence antiangiogenic targeted therapy holds promise in this disease.

Approved agents: pazopanib, sunitinib
Investigational agents:

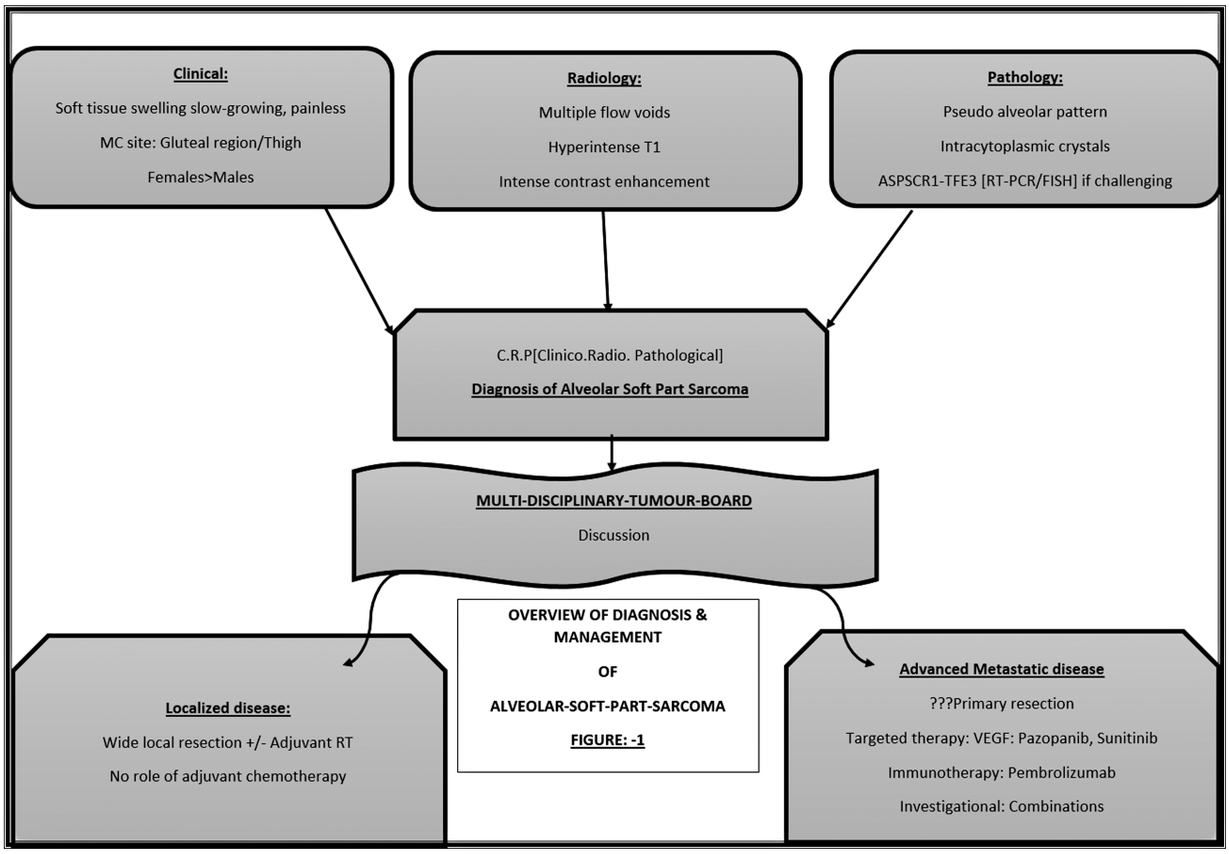


Fig. 1 Overview of management.

Table 1 NCCN 2021 evidence blocks

Sunitinib					
	3/5	3/5	2/5	3/5	2/5
	Efficacy	Safety	Quality of evidence	Consistency of evidence	Affordability
Pazopanib					
	3/5	3/5	2/5	3/5	2/5
	Efficacy	Safety	Quality of evidence	Consistency of evidence	Affordability
Pembrolizumab					
	3/5	3/5	2/5	2/5	1/5
	Efficacy	Safety	Quality of evidence	Consistency of evidence	Affordability

Table 2 Systemic treatment with targeted therapy in ASPS

Sunitinib			
Author	**Year**	**Number of patients**	**Outcomes**
Stacchiotti[11]	2011	9	5PR/3SD/1PD Median TTP: 17months
Li[12]	2016	14	4PR/10SD Median PFS:41months
Jagodzinska[13]	2017	15	6PR/8SD/1PD MedianPFS:19months Median OS:56months
Pazopanib			
Year	**Author**	**Number of patients**	**Outcomes**
Stacchiotti[14]	2018	30	1CR/7PR/17SD/4PD/1NE Median PFS:13.6months
Kim[15]	2019	6	ORR:17% Median PFS:5.5 months
Cediranib			
Kummar[16]	2013	43	ORR:35%
Judson[17]	2014	6	2PR/4SD
Judson [RCT, Ph2] CASPS[18]	2019	32/16	3PR/14SD Median PFS:10.8months
Dasatinib			
Schurtze[19]	2017	12	Median PFS:11months 5yr OS:30%
Crizotinib			
Schoffski[20]	2018	45	1PR/35SD 1year PFS:38%
Tivantinib			
Wagner[21]	2012	27	21SD/5PD/1NE Median PFS:5.5 months
Combination of targeted therapy			
Flores[22]	2018	69 [11 targetted/ 15chemo/ 6observation]	2PR/6SD/3PD Median TTP: - Targetted:12months Chemo:7months Observation:4months
J.Bajpai[23]	2019	54[6 with sunitinib/pazopanib]	2CR/2PR Median PFS:23 months

Anti-VEGF: cediranib, anlotinib
Anti-MET: crizotinib
The following table gives a broad overview of systemic targeted therapy in ASPS. [Selection of studies with at least 5 patients] ►**Table 2**.

Immunotherapy

Rationale

ASPS is a cold tumor with low TMB and low PDL1 expression. The responses seen with immunotherapy are postulated to be due to neoantigens created by the unique fusion gene in ASPS.

Pembrolizumab

A retrospective series[24] by Roman et al of 50 patients with advanced STS at the Phase1 clinic at MD Anderson included 4 ASPS patients. All 4 ASPS patients showed clinical benefit, and the best response seen in this study of mixed histologies was partial response in 2 ASPS patients. This has led to the approval and recommendation for advanced ASPS.

Atezolizumab

A phase-2 study by Coyne et al,[25] presented at the ASCO 2021 of 43 patients, ORR was 37% (16/43). [CR:1/PR:15/SD:25], with the median time to response of 3.5 months (range, 2.1–14.9 months) and the median duration of response of 16.5 months (range, 4.9–38.1 months).

Combination Regimens

Immune checkpoint inhibitor with antiangiogenic targeted therapy:

Table 3 Therapeutic journey of ASPS from nihilism to cautious optimism

Year	Author	Number	Outcome localized disease	Outcome metastatic disease
1989	Lieberman[28]	91 [69/22]	Median OS = 11 y OS at 2 y-77% OS at 5 y-60% OS at 10 y-38% OS at 20 y-15%	Median OS = 3 y
2018	Flores[22]	69 [31/38]	OS at 5 y-87%	OS at 5 y-61%

VEGF mediates neo-angiogenesis and an immunosuppressive tumor microenvironment. VEGF inhibitors would evade the immunosuppressive microenvironment and thus show synergism with immunotherapy.

Pembrolizumab with axitinib, in a phase-2 study of 36 advanced STS with 12 ASPS, showed overall response rate of 55% and 3 months PFS of 75%. This was independent of the PDL1 status.[26]

Systematic review and meta-analysis of immune checkpoint inhibitors in soft tissue sarcoma[27]:

Sarens et al have published a meta-analysis in 2021, evaluating 900 patients with advanced soft tissue sarcoma including 109 ASPS patients. The ORR by RECIST and Choi criteria was 0.35 [95%CI 0.27–0.44]. Exploratory analysis of ORR showed:

Checkpoint inhibitor monotherapy: 0.31 [0.22–0.42 CI]
Checkpoint inhibitor +TKI: 0.47 [0.26–0.69]
Checkpoint inhibitor+ others: 0.55 [0.28–0.79]

Therapeutic Journey from Nihilism to Cautious Optimism

The progress in systemic therapy with targeted agents has led to improvement in survival as shown in ►**Table 3**. The 5 years overall survival of patients with the localized disease was 60%. Now over three decades later, patients with metastatic disease, treated with targeted therapy have the same survival. This clearly shows the progress in our therapeutic journey.

With many novel agents in the pipeline and pathway-driven basket trials and collaborative prospective clinical trials, the future of management of ASPS looks bright and promising.

Take Home Messages

- ASPS is a rare orphan disease, with an indolent yet relentless clinical course.
- A detailed clinico–radio-pathological evaluation is the key to diagnosis.
- It usually presents as a painless slow-growing vascular soft tissue mass in the lower limb of adolescents and young adults, predominantly females.
- It has characteristic histopathology with Pseudo-alveolar patterns and intracytoplasmic crystals. IHC with TFE3 and Molecular studies for ASPSCR1-TFE3 help in challenging situations.
- Metastatic disease to lung/bone/brain leads to poor prognosis. It is unique among STS to have brain metastasis.
- Localized disease is managed with wide local excision followed by adjuvant radiotherapy if microscopic or macroscopic residual disease.
- It is essentially a chemoresistant disease with an almost negligible role for Adjuvant chemotherapy.
- Metastatic disease is treated with targeted anti-VEGF agents such as pazopanib/sunitinib and immunotherapy such as pembrolizumab or combination.
- With many novel agents in the pipeline and pathway-driven Basket trials with collaborative prospective clinical trials, the future of management of ASPS looks promising. It is truly a therapeutic journey from Nihilism to cautious optimism.

Conflict of Interest
None declared.

References

1 Christopherson WM, Foote FW Jr, Stewart FW. Alveolar soft-part sarcomas; structurally characteristic tumors of uncertain histogenesis. Cancer 1952;5(01):100–111
2 Reichardt P, Lindner T, Pink D, Thuss-Patience PC, Kretzschmar A, Dörken B. Chemotherapy in alveolar soft part sarcomas. What do we know? Eur J Cancer 2003;39(11):1511–1516
3 McCarville MB, Muzzafar S, Kao SC, et al. Imaging features of alveolar soft-part sarcoma: a report from Children's Oncology Group Study ARST0332. AJR Am J Roentgenol 2014;203(06):1345–1352
4 Li X, Ye Z. Magnetic resonance imaging features of alveolar soft part sarcoma: report of 14 cases. World J Surg Oncol 2014;12:36
5 Cui JF, Chen HS, Hao DP, Liu JH, Hou F, Xu WJ. Magnetic resonance features and characteristic vascular pattern of alveolar soft part sarcoma. Oncol Res Treat 2017;40(10):580–585
6 Ladanyi M, Lui MY, Antonescu CR, et al. The der(17)t(X;17)(p11;q25) of human alveolar soft part sarcoma fuses the TFE3 transcription factor gene to ASPL, a novel gene at 17q25. Oncogene 2001;20(01):48–57
7 Williams A, Bartle G, Sumathi VP, et al. Detection of ASPL/TFE3 fusion transcripts and the TFE3 antigen in formalin-fixed, paraffin-embedded tissue in a series of 18 cases of alveolar soft part sarcoma: useful diagnostic tools in cases with unusual histological features. Virchows Arch 2011;458(03):291–300

8 Wang Y, Cui J, Yan X, Jin R, Hong X. Alveolar soft part sarcoma with multiple brain and lung metastases in pregnancy: a case report and literature review. Medicine (Baltimore) 2017;96(46):e8790
9 Wang H, Jacobson A, Harmon DC, et al. Prognostic factors in alveolar soft part sarcoma: A SEER analysis. J Surg Oncol 2016;113 (05):581–586
10 Ogura K, Beppu Y, Chuman H, et al. Alveolar soft part sarcoma: a single-center 26-patient case series and review of the literature. Sarcoma 2012;2012:907179
11 Stacchiotti S, Negri T, Zaffaroni N, et al. Sunitinib in advanced alveolar soft part sarcoma: evidence of a direct antitumor effect. Ann Oncol 2011;22(07):1682–1690
12 Li T, Wang L, Wang H, et al. A retrospective analysis of 14 consecutive Chinese patients with unresectable or metastatic alveolar soft part sarcoma treated with sunitinib. Invest New Drugs 2016;34(06):701–706
13 Jagodzińska-Mucha P, Świtaj T, Kozak K, et al. Long-term results of therapy with sunitinib in metastatic alveolar soft part sarcoma. Tumori 2017;103(03):231–235
14 Stacchiotti S, Mir O, Le Cesne A, et al. Activity of pazopanib and trabectedin in advanced alveolar soft part sarcoma. Oncologist 2018;23(01):62–70
15 Kim M, Kim TM, Keam B, et al. A Phase II trial of pazopanib in patients with metastatic alveolar soft part sarcoma. Oncologist 2019;24(01):20–e29
16 Kummar S, Allen D, Monks A, et al. Cediranib for metastatic alveolar soft part sarcoma. J Clin Oncol 2013;31(18):2296–2302
17 Judson I, Scurr M, Gardner K, et al. Phase II study of cediranib in patients with advanced gastrointestinal stromal tumors or soft-tissue sarcoma. Clin Cancer Res 2014;20(13):3603–3612
18 Judson I, Morden JP, Leahy MG, et al. Activity of cediranib in alveolar soft part sarcoma (ASPS) confirmed by CASPS (cediranib in ASPS), an international, randomized phase II trial [abstract 11004]. Proc ASCO. 2017;35(15).
19 Schuetze SM, Bolejack V, Choy E, et al. Phase 2 study of dasatinib in patients with alveolar soft part sarcoma, chondrosarcoma, chordoma, epithelioid sarcoma, or solitary fibrous tumor. Cancer 2017;123(01):90–97
20 Schöffski P, Wozniak A, Kasper B, et al. Activity and safety of crizotinib in patients with alveolar soft part sarcoma with rearrangement of TFE3: European Organization for Research and Treatment of Cancer (EORTC) phase II trial 90101 'CREATE'. Ann Oncol 2018;29(03):758–765
21 Wagner AJ, Goldberg JM, Dubois SG, et al. Tivantinib (ARQ 197), a selective inhibitor of MET, in patients with microphthalmia transcription factor-associated tumors: results of a multicenter phase 2 trial. Cancer 2012;118(23):5894–5902
22 Flores RJ, Harrison DJ, Federman NC, et al. Alveolar soft part sarcoma in children and young adults: a report of 69 cases. Pediatr Blood Cancer 2018;65(05):e26953
23 Simha V, Bajpai J. Alveolar Soft Part Sarcomas(ASPS): A tertiary cancer care center experience from India. Journal of Clinical Oncology 2019;37(15):e22553
24 Groisberg R, Hong DS, Behrang A, et al. Characteristics and outcomes of patients with advanced sarcoma enrolled in early phase immunotherapy trials. J Immunother Cancer 2017;5(01): 100
25 Naqash AR, Coyne GHO, Moore N, et al. Phase II study of atezolizumab in advanced alveolar soft part sarcoma (ASPS). Journal of Clinical Oncology 2021;39(15): suppl. 11519
26 Wilky BA, Trucco MM, Subhawong TK, et al. Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial. Lancet Oncol 2019;20(06):837–848
27 Saerens M, Brusselaers N, Rottey S, Decruyenaere A, Creytens D, Lapeire L. Immune checkpoint inhibitors in treatment of soft-tissue sarcoma: A systematic review and meta-analysis. Eur J Cancer 2021;152:165–182
28 Lieberman PH, Brennan MF, Kimmel M, Erlandson RA Garin-Chesa P, Flehinger BY. Alveolar soft-part sarcoma. A clinico-pathologic study of half a century. Cancer 1989;63 (01):1–13

TP53 Mutations R175H and R249S Are Rare in Indian Head and Neck Cancer Patients

Arjita Ghosh[1] Anbalagan Moorthy[1]

[1] Department of Integrative Biology, School of Bioscience and Technology (SBST), Vellore Institute of Technology, Vellore, Tamil Nadu, India

Address for correspondence Anbalagan Moorthy, PhD, Department of Integrative Biology, School of Bioscience and Technology (SBST), Vellore Institute of Technology, Vellore 632014, Tamil Nadu, India (e-mail: anbalagan.m@vit.ac.in).

Ind J Med Paediatr Oncol 2024;45:74–79.

Abstract

Introduction Mutations in tumor suppressor gene TP53 are considered as one of the main causes for different types of cancer. Head and neck squamous cell carcinoma (HNSCC) is one of the common cancers found in India. Among the several mutations reported in the TP53 gene, R175H and R249S are linked to cause of several cancers. This work was carried out to study the prevalence of R175H and R249S mutations in HNSCC patients of Indian origin.

Method Tumor samples were collected from 50 HNSCC patients and good quality genomic deoxyribonucleic acid (DNA) were obtained from 41 samples. Using this genomic DNA, polymerase chain reaction-linked restriction fragment length polymorphism technique was used to screen both the mutations in the TP53 gene of the patients.

Result The results revealed that out of the 41 samples analyzed, all the samples were negative for the mutations both in homozygous and heterozygous condition. This experiment was repeated three times, and the representative image is shown.

Conclusion This study suggests that mutations in codon 175 (R175H) and 249 (R249S) are rare in HNSCC patients of Indian origin.

Keywords
- head and neck cancer
- mutations
- TP53
- polymerase chain reaction coupled restriction fragment length polymorphism
- R175H
- R249S

Introduction

TP53 is a tumor suppressor gene which protects the genome from mutations and prevents proliferation of mutated cell in the organism by inducing apoptosis in the mutated cell there by preventing cancer.[1] Mutations in the TP53 gene are implicated in etiopathogenesis of many cancers.[2] TP53 mutations were widely seen in different type of cancers such as brain, breast, colon, lungs, ovaries, esophagus,[3] and head and neck squamous cell carcinoma (HNSCC).[1]

Polymerase chain reaction-linked restriction fragment length polymorphism (PCR-RFLP) is a rapid and cost-effective method for screening mutations/variants of a gene. This technique was used to screen for two different hotspot mutations in the TP53 gene of head and neck cancer (HNC) patients.

Among the different cancers, HNSCC is the sixth most common cancer reported in the world. Each year, almost 6 lakh cases of HNSCC are reported, out of which 3.5 lakh patients are reported to die.[4] The anatomical occurrences of HNSCC include sites in the head and neck region such as the larynx, oral cavity, pharynx, nose/paranasal sinuses, oropharynx, etc.[1]

The cause of HNSCC is mainly due to cultural or habitual related risk factors.

Smoking, alcohol consumption, betel nut chewing, human papillomavirus infections due to unnatural sexual practices, etc. are the risk factors associated with HNSCC. Other minor causes include exposure to carcinogens, irradiations, diet, genetic disposition, and immunodeficiency.[1]

article published online
September 22, 2023

DOI https://doi.org/10.1055/s-0043-1774776.
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

Since TP53 mutations are considered to be one of the major causes of cancer, and it has been reported that in HNSCC, incidences of mutation in TP53 ranges from 30 to 70% [1], in this study, we investigated the prevalence codon 175 mutation present in exon 5[5] and codon 249 mutation present in exon 7 of the TP53 gene of Indian HNSCC patients.[6]

p53 protein consists of (1) N-terminal transcriptional activation domain, (2) central deoxyribonucleic acid (DNA) binding domain, (3) tetramerization domain, and (4) C-terminal regulatory domain.[2] Some of the mutations like frameshift, nonsense, and missense mutations are reported in different types of cancers; it has been observed that 90% of these mutations occur in the DNA binding domain of TP53, of which majority are missense mutations.[7] Among the missense mutations, R175, V157, Y220, G245, R248, R249, R273, and R282 are considered as hotspot mutations.[8]

In HNSCC, most of the TP53 mutations are reported in "hotspots" located between the exons 5 to 8.[9] In HNSCC, R273, R248, G245, R175, R282, and H179[1] are some of the reported mutations in TP53 and the distribution tends to vary depending on geographical locations and ethnicity.

Codon 175 and 249 are hotspot sites for mutation in the TP53 gene, the codons are present in the DNA sequences that encode DNA binding domain of the protein, though these amino acids are not in direct contact with DNA, but these mutations alter the architecture of DNA binding domain and also affect the composition of interacting proteins which make the variant TP53 protein oncogenic.[1]

Transition from G > A in codon 175 leads to the substitution of histidine to arginine (R175H) and this mutation is the most prevalent in the TP53 gene among other mutations, found in several cancers and causes impairment of the protein's biological and biochemical functions.[5] R175 mutation is also associated with chemoresistance of cancer cells.[5] Transition from G > T in codon 249 leads to the substitution of arginine to serine (R249S), this is also another common and frequent mutations in the TP53 gene found in cancer, especially in certain regions of China and South Africa. [10] R249S mutation is known to induce transition of G0 to G1 or M to G1 during cell cycle.[6] It is also observed that this mutation occurs largely in hepatocellular carcinoma that too in particular is associated with aflatoxin toxicity .[11]

In the present study, PCR-RFLP was used to examine mutations in codon R175H and R249S in the TP53 gene of Indian HNSCC patients.

Materials and Methods

Patients and Specimens

All the tumor samples were excised surgically from HNC patients and transported to the lab under frozen conditions. All the patient data were followed up, and an informed consent was obtained from all individuals who participated in the study. The institute's human ethical committee approved the study (IEC/IRB No: IECH/2013/Dec18-006). Patients from different states of India, such as Tamil Nadu, Pondicherry, West Bengal, Manipur, and Andhra Pradesh, were included in the study and the study was carried out in accordance with the ethical standards laid down by 1964 Declaration of Helsinki and its later amendments.

DNA Extraction

The tumor tissues were processed by grinding the fresh samples using mortar and pestle in the presence of liquid nitrogen. The tissues were digested in individual tubes containing 1 mL of buffer (6 M NaCl, 100 mM ethylenediaminetetraacetic acid, 10 mM Tris, 0.6% sodium dodecyl sulfate) and proteinase K (20 mg/mL) overnight at 45°C. After digestion, 227 µL of 6 M NaCl was added to precipitate the DNA. The insoluble components were pelleted down by centrifuging the tubes at 12,000 revolutions per minute (rpm) for 10 minutes. The pellet was discarded and supernatant was transferred into a fresh microfuge tube. The genomic DNA was precipitated by adding equal volume of 100% ethanol and the precipitated DNA was pelleted by centrifuging tubes at 12,000 rpm for 10 minutes. The supernatant was discarded and DNA pellet was washed with 70% ethanol and air-dried. The DNA was suspended in 40 to 100 µL of sterile distilled water. The DNA quantity was measured using the NanoDrop instrument (Thermo Fisher Scientific) and the quality of the DNA was tested on agarose gel electrophoresis and visualized under ultraviolet (UV) light in a gel documentation system (Axygen). Control sample testing was not done as we only tested genotyping of genomic DNA isolated from tumor samples.

PCR-RFLP

Using specific set of primers, a 214-base pair (bp) PCR product (for codon 175) and 236-bp PCR product (for codon 249) was PCR amplified using each patient's genomic DNA as template. The primer sequence and PCR conditions used for both the codons are as follows:

Codon 175 forward primer was CACTTGTGCCCTGACTTTCAAC and reverse primer was GCGCTCATGGTGGGGG. The annealing temperature used was 60.1°C. Codon 249 forward primer sequence was CTTGCCACAGGTCTCCCCAA and reverse primer used was AGGGGTCAGCGGCAAGCAGA. The annealing temperature for PCR was 65.1°C. A 50-µL of PCR reaction mixture was made consisting of 5 µL of 10× buffer, 2 µL each primers of 100 µM concentration, 2 µL of deoxynucleotide triphosphate (dNTP) (2.5 mM each dNTP), 0.35 µL of Taq polymerase (3 units/µl) (Genei, India), 0.5 µL of dimethyl sulfoxide, 1 µL of DNA sample (50 ng/µL), and 37.15 µL of sterile water. After PCR, all the PCR products were separated on a 2.5% agarose gel, and the DNA bands were visualized under the UV light and documented using a gel documentation system (Axygen). For screening of R175H mutation, the 214-bp PCR products were digested with HhaI restriction enzyme (Thermo Fisher Scientific), and for screening of R249S mutation, the 236-bp PCR products were digested with HaeIII restriction enzyme (Thermo Fisher Scientific). The restriction-digested PCR products were separated on a 5% gel (for R249S) or 10% polyacrylamide gel electrophoresis (PAGE) gel (for R175H) and the banding

patterns of each sample were visualized and documented. This PCR-RFLP method was standardized.

Primary and Secondary Outcome

The primary outcome was the detection of mutation in the TP53 gene in the codon 175 and 249. Secondary outcome was to correlate the mutational status to HNC patient's disease progression and response to treatment.

Exclusion and Inclusion Criteria

Inclusion criteria of the patients for the study include:

- Patients with nonnasopharyngeal HNC such as cancers of the oral cavity, oropharyngeal and laryngeal origin.
- Patients with biopsy-proven squamous cell cancer and undergoing radical intent treatment with either surgery or radical radiation therapy (concomitant chemo-radiation therapy).
- Patients with potentially curable diseases from stage I to IVA.
- Patients who consent to be a part of the study as well as follow-up.

Exclusion criteria of the patients for the study include:

- Patients with thyroid or nasopharyngeal cancer.
- Patients with metastatic disease in any visceral organ (lung, liver, and bone).
- Patients with history of previous malignancies or previously treated with radiation or chemotherapy.
- Patients with poor performance status (Karnofsky Performance Scale < 70) and expected survival less than 6 months.
- There was no age cutoff. The Li–Fraumeni syndrome was not included.

Statistical Analysis

All the samples were analyzed at least three times and the images represent the best presentable image. Since there were no mutations detected, overall survival and progression-free survival were not calculated.

Ethics Committee

The institute's human ethical committee approved the study (IEC/IRB No:

IECH/2013/Dec18-006). All the patients were Indians hailing from different parts of the country such as Tamil Nadu, West Bengal, Andhra Pradesh, Manipur, and Pondicherry. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Screening of R175H Mutation

At codon 175 CGC (R) is mutated to CAC (H), this change in the mutation is recognized by the restriction enzyme HhaI (recognition sequence: G**CGC**). The 214-bp PCR product

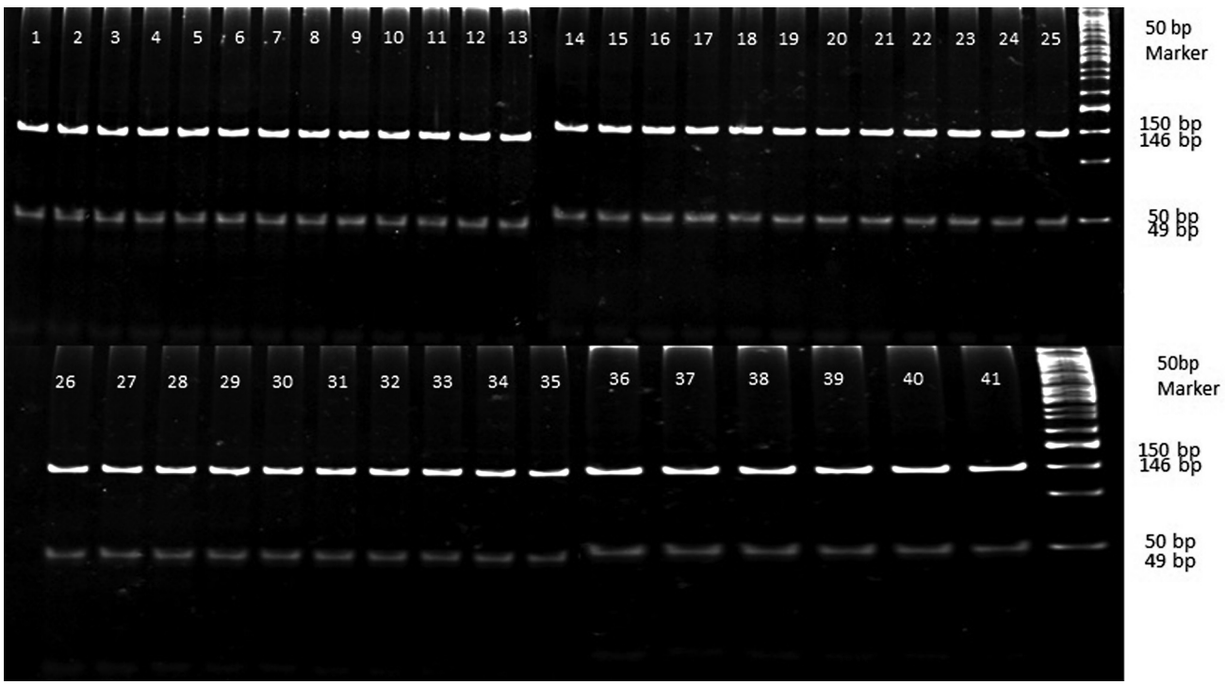


Fig. 1 Screening of Tp53 gene R175H. Polymerase chain reaction (PCR) product from genomic deoxyribonucleic acid (DNA) was digested with HhaI enzyme and separated in 10% polyacrylamide gel electrophoresis (PAGE). All samples show only 146 and 49 base pair (bp) bands (18 and 1 bp too small to be visualized). A 50-bp ladder is used as reference.

consists of three restriction sites for HhaI, digestion of the PCR product with enzyme creates four fragments (146, 49, 18, and 1 bp). Presence of R175H mutation in the PCR product abolishes a restriction site leading to the production of three fragments instead of four (146, 67, and 1 bp) which can be detected on 10% PAGE. As can be seen in ►**Fig. 1**, out of 41 samples screened, all the samples produced 146, 49, 18, and 1 bp product, out of which we are able to see 146 and 49 bp product on the gel and the other products (18 and 1 bp products) are too small to see them on gel.[12]

Screening of R249S Mutation

At codon 249 AGG (R) is mutated to AGT (S), this change in base sequence is recognized by the HaeIII enzyme (recognition sequence: G**GC**C). The 236-bp PCR product consists of four restriction sites for HaeIII, digestion of the PCR product with enzyme creates five fragments (91, 66, 37, 30, and 12 bp). The wild-type PCR product is cut into 91, 66, 37, 30, and 12 bp. In R249S mutation, one recognition site is abolished (AGG to AGT) resulting in the production of four fragments of sizes 157, 37, 30, and 12 bp. As seen in ►**Fig. 2** in all the samples, only 91 and 66 bp products are seen on 5% agarose gel (37, 30, and 12 are not clearly visible due to their lower size), and none of the samples produced 157 bp product, suggesting that all the samples are wild-type without either heterozygous or homozygous mutation.[6]

Discussion

Genetic alterations in specific signaling pathways, including those of the TP53 gene, play an important role in cancer progression. Analysis of these changes in cancer patients

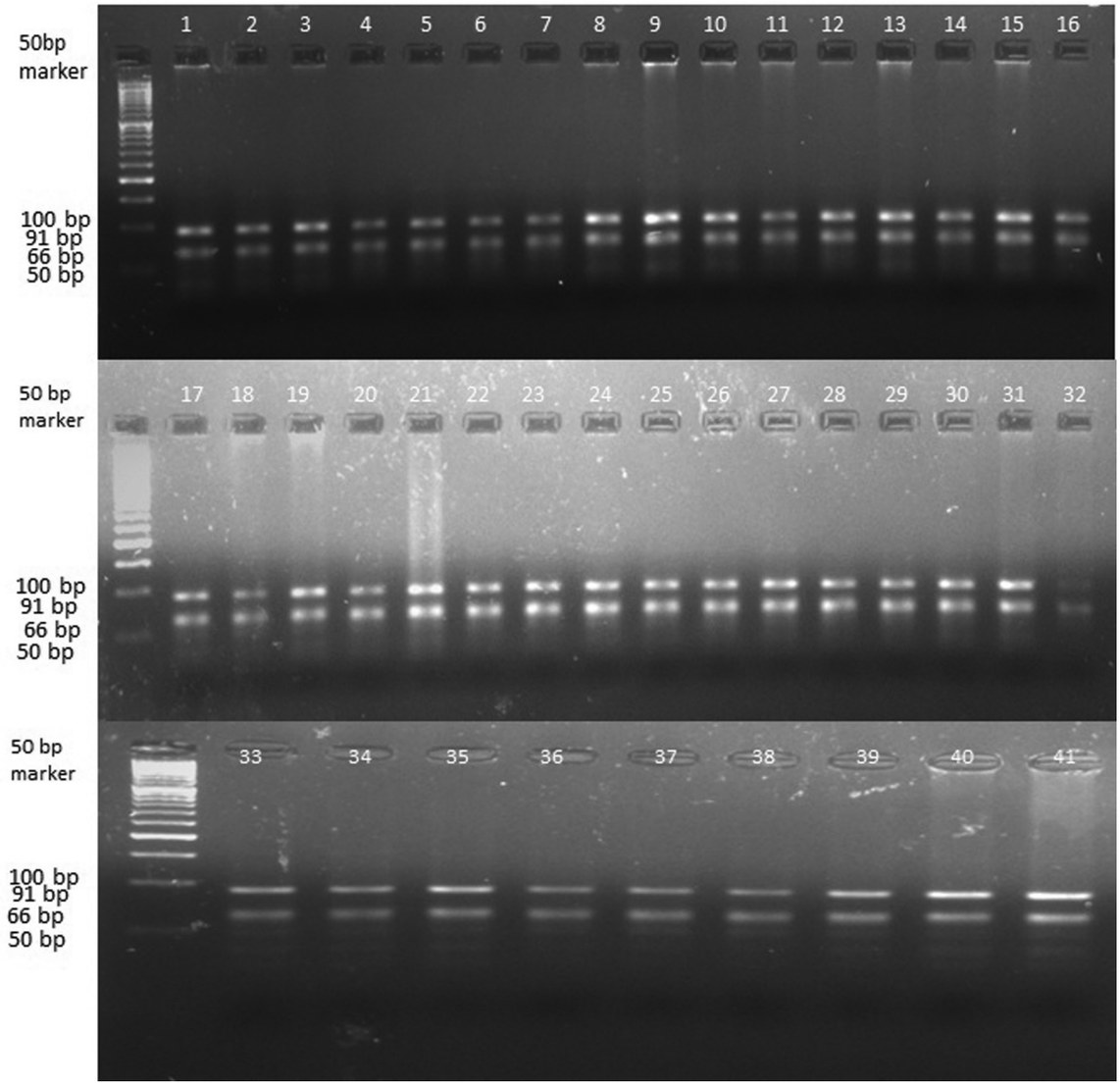


Fig. 2 Screening of Tp53 gene R249S. Polymerase chain reaction (PCR) product from genomic deoxyribonucleic acid (DNA) was digested with HaeIII enzyme and separated in 5% agarose gel. All samples show only 91 and 66 base pair (bp) bands (37, 30, and 12 bp too small to be visualized). A 50-bp ladder was used as reference.

helps us to correlate the role of mutations to cause, response to treatment, severity of the disease, and designing treatment protocols. Our laboratory has been interested in the identification of mutations in various genes of HNSCC patients of Indian origin.[13–16] Since the TP53 gene is one of the most commonly mutated genes in cancer, this study was directed to screen for commonly occurring mutations in the HNSCC patients of Indian origin. In relation to this, our previous study revealed that one of the common mutations in the TP53 gene, R248W, is rare in these patients. In order to further identify other common mutations in the TP53 gene in this cohort, we have examined for two other hotspot mutations R175H and R249S in this gene.

PCR-RFLP is one of the widely used and reliable techniques to screen for mutations in genomic DNA; using this technique, screening of 41 HNSCC patients for TP53 R175H and R249S mutations did not reveal any such mutations, suggesting that these mutations are rare in these patients. Other studies done around the world involving the screening of HNSCC patients for TP53 R175 and R249S also suggested that these mutations were absent or rare. For example, studies done in countries like the United Kingdom,[10] Sweden,[17] and the United States[18] showed these two mutation were absent among their population. Whereas screening of these two mutations in Asian countries like Iran (R249S, 8.3%)[19] and Taiwan (R175H, 2.0%)[20] also shows these mutations have low prevalence among HNSCC patients.

Two studies in Indian population cohort show that these two mutations are almost absent in their study sample. One study done by Vora et al[9] showed 0% of these two mutations ($n = 49$). Another study done by Saranath et al[21] showed R175H mutation in 2.4% and no R249S mutation in their samples ($n = 83$).

The genome makeup and hence the distribution of mutations also depends upon the geographical location as well as ethnicity.

Taking altogether, it is evident that mutations at these two codons of TP53 are not regular and thus may not be considered for prognosis in HNSCC patients.

As it is generally accepted that cancers are caused due to activating mutations in oncogenes and inactivating mutations in tumor suppressor genes, with respect to the cohort of HNSCC patients included in this study, our previous observations suggest that more than 90% of patients either carried homozygous or heterozygous activating mutations in B-Raf and Ras G12A, suggesting that activating mutations in oncogenes could be a molecular mechanism behind the cause of HNSCC.[13,16] More studies are progressing in our lab to further get an insight into the cause of HNSCC.

Though PCR-RFLP provides rapid and easy way to screen for gene variants/mutations, this technique focuses only in the restriction enzyme recognition sequences. While using Sanger's method of DNA sequencing would have provided more information about other mutations in the TP53 gene of the patients, use of next-generation DNA sequencing technique would have provided global mutations in the whole genome of the patients. Also, we could not check this mutation in heavily pretreated or progressive HNSCC as the sampling of this study was completed and more than 70% of patients in the cohort are dead. Hence, it was not possible to check further.

Conclusion

In order to understand the contribution of R175 and R249 TP53 mutations in Indian HNC patients, prevalence of these mutations in the cohort was screened by PCR-RFLP, the results reveal that these mutations are rare in these patients and they may not have any role in the cause of cancer.

Note

The manuscript has been read and approved by all authors, and the requirement of authorship has been met by each author. Each author believes that the manuscript represent honest work.

Funding

None.

Conflict of Interest

None declared.

Acknowledgment

The authors acknowledge Dr. Debnarayan Dutta, Apollo Hospital Chennai, for his valuable support for this study.

References

1 Zhou G, Liu Z, Myers JN. TP53 mutations in head and neck squamous cell carcinoma and their impact on disease progression and treatment response. J Cell Biochem 2016;117(12):2682–2692
2 Harms KL, Chen X. The functional domains in p53 family proteins exhibit both common and distinct properties. Cell Death Differ 2006;13(06):890–897
3 Higginson J, Muir CS, Munoz N. Human cancer. Eur J Cancer Prev 1993;2(03):285
4 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70(01):7–30
5 Chiang YT, Chien YC, Lin YH, Wu HH, Lee DF, Yu YL. The function of the mutant p53-r175h in cancer. Cancers (Basel) 2021;13(16): 1–18
6 Mohamadkhani A, Naderi E, Sharafkhah M, Fazli HR, Moradzadeh M, Pourshams A. Detection of TP53 R249 mutation in Iranian patients with pancreatic cancer. J Oncol 2013;2013:738915
7 Olivier M, Hollstein M, Hainaut P. TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol 2010;2(01):a001008
8 Leroy B, Anderson M, Soussi T. TP53 mutations in human cancer: database reassessment and prospects for the next decade. Hum Mutat 2014;35(06):672–688
9 Vora HH, Mehta SV, Shukla SN, Shah PM. No mutation detected in five hot spot codons of the TP53 gene by restriction site mutation analysis in patients with carcinoma of the tongue. Int J Biol Markers 2010;25(01):46–51
10 Field J, Malliri A, Jones A, Spandidos D. Mutations in the P53 gene at codon 249 are rare in squamous-cell carcinoma of the head and neck. Int J Oncol 1992;1(03):253–256
11 Kirk GD, Lesi OA, Mendy M, et al. 249(ser) TP53 mutation in plasma DNA, hepatitis B viral infection, and risk of hepatocellular carcinoma. Oncogene 2005;24(38):5858–5867

12 Nigam P, Misra U, Negi TS, Mittal B, Choudhuri G. Alterations of p53 gene in gallbladder cancer patients of North India. Trop Gastroenterol 2010;31(02):96–100
13 Gauthaman A, Moorthy A. Prevalence of K-ras codon 12 mutations in Indian patients with head and neck cancer. Indian J Clin Biochem 2021;36(03):370–374
14 Gauthaman A, Moorthy A. R248W mutations in p53 gene are rare among Indian patients with head-and-neck cancer. Indian J Med Paediatr Oncol 2020;41(04):519–522
15 Dutta D, Abarna R, Shubham M, et al. Effect of Arg399Gln single-nucleotide polymorphism in *XRCC1* gene on survival rate of Indian squamous cell head-and-neck cancer patients. J Cancer Res Ther 2020;16(03):551–558
16 Gauthaman A, Moorthy A. High incidence of BRAF V600 mutation in Indian patients with head and neck cancer. Front Biosci (Elite Ed) 2018;10(03):520–527
17 Mineta H, Borg A, Dictor M, Wahlberg P, Akervall J, Wennerberg J. p53 mutation, but not p53 overexpression, correlates with survival in head and neck squamous cell carcinoma. Br J Cancer 1998; 78(08):1084–1090
18 Xu J, Gimenez-Conti IB, Cunningham JE, et al. Alterations of p53, cyclin D1, Rb, and H-ras in human oral carcinomas related to tobacco use. Cancer 1998;83(02):204–212
19 Rogha M, Berjis N, Lajevardi SM, Alamdaran M, Hashemi SM. Identification of R249 mutation in P53 gene in tumoral tissue of tongue cancer. Int J Prev Med 2019;10:129
20 Wong YK, Liu TY, Chang KW, et al. p53 alterations in betel quid- and tobacco-associated oral squamous cell carcinomas from Taiwan. J Oral Pathol Med 1998;27(06):243–248
21 Saranath D, Tandle AT, Teni TR, et al. P53 inactivation in chewing tobacco-induced oral cancers and leukoplakias from India. Oral Oncol 1999;35(03):242–250

 © 2023. The Author(s).

A Case Report and Literature Review of Primary Central Nervous System Lymphoma in a Patient with Crigler–Najjar Syndrome: How We Managed

Udip Maheshwari[1] Disha Morzaria[1] Seema Jagiasi[1] Vashishth Maniar[1] Ashish Joshi[1] Sameer Soneji[2]

[1] Medical Oncology Department, Mumbai Oncocare Centre, Mumbai, Maharashtra, India
[2] Infinity Scan Centre, Mumbai, Maharashtra, India

Address for correspondence Dr. Udip Maheshwari, 1st Floor, Shreepati Arcade, August Kranti Rd, Nana Chowk, Grant Road West, Kemps Corner, Grant Road, Mumbai, Maharashtra 400036, India (e-mail: drudipdm@mocindia.co.in).

Ind J Med Paediatr Oncol 2024;45:80–82.

Abstract

Primary central nervous system lymphoma (PCNSL) is a rare form of CNS tumor that can be managed with curative intent using high-dose chemotherapeutic drugs. High-dose methotrexate is an essential drug for the management of PCNSL. We present a case of a 26-year-old man with a known comorbidity of Crigler–Najjar syndrome type II and a baseline bilirubin of 13.5 mg/dL, presented with somnolence and ataxia. In view of hyperbilirubinemia, the optimal treatment for CNS lymphoma, the De Angelis protocol, was modified for this patient. The patient tolerated the chemotherapy well with manageable fluctuations in bilirubin levels, followed by consolidation with whole-brain radiotherapy. He remains asymptomatic 6 months after the onset of the symptoms with the disease in complete remission. We highlight here this unusual case of PCNSL where high-dose methotrexate was used with close observation of liver function in view of hyperbilirubinemia in a known case of Crigler–Najjar syndrome.

Keywords
- Crigler–Najjar syndrome
- DeAngelis protocol
- hyperbilirubinemia
- primary CNS lymphoma

Introduction

A rare form of non-Hodgkin lymphoma, primary central nervous system lymphoma (PCNSL) is confined to the CNS. Around 90% of PCNSLs consist of B-cell lymphomas that account for 2 to 3% of all brain tumors and less than 1% of all non-Hodgkin lymphomas.[1] PCNSL is a curable malignancy with a 5-year survival rate of 30%, and standard chemotherapy regimens consisting of high-dose methotrexate and high-dose cytarabine are used for its treatment.[2] Hepatic dysfunction in such patients could be detrimental, as high-dose methotrexate has been associated with a range of liver-related adverse effects that may lead to progressive fibrosis and cirrhosis.[3] Crigler–Najjar is a syndrome wherein indirect bilirubin is high with no liver dysfunction. Our present report elucidates a case of PCNSL in a known case of Crigler–Najjar syndrome with a baseline bilirubin of 13.5 mg/dL, and we highlight modifications in the treatment protocol of this curable malignancy.

Case Report

A 26-year-old man with a history of the consanguineous marriage of parents presented with somnolence, ataxia, and forgetfulness for a duration of 4 weeks, which was progressing. His medical history included a diagnosis of Crigler–Najjar syndrome, type II, and on examination icterus was present with vital signs being in the normal range. Magnetic resonance imaging (MRI) scan of the brain demonstrated a lesion in the bilateral medial thalami extending along the posterior wall of the third ventricle and proximal aqueduct of Sylvius measuring $2.7 \times 1.8 \times 2.5$ cm with mild perilesional

article published online
September 22, 2023

DOI https://doi.org/10.1055/s-0043-1770926.
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

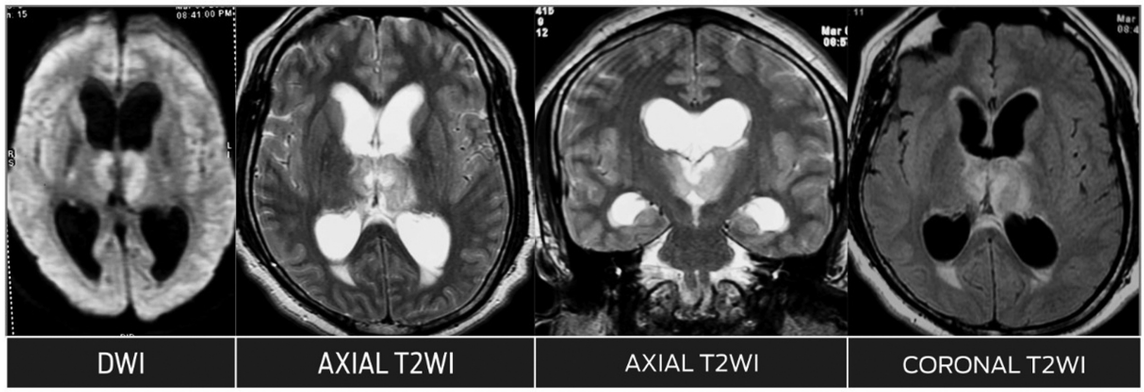


Fig. 1 Pretreatment MRI shows mass lesion in the region of the third ventricle with involvement of bilateral thalami, with perilesional edema in the thalami showing restricted diffusion with diffuse T2, fluid-attenuated inversion recovery (FLAIR) hyperintensity, and postcontrast enhancement and dilatation of the lateral ventricles with periventricular hyperintensity.

edema (►**Fig. 1**). This was followed by an endoscopic third ventriculostomy and a biopsy of the space-occupying lesion, which was suggestive of diffuse B-cell lymphoma of the CNS. No atypical or malignant cells were detected on cerebrospinal fluid cytology. Whole-body positron emission tomography–computed tomography (PET-CT) scan was done to exclude systemic diffuse large B-cell lymphoma.

Given his present history of Crigler–Najjar syndrome and a raised indirect bilirubin, magnetic resonance elastography was done to evaluate the status of the liver before starting the treatment for PCNSL. It demonstrated hepatomegaly with diffuse hepatic steatosis with a fat fraction of 12 to 17% (normal range: <5%) and a mean shear stiffness value of 2.4 kPa (reference range: 2.6–6.1 kPa). Blood work-up was normal, except for the liver function test where hyperbilirubinemia was observed with total bilirubin levels of 13.5 mg/dL and normal direct bilirubin, serum glutamic-oxaloacetic transaminase (SGOT; 21 U/L), serum glutamic-pyruvic transaminase (SGPT; 47 U/L), serum albumin (5.6 g/dL), and international normalized ratio (1.0), and the patient was categorized as Child–Pugh status B. After consultation with the hepatology team, considering PCNSL is a rare tumor with aggressive biology in conjunction with Crigler–Najjar syndrome, all the available treatment options including high-dose methotrexate as a part of the DeAngelis protocol was discussed. In view of hyperbilirubinemia, the DeAngelis protocol was modified and he was treated with high-dose cytarabine (3 g/m^2) at weeks 1 and 3 to begin with. After the first cycle of cytarabine, the patient's bilirubin increased to 20 mg/dL with normal direct bilirubin, SGOT, and SGPT. The bilirubin levels over the period of 2 weeks dropped to 11.5 mg/dL, and the second cycle of high-dose cytarabine was given. The patient had responded very well clinically, and further decision of continuing with high-dose methotrexate (3,500 mg/m^2 at weeks 7, 9, 11, 16, 18), vincristine, and procarbazine was taken. The patient's creatinine and estimated glomerular filtration rate values before high-dose methotrexate administration were 1.09 and 147, respectively; he tolerated high-dose methotrexate well with no clinically significant deterioration of the liver function and also no added hematological toxicity was seen. Whole-brain radiotherapy (36 Gy/20 fractions) was later given as a consolidation therapy. He remains asymptomatic 6 months after the onset of the symptoms with a clinically well-responding disease and improving functional status with MRI scan suggestive of signal intensity in the right middle cerebellar peduncle without postcontrast enhancement with a new area of gliosis (►**Fig. 2**).

Discussion

PCNSLs are unusual tumors and are recorded as 0.7 to 0.9% of all lymphomas, with only 0.3 to 1.5% of all intracranial tumors. These are diagnosed in immunocompromised as well as immunocompetent individuals, with a more common occurrence in men than women, in a ratio of 3:2.[4] Intracranial lesions in the brain parenchyma are the most observed imaging of PCNSL, with the common presentation of neuropsychiatric and behavior changes in 43% of patients,[5] corroborating with the clinical presentation in the present case. The present-day treatment of PCNSL includes two phases: induction and consolidation; however, age and performance status are important prognostic factors and other details, such as comorbidity, frailty, organ function, and risk of neurotoxicity, should be considered in the selection of the better treatment.

The present case had a baseline diagnosis of Crigler–Najjar syndrome, type II, which is a rare genetic disorder, and an inborn error of bilirubin metabolism noticeable by persistent rising of unconjugated bilirubin. It is an autosomal recessive disorder, where the fundamental pathogenesis of partial mutation in the *UGTA1* gene, which contains instructions for encoding liver enzyme, if characterized by type II is less severe and has good prognosis.[6] Crigler–Najjar syndrome presents with persistent jaundice and is exacerbated by intercurrent illness, stress, or drug use and the bilirubin level could go as high as 40 mg/dL.[7] Similarly, our patient presented with a bilirubin of 13.5 mg/dL and a normal direct bilirubin with subsequent rise to 20 mg/dL following the first cycle of chemotherapy; however, there was no derangement

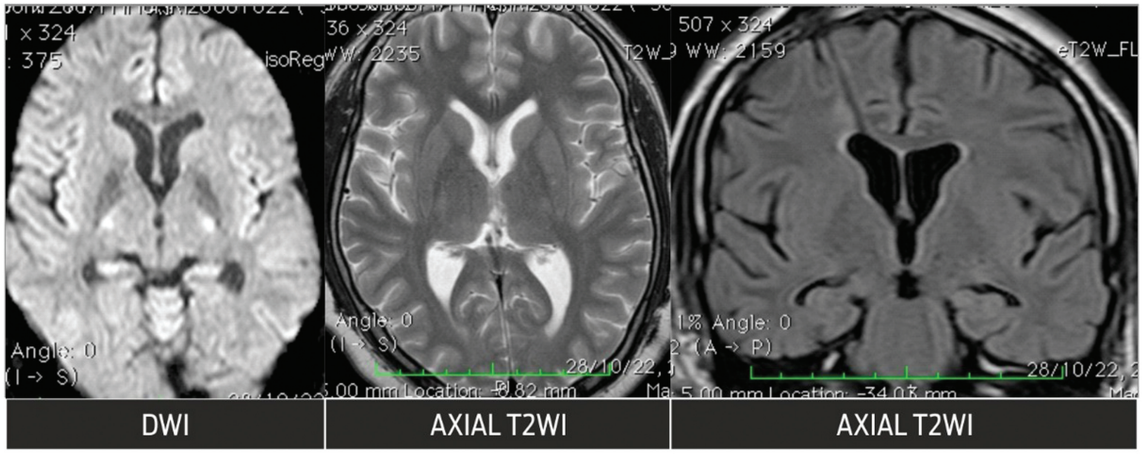


Fig. 2 Posttreatment MRI shows complete resolution of the mass lesion in the region of the third ventricle and bilateral thalami.

of the functional status of the liver. High-dose cytarabine has negligible hepatotoxicity and hence was chosen to begin the therapy.[8] Drugs that displace bilirubin from albumin such as penicillin,, salicylates, furosemide, sulfonamides, and ceftriaxone were avoided as they can affect bilirubin levels.[7]

High-dose methotrexate or long-term use of methotrexate leads to hepatotoxicity and hence there is significant restriction on its use in the doses desired and as a consequence is avoided in patients with hepatotoxicity[3]; however, in the present case, after hepatology consult and MRI elastography report and in view of the curable nature of the disease in a young patient, we started with high-dose methotrexate following two cycles of cytarabine as per the DeAngelis protocol (intravenous methotrexate, leucovorin, vincristine, procarbazine, dexamethasone, intrathecal methotrexate), and the patient tolerated chemotherapy well and was able to complete the whole course of treatment with significant clinical and radiological improvement and without any significant hepatotoxicity or hematological toxicity. The patient was later consolidated with whole-brain radiotherapy and now continues to stay in complete remission. There is paucity of data for the use of high-dose methotrexate in patients with Crigler–Najjar syndrome and hence this experience can help in taking the treatment decisions in such challenging clinical scenarios. However, the limitation of this study is that it is a single case–based report and not a case series. The major outcome is we could give all the drugs safely. Furthermore case series and research would help in future to establish the benefit of using high-dose methotrexate in patients with Crigler–Najjar syndrome.

Conclusion

PCNSL is a curable malignancy and hence completing treatment especially in younger patients is imperative. Comorbidities such as Crigler–Najjar syndrome with hyperbilirubinemia can affect the treatment decisions in view of dearth of data on the use of high-dose chemotherapy in such patients. Based on the current case, we suggest the use of standard chemotherapeutic drugs for PCNSL in Crigler–Najjar syndrome is safe; however, it requires close observation on liver function and involvement of a multidisciplinary team.

Patient's Consent

Informed consent was obtained from all individual participants included in the study.

Funding

None declared.

Conflicts of Interest

None declared.

References

1 Zeng X, Lu X, Li X, Peng L, Chen L. A case report of primary central nervous system lymphoma. J Int Med Res 2020;48(07): 300060520937839
2 Green K, Hogg JP. Central Nervous System Lymphoma. StatPearls Publishing; 2022. Accessed December 5, 2022 at: https://www.ncbi.nlm.nih.gov/books/NBK545145/
3 Kumari S. Methotrexate induced hepatotoxicity and its. management. Int J Sci Res 2013;5(09):1477–1481
4 Sasani M, Bayhan M, Sasani H, et al. Primary central nervous system lymphoma presenting as a pure third ventricular lesion: a case report. J Med Case Reports 2011;5(01):213
5 Song KW, Issa S, Batchelor T. Primary central nervous system lymphoma: epidemiology and clinical presentation. Ann Lymphoma 2021;5:16
6 Rahman MA, Islam MSU, Tasnim N. Crigler Najjar syndrome type 2: a case of unexplained jaundice in an adult. Faridpur Med Coll J 2020;15(01):43–45
7 Kumar P, Sasmal G, Gupta S, Saxena R, Kohli S. Crigler Najjar syndrome type 2 (CNS type 2): an unwonted cause of jaundice in adults. J Clin Diagn Res 2017;11(07):OD05–OD06
8 Barker JA, Marini BL, Bixby D, Perissinotti AJ. Successful use of high-dose cytarabine in a patient with acute myeloid leukemia and severe hepatic dysfunction. J Oncol Pharm Pract 2016;22(06): 811–815

Complete Remission of Cutaneous Metastasis from Invasive Breast Cancer with Abemaciclib plus Letrozole

Shaunak N. Valame[1] Dhruti D. Manek[2]

[1] Department of Medical Oncology, Jawaharlal Nehru Cancer Hospital and Research Centre, Bhopal, Madhya Pradesh, India
[2] Department of Pathology, CARE Pathology, Bhopal, Madhya Pradesh, India

Address for correspondence Shaunak Valame, DNB, Department of Medical Oncology, Jawaharlal Nehru Cancer Hospital and Research Centre, Cancer Hospital Road, Idgah Hills, Bhopal, 462001 Madhya Pradesh, India (e-mail: shaunak_valame@hotmail.com; manek.dhruti89@gmail.com).

Ind J Med Paediatr Oncol 2024;45:83–86.

Abstract

Skin metastases from internal malignancies can be the first clinical finding of cancer recurrence. If presentation is delayed, they may ulcerate and develop secondary infection. Through this case, we will highlight a case of breast cancer recurrence with extensive cutaneous metastases that clinically completely responded to oral systemic therapy, thereby obviating the need for chemotherapy and leading to stark improvement in performance status and quality of life.

Keywords
- breast neoplasms
- cyclin-dependent kinase inhibitor proteins
- remission induction

Introduction

Skin metastases from primary internal malignancies are uncommon, with an incidence of 0.6 to 10.4% of all patients with cancer.[1,2] However, it can be the first clinical finding of cancer recurrence. The most common sites of cutaneous involvement from breast carcinoma are the chest wall and the abdomen.[3] Other organs may have already been affected by the time skin lesions are identified.[4] Here we discuss a patient whose breast carcinoma recurred after 14 years with disfiguring chest and abdominal wall metastases and the exceptional therapeutic response.

Case Report

A 58-year-old postmenopausal woman, teacher by occupation, is a known case of carcinoma of the left breast treated with breast conservation surgery in 2008. Histopathology showed invasive breast carcinoma pT2N1. Immunohistochemistry (IHC) was positive for estrogen receptor (ER) and progesterone receptor (PR) but negative for Her2neu. She had received six cycles of adjuvant chemotherapy (fluorouracil, epirubicin, and cyclophosphamide) followed by adjuvant radiotherapy. She had completed 5 years of tamoxifen till 2014 and was on routine follow-ups till 2019. She presented in May 2022 with complaints of pustular discharge from a lesion on the left chest wall and left side of the abdomen for 3 months and chest pain for 6 months. She had also noticed heaviness in the right breast and nodular lesions developing over the skin of the right breast and sternum since the past 1 year.

At presentation, her Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 3. General physical examination revealed a 6×5 cm fungating left breast lesion with foul-smelling sanguinopurulent discharge, a 2×3 cm fungating lesion on anterior abdominal wall below the xiphisternum, multiple modular lesions over skin of the right breast (►**Fig. 1A, B**), and a 3×4 cm lump in the right breast upper outer quadrant. Biopsy from the right breast skin lesion and the left chest wall lesions were suggestive of invasive breast carcinoma. IHC of the right breast skin lesion showed ER 7/8, PR 6/8, and negative Her2neu, while that of the left chest wall lesion was ER 5/8, PR 6/8, and negative Her2neu. Fluorodeoxyglucose positron

article published online
September 18, 2023

DOI https://doi.org/10.1055/s-0043-1771046.
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 (**A**,**B**) Chest wall and abdominal skin lesions prior to initiation of abemaciclib + letrozole (May 2022) and (**C–E**) its regression with treatment to date.

emission tomography computed tomography (FDG PET CT; ►**Fig. 2A, C**) revealed a 3.3 × 3.6 cm left breast upper inner quadrant mass infiltrating the overlying skin with ulceration (maximum standardized uptake value [SUVmax] 11.24), multiple cutaneous deposits below the xiphisternum, largest 3.9 × 6.0 cm (SUVmax 12.02), right breast lesion 4.1 × 3.7 cm (SUVmax 11.87), right axillary lymph node 2.5 × 2.2 cm (SUVmax 9.43), right anterior diaphragmatic lymph nodes 2.8 × 3.2 cm (SUVmax 5.27), periportal lymph node 1.5 × 2.6 cm (SUVmax 8.27), lytic lesion in the manubrium and the body of the sternum with soft-tissue component 3.1 × 5.1 cm (SUVmax 7.63), multiple subpleural and parenchymal lung lesions (SUVmax 5.98), and an FDG avid lesion (SUVmax 4.47) in segment IVB of the liver without associated CT changes. Blood panel for renal and hepatic functions were adequate. Thus, she was diagnosed as metastatic hormone receptor positive breast cancer without visceral crisis.

She was started on abemaciclib 150 mg twice daily + letrozole 2.5 mg once daily in June 2022 along with bisphosphonate and calcium support. Aerobic culture of the pustular discharge showed *Proteus vulgaris* and *Klebsiella pneumoniae*, which were treated as per the sensitivity profile using piperacillin + tazobactam intravenous (IV), and amikacin IV for 7 days. Daily dressing and cleansing of the pustular discharge were done with povidone-iodine solution. The discharge receded, along with the foul smell, by the end of 1 month of therapy. By October 2022, the abdominal wall and left chest wall lesions (►**Fig. 1C**) showed healing with reduction in size. FDG PET CT (►**Fig. 2B, D**) reassessment showed complete metabolic response of all previously viable lesions. Complete morphologic resolution was observed in the left and right breast lesions, cutaneous deposits, lymphadenopathy, skeletal lesions, and pleural deposits. She developed a rash associated with pruritis over the right chest wall, which was managed conservatively, but by November 2022 (►**Fig. 1D**) it had not resolved. Thus, dose reduction of abemaciclib to 100 mg twice daily was done. The rash and pruritis responded to the dose reduction. Treatment was continued without interruptions. She had two episodes of grade 2 neutropenia in December 2022 and January 2023, and grade 2 diarrhea in February 2023. By March 2023 (►**Fig. 1E**), her skin lesions had shown complete

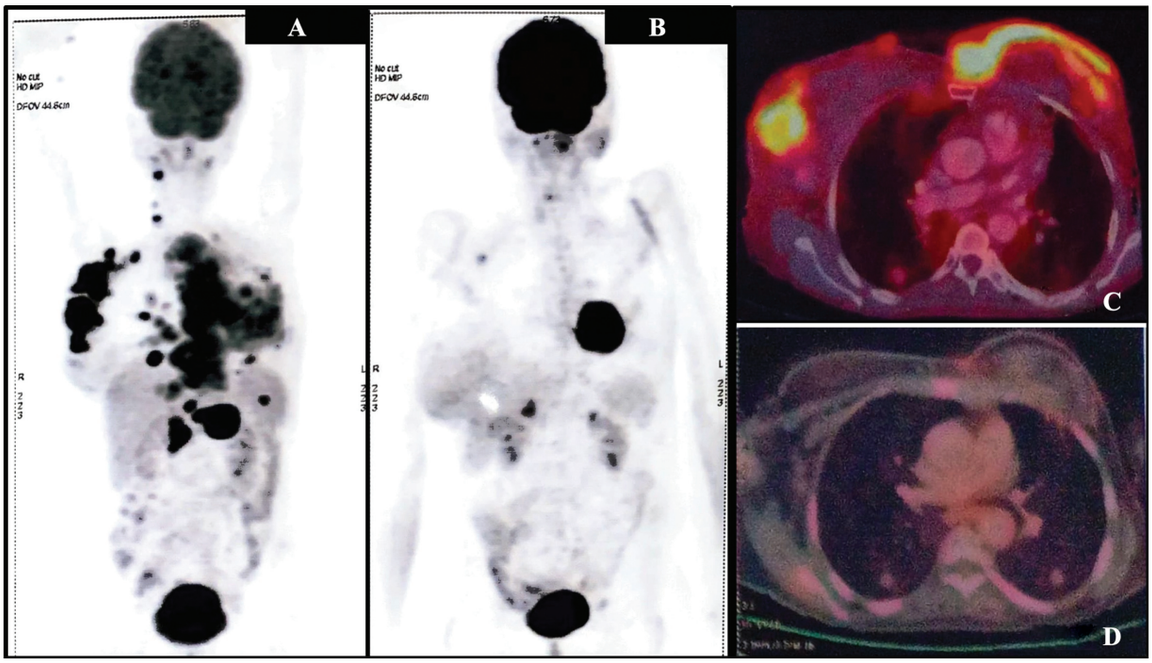


Fig. 2 Positron emission tomography (PET) at (**A**,**C**) baseline (May 2022) and (**B**,**D**) after completion of 5 months of therapy (October 2022).

clinical response, with improvement in ECOG PS to 1. As of her last visit in June 2023, she continues to be on abemaciclib 100 mg twice daily plus letrozole 2.5 mg/d.

Discussion

Cutaneous metastases from breast carcinoma occur in 23.9% of patients as per the largest reported series.[2] Nodules are the most common clinical presentation, ranging from 1 to 3 cm in size, firm consistency, solitary or multiple, and located in dermis or subcutaneous tissue.[5] Nodules are generally asymptomatic but may ulcerate and develop secondary infection.[6] Our patient initially developed skin nodules 1 year prior to her presentation. They gradually progressed leading to large ulceration with pustular discharge.

The decision to start with endocrine therapy (ET) + CDK4/6 inhibitors (CDK4/6i) was based on multiple factors. First, although skin is the largest bodily organ, extensive cutaneous metastasis is not considered a defining event of visceral crisis as per the ABC5 guidelines.[7] ET + CDK4/6i is the preferred option for hormone-receptor-positive advanced breast cancer in the absence of visceral crisis. Our patient had visceral metastasis in the liver and lungs, but there was no organ dysfunction. Second, the use of chemotherapy, for rapid efficacy may have been a prudent option as well, before switching eventually to ET + CDK4/6i, but the concurrent secondary infection was concerning. It took 8 to 10 weeks for the skin lesions to show reduction in size, although the pustular discharge was resolving by the end of 1 month of therapy. Third, among the three available CDK4/6i, abemaciclib causes the least neutropenia,[8] keeping in mind the concurrent skin infection. Fourth, our patient has an endocrine-sensitive disease, which usually indicates a favorable prognosis with this combination therapy. In the authors' region of practice, accessibility to CDK4/6i is dependent on the eligible patient's out-of-pocket expenditure. With availability of generic options, an increasing number of patients are reaping the benefit of these molecules. A detailed counseling regarding these options goes a long way in helping the patient choose the most suitable modality of treatment.

Overall, cutaneous metastases portend a poor prognosis with a median survival of 6.5 months. The median survival of patients of primary breast cancer presenting with cutaneous metastases is 13.8 months.[9] Data for overall survival in the era of CDK4/6i are, however, lacking. Our patient has completed 12 months of treatment (as of June 2023) and she showed a steady regression. It does remain to be seen how long it sustains. With her disease predominantly involving skin rather than viscera, it would be interesting to see her progression-free survival in comparison to the MONARCH3 data.[10]

The improvement in our patients' quality of life (QoL) from ECOG PS 3 to 1 cannot be understated. At presentation, she was unable to sleep due to frequent awakenings related to pain. Her decubitus for sleeping was on her knees bent forward. Due to the skin fungation and odor, her social activities had been severely compromised. With stark improvement due to therapy, she has currently resumed her teaching activities, socializing with friends and family, and has an uninterrupted sleep. Rash was observed in 15.3% of cases in MONARCH3,[10] but only three cases were of grade 3. For our patient, it responded to dose reduction of abemaciclib. The grade 2 diarrhea and neutropenia she experienced did not have a major detrimental impact on her QoL.

However, patients must be counseled to seek medical attention at the earliest new symptom onset. Our patient had a delayed presentation as she was aware that skin lesions could be a sign of cancer recurrence but did not want to undergo chemotherapy and experience its adverse events once again. The utility of CDK4/6i in obviating the need for chemotherapy is also one of its advantages.

Conclusion

Thus, our case report shows that CDK4/6i and ET have an important role to play in cutaneous metastasis of advanced breast cancer. To our knowledge, this is the first report of cutaneous metastasis showing complete metabolic and clinical response to CDK4/6i + ET.

Patient's Consent

Patient's consent was obtained to use her clinical images and PET scan images during publishing of this Case Report.

Contribution by Authors

Shaunak N. Valame was responsible for identifying the appropriate patient for treatment, counselling of patient, treatment protocols, starting of treatment and follow-ups, and providing the necessary data for compiling the article. Dhruti D. Manek contributed to reviewing the reports, literature search, and manuscript preparation and editing. The manuscript has been read and approved by both the authors.

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

The authors would like to thank our patient and her family for giving support and permission for publishing her case.

References

1 Schwartz RA. Cutaneous metastatic disease. J Am Acad Dermatol 1995;33(2, Pt 1):161–182, quiz 183–186
2 Lookingbill DP, Spangler N, Helm KF. Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. J Am Acad Dermatol 1993;29(2, Pt 1):228–236
3 De Giorgi V, Grazzini M, Alfaioli B, et al. Cutaneous manifestations of breast carcinoma. Dermatol Ther 2010;23(06):581–589
4 Hussein MR. Skin metastasis: a pathologist's perspective. J Cutan Pathol 2010;37(09):e1–e20
5 Pipkin CA, Lio PA. Cutaneous manifestations of internal malignancies: an overview. Dermatol Clin 2008;26(01):1–15, vii
6 Alcaraz I, Cerroni L, Rütten A, Kutzner H, Requena L. Cutaneous metastases from internal malignancies: a clinicopathologic and immunohistochemical review. Am J Dermatopathol 2012;34(04): 347–393
7 Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020;31(12):1623–1649
8 Roncato R, Angelini J, Pani A, et al. CDK4/6 inhibitors in breast cancer treatment: potential interactions with drug, gene, and pathophysiological conditions. Int J Mol Sci 2020;21(17):6350
9 Schoenlaub P, Sarraux A, Grosshans E, Heid E, Cribier B. Survival after cutaneous metastasis: a study of 200 cases. Ann Dermatol Venereol 2001;128(12):1310–1315
10 Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. NPJ Breast Cancer 2019;5:5

Bleeding Diathesis Secondary to a Heparin-Like Anticoagulant in a Patient with Multiple Myeloma—A Case Report and Review of Literature

Nihar Desai[1] Seema Biswas[1] Dinesh Chandra[1] Ruchi Gupta[1] Anshul Gupta[1] Rajesh Kashyap[1]

[1] Department of Hematology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Ind J Med Paediatr Oncol 2024;45:87–91.

Address for correspondence Dinesh Chandra, DM, Department of Hematology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, 226014, Uttar Pradesh, India (e-mail: dinesh3224@gmail.com).

Abstract

Multiple myeloma (MM) is a clonal plasma cell disorder that commonly presents with anemia, renal failure, hypercalcemia, and lytic bone lesions. MM is also frequently associated with thrombotic complications; however, it may rarely present with bleeding diathesis. We report a case of a 42-year-old gentleman with relapsed immunoglobulin G lambda MM who presented with epistaxis, gingival bleeding, and oozing at the venepuncture site. Routine tests of coagulation revealed a prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time. The PT and aPTT failed to correct with pooled normal plasma and the patient was thus diagnosed to have an acquired heparin-like anticoagulant (HLAC). The source of this HLAC has long been debated, but recent data have demonstrated that this HLAC may be the paraproteins produced by the malignant plasma cells. The patient was treated with intravenous protamine sulfate, repeated cycles of plasma exchange, and a daratumumab-based quadruplet regimen but eventually succumbed to an intracranial hemorrhage. HLAC is a rare but potentially fatal complication of MM that must be considered when patients with MM present with bleeding diathesis.

Keywords
- bleeding
- multiple myeloma
- daratumumab
- heparin

Introduction

Multiple myeloma (MM) is a clonal plasma cell disorder that commonly presents with anemia, renal failure, hypercalcemia, and lytic bone lesions. MM also affects the hemostatic system and contributes to thrombosis and bleeding. Hemorrhagic manifestations usually have a multifactorial etiology with thrombocytopenia, dysfibrinogenemia, platelet dysfunction, and acquired coagulation factor deficiencies being commonly reported.[1] Rarely, paraproteins with heparin-like anticoagulant (HLAC) activity can also cause bleeding. HLAC has also been rarely identified in patients with nonhematological malignancies like metastatic bladder, breast carcinoma and in patients with acquired immunodeficiency syndrome.[2–4]

We report a case of a middle-aged man with relapsed MM who presented with epistaxis and eventually developed a fatal right parietal lobe hemorrhage. The challenges in establishing the diagnosis and management of these rare HLAC are discussed along with a brief review of the literature.

Case Report

A 42-year-old gentleman was diagnosed with MM in January 2019 when he presented with anemia, low back pain, and hypercalcemia. Investigations revealed immunoglobulin G

article published online September 18, 2023

DOI https://doi.org/10.1055/s-0043-1769789.
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

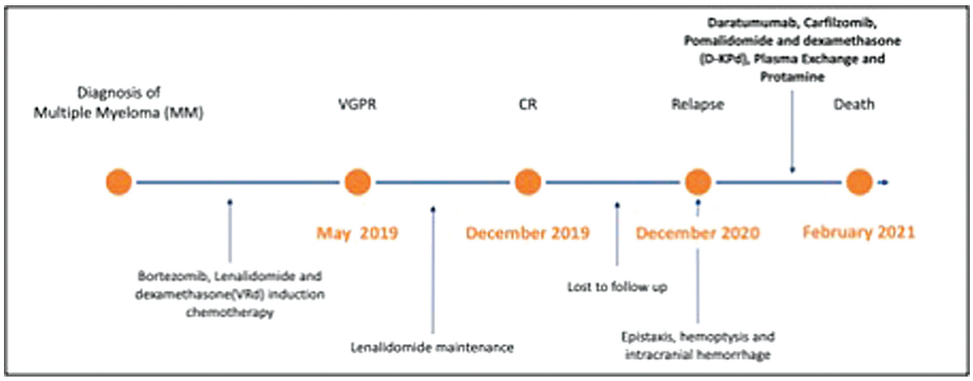


Fig. 1 Course of the disease. Complete response (CR); Very Good Partial Response (VGPR).

(IgG) lambda monoclonal protein at a concentration of 62 g/L and the bone marrow biopsy showed 80% clonal plasma cells. He was risk stratified as Revised International Staging System (R-ISS) stage II and received eight cycles of triplet induction therapy with bortezomib, lenalidomide, and dexamethasone. He attained a very good partial response but deferred autologous stem cell transplantation. Thereafter, he remained on lenalidomide maintenance for 16 months. The course of disease has been shown in ►**Fig. 1**. In his present visit, the patient complained of epistaxis, gingival bleed, and oozing at the venepuncture site.

Laboratory investigations at this time, approximately 2 years from the time of initial diagnosis, were suggestive of disease relapse with IgG lambda monoclonal band of 35 g/L and serum free light chain kappa, 1.07 mg/L; lambda, 3310mg/L; the kappa/lambda ratio, 0.0003. The platelet count was normal (183×10^9/L), but the results of his coagulation tests were deranged (►**Table 1**). The addition of an equal volume of normal plasma did not correct the elevated activated partial thromboplastin time (aPTT) and thrombin time (TT) indicating the presence of an inhibitor. Plasma levels of factor VIII, IX, and X were normal as was the fibrinogen level (Clauss assay) and D-dimer, ruling out disseminated intravascular coagulation. The addition of protamine sulfate (concentration of 100 µg/mL) to the patient's plasma in a 4:1 ratio normalized the TT. This indicated a possibility of a heparin like mechanism contributing to the derangement. A detailed review of the patient's drug chart did not identify the use of exogenous heparin. Considering this background, it was thought that an endogenous heparin activity attributable to the paraprotein was the causative factor.

Local hemostatic measures and infusion of fresh frozen plasma (15 mL/kg) did not arrest the bleeding. He was treated with a continuous infusion of protamine sulfate (5mg/hour) that led to a slight improvement in his TT in vitro (75 seconds) but did not stop his bleeding manifestations. Given the lack of evidence available for the ideal management of this rare complication, we considered managing the underlying disease aggressively with a quadruplet regimen consisting of daratumumab, carfilzomib, pomalidomide, and dexamethasone. This led to a significant reduction in his bleeding manifestations and further treatment was administered on an outpatient basis.

Table 1 Coagulation studies at the time of onset of bleeding

Test	Result	Normal value
Hemoglobin (g/L)	76	120–140
Platelet count ($x10^9$/L)	183	150–400
Prothrombin time (s)	24.6	10.8–13.6
Activated partial thromboplastin time (s)	65.8	28.6–32.6
Thrombin time (s)	154	16–21
Fibrinogen (g/L)	5.92	2–4
Mixing studies with pooled normal plasma	Not corrected	–
Factor X assay	72%	50–150%
Factor VIII assay	66%	50–150%
D-dimer	Negative	Negative
Dilute Russel viper venom test (dRVVT)	Negative	<1.20
Thrombin time with 100 µg/mL protamine sulfate mixed in a 1:4 ratio	16.6	16–21

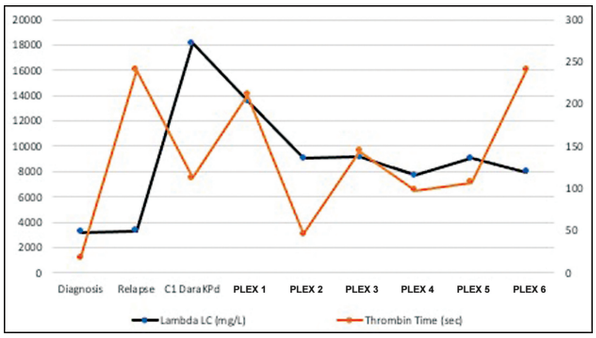


Fig. 2 Change in light chain burden and thrombin time with treatment. DaraKPD, daratumumab-carfilzomib, pomalidomide, dexamethasone; PLEX, plasma exchange (plasmapheresis).

However, he returned to us 2 weeks later with complaints of epistaxis, gingival bleed, headache, and vomiting, and a right parietal hematoma was seen on a noncontrast computed tomography of the brain. His coagulation parameters were deranged again and there was a significant increase in his lambda light chain (18,600mg/L; ►**Fig. 2**). He underwent six cycles of plasma exchange as a means to reduce his light chain burden but his clinical condition continued to worsen and he developed status epilepticus for which he was intubated. Despite continuing supportive care his hemorrhagic manifestations worsened and he could not be salvaged.

Discussion

Contrary to the more common predisposition to thrombotic complications, patients with MM have been reported to have clinically significant bleeding diathesis ranging from 13 to 36%.[5] The underlying etiology is not identified but thrombocytopenia, platelet function defects, acquired factor VIII and X deficiency, and inhibition of fibrin polymerization are some of the mechanisms proposed.[6,7] A rarely reported cause of bleeding is the presence of a circulating HLAC with less than 30 cases being reported to date (►**Table 2**).

HLAC is usually suspected when patients with monoclonal gammopathies present with hemorrhagic manifestations and an elevated prothrombin time (PT), aPTT, and TT. The aPTT remains prolonged despite mixing studies with normal plasma suggesting the presence of an inhibitor. The correction of TT on the addition of protamine sulfate further supports the diagnosis.

The mechanism by which HLAC causes hemorrhagic manifestations is unclear. It has been hypothesized that the negatively charged, sialic acid-bearing monoclonal immunoglobins bind the heparin-binding domain of antithrombin and cause a similar activation to that caused by exogenous heparin.[8] However, Khoory et al proposed that the coagulopathy was not due to a myeloma protein, but a circulating proteoglycan functioning as a cofactor for antithrombin III.[9] The source of this acquired anticoagulant is also debated with neoplastic plasma cells, their paraprotein product, damaged endothelial cells, and soluble CD138 (syndecan) being implicated by various authors.[10] Patients with primary amyloidosis also frequently present with clinically significant bleeding and a prolonged TT, suggesting that the HLAC may not always be derived from the myeloma protein.[11]

Of the reported cases, most patients presented with bleeding manifestations at the time of their initial diagnosis. However, our patient had no coagulation abnormalities at the time of diagnosis and developed fatal hemorrhage at the time of disease relapse. Patients most frequently presented with mucocutaneous bleeding, deep-seated hematomas, and bleeding from surgical/biopsy sites.[12] The severity of bleeding does not correlate with the disease burden and severe bleeding has been reported in patients with monoclonal gammopathy of underdetermined significance and smoldering multiple myeloma as well.[12] Earlier studies did report a high frequency of HLAC in patients with high disease burden like plasma cell leukemia but most contemporary reports show no such association. The impact of HLAC on the prognosis is also not known. Most of the studies have reported deaths due to bleeding and sepsis, rather than the primary disease.[13]

There is a paucity of data to guide the management of this rare complication and the treatment is usually decided by the degree of bleeding. Given the mechanism of action of this inhibitor, protamine sulfate has been used by many authors with variable success, but the optimal dose and duration of protamine therapy have not been determined.[14,15] Studies have also demonstrated an improvement in the coagulation parameters with reduction in the tumor burden and successful treatment with plasma exchange has been reported by Goddard et al.[16,17] To the best of our knowledge, this is the first report on the use of novel agents like monoclonal antibodies for these patients and also the first report from India. Our patient was treated with daratumumab, carfilzomib, pomalidomide, and dexamethasone as a means of rapidly reducing his plasma cell burden. He also underwent plasma exchange with minimal improvement in his laboratory parameters but without any clinical benefit. However, our approach was limited as experimental studies to isolate and characterize the HLAC activity of the paraprotein were not carried out. There is a paucity of literature regarding its mechanism, and treatment is largely supportive. Future research is warranted to better understand the mechanism, source, and optimal management of patients with this dreaded complication.

Conclusion

HLAC is an uncommon cause of bleeding in patients with plasma cell disorders that should be considered in those who present with bleeding diathesis and a prolonged TT. It may manifest at the time of initial presentation or later in the disease course and its severity may not correlate with the disease burden.

Indian Journal of Medical and Paediatric Oncology Vol. 45 No. 1/2024 © 2023. The Author(s).

Table 2 Summary of coagulation abnormalities, treatment, and outcome of patients with heparin-like anticoagulant—literature review

	Author	Age	Gender	Diagnosis	Subtype	PT (s)	aPTT (s)	TT (s)	Fibrinogen (mg/dL)	At the time of diagnosis	Treatment	Outcome
1	Shen et al[13]	48	M	MM	IgD lambda	14	118	28.5		Yes	VCD	Alive
2	Torjemane et al[10]	55	M	MM	IgG lambda	14	63	65	267	No	VAD + protamine	Alive
3	Khoory et al[9]	68	F	MM	IgA kappa	12	58	>600	250		L phenylalanine mustard + corticosteroids	–
4	Chapman et al[6]	54	M	MM	IgG kappa	13.5	59	38	300	No	VMP	–
5	Kaufman et al[14]	55	M	PCL	–	14	>150	>120	345	Yes	FFP+ protamine + chemotherapy	Dead
7	Martínez-Martínez et al[18]	73	F	MM	IgG	–	75–97 at various time points	>180	–	Yes	Recombinant VIIa + chemotherapy	No further bleeds
8	Tefferi et al[12]	68	F	MM	IgA kappa	21	48	>600	138	No	Cryoprecipitate+ plasmapheresis + protamine	Dead (sepsis)
9	Tefferi et al[12]	47	M	MM	IgG lambda	25	44	>600	432		None	Dead (renal failure)
10	Tefferi et al[12]	78	F	MM	Kappa LC	28	48	>600	883			Death (bleeding)
9	Shen et al[13]	47	M	MM	IgG lambda	25	44	>600	432	Yes	Corticosteroids	Dead
10	Willner and Chisti[19]	62	F	MM	IgG kappa	12	44.3	32.3	228	No	Protamine	No further bleeds
11	Goddard et al[17]	57	M	MM	–	16		180		No	Protamine+ PLEX+ chemo	Dead

Abbreviations: aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma; IgG, immunoglobulin G; MM, multiple myeloma; PCL, plasma cell leukemia; PLEX, plasma exchange; PT, prothrombin time; TT, thrombin time; VAD, vincristine, adriamycin, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VMP, bortezomib, melphalan, prednisolone.

Declaration of Patient Consent
Yes.

Funding
None.

Conflict of Interest
None.

References

1 Saif MW, Allegra CJ, Greenberg B. Bleeding diathesis in multiple myeloma. J Hematother Stem Cell Res 2001;10(05):657–660
2 Tefferi A, Owen BA, Nichols WL, Witzig TE, Owen WG. Isolation of a heparin-like anticoagulant from the plasma of a patient with metastatic bladder carcinoma. Blood 1989;74(01):252–254
3 Rodgers GM, Corash L. Acquired heparinlike anticoagulant in a patient with metastatic breast carcinoma. West J Med 1985;143 (05):672–675
4 de Prost D, Katlama C, Pialoux G, Karsenty-Mathonnet F, Wolff M. Heparin-like anticoagulant associated with AIDS. Thromb Haemost 1987;57(02):239–239
5 Perkins HA, MacKenzie MR, Fudenberg HH. Hemostatic defects in dysproteinemias. Blood 1970;35(05):695–707
6 Chapman GS, George CB, Danley DL. Heparin-like anticoagulant associated with plasma cell myeloma. Am J Clin Pathol 1985;83 (06):764–766
7 Rahman S, Veeraballi S, Chan KH, Shaaban HS. Bleeding diathesis in multiple myeloma: a rare presentation of a dreadful emergency with management nightmare. Cureus 2021;13(03):e13990
8 Saadalla A, Seheult J, Ladwig P, et al. Sialic acid-bearing paraproteins are implicated in heparin-like coagulopathy in patients with myeloma. Blood 2020;136(17):1988–1992
9 Khoory MS, Nesheim ME, Bowie EJ, Mann KG. Circulating heparan sulfate proteoglycan anticoagulant from a patient with a plasma cell disorder. J Clin Invest 1980;65(03):666–674
10 Torjemane L, Guermazi S, Ladeb S, et al. Heparin-like anticoagulant associated with multiple myeloma and neutralized with protamine sulfate. Blood Coagul Fibrinolysis 2007;18(03): 279–281
11 Mumford AD, O'Donnell J, Gillmore JD, Manning RA, Hawkins PN, Laffan M. Bleeding symptoms and coagulation abnormalities in 337 patients with AL-amyloidosis. Br J Haematol 2000;110(02): 454–460
12 Tefferi A, Nichols WL, Bowie EJ. Circulating heparin-like anticoagulants: report of five consecutive cases and a review. Am J Med 1990;88(02):184–188
13 Shen H, Wu C, Chen L, Zhang R. Acquired heparin-like anticoagulation process in a patient with multiple myeloma: a case report and literature review. Transl Cancer Res 2020;9(11): 7366–7371https://tcr.amegroups.com/article/view/45909 cited 2022Mar27 [Internet]
14 Kaufman PA, Gockerman JP, Greenberg CS. Production of a novel anticoagulant by neoplastic plasma cells: report of a case and review of the literature. Am J Med 1989;86(05):612–616
15 Palmer RN, Rick ME, Rick PD, Zeller JA, Gralnick HR. Circulating heparan sulfate anticoagulant in a patient with a fatal bleeding disorder. N Engl J Med 1984;310(26):1696–1699
16 Llamas P, Outeiriño J, Espinoza J, Santos AB, Román A, Tomás JF. Report of three cases of circulating heparin-like anticoagulants. Am J Hematol 2001;67(04):256–258
17 Goddard IR, Stewart WK, Hodson BA, Dawes J. Plasma exchange as a treatment for endogenous glycosaminoglycan anticoagulant induced haemorrhage in a patient with myeloma kidney. Nephron J 1990;56(01):94–96
18 Martínez-Martínez I, González-Porras JR, Cebeira MJ, et al. Identification of a new potential mechanism responsible for severe bleeding in myeloma: immunoglobulins bind the heparin binding domain of antithrombin activating this endogenous anticoagulant. Haematologica 2016;101(10):e423–e426
19 Willner CA, Chisti MM. Treatment of bleeding diathesis associated with a heparin-like anticoagulant in plasma cell neoplasia using protamine. Case Rep Hematol 2018;2018:4342301

SETBP1 in Myeloid Malignancies—Putting Breadcrumbs Together in Rare, Uncommon, and Common Pediatric Cases

Aroonima Misra[1,*] Bhavika Rishi[1,*] Srilatha Bajaj[2] Sumita Saluja[3] Amitabh Singh[4]

[1] Scientist-C, Indian Council of Medical Research (ICMR)-National Institute of Pathology, New Delhi, India
[2] Department of Pediatrics, Vardhman Mahavir Medical College (VMMC) and Safdarjung Hospital, New Delhi, India
[3] Department of Laboratory Hematology, Vardhman Mahavir Medical College (VMMC) and Safdarjung Hospital, New Delhi, India
[4] Department of Pediatrics, Division of Pediatric Hematology/Oncology, Vardhman Mahavir Medical College (VMMC) and Safdarjung Hospital, New Delhi, India

Address for correspondence Amitabh Singh, MD, Pediatrics, Department of Pediatrics, Division of Pediatric Hematology/oncology, Vardhman Mahavir Medical College (VMMC) and Safdarjung Hospital, New Delhi 110029, India (e-mail: doc.amitabh@gmail.com).

Ind J Med Paediatr Oncol 2024;45:92–94.

In resource-constraint settings, genetic testing is rarely available for patients. We report the association of SETBP1, a major oncogene of interest in myeloid malignancies, with juvenile myelomonocytic leukemia (JMML) and with GATA 1 mutation. The modulating role of SETBP1 in Rat sarcoma virus (RAS)-driven myeloid malignancies, especially JMML, is unknown. In vivo and in vitro studies point to the role of SETBP1 in aggressive leukemogenesis.[1] SETBP1 mutation is not considered the primary event.[2] The association of SETBP1 with RAS and PTPN11, protein tyrosine phosphatase nonreceptor type 11 (PTPN11) confers both self-renewal and oncogenic transformation. The outcome of SETBP1 with confounding mutations like PTPN11 and interlinked pathways of Mitogen-activated protein kinase (MAPK) may be difficult to predict.[3,4] PTPN11 in co-association with RAS in JMML is an independent poor prognostic factor[5] and confounds the effects of those associated with SETBP1. PTPN11 also has poor prognostic outcomes post-hematopoietic stem cell transplantation in JMML patients.[3]

We present three cases of rare associations of SETBP1 with GATA1 mutation, JMML, and one with concomitant PTPN11 mutation. Our first case was a novel association of SETBP1 in transient abnormal myelopoiesis (TAM) with a fatal outcome, the second case was JMML with a blastic transformation-like presentation with tumor lysis, and the third case was a case of JMML. These different outcomes could be attributed to the association of an underlying SETBP1 or one of the pathway mutations downstream of myeloid leukemogenesis. The presentation, however, in all cases was similar: severe anemia, massive organomegaly, presentation with high leucocyte count, and tumor lysis syndrome in one patient (another rare occurrence in JMML) (►**Table 1**). Two of the patients died within 4 days despite the best supportive treatment. One of the JMML cases with isolated SETBP1 mutation has an indolent course compared to the other two and is alive on follow-up awaiting transplantation (►**Table 1**). SETBP1 may not confer a dismal outcome and is just evidence of complex mutagenesis and could also mean heterogeneous clones with isolated mutations rather than co-existent mutations.

SETBP1 co-expression leads to increased phosphorylated-driven MAP kinases, with a possible role of trametinib in these disorders.[2] Co-occurrence with other known mutations highlights the interrelated roles of the downstream leukemoid pathogenesis in these strikingly different neoplasms. The case of TAM with SETBP1 could initiate new insight into myeloid leukemogenesis. Next-generation sequencing is essential in the diagnostic management of all pediatric myeloproliferative disorders and can improve outcomes with better risk stratification.

Ethical Statement

All ethical consideration and permissions were obtained for preparation of manuscript.

* *Joint first authors-Both contributed equally.*

article published online
June 9, 2023

DOI https://doi.org/10.1055/s-0043-1769491.
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 Clinicopathological characteristics of the novel, uncommon, and common case with *SETBP1* mutation

Case	1. TAM with *SETBP1* case	2. Uncommon *SETBP1* mutated JMML case	3. Common *SETBP1* in JMML
Brief history	A 2-day-old baby boy born out of nonconsanguineous marriage, 3rd in birth order presented with leucocytosis, thrombocytopenia and anemia with myeloid blasts	A 1-year-old child presented with a history of progressive paleness of the body, frequent infections, fever, and abdominal distension for 1 month. The child had monocytic leucocytosis, 20% blasts on peripheral smear with laboratory evidence of tumor lysis syndrome	A 1-year-old male child born out of nonconsanguineous marriage, presented with complaints of fever with abdominal distension for 3 months
Primary investigations	Flow cytometry: AML with MPO + CD34 + CD117 + CD33 +, CD56 +, and CD7dim+ (►**Fig. 1**)	Investigations suggested myeloid blast crisis in a known case of JMML with tumor lysis syndrome	Investigations showed leucocytosis with monocytosis, thrombocytopenia, and massive hepatosplenomegaly. The child met the criteria for JMML on the investigations (Splenomegaly, 8% blasts on Peripheral smear, leucocytosis, absolute monocytosis, myeloid precursors
Sequencing result	*GATA1, SETBP1*	*PTPN11, SETBP1*	*PTPN11, SETBP1*
Details of variants	1. Delins variant (chrX:g.48791258_48791271delinsTCAGGCAGT; c.149_162delinsTCAGGCAGT) in the GATA1 gene (561X, 8.4% MAF). 2. Frameshift deletion (chrX: g.48791243_48791246del; c.134_137del) 560X, 24.8% MAF in GATA1 gene (►**Fig. 1**) 3. *SETBP1* gene mutation at c.2843G > A (ENST00000649279.2) in Exon 4 was found (859X, MAF- 48.9%) (►**Fig. 1**)	1. *PTPN11* mutation [(chr12: g.112450406G > A; c.226G > A) not reported in ExAC and 1000 genomes databases[VCV000013336.5]] 2. *SETBP1* mutation [(chr18: g.44951942G > A; c.2602G > A) gain-of-function mutation MAF-0.002%, not reported in 1000 genomes database] (►**Fig. 2A** and **B**)	1. *PTPN11* gene [c.179G > T (ENST00000635625.1) 51X, MAF- 49.3%]. 2. *SETBP1*mutation [c.1102A > G (ENST00000649279.2) with heterozygous allele burden (50%) and 258X depth read (►**Fig. 3A** and **B**)
Treatment	Supportive	Supportive	On supportive transfusion care, awaiting BMT
Outcome	Mortality at day 2 of admission	Mortality at day 4 of admission	Alive and hemodynamically stable on transfusion
Remarks	Never reported in literature co-association of *SETBP1* with *GATA1*in a patient could highlight the inter-related myeloid pathway in Leukemia and MPNS	The child was detected to have concurrent. The rare presentation as tumor lysis syndrome could be attributable to co-existent *PTPN-11* and *SETBP1* mutation in the same clone by simultaneous or additional hit	*SETBP1* in JMML in our case three did not have a dismal outcome, suggesting the *SETBP1* and *PTPN11* could be heteroclonal or subclonal, rather than concomitant in single malignant clone

Abbreviations: AML, acute myeloid Leukemia; BMT, bone marrow transplant; GATA 1, GATA binding protein 1; JMML, juvenile myelomonocytic leukemia; PTPN11, protein tyrosine phosphatase nonreceptor type 11; SETBP1, SET binding protein 1.

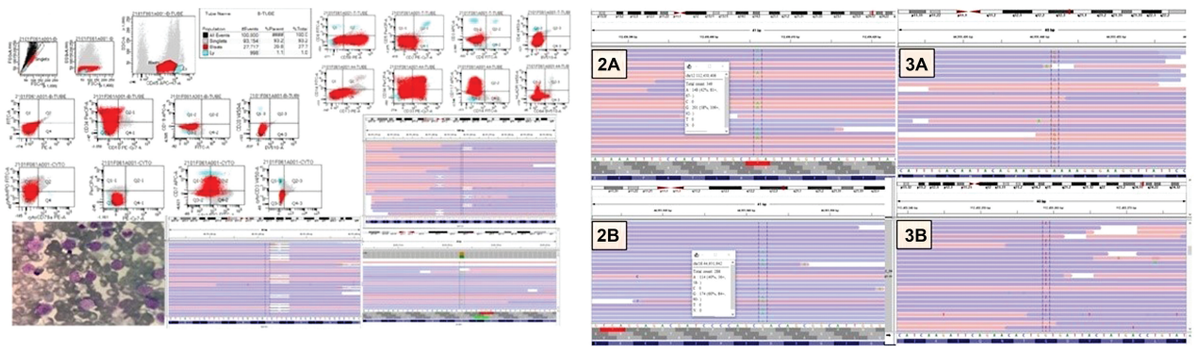


Fig. 1 The morphological features, flow-cytometry characters, and sequencing result of patient 1 in the left-side plane and the sequencing results for patients 2 (2**A** and **B**) and patient 3 (3**A** and **B**) on the right-side pane.

Conflict of Interest
None declared.

Acknowledgment
The sequencing panel for JMML and TAM for these patients supported by our NGO partner Cankids Kidscan, New Delhi, performed at a CAP-accredited laboratory.

References

1 Shiba N, Ohki K, Park MJ, et al. SETBP1 mutations in juvenile myelomonocytic leukaemia and myelodysplastic syndrome but not in paediatric acute myeloid leukaemia. Br J Haematol 2014; 164(01):156–159
2 Carratt SA, Braun TP, Coblentz C, et al. Mutant SETBP1 enhances NRAS-driven MAPK pathway activation to promote aggressive leukemia. Leukemia 2021;35(12):3594–3599
3 Locatelli F, Niemeyer CM. How I treat juvenile myelomonocytic leukemia. Blood 2015;125(07):1083–1090
4 Piazza R, Magistroni V, Redaelli S, et al. SETBP1 induces transcription of a network of development genes by acting as an epigenetic hub. Nat Commun 2018;9(01):2192
5 Alfayez M, Issa GC, Patel KP, et al. The clinical impact of PTPN11 mutations in adults with acute myeloid leukemia. Leukemia 2021;35(03):691–700

 © 2023. The Author(s).

INDIAN SOCIETY OF MEDICAL & PAEDIATRIC ONCOLOGY

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

INDIAN SOCIETY OF MEDICAL & PAEDIATRIC ONCOLOGY

Membership Benefits

EASY ACCESS TO INTERNATIONAL ONCOLOGY FORUMS

International oncology forums such as ASCO, ESMO, and others are linked on the website. These educational links will only be available to members.

CONNECTION TO ABOUT 2500 JOURNALS

The ISMPO is joining the National Cancer Grid (NCG) as an association member. As a result, ISMPO will have access to around 2500 journals that are only available to our members.

THE EARLIER, THE BETTER

Introduction Trainee Membership soon during DM/DNB medical oncology training period. This will be mandatory for participating in competitions like ISMPO-TYSA.

A CONVENIENT WAY TO SUBMIT AN ABSTRACT

The ISMPO member will be able to submit abstracts for various ISMPO meetings and conferences directly through the website. Also, eligible for several Awards.

REGISTER NOW AT THE BEST RATES

The membership fees will be revised once medical oncologists from SAARC and other countries are included.
Thus, register now

FREE LIFE MEMBERSHIP

Complimentary Life membership for DM, DNB, and DrNB medical oncology students.