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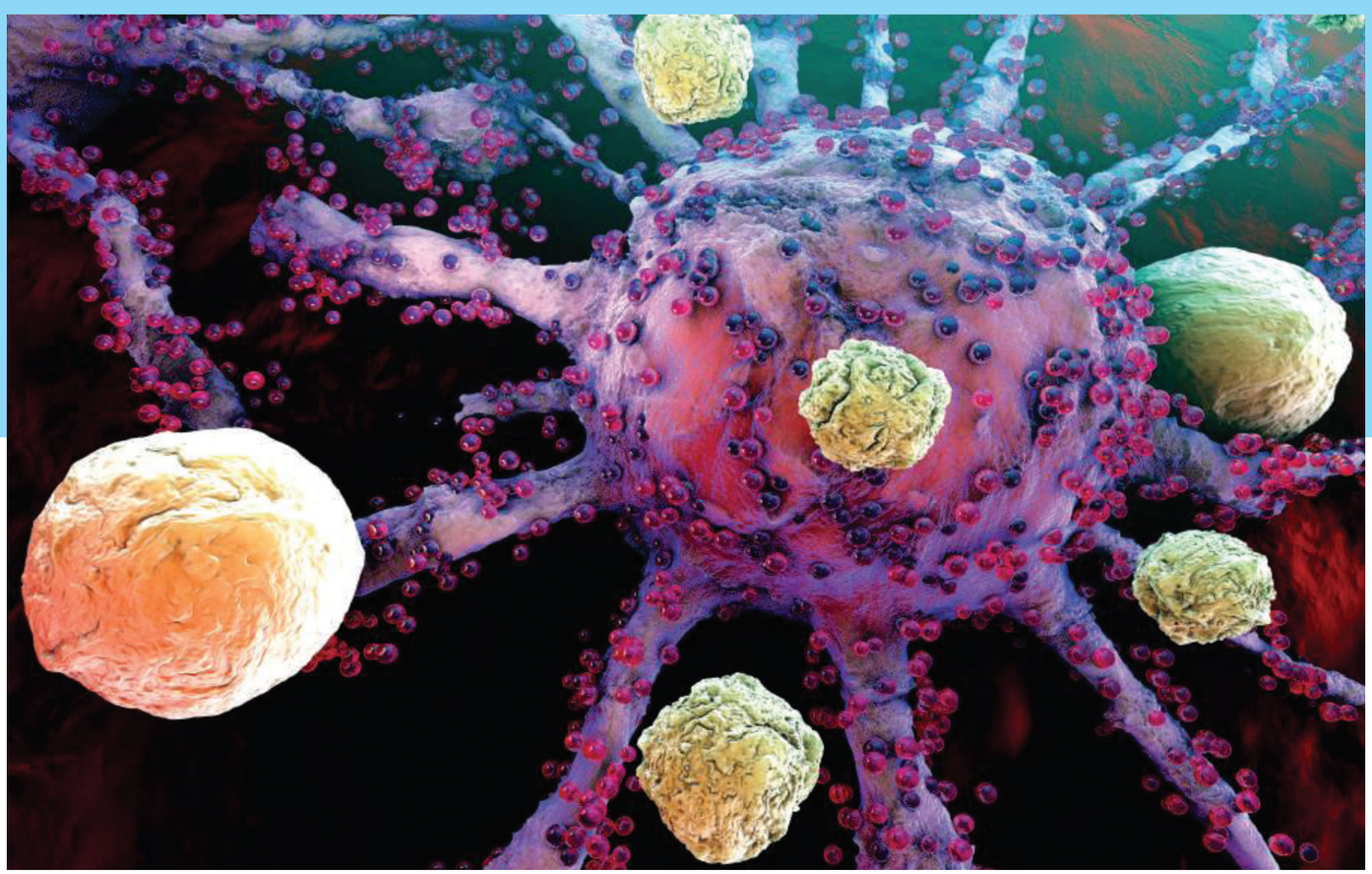

Special Issue: Imaging recommendations for diagnosis, staging and management of Cancers

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Editorial

Editorial

Dr. Abhishek Mahajan[1]

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Indian Journal of Medical and Paediatric Oncology (IJMPO) is an international peer-reviewed open-access journal under the aegis of Indian Society of Medical and Paediatric Oncology (ISMPO) catering to and disseminating knowledge on all aspects of oncology among the medical fraternity with Dr. Padmaj Kulkarni being the Editor-in-Chief. The idea of having an exclusive edition dedicated to imaging guidelines in oncology was conceived by Dr. Abhishek Mahajan, Consultant Radiologist at Clatterbridge Cancer Centre, Liverpool, United Kingdom, and ex-Consultant Radiologist at Tata Memorial Hospital, Mumbai, Maharashtra, India, having more than 15 years of experience in oncoimaging, with the aim of providing a comprehensive one-stop reference guide to the clinicians and radiologists alike on practical aspects of site-specific imaging in oncology. Dr. Padmaj Kulkarni, Editor-in-Chief of IJMPO, Dr. Abhishek Mahajan, Editor of this special edition on imaging guidelines in oncology, along with the associate editors Dr. Nivedita Chakrabarty and Dr. Jinita Majithia, have brought forth two issues pertaining to imaging guidelines in oncology authored by radiologists and clinicians having expertise in their respective domain across the country.

Each site-specific article in this edition has been structured to include risk factors and etiopathogenesis, epidemiology, imaging guidelines, and consensus statements issued by international and national organizations responsible for policy making on screening, diagnosis (including interventions), staging, management, and follow-up of cancer, and a summary of recommendations at the end for ease of reference. Such a comprehensive article is aimed to keep the clinicians and radiologists updated on the current cancer imaging guidelines and management and also to address the lacunae in knowledge between cancer institutes and general hospitals by disseminating awareness among the entire medical fraternity. In addition, synoptic reporting templates have been provided at the end of each of the articles to bring about uniformity and quality in radiology reports pertaining to oncology. Each article has been double-blind peer-reviewed predominantly by the clinicians so that the radiologists and clinicians can speak a common language in terms of content.

Such a mammoth task would not have been accomplished without the relentless efforts by the esteemed authors and the untiring efforts of the entire editorial team to bring forth impactful and utilitarian content.

Conflict of Interest
None declared.

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Multisystem Imaging Recommendations/Guidelines: In the Pursuit of Precision Oncology

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Abstract

With an increasing rate of cancers in almost all age groups and advanced screening techniques leading to an early diagnosis and longer longevity of patients with cancers, it is of utmost importance that radiologists assigned with cancer imaging should be prepared to deal with specific expected and unexpected circumstances that may arise during the lifetime of these patients. Tailored integration of preventive and curative interventions with current health plans and global escalation of efforts for timely diagnosis of cancers will pave the path for a cancer-free world. The commonly encountered circumstances in the current era, complicating cancer imaging, include coronavirus disease 2019 infection, pregnancy and lactation, immunocompromised states, bone marrow transplant, and screening of cancers in the relevant population. In this article, we discuss the imaging recommendations pertaining to cancer screening and diagnosis in the aforementioned clinical circumstances.

Keywords

- AI
- BMT
- CI-RADS
- COIN
- COVID-19
- Immuno-compromised
- iTNM
- oncology
- Lactation
- pregnancy

Multisystem Imaging Recommendations/ Guidelines: In the Pursuit of Precision Oncology

(1) Imaging tumor, node, metastasis (iTNM), Cancer Imaging Reporting and Data Systems, Comprehensive Onco-Imaging Network.

(2) Imaging recommendations in special circumstances in oncology—coronavirus disease 2019, pregnancy and lactation, immunocompromised state, screening for cancers, and bone marrow transplant.

(3) Imaging recommendations for artificial intelligence in oncological imaging.

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Imaging Tumor, Node, Metastasis, Cancer Imaging Reporting and Data Systems, and Comprehensive Onco-Imaging Network

Addressing the Need

Cancer is a leading cause of morbidity and mortality worldwide, irrespective of the level of human development. As per the estimations of Global Cancer Observatory 2020, approximately 19.3 million new cancer cases and 10 million cancer-related deaths occurred worldwide in 2020.[1] The health care industry is overwhelmed by the sheer number of residual cancer cases and is under immense pressure for not only promptly diagnosing and treating cancer but also developing newer modalities to address the growing needs. Tailored integration of preventive and curative interventions with current health plans and global escalation of efforts for timely diagnosis of cancers will pave the path for a cancer-free world.

With the development of advanced radiological techniques, medical practice is becoming increasingly dependent on imaging. From providing morphological, physiological, to functional information, imaging has grown by leaps and bounds in the past few decades and continues to innovate. Medical imaging plays a significant role in cancer management and directing targeted therapy with a positive influence on the quality-adjusted survival of cancer patients.[2] A simulation-based analysis by Ward et al studied the positive impact of scaling up imaging and treatment availability on the synergistic survival gains for patients with cancer.[3]

The radiology report serves as a document for means of communication between a radiologist and the treating physician or surgeon, describing imaging characteristics of the tumor and providing information on the stage of cancer. For centuries, elaborated and descriptive reporting was the norm in oncoimaging as it allowed the radiologist freedom of expression to emphasize on key findings with the use of free text. However, various pitfalls were identified with narrative reporting. Variability in the length, ambiguity in terminology, and inconsistency in form of the report served as potential sources of confusion among treating oncologists.

Inception of comprehensive synoptic reporting systems has opened up new avenues for a more uniform and simplified approach to oncoimaging. An organized workflow algorithm using structured templates can establish consistency in reports, prevent errors, and promise quality assurance. The use of different categories and subcategories in a report, usually related to organ systems or anatomic structures, can allow clear communication, improve readability, and reduce omission of pertinent information, all of which are expected to contribute to evidence-based medicine.[4]

Since it is well known that imaging can influence the management of cancer by altering the locoregional staging (for example, upstaging of oral cancer by the depiction of mandibular erosion and perineural spread or high infratemporal extension on imaging, both of which are not evident clinically), the introduction of a concise reporting format in oncoimaging is the need of the hour and can be achieved by implementing iTNM staging, i.e., imaging tumor (T), node (N), metastasis (M) staging. Some studies have found that the clinical TNM (cTNM) and the pathological TNM (pTNM) do not always corroborate,[5,6] highlighting the role of imaging in accurate TNM staging, pre- or posttreatment. A comparative study by Frommhold et al investigated the agreement between pTNM and iTNM in renal tumors; in about 67% cases, iTNM and pTNM were matching, whereas in only 53% cases, the cTNM matched with pTNM, proving the higher efficacy of imaging in TNM staging.[7] The major drawback of interobserver and intraobserver variations in radiology reporting can be mitigated by standardization.

Reporting and Data Systems

Reporting and Data Systems (RADS) was conceptualized and endorsed by the American College of Radiology (ACR) for providing standardized terminologies and well-defined classification algorithms for concise interpretation of lesions. It is modality and technique dependent and ensures uniformity in lesion description.[8] It uses a stepwise numerical scoring system, based on the degree of suspicion of disease, with management recommendations based on the score. Committees worked to build structured terminology and algorithms to measure the risk of malignancy or disease. The risk assessment criteria are provided in terms such as "normal" or "negative," "benign," "probably benign," "intermediate risk," to "definitely malignant," or "high risk." Tools are provided through a range of products from lexicon, risk stratification system, atlas, flash cards, report templates, and white papers. Certain systems also allow modifiers to convey specific details, such as inadequate examination, negative examination, post-treatment findings, and nondisease-related findings. The prototype system first published by ACR in 1993 was the Breast Imaging Reporting and Data System (BI-RADS) for the stratification of breast cancer patients.[9] Following this, several RADS, oncology, and nononcology have been developed as depicted in ►**Table 1**, and few are under active development with the primary focus on oncological disease.

The main purpose for the development of RADS was for the assessment of disease probability. However, it has been observed that currently there are no existing standardized reporting formats in cancer imaging that can provide a comprehensive overview of the stage of an already diagnosed cancer in a single, readable, and reproducible document. Hence, we propose the introduction and use of Cancer Imaging Reporting and Data Systems (CI-RADS) which will standardize oncoradiology reports globally. The aim is to provide optimum guidelines for reporting a scan of an already diagnosed case of cancer, usually on cross-sectional imaging like computed tomography (CT) or magnetic resonance imaging (MRI), but also ultrasound, especially for lesion characterization in breast, ovarian, and thyroid cancers. A standard and universally accepted scaffolding for the radiologist to build a report on will ensure that the imaging TNM or iTNM is correctly addressed. Each report will have ensured quality in terms of information on tumor characterization, extent, locoregional and vascular relations, nodal metastasis, and distant spread, all of which will individually

Table 1 Various Reporting and Data Systems (RADS)

RADS Disease		Modality
BI-RADS	Breast cancer	Mammography, MRI, Ultrasound
C-RADS	Colon cancer	CT colonography
LI-RADS	Liver cancer	MRI, CT, US, and contrast-enhanced US
Lung-RADS	Lung cancer	Low dose CT
NI-RADS	Head and neck cancers	PET, CT, MRI
O-RADS	Adnexal masses	Ultrasound
PI-RADS	Prostate cancer	MRI
TI-RADS	Thyroid cancer	Ultrasound
BT-RADS	Brain tumor	MRI
CAD-RADS	Coronary artery disease	CT coronary angiography
CO-RADS	COVID	CT chest

Abbreviations: BI, brest imaging; COVID, coronavirus disease; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; US, ultrasound.

influence patient management. Thus, while RADS defines the nature of a lesion as benign or malignant, the aim of CI-RADS will be to create a process for analyzing a tumor in terms of T, N, and M stages that will ensure that even the minor of details of the tumor nature and extent, which can impact management, not be missed. It can also reduce the turn-around-time of reports as it simplifies the approach to even larger complicated masses. A synoptic reporting template aims at making reporting of even the most complicated lesions, much simpler and more systematic. RADS discusses the probability of a lesion being malignant or not, and CI-RADS talks about the disease extent or a diagnosed case, usually malignant, so as to infer the iTNM staging.

A CI-RADS that already exists is the Lung Cancer Reporting and Data System (LC-RADS).[10] The LC-RADS algorithm not only provides a template for reporting a primary lung neoplasm but also standardizes the follow-up scans with special reference to the possible complications of a particular treatment regimen such as radiation-related lung injury, immunotherapy-related toxicity, and surgical complications requiring urgent interventions. The introduction of this standardized template for reporting lung cancers highlights the impact of a comprehensive report in allowing the treating physicians and surgeons to plan the further course of action.[10] Thyroid Cancer Reporting and Data System (T-CIRADS) for thyroid cancer imaging and Head and Neck Cancer Reporting and Data System (HN-RADS) for head and neck cancer imaging have also paved the path for the journey of standardization in oncoimaging.[11,12] Standard reporting templates ensure high-quality and clear communication.

There has always been a motivation to integrate radiological and molecular investigations with clinical data so as to create a single document to overview the entire disease that is being dealt with. The creation and implementation of a comprehensive combined report for a patient's baseline and response assessment scan can help treat the patient and not the cancer.

Future Applications of Cancer Imaging Reporting and Data Systems

The development of models based on artificial intelligence (AI), for image perception, is one of the foreseeable applications of CI-RADS. Data mining and its optimal utilization can only be successful in the case of standardization. The use of structured data in various domains, like, the development of predictive models, imaging biobanking, and machine learning, will form an essential part of precision medicine. For example, the use of computer-aided techniques like artificial neural network (ANN) for BI-RADS was developed for application in mammographic interpretation and diagnostic decision-making.[13]

The development of high-accuracy clinical predictive models can help individualize diagnostic and prognostic decision-making and risk stratification in oncology practice.[14] The predictive ability of a clinical predictive model enhances significantly with the incorporation of diagnostic imaging. There is a growing trend of machine learning algorithms in the development of predictive models. Implementation and merger of synoptic radiology reports with machine learning algorithms in predictive models are expected to behave as automated "second opinions" in order to augment human performance. This can make it robust by improving the diagnostic accuracy, providing prognosis, and quantitating risk,[15] all of which can be addressed by the implementation of CI-RADS. Imaging biobanks which are defined by the European Society of Radiology as "organized databases of medical images and associated imaging biomarkers (radiology and beyond) shared among multiple researchers and linked to other biorepositories"[16] are massive reserves of data for research. However, the creation of a network of biobanks from different geographical distributions and diversities, to form a repository of information, can be realized by utilization of standard reporting systems like CI-RADS. Recent advances in medical image processing, such

as texture analysis, deep learning, and AI[17] along with the aid of an integrative CI-RADS methodology for the approach to imaging, show a promising future.

Tumor Response Criteria

Imaging-based response criteria are the crucial aspect of oncological imaging, patient care, and clinical trials. They provide a set of guidelines to assess tumor burden for objective assessment of response to therapy. World Health Organization (WHO) published the first standardized response criteria in 1981, called the WHO criteria.[18] This was followed by the launch of Response Evaluation Criteria in Solid Tumors (RECIST) criteria in 2000 and revised in 2009 as RECIST 1.1.[19] Both these criteria were developed during the era of cytotoxic chemotherapeutic agents and monitored only the change in the tumor size during the course of treatment as a benchmark for response evaluation without consideration of the change in tumor attenuation to distinguish viable and nonviable components. Both these criteria are still commonly used in clinical trials.

- WHO criteria: WHO criteria used bidimensional measurements of the tumor for response assessment, that is, the sum of the products of the longest overall diameters—which means the sum of the longest overall tumor diameter and longest diameter perpendicular to the longest overall diameter and classified the tumor burden. The major pitfall with WHO criteria was the use of two dimensions (increasing the probability of progressive disease) and not defining the number of lesions to be measured.
- RECIST 1.0 criteria: RECIST 1.0 criteria shifted to unidimensional measurements with the use of the longest diameter of the lesion. It addressed the pitfalls of the WHO criteria with the definition for the minimum size of measurable lesions (10 mm at spiral CT and 20 mm at conventional CT), number of lesions to be measured (10 lesions with < 5 in any one organ), and details on the usage of new imaging technologies (spiral CT).
- RECIST 1.1: RECIST 1.1 made modifications in RECIST 1.0 criteria, like measurement of lesions (target lesions measured in longest dimension, at least 10 mm, and target lymph nodes measured in short axis at least 15 mm), measurements taken in axial planes (other planes may be used if isotropic CT reconstruction/MRI are available), and soft tissue component of bone lesions qualifying for measurements and maximum number of lesions (five lesions with up to two in any one organ).

A major drawback with the use of WHO guidelines and RECIST was their dependence only on anatomic changes based on CT and MRI findings. Another important drawback was their selective use in patients receiving cytotoxic therapy and thus not being validated for use in patients receiving targeted or immunotherapy which are known to bring about a necrotic or cystic change in the tumor rather than shrinkage.[20] The advent and widespread use of molecular imaging and whole-body MRI with diffusion-weighted imaging has made a significant impact on the response assessment criteria as well as the development of new anticancer therapies.[20] Positron emission tomography (PET) CT is also increasingly used as an imaging biomarker to determine the early therapeutic response to novel anticancer therapies with the development of quantitative and semiquantitative methods for objective measurements and response categorization.[21,22]

A summary of these response criteria has been given in ►**Table 2**.[23]

Table 2 Tumor response criteria

WHO criteria		RECIST v1.0	RECIST v1.1
	Sum of products of two longest diameters in perpendicular dimensions (*bidimensional; surface area)*	Sum of longest diameters of target lesions (*unidimensional*)	Sum of longest diameters of nonnodal target lesions and short axis of nodal target lesions (*unidimensional*)
No. of lesions measured	All lesions	Target lesions: maximum 5 per organ, 10 in total	Target lesions: Maximum 2 per organ, 5 in total
		Nontarget lesions: Not specifically addressed. Increase in size of one or a few nontarget lesions is PD, even when target lesions are stable or responding	Nontarget lesions: Imaging of nontarget lesions not necessary at every protocol-specified time point for declaration of partial response or stable disease. Increase in nontarget lesions is only PD, if the increase is representative of change in overall tumor burden.
Response			
Complete response (CR)	No lesion for at least 4 wk	No lesion for at least 4 wk	Disappearance of all target lesions or lymph nodes <10 mm in the short axis

Abbreviations: RECIST, response evaluation criteria in solid tumors; WHO, World Health Organization.

Table 3 Tumor response criteria in immunotherapy

Response	irRC	irRECIST	iRECIST	imRECIST
CR	Complete disappearance + confirmation not confirmation at mandatory 4 wk		Confirmation only in nonrandomized trials	Disappearance of all lesions
PR	≥30% decrease + ≥50% decrease + No unequivocal confirmation at progression in 4 wk nonmeasurable disease		≥30% decrease + No unequivocal progression in nonmeasurable disease	≥30% decrease
PD	>20% increase + ≥25% increase + > 5 mm absolute confirmation at increase in MTB 4 wk + confirmation at 4 wk		Immune unconfirmed progressive disease (iUPD) and immune confirmed progressive disease (iCPD)	≥20% increase or > 5 mm absolute increase
SD	None	None	None	None

Abbreviations: CR, complete response; imRECIST, immune-modified response evaluation criteria in solid tumors; irRC, immune-related response criteria; irRECIST, immune-related response evaluation criteria in solid tumors; iRECIST, immunotherapy response evaluation criteria in solid tumors; MTB, mycobacterium tuberculosistuberculosis; PD, progressive disease; PR: partial response; SD, stable disease.

Tumor Response Criteria in Immunotherapy

With the introduction of immune-oncology drugs, like the immune check-point inhibitors, there has been an observation of atypical and unique tumor responses. The phenomenon of pseudoprogression was described to indicate an initial radiological progression by RECIST and subsequent delayed tumor shrinkage. This often led to premature discontinuation of treatment which led to the introduction of certain criteria to address the insufficiencies of RECIST. This includes immune-related response criteria, immune-related response evaluation criteria in solid tumors, immunotherapy response evaluation criteria in solid tumors, and immune-modified response evaluation criteria in solid tumors. The various aspects of these response categories are described in ►**Table 3**.[24]

Tumor Response Criteria in Targeted Therapy

With the advent of targeted therapy, various criteria have been developed as below.

- Choi response criteria for gastrointestinal (GI) stromal tumor utilizes the change in tumor attenuation in addition to tumor size, considering a minimal decrease or even an increase in the size of the lesion in early stages of treatment secondary to internal hemorrhage, necrosis, or myxoid degeneration, proving to be a better predictor of clinical response to imatinib than RECIST.[25]
- Modified RECIST for hepatocellular carcinoma accounted for arterial phase enhancement of the lesion in dynamic CT or MRI as transarterial radioembolization may lead to disease stabilization without actual shrinkage of tumor size, but with a significant decrease in the hypervascularity and the presence of necrosis.[26]
- European Organization for Research and Treatment of Cancer (EORTC criteria) and PET Response Criteria in Solid Tumors (PERCIST) account for tumor metabolism and use fluorodeoxyglucose (FDG) PET/CT for tumor response assessment.[20,27]
- Macdonald criteria for glioblastoma with response interpretation based on changes in tumor size/enhancing lesions, interpreted in light of steroid use and neurological findings.[28]
- Response Assessment in Neurooncology (RANO) has superseded Macdonald criteria by addressing the issues and taking into consideration nonenhancing components and T2-weighted/fluid-attenuated inversion recovery lesions.[28]
- RANO-BM criteria (Response Assessment in Neuro-Oncology Brain Metastasis) are recommendations for standardized tumor response and progression assessment in clinical trials involving brain metastasis.
- Cheson response criteria for malignant lymphomas uses FDG PET, immunohistochemistry, and flow cytometry.[29]
- Deauville criteria for lymphoma simplifies the 5-point scale to standardize interpretation.[29,30]
- Lugano recommendations are revised recommendations regarding the use of the Cheson and Deauville criteria. It formally incorporated FDG PET into staging and response evaluation for FDG-avid lymphomas.[31]
- MD Anderson Bone Response Criteria is for response assessment in bone lesions.[32]

A summary of the response criteria with their advantages and disadvantages has been given in ►**Table 4**.[33,34]

Comprehensive Onco-Imaging Network

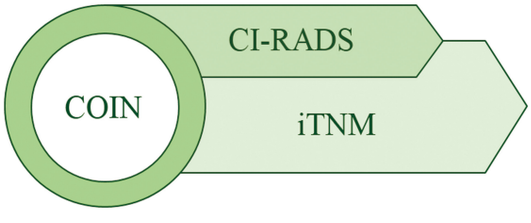
We also propose the formation of COIN, a Comprehensive Onco-Imaging Network, an alliance that will coordinate the expertise and leadership of oncoradiologists in order to form a coalition for the exchange of valuable information which will eventually augment the practice of oncoimaging. The objectives of this network will not be limited to improving patient management via imaging but also for ensuring continued research and education. By ensuring high-quality radiology practice, this network can stress upon the importance of standardized reporting and its impact on cancer care.

Table 4 Advantages and disadvantages of various response criteria

Response assessment criteria	Year	Imaging modalities	Assessment type	Advantages	Disadvantages
WHO	1979 and 1981	CT	Anatomic, size-based	First objective measurements of images of all lesions	Time-consuming procedure; interobserver variability
RECIST v1.0	2000	CT, MRI	Anatomic, size-based	Easier than WHO; measurement of "target" and "nontarget" lesions; less measurement errors	Only anatomic assessment
RECIST v1.1	2009	CT, MRI, PET	Anatomic, size-based	Easier than RECIST v1.0 Lymph nodes incorporated	Only anatomic assessment
mRECIST	2006	CT, MRI	Anatomic, size-based	Simpler than RECIST v1.1	Only anatomic assessment, not prospectively validated
mRECIST for HCC	2010	CT, MRI	Anatomic and functional; based on contrast enhancement	Measurement of a viable tumor. Appropriate for loco-regional therapies	Only for HCC
EASL and qEASL	2000 and 2012	CT, MRI	Anatomic and functional; based on contrast enhancement	qEASL is better than RECIST to predict OS; measurement of a viable tumor	Only for HCC
Choi criteria	2007	CT	Anatomic and functional; based on tumor density	Validated for GIST, more precise than RECIST; Measurement of a viable tumor	Only for GIST
Morphologic response	2009	CT	Anatomic and functional; based on morphologic changes	Appropriate for bevacizumab treatment	For CRC liver metastases, not prospectively validated
irRC	2009	CT, MRI	Anatomic, size-based	For the treatment with immune- checkpoint inhibitors, capture of atypical response (pseudoprogression)	The variability of interpretation
irRECIST	2013				
iRECIST	2017				
imRECIST	2018				

Abbreviations: CRC, colorectal cancer; CT, computed tomography; EASL, European Association for the Study of the Liver; GIST, gastro-intestinal stromal tumor; HCC, hepatocellular carcinoma; imRECIST, immune-modified response evaluation criteria in solid tumors; mRECIST, modified RECIST; MRI, magnetic resonance imaging; irRC, immune-related response criteria; irRECIST, immune-related response evaluation criteria in solid tumors; iRECIST, immunotherapy response evaluation criteria in solid tumors; MTB, mycobacterium tuberculosis; OS, overall survival; PET, positron emission tomography; qEASL, quantitative EASL.

COIN will also aspire to promote improvement in clinical practice by providing a common ground for various specialties in order to have a multidisciplinary approach to cancer management. The formation of disease management groups under this network will allow individualization of treatment and will be a step forward in precision medicine.



Cancer Imaging Recommendations in Special Circumstances—Coronavirus Disease 2019, Pregnancy and Lactation, Immunocompromised State, Screening for Cancers, and Bone Marrow Transplant

Coronavirus Disease and Cancer

Globally, by the end of May 2022, there have been 525,467,084 confirmed cases of COVID- 19, including 6,285,171 deaths, reported to WHO. Patients diagnosed with, suspected of, or at risk of developing cancer are especially vulnerable during this pandemic as there can be delay in early detection, delay in treatment initiation, and progression of cancer[35,36] These patients have more adverse

Table 5 Indications and common findings of COVID-19 in various imaging modalities

Imaging modality	Indication	Common findings
Lung ultrasound (LUS)	Triage Severity of lung damage Evolution of the disease Safely used in children and pregnant women	B-Line Pleural line irregularity White lung Consolidation Broncho-grams
CT	More sensitive and specific	GGO GGO + Consolidation Crazy paving Broncho-grams Reversed halo sign
Chest X-ray	Less sensitive than a CT scan, it may be used as a first-line approach In very critical patients	Bilateral consolidation GGO White out lungs
MRI	Not relevant for the evaluation of lung disease	Diagnostic pathway COVID-induced thrombogenic acute stroke, impaired consciousness, acute necrotizing hemorrhagic encephalopathy
FDG-PET	Not used in an emergency	Cancer staging

Abbreviations: COVID, coronavirus disease; CT, computed tomography; FDG-PET, fluorodeoxyglucose-positron emission tomography; GGO, ground glass opacities; MRI, magnetic resonance imaging.

outcomes as compared to the general population due to COVID-19 induced immunosuppression.[37]

Coronavirus Disease Imaging

Cancer treatments like chemotherapy and immunosuppressant taken after surgical cancer removal usually weaken the patient's immune system rendering them more vulnerable COVID infection.[38] Among cancer patients, patients with hematolymphoid malignancy have a maximum risk of getting affected by COVID.[39] Lung ultrasound and CT have a high sensitivity in detecting pulmonary interstitial involvement.[40] Chest radiography is an easily available and affordable tool in COVID care but it is less sensitive for early lung changes due to infection.[41] ►**Table 5** summarizes the indication and common findings of various imaging modalities.

Management of Cancer Patients During the Coronavirus Disease 2019

Cancer patients have been reported to be at increased risk of contracting COVID-19 infection and a higher proportion require greater levels of intensive care, having a more rapidly evolving disease and an increased risk of death.[36] Here, we classify the patients seeking cancer treatment into three categories and discuss the impact of COVID pandemic and recommendations for each.

New Suspected and Diagnosed Case of Cancer

The COVID-19 pandemic prompted significant reductions in procedures used to diagnose cancers including imaging, resulting in a decrease in new cancer diagnoses. For newly suspected or diagnosed cancer cases, initial assessment becomes the crucial step for detection, staging, and future management.[42] Initial imaging modalities for workup include radiograph, CT scan, MRI, and PET CT. New patients walking into the radiological procedure room should be screened for COVID symptoms. Overcrowding should be avoided by modifying waiting rooms and streamlining registrations. Patients and staff should be encouraged to wear masks, perform hand hygiene, and appropriately use personal protective equipment (PPE). If positive for symptoms, the patient should be advised an reverse transcription polymerase chain reaction test. Once a swab is confirmed as negative, the patient can proceed with a routine workup. Usage of high-level PPE, including gown, gloves, eye protection, and at least an N-95 respirator is suggested during clinical examination and imaging of COVID-19-positive patients. During the COVID wave, all patients undergoing imaging should be treated as if they are COVID-19 positive to minimize the risk of unknown exposure.[43]

Cancer Imaging in Patients Receiving Curative Therapies

Cancer curative therapies were affected worldwide due to lockdowns; many patients could not undergo planned surgery and experienced longer preoperative workup delays including imaging. Many of the proposed triages are based on experience or expert consensus. In some centers, the decision to schedule or delay surgery and adjuvant and neoadjuvant therapies has been made by experts (surgeons, oncologists, pathologists, and radiologists). The European Society for Medical Oncology has proposed a 3-tier classification for prioritization of treatment during the COVID-19 pandemic. The high-priority group comprises patients with vital commitment or who could gain a significant improvement in mortality or quality of life with treatment. The medium-priority group is noncritical patients, but a delay in starting their therapy beyond 6 weeks could have consequences. Finally, the low-priority group could be treated after the pandemic since the benefit of treatment is marginal.

Treated Case of Cancer Patient Who Are on Followup

Lockdown due to COVID waves has caused a disturbance in the routine follow-up of treated cancer patients. Teleconsultation including real-time video consultation is an

excellent tool for following cancer patients. Imaging done at patients' native places can be reviewed by expert radiologist with the help of teleradiology.[44]

Imaging Findings of Coronavirus Disease 2019Impacting Cancer Imaging

►**Table 6** compiles the impact of imaging findings of COVID-19 on cancer imaging and recommendations for mitigating the same. [45]

Imaging Recommendations During Pregnancy and Lactation

Radiological imaging during pregnancy has been a hot topic of discussion among clinicians, and it has been observed that the lack of knowledge or confusion across almost entire medical fraternity leads to either unrequired avoidance of useful procedures/diagnostic tests or needless interruption of breastfeeding. Taking diverse applications of imaging into consideration, it is not uncommon for women with diagnosed or undiagnosed pregnancy to be evaluated by one of these imaging modalities.

While MRI and ultrasounds are universally recognized as safe imaging options during pregnancy, sometimes they end up being overprescribed. Clinicians should be encouraged to make prudent use of these diagnostic tests only in cases where the test is expected to provide a health benefit to the patient. It is also essential that we educate ourselves as well as other clinicians about the fact that the radiation exposure with most radiological procedures (except a few), CT scans, and nuclear imaging techniques are at a dose much lower than the exposure needed to harm the fetus[46]; hence, radiography, CT scans, and nuclear imaging studies should not be withheld if the benefits outweigh the possibilities of fetal harm. Care should be taken that these procedures are carried out only by trained/experienced personnel and in accordance with set guidelines/protocols and at minimum required frequency.

Ultrasound

Although there has been no documentation of adverse effects on the fetus following diagnostic ultrasound procedures, including duplex Doppler imaging, it is advisable to keep the fetal exposure to the minimum by keeping the acoustic outputs to as low as reasonably achievable. For instance, in the United States, the Food and Drug Administration limits the spatial-peak temporal average intensity of U.S. transducers to 720 mW/cm^2 which theoretically has the potential to increase the temperature of the fetus as high as 2 °C but unlikely at a single fetal anatomical site.[47] Although color Doppler has the maximum potential to increase the tissue temperature, it has no detrimental effect on the health of the pregnancy when used appropriately.[48]

Magnetic Resonance Imaging

The main benefits of MRI over ultrasound sonography (USG)/CT scans are superior soft tissue resolution, negligible operator dependency, and no use of ionizing radiations. Some theoretical concerns exist for fetus raised such as teratogenesis, acoustic damage, and tissue heating, but there is very little supporting evidence. Proximity to the scanner decides tissue heating which is negligible near the uterus.[49,50] The ACR recommends no special consideration for the first (as compared to any other) trimester of pregnancy.[51] The use of gadolinium-based agents is highly beneficial in the imaging of the nervous system because they readily cross the blood–brain barrier when pathologies such as presence of a tumor, abscesses, or demyelination disrupt the blood–brain barrier. Although gadolinium-based contrast provides a better idea on imaging of tissue margins and invasion in cases of placental abnormalities, noncontrast MRI gives comparable results with the added benefit of no contrast-related adversities.[50] Even though gadolinium adds a great value to MRI, there have been some concerns raised regarding the water solubility and breast milk excretion of the same. Free gadolinium has been

Table 6 Impact of imaging findings of COVID-19 on cancer imaging and recommendations for mitigating the same

	Impact on imaging	Recommendation
Lung imaging	COVID-19 lung findings can mimic therapy- associated pneumonitis and other viral infections. 18F-FDG uptake in mediastinal lymph nodes in a patient with COVID-19 has been described, consistent with active inflammation	Discussion with treating clinician, careful history, and appropriate evaluation for infection should be considered.
Neurologic imaging	Ischemic and hemorrhagic complications due hypercoagulopahthy. Meningoencephalitis, demyelinating lesions and acute leukoencephalopathy. Can rarely confused with immunotherapy-associated or tumor induced autoimmune and/or limbic encephalitis.	Assessing the exact etiology of brain imaging findings inpatients on immunotherapy and COVID-19 is suggested.
Abdominal findings	Abdominal manifestations in patients result in imaging findings most of which are nonspecific.	No evidence suggesting mimic of cancer.

Abbreviations: COVID-19, coronavirus disease 2019; FDG, fluorodeoxyglucose.

proven to have teratogenic effects in few animal studies on repeated use and thus should be used with caution until proven otherwise in human studies.[49]

There are very little data published on the duration of fetal exposure because the contrast present in the amniotic fluid undergoes repeated swallowing and excretion by the fetus in utero, increasing the potential to dissociate from the chelating agent and causing harm to the fetus.[51]

De Santis et al[52] concluded no adverse perinatal or neonatal outcomes among 26 pregnant women who received gadolinium-based contrast agents in first trimester of the pregnancy. They also recommended further studies in order to exclude any teratogenic risk and to further improve the counseling of pregnant women accidently exposed to gadolinium-based contrasts. A recent study by Ray et al concluded no association between fetal harm or early childhood disabilities and MRI exposure during the first trimester of pregnancy. Gadolinium-based contrast use in MRI at any time during pregnancy showed an increased risk of a broad set of rheumatological, inflammatory, or infiltrative skin conditions and for stillbirth or neonatal death. The limitation of this study lies in the fact that the researchers might not have been able to detect any rare adverse outcomes.[53]

There is very little evidence presented by any animal or human studies to evaluate the use of superparamagnetic iron oxide contrast, especially during pregnancy and lactation. The water solubility of gadolinium-based agents accounts for the excretion of less than 0.04% of the intravenous dose of gadolinium dose in the breast milk, out of which less than 1% will get absorbed from the GI tract of the infant making it nearly negligible to cause any substantial harm. It is thus advised that there should be no interruption in breastfeeding after the use of gadolinium-based agent.[54]

Radiation in Pregnancy and Lactation

Imaging involving radiation exposure, in pregnancy and lactation, is a prevalent yet controversial clinical scenario which remains improperly understood and poorly addressed till date. This is attributed to the major lack of awareness among the patients as well as physicians regarding the adverse effects of radiation at the routinely used doses in diagnostic imaging.

The effects of radiation exposure can be divided into four major categories based on the observations made from the victims of high levels of radiation exposure, including—pregnancy loss, deformity, developmental delay or retardation, and carcinogenesis. The fetus is most susceptible to the effects of radiation between 8 and 15 weeks of gestation relating to the phase of organogenesis.[55,56]

Pregnancy loss is an all or none phenomenon occurring with radiation exposures during early pregnancy, that is, within 2 weeks of conception; radiation exposure to the fetus between 50 and 100 mGy may prevent blastocyst implantation and result in spontaneous abortion. Congenital deformities and developmental delays are also dose dependent and occur during the organogenesis period, that is, 2 to 8 weeks; fetal dosages above 150 to 200 mGy considerably increase the likelihood of malformations, while exposures above 500 mGy result in gross fetal damage. Carcinogenesis, on the contrary, is a stochastic effect indicating that radiation exposure of any degree can cause cancer. However, when radiation exposure rises, the likelihood of getting cancer rises as well. The risk of malignancy, miscarriage, or major malformations is negligible in fetuses exposed to 50 mGy or less, according to consensus statements from the pertinent major organizations (National Commission on Radiological Protection, International Commission on Radiological Protection, Biologic Effects of Ionizing Radiation VII, Centre for Disease Control and Prevention, ACR, and American Congress of Obstetricians and Gynecologists). For carcinogenesis, at radiation doses below 100 mSv, the linear-no-threshold risk model has statistical constraints that make it challenging to predict cancer risk. The ACR Practice Guidelines state: "A dose of 20 mGy represents an additional projected lifetime risk of about 40 additional cancers or fewer per 5000 babies, or about 0.8%."[57]

Ionizing radiation doses from almost all diagnostic imaging investigations are substantially below 50 mGy (►**Fig. 1**). It has not been demonstrated that exposure to ionizing radiation doses less than 50 mGy is related to altered pregnancy outcomes from fetuses exposed to background radiation alone. Hence, medical professionals involved in the care of pregnant and nursing women requiring diagnostic imaging should compare the dangers of radiation and contrast agent exposure to the risk of illness nondiagnosis and progression. When ionizing radiation investigations are necessary, planning and coordination with a radiologist are frequently helpful in changing techniques to reduce overall radiation dosage.[46,47,56–62]

Recommendations

The following recommendations are made regarding diagnostic imaging methods during pregnancy and breastfeeding by the Committee on Obstetric Practice of the American College of Obstetricians and Gynecologists[63]:

- The preferred imaging methods for pregnant patients are ultrasound and MRI, which are both low risk. However, these methods should only be utilized carefully and when they are anticipated to provide the patient with medical benefits.
- With very few instances, radiation exposure by radiography, CT scans, or nuclear medicine imaging methods is at a dose significantly lower than the exposure linked to harm to fetuses. A pregnant patient should not be denied access to these procedures if they are required in addition to ultrasonography or MRI or are more accessible for the diagnostic at hand.
- Gadolinium contrast should only be used sparingly in MRI procedures; it should not be utilized as a contrast agent in pregnant women unless it greatly enhances diagnostic accuracy and is anticipated to have positive effects on the fetus or the mother.

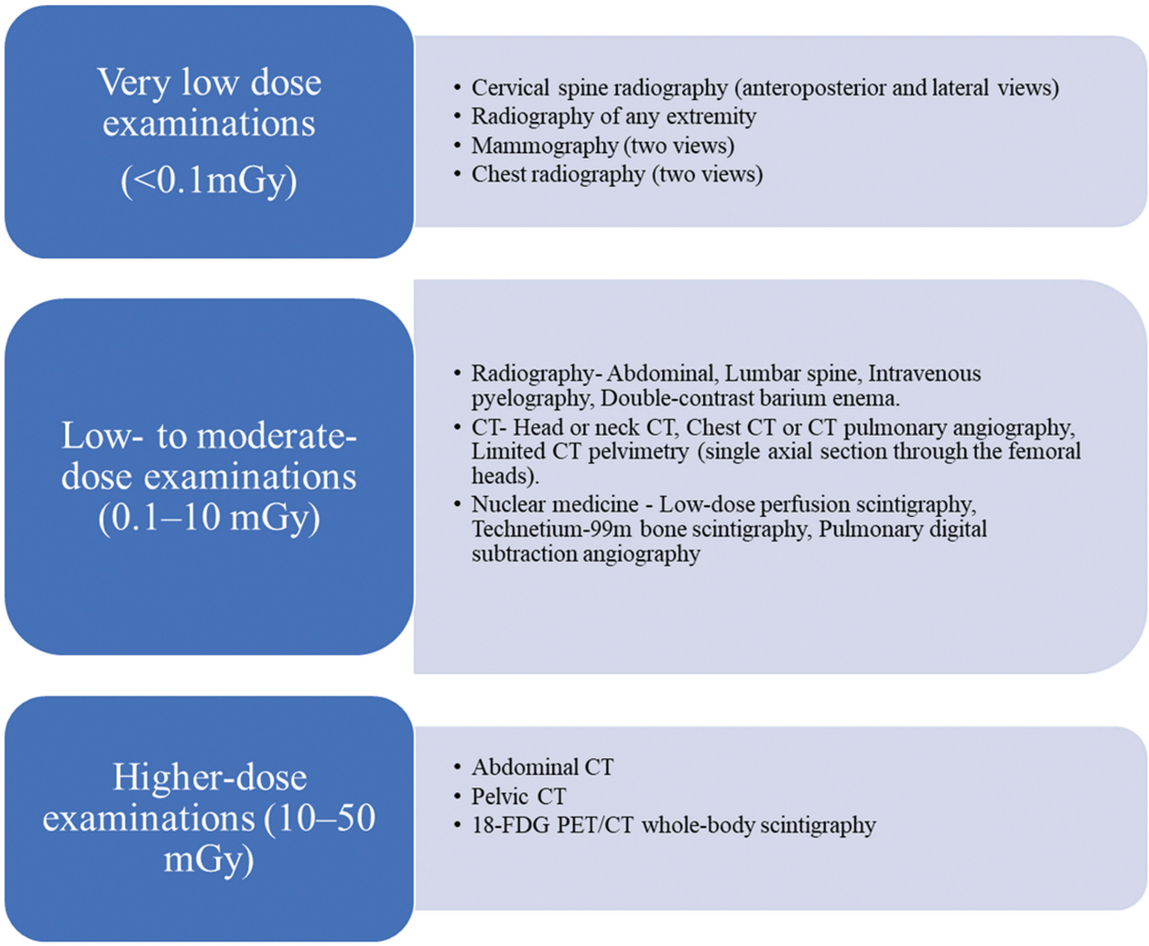


Fig. 1 Radiation doses associated with common radiologic examinations.

- Gadolinium administration should not be followed by a break in breastfeeding.

Imaging Recommendations for Bone Marrow Transplant

Bone marrow transplantation (BMT)/hematopoietic stem cell transplantation is the procedure in which patient's diseased stem cells or stem cells destroyed due to the high dose of chemotherapy/radiotherapy are replaced by healthy stem cells. BMT destroys tumor cells in case of malignancy and replaces dysfunctional cells by generating functional cells in nonmalignant hematological disorders (immune deficiency syndromes and hemoglobinopathies).

Indications

Broadly there are three indications of BMT: (1) curative for certain types of hematological malignancies, (2) supportive for those undergoing high-dose chemotherapy, and (3) nonmalignant hematological disorders.[64,65] The various indications are enumerated in ►**Table 7**.[64,66]

Definitions

Treatment of various malignant and nonmalignant hematological disorders by infusion of healthy hematopoietic progenitor cells, in order to augment hematopoietic and immune functions, is known as BMT. There are three types of BMT[64,65]:

(1) Autologous BMT: BMT using patient's own stem cells after purification is known as autologous BMT. There is no graft versus host disease (GVHD), but relapse can occur in case of malignancy.
(2) Allogeneic BMT: BMT using stem cells from human leukocyte antigen (HLA)—compatible donor is known as allogeneic BMT.
(3) Syngeneic BMT: BMT using stem cells of identical twin is known as syngeneic BMT. There is no GVHD and no graft failure with this type of BMT.

Patient Information and Consent

Physician should obtain informed consent of the patient after explaining the entire procedure of BMT, stating the risk/benefit ratio, complications associated with BMT, and specifying available alternative treatment options. The

Table 7 Indications of BMT

Various Indications for BMT
1. Acute lymphoblastic leukemia (ALL)
2. Acute myeloid leukemia (AML)
3. B-cell lymphomas
4. Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma
5. Chronic myeloid leukemia (CML)
6. Gestational trophoblastic neoplasia (GTN)
7. Hodgkin lymphoma (HL) 8. Multiple myeloma (MM)
9. Myelodysplastic syndromes (MDS)
10. Myeloproliferative neoplasms
11. Primary cutaneous lymphoma
12. T-cell lymphomas
13. Germ cell tumors (testicular tumors) refractory to chemotherapy
14. Systemic light chain amyloidosis
15. Systemic mastocytosis
16. Waldenstrom macroglobulinemia
17. Non-malignant hematological disorders, e.g., severe combined immune deficiency syndrome (SCID), thalassemia, sickle cell anemia
18. Other diseases: Chronic granulomatous disease, leukocyte adhesion deficiency, Chediak–Higashi syndrome, Kostman syndrome, Fanconi anemia, Blackfan–Diamond anemia, and enzymatic disorders.

Abbreviation: BMT, bone marrow transplantation.

patient should be in a sound mental state to understand the procedure and comprehend the risks and complications associated with BMT.[66]

Protocol

Donor workup: The donor workup includes infectious disease markers, renal and liver function test, complete blood count, ABO and Rh typing, and HLA Class I and HLA Class II typing. Imaging studies on a case-to-case basis are required.

In case the graft is from the bone marrow, the donor in addition to that would require an electrocardiogram, echocardiogram, chest X-ray, and thyroid function test.

Pretransplant imaging: Pre-transplant imaging is done following central line placement either in the internal jugular vein or subclavian vein to identify the position and to evaluate for complications such as pneumothorax. Screening CTs are done for selected diseases like acute myelogenous leukemia, prolonged pancytopenia, previous history of infection like pneumonitis, and prior mediastinal radiation. Imaging is also helpful to know the response status prior to a transplant for example lymphoma patients. MRI is helpful in evaluating iron overload status in heavily transfused patients.

Complications

Allogeneic BMT recipients are prone to develop GVHD, whereas autologous BMT recipients are prone to develop infections and relapses. Posttransplantation period can be divided into three phases: (1) preengraftment phase (0–30 days posttransplant), (b) early posttransplant phase (30–100 days posttransplant), and (c) late posttransplant phase (>100 days posttransplant). Pulmonary complications are most frequent.[67] Various complications of BMT are enumerated in ►**Table 8**.

Posttransplant Imaging

The common imaging studies and their indications are summarized in ►**Table 9**.

Quality Control, Interinstitution Performance Harmonization, and Regulatory Issues

Indian Council of Medical Research (ICMR) has laid down National Guidelines for Hematopoietic Cell Transplantation-

Table 8 Post-BMT complications

Organs affected	Complications
Pulmonary complications	*Preengraftment phase* -Fungal infection -Diffuse alveolar hemorrhage -Pulmonary edema -Engraftment syndrome *Early posttransplantation phase* -Cytomegalovirus infection -Pneumocystis jiroveci pneumonia -Idiopathic pneumonia syndrome *Late posttransplantation phase* -Bronchiolitis obliterans -Cryptogenic organizing pneumonia
Hepatic complications	-Acute GVHD -Drug-induced hepatotoxicity -Viral hepatitis -Liver abscess -Hepatic sinusoidal obstruction syndrome
Gastrointestinal complications	-GVHD (acute and chronic) -Neutropenic enterocolitis
Genitourinary complications	-Renal function impairment -Hemorrhagic cystitis -Renal parenchymal infections
Central nervous	-CNS infections
system (CNS)	-Intraaxial hematomas
complications	-Infarction -Posterior reversible encephalopathy syndrome
Musculoskeletal complications	-Osteoporosis -Avascular necrosis
Secondary malignancies	-Solid tumors -Hematological malignancies -Posttransplant lymphoproliferative disease

Abbreviations: BMT, bone marrow transplantation; GVHD, graft versus host disease.

Table 9 Common postbone marrow transplant imaging studies and their indications

Imaging studies	Indications
Radiography	• In suspected Engraftment Syndrome and pulmonary edema. • Postline placement to identify the position and to evaluate any complications such as a pneumothorax.
CT Chest	• In suspected lung infection, diffuse alveolar hemorrhage and idiopathic pneumonia syndrome. • In suspected chronic GVHD, posttransplant lymphoproliferative disorder (PTLD) and veno-occlusive disease (late posttransplant period) • I.V. contrast study is recommended for imaging in venoocculusive disease.
USG abdomen	• In suspected sinusoidal obstruction syndrome, Budd–Chiari syndrome, neutropenic colitis, pyelonephritis, and hemorrhagic cystitis.
CT abdomen with contrast	• In suspected acute GVHD and infection. • In suspected PTLD and chronic GVHD (late posttransplant period).
CT brain	• In suspected intracranial hemorrhages, PRES, and infection. • I.V Contrast study is recommended for imaging in infection.
MRI Brain	• In suspected metabolic encephalopathy, PRES and infection. • Post-HSCT carcinogenesis (late posttransplant period) • I.V. contrast study is recommended for imaging in infection and post-HSCT carcinogenesis.

Abbreviations: CT, computed tomography; GVHD, graft versus host disease; HSCT, hematopoietic stem-cell transplantation; I.V. intravenous; MRI, magnetic resonance imaging; PRES, posterior reversible encephalopathy syndrome; USG, ultrasound.

2021 for highlighting indications for BMT in both adult and pediatric patients, HLA typing in BMT, handling, processing, and preservation of stem cells and follow-up of patients after transplant. ICMR has developed these guidelines after referring to the European Society for Blood and Marrow Transplantation and the American Society of Transplantation and Cellular Therapy. A quality management system should be in place and internal and external audits should be conducted to ensure that implementation of the BMT procedure is in accordance with the agreed standards and with the complete involvement of all the staff members.[68]

Summary of Recommendations

(1) Indications for BMT should be in accordance with the existing national and international guidelines.
(2) Patients should be explained in details about the procedure of BMT and its potential complications so that they can take a call on whether to proceed for the procedure or not.
(3) Proper diagnostic work-up prior to and after the transplantation forms the backbone of BMT.
(4) Quality control checks and audits should be regularly performed to ensure proper implementation of the BMT procedure in accordance with the established guidelines.

Imaging Recommendations for Cancer Screening

A screening test is a medical test or procedure performed on subjects of a defined asymptomatic population or population subgroup to assess the likelihood of their members having a particular disease with a major objective to reduce morbidity or mortality in the population group by early detection, when treatment may be more successful.[69] Screening program for a disease needs justification for its existence and application to a population. Important points of consideration depend upon the disease, the screening test devised, and treatment of the disease if detected during screening.[70] The principle of screening in cancer is rooted in the philosophy of detecting cancer at the earliest, keeping in mind the underlying hypothesis that diseases follow progressive linear paths of increasing abnormalities.[71]

Cancer Screening in India

In India, there are approximately 948,900 new cancer cases and 633,500 deaths annually.[72] Cancer screening in India remains mainly opportunistic and consequently the majority of cancers are diagnosed at advanced stages. Due to a lack of resources and a skilled workforce, developing nations cannot directly use the conventional techniques and technology used for cancer screening in developed nations (such as cytology for cervix cancer and mammography for breast cancer screening). Hence, simple, socioculturally acceptable, and cost-effective technologies are required for organized cancer screening in the Indian scenario.[73] Screening for cervical, breast, and oral cancers with visual inspection with acetic acid, clinical breast examination, and oral visual examination, respectively, has been used.

Worldwide screening programs have been devised for the following cancers.

Breast Cancer Screening

The most frequent malignancy among women worldwide is breast cancer. It is the most frequent cancer in both developed and developing regions.[74] Modifiable risk factors for breast cancer include older age at first childbirth, lack of breastfeeding practices, obesity, menopausal hormone therapy, and alcohol intake. Nonmodifiable risk factors include older age, history of benign breast disease, genetic predisposition, family

history, early menarche/delayed menopause, increased breast density, and chest irradiation.[75] The guidelines for breast cancer screening and diagnosis vary in different parts of the world. As familial cancer predisposition plays an important role in this disease, family history can pave the way for decision-making in the screening and management of breast cancer.

The National Comprehensive Cancer Network lays down the following guidelines: at the first clinical encounter, risk assessment is important. Asymptomatic women with increased risk, for example, those having prior history of breast cancer, history of thoracic radiation therapy, genetic predisposition, history of lobular carcinoma in situ (LCIS), etc, should undergo clinical examination every 6 to 12 months starting from the age of 35 years. Annual screening mammogram is advised with consideration of tomosynthesis. Breast awareness is important in this group with consideration of risk reduction strategies.[76]

Asymptomatic women with average risk can undergo clinical encounter every 1 to 3 years. Above ≥40 years of age should undergo annual screening mammogram with consideration of tomosynthesis in addition to annual clinical examination.

For symptomatic women with palpable mass, skin changes or nipple discharge, irrespective of age, mammography followed by ultrasound of the breast is advised, followed by core needle biopsy in highly suspicious cases. If the appears benign then follow-up is suggested to assess stability and core needle biopsy is advised if there is an increase in size or suspicion.

For women between the ages of 40 and 49 years, the United States Preventive Services Task Force (USPSTF) advises avoiding routine mammography screening. A patient's context, including their values toward certain advantages and hazards, should be taken into consideration when deciding whether to begin regular, biennial screening mammography before the age of 50 years. The USPSTF recommends biennial screening mammography for women between the ages of 50 and 74 years. Individual preference of weighing potential benefit versus harm is given to women between 40 and 49 years.[77]

The WHO recommends mammography for women aged 50 to 69 years in well- resourced settings; however, in limited-resource settings, population-based mammography may not be cost-effective, and hence, early detection should focus on reducing the stage at diagnosis through awareness.

►**Table 10** shows the guidelines, laid by American Cancer Society, depending upon the age group and risk assessment.[78]

The breast cancer screening programs in the United Kingdom currently invite women aged 50 to 70 years for screening mammography every 3 years.[79]

Breast Cancer Screening in Indian Scenario

The incidence of breast cancer has overtaken cervical cancer in our country[80] and has disproportionately high mortality rates. On the contrary, incidence of breast cancer in India is still significantly lower than in Western countries even after adjusting for the age structure of the population.[81]

In contrast to the widespread community-based screening programs in the Western world, no such screening program exists in our country.[82] Opportunistic screening is also difficult as most of the time the disease is totally asymptomatic at an early stage. Women from low socioeconomic strata, with low-income and less education may not seek care even if a lump is felt. This could be attributed to their unawareness of what the lump represents, stigma of being rejected by the community and partner, potential fear of loss of the breast, prevailing taboo of not discussing breast cancer topic openly, and disbelief of the existence of any effective therapy for the disease.[83]

Again, even in the West, the role of screening mammography has been challenged. Despite substantial increases in the number of cases of early-stage breast cancer detected, screening mammography has only marginally reduced the rate at which women present with advanced cancer and in turn has had a minor implication in reducing death rates.[84] Data from many randomized trials have shown that mammography can lead to overdiagnosis to the extent of 25 to 30%.[85] Cancer literacy regarding the risk factors of breast cancer is low irrespective of socio-economic or educational background,[86] and breast awareness programs

Table 10 American Cancer Society breast cancer screening guidelines

Age group and risk assessment	Recommendations
40–44 y	Choice to start annual breast screening should be given explaining the risks and potential benefits.
45–49 y	Annual mammograms
50–54 y	Clinical breast examination with annual mammograms
55–74 y	Clinical breast examination with mammograms every 2 y, choice to continue yearly screening.
75 y and older	Screening should continue as long as a woman is in good health and is expected to live 10 more years or longer.
Women at higher-than-average risk (family history or with predisposing genetic mutation)	MRI and mammogram every year

Abbreviation: MRI, magnetic resonance imaging.

with cognizance of breast self-examination and clinical breast examination can be helpful in our population.[87]

Methods of Breast Screening

Breast examination: Breast self-examination once monthly may help detect any irregularity or lumps. Clinical breast examination is done by a trained medical staff. Warning signs of breast cancer are lump, hard knot, or thickening in the breast or underarm, swelling, warmth or redness, change in size and shape of breast, dimpling or puckering of overlying skin, itchy, scaly sore or rash and nipple discharge.

Role of mammography: Mammography plays a central role in screening and detection. Low-dose film-screen mammography has now been superseded by full-field digital mammography due to its higher sensitivity and superior screening accuracy.[88] BI-RADS has been designed to standardize breast imaging reporting. This includes indication, breast composition, important findings, and comparison with the previous study if any. Standardized terminology/descriptors are used to avoid confusion.[89]

Diagnosis of ductal carcinoma in situ (DCIS) has increased dramatically increased in parallel with the increased use of screening mammography.[90] As mammography depicts microcalcification better than other breast imaging methods, it scores over other techniques in mass screening.

Role of breast tomosynthesis: Digital breast tomosynthesis is a pseudothree- dimensional digital mammography imaging system that produces a series of 1-mm-slice images with multiple very low-dose X-ray projections to reveal the inner architecture of the breast after eliminating interference from overlapping breast tissue[91] and potentially reduce recall rates at screening. The consideration of adding tomosynthesis has now been incorporated into the screening protocol to enhance cancer detection.

Role of ultrasound: Dense breast can pose a challenge by decreasing the sensitivity of mammography which may be as low as 30 to 48%. Ultrasound of the breast is important in screening as an add-on to mammography, especially in high-risk cases, significantly increasing the yield in case of small lesions and node-negative disease.[92] Ultrasound is preferable for screening (if needed) in the younger age group ($\leq$30 years of age), as there is no exposure to radiation and better delineation of lesions which may be obscured due to dense parenchyma in mammography. However, there is an increase in the number of false-positive cases also.[93]

Role of MR mammogram: Breast MRI is mostly used in diagnosis and staging, rather than screening. However, there is growing evidence that breast MRI in combination with mammography, compared with mammography alone, can increase the detection of breast cancer in high-risk patients. Breast MRI as an adjunct to mammography has been advised in the following conditions.

- Above age 25 every year in women with BRCA1 or BRCA2 mutation or a first-degree relative with a BRCA1 or BRCA2 mutation
- Above age 30 every year in women with a strong family history of breast or ovarian cancer.
- In women who received radiation treatment to the chest area during childhood or young adulthood every year starting 8 to 10 years after radiation treatment or at age 40 years (whichever age comes first).
- Li-Fraumeni, Cowden, or Bannayan–Riley–Ruvalcaba syndrome (or family has a known mutation in the *TP53* or *PTEN* genes) every year starting between ages 20 and 25 years.
- A personal history of invasive breast cancer.
- A personal history of DCIS, LCIS, or atypical hyperplasia.
- Very dense breast tissue.[94]

A recent randomized controlled trial comparing MRI versus mammography for breast cancer screening in women with familial risk[95] showed that MRI detected breast cancers at an earlier stage than mammography, thus reducing adjuvant chemotherapy and breast cancer-related mortality. However, the higher cost may preclude the use of MRI for screening in our country. More false positives in highly dense breasts are another disadvantage.

Lung Cancer Screening

Lung cancer is the leading cause of cancer death in men and the second leading cause of cancer death in women worldwide.[96] In India, it has emerged as a major cause of cancer-related deaths after 1980s. It is significantly more prevalent in males, with male: female ratio ranging from 5.76:1 to 6.67:1.[97]

Smoking is the most important contributing factor in the development of lung cancer. Most lung cancer cases are nonsmall cell lung carcinomas (NSCLCs), and most screening programs focus on the detection and treatment of early-stage NSCLC.[98] For lung cancer

screening, sputum cytology analysis and chest radiography have both been employed. Low-dose CT chest (LDCT) has been found to be more sensitive for detecting early-stage cancer.[99]

Planning for screening depends upon the risk assessment. The most significant risk factors for lung cancer are age, total lifetime tobacco smoke exposure, and the number of years since smoking cessation. Other risk factors include specific occupational exposures, radon exposure, family history, and history of pulmonary fibrosis or chronic obstructive lung disease.[98]

High-risk status (which includes age $\geq$55 to 77 years, $\geq$30 pack-year smoking history, and current smokers or have quit smoking within last 15 years) warrants screening with LDCT. Detection of a solid nodule on LDCT warrants further screening depending upon the size ($\leq$5 mm—annual, 6–7 mm—every 6 months, 8–14 mm—every 3 months/PET-CT). Management of larger nodules needs further evaluation with CT chest with contrast and/or PET-CT followed by repeated evaluation with LDCT in case of low suspicion and biopsy or surgical excision in case of high suspicion of cancer. Solid endobronchial nodule may need evaluation with bronchoscopy if there is no resolution on LDCT at 1 month.[100]

Disadvantages of LDCT screening include false-negative (up to 20%) and false-positive results, incidental findings,

overdiagnosis, radiation exposure, and psychological distress. The specificity of LDCT ranges from 28 to 100%.

People with serious comorbidities or unwilling to have curative lung surgery may not have a net benefit from screening, hence should be excluded. Individuals with a moderate risk (aged $\geq$50 years and $\geq$20 pack-year smoking history or second-hand smoke exposure but no additional lung cancer risk factors) or low risk (younger than 50 years or smoking history of $\leq$20 pack-years) should be excluded from screening.

Colorectal Cancer Screening

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide and accounts for 10% of cancers.[101] The burden of the disease has been significantly affected due to patients being diagnosed early, by an effective screening process. The effectiveness of screening is, however, jeopardized by a multitude of factors including the limitations of test performance, lack of accessibility, and suboptimal screening compliance.

Available methods for screening colon cancer include biochemical, endoscopy, and radiological tests. Biochemical tests include stool guaiac test or fecal occult blood tests, fecal immunohistochemical test (FIT), and stool DNA testing. Colonoscopy is an outdoor albeit invasive procedure requiring sedation. However, it is considered the gold standard for viewing the lumen, sampling, or removal of any suspicious lesion.[102] Radiological techniques include double-contrast barium enema, CT colonography (CTC), and MR colonoscopy. However, only CTC has been approved for screening in selected cases.[103] CTC scores over direct colonoscopy as it is minimally invasive and provides information about the proximal colon especially if colonoscopy is incomplete due to obstructive lesion. It can provide insight into extracolonic pathologies. Patients with a personal history of adenoma or sessile serrated polyps, colorectal carcinoma, and inflammatory bowel disease or family history of CRC are considered high risk. Polyps are generally managed according to their size and histology and followed up with a colonoscopy. People with inflammatory bowel disease may undergo targeted biopsy and followed up with colonoscopy.

CRC is associated with high-risk syndromes like Lynch syndrome, familial adenomatous polyposis, Peutz–Jeghers syndromes, etc, and people with these syndromes warrant more vigilant screening. Lynch syndrome is associated with CRC and extracolonic cancers like gastric and small bowel cancer, urothelial cancer, CNS tumors, breast cancer, and prostate cancer. Screening of CRC as well other systems should start early in these patients as early as 20 to 25 years.

Cervical Cancer Screening

Viral infections have been implicated in contributing to around 5 to 20% of all human cancer. Several viruses play considerable roles in the multistage development of malignant cancers.[70] Human papilloma virus (HPV) contributes to the statistics of cancerous diseases. High-risk HPV DNA is found to be present in 99.7% of cervical cancer specimens.[104]

Cervical cancer incidence and prevalence is high in developing countries as HPV infection rates continue to persist. Low socioeconomic status, lack of population awareness, and inadequately implemented screening and vaccination programs contribute to this. Primary prevention for this disease is considered to be a vaccination against HPV, whereas secondary prevention is constituted by screening. The usual long natural history of progression from mild dysplasia to carcinoma cervix makes it a relatively early preventable disease and provides the rationale for screening.[105]

Various cervical cancer screening strategies are in place. Some countries have population-based programs, whereby women in the target population are individually identified and invited to attend the screening, whereas in opportunistic screening, invitations depend on the individual's decision or on encounters with health care providers.[104]

American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology provide guidelines for the screening of cervical cancer, which is mainly limited to HPV with/or without cytology, depending upon the age of the patient. Imaging does not have a role in the screening of cervical cancer.[106]

In India, cervical carcinoma is a major health problem with approximately 120,000 women getting affected every year, predominantly in the rural population. Despite the existence of national guidelines, which advises screening for women between 30 and 65 years of age, the screening coverage in India is appalling low. Hence, the diagnosis of carcinoma cervix is based on opportunistic screening or after the onset of the symptoms. Rural cancer registries and camp-based approaches have been implemented; visual inspection of the cervix followed by pap smear examination and HPV-DNA detection have been undertaken.[107]

Prostate Cancer Screening

Prostate cancer is the second most frequent cancer diagnosis made in men. The disease may be asymptomatic at the early stage and often has an indolent course that may require only active surveillance. Incidence and mortality rates are strongly related to age with the highest incidence being seen in elderly men (>65 years of age). African American men have the highest incidence rates and more aggressive type of prostate cancer compared to Caucasian population.[108]

Screening has been recommended after baseline evaluation including family history, race, high-risk germ line mutations, medications (like 5-alpha reductase inhibitors), history of prior prostate disease, and prior prostate-specific antigen (PSA) evaluation. Risk stratification includes the age of the patient with concurrent PSA values and digital rectal examination.[109]

Imaging does not have any significant role in screening. However, transrectal ultrasound-guided biopsy and/or multiparametric MRI are done for evaluation and management if screening results are suspicious.

Familial Cancers and Cancer Syndromes

High-penetrance breast and/or ovarian cancers warrant vigilant screening in the affected/at-risk individuals. These includes BRCA1, BRCA2, CDH1, PALB2, PTEN, and TP53 genes among others. High-risk cases include personal history of breast cancer at age $\leq$45 years, history of second breast cancer at any age, triple-negative breast cancer at age $\leq$60 years, male breast cancer, one or more close blood relative with breast, ovarian, pancreatic or high grade or intraductal prostatic cancer, epithelial ovarian cancer, exocrine pancreatic cancer and individuals with first- or second-degree blood relative meeting the criteria described above.[110]

Genetic testing is of paramount importance in these individuals. Screening protocols for some important genetic syndromes are as follows.

BRCA1 and BRCA2: Breast awareness is important in these women and should start as early as 18 years of age if the mutation is known to exist in the family or the patient. Clinical breast examination should start every 6 to 12 monthly at 25 years of age. Breast screening with annual breast MRI should start at 25 years of age, with annual mammograms and consideration of tomosynthesis $\geq$30 years of age. Options for risk-reducing mastectomy (RRM) and salpingo-oophorectomy (RRSO) should be given. Those patients not opting for RRSO may undergo transvaginal ultrasound and CA-125 evaluation at clinician's discretion. In men, breast self-examination should start at 35 years of age with the screening of prostate cancer at 40 years of age. Pancreatic cancer screening is also recommended in both men and women especially with known family history and proven genetic mutation with contrast enhanced magnetic resonance imaging, magnetic resonance cholangiopancreatography, and/or endoscopic ultrasonography.

CDH1: Increased risk of lobular breast carcinoma is seen in females in this group. Screening annual mammogram with consideration of tomosynthesis is suggested at 30 years of age. MRI of the breast may also be considered. RRM may be advised if strong family history is there. Other cancers like gastric cancer may be prevalent in this group. Prophylactic gastrectomy has been advised over 18 years of age.

PTEN: Cowden Syndrome is associated with this genetic mutation. Lhermitte–Duclos disease, breast cancer, endometrial cancer, follicular thyroid cancer, genito-urinary hamartomas or ganglioneuromas, thyroid lesions, colon cancer, renal cell cancer, and vascular abnormalities are found in this condition.

In women breast awareness and breast self-examination should be started as early as 18 years of age. Clinical breast examination should be initiated at 25 years of age every 6 to 12 months. Annual mammography with consideration of tomosynthesis and breast MRI screening with contrast should be considered starting at 30 to 35 years of age. RRM should be offered. Endometrial cancer screening should also be started at 35 years of age with consideration of prophylactic hysterectomy. Endometrial biopsy is the screening tool used. Transvaginal ultrasound is not sensitive for screening.

In both sexes, thyroid screening with clinical examination is important from 18 years of age. Thyroid USG has been advised as early as 7 years of age. Colonoscopy and renal ultrasound initiated from 35 to 40 years of age help in the early detection of cancers of respective regions.

TP-53: Li-Fraumeni syndrome forms an important hereditary cancer syndrome associated with TP-53 mutation. The most common malignancy in this syndrome is the early onset sarcomas ($\leq$45 years). Strong positive family history in first- or second-degree relatives is found. Other neoplasms associated with this condition include CNS tumors like choroid plexus carcinomas, breast cancer, pancreatic carcinoma, and adrenocortical carcinoma.

As seen in *PTEN* mutation, breast awareness as early as 18 years of age is initiated. Clinical breast exam has to be started from 20 years of age. Breast screening with annual breast MRI with contrast is suggested from 20 to 29 years of age, with MRI and mammogram from 30 to 75 years group. Consideration of tomosynthesis should be given in the latter group. RRM should be advocated.

Screening of other cancers includes colonoscopy and upper GI endoscopy every 2 to 5 years starting at 25 years, annual dermatologic examination, and annual whole body and brain MRI.

Cancer has always been an enigma for the medical fraternity. As screening involves asymptomatic population, knowledge needs to be imparted at the community level about the need for screening to increase participation of the target population. Simultaneously, it becomes the responsibility of the policymakers to devise a screening test which is sensitive, specific, has a good cost-benefit ratio, does not increase morbidity of the population screened, and has actual value in real world by benefitting the target population, not only by increasing the longevity but also the quality of life. For a resource-poor country like ours, judicious use of available resources by educating the at-risk population and community-based mass screening is the way now. Opportunistic screening by a health care worker is still at large the method of detecting preclinical phase of cancer in our country.

Imaging recommendations for Artificial Intelligence in oncological imaging

Abstract

Artificial intelligence (AI) has revolutionized the field of oncological imaging by providing precision/personalized medicine with the help of radiomics, machine learning, and deep learning, and this has largely been possible because of the availability of big data, powerful hardware, and robust algorithms. The role of AI in screening, diagnosis, response prediction, survival outcome prediction, and recurrence prediction, on imaging, has taken patient management to a level previously unfathomable. However, there are certain guidelines laid down by international bodies, for example, the Canadian Association of Radiologists and Royal College of Radiologists, which should be adhered to, before embarking on a journey involving AI. Also, the collaboration of radiologists, pathologists, and clinicians with the key stakeholders,

industrial partners, and scientists is imperative for the successful implementation of AI. In this manuscript, we introduce the basic concepts and workflow of AI, mention the applied uses of AI in oncology on imaging, and then delve into the ethical issues and guidelines in place for using AI.

Introduction

Artificial intelligence (AI) refers to the ability of the machine to obtain and apply knowledge to simulate the human brain in performing cognitive tasks, by using advanced technologies, powerful hardware, and enhanced algorithms.[111] Patient management in oncology has received a boost by the potential role of AI, not only in cancer diagnosis and screening, but also in the prediction of response to treatment, survival outcome prediction, and recurrence prediction, on imaging with the help of radiomics, machine learning (ML), and deep learning (DL).[112–115] Noninvasive assessment of tumor biology on imaging using AI could help in providing precision/personalized medicine.[113,114] However, before embarking on a journey of AI, ethical issues should be well addressed, and guidelines should be well adhered to. In this manuscript, we have provided existing guidelines on quality control and ethical issues, in addition to the various concepts, applied uses, and workflow pertaining to AI in cancer imaging. At the end, we have summarized the recommendations for successful implementation of AI-based research in cancer imaging.

Concepts and Definitions

Radiomics: It is a process of extracting features from medical imaging data using advanced mathematical analysis for diagnosis, prognostication, clinical decision-making, and prediction of outcomes. Radiomics can also be used to assess tumor gene expression, in which case it is known as radiogenomics.[113]

Machine learning (ML): It is a subset of AI which enables the computer to automatically learn from data and improve performance from experiences by developing algorithms, thus making predictions and decisions without being explicitly programed.[116–118]

ANN: It is a subgroup of ML which uses a statistical and mathematical technique simulating interconnected neurons in a human brain. It comprises of the input layer, one or more hidden layer, and an output layer.[117]

Deep learning (DL): It is a subset and an enhanced version of ML, which uses neural network architecture with more than two hidden layers to perform complex tasks.[116,117] Convolutional neural network is the core of DL, with weighted connections between neurons that are iteratively adjusted to improve performance from continual exposure to training data.[119] Transfer learning: application of knowledge gained from a previously labeled data for performing different but related task.[117]

Federated learning: Multiple organizations/institutions/hospitals coming together, irrespective of geographical boundaries, to train a model on a huge data after anonymization of patient information, with the aim to build a robust deployable model.[120]

Both ML and DL can be supervised or unsupervised depending on whether labeled datasets are used to train computational models or algorithms are used to learn patterns from unlabeled datasets.[113,116] Relationship between AI, ML, DL and NN, and types of ML and DL algorithms are shown in ►**Fig. 2**.[6,7] ►**Table 11** enumerates the difference between radiomics combined with the ML model and DL.[113,121] The choice of radiomics or DL depends upon the complexity of task at hand and availability of sufficient data for model training in DL.

Applications of Artificial Intelligence in Oncology

Screening, diagnosis, lesion characterization (e.g., classification task into benign or malignant), prediction of tumor genome status, response to therapy, prognosis, outcome and recurrence prediction are the major applications of AI (radiomics, ML, and DL) in oncology on imaging.[112–115] Besides, pretrained DL models can be used to perform automatic segmentation (delineation of tumor boundaries). ►**Fig. 3** depicts the overview of AI application in oncological imaging.

Few studies involving AI in cancer diagnosis and management include:

- Histology prediction and screening of breast cancer on mammography.[122,123]
- Brain tumor segmentation.[124–127]
- Lung nodule segmentation on computed tomography (CT).[128–130]
- Liver tumor segmentation on CT.[130,131]
- Prostate gland tumor detection on magnetic resonance imaging (MRI).[112,132,133]
- Brain tumor survival prediction[134–136]:
- Glioblastoma recurrence prediction.[137]

DL Workflow in Radiology

A DL-based study should be undertaken if it has the potential to alter patient management, and sufficient data are available for its execution. A typical DL workflow comprises of the following steps.

Collaboration: Radiologist, clinician, software developers (technical expertise), and data scientist need to collaborate for the execution of a DL-based study.[115]

Ethics committee approval: Approval of institutional ethics committee should be sought.[115]

Image acquisition and data deidentification: CT, PET, MRI, ultrasonography (USG), radiographs, and mammogram can be used for image acquisition based on the requirement of the study. Images should be anonymized to remove patient identity and should be exported as Digital Imaging and Communication in Medicine file.[115] Alternatively, imaging biobanks, which are open source image data repository, can be used for research.[138] Images should be annotated for training the DL models.

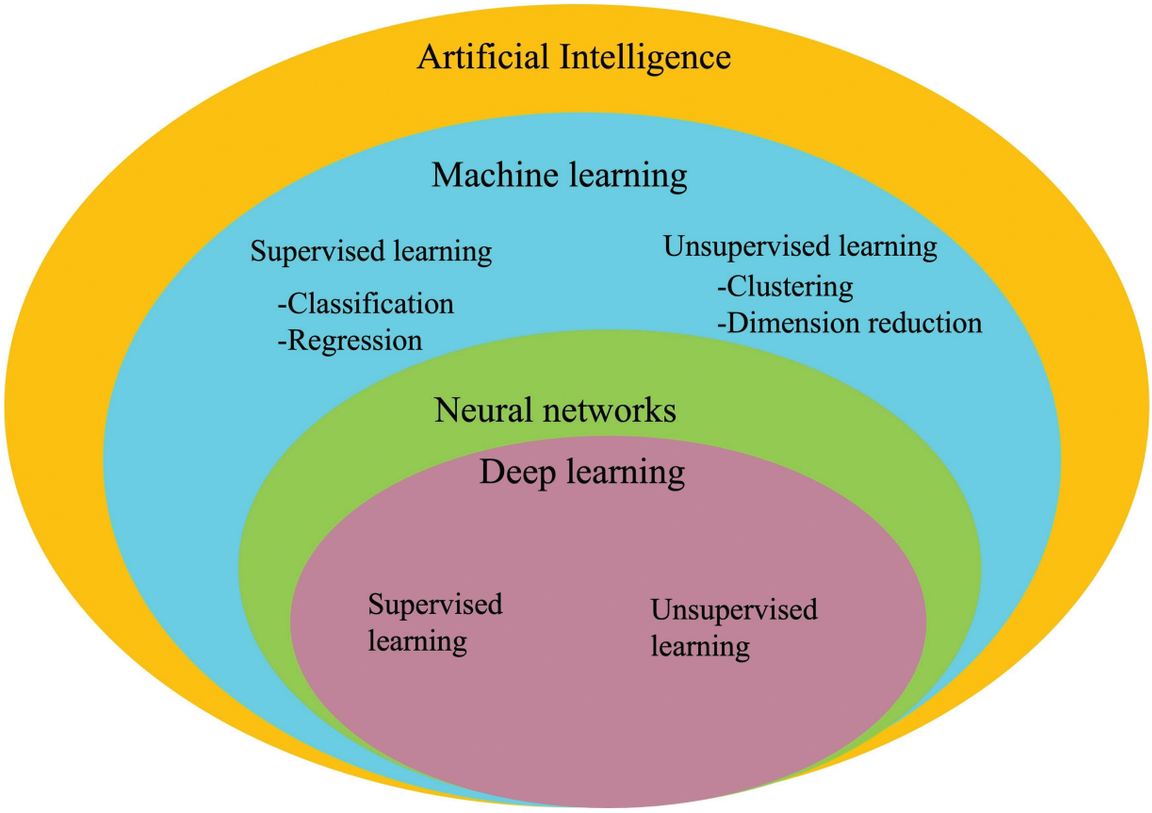


Fig. 2 Relationship between artificial intelligence, machine learning (ML), neural network, and deep learning (DL).

Nonimaging data collection and curation: This includes other nonimaging data that need to be collected, for example, clinical data, radiology, and pathology reports.

Segmentation: Automatic and semiautomatic segmentation, that is, DL-based delineation of tumor boundaries, can be achieved, after training models for segmentation.[115,117,139]

Model training, validation, and testing: DL autoextracts features from imaging data. Appropriate model should be selected after training based on performance using the receiver operating characteristic (ROC) curve and area under the ROC curve. The model should be fine-tuned on validation datasets. Test dataset should be used for evaluating the performance of a model for practical deployment.[115]

Hardware selection: It is based on the quantity of data available and the complexity of model. Central processing unit has huge memory but limited bandwidth, whereas graphics processing unit (GPU) and tensor processing units (TPU) have limited memory but high bandwidth.[115]

Radiomics Workflow

For a radiomic study, as a general rule, 10 to 15 samples per feature are required for classification studies, though the number of features cannot be predetermined.[113] After institutional ethics committee approval, the following steps should be followed for a radiomic study.

Table 11 Difference between radiomics combined with machine learning (ML) model and deep learning (DL)

Radiomics combined with the ML model	DL
Large data required, but can work in lesser data in comparison to DL.	Cannot perform without huge data.
Can work on low-end machines	Need high-end machines to process high data.
For solving simple and less complex problems.	For solving complex problems.
Model training takes less time but validation requires a longer time	Model training requires a longer time but validation is less time consuming.
Radiomics uses manual feature extraction step to proceed further.	DL autolearns from data, so manual feature extraction step not required.
Result interpretation and reasoning is comprehensible.	As DL autolearns and has many hidden layers, reasoning behind result is not comprehensible.

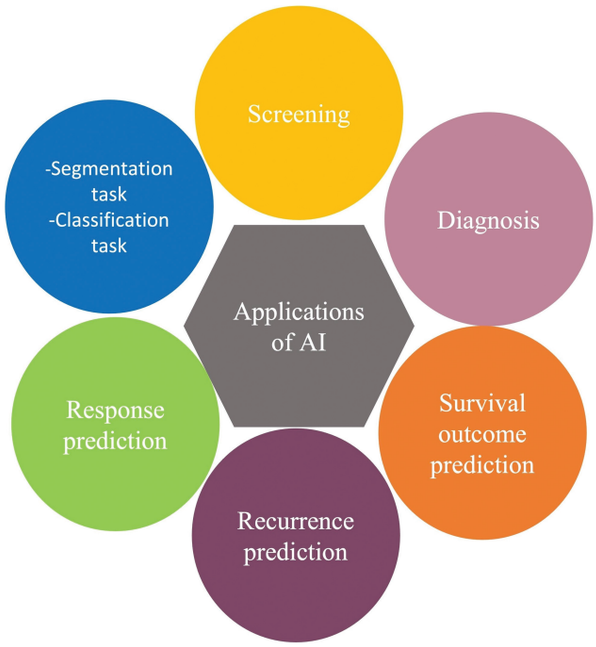


Fig. 3 Applications of artificial intelligence in oncological imaging.

- *Image acquisition and data curation*: It is the same as described in DL workflow.
- *Segmentation and feature stability*: Region of interest (ROI) is drawn within the tumor, or peritumoral zones, in two dimension (2D) or 3D. With manual segmentation, radiomic features sensitive to interreader variations should be rejected. The intraclass correlation coefficient should be used to reject nonreproducible features after repeating tumor segmentation by one or more readers.[113,140]
- *Image preprocessing*: Raw image data need to be homogenized and enhanced before radiomic features can be extracted.[3,30] Various preprocessing steps include signal intensity (SI) normalization, image interpolation, range resegmentation, denoising, bias field correction, motion correction, image thresholding, and discretization.[113,140]
- *Feature extraction*: It refers to calculation of features using feature descriptors to quantify characteristics of gray levels within ROI in accordance with Image Biomarker Standardization Initiative guidelines.[140] In radiomics, feature extraction is handcrafted that is chosen by a data scientist.[116] The various feature classes are as follows.
  - I. *Morphologic features:* It includes volume, diameter, area, and elongation features.
  - II. *Intensity-based features (first order features):* This describes distribution of intensities within an ROI and are further grouped based on location, spread, and shape of distribution. Images from MRI and USG require standardization before calculation of first order features as they generate arbitrary intensity images.
  - III. *Texture features (second order features):* In this, spatial location as well as signal intensities are used for calculating features.
  - IV. *Higher order features:* These are imaging features acquired after applying filters or mathematical transforms using statistical methods.[141]

►**Table 12** describes the various feature extraction classes.[113,141]

- *Feature selection/dimensionality reduction:* It is imperative to select optimal number of features by reducing excess features and also important to reduce dimension, so as to exclude nonreproducible and redundant features, during building of ML models, to enable generation of valid and generalizable results.[140]
- *Model building and performance evaluation:* After collecting radiomic features and clinical data as input features, statistical models are fitted to predict study results. The hold-out method and cross-validation are two types of methods to estimate performance. In hold-out method, there are separate training and validation datasets to develop a model and evaluate performance on a new data, respectively. The hold-out method is used in case of larger sample size (>200), whereas cross-validation can evaluate performance on a smaller sample size.[113] As a rule, one third of the training sample size should be available for adequate validation.

Classification models which generate linear or quadratic decision boundaries include linear discriminant analysis, Gaussian naïve Bayes and quadratic discriminant analysis, and logistic regression with Least Absolute Shrinkage and Selection Operator regularization. Classification models

Table 12 Feature extraction classes and their descriptions

Feature class	Description
Morphologic features	Volume, diameter, area, sphericity can be quantitative or descriptive.
Intensity-based features (first-order features)	These features measure a. location of distribution (mean, median, mode). b. Spread of distribution (variance, interquartile range). c. Shape of distribution (skewness, kurtosis).
Texture features (second order features):	These describe spatial complexity and relationships of SI between adjacent pixels. These include gray-level co-occurrence matrix, gray-level run-length matrix, gray-level size-zone matrix, gray-level distance-zone matrix, neighborhood gray-tone difference matrix, and

which generate complex nonlinear decision boundaries include support and relevance vector machines, random forest, and neural network classifiers. Time-to-event models include Cox regression and random forest survival.[113] Radiomics can be combined with ML, where features are extracted using radiomics and models are trained, validated and tested using ML techniques.[137]

Imaging Biobanks

Imaging biobank refers to the collection of anonymized imaging data.[142] Open access platforms like The Cancer Genome Atlas program, The Cancer Imaging Archive, and European Genome–phenome Archive have a collection of deidentified imaging data for public use, to cater to the problem of huge data requirement for DL-based research.[143,144] The Tata Memorial Center Imaging Biobank is also one such project and is the result of collaboration between the Department of Biotechnology (Government of India) under the guidance of the National Institution for Transforming India (NITI) Aayog, and Tata Memorial Centre.[112]

Quality Control

- AI applications developed by the team of expertise should follow the principles of evidence-based medicine.[145]
- AI tools developed for diagnosis and prognostication should follow the existing consensus statements. For example, diagnostic tools developed using AI should be compliant with Standards for Reporting Diagnostic Accuracy statement, and predictive models should follow Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis statement.[139,146,147]
- Validated and reproducible AI tools impermeable to the unevenness in the equipment and imaging protocol should be encouraged.[139] Open-source data and federated learning can provide the datasets necessary for validation.
- There should be published results on the sensitivity and specificity of the AI tool developed prior to its use in clinical practice.[148]
- Radiomics Quality Score (RQS): Radiomics studies should be assessed based on RQS which consists of 36 points and 16 criteria.[149]

National Recommendations on Artificial Intelligence

There are no existing guidelines governing AI-based research in India. National Strategy for Artificial Intelligence was released by the NITI Aayog in June 2018, for promoting the theme "AI for All," and it recommends the promotion of AI-based research, workforce training, finding AI solutions, and development of guidelines for 'responsible AI'.[150] AI in health care is a collaborative effort of various stakeholders like researchers, software developers (technical expertise), Government, scientists, and general public. Data privacy, accountability by stakeholders, and transparency of developed AI tools are some of the recommendations made by NITI Aayog.[150]

Ethical Framework for Artificial Intelligence in Radiology

Ethical framework for AI in radiology should be based on the following biomedical ethics[111,142]:

- *Autonomy:* Patients have the right to take decisions, as medical images contain patient data and are not just pixels.
- *Beneficence and nonmaleficence:* Beneficence (do good) and nonmaleficence (do no harm) principles should be impartially followed towards patients.
- *Justice:* Just distribution of medical goods and services among patients.

Explicability (transparency and accountability): AI-based decision-making should have logical explanations, and there should be transparent communication regarding the same with patients. There should be an accountable body in case any medicolegal issue arises. Consensus statements issued by the American College of Radiology, European Society of Radiology, Radiological Society of North America, Society for Imaging Informatics in Medicine, European Society of Medical Imaging Informatics, Canadian Association of Radiologists, and American Association of Physicists in Medicine emphasize that AI in radiology should foster well-being, reduce harm, ensure just distribution of benefits and harm among stakeholders and that AI in radiology should be transparent, dependable with curtailment of bias in decision-making, and the responsibility and accountability should rest with humans.[151]

Systematic Review and Meta-Analysis Data

A systematic review of 734 original studies on applied ML in patient diagnosis, classification, and prognostication studies from January 2016 to December 2020 concluded that ML has helped in understanding the principles underlying oncogenesis and in serving as a noninvasive biomarker for cancer diagnosis, prognosis, prevention, and treatment; however, robustness and explainability of the models need to be improved.[152] Another systematic review from articles published between 2009 and April 2021 on AI techniques in cancer diagnosis and prediction revealed 13 articles on breast cancer, 10 articles on brain tumors, 8 articles each on cervical, liver, lung, and skin cancers, 7 articles on stomach cancer, 6 articles on colorectal cancer, 5 articles each on renal and thyroid cancers, 2 articles each on oral and prostate cancers, and 1 article each on neuroendocrine tumors and lymph node metastasis.[153]

Summary of Recommendations

- AI-based research in imaging is a collaborative effort of radiologists, clinician, software developers (technical

expertise), and data scientist, and it should be undertaken only if it has the potential to alter patient management as it involves additional workforce and consumes a lot of time.
- Anonymization of patient images and clinical data is a compulsory step of AI-based research.
- Open-source data (imaging biobanks) should be encouraged after proper deidentification, to cater to the need of huge data requirements and so as to benefit a larger population worldwide. As little medical data should be retained as reasonably acceptable. Transfer learning may be employed when there is data constraint.
- Developed AI model should be appropriately validated prior to its deployment in an institution. Federated learning can help in validation and building a robust model.
- Updated data storage systems and data encryption is a necessity to prevent data breach.

Standard operating procedure for AI workflow, and data sharing and ethics, are attached in the ►**Supplementary Material Figure 1** and **2**.

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Imaging Recommendations for the Diagnosis, Staging, and Management of Adult Brain Tumors

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Abstract

Neuroimaging plays a pivotal role in the clinical practice of brain tumors aiding in the diagnosis, genotype prediction, preoperative planning, and prognostication. The brain tumors most commonly seen in adults are extra-axial lesions like meningioma, intra-axial lesions like gliomas and lesions of the pituitary gland. Clinical features may be localizing like partial seizures, weakness, and sensory disturbances or nonspecific like a headache. On clinical suspicion of a brain tumor, the primary investigative workup should focus on imaging. Other investigations like fundoscopy and electroencephalography may be performed depending on the clinical presentation. Obtaining a tissue sample after identifying a brain tumor on imaging is crucial for confirming the diagnosis and planning further treatment. Tissue sample may be obtained by techniques such as stereotactic biopsy or upfront surgery. The magnetic resonance (MR) imaging protocol needs to be standardized and includes conventional sequences like T1-weighted (T1W) imaging with and without contrast, T2w imaging, fluid-attenuated axial inversion recovery, diffusion-weighted imaging (DWI), susceptibility-weighted imaging, and advanced imaging sequences like MR perfusion and MR spectroscopy. Various tumor characteristics in each of these sequences can help us narrow down the differential diagnosis and also predict the grade of the tumor. Multidisciplinary co-ordination is needed for proper management and care of brain tumor patients. Treatment protocols need to be adapted and individualized for each patient depending on the age, general condition of the patient, histopathological characteristics, and genotype of the tumor. Treatment options include surgery, radiotherapy, and chemotherapy. Imaging also plays a vital role in post-treatment follow-up. Sequences like DWI, MR perfusion, and MR spectroscopy are useful to distinguish post-treatment effects like radiation necrosis and pseudoprogression from true recurrence. Radiological reporting of brain tumor images should follow a structured format to include all the elements that could have an impact on the treatment decisions in patients.

Keywords
- brain tumors
- neuroimaging
- radiology

Introduction

Following the discovery of X-rays, there were a few reports of imaging being utilized for the diagnosis and localization of brain tumors, although of very limited utility.[1] A major leap in the field of neuroimaging came with the invention of computed tomography (CT).[1] In the 1980s, when it was recognized that nuclear magnetic resonance (MR) could be applied to medical imaging, magnetic resonance imaging (MRI) was introduced.[2] MRI has become a cornerstone in

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neuroimaging, based on its capability to demonstrate soft tissues, with exquisite detail. Advanced MRI sequences, along with modalities like positron emission tomography (PET), can now further help us by demonstrating the pathophysiological underpinnings of brain tumors and be useful for preoperative planning.

Epidemiology, Clinical Presentation in India and Global

The most common brain tumors seen in adults are extra-axial lesions like meningiomas, intra-axial lesions like gliomas, and pituitary gland tumors.[3] A published meta-analysis on primary brain tumors has estimated the worldwide incidence rates to be 10.82 per 1,00,000 person-years.[4] Primary brain tumors are a very heterogeneous group with the incidence and prevalence rates differing across tumor types. According to Porter et al, in the United States, the highest incidence was for gliomas and meningiomas, measuring 6 per 1,00,000 person-years for each.[5] The overall incidence of brain and spinal cord tumors is 5 to 10 per 1,00,000 in India.[6] The majority (38.7%) of these lesions were astrocytomas.[6]

Clinically, presenting symptoms may be related to lesion localization. Examples include focal seizures, sensory impairment, motor weakness, ataxia and cognitive disturbances or personality changes.[7] Symptoms may also be generalized and nonspecific like headaches with vomiting, which may point toward the underlying raised intracranial pressure.[7] Visual disturbances may occur either due to the former or the latter.

Clinical and Diagnostic Workup Excluding Imaging

On clinical suspicion of a brain tumor, the primary investigative workup focuses on imaging.[8] When the patient presents with a headache, a fundoscopy may be performed to look for papilledema, which could be a sign of raised intracranial tension due to a brain tumor. When a seizure is an initial presentation, electroencephalography is usually performed.[8] Further, cerebrospinal fluid (CSF) markers based on the tumoral genetic material and proteins like circulating tumor DNA and microRNA have been shown to aid in brain tumor diagnosis.[9]

Obtaining a tissue sample after the identification of a brain tumor on imaging is crucial for confirming the diagnosis and planning further treatment.[8] This importance is even more in the era of molecular diagnostics, where genotyping is necessary for accurate prognostication.[8,10] The tissue sample is usually obtained by biopsy or upfront surgery.[8] Stereotactic biopsy has a low risk of morbidity and a good sampling rate with higher chances of an accurate tissue diagnosis.[8,11] The genetic makeup of glioma may be identified by methods like DNA sequencing or cheaper, more widely available alternatives like immunohistochemistry (IHC).[12] The diagnosis and classification of a brain tumor should be based on the World Health Organization (WHO) 2021 classification system.[13]

Recommendations

- The diagnostic modality of choice on clinical suspicion of a brain tumor is contrast-enhanced MRI.[8]
- The tissue sample from a diffuse infiltrative glioma is to be routinely subjected to IHC for the detection of Isocitrate Dehydrogenase (IDH) 1 R132H mutant protein and alpha-thalassemia mental retardation X-linked (ATRX) nuclear expression.[8]
- When IDH1 mutation is not detected by IHC, DNA sequencing must be performed for the detection of IDH1 or IDH2 mutations in all diffuse astrocytomas and oligodendrogliomas. It should also be done in patients less than 55 years old with glioblastomas.[8,14]
- All IDH-mutant gliomas should be tested for 1p/19q codeletion status when there is ATRX retention.[8,15]
- IDH-mutant astrocytomas must be interrogated for cyclin dependent kinase inhibitor (CDKN) 2A/B homozygous deletions.[8,15]
- To label an IDH-wild diffuse glioma as a glioblastoma, testing should be done for a gain of chromosome 7 with a loss of chromosome 10, epidermal growth factor receptor amplification and telomerase reverse transcriptase promoter mutation when there is an absence of microvascular proliferation and necrosis.[8,15]
- In diffuse midline gliomas, testing should be done for Lys27-Met mutations in histone 3 genes (H3K27M) mutation.[8]

Imaging

Current recommendations for brain tumor MRI protocol include the following sequences: 2D T1-weighted imaging (T1WI), fluid-attenuated inversion recovery (FLAIR) 2D axials, axial susceptibility-weighted imaging (SWI), DWI 2D axials, 3D T1 postcontrast. Advanced imaging includes dynamic susceptibility ($T2^*$) and dynamic contrast enhancement (T1) perfusion-weighted imaging (PWI), magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), and functional MRI (fMRI). Similarly, 3D T2WI and 3D postcontrast T1W spoiled gradient recalled imaging are useful for neuronavigation/presurgical biopsy planning.

Standard MRI brain tumor protocol is required to reduce the quantitative and qualitative differences due to different protocols followed at various institutes.

►**Table 1** gives an overview of the adult brain tumor protocol followed at our institute.

On imaging, larger lesions that show hemorrhage, necrosis, mass effect, profuse edema, and a thick heterogeneous enhancement are usually aggressive and of higher grade.[16] Various tumors can be distinguished using structural imaging features such as calcifications. For instance, calcifications, a feature of oligodendroglioma, may be seen in 90% of cases while not so common in higher-grade gliomas (HGG).[17] Calcifications are also useful in differentiating between extra-axial dural-based masses as meningiomas frequently have calcifications while solitary fibrous tumors do not.[18]

Further, patterns of enhancement can also predict the type of tumor. Primary central nervous system lymphoma (PCNSL) lesions, for example, enhance homogenously, along

Table 1 Brain tumor protocol parameters

MR sequence	TE	TR	TI	FOV	Matrix	Slice thickness	Flip angle
2D axial T1 precontrast	20 milliseconds	2,200 milliseconds	NA	240 mm	320 × 256	3 mm	10–15 degrees
2D axial and sagittal T2WI	120 milliseconds	>2,600 milliseconds	NA	240 mm	480 × 480	3 mm	90 degrees
2D axial FLAIR	120 milliseconds	>6,500 milliseconds	2400 milliseconds	240 mm	320 × 256	3 mm	90 degrees
2D axial DWI (b = 0,1000 second mm^2)	70 milliseconds	>6,000 milliseconds	NA	240 mm	128 × 254	3 mm	90 degrees
3D axial T1 postcontrast	20 milliseconds	2,200 milliseconds	NA	256 mm	320 × 256	<1.5 mm	10–15 degrees
DSC (T2*) perfusion	25–23 milliseconds	2,400 milliseconds	NA	256 mm	320 × 256	<1.5 mm	30 degrees

Abbreviations: 2D, two-dimensional; FLAIR, fluid-attenuated axial inversion recovery; FOV, field of view; DSC, dynamic susceptibility contrast; DWI, diffusion-weighted imaging; MR, magnetic resonance; NA, not available; T2WI, T2-weighted imaging; TE, echo time; TI, inversion time; TR, repetition time.

Fig.1 Characteristic imaging features in a case of glioblastoma. Fluid-attenuated axial inversion recovery mixed signal intensity lesion **(A)** crossing across the midline via corpus callosum showing central blooming (compatible with bleed) **(B)** along with diffusion heterogeneity **(C)**. On postcontrast images **(D)** irregular peripheral enhancement noted and on relative cerebral blood volume maps **(E)**, increased perfusion noted in the corresponding region.

the ventricles, or show linear enhancement along perivascular spaces; on the other hand, immuno-deficient patients show ring-like enhancement.[19] "Notch sign" in lymphomas can be used to differentiate them from glioblastoma.[20] Glioblastoma is necrotic in the center and has thick enhancement near the periphery.[16]

Though structural imaging may narrow down the diagnostic possibility to a particular tumor, the combination of DWI along with PWI (►**Fig. 1**) can help predict the grade of the neoplasm and enhance diagnostic confidence. A greater tumor grade may be determined by an increased cell density, which is shown by hyperintensity on DWI and low apparent diffusion coefficient (ADC) values.[21–23] Higher ADC values are found in metastases and HGG compared with PCNSL.[21]

Recommendations for T1W Pre- and Postcontrast Images

- Before contrast administration, T1 shortening may be seen due to broken-down blood products, mineralization, fat, and melanin.

- The integrity of the blood–brain barrier can be demonstrated by T1 postcontrast imaging.
- The degree/pattern of contrast enhancement may not be useful to predict the grade of neoplasm.
- Recommendations for T2W image/FLAIR images:
- T2/FLAIR hyperintensity may be seen in vasogenic and cytotoxic edema/nonenhancing regions of the tumor/white matter pathology.
- T2/FLAIR mismatch is highly specific for IDH mutant 1p/19 q non-co deleted diffuse astrocytoma.[24] This, however, needs to be differentiated from the "bright rim" sign of dysembryoplastic neuroepithelial tumor.

Recommendations for SWI/GRE (Gradient Echo)

- For identifying regions of increased MR susceptibility. Blooming can be seen in areas of broken-down blood products, increased tumoral vascularity (higher percent of deoxyhemoglobin), and mineralization.
- Recommendations for DWI/ADC map:
- The image is weighted by the degree of water molecule diffusion and can be represented as an ADC map.
- A bright signal on DWI with a low ADC may be seen in densely packed cellular tumors/cytotoxic edema.
- Kitis et al showed that lower-grade gliomas (LGG) have considerably high minimum ADC values than HGGs.[25]
- Apart from gliomas, it was found by Bozdağ et al that high-grade meningiomas had a lower mean, minimum, and maximum ADC values than low-grade meningiomas (900, 850, 950 $\times 10^{-6}$ mm^2/s). This was in addition to a notable relation with tumor grading and proliferation (K_i-67, mitotic indices).[26]
- Differentiating lymphoma from glioblastoma can at times be challenging. ADC values are lower in lymphoma than those in HGG. In a study by Makino et al, with an ADC cutoff of $1.0 \times 10 - 3$ mm2/s, it was possible to differentiate PCNSL from glioblastoma.[27]

Recommendations for MRS

- Lower N-Acetylaspartate (NAA) and creatine levels, higher lactate along with lipid levels, and higher NAA/choline, as well as choline/creatine ratios, were found in HGGs, implying that metabolite measurement can be used to predict tumor grade, although metabolically active non-neoplastic etiologies like demyelination may have a similar pattern.[28]

Recommendations for MR Perfusion—DSC (Dynamic Susceptibility Contrast)/ T2*Perfusion

- An important perfusion parameter in T2 * perfusion is relative cerebral blood volume (rCBV). It is common to find high-grade tumors to have enhanced perfusion, as shown by elevated rCBV.[28,29]
- In a meta-analysis that compared nine studies, HGGs were shown to have considerably higher absolute and relative tumor blood volumes compared with LGGs.[30]
- In comparison to traditional MRI findings, Law et al observed increased rCBV (1.75) in HGGs compared with LGGs; however, oligodendroglioma is an exception among gliomas, where increased rCBV may be linked to fine intratumoral capillaries rather than malignant potential and neo-angiogenesis.[28]
- A steady increase in rCBV within a tumor over time may forecast the interval change of a previously low-grade neoplasm to a higher grade.[31]
- PWI is less useful for grading in meningiomas as all grades show elevated perfusion due to the common expression of vascular endothelial growth factor (VEGF), an angiogenesis marker.[32]
- PCNSL lesions can also be distinguished from metastases and glioblastomas using DSC-MRI. PCNSL has reduced rCBV compared with metastases and glioblastomas. This is because PCNSL lesions are angiocentric rather than angiogenic, meaning that they surround pre-existing blood vessels rather than create new ones.[33–35] Metastases might have variable rCBV values depending on the primary lesion.
- The dynamic passage of contrast through a region can be plotted as a signal intensity to time or a mean curve (MC). Another useful perfusion metric in MC analysis is percentage signal recovery (PSR), which measures the tendency of the MC to return to the baseline. The PSR may be used to evaluate the integrity of the blood–brain barrier.[34–36] Studies in which preloading has not been utilized for minimizing the T1 impact of gadolinium-based contrast agents in DSC-perfusion images found that lymphoma has the greatest PSR, followed by metastases and glioblastoma.[34–37] The elevated PSR in PCNSL (►**Fig. 2**) is due to T1 effects associated with the accumulation of contrast in the tumor interstitium dominating T2* effects.[35]
- PSR normally returns close to baseline in gliomas, while in brain metastases and extra-axial tumors, PSR may not return to baseline due to increased contrast extravasation.

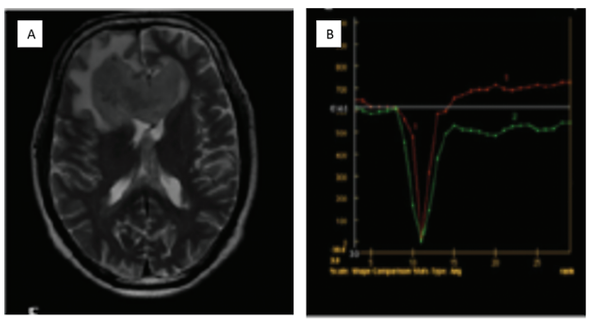


Fig. 2 Case of diffuse large B cell lymphoma. T2-weighted imaging reveals a small area of hyperintensity in the genu of the corpus callosum. **(A)**. Percentage signal recovery is high (red curve) on dynamic susceptibility contrast perfusion imaging in lymphoma with mild elevation in relative cerebral blood volume **(B)**.

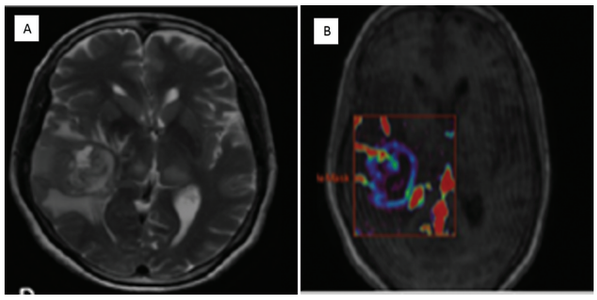


Fig. 3 Case of IDH wild glioblastoma in the right temporal lobe. The lesion represents heterogeneous hyperintensity on T2-weighted imaging **(A)** as well as elevated K trans value of 0.322 on dynamic contrast enhancement perfusion imaging **(B).**

Recommendations for MR Perfusion—Dynamic Contrast Enhancement (DCE) / T1 Perfusion

- Another PWI technique that can be used for tumor grading is DCE, a T1-based approach to estimate tumor capillary permeability (►**Fig. 3**). Higher K-trans values suggest a high grade/recurrent/progressive tumor and are extremely useful to discriminate tumor recurrence from radiation necrosis. However, the complexity of postprocessing, poor technique standardization, and lack of clinical validation are the drawbacks to widespread use.[38]

Recommendations for MR Perfusion—Arterial Spin Labeling (ASL)

- The parameter that is obtained is cerebral blood flow (CBF) without contrast administration. Increased CBF indicates a higher grade/recurrent lesion.
- eASLhas an additional advantage over ASL in terms of more accurate quantification of various metrics of tissue perfusion.

Recommendations for Diffusion Tensor Imaging (DTI)

- Imaging of white matter fiber arrangement using the property of anisotropic diffusion of water molecules.
- Fractional anisotropy (FA), an important DTI metric is a measure of the integrity of white matter tracts. Other metrics include mean diffusivity, and planar anisotropy.
- Tractograms are used to visualize the white matter tract directionality and predict displacement/ infiltration by the tumor. This can be used for preoperative planning.
- In addition, within brain neoplasms, disrupted tissue architecture results in altered FA that correlates with tumor cellularity.[39] Glioblastoma patients who show higher DTI abnormality in preoperative images have a long tumor progression-free survival and increased overall survival.[40,41]
- The limitations of tractography are the ability to resolve only a single fiber direction for a given voxel, while most voxels in the image contain multiple fiber directions[42,43] and the crossing fiber problem that can be overcome with higher-order models like high angular resolution diffusion imaging that are more time-consuming.

Recommendations for Functional Magnetic Resonance Imaging (fMRI)

- Areas of functional activation can be detected from the local fluctuations in the blood-oxygen levels in the brain.
- This property is exploited by task-based fMRI for preoperative identification of functional areas, useful in surgical planning.
- Resting-state fMRI at present is used as a research tool.

Recommendations for the Screening of the Entire Neuraxis

- The primary intracerebral malignancies that may need entire neuraxial screening for drop metastases or multicentricity include medulloblastoma, ependymoma, pineal gland malignancies, germinoma, choroid plexus carcinoma.[44]

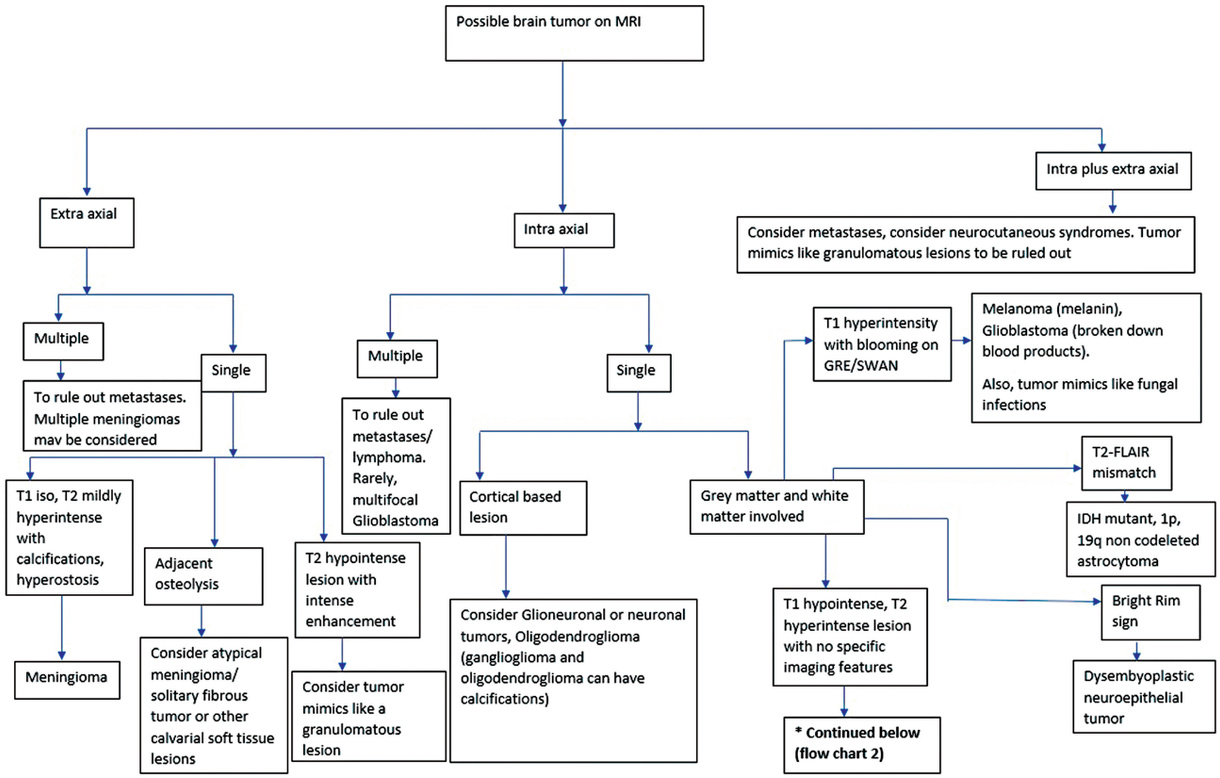
Flowcharts 1 and **2** show an algorithm for the interpretation of MR images in patients with a suspected brain tumor.[45] Postchemoradiotherapy effects may be classified as early and late effects. Early effects may occur in the first 3 to 4 months after treatment, while delayed effects can occur from 6 months to years after treatment.[46] Chemotherapy further exacerbates these effects by increasing the disruption of the blood-brain barrier.

Pseudoprogression is a type of early post-treatment effect that can occur in the first 3 to 6 months. Pseudoresponse is again an early type of reaction seen when HGGs are treated with anti-VEGF agents.[47]

Radiation necrosis (►**Fig. 4**) is due to severe local tissue response to radiation. Although it usually occurs 3 to 12 months after radiotherapy, it can even occur several years or decades later.[47] It has been described as having a Swiss cheese enhancement pattern.[46] However, the identification of radiation necrosis based on the pattern of enhancement alone can prove to be difficult.[46] DWI and advanced MRI sequences like PWI and MRS can help with the diagnosis in these cases. Studies on post-treatment DWI and PWI have shown that recurrent tumors have reduced ADC and increased rCBV values compared with post-treatment effects (►**Fig. 5**).[46] Chemical exchange saturation transfer MRI and PET using amino acid radiotracers (rather than fluorodeoxyglucose) have demonstrated the capability to differentiate tumor recurrence/residue and post-therapy changes.[48,49]

Recommendations in the Imaging of Treated Brain Tumors

- Identification of post-treatment effects is of importance as these can be followed up with or without medical management while the recurrence warrants treatment.



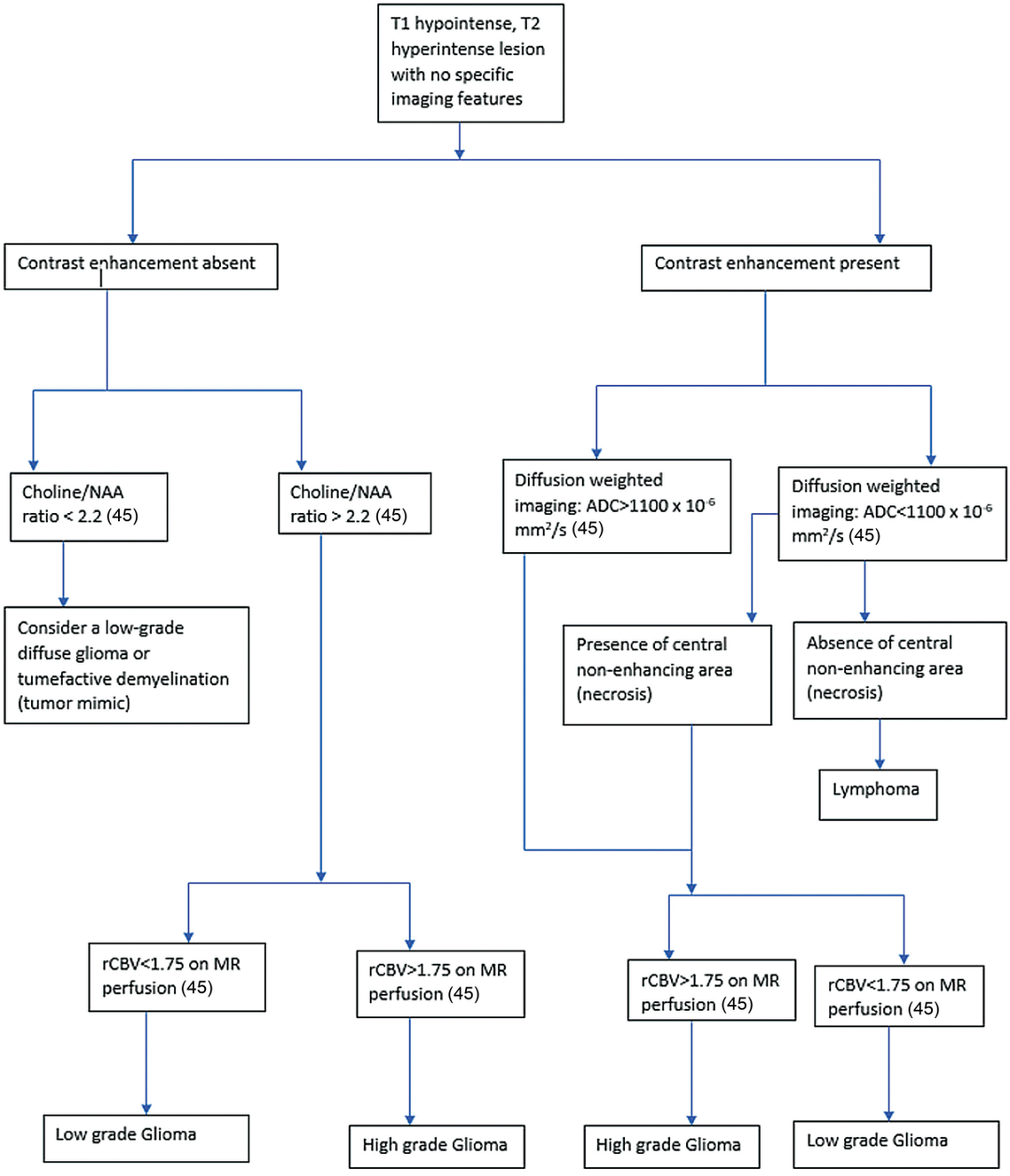
Flowchart 1 Image interpretation algorithm 1. FLAIR, fluid-attenuated axial inversion recovery; MRI, magnetic resonance imaging.

- Advanced MRI sequences like DWI, PWI, MRS, and PET-CT may be used to differentiate post-treatment changes from recurrence or residual lesions.[46]

Radiographic response assessment: Given the wide range of interpretations, it is not unexpected that tumor response reporting in radiology varies as well. An evaluation of post-therapeutic response in gliomas is done using modified Response Assessment in Neuro-Oncology (mRANO) criteria.[50,51]

Recommendations for mRANO Criteria

- Response of the tumor is determined in comparison to baseline images (pretreatment image for recurrent glioblastoma and postradiation scan for newly detected glioblastoma).
- Lesions can be measurable and/or nonmeasurable. Measurable lesions demonstrate contrast enhancement with clearly defined margins, on 2 or more axial sections (preferably 5 mm axial slices with no interslice gap). The lesion should be at least 10 mm in size (maximum diameter) if the slice thickness is less than 5 mm and twice the slice thickness if the slice thickness is more than 5 mm. Nonmeasurable lesions show poorly defined margins that cannot be measured, lack contrast enhancement, and/or are too small to measure (<10 mm in maximum diameter).
- It divides the radiographic/clinical response into four types: (1) Complete response (CR), (2) partial response (PR), (3) progressive disease (PD), (4) stable disease (SD).
- CR: Disappearance of all measurable enhancement and nonmeasurable disease, with scans done at least 4 weeks apart. CR seen on the first scan is preliminary and on the second scan is durable. If the second scan shows enhancing lesion compared with the preliminary CR, then it is a pseudoresponse and preliminary PD. Clinically with CR, the patient should improve/be stable with no corticosteroid usage (except for physiological dose).
- PR: Measurable enhancement showing more than or equal to50% reduction in the sum of perpendicular diameter and/or more than or equal to 65% reduction in total lesion volume with scans done at least 4 weeks apart. The first scan showing PR compared with baseline is preliminary PR. If the second scan shows progression compared with preliminary PR, then it is pseudoresponse and preliminary PD and for a confirmed PD, at least two sequential scans must show an increase in tumor size. If the second scan shows a PR, then it is a durable PR. Clinically, with PR the patient should improve/be stable with no corticosteroid usage (except for physiological dose).
- PD: Measurable enhancement showing more than or equal to 25% increase in the sum of perpendicular diameter or more than or equal to 40% increase in lesion volume in 2 sequential scans done more than or equal to 4 weeks apart. The first scan showing PD is preliminary PD and if the second scan also shows PD, then it is confirmed PD. If a second scan done 4 weeks later shows SD or PR/CR, then it is pseudoprogression and is labeled as preliminary PD.



Flowchart 2 Image interpretation algorithm 2. ADC, apparent diffusion coefficient; MR, magnetic resonance; NAA,—; rCBV, relative cerebral blood volume.

Clinically with PD, the patient should have significant worsening not attributable to any other illness/steroid dose.

- SD: The patient not qualifying for CR/PR/PD is clinically stable with reduced/stable steroid dose intake compared with baseline.

mRANO criteria are yet to be widely adopted in clinical radiology practice, owing in part to the strict guidelines that must be followed, and limitations such as high interobserver variability in interpretation, dependence on clinical status and treatment history, and consistency in taking multiple measurements over time. Relying on gadolinium enhancement for assessing therapeutic response was a fundamental shortcoming of the RANO criteria as both tumor progression and post-treatment change can show enhancement.

After the advent of immunotherapy for glial neoplasms, immunotherapy response assessment for neuro-oncology has been introduced to overcome the challenges in radiology reporting which is a slight modification of the mRANO criteria. The main differences are 1. Patients on

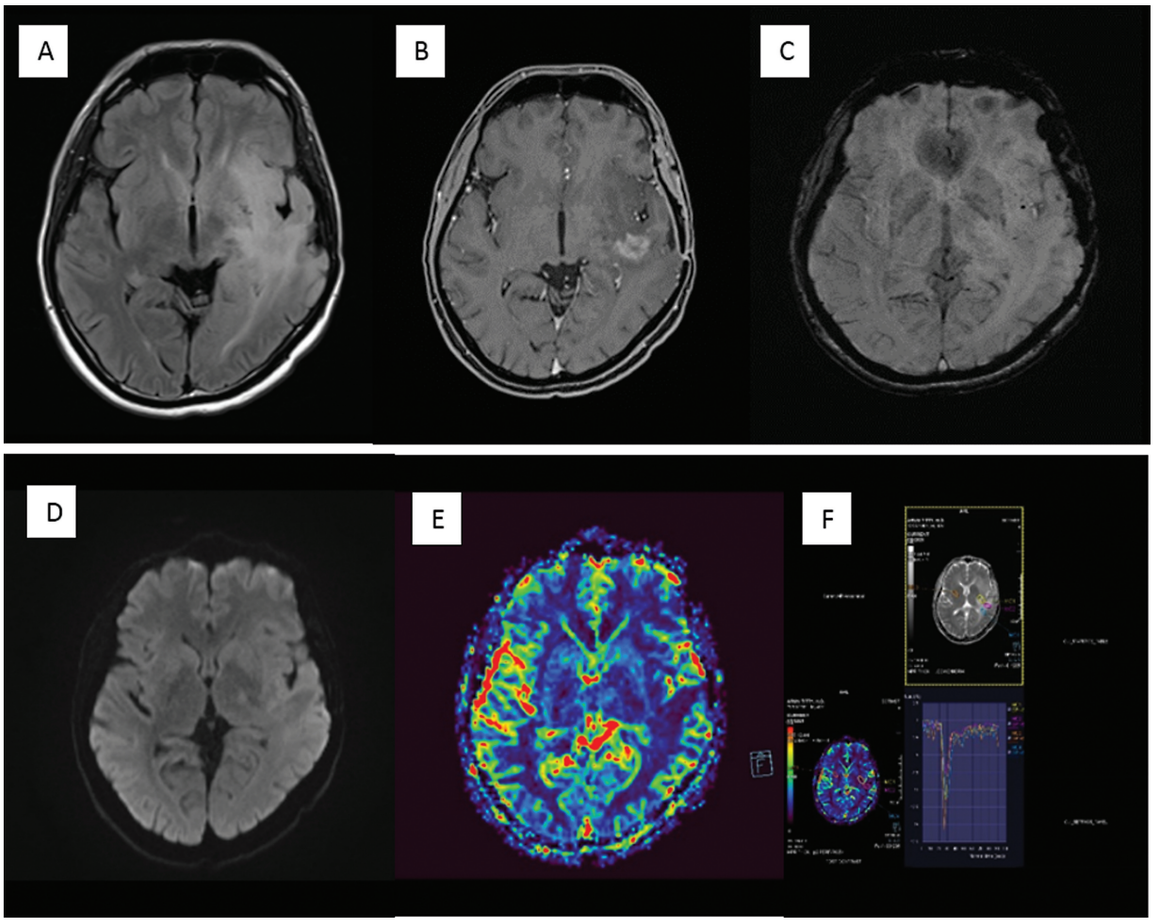


Fig. 4 Post-treatment change in the form of radiation necrosis in a patient after resection of a higher-grade glioma followed by postoperative radiotherapy. **(A)** There is fluid-attenuated axial inversion recovery (FLAIR) hyperintensity surrounding the operative cavity. **(B)** There is heterogeneous "swiss-cheese" enhancement within. **(C)** On susceptibility-weighted imaging, there are multiple foci of blooming in the hyperintensity that most likely represent postradiotherapy cavernomas. **(D)** No restriction on diffusion-weighted imaging and **(E, F)** no elevated relative cerebral blood volume on perfusion imaging within the FLAIR hyperintensity and the enhancing area as compared with the contralateral side on perfusion color map and dynamic susceptibility contrast -curves.

immunotherapy with new contrast-enhancing lesions outside the radiation field will not fall under the PD category, 2. Unlike RANO, a follow-up scan after 3 months is required to confirm disease progression as the therapeutic effect of immunotherapy may be delayed.

Brain tumor reporting and data system (BT-RADS) was created to make MRI reporting of post-treatment brain tumors easier and more consistent by assigning scores from 0 to 4 to the patients' images.[51,52] Score 0—new baseline study, score 1—improvement in imaging findings, score 2—stable imaging findings, score 3—worsening imaging findings and is divided into three subgroups depending on the underlying cause (post-therapy effect= 3a, the combined effect of treatment changes and tumor progression= 3b, tumor progression favored= 3c). Score 4—worsening of imaging findings likely indicating tumor progression. T2* perfusion and DWI can help categorize patients better, into individual subgroups in BT-RADS score 3. Each category in BT-RADS is linked to a specific management decision leading to better communication between the referring physician and the radiologist.[53,54]

Principles of Management

General management should precede definitive treatment. When the presentation is in the emergency setting with a depressed sensorium or status epilepticus, the initial measures should focus on the maintenance of the airway, respiratory efforts, blood pressure, heart rate, and seizure control.[53–55] Dexamethasone may be used to treat peritumoral edema.[56]

Recommendations

- In a diffuse infiltrating glioma seen on imaging, the treatment of choice is the maximum possible safe resection followed by radiotherapy and chemotherapy. If resection is not feasible due to the eloquence of adjacent areas or the poor general condition of the patient, a stereotactic biopsy may be considered for deciding on further management.[8,11,57] Management decisions without histological diagnosis should be stringently avoided and may only be taken in unusual situations like difficulty

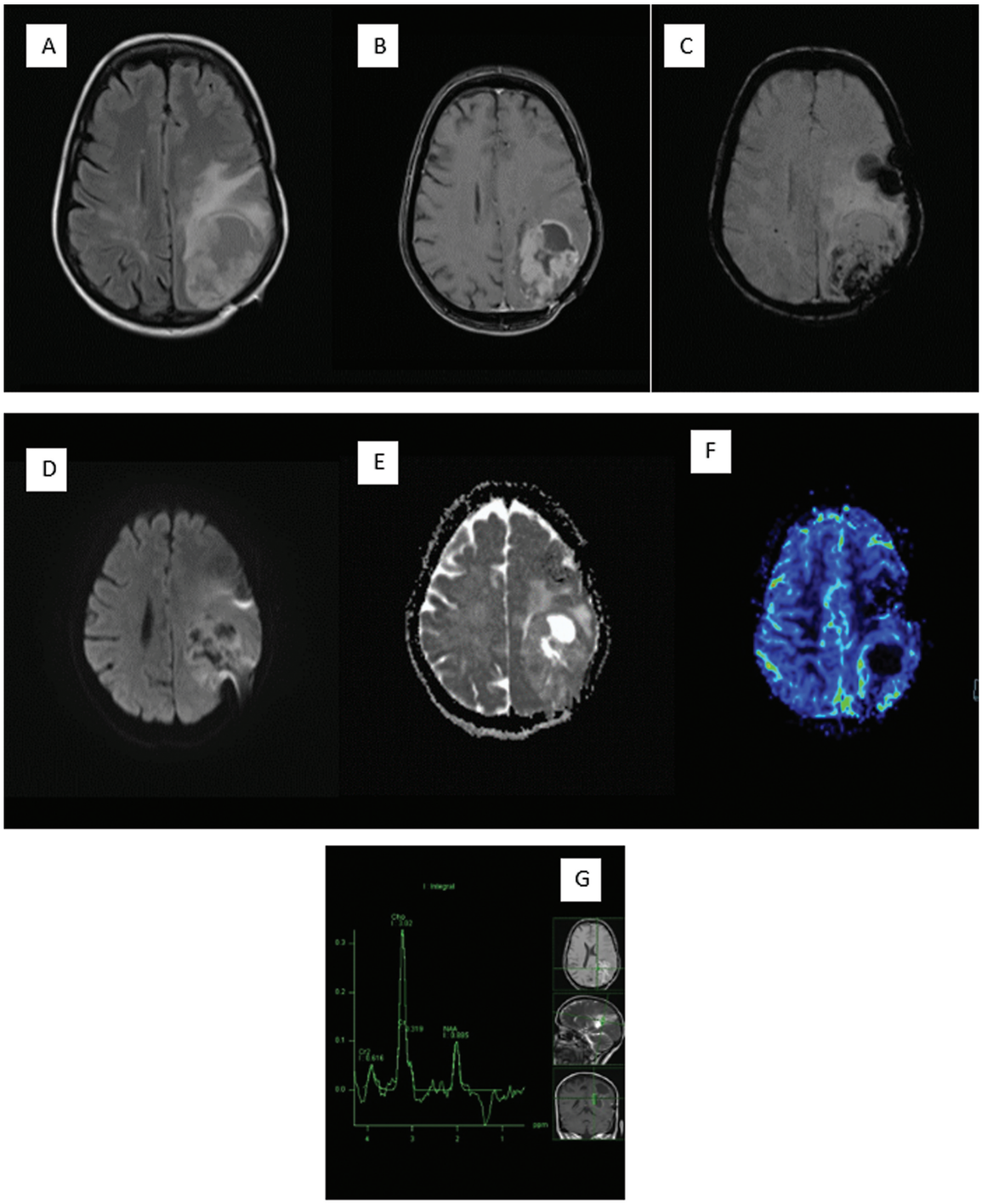


Fig. 5 Recurrence in the postoperative higher grade glioma patient. **(A)** Fluid-attenuated axial inversion recovery image is noted to show a heterogeneous hyperintensity in the left parietal lobe. **(B)** Heterogeneous enhancement on postcontrast scan has been seen. **(C)** Susceptibility-weighted imaging shows blood products that are most likely postoperative. **(D, E)** There is heterogeneous diffusion on diffusion-weighted imaging and apparent diffusion coefficient with a few areas of restriction. **(F)** Dynamic susceptibility contrast-perfusion image shows elevated relative cerebral blood volume within the enhancing region. **(G)** Spectroscopy with intermediate echo time shows significantly elevated choline with a lactate peak.

in biopsy as in elderly patients with comorbidities or where imaging very apparently shows a large HGG.[8]

- For IDH-mutant astrocytoma, WHO grade 2 the treatment is the maximum possible resection. This is followed by radiotherapy and chemotherapy with the PCV (lomustine, procarbazine, and vincristine) regimen in patients with subtotal resection and/or when the patient is over 40 years old.[8,57,58]
- For IDH-mutant astrocytoma, WHO grade 3 and grade 4, maximum possible resection, followed by radiotherapy and chemotherapy with temozolomide.[8,57,58]

- For IDH-mutant, 1p/19q-co deleted oligodendroglioma, WHO grade 2 and 3, treatment is the maximum possible resection. If further treatment is needed, it is radiotherapy, followed by chemotherapy with the PCV regimen.[8,57,58]
- For IDH-wild glioblastoma, aged less than 70 years, the standard of care is maximum possible resection, followed by concomitant radiotherapy and daily chemotherapy with temozolomide plus 6 cycles of maintenance temozolomide. Elderly patients who are not suitable candidates for combined radio and chemotherapy are to be managed based on O^6-methylguanine-DNA methyl-transferase (MGMT) methylation status.[8,57–59]
- For incidentally detected, asymptomatic meningiomas, conservative management with follow-up is recommended. Surgery, with Simpson grade 1 resection, is indicated for meningiomas that grow or become symptomatic. Radiosurgery may be offered in patients who cannot undergo surgery when the tumor is relatively small with no significant mass effect. Patients with subtotally resected WHO grade 1 meningiomas or WHO grade 2 meningiomas with Simpsons grade 1 to 3 resection may be followed up or given adjuvant radiotherapy. WHO grade 2 meningiomas with Simpsons grade 4 or 5 resections should be given adjuvant radiotherapy. Maximal possible resection, followed by radiotherapy, is recommended in WHO grade 3 meningiomas.[59,60]
- Transsphenoidal resection is recommended for enlarging, symptomatic, nonfunctioning pituitary adenomas with mass effect and for functional adenomas. Radiotherapy may be used as adjuvant therapy for residual lesions. Follow-up is recommended for pituitary incidentalomas that are asymptomatic and surgery, if there is significant tumor growth on follow-up. Prolactinomas are generally treated with dopamine agonists. Surgery is reserved for cases with inadequate response. Radiotherapy may be used for residue after dopamine agonists or surgery.[61]
- For primary CNS lymphoma, systemic chemotherapy is the first line of management.[62,63] Surgery may be considered in a superficially located large lesion that is causing a significant mass effect. For induction chemotherapy, high-dose intravenous methotrexate is the agent of choice and it may be combined with other chemotherapeutic agents. For consolidation, high-dose chemotherapy with autologous stem cell transplantation is as efficacious as whole-brain radiotherapy (WBRT).[63]
- Brain metastases are to be treated with the best combination of multimodality treatment. Surgery may be considered in solitary brain metastases or when there is a significant mass effect with raised intracranial pressure. Surgery may also be considered in patients with multiple brain metastases, especially when the prognosis is favorable. Stereotactic radiosurgery, WBRT, or systemic chemotherapy with agents based on the primary tumor may also be considered.[64]

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

The imaging appearance after tumor resection, chemotherapy, and radiotherapy is very complex and is influenced by multiple factors. These include blood products after the surgery, inflammatory response, and edema caused by the surgery or chemoradiation.[46] Apart from post-treatment changes like radiation necrosis, pseudoprogression, and pseudoresponse, there may be residual or a recurrent tumor (►**Fig. 5**) at the margins of the resection cavity that is of particular concern.

Recommendations

- In diffuse infiltrating gliomas, a postoperative scan within 24 to 48 hours is recommended, preferably with contrast-enhanced MRI to assess the extent of resection.[8,65] A baseline MRI is done after 3 to 4 weeks after the completion of radiotherapy.[8] After the completion of therapy, imaging may be performed in 2- to 6-month intervals. But, the duration of intervals may be prolonged or shortened, depending on the extent of residual disease, and histological and genetic characteristics of the tumors. For example, IDH mutant gliomas may be followed up at 3- to 6-month intervals while IDH-wild gliomas at 2- to 3-month intervals. However, in the event of suspected disease progression, a shorter interval of 4 to 8 weeks may be adopted to confirm the same. In the rare event of a possible glioma being followed up without proper histological diagnosis, a shorter interval of approximately 2 to 3 months between imaging sessions is recommended.[8] When there is a recurrence, the prior treatment and the patient's functional status usually are considered for decision-making. A second surgery may be considered.[8]
- Patients with incidentally detected, suspected meningiomas that are asymptomatic and patients with treated WHO grade 1 meningiomas are to be followed up with annual MR examinations for 5 years. Thereafter, follow-ups may be farther apart depending on the age, and the clinical condition of the patient. For treated WHO grade 2, biannual follow-up is recommended for 5 years as they have an increased risk of recurrence. Following this, yearly follow-up is recommended.[60] Fractionated radiotherapy may be used in patients with recurrent meningiomas.[60]
- For pituitary incidentalomas that are microadenomas, an annual scan for 2 to 3 years is recommended. After this, the follow-up intervals may be prolonged if there is no increase in size. For incidentally detected pituitary macroadenomas, annual imaging follow-up with visual field charting every 6 to 12 months is recommended.[61] Aggressive pituitary lesions, after the completion of treatment, are to be followed up every 3 to 12 months by imaging depending on the rate of tumor growth and

proximity to important anatomical structures. This may be coupled with endocrine evaluation depending on the clinical scenario.[66]

- Brain metastases are to be followed up at intervals of 3 months. If there is any recurrence or progression during follow-up, the treatment decision depends on the patient's general condition, degree of progression, and the initial treatment. Treatment options include surgery, radiotherapy, and systemic chemotherapy.[64]

Synoptic Reporting Formats

Structured reporting better conveys the anatomical and pathophysiological information from the radiologist to the referring physician. A CT or an MR scan report for a brain tumor should have a detailed description of the number of tumors, their specific location, and their distance from eloquent structures as this plays a very important role in preoperative decision-making. The dimensions of the tumor along three different axes are to be mentioned; more specifically the sizes of the T2, FLAIR abnormality, and the enhancing area on the postcontrast T1W image are to be mentioned separately when the tumor is partially enhancing.[67]

Information about the extent of T2, FLAIR white matter hyperintensity adjacent to the tumor which may represent edema, the mass effect due to the tumor visible as effacement of ventricles, CSF spaces and midline shift are also to be conveyed in the report. Tumoral characteristics on DWI, SWI, PWI, and the effect of the tumor on adjacent vascular structures are also very important.

The presence of additional pathology in the neuroparenchyma like white matter disease or diffuse neuroparenchymal volume loss and calvarial pathology are all significant clinically and need to be mentioned. Finally, the radiological impression should include a possible list of differentials based on the imaging findings following the recent WHO 2021 nomenclature of brain tumors.

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Imaging Guidelines and Recommendations for Diagnosis, Surveillance, and Management of Pediatric CNS and Spinal Tumors

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Abstract

Central nervous system (CNS) tumors are the second most common cause of cancer in children when incidence rates of cancer are estimated according to the Indian population dynamics based on 2011 consensus. As per the estimates, CNS tumors account for 20.1% of cancer burden in children aged between 0 and 14 years and 16.8% when 0 to 19 years age group is considered. The most common pediatric brain tumors are astrocytoma and medulloblastoma followed by other embryonal tumors, craniopharyngioma, and ependymal tumors. The incidence of CNS tumors in children from India is similar to the western high-income countries, other than slightly higher incidence of craniopharyngioma in Indian children.

Keywords
- MRI
- pediatric brain tumors
- protocol
- spinal tumor

Introduction

Central nervous system (CNS) tumors are the second most common cause of cancer in children when incidence rates of cancer are estimated according to the Indian population dynamics based on 2011 consensus. As per the estimates, CNS tumors account for 20.1% of cancer burden in children aged between 0 and 14 years and 16.8% when 0 to 19 years age group is considered.[1] The most common pediatric brain tumors are astrocytoma and medulloblastoma followed by other embryonal tumors, craniopharyngioma (CP), and ependymal tumors.[2] The incidence of CNS tumors in children from India is similar to the western high-income countries

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(HIC), other than slightly higher incidence of CP in Indian children.[2,3]

Symptoms/Presentation

Central nervous system (CNS) tumors are the most common solid tumors in children. The worldwide incidence of pediatric CNS tumors varies from 1.12 to 5.14 per 1,00,000 individuals.[4] The peak age for pediatric CNS tumors is less than 5 years after which the incidence of CNS tumors is less till up to 15 years of age after which the incidence rates are almost like adults.[5] In the Indian population, the age-adjusted rates for the incidence of childhood CNS tumors range from 6.6 to 19.8 per million for boys and 3.0 to 16.0 per million for girls.[6]

The common presenting symptoms of pediatric CNS tumors are headache, vomiting, seizures, or cranial nerve deficits, which are quite nonspecific. This can lead to delayed or missed diagnosis.

Prognosis/Survival

The data to evaluate prognosis or study survival statistics in children with CNS tumors in India is scarce. The overall incidence of pediatric CNS tumors in India is low compared to the HIC, probably due to missed diagnosis or failure to recognize symptoms attributable to CNS tumors. As per a study from South India with data on institutional follow-up for pediatric CNS tumors, the mortality was found to be approximately 15.3% with significant treatment drop-out.[7] The 5-year survival data from a systematic review of worldwide literature from 1980 to 2009 concludes variability in survival statistics over the decades depending on tumor grade. There was significant improvement in survival for embryonal tumors (37% in 1980 to 60% in 2009), whereas the survival for astrocytoma changed very little (78% in 1982 to 89% in 2009) over the years.[8]

Role of Imaging

Magnetic resonance imaging (MRI) is the modality of choice for initial baseline assessment of a brain tumor and for follow-up imaging to assess for treatment response. Computed tomographic (CT) scan can be useful for certain cases when the intracranial lesion is heavily calcified (e.g., CP) and for tumors near the skull base or involving the skull vault to assess for bony changes. However, CT scan is usually always performed in conjunction with an MRI for complete assessment.

Across India, there are multiple cancer treatment hospitals, either managed by the government or run privately. The various institutions have a variety of MRI/CT scanners from different vendors with the MRI field magnet strength ranging from 0.5T to 3T. Also, many scans are performed at standalone private diagnostic centers and images are provided as hard prints on films. Some of the other challenges in pediatric brain/spine imaging are lack of anesthetic support or lack of expertise in reporting those scans. This greatly limits the prospect of multicenter study trials due to the inhomogeneity in scan planning and acquisition. It is a pressing priority to have a standardized imaging protocol across various institutions to be able to include more patients in pediatric CNS tumor trials and improve treatment outcomes.

The Response Assessment in Pediatric Neuro-Oncology (RAPNO) committee have recently published recommendations for image acquisition and have clearly defined response criteria for the pediatric brain tumors.[9–12] Based on these recommendations, the European Society of Paediatric Oncology Brain Tumour imaging Working Group has provided their own recommendations for pediatric brain tumor imaging that consists of minimal essential/mandatory sequences and additional sequences including advanced imaging methods that can be performed as per local imaging policy.[13] Applying these recommendations to the Indian scenario poses unique challenges as discussed above and thus we have formed imaging guidelines that will most suite to the Indian subcontinent in terms of utilizing the limited imaging capacity and improvise on the reporting standards with a clear guideline for timing the scans. We have also included templates for reporting formats to achieve minimal variability in reporting standards and facilitate wider acceptance of cases for future pediatric CNS tumor trials.

Pediatric CNS Tumor Grade on Imaging

The conventional T2-weighted (T2W) and fluid-attenuated inversion recovery (FLAIR) sequences give a good overview of the extent as well as the characteristics of the lesion with information on perilesional edema and mass effect on surrounding structures. The highly cellular lesions cause T2 shortening and generally appear iso to hypointense on T2W images. FLAIR signal changes combined with diffusion-weighted imaging/apparent diffusion coefficient (DWI/ADC) maps give information on perilesional edema versus tumor infiltration. Some low-grade gliomas (LGGs) have a bubbly appearance on imaging with a FLAIR hyperintense rim (highly suggestive of a dysembryoplastic neuroepithelial tumour [DNET]). Calcifications can be seen in low-grade tumors like pilocytic astrocytoma (PA), intermediate grade lesions like supratentorial ependymomas (EP) and in high-grade tumors like atypical teratoid rhabdoid tumor (ATRT). However, when the lesion is largely calcified with no associated enhancing component or abnormal diffusion changes, it is usually a low-grade lesion. T1W imaging is helpful specially to look for hemorrhage or calcification in the lesion as gradient or susceptibility imaging sequences are not generally part of tumor imaging protocol. The other important utility of precontrast T1W imaging is on the postoperative scan to distinguish postoperative hemorrhage from abnormal postcontrast enhancement along the resection margins that can indicate residual disease.

Postcontrast enhancement at baseline imaging in a pediatric CNS tumor does not play as big a role as it does for adult CNS tumors, as it does not reflect tumor grade in pediatric cases. However, postcontrast enhancement is particularly important in some metastasizing low-grade tumors (e.g., 5–10% of PA can metastasize) that only show enhancement

and this can be the only feature on imaging to pick up smaller lesions or leptomeningeal spread.[14] Enhancement plays an important role for tumor follow-up (f/u) for the lesions that showed enhancement at baseline imaging, to map the tumor extent or recurrence on f/u imaging (e.g., PA) and also for nonenhancing lesions at baseline that show abnormal postcontrast enhancement on f/u suggesting progression or change in lesion grade (e.g., World Health Organization [WHO] grade I diffuse astrocytoma *MYB or MYBL1 altered*).[14] Postcontrast imaging can also help to assess tumor response as LGG show significantly reduced enhancement after treatment with MEK inhibitors or BRAF inhibitors; however, this should be weighed with tumor size measurement on T2W/FLAIR imaging.[9]

DWI with ADC maps is one of the most important sequences for pediatric CNS tumor grading. Tumors can be graded by obtaining ADC value of the lesion by drawing a region of interest on the ADC map where the lower ADC values correspond to higher grade and cellularity. Some higher grade lesions do not show postcontrast enhancement and in such cases a lower ADC value can help assess for high tumor cellularity as well as for nonenhancing metastasis, a classic example being leptomeningeal and spinal metastasis in grade 4 medulloblastoma showing a contrast enhancement-DWI mismatch.[15] Diffusion has a crucial role in determining progression for the nonenhancing tumors on antiangiogenic therapy and to distinguish recurrence from pseudo-progression in high-grade tumors.[16,17]

Pediatric Brain Tumor Types

The pediatric brain tumors have several classification systems that are based on histology, molecular features, and/or site of origin of the lesion. Approximately two-third of CNS tumors in adults are supratentorial, whereas, in children approximately two-third of CNS tumors are infratentorial. Some genetic syndromes like neurofibromatosis (NF) type 1 and 2, tuberous sclerosis and Li-Fraumeni syndrome show propensity to develop brain tumors.

The most recent update by the new WHO 2021 classification of CNS tumors (WHO CNS 5) have introduced and merged many categories form the previous classification. The WHO CNS5 have classified brain tumors mainly based on the combination of histological and molecular features. The common pediatric infratentorial tumors are medulloblastoma, cerebellar astrocytoma, EP, brain stem diffuse midline glioma (including diffuse intrinsic pontine glioma [DIPG]), and ATRT. The common pediatric supratentorial tumors are LGG, high-grade gliomas (HGG), embryonal tumors, pituitary tumors, and pineal tumors.

Low-Grade Gliomas and Other Low-Grade Tumors (WHO grade I/11)

LGG are tumors of glial origin and are WHO grade I and II tumors. LGG are the most common pediatric CNS tumors accounting for nearly 40 to 50% of all CNS tumors.[18] In the WHO CNS5 classification, pediatric LGGs are classified as circumscribed, diffuse, and glioneuronal tumors. The LGG commonly arise in the hypothalamic-chiasmatic region (40%), cerebellum (25%), and cerebral hemispheres (17%), with a small proportion occurring in the brain stem (9%).[18,19] Optic pathway lesions are generally more diffuse and quite extensive in children often involving the hypothalamic–chiasmatic axis when sporadic. When associated with a cancer predisposition syndrome, the LGG are classically seen involving the optic pathway and brain stem (10–15% of NF type 1 patients).[20] PA is the most common LGG (~16%).[21] The other less common low-grade lesions are diffuse astrocytoma, pilomyxoid astrocytoma, pleomorphic xanthoastrocytoma, and DNET. The recent 2021 WHO classification of CNS tumors have added a new category for diffuse LGGs with four entities under this category: diffuse astrocytoma, MYB- or MYBL1-altered; angiocentric glioma; polymorphous low-grade neuroepithelial tumor of the young; and diffuse LGG, MAPK pathway-altered.[22]

High-Grade Gliomas and Embryonal Tumors

HGG encompass a variety of WHO grade III and IV glial tumors and the second most common pediatric CNS tumors. The common HGG gliomas are anaplastic astrocytoma (WHO III), glioblastoma multiforme (WHO IV), and diffuse midline gliomas. The new diffuse pediatric HGG category in the new 2021 WHO CNS tumor classification has four entities under it: diffuse midline glioma (H3 K27-altered), diffuse hemispheric glioma (H3 G34-mutant), diffuse pediatric-type HGG (H3-wild-type and IDH-wild-type), and infant-type hemispheric glioma.[22]

Embryonal tumors are one of the most common high-grade CNS lesions in children and medulloblastoma is the most common CNS embryonal tumor accounting for 10-15% of pediatric CNS tumors.[12] The new WHO CNS5 classification has molecularly divided medulloblastoma (MBL) into four categories (WNT-activated, sonic hedgehog [SHH]-activated TP53 wild-type, SHH-activated TP53-mutant, and non-WNT/non-SHH group that mainly comprises group 3 and 4 lesions) and the previously described histological subtypes are now combined in one category, MBL histologically defined.[22] The other common embryonal tumors are ATRTs and embryonal tumors with multilayered rosettes.

Ependymal and other Pediatric CNS Tumors (WHO I–III)

EP are classified according histopathological/molecular features as well as anatomic site, and are divided into molecular groups across the supratentorial (ZFTA fusion-positive and YAP1 fusion-positive), posterior fossa (two groups PFA and PFB), and spinal compartments (MYCN amplified and myxopapillary EP).[22] The supratentorial EP are associated with calcification and cysts. Leptomeningeal spread can be seen in EP and is not limited to any particular tumor location. The intracranial EP have a significant risk for recurrence and the 5-year overall survival is approximately 50 to 70%.[23]

The most common pituitary tumor in children is CP accounting for 6 to 9% of pediatric CNS tumors.[24] CP arises from Rathke's pouch remnant and can be sellar or suprasellar and follows the rule of 90% (approximately 90% have calcification, 90% are cystic, and 90% show enhancement). Pituitary microadenoma and macroadenoma are the less common

tumors in this category. The adamantinomatous variety of CP is more common in children and papillary variant is more common in adults.

The common pineal tumors are germ cell tumors that can sometimes present as a bifocal tumor and can involve the neurohypophyseal region.[25] Tumor markers show good correlation with different types of germ cell tumors. Calcification is common in pineal tumors. The usual clinical presentation is due to obstructive hydrocephalus due to mass effect on the cerebral aqueduct.

Management of Pediatric CNS Tumors

Surgery, chemotherapy, and radiotherapy (RT) are the main treatment options for pediatric CNS tumors and the choice of treatment depends on the stage of the disease, lesion grade, and anatomical location of the lesion.

Surgery is often the initial treatment choice especially when the tumor is causing significant mass effect or hydrocephalus or raised intracranial pressure. Surgery planning is mostly done on MRI with assistance from other advanced imaging techniques like diffusion-tensor imaging (DTI), functional MRI, and intraoperative monitoring with ultrasonography or intraoperative MRI. Surgery for pediatric CNS tumors is undertaken with curative intent and is extremely valuable in most of the nondiffuse CNS tumors (e.g., medulloblastoma or PA). However, the immediate postoperative MRI (<72 hours) is extremely useful to classify the surgery into subtotal, gross total, supramaximal, or complete resection. The extent of resection is particularly important in higher grade lesions for prognostication.

An extraventricular drain or a ventriculoperitoneal shunt is often required for hydrocephalus and for tumors around the cerebral aqueduct or in the posterior fossa, a third ventriculostomy may be required. For certain tumors like CP, achieving complete resection is often difficult due to its extent and involvement of adjacent structures making surgical debulking a suitable option. However, the CP cysts often fill up and in such cases an Omaya reservoir is inserted to achieve cyst drainage and can also be used for chemotherapy administration.[26]

RT is one of the main treatment modalities for unresectable pediatric CNS tumors and residual disease or for preventing recurrence. Various forms of RT can be used including the conventional photon bean therapy or brachytherapy or the upcoming proton beam therapy. Proton beam therapy is more focused with less complications due to less irradiation of the adjacent uninvolved structures.[27]

Role of chemotherapy in pediatric brain tumors is limited due to poor permeability of chemotherapeutic drugs across the brood–brain barrier; however, it is useful adjunct for certain tumors. Intrathecal chemotherapy is useful for intracranial hemato-lymphoid tumors.

Timing for Imaging

A presurgical baseline MRI brain or spine imaging should be performed for all patients. For patients undergoing surgery, a postoperative MRI scan to assess for residual disease should be performed around 48 hours (within 24–72 hours) as per RAPNO recommendations.[9,10] This postoperative scan will then be the baseline scan for further imaging follow-up. If only biopsy is performed, then a postbiopsy scan is not required. Follow-up imaging is recommended every 3 months for surveillance in the first year and the interval can be then be slowly increased.[20,28] In some cases of relapse, follow-up imaging can be performed every 2 months.[10] Approximately 5 to 10% of pediatric CNS low-grade tumors and 10 to 30% HGG[29] present with metastasis on presentation or develop secondarily.[30] Thus, spine MRI for brain tumors should be performed at baseline; similarly, baseline brain imaging should be performed for primary spinal cord tumors (SCT). If metastasis is detected, then repeat surveillance MRI of the spine or brain is recommended by the RAPNO committee at the same intervals as the primary tumor site.[9]

NF-1-related low-grade CNS lesions should have similar imaging protocols with additional sequences specific for site, like for orbital imaging (►**Supplementary Table S1**).[9] RAPNO has defined the radiological response assessment criteria for pediatric LGG and HGG (►**Supplementary Tables S2** and **S3**).

The largest measurable lesion or lesions or the most symptomatic/actively growing lesion should be the target lesion. Measurements are usually done in two or three dimensions and the most reproducible way is to measure the longest dimension in perpendicular planes.[9]

Introduction to Spinal Cord Tumors

SCT are classified based on location as intramedullary (IM), intradural–extramedullary (IDEM), or extradural (ED).[31] Spinal cord neoplasms are comparatively rare. They account for 5 to 10% of all central nervous system tumors, of which 70 to 80% are IDEM in location.[32] The intramedullary neoplasms can be glial and nonglial histopathologically. The glial neoplasms include EP, myxopapillary EP, subependymoma, astrocytoma, and ganglioglioma. The nonglial neoplasms include hemangioblastoma, paraganglioma, dermoid, epidermoids, lipomas, hemangiomas, metastasis, and lymphoma.[33,34] EP are the most commonly seen in adults, while astrocytomas are more common in the pediatric population. The IDEM and ED neoplasms primarily include meningioma and nerve sheath tumors.[32] Other lesions include cysts, metastases, paraganglioma, dermoid, and epidermoids. ED tumors also include the spinal column, of which bone metastasis is the most common.

Etiopathogenesis and Epidemiology

The etiopathogenesis of most primary spinal tumors is unknown. However, exposure to cancer-causing agents may be attributed to some. A genetic role is suspected as these tumors are linked to known inherited syndromes. NF 2 and von Hippel-Lindau disease are the common ones associated with neurofibromas/meningiomas and hemangioblastomas, respectively.

There is scarce data on the incidence of primary SCT. Schellinger et al quoted an overall incidence of spinal cord tumors as 0.74 per 100,000 person-years, with an incidence of 0.77/100,000 in females and 0.70/100,000 in males.[35] Two-third of all spinal tumors are IDEM, and 10% are IM SCT.[36] According to literature, the primary spinal tumors are more commonly seen in females in the Western population, whereas a slight male preponderance is seen in Asian studies.[37,38] Male to female ratio of nearly 1.4:1 has been reported in Indian studies.[39,40] The mean age of presentation of IDEM tumors was 35.8 years, IM was 25.7 years, and ED tumors was 30.7 years.[41] In a study by Chamberlain and Tredway, the mean age of patients with intramedullary spinal cord tumor (IMSCT) was 41 years, which is higher than Indian data.[36]

Clinical Presentation

Back pain, paresthesias, weakness in limbs, and sensory loss are the most frequent presenting symptoms. Scoliosis or other spinal deformities may occur due to weakness of paraspinal muscles when anterior horn cells of the spinal cord are involved. Autonomic dysfunction, including loss of bowel or bladder control and erectile dysfunction may also occur.[40,42,43]

Clinical/ Diagnostic Workup Excluding Imaging

A thorough clinical history and examination with a detailed neurological assessment mark the beginning of the assessment. IM tumors have a longer duration of clinical history as compared to IDEM tumors. IDEM tumors commonly have radicular pain, whereas IM tumors present with dull aching pain. Paralysis may occur in different body parts, depending on which level of the spinal cord or corticospinal tracts are involved (distal to proximal muscle weakness occurs in IDEM and proximal to distal weakness in IM tumors). Loss of sensation in the legs, arms, or chest may occur when spinothalamic tracts are involved. Dissociative anesthesia and suspended sensory loss are the classical presentations of IM tumors. Loss of bowel or bladder function occurs earlier in intramedullary tumors than in IDEM tumors. Anterior horn cell involvement, which occurs more commonly in IM tumors, leads to paraspinal muscle wasting causing secondary scoliosis.[40,42,43]

Cerebrospinal fluid (CSF) analysis may be considered to assess tumor cells. Laboratory studies are usually not helpful in establishing the diagnosis.

To identify the location and appearance of the tumor, imaging is required in the form of an MRI or CT scan.

Imaging Guidelines

MRI without and with intravenous gadolinium contrast is the modality of choice. It helps differentiate various spinal cord neoplasms; however, the appearances are not always pathognomic.[33] Radiographs and CT scans do not have a role in assessing the primary tumor. They may reveal associated bony changes like scoliosis, widened interpeduncular distance, and bone erosion.[33]

MRI protocol should include T2W sagittal images through the whole spine with tailored down T2 and T1 axials through the area of abnormality. Postcontrast images are at least obtained in sagittal and axial planes with an additional whole spine postcontrast screening to look for additional lesions or drop metastasis. In selected cases, DWI or DTI may be performed.[44] The recommended brain tumor protocol and spinal tumor protocol and metastatic workup imaging evaluation have been described in ►**Tables 1** and **2**, respectively.

MRI helps distinguish IM versus IDEM versus ED tumors in most cases. It helps identify the characteristic features, tailoring down the diagnostic considerations to one most likely diagnosis to be posited. Among IM neoplasm, EP is most common in adults, followed by astrocytoma. Central location, well-circumscribed lesion, presence of hemorrhage (cap sign), presence of cysts, and focal intense homogeneous enhancement are the features favoring EP. Myxopapillary EP is the most common neoplasm of the conus medullaris/filum terminale. Astrocytomas, as opposed, are poorly defined and eccentric with patchy irregular enhancement.[33,44] Meningiomas and schwannomas are the common IDEM tumors associated with NF. Meningiomas are more common in the thoracic spine followed by the cervical spine and reveal intense enhancement with a dural tail. Schwannomas are common in the dorsal spinal nerve root, reveal foraminal extension with intense enhancement, which may be heterogeneous in larger lesions.[32] Both of these can also present as ED masses.

Principles of Management

A multidisciplinary treatment decision making is often required, comprising neurosurgeons, spinal surgeons, medical oncologists, radiation oncologists, and other medical specialists. Preoperative imaging diagnosis is essential as it guides the surgeon in appropriate planning for the excision of the tumor. Intraoperative neuromonitoring (motor evoked potentials & somatosensory evoked potentials) plays an important role in SCT surgery, especially in intramedullary tumors where tracts are in extremely close proximity to the tumor. A meticulous dissection of the tumor from the cord interface is carried out. Any intraoperative drop in motor evoked potentials or somatosensory evoked potentials alarms the surgeon and allows maximum safe resection of tumors. The main aim of surgery in SCT, especially in IMSCT, is maximum safe resection with preservation of motor and sensory function. Histopathology report guides the further line of management. Adjuvant treatment in the form of radiation therapy and chemotherapy is suggested in malignant SCT and cases of drop metastases to the spinal cord.[40,42,43,45]

Follow-Up Imaging

MRI is the modality of choice for postoperative imaging. In the immediate postoperative period, MRI may be performed

Table 1 Pediatric brain tumor MRI protocol recommendations (adapted from the recent RAPNO and SIOPE recommendations)[2–6]

MRI sequence	Slice thickness/parameters	Imaging plane	Comments
Basic protocol (essential)			
a. T1W TSE/FSE or b. 3D T1W	a. Slice thickness $\leq$ 4 mm and slice gap $\leq$1 mm or b. Slice thickness <1mm and no slice gap	a. Axial or b. Sagittal	The 3D MPR sequence should be isotropic. Avoid fat saturation technique
T2W TSE/FSE	Slice thickness $\leq$ 4 mm and slice gap $\leq$1 mm	Axial	None
T2 FLAIR TSE/FSE	Slice thickness $\leq$ 4 mm and slice gap $\leq$1 mm	Axial	None
DWI/ADC	Slice thickness $\leq$ 4 mm and slice gap $\leq$1 mm	Axial	A minimum of two *b*-values ($b = 0$ and $b = 1000$), preferably three b-values ($b = 0$, $b = 500$, $b = 1000$)
Postcontrast a. T1W TSE/FSE or b. 3D T1W	a. Slice thickness $\leq$ 4 mm and slice gap $\leq$1 mm or b. Slice thickness <1mm and no slice gap	a. Axial, sagittal and coronal or b. Sagittal	The 3D MPR sequence should be isotropic. Avoid fat saturation technique
Additional sequences			
MRI sequence	Slice thickness / parameters	Imaging plane	Comments
Postcontrast T2 FLAIR TSE/FSE	Slice thickness $\leq$ 4 mm and slice gap $\leq$1 mm	Axial	
Advanced MRI sequences	Perfusion, MR spectroscopy and DTI		

Abbreviations: 3D, three-dimensional; ADC, apparent diffusion coefficient; DTI, diffusion-tensor imaging; FLAIR, fluid-attenuated inversion recovery; FSE, fast spin echo; MPR, multiplanar reconstruction; MRI, magnetic resonance imaging; RAPNO, Response Assessment in Pediatric Neuro-Oncology; SIOPE, European Society of Paediatric Oncology; T1W, T1-weighted; TSE, turbo spin echo.

Table 2 Pediatric spine MRI protocol guidelines for brain tumors and for primary spinal tumors (adapted from the recent RAPNO and SIOPE recommendations)[2–6]

MRI sequence	Slice thickness/parameters	Imaging plane	Comments
Spine imaging for brain tumors (metastatic workup)			
T1W postcontrast SE/TSE	Slice thickness $\leq$ 3 mm and slice gap $<$ 0.5 mm	Sagittal	Whole spine (will need two blocks for older kids)
T1W postcontrast SE/TSE	Slice thickness 4–5 mm and no slice gap	Axial	Will require two blocks (upper and lower spine)
Spine imaging for primary spinal tumors			
T2W SE/TSE	Slice thickness $\leq$ 3 mm and slice gap $<$ 0.5 mm	Sagittal	Whole spine (will need two blocks for older kids)
T1W SE/TSE	Slice thickness $\leq$ 3 mm and slice gap $<$ 0.5 mm	Sagittal	Whole spine (will need two blocks for older kids)
Postcontrast			
T1W SE/TSE	Slice thickness $\leq$ 3 mm and slice gap $<$ 0.5 mm	Sagittal	Whole spine (will need two blocks for older kids)
T1W SE/TSE or T1W VIBE/THRIVE/LAVA	Slice thickness 4-5mm and no slice gap or Slice thickness $\leq$ 3 mm and no slice gap	Axial	Will require two blocks (upper and lower spine)
Additional sequences			
T2W SE/TSE	Slice thickness 4–5mm and no slice gap	Axial	At the level of abnormality
Heavily T2W	3D FIESTA/CISS/SPACE/VISTA	Sagittal	At the level of abnormality

Abbreviations: 3D, three-dimensional; MRI, magnetic resonance imaging; RAPNO, Response Assessment in Pediatric Neuro-Oncology; SIOPE, European Society of Paediatric Oncology; T1W, T1-weighted; TSE, turbo spin echo.

to assess the extent of resection. This also serves as a baseline imaging for further follow-up (pre-RT and chemotherapy baseline). It is usually performed within 24 hours following surgery before neovascularity and scarring develops. It also helps assess complications like hematoma, ischemia, infection, CSF leak, and malpositioning of hardware in symptomatic patients. Hardware positioning and integrity are better evaluated with CT.[46]

In asymptomatic patients, a routine follow-up MRI imaging is performed at 4 to 6 months postsurgery to assess for tumor recurrence or disease progression. In symptomatic patients, it again helps assess tumor recurrence, hardware failure, and treatment-related complications like compression fracture, radiation myelitis, and radiation myositis. Radiation myositis on MRI reveals edema in the radiation field with straight sharp margins extending across the muscle and subcutaneous fat. Radiation myelopathy is a rare and late complication, usually seen within 4 years after radiation therapy and dependent upon the radiation dose. MRI reveals cord edema in the early course with atrophy in delayed phase.[17]

Conflict of Interest
None declared.

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Imaging Recommendations for Diagnosis, Staging, and Management of Sinonasal Tumors

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Abstract

Sinonasal tumors are a relatively rare and heterogeneous group of tumors. Owing to their nonspecific presentation and rarity, they can be potentially overlooked resulting in delayed diagnosis and management, and increased patient morbidity. Imaging is crucial for the detection, staging, surgical planning, follow-up as well as surveillance of sinonasal masses, wherein computed tomography (CT) and magnetic resonance imaging (MRI) play complementary roles. CT is better at depicting bony changes, while MRI is useful for delineating the extent of soft tissue lesion, detect perineural, intracranial, or intraorbital spread as well as differentiate trapped sinus secretions from tumor tissue. Other modalities like fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) and arteriography can be selectively employed. FDG-PET is useful for metastatic workup and detection of residual/recurrent disease. Arteriography and endovascular image-guided interventions are useful to delineate supply of vascular tumors and perform preoperative embolization. A systematic evidence-based approach to a possible case of sinonasal tumor can go a long way in streamlining the detection and management of these tumors, while optimizing the use of available healthcare resources.

Keywords
- guidelines
- malignancy
- tumors
- neoplasms
- paranasal sinus
- radiology
- sinonasal imaging

Introduction

Sinonasal tumors are rare with sinonasal malignancies accounting for about 3% of the head and neck cancers.[1] Many are diagnosed in advanced stages owing to innocuous symptoms until late into disease. The clinical manifestation often is similar to inflammatory sinus conditions including nasal discharge, nasal blockade, headache or epistaxis, thereby making a clinical diagnosis difficult. At times, a mass may be visualized on clinical examination or nasal endoscopy. Even when a mass is visualized, cross sectional imaging is essential to elucidate the origin and extent of the mass.

Computed tomography (CT) and magnetic resonance imaging (MRI) play a complementary role with bony and cartilaginous lesions better depicted by CT, whereas soft tissue extension of tumor, differentiation between tumor and trapped secretions, perineural spread, intraorbital, dural, cavernous sinus, and intracranial involvement are better seen on MRI.

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Although pointing out a histological diagnosis is often impractical on imaging, it does help characterize the lesion into benign versus malignant and guide further management.

Risk Factors and Etiopathogenesis

Predilections and risk factors of the sinonasal tumors vary by the histological subtype.

Notable associations are that of the juvenile nasal angiofibroma (JNA) occurring exclusively in males, bimodal distribution of olfactory neuroblastoma with a peak at age 45-55 years and smaller peak at 10 to 25 years, human papillomavirus (HPV) association of inverted papilloma, Epstein-Barr virus association of sinonasal lymphoepithelial carcinoma.[2]

Important risk factors for malignant sinonasal tumors are inhaled wood dust (particularly hardwood), leather dust, nickel and chrome pigments. The aforementioned reportedly cause 600-fold increased risk for adenocarcinoma and 20-fold increased risk for squamous cell carcinoma (SCC).[3] HPV infection and smoking are the other lesser risk factors.[4] Carcinogens like formaldehyde, diisopropyl sulfate, dichloroethyl sulfide, and thorotrast have also been implicated.

Sinonasal malignancies are not notable for lymphadenopathy or distant metastases. They, however, tend to demonstrate contiguous multicompartmental local invasion with destroyed intervening bones.[5]

Epidemiology, Clinical Presentation in India and Globally

Sinonasal tumors are rare with incidence of less than 1 in 100,000 per year.[6] The sinonasal malignancies comprise 3% of the head and neck cancers and 1% of all malignancies. Peak incidence is in the fifth to seventh decade with a male preponderance.[1] SCC is the most common malignancy accounting for 50 to 80% of epithelial sinonasal malignancies.[2] The nasal cavity, maxillary and ethmoid sinuses are common sites, whereas frontal and sphenoid sinuses are rarely involved. Benign tumors are commoner in the second to third decade, with papilloma being the most common benign epithelial neoplasm.

Studies investigating the epidemiology of sinonasal tumors in India are limited. Few retrospective studies done have found a similar distribution of these tumors as seen globally. A study by Satarkar and Srikanth in North India retrospectively analyzed 206 cases of sinonasal tumors and tumor-like conditions during a period of 5 years, and found similar results. In their study, JNA was the most common benign tumor and SCC the most common malignant tumour.[7]

Clinical manifestations of sinonasal tumors are often ambiguous and mimic rhinosinusitis, thereby delaying presentation and diagnosis. Advanced disease with orbital or skull base involvement may present with visual impairment, proptosis, diplopia, epiphora, anosmia, or cranial neuropathies.

Imaging Referral Guidelines

Guidelines proposed by various societies around the world for referral and imaging in sinonasal tumors primarily advocate CT and MRI of the head and neck in complementary roles.

Imaging in the form of combination of CT and MRI is recommended by the Royal College of Radiologists (RCR) in all biopsy proven cases of sinonasal cancer to stage disease (►**Fig. 1**).[8] CT with contrast or MRI with contrast of head and neck is indicated in suspected cases of paranasal sinus (PNS) tumors by the National Comprehensive Cancer Network (NCCN).[9] Maxillofacial CT with or without intravenous (IV) contrast and MRI of orbits face neck with and without IV contrast are usually appropriate as initial imaging for suspected sinonasal mass, as per the American College of Radiology (ACR) appropriateness criteria.[10] If an MRI is planned, then a complementary noncontrast maxillofacial CT is usually sufficient as only bony changes need be assessed on CT. Imaging is to be done ideally before biopsy, if possible, as a biopsy procedure may lead to edema of the tumor and surrounding mucosa and so spuriously overstage disease extent. If advanced disease is detected on CT making a poor surgical candidate, further sinonasal imaging is not recommended by the RCR. It is frequent for tumors to cause obstruction of sinus drainage thus leading to inspissated secretions clogging the sinuses with blocked drainage pathways. Noncontrast CT may not clearly differentiate clogged secretions from tumor, and it is therefore necessary to image with either contrast enhanced CT or with MR for this differentiation.

Noncontrast MRI orbits face neck may be appropriate conditionally, if contrast is contraindicated. Noncontrast CT head or combined pre- and postcontrast maxillofacial CT imaging is not appropriate. Radiography of PNS, fluorodeoxyglucose-positron emission tomography (FDG-PET) whole body, single-photon emission computed tomography of PNS, CT cone-beam PNS and computed tomography angiography/magnetic resonance angiography (CTA/MRA) of head are considered usually not appropriate for initial imaging. CT and MRA may be useful for preoperative planning of a vascular mass. Similarly, craniofacial arteriography is not appropriate as initial imaging, and may be employed in cases of vascular tumors for preoperative embolization, preoperative planning and to control severe epistaxis.

While the RCR recommends CT chest in all clinical stages to rule out lung metastases, the NCCN recommends chest CT with or without contrast in cases of advanced nodal disease to screen for lung metastases.

FDG-PET is not generally indicated for staging. It serves to screen for lymph nodal and distant metastases in advanced disease (stage III or IV)[9] and as a problem-solving modality in cases of suspected recurrence and for suspected cancerous lymph nodes not accessible for fine-needle aspiration (FNA) or with equivocal FNA cytology results.[8]

Contrast CT or FDG-PET/CT of the abdomen and chest as well as contrast MR of the brain is indicated to rule out distant metastases if biopsy reveals a sinonasal mucosal melanoma.[9]

Clinical/Diagnostic Workup (Excluding Imaging)

As per NCCN guidelines, the workup comprises history including documentation and quantification of tobacco use

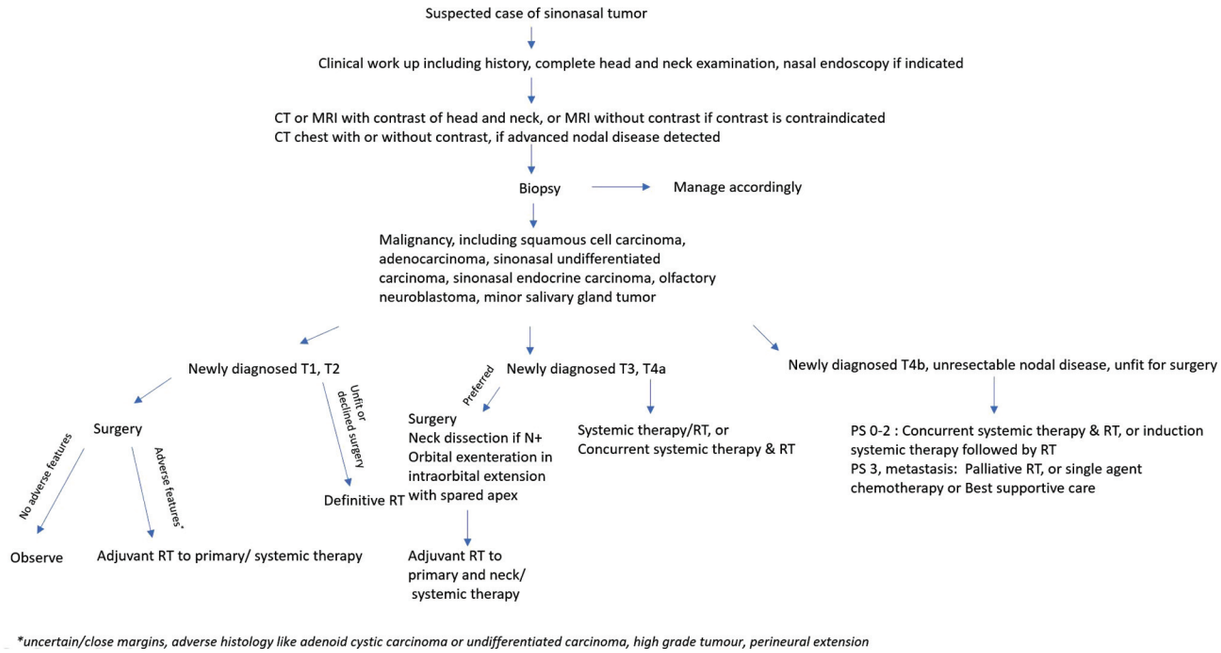

Fig. 1 Simplified flowchart for the management of suspected sinonasal mass (adapted from the NCCN v1.2022 guidelines[9]). CT, computed tomography; MRI, magnetic resonance imaging; RT, radiotherapy.

(pack years smoked) and physical examination including complete head and neck examination with nasal endoscopy as clinically indicated. Dental consultation, nutritional, speech and swallowing evaluation, screening for depression, smoking cessation counselling, and fertility/reproductive counselling are also to be considered as clinically indicated.

Although most tumors require biopsy to establish a histopathological diagnosis, exceptions do exist, like JNA wherein the diagnosis is clinicoradiological and biopsy is usually avoided. Transnasal route for endoscopic/punch biopsy is preferred, when performed. Needle biopsy is acceptable. In sampling of maxillary tumors, canine fossa puncture and Caldwell-Luc approach are to be avoided for biopsy.

Imaging Guidelines

Screening

Sinonasal cancers are rare, and general population screening is ineffective, with a potential for false positive diagnoses. Currently, there is no evidence to support screening of head and neck cancers in general as well as high-risk populations.[11–14]

Diagnosis

Imaging is done with contrast unless contraindicated.[9] The diagnostic CT protocol entails spiral CT following intravenous contrast administration from skull base to thoracic inlet with hands by the sides of the patient. The slice thickness should be no greater than 3 mm. It is viewed in the axial and coronal reformatted planes in soft-tissue as well as bone windows for local extent of tumor and lymph nodal disease.

MRI is better for assessing skull base invasion, soft tissue intracranial, or intraorbital extension, differentiating retained secretions from tumor and perineural spread (►**Figs. 2** and **3**). CT is complementary to MRI to assess bony destruction/remodeling (►**Figs. 4** and **5**). The basic MR sequences acquired are pre- and post-gadolinium T1-weighted (T1W), post-gadolinium T1-fat suppressed, T2W, and short tau inversion recovery images in orthogonal planes (axial and coronal) with slice thickness no greater than 4 mm. Additionally, T2W sagittal images and T2W coronal images with increased matrix (512×512) may also be acquired. MRA may be done to delineate arterial involvement, and volumetric post-gadolinium images acquired for radiotherapy (RT) planning.[8]

Ultrasonography (US) may be used for the assessment of clinically occult neck nodes and post-treatment surveillance

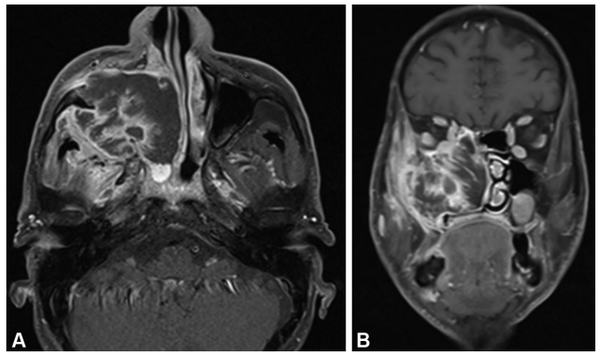

Fig. 2 Well-differentiated squamous cell carcinoma of maxillary sinus. **(A)** Axial post-gadolinium T1-weighted image with fat suppression shows heterogeneously enhancing irregular mass in the right maxillary sinus with destruction of its anterior and posterior walls and invasion of the subcutaneous tissue and pterygoid fossa, respectively. **(B)** Coronal post-gadolinium T1-weighted image with fat suppression shows the mass invading into the orbital fat and ethmoid sinus.

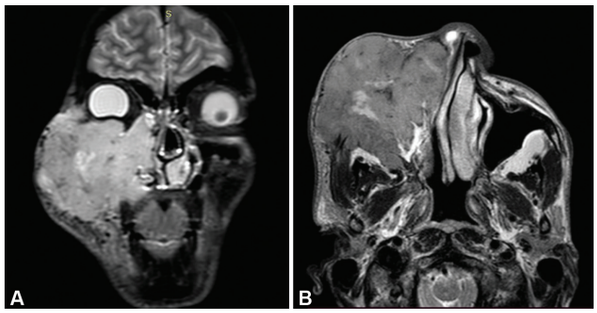

Fig. 3 Nonkeratinizing squamous cell carcinoma of right maxillary sinus. **(A)** Coronal short tau inversion recovery image shows hyperintense irregular mass lesion of the right maxillary sinus invading the subcutaneous tissue and skin of cheek, hard palate, nasal cavity, right ethmoid sinus, and right orbit. **(B)** Axial T2-weighted image shows extension of mass into the right infratemporal fossa as well.

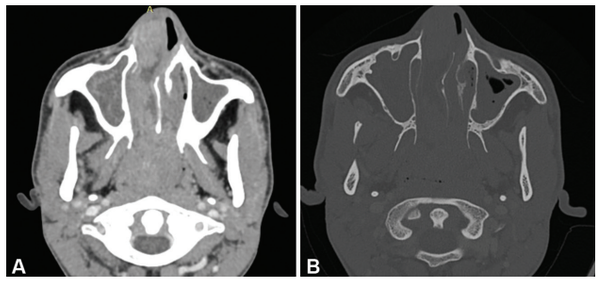

Fig. 4 Sinonasal adenocarcinoma. **(A)** Axial contrast computed tomographic image in soft tissue window shows irregular lobulated mass in the right nasal cavity protruding as far as the anterior choana, and the nasopharynx. Retained secretions in the maxillary sinus noted. (**B)** Axial bone window image shows destruction of the right turbinate.

of neck nodes. In nodal assessment by US, it is noteworthy that size criterion (short axis diameter >1.0 cm) has poor sensitivity and additional features in form of shape, contour, echogenicity, grouping, internal architecture, necrosis and pattern of Doppler vascularity must be taken into account to achieve greater accuracy (reportedly more than 90%).[15] US-guided FNA cytology is useful to detect metastatic nodes with high specificity.

In resource-poor settings, a holistic workup might not always be practical. The bare minimum investigations as recommended by the National Cancer Grid in such scenarios include diagnostic nasal endoscopy with biopsy and IHC, CT PNS, and chest X-ray.[16] It recommends MRI of face and neck, CT Thorax, ophthalmic and endocrine evaluation for optimal assessment. PET CT is deemed optional in initial assessment.

The synoptic reporting formats for CT PNS have been provided in ►**Supplementary Material.**

Staging

More than 70 histopathological entities of sinonasal neoplasms have been classified by the World Health Organization, based on tissue of origin and differentiation, and grouped under benign and malignant tumours.[2]

The American Joint Committee on Cancer—Tumour Node Metastasis (AJCC TNM) staging system for malignancies of the nasal cavity and PNS is referred to for staging of epithelial (non-melanoma) sinonasal tumours.[17] TNM staging of head and neck mucosal melanomas is separately described to stage them. The current edition (8th at the time of publication) distinguishes and separately describes the staging of maxillary sinus and ethmoid sinus tumors (►**Table 1**). No system for staging of malignancies of the frontal and sphenoid sinus is defined. Staging systems other than the TNM exist too for certain tumor histologies, like the Kadish staging for olfactory neuroblastoma.

Follow-Up

For follow-up, the NCCN recommends complete head and neck physical examination including mirror and fiberoptic examination as per the following schedule—every 1 to 3 months in year 1, 2 to 6 months in year 2, 4 to 8 months in years 3 to 5, and annually thereafter.

In the early postoperative period ($\leq$ 6 months), the preoperative baseline imaging modality can be conveniently repeated to establish a baseline postoperative scan. However, MRI has been found more helpful than CT for follow-up. FDG-PET/CT is to be done within 3 to 6 months of definitive RT or systemic therapy/RT for response assessment and to identify residual tumor. Early FDG-PET before 12 weeks is prone to false positives, and therefore the optimal timing is 3 to 6 months.

Surveillance (6 Months to 5 Years)

Most of the post-treatment recurrences occur in the first 2 years. Various modalities are employed across various centers for surveillance. FDG-PET/CT is reportedly the most sensitive modality for surveillance.

Surveillance using imaging is not supported by evidence for asymptomatic cases with negative initial PET (at 3–6 months post-treatment) and no worrisome features on clinical examination.[9] Clinical nasal endoscopy is now routinely available and enables a full evaluation of the surgical cavity, thus limiting somewhat the additional value of imaging. Another recent trend has, however, been for the use of free flaps for reconstruction of the surgical defect and the palate. Free flap reconstruction may potentially hide early recurrences emerging under the flap, and imaging for surveillance has therefore to be used more frequently in this setting. Hence, further imaging is tailored based on the presence of worrisome features, equivocal signs/symptoms on physical examination, smoking history and to assess areas inaccessible to clinical examination. Annual imaging (CT or MRI) may be done to assess for areas difficult to assess on clinical examination. US examination of the neck is useful for nodal surveillance. Annual chest CT is recommended in those with a smoking history or at high risk for lung metastases.

Principles of Management

No randomized trial exists investigating the optimal treatment for PNS tumors owing to rarity and heterogeneity of this group of neoplasms. Therefore, the general guidelines for

Table 1 TNM staging for epithelial PNS cancers other than mucosal melanomas (adapted from AJCC Cancer staging manual, 8th edition, 2017[17])

T staging	Maxillary sinus	Nasal cavity and ethmoid sinus	
Tx	Primary tumor cannot be assessed		
Tis	Carcinoma in situ		
T1	Limited to mucosa with no bony erosion/destruction	Limited to one subsite with or without bony invasion	
T2	Bony destruction including extension to hard palate and/or middle meatus, but not including posterior wall of maxillary sinus and pterygoid plates	Tumor involves two subsites within the same region or extends to an adjacent region within the nasoethmoidal complex ± bony invasion	
T3	Involvement of one of the following —bone of posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses	Invasion of medial wall or floor of orbit, maxillary sinus, palate or cribriform plate	
T4	T4a—termed moderately advanced local disease. Invasion of anterior orbital contents, skin of cheek, pterygoid plates, infra-temporal fossa, cribriform plate, sphenoid or frontal sinuses T4b—termed very advanced local disease. Invasion of orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx or clivus	T4a—termed moderately advanced local disease. Invasion of anterior orbital contents, skin of cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses. T4b—termed very advanced local disease. Invasion of orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx or clivus	
N staging (clinical)			
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Single ipsilateral lymph node metastasis < 3cm in greatest dimension and no extranodal extension (ENE)		
N2	N2a—Single ipsilateral lymph node metastasis (3-6 cm) with ENE (−) N2b—Multiple ipsilateral lymph node metastasis, all < 6 cm and ENE (−) N2c—Bilateral or contralateral lymph node metastasis < 6 cm and ENE (−)		
N3	N3a—Metastasis in a lymph node with greatest dimension > 6 cm and ENE (−) N3b—metastasis in any node(s) with clinically overt ENE		
M staging			
M0	No distant metastasis		
M1	Distant metastasis		
Prognostic stage groups			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, 2	N1	M0
	T3	N0, 1	M0
Stage IVA	T1, 2, 3	N2	M0
	T4a	N0, 1, 2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

head and neck cancers are often referred to and treatment is tailored to the individual patient.

In general, surgical resection is recommended in all operable cases regardless of nodal status or histology (►**Fig. 1**). An exception is lymphoma that is treated with chemotherapy alone. Transnasal endoscopic surgery is recently gaining preference over open surgical approaches due to reduced post-surgical morbidity and complications while achieving comparable prognosis in carefully selected situations.[18,19] This, however, mandates careful imaging to ensure that the endoscopic minimally invasive surgery would be effective in fully encompassing the tumor with appropriate margins. Post-surgery RT is administered in T1 and T2 cases with positive/uncertain margins, or with adverse prognostic factors (adverse histology like adenoid cystic carcinoma or undifferentiated carcinoma, high grade tumor, perineural extension). Adjuvant RT is recommended in all advanced cases (T3, T4) due to high risk of recurrence.[20] Orbital exenteration is indicated in cases with tumor transgressing the periorbita into the intraorbital fat. Breach of the lamina papyracea and invasion of the orbital periosteum alone do not mandate exenteration.[21]

Lymph nodal involvement is uncommon, unless tissues with rich lymphatic supply like the anterior skin, nasopharynx, oropharynx, and hard palate are invaded. The retropharyngeal lymph nodes, followed by periparotid, level 1b and 2 nodes are the most common to be involved. Cases with clinical lymph nodal disease are treated with lymph node dissection and adjuvant RT. Prophylactic nodal dissection in clinically node negative cases is not recommended. However, prophylactic RT to ipsilateral neck or ipsilateral node dissection may be advocated in advanced (T3, T4) disease.[22]

Radical RT or chemoradiotherapy without surgery is not usually recommended but may be instituted in the subsets of unresectable cases, or patients unwilling or unfit for surgery. Neoadjuvant chemotherapy might shrink the tumor size and save surgical morbidity from an otherwise more extensive resection; however, supporting evidence is scarce. Recurrent disease is treated with a combination of surgery and chemoradiation.

Prognosis

The overall 5-year survival rates average to about 50%, but vary across various histologies and stages.[23] The better prognostic factors include lower stage, absence of lymph nodal involvement, maxillary sinus tumor over ethmoid sinus tumor, and adenocarcinoma over SCC/undifferentiated carcinoma.

Summary of Recommendations

- Imaging with CT and/or MRI of the head and neck is indicated in patients of suspected as well as biopsy proven sinonasal tumors for staging. CT and MRI have complementary roles. Imaging is done with contrast, unless contraindicated. FDG-PET/CT, CT/MRA, and arteriography are not appropriate for initial imaging and may be considered selectively.
- Chest CT is recommended to screen for lung metastases in advanced disease. FDG-PET/CT is useful for surveillance to detect recurrence, and for metastatic workup.
- There is no role of screening in the general population or high-risk population owing to the rarity of these tumors.
- Surgical resection is preferred across all histologies except lymphoma, with adjuvant RT in advanced disease (T3, T4) as well as early disease with adverse prognostic factors (adverse histology, high grade, perineural spread). Lymph node dissection and adjuvant RT are warranted in clinically node positive cases. Prophylactic lymph node dissection is rarely advocated, but prophylactic neck RT may be selectively done in advanced disease (T3, T4) with no clinically apparent nodes.
- Post-surgical baseline CT or MRI is acquired within the first 6 months for follow-up. FDG-PET/CT is used for early follow-up within 3 to 6 months of completing adjuvant RT to detect residual tumor. Surveillance is essentially clinical, unless the surgical cavity is not entirely clinically accessible. In such cases, annual CT/MR is advisable. US of the neck is useful for nodal surveillance.

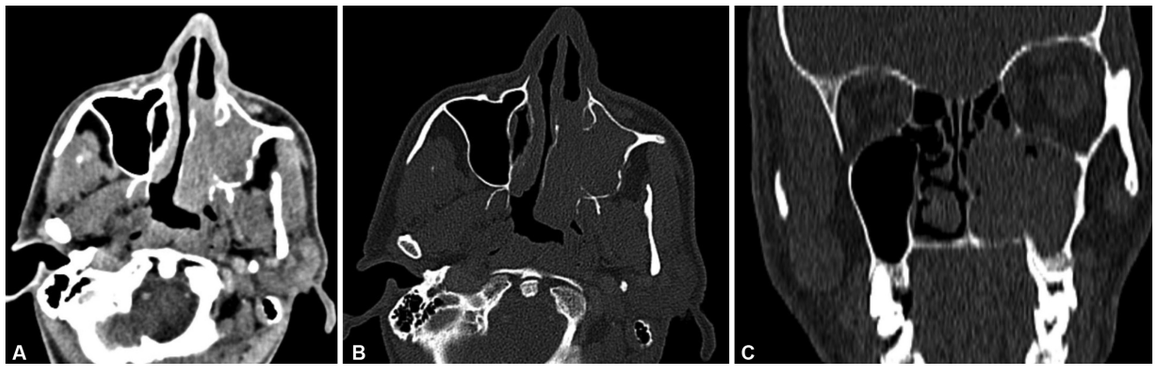

Fig. 5 Sinonasal undifferentiated carcinoma. **(A)** Axial contrast computed tomographic image in soft tissue window shows enhancing mass in the left maxillary sinus invading the left nasal cavity. **(B)** Bone window image better depicts the erosion of the posterior wall of left maxillary sinus, and the left medial pterygoid plate. The turbinates are destroyed. **(C)** Coronal reformatted bone window image shows erosion of the hard palate.

Authors' Contributions
ASB, GMNI, SM contributed in the concept, design, literature search, manuscript preparation, editing, and review. AG, RK, AS, AT, and AI contributed to the manuscript editing and review.

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None declared.

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Imaging Recommendations for Diagnosis, Staging and Management of Larynx and Hypopharynx Cancer

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Abstract

We discussed the imaging recommendations for diagnosis, staging, and management of larynx and hypopharynx cancer. Carcinoma of the larynx is a common cancer, with males being affected more. Hypopharyngeal carcinoma is less common than laryngeal malignancies. Squamous cell carcinoma is the most common histological type. Non-squamous cell malignant lesions are rare and mostly submucosal lesions. Clinical examination and endoscopy play an integral role in its detection and staging. Imaging also plays a major role in its staging, including local disease extent, nodal and distant metastatic status, as well as to assess response to therapy. Follow-up of treated cases and differentiation of recurrence from post treatment changes can be done on imaging. Early stage disease is treated with single modalities such as radiotherapy or surgery. Advanced disease is treated with multimodality of either chemoradiotherapy or surgery followed by adjuvant radiotherapy with or without concurrent chemotherapy.

Keywords
- general surgery
- pathology
- radiology

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Introduction

Carcinoma of the larynx is the second most common head and neck cancer after oral cavity. It is commonly diagnosed in patients above 50 years of age. The incidence of this cancer is more in males.[1] Hypopharyngeal carcinoma is relatively less common than laryngeal malignancies.[2] Histologically, squamous cell carcinoma is the most common type. These cancers are commonly associated with lungs and aerodigestive malignancies due to common risk factors.[1]

Endoscopy can detect mucosal lesions; however, cross-sectional imaging (computed tomography and/or magnetic resonance imaging) improves the accuracy of loco-regional staging of the disease.[1–3] Submucosal extension of the disease including involvement of the spaces and cartilages cannot be assessed on endoscopy and therefore supplementation of the clinical examination with imaging is essential for appropriate treatment planning. Cross-sectional imaging also gives information about nodal status and distant metastases and helps in restaging and follow-up of treated patients. Distorted anatomy and post treatment fibrosis may make the clinical examination challenging. Functional imaging techniques such as PET CT play a crucial role in response assessment after organ preservation protocols.

Risk Factors and Etiopathogenesis

Smoking, tobacco, and alcohol are the major risk factors[2,4]; others being indoor air pollution and meat rich, low-fiber diet.[5,6]

These carcinomas are usually mucosal in origin and then infiltrate into the submucosal tissues. The anatomical barriers produced by the laryngeal compartments and intercartilaginous membranes restrict their initial spread by forming a rigid barrier, due to which they tend to spread along pathways of least resistance into the soft tissue. However, in the later stages, invasion of the bone and/or cartilage is seen.[2] A careful evaluation of the lungs must be done for concurrent primary bronchogenic malignancies.

Lymphatic spread to neck nodes is very common in supraglottic and hypopharyngeal cancers. Glottic carcinomas do not have nodal spread commonly,[2] being 0 to 10% in early cancers and 10 to 35% in advanced cases.[7] Distant metastasis is less common, ~6.5 to 8.5%.[8–10] Lungs are the most common site of distant metastasis, followed by bones and liver.[2]

Epidemiology, Clinical Presentation in India and Global

Laryngeal cancer forms 2% of all cancers with more than 1,59,000 new cases and 90,000 cancer deaths worldwide.[11] In India, laryngeal cancer contributes to ~3 to 6% of all cancers in men, varying in different regions of the country.[5] The 5-year survival for laryngeal cancer in India is ~28%.[5]

The incidence of hypopharyngeal cancers is relatively higher in India (~11% against 1% worldwide).[11] Dietary variation has been proposed as a likely cause of this difference.

Common presenting symptoms are hoarseness, difficulty in breathing, dysphagia, or odynophagia, foreign body sensation, ear ache, and advanced disease may lead to stridor or aspiration.[11]

Imaging Referral Guidelines

As per the NCCN (National Comprehensive Cancer Network) guidelines, version V.1.2021, the following investigations are to be done for patients with larynx or hypopharynx cancer[12]:

1. Examination under anesthesia with endoscopy.
2. CECT and/or MRI for primary and neck (thin angled cuts through larynx for laryngeal carcinoma).
3. Chest CT (with/without contrast) for advanced nodal disease to screen for distant metastasis and screen for lung cancer in smokers.
4. FDG PET-CT for stage III-IV disease.

Clinical and examination findings are suggestive of the diagnosis of laryngeal carcinoma. Direct laryngoscopy with a confirmatory biopsy establishes the diagnosis. Direct laryngoscopy helps to assess the mucosal extent of disease as well as certain areas that may not be amenable to examination in routine OPD examination such as ventricles, subglottis, pyriform sinus, and post cricoid area. Imaging complements endoscopy and helps in accurate assessment and staging of disease. Contrast-enhanced CT scan is the modality of choice for initial evaluation due to its wider availability, and cheaper and faster acquisition. CT is less prone to swallowing artifacts and provides better spatial resolution compared with MRI.[1] It may be complemented with MRI in cases with dilemma, especially related to cartilage involvement.

Contrast-enhanced MRI is better to assess early cartilage involvement, pre epiglottic space, and tongue base involvement. MRI offers advantages of higher contrast resolution, differentiates tumor from peri-tumoral inflammatory response, thus helping in accurate disease assessment.[1] MRI has a higher sensitivity (89–96%) and a higher accuracy (84–76%) in detecting cartilage erosion,[1,13] but has lower specificity (74–84%) as compared with CT.[1] It has disadvantage of images being degraded by motion artifact and larger acquisition times.

FDG-PET CT is done in cases of advanced loco-regional disease to assess distant metastases. PET CT is also more helpful than CT and MRI to differentiate recurrence from treatment-related changes.[14]

All patients diagnosed with hypopharyngeal carcinoma should also be imaged because submucosal spread is common, and hence volume of disease can be underdiagnosed on endoscopy. Contrast-enhanced CT or MRI is used for detecting the extent of disease and its size. FDG PET CT is especially useful in differentiating recurrence from post treatment changes such as in laryngeal cancers.[10]

Clinical/Diagnostic Work-up Excluding Imaging

Cancer of the larynx and hypopharynx differ in many clinical aspects. Laryngeal cancer is more common than

hypopharyngeal cancer. Because hypopharyngeal cancer can be asymptomatic for a long time, these cases more frequently present with advanced cancers compared with laryngeal carcinoma. Nodal and systemic metastatic involvement is more common in hypopharyngeal than laryngeal carcinoma and neck mass may even be the first presentation in hypopharyngeal cancer. Relapse rates are also higher with carcinoma of the hypopharynx.[11] Despite these differences, the clinical/diagnostic work up is similar.

The clinical examination begins with a detailed evaluation of the primary lesion with an indirect laryngoscopy, which should be supplemented with the findings of direct laryngoscopy performed under general anesthesia. Indirect laryngoscopy is an office procedure that uses video camera or mirrors to indirectly visualize the lesion and assess cord/larynx mobility. Direct laryngoscopy directly visualizes the larynx and hypopharynx using rigid laryngoscopes.[15] Certain areas such asventricle, pyriform sinus apex, post cricoid area, and subglottis, which are suboptimally visible on indirect laryngoscopy are better visualized with direct laryngoscopy. Tissue biopsy is performed to establish the diagnosis. Neck should be meticulously examined for lymph nodes.[11]

Squamous cell carcinoma is the commonest epithelial tumor. Nonsquamous cell malignant lesions are rare and mostly submucosal lesions. These include chondrosarcoma, lymphoma, myelomas, and metastases. The clinical and endoscopic diagnosis of submucosal lesions is more difficult, and the initial biopsy if not taken from the submucosal lesion may be inconclusive or negative.[2] Imaging plays a strong role in detecting these lesions and can guide accurate biopsy in such cases.

Imaging Guidelines

a) Screening: There is no recommended screening test for laryngeal and hypopharyngeal cancers as of today.

b) Diagnosis: The CT and MRI protocol has been explained in ►**Table 1**.[1–3,16]

CT of the neck should be obtained ideally in the venous phase, so that the contrast gets enough time to reach the normal and pathologic soft tissues. The scan is taken with the patient breathing quietly to allow better evaluation of anterior and posterior commissures when the vocal cords are abducted. The scan should be viewed in soft tissue and bone windows.[1–3,16] Reformations are important.

MRI with contrast is useful in indeterminate scenarios with dilemma of cartilage erosion versus tumoral inflammation in borderline cases of T3 tumors. MRI also adds information for bulky tumor and its relationship with prevertebral fascia as well as carotid sheath in exolaryngeal spread.[1,3,16] Diffusion-weighted MRI may help in differentiating carcinomas from benign lesions and metastatic from reactive neck nodes.[17,18]

The normal CT and MR anatomy of the larynx is shown in ►**Fig. 1**. The normal appearance of the hypopharynx on CT has been demonstrated in ►**Fig. 2**.

PET CT using fluorine-18-labeled 2-fluoro-2-deoxy-D-glucose (FDG) can be used in initial staging, especially in cases with advanced locoregional disease.[2,3,16] It can help locate distant metastases or synchronous primary malignancy. It has also proved superior to CT/MRI in initial staging of lymph node metastases.

Ultrasonography can detect the primary laryngeal tumor; however, artifacts caused by thyroid cartilage calcification and by air within the laryngeal cavities are unfavorable factors.[19] Ultrasound is an excellent modality to assess neck nodes in both laryngeal and hypopharyngeal carcinomas. It can also be used to guide fine needle aspiration cytology/biopsy from indeterminate neck nodes, nodal metastases being the most accurate prognostic factor for SCC.[2,16] The appearance of a metastatic node on ultrasound

Table 1 CT and MRI protocols for imaging of the larynx and hypopharynx

CT protocol	MRI protocol
Multidectector CT (MDCT, 16 slice or above)	Multiplanar non-contrast T1-weighted, T2-weighted, T2-weighted fat-saturation images with post-contrast T1 fat-suppressed images
Iodinated contrast agent (35–40 g iodine) injected at rate of 1–1.5 mL/s; with subsequent saline injection at the same rate	Section thickness of 4 mm with an interslice gap of 0 to 1 mm
Scan should be started after the entire contrast volume injected, ideally in the venous phase with a 60–90 s delay	A dedicated neck coil
In supine position with the patient breathing quietly; with patient instructed not to cough or swallow	Instructions of not coughing and swallowing during the scan
Axial images obtained from the skull base to the aortic arch; reconstruction parallel to the hyoid bone, to get images parallel to the true vocal cords. Additional maneuvers such as modified Valsalva or phonation for better visualization of the hypopharynx or laryngeal ventricle respectively.	From the skull base to the thoracic inlet, with scan orientation parallel to the true vocal cords.
Sagittal and coronal plane reformats important	The pre-epiglottic space is better seen in the sagittal plane, while the paraglottic space and the ventricle are better assessed in the coronal plane.

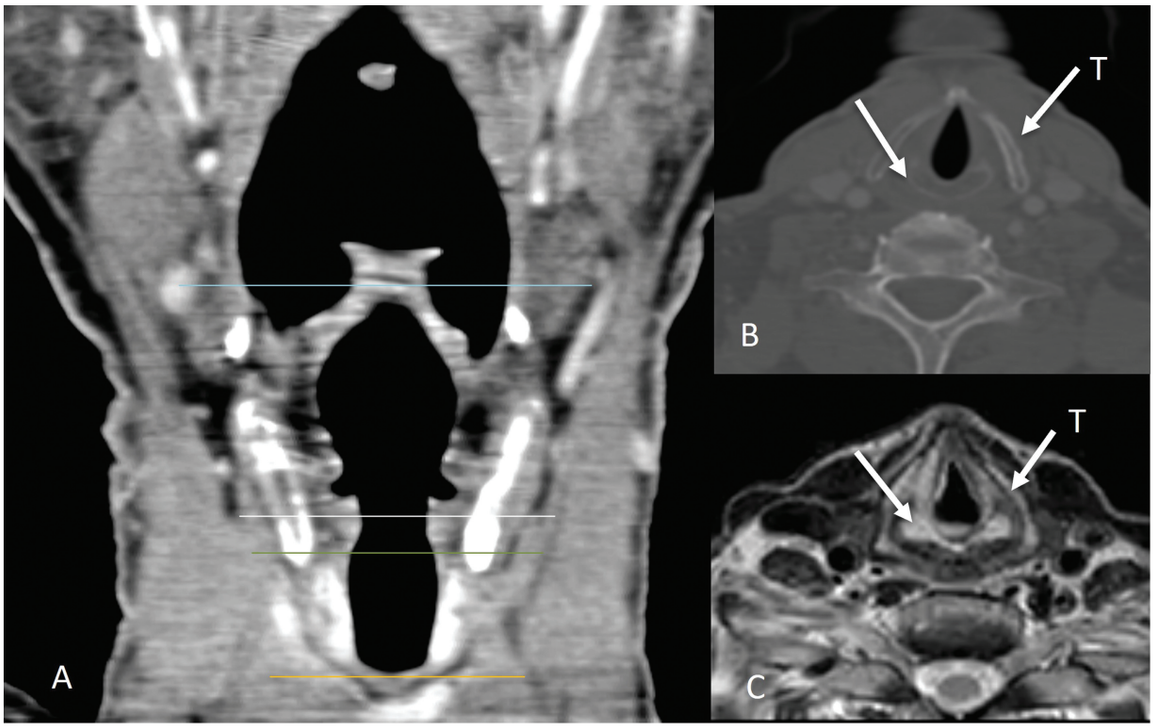

Fig. 1 Normal laryngeal anatomy. Coronal CT image (**A**) showing normal anatomy of the larynx and its subdivisions (supraglottis between blue and white lines; glottis between white and green lines; subglottis between the green and orange lines). Normal appearance of the thyroid cartilage (straight arrow labeled T) and cricoid cartilage (straight arrow) shown on image (**B**) and on axial T2W MRI image (**C**).

is shown in ►**Fig. 3**. It can also be used for surveillance post treatment;[14] however, it is operator dependent.

The primary tumor can be detected as a soft tissue thickening or mass-forming disease showing abnormal contrast enhancement with or without infiltration of fatty tissue.[2] Associated inflammatory and edematous changes may overestimate the tumor extent. This is a common pitfall of CT imaging.

Carcinoma of the larynx arises in the supraglottic region (30%), glottis (65%), or subglottic region (5%).[1,3]

Supraglottic laryngeal cancers tend to be detected in advanced stages because symptoms occur late. Supraglottic larynx has a rich lymphatic network; hence, nodal metastasis is a common finding in these patients. Supraglottic tumors may arise from the anterior components such as epiglottis, or the postero-lateral components such as aryepiglottic fold and false cords. The epiglottic lesions are usually seen along the midline anteriorly, that primarily invade into the pre-epiglottic space (PES) and laterally into the paraglottic space. The lesions arising from the stem of epiglottis often invade the low PES and then reach the glottis and subglottis via the anterior commissure. PES invasion is seen as replacement of the normal fat by abnormal enhancing soft tissue.[1–3] ►**Figs. 4** and **5** show examples of the imaging appearance of supraglottic cancer.

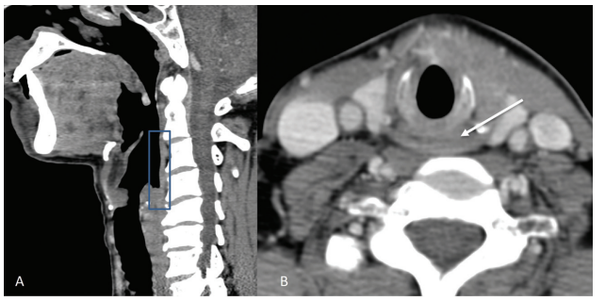

Fig. 2 Normal anatomy of the hypopharynx. Figure showing normal appearance of the hypopharynx (box) on sagittal CT image (**A**) and of the post cricoid region (arrow) on the axial CT image (**B**).

The commonest site of glottic cancer is the anterior aspect of vocal cord (►**Fig. 6**). Involvement of the anterior commissure is common, and these lesions tend to cross to the contralateral vocal cord through the midline. Anterior commissural disease is seen on CT or MRI as soft tissue thickening of more than 1 to 2 mm. Lesions involving the anterior commissure may directly spread to the anterior subglottis, lower pre-epiglottic space. Tumors in the anterior commissure have a propensity to spread to the thyroid cartilage in the midline and hence advance to T3 stage quickly. When the tumor arises from the posterior vocal cord, posterior extension to arytenoid cartilage, and posterior commissure can occur. Further spread to the post cricoid hypopharynx and esophagus may occur. Laterally, the disease can involve the vocal ligament and muscle, followed by paraglottic space and thyroid cartilage. The tumor is diverted superiorly or

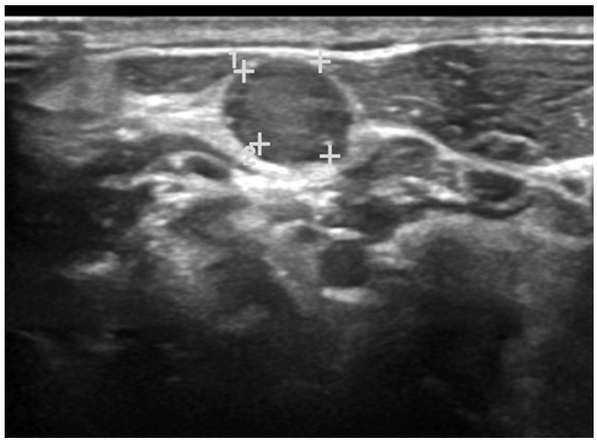

Fig. 3 Ultrasound image showing a round neck node with loss of fatty hilum, suggestive of an involved node.

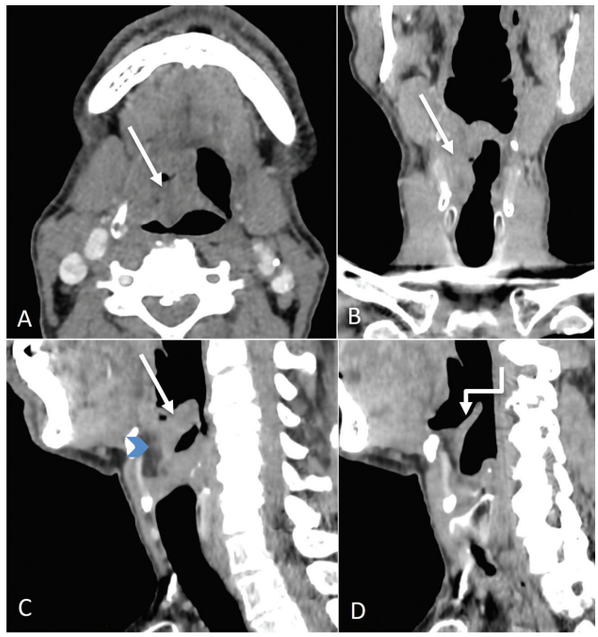

Fig. 5 Supraglottic laryngeal cancer. Axial, coronal, and sagittal CT images (**A**–**C**) showing the proliferative irregular mass (straight arrows) involving the right vallecula and supra and infrahyoid epiglottis on the right with involvement of the median glosso-epiglottic fold. There is involvement of the pre-epiglottic space also (blue arrowhead). Sagittal left paramedian CT image (**D**) showing normal uninvolved epiglottis on the left (shouldered arrow).

inferiorly by the thyroid cartilage, into the paraglottic space or the subglottis respectively. Usually, glottic cancers metastasize to the neck lymph nodes when they have transglottic extension either into supraglottis or extension into subglottis.[1–3]

Subglottic cancers, although less common, are clinically silent and present late with a poor prognosis. Lymph node metastases are commonly seen and also affect the superior mediastinal nodes. Hence, the CT should be extended to include the pre and para-tracheal region of mediastinum in such patients. Subglottic cancer is detected by the presence of any mucosal thickening between the airway and the cricoid cartilage. Invasion of the cricoid cartilage, trachea, and the cervical esophagus with extra-laryngeal spread are common in these patients at presentation.[1,3] ►**Figure 7** shows the imaging features of subglottic cancer. Apart from squamous cell carcinoma, adenoid cystic carcinoma is also common at the subglottic level.[2]

Transglottic cancer is when the disease involves both the glottis and supraglottis, irrespective of subglottic involvement.[1,3] The CT appearance of transglottic cancer has been shown in ►**Figs. 8** and **9**, and its appearance on MRI in ►**Fig. 10**.

Gross cartilage invasion is easily detected with CT. Erosion (minor areas of osteolysis) or lysis (major areas of osteolysis) of the cartilages are pointers toward cartilage involvement, while extra-laryngeal spread is highly specific. Cartilage invasion on CT is demonstrated in ►**Fig. 11**. Because ossification pattern of the laryngeal cartilages is highly variable, CT can fail to detect early cartilage invasion. MRI is more sensitive, but not as specific, to detect cartilage abnormalities. Areas of cartilage involvement will be seen as increase in

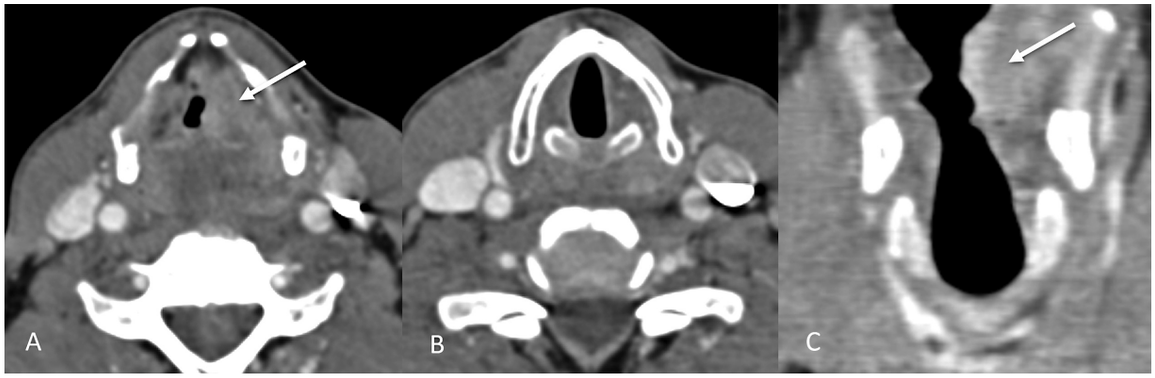

Fig. 4 Supraglottic laryngeal cancer. Axial and coronal CT images (**A, C**) showing a heterogeneously enhancing lesion (straight arrows) involving the left false vocal cord. The true vocal cords are normal in appearance and not involved as shown by the other axial image (**B**).

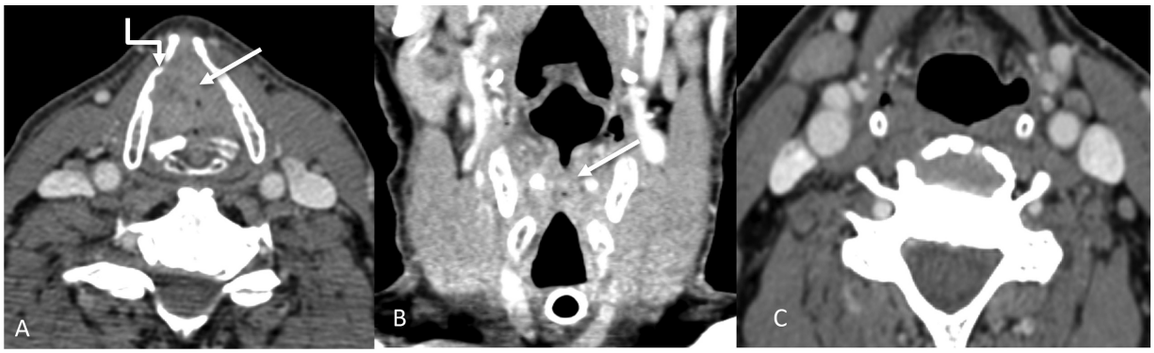

Fig. 6 Glottic laryngeal cancer. Axial and coronal CT images (**A** and **B**) showing a proliferative lesion (straight arrows) involving the true vocal cords bilaterally, with almost complete obliteration of the airway, necessitating a tracheostomy. The inner cortex of the right thyroid cartilage lamina is also involved (shouldered arrow) by the mass. No suspicious neck nodes were seen (**C**), which is usually the case in glottis cancers.

signal intensity on T2-weighted images and contrast-enhanced T1-weighted MRI images that matches the signal intensity of the tumor.[1–3,16]

Carcinoma of the hypopharynx may arise from the pyriform sinus (65%), postcricoid area (20%), and posterior pharyngeal wall (15%).[3] Imaging features of carcinoma hypopharynx have been shown in ►**Fig. 12**.

Tumors arising from the medial wall of the pyriform sinus tend to spread anteriorly into larynx through the paraglottic space. Tumors epicentered in the lateral wall of the pyriform sinus commonly infiltrate the soft tissues of the neck in early stages.[2,3]

Post-cricoid carcinoma is rare and seen in certain high-risk groups such as patients with the Plummer–Vinson syndrome. This subtype tends to be commoner in females. These lesions show submucosal spread, most commonly toward the cervical esophagus. Due to the submucosal spread, its true extent becomes more apparent with axial or sagittal MR images.[2,3] ►**Figure 13** shows an example of post cricoid carcinoma.

Posterior pharyngeal wall carcinoma commonly involves the oropharynx too. These appear as asymmetrical thickening of the posterior pharyngeal wall. Prevertebral space involvement is rare and can be reliably excluded on CT and MRI by observing the retropharyngeal fat plane.[2,3]

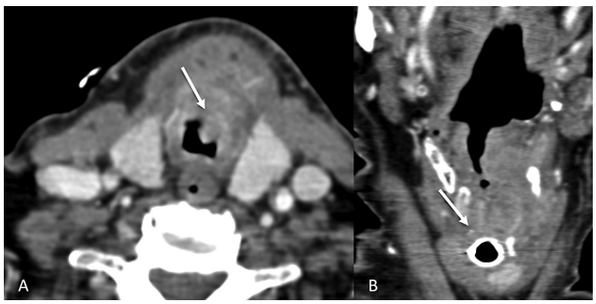

Fig. 7 Subglottic involvement. Axial and coronal CT images (**A and B**) showing subglottic involvement (straight arrows) of the laryngeal mass.

A short axis diameter of at least 10 mm, round shape, presence of necrosis (irrespective of size) and extranodal extension (node showing indistinct spiculated margins) are the general criteria to detect involved nodes on CT and MRI.[1,2]

The most common site of distant metastasis is lung. Bone and liver are the other frequent sites.[1,2]

c) Staging[1,3,12]: ►**Table 2**.

d) Response assessment imaging and follow-up:

Imaging is critical in assessing response to therapy and also for detecting recurrence. Surveillance is especially vital in the first 2 to 3 years because about two-thirds of local recurrences occur during this time period.[16,20]

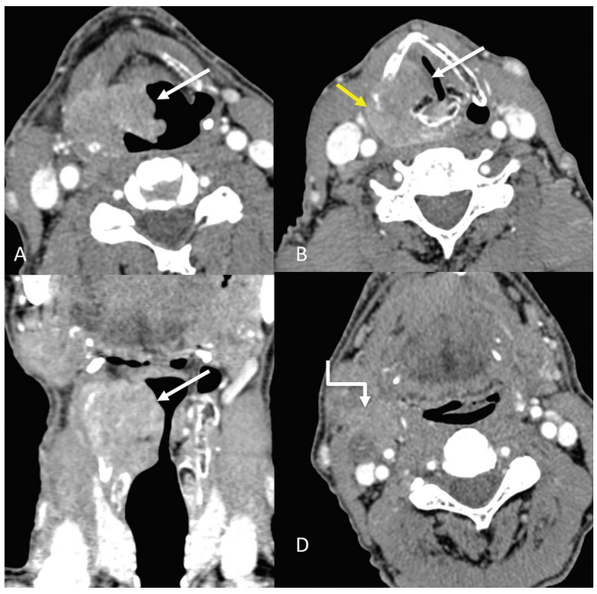

Fig. 8 Transglottic cancer involving supraglottis and glottis. Axial and coronal CT images (**A–C**) showing an enhancing exophytic mass (straight arrows) involving the right aryepiglottic fold and right vocal cord, with involvement of the right paraglottic space. Extralaryngeal spread of disease is seen (yellow arrow in B). An enlarged metastatic necrotic right level II node (shouldered arrow) is also seen (**D**).

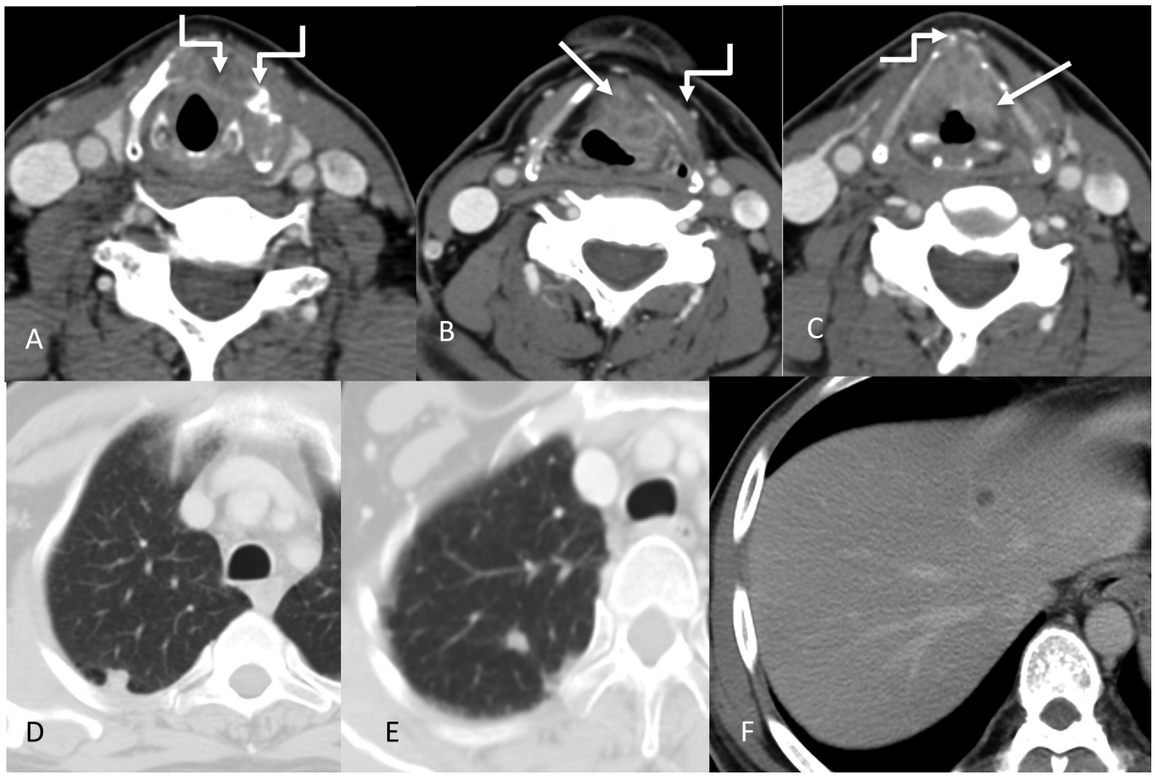

Fig. 9 Transglottic laryngeal cancer. Axial CT images (**A–C**) showing the primary enhancing mass (straight arrows) involving the true vocal cords bilaterally and left false cord. There is gross involvement of the thyroid cartilage (more on the left side) with subtle extralaryngeal spread anteriorly (shouldered arrows). Right arytenoid cartilage appears sclerosed. The left para glottic space is also involved. In addition, lung nodules and liver lesions were also identified (**D–F**).

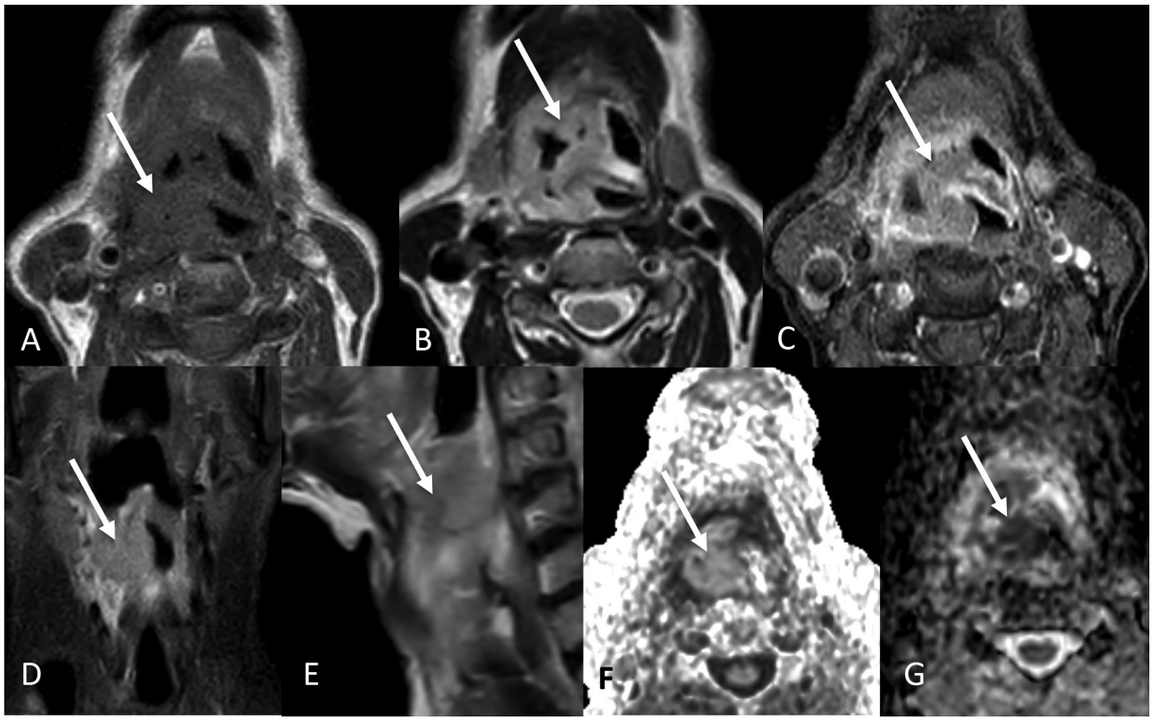

Fig. 10 Transglottic cancer. Axial T1W (**A**), T2W (**B**), post contrast T1W (**C**), coronal STIR (**D**), sagittal T2W (**E**) images showing the T1 isointense, T2 intermediate intensity, STIR hyperintense heterogeneously enhancing mass (arrows) involving the supraglottis and glottis. The mass shows restricted diffusion as seen on axial DWI and ADC images (**F and G**).

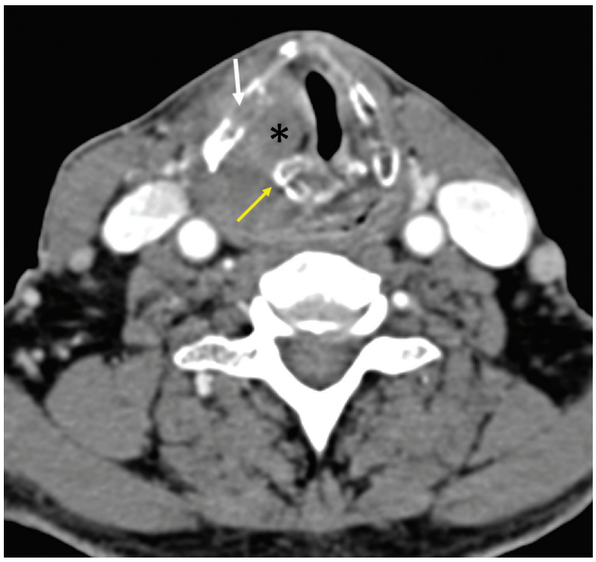

Fig. 11 Cartilage involvement-axial CT shows an enhancing mass (*) involving the right true cord, invading the thyroid cartilage on the right side (white arrow) and encasing the right arytenoid cartilage (yellow arrow).

Endoscopy is preferred to diagnose mucosal recurrences, while imaging contributes to the detection of its deeper extent.

Response assessment can be done using the modality that was used for baseline staging, be it CT or MRI or PET-CT. On CT and MRI, response to therapy can be assessed by comparing the size and extent of the mass as well as enhancement characteristics. ►**Figure 14** shows a post-chemotherapy CT that demonstrates response to treatment as compared with the pre-treatment imaging. A decreased FDG activity post treatment is a feature of response to treatment on PET-CT. PET CT is not accurate in staging and monitoring response to cystic nodes and can over estimate disease in benign reactive nodes.[16,20] Equivocal FDG uptake in neck nodes post CTRT may warrant neck dissection, however, if there is no FDG uptake after chemoradiotherapy, the patient can be kept on follow-up.[21] ►**Figure 15** shows an example of nodal recurrence in a post laryngectomy patient.

As per the NCCN guidelines in oncology for head and neck cancers,[22] a clinical assessment is to be done 4 to 8 weeks after chemotherapy or radiotherapy. If there is response clinically, a CT and/or MRI of the primary site and the neck should be performed within 8 to 12 weeks or an FDG PET/CT should be performed within 12 weeks to assess the extent of the disease. If there is residual primary tumor or disease progression clinically, a CT and/or an MRI within 4 to 8 weeks or an FDG PET/CT should be performed.[23]

Surgery causes significant distortion of the anatomy, thus the diagnosis of recurrence becomes challenging. Differentiating disease from postoperative change is difficult in view of redundant mucosa, obliteration of the paralaryngeal fat planes during surgery or postoperative granuloma. Recurrence post-surgery is generally seen as focal nodular areas or soft tissue at the surgical site. Obvious cartilage destruction and soft tissue masses greater than 1 cm in size are suggestive of recurrent tumor. Recurrence is commonly seen at the cut margins of the surgery where the tumor was previously located.[16,20]

Radiation therapy, if successful, decreases the tumor volume within 4 months. In case, at least 50% of the mass is visible 4 months after radiation, treatment failure should

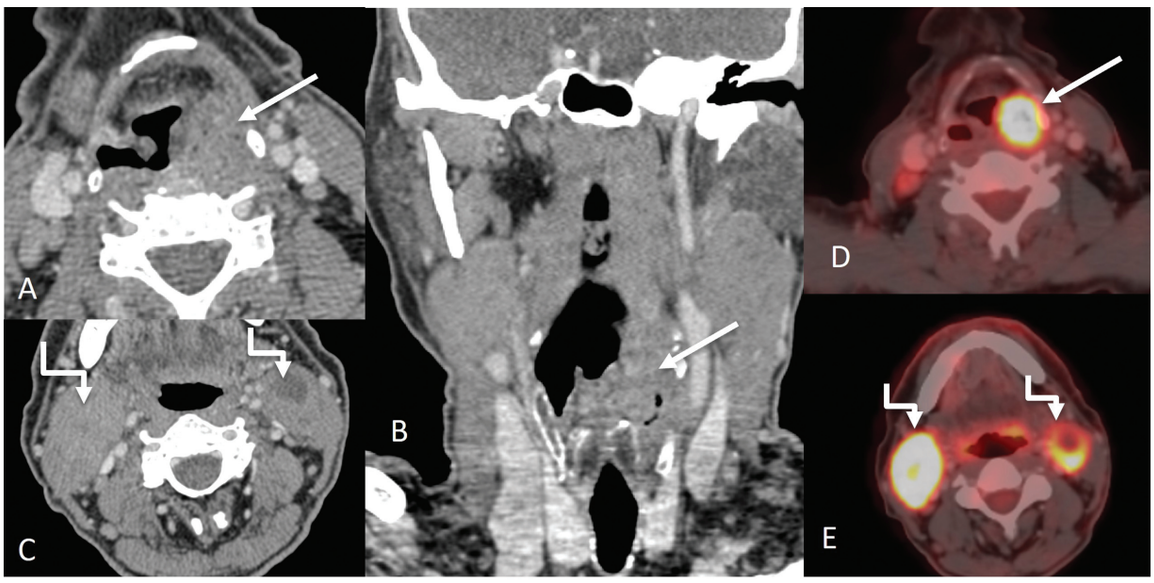

Fig. 12 Hypopharyngeal carcinoma involving pyriform sinus. Axial and coronal CT images (**A, B**) showing a proliferative mass (straight arrows) involving the left pyriform sinus. Enlarged metastatic bilateral level II nodes (shouldered arrow) are also seen on the axial CT image (**C**). Corresponding PET CT images (**D** and **E**) show significant uptake in the primary mass and metastatic neck nodes.

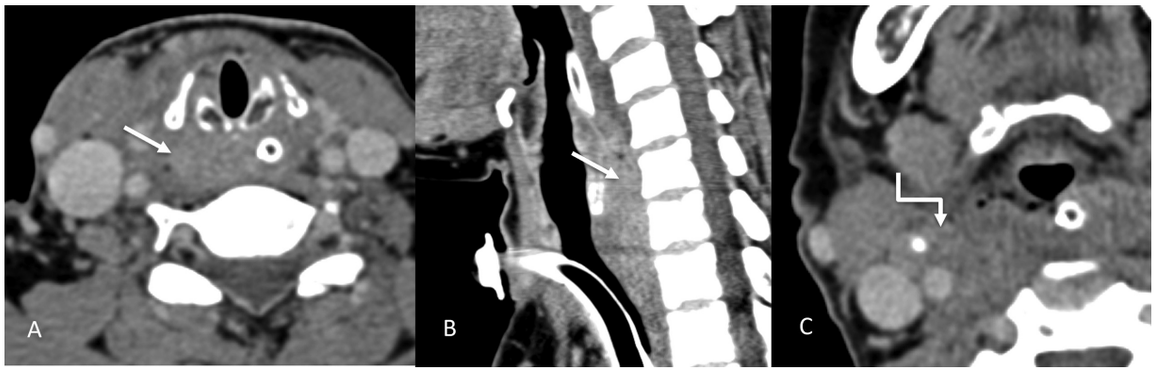

Fig. 13 Imaging of post cricoid cancer. Axial and sagittal CT images (**A**–**C**) showing a mass (straight arrows) involving the post cricoid region and a metastatic right level II node (shouldered arrow).

be considered. Radiation therapy produces edema of the laryngopharynx, thickening of the epiglottis, arytenoids, and aryepiglottic folds with abnormal enhancement. The normal fat appears stippled. These appearances may be marked and persistent beyond 6 months.[16,20] ►**Figure 16** shows typical post radiation therapy changes.

Radiation-induced chondronecrosis causes fragmentation, sclerosis and/or lysis of the cartilages. Differentiating this from recurrence is again a dilemma because both occur within a year of radiotherapy.

Knowledge of post-treatment appearances on CT and MRI scans is important to avoid unnecessary biopsies. PET-CT has more diagnostic accuracy in detecting tumor recurrence, especially when done 2 to 3 months after the completion of treatment.[16,20]

Carcinogens have been known to induce premalignant changes at more than one site in the aerodigestive tract, resulting in multiple primary tumors or secondary primary tumors, a concept known as 'field cancerization'[24]. Proposed mechanisms for this include multiple genetic aberrations, or alternatively, migration of transformed clonal cells.[24] CT, MRI, and FDG PET-CT play an important role in detecting multiple primary tumors and second primary tumors at a distant site.[25] This prevents unnecessary radical treatment of the tumor. Other methods to detect multiple/second primary tumors include fluorescence visualization.[25] Chemopreventive agents such as 13-cis retinoic acid are used to treat and prevent field cancerization.[24]

Principles of Management

Early stage I-II is treated with single modality either radiotherapy or surgery. Advanced disease with stage III-IV is treated with multimodality of either chemoradiotherapy or surgery followed by adjuvant radiotherapy with or without concurrent chemotherapy.[12] The treatment of choice for functional larynx with T1-T3 disease is organ preservation protocol of chemoradiotherapy (VA trial, RTOG 9111).[26] In select young patients with good performance status conservation, laryngeal surgery can be considered if surgical expertise is present. Early laryngeal cancers can also be treated with transoral laser surgery. Total laryngectomy is the treatment of choice in locally advanced T4 disease along with bilateral neck dissection[27] Positive node, perineural invasion, lymphatic invasion, vascular embolism, pT3 or pT4 primary disease are indications for adjuvant radiotherapy, which should be supplemented with chemotherapy in cases with extranodal extension and positive margins.[27]

In cases of carcinoma of the hypopharynx, early disease is treated with radiotherapy alone. Partial laryngectomy or transoral laser surgery can be offered in select cases. Locally advanced disease without exolaryngeal spread or cartilage erosion is treated with either chemoradiotherapy or neoadjuvant chemotherapy followed by chemoradiotherapy in responders (EORTC 24891).[28] For disease with exolaryngeal spread/cartilage erosion (T4 disease) and/or a dysfunctional larynx total laryngopharyngectomy with bilateral neck dissection should be offered. The indications of adjuvant treatment are same as mentioned above.

Patients with distant metastasis are treated with palliative intent for symptomatic relief. Treatment for the metastatic disease depends on the performance status of the patient. If good, systemic therapy is considered and if the performance status is adverse, best supportive care is advised.[12]

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

In cases of resectable locoregional recurrence, these patients should be offered surgery. If any adverse feature is identified on histopathology, adjuvant treatment with chemotherapy/RT should be considered. If the locoregional recurrence is not resectable, then these patients should be treated with systemic therapy/radiotherapy. Treatment for the metastatic recurrent disease depends on the performance status of the patient. Systemic therapy is considered if it is good and if the performance status is poor, the best supportive care is advised.[12]

Table 2 TNM staging of larynx and hypopharynx carcinoma

T staging	
Supraglottic SCC	
T1	Tumor confined to one supraglottic subsite with normal vocal cord mobility
T2	Tumor involving mucosa of more than one supraglottic subsite, with no cord fixation
T3	Tumor limited to the larynx, with vocal cord fixation and/or invasion of post cricoid region or pre-epiglottic space
T4A	Tumor invading through cricoid cartilage and/ or other extra-laryngeal tissues (trachea, cervical soft tissue, strap muscle, thyroid, esophagus) (resectable)
T4B	Tumor invading prevertebral space, encasing carotid artery or invading mediastinal structures (unresectable)
Glottic SCC	
T1	Tumor confined to vocal cord(s) with normal mobility (may involve anterior or posterior commissure) T1A-Limited to one cord T1B-Involving both cords
T2	Tumor extending to supra and/or subglottis with impaired vocal cord mobility
T3	Tumor limited to larynx, with vocal cord fixation and/or invasion of paraglottic space and/ or inner cortex of thyroid cartilage
T4A	Tumor invading through thyroid cartilage and/ or other extra-laryngeal tissues (trachea, cervical soft tissue, strap muscle, thyroid, esophagus, deep extrinsic muscles of tongue) (resectable)
T4B	Tumor invading prevertebral space, encasing carotid artery or invading mediastinal structures (very advanced local disease)
Subglottic SCC	
T1	Tumor confined to subgottis
T2	Tumor extending to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4A	Tumor invading through cricoid and/or thyroid cartilage and/or other extralaryngeal tissues (trachea, cervical soft tissue, strap muscle, thyroid, esophagus, deep extrinsic muscles of tongue) (resectable)
T4B	Tumor invading prevertebral space, encasing carotid artery or invading mediastinal structures (Unresectable)
Hypopharyngeal SCC	
T1	Tumor limited to one subsite of hypopharynx and/or $\leq$ 2 cm in greatest dimension
T2	Tumor extends into adjacent subsite of hypopharynx or adjacent site (larynx, oropharynx) and/or $>$ 2 cm but $\leq$ 4 cm without fixation of hemilarynx
T3	Tumor $>$ 4 cm, or clinical fixation of hemilarynx, or extension to esophageal mucosa
T4a	Tumor invades thyroid cartilage and/or cricoid cartilage and/or hyoid bone and/or thyroid gland and/or esophageal muscle and/or central compartment soft tissue (prelaryngeal strap muscles and subcutaneous fat) (moderately advanced local disease)
T4b	Tumor invading prevertebral space, encasing carotid artery or invading mediastinal structures (very advanced local disease)
N staging	
Nx	Regional nodes cannot be assessed
N0	No regional nodal metastasis
N1	Metastasis in single ipsilateral lymph node $\leq$ 3 cm in greatest dimension with no extranodal extension (ENE)
N2a	Metastasis in single ipsilateral lymph node $>$ 3 cm but $\leq$ 6 cm in greatest dimension with no ENE; or single ipsilateral lymph node up to 3 cm in the greatest dimension with ENE
N2b	Metastasis in multiple ipsilateral lymph nodes, $\leq$ 6 cm in greatest dimension with no ENE
N2c	Metastasis in bilateral or contralateral lymph nodes, $\leq$ 6 cm in greatest dimension with no ENE
N3a	Metastasis in a lymph node $>$ 6 cm in greatest dimension with no ENE
N3b	

(*Continued*)

Table 2 (*Continued*)

T staging	
Supraglottic SCC	
	Metastasis in a single ipsilateral lymph node > 3 cm with ENE; or multiple ipsilateral, contralateral or bilateral nodes with ENE; or single contralateral node with ENE
M staging	
M0	No distant metastasis
M1	Distant metastasis

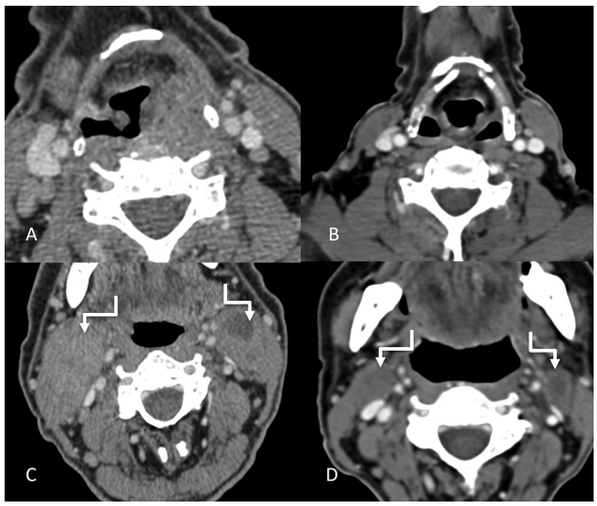

Fig. 14 Pre-chemotherapy (**A** and **C**) and post chemotherapy (**B** and **D**) imaging of the previously shown pyriform sinus cancer. Post chemotherapy axial CT images (**B** and **D**) showing near complete resolution of the primary mass and the metastatic bilateral level II nodes (shouldered arrows).

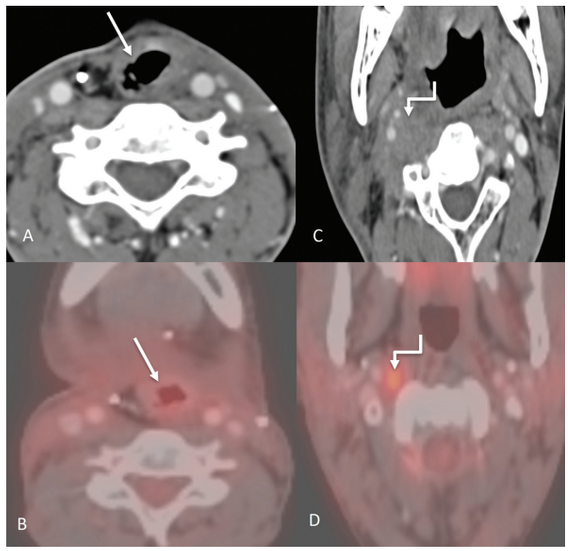

Fig. 15 Post treatment imaging. Axial CT image (**A**) of a post laryngectomy patient showing the altered anatomy postsurgery (straight arrow) with a corresponding PET CT image (**B**) showing no significant uptake to suggest recurrence at the locoregional site. However, an enlarged right retropharyngeal node is seen on axial CT image (**C**), (marked with shouldered arrow) which also showed uptake on the corresponding PET CT image (**D**).

Summary of Recommendations

- CT is generally used for assessing the primary disease, with MRI being used in doubtful cases especially for cartilage erosion.
- Ultrasound is useful for assessing neck nodes and also guide their fine needle aspiration.
- CT chest is used to rule out lung metastasis in advanced cases of laryngeal cancer; FDG PET-CT is used for distant metastases in cases with high locoregional burden and for detection of lymph node metastatic disease.
- Response assessment should ideally be done with the modality with which the baseline evaluation was done.
- Recurrence can be detected with CT or MRI or FDG PET-CT.

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

Conflict of Interest
None declared.

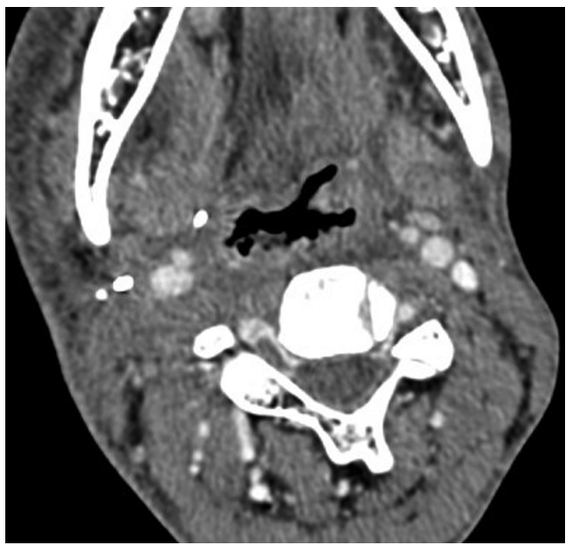

Fig. 16 Post treatment imaging. Axial CT image showing the changes caused by radiation therapy in the form of diffuse mucosal edematous changes and thickening of the skin and subcutaneous soft tissues.

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

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Abstract

Gastric cancer is the second most common cause of cancer-related death in Indian men and women aged between 15 and 44 years. Most patients present at an advanced stage of disease. Surgically resectable disease usually requires a standard gastric resection and D2 lymphadenectomy. Imaging, especially with computed tomography scan of abdomen as well as thorax, is necessary for localization, nodal mapping, and metastatic workup of gastric cancer. In this review, we discuss current imaging recommendations for gastric carcinoma.

Keywords
- computed tomography
- gastric carcinoma
- imaging

Introduction

Gastric cancer is the second most common cause of cancer-related death in Indian men and women aged between 15 and 44 years.[1] Most patients present at an advanced stage of disease. Surgically resectable disease usually requires a standard gastric resection and D2 lymphadenectomy. Imaging, especially with computed tomography (CT) scan of abdomen as well as thorax, is necessary for localization, nodal mapping, and metastatic workup of gastric cancer.

Risk Factors and Etiopathogenesis

Risk factors may differ for proximal and distal gastric cancers. The important risk factors include gastric adenomas or dysplasia, chronic atrophic gastritis, previous gastric surgery, *Helicobacter pylori* infection, high intake of pickled, smoked, salted, or preserved foods, smoking and alcohol consumption, obesity, and family history.[2–4]

Epidemiology and Clinical Presentation—India and Global

Gastric carcinoma is currently the fifth most common cancer worldwide and accounts for 8.2% of all cancer-related deaths globally.[5] There is substantial geographic variation in gastric cancer incidence. High age-standardized incidence rate is seen in the high-income Asia Pacific region (Japan, South Korea), with incidences of 29.5 per thousand population, followed by Eastern Europe and Andean Latin America. In contrast, India has relatively low rates of gastric carcinoma, with an age-standardized incidence rate of 7.5 per 100,000 population.[6] Gastric cancer is the second most common cause of cancer-related death in Indian men and women aged between 15 and 44 years.[1] Highest incidence is reported from north-eastern and southern parts of India.[7] Most patients present at an advanced stage of disease. Standard gastric resection and D2 lymphadenectomy offer the best chance of survival. The overall survival for gastric

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carcinoma is poor and the 5-year survival rate with surgical treatment alone ranges between 23 and 25%.[8]

Clinical features of gastric carcinoma include weight loss, persistent abdominal pain, dysphagia (proximal tumors), gastric outlet obstruction and/or vomiting (distal tumors), occult gastrointestinal bleeding with or without iron deficiency anemia, and signs or symptoms of distant metastases that include palpable nodes such as left supraclavicular node (Virchow's node), periumbilical nodes (Sister Mary Joseph node), and left axillary node (Irish node). Patients may also present with ascites from peritoneal spread.

Diagnostic Workup

Other than history, physical examination, and cross-sectional imaging, the diagnostic workup of suspected gastric cancer includes:

- Complete blood count and comprehensive chemistry profile.
- Endoscopy and biopsy. In case of metastatic disease, human epidermal growth factor receptor 2 (HER-2), Programmed cell death protein 1 (PD-1) and Microsatellite instability (MSI) testing are recommended. Histology should be reported according to the World Health Organization criteria. A histopathology confirmation is mandatory before definitive treatment.
- Biopsy of metastatic disease, as clinically indicated.
- Staging laparoscopy: Staging laparoscopy can upstage up to 30% of tumors. It is indicated for stage IB to III gastric cancer (as assessed by clinicoradiological examination) to determine treatment intent before commencement of neoadjuvant therapy.[9] It is desirable to collect peritoneal washings during laparoscopy.[10]

Imaging Guidelines

Screening

Some countries with high incidence of gastric carcinoma (such as Japan) have national screening programs. These programs allow early diagnosis of gastric carcinoma when the disease is potentially curable.[11] Japanese guidelines recommend screening endoscopy for adults more than 50 years of age.[12]

Diagnosis and Staging

Goal of Imaging

I. Identify resectable disease.
II. Plan resection:
   A. Siewert classification (Location of midpoint of the tumor in relation to the gastroesophageal junction).
   B. Determine nodal involvement (N+ or not) and nonregional, metastatic nodes.
   C. Vascular and root of mesentery encasement. Encasement of aorta or its major branches, except splenic artery, is a contraindication to curative surgery.
III. Identify and assess the burden of metastases.
IV. Response assessment (following neoadjuvant chemotherapy or palliative chemotherapy)
V. Identify postoperative complications.

Imaging Methods

Endoscopic ultrasound is the most accurate preoperative staging modality of early gastric carcinoma with an accuracy ranging between 78 and 94%.[13]

Method of choice of cross-sectional imaging for staging of gastric cancer is *contrast-enhanced CT (CECT) scan* thorax including lower neck, abdomen, and pelvis (CT TAP). CT scans perform better at T-staging of advanced (T3 and T4) carcinomas versus early (T1 and T2) carcinomas.

Positron emission tomography (PET-CT) evaluation from skull base to midthigh is recommended in locally advanced gastric cancer for metastatic workup especially if metastases are not evident on conventional CECT. Routine use of ^{18}F-fluorodeoxyglucose (FDG) PET-CT offers no significant incremental value over and above CECT as up to one third of cases of gastric cancer are not FDG avid.[7] In one retrospective study, only a small percentage of nodes were spotted in PET-CT that were not identified by conventional staging CT.[14] Some studies support the use of PET in gastric cancer staging, particularly in characterizing distant metastases or lymphatic metastases beyond D1 or D2 compartment. In postoperative cases with suspected recurrence, equivocal findings on CECT can be better characterized with the added metabolic information of FDG-PET as disease recurrence may be difficult to identify in some cases due to altered anatomy.

Technique of CECT

CECT for gastric cancer is done in two phases: noncontrast and portal venous phase (►**Table 1**). An additional arterial phase is optional and may be helpful in the evaluation of arterial anatomy and detection of very early lesions. Iodinated contrast media (Iodine concentration 300/320/350) is usually given as intravenous (IV) contrast at a dose of 1.5 mL/ kg body weight through the antecubital vein at a rate of 3 mL/s. Neutral or negative oral contrast is preferred for optimal distension of stomach and duodenum. Approximately 1,000 to 1,200 mL of plain water usually provide sufficient distension. Injection Buscopan is not recommended.

Primary Tumor Staging

The primary tumor, if identified in CT, is to be described according the following subheadings:

Site

Gastric cardia, proximal stomach, distal stomach. For proximal tumors, the relation of the epicenter of the cardia according to the Siewert classification is to be mentioned (►**Fig. 1**).

Extent

Focal, segmental, or diffuse.

Size

Three dimensions of focal lesions; maximum length of the involved segment in segmental lesion.

Relationship with adjacent structures: Involvement of surrounding structures especially gastrohepatic ligament, duodenum, pancreas, left adrenal, and colon.

Table 1 Imaging parameters of CT scan of abdomen in gastric carcinoma

	Noncontrast	Arterial	Portal venous
Purpose	Baseline	Vascular anatomy for surgical planning. Delineation of early tumors	Extent of tumor, liver metastases, other metastases
Area covered	Xiphisternum to symphysis pubis	Xiphisternum to iliac crest	Xiphisternum to symphysis pubis
FOV (mm)	422–500	380	450
kV	100	100	100
mAs	Auto	Auto	Auto
Slice thickness (mm)	5	5	5
Interslice gap (mm)	5	5	5
Reconstruction thickness (mm)	1	1	1
Reconstruction interval (mm)	0.5	0.5	0.5

Abbreviations: CT, computed tomography; FOV, field of view.

Identify periarterial cuffing /thickening along celiac axis and its branches/identify small perigastric veins and extramural venous invasion; optional).[15]

Nodal Status

Lymphatic spread is found in 74 to 88% of gastric cancers at diagnosis.[16] Presence of nodes in preoperative staging warrants perioperative chemotherapy and indicates higher chance of local recurrence. In staging CT, nodes larger than 6 to 8 mm in the short axis are considered significant.[17]

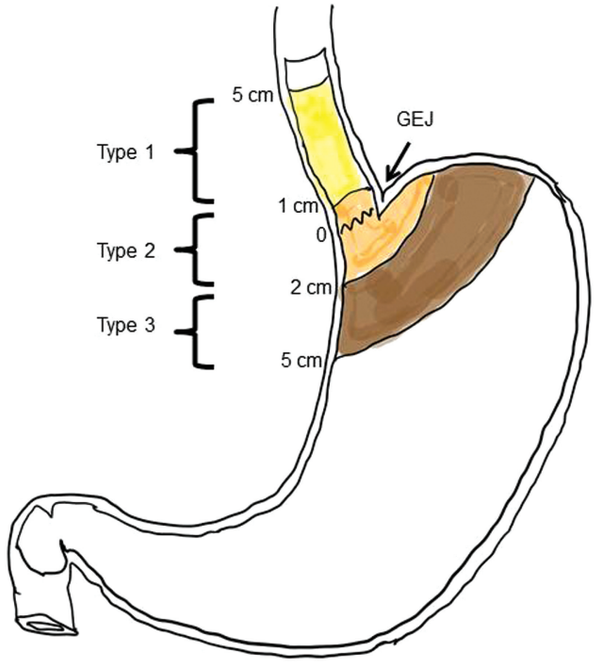

Fig. 1 Siewert classification of gastroesophageal junction (GEJ) carcinoma. Type I, epicenter of the lesion 1 to 5 cm above the GEJ; type II, epicenter of the lesion within a point 1 cm above to a point 2 cm below the GEJ; and, type III, epicenter of the lesion is 2 to 5 cm below GEJ (arrow).

Radiology report should mention the location and approximate number of significant nodes. Dimensions of the largest node are mentioned in two axes. Nodes can be described in two large groups.

- Regional (D1 and D2 nodes): Perigastric, along left gastric artery, common hepatic artery, celiac artery, splenic artery, splenic hilar and hepatoduodenal nodes. Superior mesenteric vein nodes are also considered regional node.[17]
- Nonregional nodes: para-aortic, aortocaval, mediastinal, and left supraclavicular nodes.

Metastasis

- Liver, omentum, peritoneum, lungs, bone, ovaries, and rectovesical pouch.
  - Presence of ascites and if present, its predominant location and nature (attenuation and internal septations).
  - Synchronous primary lesion elsewhere in the esophagus or stomach.

Arterial Anatomy

Celiac artery and its branches and any anatomic arterial variation thereof is desirable to be mentioned in the preoperative evaluation.

Chemotherapy Response Assessment

Assessment of response following perioperative chemotherapy is currently performed with multidetector computed tomography (MDCT) and/or FDG-PET/CT. On CT, the Response Evaluation Criteria in Solid Tumors (RECIST) criteria is considered the method of choice in the assessment of response; however, the primary gastric tumor has been considered unmeasurable according to RECIST. Response assessment focuses on short axis measurement of involved lymph nodes and exclusion of disease progression. CT tumor volumetry (TV) to accurately measure the primary tumor is shown to be useful. A 15% reduction in tumor

volume evaluated with MDCT has been shown to correlate with histologic response.[18] FDG-PET/CT is not routinely used for treatment response. More evidence is needed to use Positron Emission Tomography (PET) Response Criteria in Solid Tumors criteria in chemotherapy follow-up.[19]

Postoperative Imaging

Most advanced gastric carcinoma requires neoadjuvant chemotherapy followed by proximal, distal, subtotal or total gastrectomy, depending upon site and location of malignancy. Other than response evaluation following surgery and subsequent chemotherapy, if any, imaging is necessary in cases in immediate or early postoperative period.

Gastrectomy with D2 lymph node clearance is associated with postoperative complications such as bleeding, anastomotic leak, sepsis, duodenal blow out, intestinal obstruction, and pulmonary complications. If the patient deviates from the normal recovery pathway in the postoperative period, then the patient may require imaging.

Often a noncontrast CT of abdomen and pelvis is sufficient. Oral contrast is given when obstruction or leak is suspected. IV contrast is given when bleeding is suspected.

Reporting checklist of a postoperative CT in gastric cancer includes:

- Pleural effusion or basal atelectasis.
- Any collection at perioperative site or anastomotic site.
- Status of bowel (small/large bowel) dilatation/narrowing.
- Area of stenosis or narrowing or abnormal wall thickening in anastomotic site or bowel and to look for normal passage of oral contrast.
- Look for a stoma site, if any.
- Look for intra-abdominal drains and their position.
- Ascites.

Principles of Management

Surgery

Resectable Lesions

The standard oncological resection for gastric cancer involves resection of at least two-thirds of the stomach along with D2 lymph node clearance. The type of resection depends on the location of the tumor, which includes total gastrectomy (includes cardia and pylorus), distal gastrectomy (two-thirds of distal stomach), and proximal gastrectomy (including gastro-esophageal junction).[20] A proximal resection margin of at least 3 cm is recommended for mass-forming and ulcerative lesions and of at least 5 cm of the same for infiltrative lesions. En bloc resection of the gastric cancer along with resection of left lateral section of liver, spleen, tail of pancreas, diaphragm can be done to achieve R0 resection. However, in cases of involvement of the second portion of duodenum, an extended resection of the head or body of the pancreas or the hepatoduodenal ligament is not recommended.

Nodal resection: D1: perigastric nodes; D2: nodes along left gastric artery (LGA), common hepatic artery (CHA), splenic artery, and celiac axis.

Splenectomy is indicated when there is direct splenic involvement from a greater curvature tumor.

For selected cases of peritoneal carcinomatosis (low volume peritoneal metastases or isolated cytology positive), a multimodal and aggressive treatment, including neoadjuvant chemotherapy (systemic, intraperitoneal, or a combination of these), curative gastrectomy, D2 lymphadenectomy along hyperthermic intraperitoneal chemotherapy can be beneficial.[21]

Palliative Surgery

Palliative surgery is only indicated for relieving symptoms like bleeding or obstruction in presence of metastases. There is no advantage of cytoreductive surgery over palliative chemotherapy in the presence of metastatic disease.[22] Gastrojejunostomy is preferred over stenting in cases of obstruction, if surgery can be done, and prognosis is reasonable. Nodal resection not indicated.

Interventional Radiology

Role of interventional radiology is limited to embolization for bleeding that is not controlled by endoscopic methods or relieving of obstruction by placement of a stent or gastrostomy tube.

Chemotherapy and Immunotherapy

In case of localized or locally advanced disease, the treatment intent becomes curative. The current standard of care is FLOT regime (fluorouracil, leucovorin, oxaliplatin, and docetaxel), which comprises four cycles of neoadjuvant FLOT chemotherapy followed by surgery and another four cycles of FLOT. FLOT has shown to increase overall survival compared with the ECF/ECX (epirubicin-cisplatin-capecitabine), the previous standard of care (hazard ratio: 0·77; 95% confidence interval: 0.63–0·94].[23] In case of metastatic cancer, the treatment depends on the combined positive score. If it is high, there is a role of immunotherapies like pembrolizumab/nivolumab in combination with a standard CAPOX/FOLFOX-based regimen to improve overall survival. Treatment depends on PD-L1 combined positive score. In case of low immune score, the standard of care remains chemotherapy alone.[24,25] In the case of HER 2 positive tumors, adding trastuzumab with standard chemotherapy regimens has shown to improve survival.[26,27]

Follow-Up Imaging

For early disease (pTi, pT1) treated by endoscopic resection, CT TAP is indicated only when there is clinical concern for recurrence. In cases of pathological (Yp) stage I to III cases, CT TAP every 6 to 12 months is indicated for 2 years, then annually for up to 5 years.

Summary of Recommendations

- Diagnosis of gastric carcinoma is done by endoscopy and biopsy.
- For primary staging of early lesions, endoscopic ultrasound and/or endoscopic resection is necessary.

- For primary staging of other lesions, CT TAP is recommended. PET has a limited role.
- For T3 and above lesions, diagnostic laparoscopy with peritoneal washing is recommended.
- In follow-up after chemotherapy and postoperative cases, the imaging method of choice is CT.

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Imaging Recommendations for Diagnosis, Staging, and Management of Small Bowel and Colorectal Malignancies

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Abstract

Small bowel malignancies are rare, though colorectal cancers are common. This article reviews the current imaging recommendations for small bowel and colorectal malignancies. Contrast-enhanced computed tomography (CT) is the imaging modality of choice for diagnosis/staging/response evaluation/follow-up of the small bowel and colonic tumors. Magnetic resonance imaging of the pelvis with high-resolution T2-weighted images in sagittal, oblique axial, and coronal planes is the imaging modality of choice for staging/response evaluation of anorectal tumors. CT colonography may be utilized as a tumor screening modality, alternative to colonoscopy.

Keywords
- bowel malignancies
- gastroenterology
- general surgery
- radiology
- recommendations

Introduction

Small and large bowel tumors are a large heterogeneous group of malignancies with variable presentation and prognosis. We provide a review of various consensus guidelines and imaging recommendations for diagnosis as well as follow-up of bowel malignancies.

Risk Factors and Etiopathogenesis

While most cancers are sporadic, syndromes like familial adenomatous polyposis, Lynch syndrome, and Peutz-Jeghers syndrome have a predilection for gastrointestinal (GI) tumors. Other risk factors include old age, male gender, obesity, inflammatory bowel disease, celiac disease, decreased fiber in diet, alcohol, red or processed meat, smoked food, tobacco, human immunodeficiency virus (HIV) infection, and long-term immunosuppression.[1,2] Adenocarcinoma is by far the most common tumor, with carcinoid, gastrointestinal stromal tumor (GIST), squamous cancer (anal canal), lymphoma, non-GIST sarcoma, and metastasis being the other potential tumors.[1,2] The guidelines below pertain predominantly to adenocarcinoma.

Epidemiology and Clinical Presentation

Large bowel tumors are quite common, accounting for approximately 10% of all cancers in the world.[3] Small bowel

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tumors are relatively rare, forming less than symbol 2% of all GI tumors.[1] Small bowel tumors are often clinically silent for long, presenting with vague abdominal pain, nausea, vomiting, melena, and weight loss.[1] Colorectal tumors usually present with altered bowel habits, iron-deficiency anemia (especially right colonic primaries), obstruction, and rectal bleeding. Patients with colorectal cancer usually present between 60 and 80 years, while small bowel tumors present a decade earlier. Patients with signet cell cancers may, however, present in the second to fourth decades of life.[1,2,4]

Small Bowel Malignancies

Screening

No imaging study is recommended for screening individuals for small bowel malignancies. Patients with Crohn's disease may undergo regular magnetic resonance imaging/computed tomography (MRI/CT) for evaluating the disease activity status and to look for complications.

Diagnosis and Staging

A single-phase contrast-enhanced CT (CECT) of the thorax, abdomen, and pelvis with oral contrast is the investigation of choice for small bowel tumors (►**Table 1**).[1,5] CT enterography/enteroclysis may be performed if the primary is poorly appreciable with a standard CECT (National Comprehensive Cancer Network [NCCN], category 2A).

A contrast-enhanced MRI (CE-MRI) of the abdomen and pelvis with a noncontrast CT chest may be performed instead of the CECT in patients with a contraindication to iodinated contrast (NCCN, category 2A).

Magnetic resonance cholangiopancreatography may be performed for evaluating a duodenal primary, especially if there is obstructive jaundice (NCCN, category 2A).

MRI may also be used to further evaluate an indeterminate hepatic lesion observed on CT (NCCN, category 2A).

Positron emission tomography/computed tomography (PET/CT) is not recommended for baseline evaluation of small bowel tumors as per NCCN guidelines.[5] It may be used as a problem-solving tool in patients with equivocal CT or MRI findings, and in patients with discordantly high tumor markers and resectable disease on CT to look for occult metastases often detected in the peritoneum.

Barium or fluoroscopic upper GI studies are not performed.

Other Initial (Nonradiological) Investigations

These include upper GI endoscopy with or without endoscopic ultrasound (for proximal tumors), capsule enteroscopy, serum tumor marker levels (carcinoembryonic antigen [CEA] and carbohydrate antigen 19–9), and biopsy (usually image-guided).

Response Assessment and Follow-Up

In patients with metastatic disease, treatment response should be assessed with a CECT of the thorax, abdomen, and pelvis (NCCN, category 2A).

Table 1 Reporting format for small bowel and colonic tumors

Primary tumor	
Lesion	● Visible
	● Not visible *(i.e., lesions endoscopically resected and subsequently characterized as cancer polyps)*
Site	● Duodenum
	● Jejunum (proximal, distal)
	● Ileum (proximal, distal)
	● Cecum
	● Ascending colon
	● Hepatic flexure
	● Proximal transverse colon
	● Distal transverse colon
	● Splenic flexure
	● Descending colon
	● Sigmoid colon
	●Rectosigmoid junction
Type	● Stenosing
	● Intraluminal polypoidal
	● Infiltrating
	● Other combinations
Size	In two dimensions (D1*D2)
T stage	T2
	T3
	T4a
	T4b (specify organ/s)
Associated findings	Bowel obstruction, perforation, ascites, peritoneal thickening,
Lymph node status	
Locoregional	Yes/no
	If yes: - N1a - N1b - N1c - N2a - N2b Site:
Distant metastases	
Distant metastases	Yes/no If yes:
	- M1a - M1b - M1c
	Specify Liver: Yes/no, Number, size, site, relationship with vascular and biliary structures, and liver hilum and other organs Lung: Yes/no, number, site, size
	Other organs including nonlocoregional lymph nodes
Final stage (TNM)	

Source: Modified from Granata V, Faggioni L, Grassi R, et al. Structured reporting of computed tomography in the staging of colon cancer: a Delphi consensus proposal. Radiol Med. 2022;127[1]:21–29. doi:10.1007/s11547-021-01418-9

PET/CT may have a role in patients with rising tumor markers and a normal CECT study.

Surveillance CECT thorax, abdomen, and pelvis is recommended for patients who have completed curative treatment, similar to the colorectal primary, although enough data on this is lacking. This entails a 6 to 12 monthly surveillance scan for the first 2 years, followed by annual surveillance for 5 years.[2,5]

Principles of Management

Surgery with adequate regional nodal clearance is the bedrock of treating small bowel adenocarcinomas. If the patient has unresectable or metastatic disease, chemotherapy/chemoradiation and a palliative diversion if the patient has obstruction is offered.

Colorectal Malignancies

Colorectal carcinoma is the third most commonly diagnosed malignancy in males and the second most common in females worldwide.[6] It is a major cause of cancer-related morbidity and mortality. Imaging forms an integral part of the screening process as well as the staging of the tumor.

Diagnostic Workup

Right-sided colon cancers usually present with occult blood in stool or iron deficiency anemia, whereas left-sided colon and rectal cancer patients present with features of altered bowel habits, bowel obstruction, or frank bleeding per rectum. Digital rectal examination has a high positive predictive value for the presence of rectal tumors in symptomatic patients. Colonoscopy is usually the first investigation performed, which can visualize the tumor and also facilitate biopsy of the lesion. Serum tumor markers like CEA have low sensitivity and specificity due to significant overlap with various benign entities. However, it can provide important prognostic information and is useful in the follow-up of patients after surgery. A preoperative serum CEA level more than 5 ng/mL indicates a poor prognosis.

Imaging Guidelines

Screening

CT colonography is considered an appropriate screening modality in patients with average and moderate risk of colon cancer with efficacy similar to colonoscopy.[7] It can be repeated every 5 years after an initial negative screen.

Diagnosis

Colonoscopy or sigmoidoscopy helps to localize the tumor in a suspected patient. It also provides guidance for obtaining a biopsy that provides the histopathological diagnosis. It also helps in localizing synchronous tumors, which are not infrequent. CT colonography with adequate bowel preparation can be used for initial diagnosis in intolerant patients or those with tight strictures that do not allow the scope to pass proximal to the site of obstruction.[8]

Table 2 Reporting format for anorectal cancer

Technical details	Use of rectal gel for distension—Yes/no
Tumor visible	Yes/no
Site of tumor	Rectum: upper, mid, lower Anal canal
Distance of lowest tumor margin from anal verge	_____ mm / Cannot be measured
Distance of lower tumor margin from anorectal junction	_____mm / Cannot be measured
Anterior peritoneal reflection	Involved/ uninvolved
Circumferential tumor location	Completely encircling / Partial (describe 'o clock position)
Longitudinal tumor size	_____mm
Shortest tumor distance from mesorectal fascia/levator ani	_____mm
Sphincter involvement	Yes/no
Adjacent organ involvement	Yes/no Mention the organ/s involved
Mesorectal lymph node	Yes/no Number and size of nodes
Extramesorectal lymph node spread	Yes/no Number, site, and size of nodes
Extramural venous invasion	Yes/no
Report distant metastases	

Source: Modified from KSAR Study Group for Rectal Cancer. Essential Items for Structured Reporting of Rectal Cancer MRI: 2016 Consensus Recommendation from the Korean Society of Abdominal Radiology. *Korean J Radiol*. 2017;18[1]:132–151. doi:10.3348/kjr.2017.18.1.132.

Staging

- CECT of chest, abdomen, and pelvis should be obtained in all patients with colorectal cancer for the purpose of staging.[8,9] In cases of colon cancer, local extent, as well as distal staging, can be ascertained through a single CT acquisition (►**Table 1**) (European Society for Medical Oncology [ESMO] level 2)[1].
- Pelvic MRI is required for local T and N staging in primary rectal tumors (►**Table 2**).[10] Screening T2-weighted and diffusion-weighted imaging of the liver and retroperitoneum can be done along with to obviate the need for CECT abdomen and pelvis (NCCN category 2A).
- PET/CT is not routinely indicated but can be done as a problem-solving tool to evaluate equivocal findings.

Response Assessment

- A restaging CT chest, abdomen and pelvis should be done after neoadjuvant therapy to determine the resectability of the disease.[9,10] MRI pelvis is also required in addition to CT in patients with rectal carcinoma to look for T and N status. MRI tumor regression grading system has been proposed

Table 3 MRI tumor regression grade

MRI tumor regression grade		
Tumor regression grade 1	Complete response	No residual tumor
Tumor regression grade 2	Good response	> 75% fibrosis with minimal residual tumor
Tumor regression grade 3	Moderate response	>50% fibrosis/mucin with obvious residual intermediate signal intensity tumor
Tumor regression grade 4	Slight response	significant residual tumor with little fibrosis/ mucin
Tumor regression grade 5	No response	No interval change in tumor

Abbreviation: MRI, magnetic resonance imaging.

for response assessment based on degree of fibrosis and residual tumor on post-treatment MRI (►**Table 3**). It has shown a good correlation with pathological tumor regression grade and can help in predicting survival outcomes.[6] PET/CT can be considered in cases of metastatic colon carcinoma for response assessment and recurrence after image-guided therapies like ablation or embolization.

Follow-Up

- Routine follow-up imaging is not recommended in patients with stage I colorectal cancer. For patients with stage II or III disease, CT chest, abdomen, and pelvis is recommended every 6 to 12 months for a period of 5 years (ESMO level 2).
- For stage IV disease CT chest, abdomen and pelvis should be done every 3 to 6 months for initial 2 years followed by 6 to 12 monthly scans up to a total of 5 years.[10,11]

Principles of Management

- In resectable colon cancer without evidence of obstruction, colectomy with en bloc removal of regional lymph nodes is performed. Resection with diversion or primary diversion/stenting followed by colectomy can be performed in patients having obstruction.
- In colon cancer, neoadjuvant therapy with FOLFOX/CAPEOX can be considered in patients with bulky nodes of T4b disease. Systemic therapy is given for inoperable and locally unresectable disease followed by reassessment.
- Resectable rectal cancer with T1 to 2 and N0 disease is managed with transanal or transabdominal resection followed by adjuvant therapy.
- In rectal cancer, neoadjuvant chemotherapy/RT followed by reassessment and surgery is preferred for patients with T3 to 4 disease, presence of nodal metastasis, and surgically inoperable disease.[9–11]

Recurrence

Recurrence can be detected by routine follow-up colonoscopy, imaging, or through elevation of CEA on serial examinations. CECT of the chest, abdomen, and pelvis should be done for suspected recurrence. A PET scan should also be considered to look for metachronous metastasis. Resection or locoregional therapies are preferred for resectable disease followed by adjuvant chemotherapy. For unresectable disease, systemic therapy can be given followed by a re-evaluation for conversion to resectable disease.

Lower Rectum and Anal Canal Malignancy

Tumors with a distal margin less than 5 cm above the anal verge or an epicenter 2 cm above the dentate line are classified as low rectal cancers.[12] Perianal cancers within 5 cm of anal verge are classified and staged as anal cancers.[13] Recommendations in this section pertains to low rectal adenocarcinomas (LRAC) and anal canal squamous cell carcinoma (ASCC).

Clinical/ Diagnostic Workup

Patients present with tenesmus, rectal bleeding, anorectal pain, nonhealing ulcer, discharge, fistula-in-ano, or fecal incontinence. Diagnosis is established with biopsy and histopathology. Recommended diagnostic workup for patients with LRAC includes digital rectal examination, clinical examination of the abdomen and the inguinal regions, colonoscopy and serum CEA levels.[14] In addition, patients with anal SCC require HIV screening and gynecological evaluation, including cervical cancer screening for women.[15]

Imaging Guidelines

Screening and diagnosis

Imaging has no role in screening of anorectal malignancies but may aid in diagnosis.

Staging

Imaging Referral Guidelines

- In biopsy-proven LRAC and ASCC, MRI pelvis is the recommended imaging modality for local staging (NCCN category 2A) (►**Table 2**).
- In patients with clinically suspected early LRAC (cT1), endorectal ultrasound can be done in addition to MRI pelvis to aid T-staging by assessing depth of invasion (NCCN category 2A).
- CECT of the thorax and abdomen is recommended for metastatic workup (ESMO level 3) (►**Table 2**).
- CEMRI of the liver may be appropriate for characterizing indeterminate liver lesions (NCCN category 2A).
- PET/CT is not recommended for staging LRAC.
- PET/CT may be considered for staging ASCC, especially for characterizing lymph node metastases that are not amenable for image-guided sampling and if such information will alter radiotherapy planning.[15,16]

Imaging Protocol Guidelines

- MRI pelvis with high-resolution T2-weighted images in sagittal, oblique coronal and oblique axial planes, parallel and perpendicular to the anal canal, is recommended for evaluating precise local anatomical extent.
- Sagittal T2 MRI is the recommended imaging plane for measuring tumor length and distance of the distal margin from the anorectal junction and anal verge.
- High-resolution axial T2-weighted MRI is recommended to identify the tumor quadrant, extramural spread, mesorectal fascia (MRF) infiltration, extramural vascular invasion (EMVI) and regional nodes.
- In LRAC, it is essential to identify and report the extent of involvement of the internal anal sphincter, external anal sphincter, the intersphincteric plane, and extrasphincteric extension into the ischiorectal fossa.
- Coronal high-resolution T2-weighted MRI is recommended to assess levator ani and puborectalis infiltration.
- In LRAC, involved MRF is defined as a distance of less than or equal to 1 mm between the primary tumor, EMVI, irregular pathological node or tumor deposit and the MRF, puborectalis or levator ani muscle. MRF is not involved if this distance is more than 1mm. The term "threatened MRF" is best avoided.
- Staging system used for LRAC is similar to colorectal cancer with the following additional considerations[17]:
  - Infiltration of internal anal sphincter and intersphincteric plane is reported as T1/2/3 based on the rectal component.
  - Infiltration of the external anal sphincter, puborectalis, levator ani, piriformis, obturator muscle is staged as T4b.
  - Infiltration of extramesorectal fat including ischiorectal fossa, infiltration of neurovascular structures of the pelvic sidewall is staged as T4b.
  - Regional nodes include mesorectal nodes, obturator, and internal iliac nodes. For LRAC extending into the anal canal below the dentate line, inguinal nodes are considered regional nodes (American Joint Committee on Cancer, 8th edition).

Response Assessment

- MRI pelvis is recommended for restaging LRAC 8 to 12 weeks following neoadjuvant chemoradiation and prior to surgery. Purpose of imaging in this setting is to exclude progression to decide on the possibility of sphincter preserving surgical procedure. In a select few patients, MRI facilitates decisions regarding deferral of surgery and watchful waiting (NCCN category 2A).[12,14]
- For ASCC, the optimal time for clinical tumor response assessment after chemoradiation is 6 months. Though response assessment in ASCC is mainly clinical, MRI pelvis is recommended prior to salvage surgery in patients with incomplete clinical response.[14,15]

Principles of Management

The primary aim of treatment of anorectal malignancies is to treat the primary, prevent recurrence, and provide the best possible quality of life.

Low Rectal Adenocarcinoma

- Local excision is a treatment option for select very early LRAC (cT1) without high-risk features.
- Early LRAC (cT2c/T3a/b) are treated with upfront surgery if negative margins can be achieved. Sphincter preserving operations can be performed provided there is sufficient margin and there are no clinical contraindications.
- Locally advanced LRAC (T3c and above) and for those with high-risk features such as involved MRF, EMVI are treated with neoadjuvant chemoradiotherapy (CRT) followed by surgery.
- Restaging MRI at 8 to 12 weeks following CRT is useful to exclude progression to decide on the possibility of sphincter preserving surgical procedures and organ preserving treatment options (deferral of surgery and watchful waiting).
- Surgical treatment consists of abdominoperineal excision (APE) or a low anterior resection.
- Patients with persistent infiltration of adjacent structures will need extended resections including pelvic exenteration.[12,14]

Anal Squamous Cell Carcinoma

- Curative intent CRT with a combination mitomycin C and 5-fluorouracil is the mainstay of treatment of ASCC.
- Patients with incomplete response to CRT are treated with salvage surgery that may be APE or pelvic exenteration.[16]

Follow-Up

- Most recurrences occur within the 3 years following treatment of LRAC. Thus, 6 monthly follow-ups with clinical examination and CEA are recommended for the first 3 years and annually till 5 years. CECT of the thorax, abdomen, and pelvis is recommended for surveillance in the following durations for completion of treatment: 6 months, 1 year, 2 years, 3 years, and 5 years.
- For ASCC patients who had an optimal clinical response at 6 months, follow-up is recommended annually for 3 years with CECT of the thorax, abdomen, and pelvis (ESMO level 2).
- MRI pelvis is recommended for treated LRAC and ASCC patients with confirmed pelvic recurrence when salvage surgery is being planned (NCCN category 2A).
- PET/CT is not recommended for routine follow-up of LRAC PET/CT may be considered in patients with negative CECT and raised tumor markers.[12,16]
- PET/CT may be appropriate to exclude extraperitoneal metastases in patients being considered for pelvic exenteration.

Summary of Recommendations

1. Screening with CT colonography may be utilized as an alternative to colonoscopy for colorectal screening. Screening for small bowel tumors is not recommended.
2. CECT of the chest, abdomen, and pelvis is the imaging modality of choice for staging/response evaluation/follow-up of the small bowel and colonic tumors.
3. MRI of the pelvis with high-resolution T2-weighted images in sagittal, oblique axial, and coronal planes is the imaging modality of choice for staging/response evaluation of anorectal tumors.
4. PET/CT is not routinely recommended for diagnosis or staging of bowel or anorectal tumors.
5. MRI liver can be used as a problem-solving tool in patients with indeterminate liver lesions and to map liver metastases prior to treatment planning.

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

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Abstract

Pancreatic cancer is the fourth most prevalent cause of cancer-related death worldwide, with a fatality rate equal to its incidence rate. Pancreatic cancer is a rare malignancy with a global incidence and death ranking of 14th and 7th, respectively. Pancreatic cancer cases are divided into three categories without metastatic disease: resectable, borderline resectable, or locally advanced disease. The category is determined by the tumor's location in the pancreas and whether it is abutting or encasing the adjacent arteries and/or vein/s.

The stage of disease and the location of the primary tumor determine the clinical presentation: the pancreatic head, neck, or uncinate process, the body or tail, or multifocal disease. Imaging plays a crucial role in the diagnosis and follow-up of pancreatic cancers. Various imaging modalities available for pancreatic imaging are ultrasonography (USG), contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), and 18-fluoro-deoxy glucose positron emission tomography (FDG PET).

Even though surgical resection is possible in both resectable and borderline resectable non-metastatic cases, neoadjuvant chemotherapy with or without radiotherapy has become the standard practice for borderline resectable cases as it gives a high yield of R0 resection.

Keywords
- ablation
- biopsy
- IRE
- magnetic resonance imaging
- multi-detector computed tomography
- oncology
- pancreatic neoplasms
- PET-CT

Introduction

Pancreatic cancer is the fourth most prevalent cause of cancer-related deathworldwide,[1] with a fatality rate equal to its incidence rate.[2,3] While other cancers such as colorectal cancer, breast cancer, and prostate cancer have made significant advances in early detection and treatment, the prognosis for pancreatic cancer remains bleak. As per the latest American Cancer Society Cancer Facts & Figures Report, the 5-year survival rate is 11% across all stages and a mortality rate that has not decreased over the last few decades.[4,5] As a result, pancreatic cancer appears to be one of the most challenging cancers to combat.[6] In this article, we review the imaging findings relevant to diagnosis and surgical staging of pancreatic carcinoma. Apart of diagnosis, emphasis has been given to image guided management of pancreatic carcinoma.

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Risk Factors and Etiopathogenesis

The risk factor can be inherited and non-inherited. Inherited include hereditary pancreatitis, cystic fibrosis, Peutz–Jeghers syndrome, hereditary nonpolyposis colorectal cancer with *MLH1* mutation, familial atypical multiple mole melanoma syndromes, hereditary breast and ovarian cancer 23.1% in *BRCA1* carriers and 6% in *BRCA2* carriers,[7] and familial pancreatic cancer. Noninherited risk factors include smoking, diabetes mellitus, chronic pancreatitis, obesity, physical activity, and cystic lesions.[7] During the development and spread of pancreatic cancer, multiple groups of genes undergo genomic alterations, i.e., either activation or inactivation. Oncogene activation and tumor suppressor gene inactivation are involved in the beginning and progression of pancreatic malignancies. Furthermore, dysregulation of molecules in various cell signaling pathways, such as EGFR, Akt, NF-B, and others, and their molecular interaction, play essential roles in pancreatic cancer molecular pathogenesis.[8]

Epidemiology

Pancreatic cancer is a rare malignancy with a global incidence and death ranking of 14th and 7th, respectively. In India, pancreas ranks 24th with 10,860 new cases (1.03%) and 18th in mortality (9). The incidence is higher in the older population (more than 50% in those aged 65–75 years).[3] The incidence is the highest among Northeastern Indian regions. In India, pancreatic carcinoma is ranked 21st in males and 17th in females. Mizoram has the highest AAR (age-adjusted incidence rates), followed by Mumbai, Thiruvananthapuram, and Delhi in males and Mumbai, Delhi, Bengaluru, and Thiruvananthapuram in females.[9] In Indian registries, there is an inconsistent pattern due to the absence of reporting of all cases in registries.[9]

Staging

The TNM staging system is used by the American Joint Committee on Cancer to assess immediate and long-term clinical prognosis and to create survival data for patients based on their illness stage. The T stage is determined by the tumor's size and its relationship (abuts/encases the vessels) with the vessels when there is an extra-pancreatic disease. The lack or presence of metastasis to regional lymph nodes or other distant sites determines the regional lymph node (N) and distant metastasis (M) stages.[10] The N categories only comprise regional lymph nodes found along lymphatic drainage channels that would be included in the surgical field and would be removed along with the underlying tumor. M1 stage lymph nodes are those that have spread outside of the usual drainage channels or are not routinely included in surgical resection.[11] The NCCN consensus report guidelines describe a tumor staging system and therapy recommendations based on the amount of the tumor. The NCCN uses the American Hepato-Pancreatico-Biliary Association (AHPBA) consensus report to determine resectability status. Pancreatic cancer cases are divided into three categories without metastatic disease: resectable, borderline resectable, or locally advanced disease.[12] The category is determined by the tumor's location in the pancreas and whether it is abutting or encasing the adjacent arteries and/or vein/s. The recommendations define "abutment" as less than or equal to 180° tumor contact of the vessel circumference and "encasement" as more significant than 180° tumor contact of the vessel circumference.[12,13] The term borderline resectable had extensive debate in the literature, hence many consensus such as AHPBA, MD Anderson and others had defined it and are listed in ►**Table 1**.[14–16] A few authors tried subclassifying borderline resectable (BR) further into BR-resectable and BR-locally advanced. NCCN had defined all BR-cases were vascular reconstruction is possible as borderline resectable and the rest as unresectable-locally advanced, provided no distant metastases.[17,18]

Clinical and Diagnostic Workup

Because the pancreas is positioned in the retroperitoneum, where cancer grows slowly at first, symptoms are typically a sign of advanced disease. The stage of disease and the location of the primary tumor determine the clinical presentation: the pancreatic head, neck, or uncinate process, the body or tail, or multifocal disease.[19] Because most tumors in the pancreatic head occur in the right–upper quadrant or epigastric region, signs and symptoms may include right–upper quadrant or epigastric pain, jaundice, nausea, or vomiting due to obstruction of the gastric outlet, diarrhea,

Table 1 Borderline resectability definitions-Comparison between different consensus

Vessel involved	AHPBA/SSAT/SSO/NCCN	MD Anderson	Alliance (TVI)
Superior mesenteric vein/portal vein	Abutment/impingement/ encasement/short segment occlusion	Occlusion	TVI $\geq$ 180° of vessel wall circumference and or reconstructable occlusion
Superior mesenteric artery	Abutment	Abutment	TVI $<$ 180° of vessel wall circumference
Hepatic artery	Abutment/short segment encasement	Abutment/short segment encasement	Reconstructable short segment interface of any degree between tumor and vessel wall
Celiac artery	Uninvolved	Abutment	TVI $<$ 180° of vessel wall circumference

AHPBA/SSAT/SSO/NCCN, Americas hepatopancreaticobiliary Associations/Society for the Surgery of the Alimentary Tract/Society of Surgical Oncology/National Comprehensive Cancer Network; TVI, tumor vessel interface.

and steatorrhea from pancreatic insufficiency. Although not always linked to malignancy, new development or worsening of previously stable diabetes should alert the clinician to the risk of pancreatic cancer.[20] In pancreatic cancer, tumor markers are of little diagnostic value. CA 19-9 (sensitivity 70%–90%, specificity 68–91%), which has a weak positive predictive value in both asymptomatic (0.9%) and symptomatic (72%) individuals, and carcinoembryonic antigen (sensitivity 25%–54%), similarly has a low diagnostic yield (specificity 75–91%), have also been studied.[21]

Imaging Guidelines

Imaging plays a crucial role in the diagnosis and follow-up of pancreatic cancers. Various imaging modalities available for pancreatic imaging are ultrasonography (USG), contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), and ^{18} fluoro-deoxy glucose positron emission tomography (FDG PET). Imaging-guided interventions such as biopsy and fine needle aspiration cytology (FNAC) are essential for tissue diagnosis in this era of molecular and targeted therapies. Key imaging features and preferred modalities in various clinical settings are summarized in ►**Supplementary Tables S1** and **S2**, available online only. We will further discuss these modalities and their relevance in the following sections.

Screening

No studies have defined the role of imaging-based screening in pancreatic cancers. However, a few upcoming studies suggest that imaging-based screening can be beneficial in candidates at risk of pancreatic cancers due to hereditary causes such as *BRCA* mutations, Li Fraumeni, Lynch, and Peutz–Jegher syndromes. Strong familial history and chronic pancreatitis are other target groups that might benefit from imaging screening, as both groups have a high risk of malignancy.[22] USG is a cost-effective screening modality and is widely available. However, dual-phase CECT and MRI can also be employed in high-risk candidates.[23,24] Many studies have shown that while MRI can detect small cystic lesions, EUS may be better able to detect small solid lesions when screening high-risk individuals for pancreatic cancer. In the Canto et al. research of 216 high-risk individuals, pancreatic abnormalities (cysts, solid lesions, or chronic pancreatitis) were seen in 42.6%, 33.3%, and 11% of patients, respectively, on EUS, MRI, and CT scan. In comparison to a sensitivity of 53% for a CT scan and a sensitivity of 67% for an MRI, this corresponds to an EUS sensitivity of 93% for the detection of solid lesions less than 2 cm.[25]

Diagnosis

Both imaging and intervention play a role in the diagnosis of pancreatic cancer. The current modality of choice for diagnosis is dual-phase CECT, as preferred by the NCCN guidelines due to its superior contrast and spatial resolution. Other modalities such as USG, MRI, and PET-CT can also be employed for diagnosis in appropriate settings. Each modality's role, advantage, and drawback have been briefly explained below.

Ultrasonography: USG can be an effective and inexpensive modality for detecting a pancreatic mass. Shortcomings of USG include obese body habitus and bowel gas shadow. The overall reported accuracy of USG in pancreatic cancer detection is around 50 to 70%.[26] In the hands of an experienced radiologist, USG can be an effective initial diagnostic modality and can perform guided biopsies and FNAC. Hypoechoic hypovascular mass is the typical USG finding.[27]

Computed tomography: The NCCN criteria prefer dual-phase CECT over the conventionally performed single-phase CECT. Dual-phase CECT is now widely performed for the diagnosis of pancreatic cancer. It includes a contrast-enhanced CT scan using intravenous contrast injection at flow rates between 3 and 5 mL/s and acquiring pancreatic parenchymal phase at 35 to 40 seconds delay and the portovenous phase at 60 to 70 second delay.[27] The protocol for CT in pancreatic cancer imaging is provided in ►**Supplementary Table S3**, available online only. Optimal pancreatic parenchymal enhancement occurs in the pancreatic parenchymal phase giving better parenchymal to tumor attenuation difference as the latter is predominantly hypoenhancing. Also, the arterial anatomy and its relation to the tumor are best depicted in this phase.[28,29] The portovenous phase gives better portovenous opacification and helps identify their relationship with the tumor. Hepatic and nodal metastases can also be better studied in this phase. ►**Figure 1** depicts a radiologically resectable pancreatic cancer. CECT has a sensitivity of 76 to 92% in detecting pancreatic cancer. The major drawback of CECT is identifying isoattenuating pancreatic lesions, especially ones smaller than 2 cm.

Magnetic resonance imaging: The main indication for MRI is when an isoattenuating lesion is when no obvious lesion is appreciated on CECT in a case of suspected pancreatic cancer. Pancreatic adenocarcinoma is a hypovascular tumor rich in fibrous stroma. It appears hypointense on T1 and T2 and shows diffusion restriction, hypointense in the venous phase, and isointense in the delayed phase due to wash-in of contrast. Magnetic resonance cholangiopancreatography (MRCP) is the modality of choice to evaluate the ductal system. It is superior to CT and ERCP as it effectively demonstrates ducts both proximal and distal to the stricture.[30] The MRI protocol for pancreatic cancer imaging is provided in ►**Supplementary Table S4**, available online only. The major drawback with MRI is cost, time, and availability compared with CT. Compared to computed tomography, MRI is a non-ionizing cross-sectional imaging technique with a safer intravenous contrast profile (CT). This is crucial, especially for patients who need to have repeated imaging follow-up and are at a higher risk of radiation harm (such as younger patients). Less than 1 cm non-contour-deforming focal ductal adenocarcinomas that typically present as non-contour-deforming pancreatic lesions on CT can be well characterized using MRI.[31] With a sensitivity and specificity of 93% and 75%, respectively, the MR method using fat-suppressed T1-weighted 3D-GRE sequence is able to distinguish ductal adenocarcinoma from chronic pancreatitis.[32]

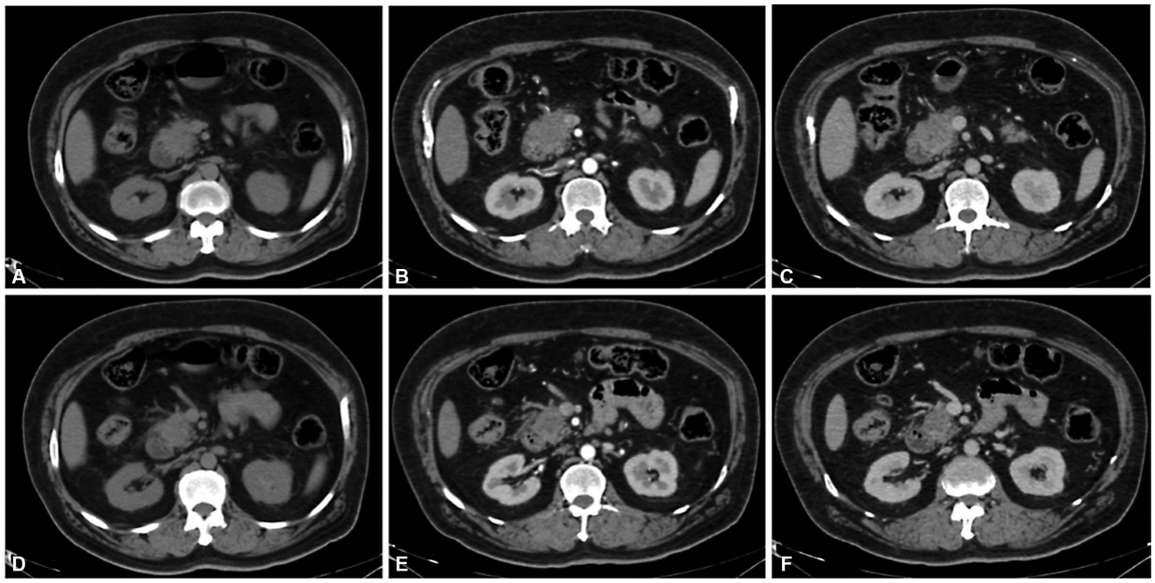

Fig. 1 Axial CT images **A, D**-plain, **B, E**-pancreatic parenchymal, and **C, F**-portovenous phase depicts a hypodense hypoenhancing mass involving the head of the pancreas. Radiologically, this represents a resectable pancreatic carcinoma.

Fluoro-deoxyglucose positron emission tomography: Integrated FDG PET-CT has incremental value in detecting subtle lesions in CT-negative or equivocal cases. A study by Heinrich et al showed the sensitivity and specificity of PET-CT versus CT alone were 89% versus 93% and 69% versus 21%, respectively.[33] NCCN criteria suggest that PET-CT cannot be substituted for the conventional dual-phase high-resolution CECT. But PET-CT has added advantage in the detection of distant metastases and staging of pancreatic cancer.[34] Neurotensin receptors are overexpressed in pancreatic cancer cells and can be specifically targeted using radiolabeled neurotensin analogs. In a study of six patients with metastatic pancreatic adenocarcinoma using a neurotensin receptor antagonist coupled to 177Lu (177Lu-3BP-227) demonstrated feasibility, improvement of symptoms, and quality of life in all patients.[35]

In the current era, tissue diagnosis, including immunohistochemistry and molecular markers, is essential before any chemotherapy. EUS-FNA is still the gold standard for sampling pancreatic masses because of its high diagnostic accuracy, especially when combined with rapid on-site evaluation (ROSE) and low-risk profile. However, FNA has some inherent flaws, which include a limited volume of tissue with poor cellularity and the difficulty of ensuring a core tissue with intact histological architecture, making immunohistochemistry and molecular profiling difficult.[36] Pancreatic tissue sampling can be performed under USG and CT guidance. The preferred modality for immunohistochemistry is the biopsy, as it requires more tissue samples than conventional FNAC. USG-guided sampling is preferred in large masses, mass involving the head of the pancreas when there is no intervening bowel shadow. CT-guided sampling is the preferred modality in many cases as the pancreas is a retroperitoneal structure and in smaller lesions or lesions involving the body and tail of the pancreas where an adequate acoustic window is not possible. In cases where good access is not available, either a transgastric approach or hydrodissection with saline can be performed to create a window. Presently, all biopsies are performed with an 18-gauge semiautomatic biopsy needle, and for FNAC 22-gauge needle is used. Post biopsy dual-phase contrast CT has to be performed routinely for all patients to rule out any possible complications.[37,38] The approach for CT-guided pancreatic biopsy is depicted in ►**Supplementary Fig. S1**, available online only. FDG PET-CT has an advantage in guiding the biopsy to the most avid part of the tumor, thereby increasing the diagnostic yield.

Staging

Dual-phase CECT is the modality of choice for the staging of pancreatic cancers and is done according to mostly followed TNM classification by AJCC or the resectability criteria proposed by the NCCN guidelines. Staging involves defining the tumor's location, extent, vascular involvement, nodal spread, and distant metastatic evaluation. The arterial and venous encasement is shown in ►**Supplementary Fig. S2**, available online only. Distant metastasis most commonly involves the liver, lungs, and peritoneum.[39] Hence, CT chest is usually acquired as a part of the venous phase of the dual-phase CECT. It is crucial to look for nodal spread and the number and location of the nodes, peritoneal disease, as these factors can affect the surgical resection. Alternative to CECT, MRI and FDG PET-CT can also be used for staging pancreatic cancer. FDG PET-CT effectively detects subtle nodal, peritoneal, and lung metastases, while MRI is better for local disease extent and liver, peritoneal and nodal metastatic evaluation.[40]

Management

Even though surgical resection is possible in both resectable and borderline resectable non-metastatic cases, neoadjuvant

chemotherapy with or without radiotherapy has become the standard practice for borderline resectable cases as it gives a high yield of R0 resection. Dual-phase CECT is the imaging modality of choice for response assessment in both neoadjuvant settings and in the immediate postoperative period. Post chemotherapy response assessment scan shown in ►**Supplementary Fig. S3**, available online only shows a decrease in the tumor size. In immediate post-surgery settings, dual-phase CECT is necessary to rule out complications such as pancreatitis, gastroduodenal artery (GDA) stump pseudoaneurysm or bleeding, abdominal collections, and anastomotic leaks.[41,42]

Imaging in the neoadjuvant and adjuvant setting is challenging as the radiological response lags behind the histological response due to persistent soft tissue around the vessels as the tumor is mainly composed of fibrous stroma even if there is no viable tumor on histology. A recent study by Lee et al concluded that a reduction in metabolic tumor parameters of FDG-PET/CT after neoadjuvant chemotherapy indicates an improved overall survival and recurrence-free survival.[43] Other challenges are local edema and inflammatory reaction induced by radiation therapy. These factors necessitate careful reading of images to avoid overcalling the resectability status. The role of imaging in a palliative setting is to assess the response to therapy and detect the presence of new lesions or metastases.[44,45]

Follow-up

NCCN recommends CECT as the modality of choice for post-treatment surveillance with a 3 to 6 monthly CECT for up to 2 years and yearly later. The average 5-year survival post curative therapy in pancreatic cancer is 20%.[45] Studies have demonstrated that routine imaging follow-up has survival benefits compared to performing imaging in symptomatic patients.

Principles of Management

The current management strategies are based on the resectability criteria. The non-metastatic pancreatic carcinomas are subdivided into resectable, borderline resectable, and non-resectable. The management of choice for resectable cancers is upfront surgical resection. However, only 20% of the newly diagnosed cases fulfill the resectability criteria.[46,47] For tumors involving the head, uncinate process, and neck of the pancreas, Whipple's pancreatoduodenectomy and pylorus-preserving pancreatoduodenectomy are performed. In contrast, distal pancreatectomy is commonly performed for pancreatic body and tail tumors.[48,49]

For borderline resectable cases, the standard practice is to downstage the tumor with neoadjuvant chemotherapy with or without radiation, increasing the likelihood of future R0 resection. The widely used first-line chemotherapy regimen is FOLFIRINOX. The average 5-year survival percentage for pancreatic carcinoma for stages I–IV is 14%, 7%, 3%, and 1%.[50,51] Moreover, most patients will develop disease recurrence after curative-intent surgery, resulting in a 5-year survival rate of only 12 to 27% and median overall survival (OS) of 16.8 months. Newer advances in radiotherapy such as stereotactic body radiotherapy (SBRT) and intensity-modulated radiotherapy (IMRT) are widely used in borderline resectable cases to improve R0 resection rates.[43] Recently, irreversible electroporation (IRE), a nonthermal ablation technique, has been used in borderline resectable cases to improve survival.[52,53] Treatment options include chemotherapy, radiotherapy, and palliative bypass surgeries in unresectable and metastatic cases. Chemotherapy with or without radiation therapy is recommended for patients with unresectable disease, followed by attempted resection if the tumor is downstaged. FOLFIRINOX and gemcitabine-based regimes are the first lines of chemotherapeutic agents, with gemcitabine having lower efficacy but with a more tolerable side effects profile compared to FOLFIRINOX. Patients who have a response or stable disease after 4 months of chemotherapy may undergo maintenance therapy. For supportive care, ERCP or PTBD can be done for biliary obstruction or celiac plexus neurolysis for pain palliation is helpful.[54,55]

Follow-Up Imaging and Management of Recurrent Disease

As per the NCCN guidelines, clinical evaluation and history for symptoms every 3 to 6 months for 2 years, then every 6 to 12 months as clinically indicated. CA 19-9 and follow-up contrast CT every 3 to 6 months is also recommended. Careful evaluation for postoperative bed soft tissue, peritoneal disease, and lung and liver metastases is essential.[56]

In a considerable percentage of patients, a multimodality approach to pancreatic cancer recurrence appears to provide effective palliation. In a small number of patients, radical excision of tumor recurrence may be possible. When compared to patients who receive chemoradiotherapy or supportive treatment, this subgroup of patients has a better chance of surviving longer. Furthermore, combining traditional therapies (e.g., chemoradiotherapy, surgery) with novel therapeutic modalities (e.g., RFA, IRE, stereotactic radiotherapy) may provide a new perspective on an otherwise fatal disease. To optimize the management of recurring tumors, accurate follow-up is required.[57,58]

Summary

Imaging is crucial for pancreatic cancer surveillance, diagnosis, resectability assessment, and response assessment. To prevent unnecessary surgery, it is crucial for the radiologist to be aware of PDAC mimics. Structured reporting for complete and accurate assessment of the primary tumor, its relationship to/involvement of neighboring structures is an effective method for reporting pancreatic cancer and that it enhances assessment and surgeons' confidence. Future pancreatic cancer care will likely see a significant increase in the utilization of novel imaging tools and therapies, such as dual-energy CT, functional MR imaging techniques, and image guided techniques such as PTBD/SEMS, celiac plexus neurolysis, and IRE.

Conflicting Interest
None declared.

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Imaging Recommendations for Diagnosis, Staging, and Management of Renal Tumors

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Abstract

Renal cell carcinomas accounts for 2% of all the cancers globally. Most of the renal tumors are detected incidentally. Ultrasound remains the main screening modality to evaluate the renal masses. A multi -phase contrast enhanced computer tomography is must for characterizing the renal lesions. Imaging plays an important role in staging, treatment planning and follow up of renal cancers. In this review , we discuss the imaging guidelines for the management of renal tumors.

Keywords
- CT scan
- MRI
- PET-CT scan
- renal cell carcinoma
- ultrasound

Introduction

Continuous advancements in various imaging modalities have revolutionized the imaging algorithm of renal masses. A majority of renal masses are detected incidentally when the patient is scanned for unrelated complaints. Radiologists need to be able to characterize renal mass on imaging. The foremost step is to differentiate between cystic and solid masses as up to 90% of solid tumors are malignant, whereas purely cystic lesions are usually benign or indolent.

Imaging is also important for staging, treatment planning, and follow-up of malignant renal masses. Ultrasound (US) is the screening modality for the evaluation of renal masses but cannot distinctly differentiate between benign and malignant lesions accurately and is also operator dependent. Contrast-enhanced US (CEUS) is a valuable addition and is especially useful in characterizing complex cystic lesions and the identification of pseudotumors. Multiphasic contrast-enhanced computed tomography (CT) is the current gold standard for the evaluation of renal masses and multiparametric magnetic resonance imaging (MRI) is used mainly as a problem-solving tool.

Risk Factors and Etiopathogenesis

Renal cell carcinoma (RCC) accounts for 2% of all cancers globally and is responsible for 2% of cancer deaths. It is the seventh most common cancer in men and the tenth most common in women[1].

Risk factors and etiopathogenesis include:[2]

1. Obesity: Obesity is a risk factor for kidney cancer in both men and women. The mechanisms by which obesity influences renal carcinogenesis are unclear, with chronic

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inflammation in adipose tissue and immune dysregulation potentially promoting carcinogenesis.
2. Smoking: Ever-smokers have a higher risk of renal cancer than never-smokers with a dose-dependent increase in risk related to the number of cigarettes smoked per day.
3. Hypertension: Hypertension is an independent risk factor for RCC.
4. Acquired cystic disease: Patients on long-term hemodialysis due to end-stage renal disease develop renal cysts and have an increased risk of renal cancer
5. Occupational exposure: Exposure to metal dyes increases the risk of developing RCCs.
6. Genetic susceptibility: Many genetic syndromes are associated with the development of RCC.

Epidemiology and Clinical Presentation

Abdominal mass, pain abdomen, and hematuria are the three cardinal clinical signs to suspect RCC. However, this constellation of symptoms is rarely seen at presentation these days and rather suggests advanced disease. About half of the RCCs are detected incidentally; such masses are small in size and pretend to have a good prognosis. Other common manifestations can be fever, leukocytosis, and weight loss. A variety of paraneoplastic syndromes may occur like polycythemia due to secretion of erythropoietin, hypercalcemia due to oversecretion of parathormone-related hormone peptide, hypertension due to renin, or Cushing syndrome due to adrenocorticotropic hormone.[3]

Clinical/ Diagnostic Workup

The initial workup of patients with suspected RCC includes history, physical examination, and blood investigations including a complete blood count with differential white blood count, serum calcium, liver functions, and renal functions. The workup allows the patient with metastatic RCC to be classified into favorable, intermediate, and poor risk categories, as per the International Metastatic RCC Database Consortium (IMDC) classification[4.] The factors include

1. Less than 1 year from the time of diagnosis to systemic therapy
2. Karnofsky performance status less than 70
3. Hemoglobin less than lower limit of normal
4. Corrected calcium more than upper limit of normal
5. Neutrophils more than upper limit of normal
6. Platelets more than upper limit of normal

The presence of none, 1 to 2, and 3 or more of the above factors categorizes the patient into favorable, intermediate, and poor risk categories, respectively. The choice of appropriate systemic therapy is based on the IMDC risk categories. For example, intermediate and poor-risk patients are treated with immune checkpoint inhibitor combinations (nivolumab and ipilimumab) or a combination of an immune checkpoint inhibitor with vascular endothelial growth factor tyrosine kinase inhibitor (VEGF TKI) pembrolizumab and lenvatinib/axitinib, nivolumab and cabozantinib, and avelumab and axitinib), while good risk patients are treated with VEGF TKIs (sunitinib or pazopanib) or a combination of immune checkpoint inhibitor and VEGF TKIs.[5]

Imaging Guidelines

RCC may be detected by an abdominal US either incidentally or in symptomatic patients. US serves as the most convenient and reliable screening tool for the detection of renal mass. It can accurately detect simple and minimally complicated cysts (Bosniak categories 1 and II). No further imaging is required in such cases. The accuracy of US falls in complex renal cysts from Bosniak 2F onwards. Differentiation of benign versus malignant masses cannot be confidently made by B mode US.

The last decade has seen an upsurge in renal applications of CEUS and it has shown fair potential in the characterization of renal tumors, especially in patients with chronic kidney disease or allergy to CT or MRI contrast. CEUS has shown great potential specifically in the differentiation of pseudotumors from renal tumors. The same enhancement characteristics along with the normal vascular pattern of the mass as the background normal kidney favor pseudotumors.[6,7] In addition, characterization of indeterminate masses, classification of the cystic renal mass into one of the Bosniak categories,[8,9] postablative treatment assessment,[10,11] differentiating bland versus malignant thrombus,[12,13] and renal transplant evaluation are other potential applications of CEUS.[14] Subtyping of the RCC by CEUS requires more studies for validation. Further characterization of the renal mass requires a dedicated tailored imaging protocol.

As per the guidelines issued by the American Association of Urology, high-quality, multiphasic, cross-sectional imaging is mandatory in any patient detected to have renal mass. This is essential for the optimum characterization and staging of the mass. Multiphasic CT forms the mainstay for the diagnosis of renal tumors. Morphology of the lesion, presence, and dynamic nature of enhancement are the important criteria in these modalities for differentiating benign from malignant masses.[14,15] In all suspected cases, a renal protocol is followed. Patient is given neutral oral contrast. A noncontrast scan is done followed by a postcontrast nephrographic phase at 40 to 70 seconds, a corticomedullary phase at 100 to 120 seconds, and an excretory phase at 7 to 10 minutes. Renal carcinoma is best identified in the nephrographic phase. The various subtypes of RCC can be better appreciated in the corticomedullary phase. The involvement of the pelvicalyceal system can be seen in the excretory phase. The split bolus technique is a newer modification that is currently followed in our institute as well. Conventional CT includes four phases in total that amounts to a high radiation dose. The split bolus technique has allowed a reduction in the number of phases with reduced total radiation dose and comparable imaging quality.

A baseline multiphasic CT is required in all diagnosed cases of RCC. The first step is to determine whether the mass is cystic or solid. If the mass is cystic, depending upon the

complexity of the lesion, it should be classified in one of the Bosniak categories. Bosniak classification, version 2019, is used on a renal mass protocol CT or MRI for predicting the risk of malignancy in cystic renal masses and guides treatment in each category. Any cystic lesion can be classified into one of the five categories namely I, II, IIF, III, and IV. Risk of malignancy increases from category IIF onwards. Bosniak III cysts can be managed with either active surveillance or primary surgery.[14,16,17] When the attenuation of the renal lesion is between −10 and +20 Hounsfield unit (HU), it is likely to be a simple cyst. If the attenuation is greater than 70 HU, it is likely to be a proteinaceous or hemorrhagic cyst. No further investigation is required for Bosniak category 1, II cysts. Bosniak category II F cysts require active surveillance and Bosniak category III and IV cysts should be considered for surgery.[18] If it is solid, it should be characterized as malignant (RCC, metastasis, lymphoma) or benign (angiomyolipoma [AML] or oncocytoma). About 90% of the solid masses are malignant. When the attenuation is between 20 and 70 HU on plain CT, contrast enhancement of greater than 15 to 20HU with less than 5% fat is highly suspicious for RCC.[16]

Such lesions mandate urological consultation for possible surgical management. Once the mass is characterized and labeled to be malignant, further staging is done to decide on the appropriate management. Essential points to consider for the staging of the mass are the size of the mass, the morphology of the mass including complexity, enhancement, and presence of fat, exophytic or endophytic nature of the mass, crossing the polar lines, involvement of PCS, invasion of perinephric fat, amount of perinephric fat, involvement of renal vein/IVC, invasion of adrenal/ surrounding organs, lymphadenopathy, distant metastasis and status of the contralateral kidney. TNM staging (8th edition) has been elaborated in ►**Table 1**.

In patients with the cT1a stage, a chest radiograph is sufficient.[16] Chest CT is recommended in all renal tumors beyond the cT1a stage for detection of lung metastases or mediastinal lymphadenopathy[12,14] as the lungs are the most common site of distant metastasis.[19,20] A bone scan is done when the patient has bony pain or elevated alkaline phosphatase. If the patient has neurological symptoms, then brain CECT or CE MRI is done to rule out metastasis. MRI is also recommended in asymptomatic patients with metastatic RCC.[14,21]

Multiparametric MRI serves as a complementary tool in the evaluation of solid renal masses. Increasingly, MRI is being used as the first modality for better characterization of

Table 1 TNM staging (8th edition)

T—Primary tumor
· **T1**—tumor < 7 cm or less in greatest dimension, limited to the kidney
o **T1a:** tumor confined to kidney, <4 cm
o **T1b:** tumor confined to kidney, >4 cm but <7 cm
· **T2:** limited to kidney >7 cm
o **T2a:** tumor confined to kidney, >7 cm but not >10 cm
o **T2b:** tumor confined to kidney, >10 cm
· T3: tumor extension into major veins or perinephric tissues, but not into ipsilateral adrenal gland or beyond Gerota fascia
o **T3a:** T3a tumor extends into the renal vein or its segmental branches, or tumor invades the pelvicalyceal system or tumor invades perirenal and/or renal sinus fat (peripelvic fat), but not beyond Gerota fascia
o **T3b:** Tumor extends into the vena cava below diaphragm
o **T3c:** T3c tumor extends into vena cava above the diaphragm or invades the wall of the vena cava
· **T4:** Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)
N—Regional lymph nodes
· NX regional lymph nodes cannot be assessed
· **N0:** no nodal involvement
· **N1:** metastatic involvement of regional lymph node(s)
M
· **M0:** no distant metastases
· **M1:** distant metastases
Stage groupings
Stage I T1 N0 M0
Stage II T2 N0 M0
Stage III T3 N0 M0 T1, T2, T3 N1 M0
Stage IV T4 Any N M0 Any T Any N M1

small renal masses, complex renal cysts, evaluation of tumor thrombus, and as a problem-solving modality in the differentiation of indeterminate renal masses diagnosed on CECT, for example, in cases of hemorrhagic cysts and papillary RCC. It is helpful in the characterization of the renal mass in case it is indeterminate on CT.[22,23] A minute amount of fat can be better appreciated in MRI than CT. Multiparametric MRI is preferable due to increased detection of small areas of subtle soft tissue enhancement with the added advantage of using subtraction techniques. It is also advocated in patients with allergy to CT contrast agents and in young or pregnant patients (where radiation exposure should be avoided).[12,24] Due to excellent soft tissue resolution, plain MRI should be done in cases when both CT and MRI contrast agents are contraindicated.[25] The standard MRI protocol done for renal mass includes T1-weighted (T1W), T2W, diffusion-weighted imaging, In and opposed phase, precontrast, and postcontrast Volumetric interpolated breath-hold examination (VIBE) images. Multiparametric MRI can be used to calculate clear cell likelihood score in small renal masses that denotes the likelihood of a renal mass is clear cell RCC.[16]

Further subtyping of RCC can be done based on their imaging characteristics. Clear cell renal cell carcinoma (cRCC) constitutes 65 to 70% of all cases of RCC.[26] The cRCC on imaging appears a large heterogenous encapsulated mass with areas of necrosis and intracytoplasmic fat. It is an intensely enhancing mass that shows steep enhancement in the corticomedullary and nephrographic phase with washout in the delayed phase (►**Fig. 1**). Papillary carcinoma, on the other hand, constitutes 10 to 15% of all RCCs.[26] These are peripheral-based, encapsulated, homogeneous masses having low signal on the T2W sequence. The enhancement is slow and less as compared with the cRCC in all the phases (►**Fig. 2**). Chromophobe RCC is the least common of the three, constituting 6 to 11% among all the RCCs.[27] These are also peripheral-based, may show a pseudocapsule, and are fairly large. Postcontrast images show moderate wash-in and washout contrast. A central area of necrosis may be present which can show segmental inversion.[28]

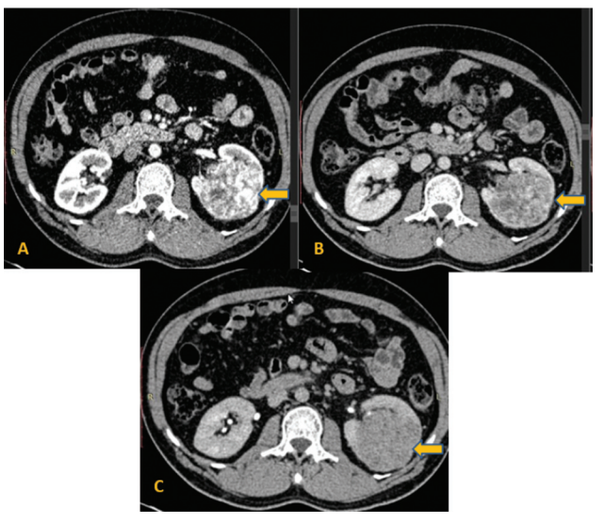

Fig. 1 Multiphase computed tomography axial images of the abdomen show an exo-endophytic mass arrow in the left kidney, showing marked enhancement in the corticomedullary phase **(A)** with relative washout in the nephrographic **(B)** and delayed phases **(C)**. Diagnosis of clear cell renal cell carcinoma was made, confirmed on postsurgical histopathology.

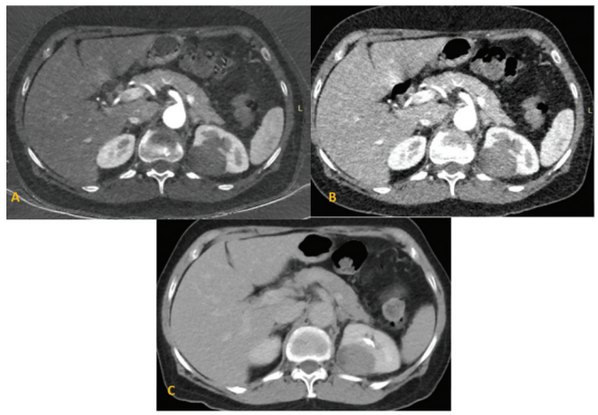

Fig. 2 Multiphase computed tomography axial images of the abdomen show an exo-endophytic mass in the right kidney, showing hypoenhancement in the corticomedullary phase **(A)** nephrographic **(B),** and delayed phases **(C)**. Diagnosis of papillary renal cell carcinoma was made, confirmed on histopathology.

Key imaging mimics of RCC are oncocytoma and fat-poor AML.[16] Due to their hypervascular nature, they are often confused with RCC due to which the patient unnecessarily undergoes surgical treatment.[29] Fat-rich AML is easy to diagnose with fat as the major component. They are hyperechoic on US and the fat component in the mass shows low attenuation (<10 HU). However, it is the lipopenic variety of AML (5%) that poses a diagnostic dilemma. Subtle points of differentiation from RCC include the homogenous nature of the mass, iso to hyperechoic on US, hyperdense on noncontrast CT, no calcification (common in RCC), T2W hypointense (RCC is T2W heterogenous hyperintense) and has rapid washout or persistent delayed enhancement on postcontrast study.[30,31] Second common benign neoplasm of the kidney is the oncocytoma that closely resembles chromophobe variety of RCC. Oncocytoma usually occurs in elderly patients, and are well-defined, homogenous masses, showing stellate scar with spoke wheel enhancement and segmental enhancement inversion on postcontrast images in different phases.[32]

In the pediatric age group, the most common tumor of the kidney (~80% cases) is Wilms tumor having a good prognosis.[33] It presents as a large heterogenous mass with hemorrhage and necrosis and infrequent areas of calcification. One should always look for multifocal/ bilateral disease (in hereditary syndromes), an extension of the mas into vascular structures, invasion of surrounding structures, lymphadenopathy, ascites, and distant metastasis.[21]

Positron Emission Tomography

Positron emission tomography (PET) is not recommended for the staging of RCC. 18F-fluoro-2-deoxy-2-d-glucose, the

substrate utilized for PET imaging, is excreted through the kidneys. The renal mass may fallaciously get obscured. The primary role of PET is in the re-evaluation of RCC post-treatment and also to detect recurrent or metastatic disease.[34] Quantitative PET helps evaluate the grade of the tumor, thereby helping in prognostication.[35]

Synoptic reporting formats for radiograph, US, CT, MRI, PET-CT scan are provided in ►**Table 2**. Also, a concise imaging algorithm for renal mass has been detailed in ►**Fig. 3**.

Renal Biopsy

A renal mass biopsy is not required for preoperative diagnosis in all cases. Only if the solid mass is suspected to be metastatic, inflammatory, infectious, or hematological, then a biopsy should be performed. A biopsy may not be done for elderly patients who are not fit for surgery and will be managed conservatively. Also, in young patients who are reluctant to conservative management if the biopsy does not show malignancy, a biopsy can be avoided.

Hereditary RCC constitutes around 4 to 6% of all cases of RCC. A high degree of suspicion should be kept when the patient presents at a young age with multiple RCCs and has a family history of RCC. The principle of management in such cases is to preserve as much renal parenchyma and hence nephron-sparing surgeries are preferred. Active surveillance and screening of other family members are also suggested.

Principles of Management

RCC is primarily a surgical disease. Despite immune-based and targeted therapy, a cure is rarely seen without complete surgical excision.[36,37] Management depends on the disease extent that is classified into localized, locally advanced, or metastatic.[38] The standard of care for localized RCC is surgical resection with the choice of surgical procedure depending upon the extent of disease, age, and comorbidity. For patients with T1 disease ($\leq$7cm), a partial nephrectomy (PN) is recommended if technically feasible. PN is also recommended for T2 disease ($>$7 cm limited to the kidney) with a solitary functioning kidney or chronic kidney disease and in bilateral renal tumors. For T2 and T3a disease (involving the perirenal tissues/renal sinus/collecting system/renal vein) and T1 disease not amenable for PN, radical nephrectomy (RN) is the standard of care.[39] The cancer-specific survival in organ-confined disease (T1 and T2) is 70 to 90% that drops to 40 to 70% in T3a disease.[40,41] Both minimally invasive and open approaches to PN and RN are available with the intent being intact removal of the specimen. Patients with inferior vena cava (IVC) thrombus (T3b/T3c) are managed aggressively with RN and IVC thrombectomy with survival rates of 45 to 60%.[42] T4 disease (extension beyond Gerota fascia or into the adrenals) portends a poorer prognosis with a survival rate of up to 30% and is managed with en bloc surgical excision to achieve negative margins.[38,43] Adjuvant therapy with systemic targeted agents does not increase overall survival and is currently not recommended for all cases.[39] Metastatic RCC carries a poor prognosis (10%

Table 2 Synoptic reporting formats for radiograph, ultrasound, CT, MRI, PET-CT scan

Ultrasound
· Presence of mass lesion
· Size
· Growth rate (if previous imaging done)
· Solid or cystic
· Simple or complex cyst
· Echogenicity of the lesion
· Necrosis
· Axial location
· Craniocaudal location
· Margins of lesion
· Capsule present or absent
· Vascularity on color and spectral doppler—present or absent, if present wave form and velocity
· Extent of the lesion
· Distance to collecting system
· Perinephric extension
· Involvement of surrounding organs
· Renal arterial and venous anatomy
· Renal vein/IVC thrombus
· Whether bland or tumor thrombus
· Tumor thrombus if present extent
· Lymphadenopathy
· Obvious metastases (liver, other abdominal organs)
· Status of opposite kidney
MPCT
· Presence of mass lesion
· Size
· Growth rate (if previous imaging done)
· Solid or cystic
· Bosniak classification if cystic
· Macroscopic fat
· Necrosis
· Presence and degree of enhancement
· Axial location
· Craniocaudal location
· Margins of lesion
· Capsule present or absent
· Extent of the lesion
· Distance to collecting system
· Perinephric extension
· Involvement of surrounding organs
· Renal arterial and venous anatomy
· Renal vein/IVC thrombus

Table 2 (*Continued*)

Ultrasound
· Whether bland or tumor thrombus
· Tumor thrombus if present extent
· Lymphadenopathy
· Distant metastases (lung, liver, bone)
MRI
· Presence of mass lesion
· Size
· Growth rate (if previous imaging done)
· Solid or cystic
· Bosniak classification if cystic
· Signal on T1W,T2W sequences, diffusion restriction
· Macroscopic fat
· Necrosis
· Microscopic fat
· Presence and degree of enhancement
· Possible histology
· Axial location
· Craniocaudal location
· Margins of lesion
· Capsule present or absent
· Extent of the lesion
· Distance to collecting system
· Perinephric extension
· Involvement of surrounding organs
· Renal arterial and venous anatomy
· Renal vein /IVC thrombus
· Whether bland or tumor thrombus
· Tumor thrombus if present extent
· Caval wall invasion
· Lymphadenopathy
· Distant metastases (lung, liver, bone)
PET-CT with IV contrast:
Presence of mass lesion
Size
FDG avid
SUVmax
Solid or cystic
Necrosis
Presence and degree of enhancement
Axial location
Craniocaudal location
Margins of lesion
Capsule present or absent
Extent of the lesion
Distance to collecting system
Perinephric extension
Involvement of surrounding organs
Renal vein/IVC thrombus
Tumor thrombus
Tumor thrombus if present extent
Lymphadenopathy
Distant metastases (lung, liver, bone)

(*Continued*)

Table 2 (*Continued*)

Abbreviations: FDG, 18F-fluoro-2-deoxy-2-d-glucose; IVC, inferior vena cava; MPCT, multiphase computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography; SUVmax, maximum standardized uptake value; T1W, T1-weighted.

survival at 5 years) and is primarily managed with targeted systemic therapy.[44] RN with metastasectomy can be considered in patients with resectable primary and oligometastases, whereas cytoreductive nephrectomy is considered in select patients based on risk stratification.[39] Algorithm for RCC management is provided in ►**Fig. 4**.

Follow-Up Imaging and Management of Recurrent Disease

Surgery is the standard of care for localized RCC with a cancer-specific survival of 70 to 90%.[40] Although rare, the recurrence rates following radical (RN) and PN are 3 and 2%, respectively.[45,46] Early diagnosis and management of local recurrences improve survival.[47] Hence, a risk-stratified approach is recommended for surveillance following surgery considering the stage, surgical procedure, cost, and radiation exposure. Patients are divided into low-risk (T1N0) and moderate-to-high-risk categories (T2-T4N0 or N1). For low-risk disease, a baseline abdominal scan (CT or MRI) at 3 to 12 months is recommended. If the baseline scan is negative, yearly repeat imaging for 3 years is done for cases who underwent a PN. Further imaging after a negative baseline scan for patients who underwent an RN is performed at the discretion of the surgeon. A yearly chest X-ray for 3 years is recommended in addition. For moderate- and high-risk diseases, a more intensive protocol is recommended. A baseline abdominal scan (CT/MRI) at 3 to 6 months followed by repeat imaging 6 monthly for 3 years and annually thereafter up to year 5 is optimal. Chest imaging with CT is also done at the same interval for up to 5 years. Further imaging of the abdomen and chest can be done beyond 5 years at the discretion of the clinician.[48] Local recurrences following PN can be due to incomplete resection, tumor emboli, nodal, or tumor multifocality.[49] Options include a repeat PN, salvage nephrectomy, thermal ablation, or cryotherapy. Residual renal parenchyma, comorbidities, life expectancy, and tumor prognostic factors are to be considered

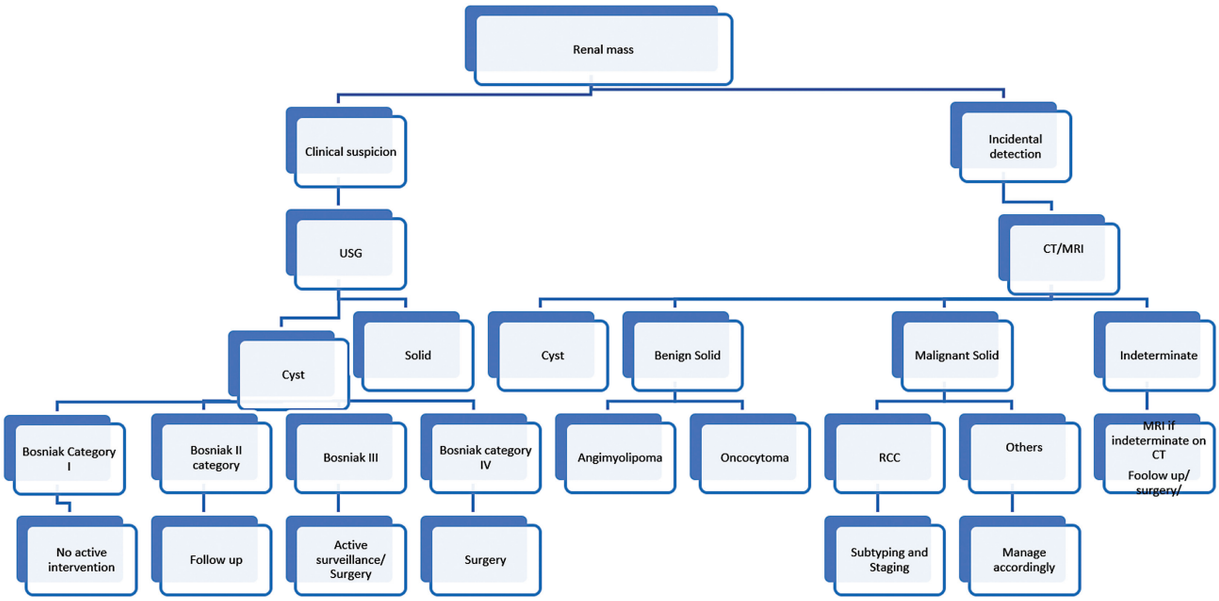

Fig. 3 Imaging algorithm. CT, computed tomography; MRI, magnetic resonance imaging; RCC, renal cell carcinoma; USG, ultrasonography.

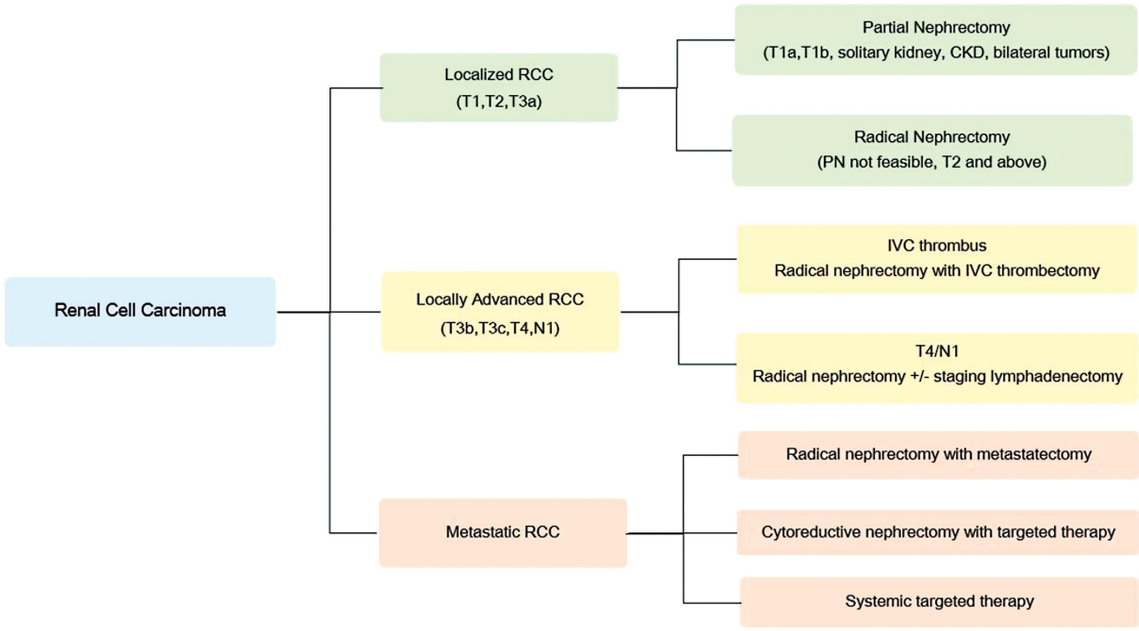

Fig. 4 Algorithm for renal cell carcinoma (RCC) management. CKD, chronic kidney disease; IVC, inferior vena cava.

before offering patients a repeat PN as it is complex and has significant postoperative morbidity (20%). The 5-year survival in these patients was found to be more than 95%.[50] Following RN, the median time to local recurrence was 20 to 36 months.[47] Surgical excision with negative margins is the only option associated with improved cancer-specific survival of 63% at 3 years.[51,52] For patients unfit for surgery, ablative therapies like cryoablation, radiofrequency, or microwave ablation can be tried pending further validation.[53] Following metastasectomy for local recurrences, adjuvant systemic therapy is recommended and in patients where the recurrence is unresectable, management is focused on palliation in the form of systemic therapy and radiation.[39]

Summary of Recommendations

- A contrast-enhanced, triple-phase helical CT scan is the preferred imaging study for evaluating renal masses.

- Chest CT should be done for the staging of renal cancers except in cT1a renal tumors.
- A multiparametric MRI can be performed as a problem-solving tool in characterizing indeterminate renal masses.
- The contrast-enhanced US can be helpful in specific cases.
- Characterization of small renal mass and response assessment following targeted therapy for advanced RCC are key challenges for current imaging modalities.

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Imaging Recommendations for Diagnosis, Staging, and Management of Adrenal Tumors

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Abstract

Adrenal glands are affected by a wide variety of tumors apart from infective and inflammatory lesions and their noninvasive characterization on imaging is important for the management of these patients. Incidentalomas form the major bulk of adrenal tumors and differentiation of benign adenomas from other malignant lesions, especially in patients with a known malignancy, guide further management. Imaging is an integral part of management along with clinical and biochemical features. The cornerstone of clinical and biochemical evaluation of adrenal tumors is to determine whether the lesion is functional or nonfunctional. Computed tomography (CT) is considered as the workhorse for imaging evaluation of adrenal lesions. CT densitometry and CT contrast washout characteristics are quite reliable in differentiating adenomas from malignant lesions. CT is also the modality of choice for the evaluation of resectability and staging of primary adrenal tumors. Magnetic resonance imaging (MRI) has superior contrast resolution compared to other morphological imaging modalities and is generally used as a problem-solving tool. MRI chemical shift imaging can also be used to reliably detect adrenal adenomas. Ultrasonography (USG) is used as a screening tool that is usually followed by either CT or MRI to better characterize the tumor and it is not routinely used for assessing the resectability, staging, and characterization of adrenal tumors. Another important role of USG is in image-guided sampling of tumors. Fluorodeoxyglucose positron emission tomography-computed tomography and other nuclear medicine modalities are a valuable addition to morphological imaging modalities. Image-guided interventions also play an important role in obtaining tissue samples where diagnostic imaging is not able to characterize adrenal tumors. In the functioning of adrenal tumors, adrenal venous sampling is widely used to accurately lateralize the secreting tumor.

Keywords
- adrenal adenoma
- adrenal incidentaloma
- computed tomography
- chemical shift imaging
- adrenal venous sampling

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Introduction

A wide variety of tumors involve adrenal glands and their variety is disproportionately high compared to the size of the gland itself. Adrenal tumors comprise a variety of benign lesions such as adrenocortical adenoma, myelolipoma, lipoma, pheochromocytoma, hemangioma, lymphangioma, schwannoma, ganglioneuroma, oncocytoma, and malignant lesions such as neuroblastoma, adrenocortical carcinoma, lymphoma, and metastases.[1] All adrenal gland tumors need biochemical and imaging evaluation.[2] The recommended modalities for the morphological evaluation of adrenal gland tumors are computed tomography (CT) and magnetic resonance imaging (MRI).[2] Most of the adrenal tumors are incidentalomas that are detected incidentally on imaging. The term incidentaloma in a strict sense is applied only to those adrenal lesions detected on imaging performed for any indication that is not directly or indirectly related to any adrenal pathology. The term will also exclude adrenal lesions detected incidentally in a patient with extra-adrenal malignancy or hereditary syndromes.[3] Also, most of the recommendations suggest additional workup only for incidentalomas more than 1 cm unless there is evidence of hormonal excess.[3–5] The incidence of incidentalomas reported in the literature is around 5%, very uncommon in children (0.5%), and the incidence steadily increases with age (up to 10% in elderly).[5–13] The reported incidence of adrenal metastasis in patients with a known primary malignancy is quite variable ranging from 2 to 71%.[14–17] Whereas the likelihood of an adrenal lesion being a metastatic lesion without any history or evidence of malignancy is extremely low.[6,18] It is important to rule out malignancy or a functioning tumor in any adrenal incidentaloma and imaging plays an important role in noninvasively characterizing these lesions that will be critical in management and prognostication. In this article, we will highlight the clinical presentation, optimal imaging modality, various imaging techniques, and interventions for the commonly encountered adrenal tumors based on the latest available evidence in the literature.

Epidemiology and Clinical Presentation

Adrenal tumors have been increasingly diagnosed in the past few decades. In a retrospective population-based cohort study from Olmsted County, Minnesota, United States, the incidence of adrenal tumors was found to increase nearly 10 times over a 22-year study period (from 4.4 per 100,000 person years in 1995 to 47.8 per 100,000 person years in 2017).[19] This dramatic increase was mainly attributed to detection of incidental adrenal lesions that comprised 82% of all adrenal tumors ($n = 1287$) reported in the study. The distribution of adrenal lesions included benign adrenocortical adenoma and nodular hyperplasia (83.7%; of these, 95% were non-functional), other benign tumors (6.6%), malignant masses (8.6%), and pheochromocytoma (1.1%). Unfortunately, there are no population-based data from India; however, there is a similar trend toward increased diagnosis of incidental adrenal lesions. In a retrospective tertiary care hospital-based study, 42 patients with a diagnosis of adrenal mass (between 2010 and 2019) were reported, of whom 20 (47.6%) had an incidentaloma.[20] Most lesions were nonfunctional (47.6%), and measured more than 4 cm in size (42.8%). Among functional tumors, pheochromocytoma was the most common (50%). A small sample size and selection bias related to the study setting explains the relative over representation of pheochromocytoma in this Indian study.

Clinical and Diagnostic Evaluation

All patients with adrenal tumors should be evaluated for clinical features of hormone excess, for example, centripetal weight gain, easy bruising, dehiscent striae and proximal myopathy (Cushing syndrome), hyperadrenergic spells (pheochromocytoma), hypertension and periodic paralysis (primary aldosteronism), hirsutism, virilization, oligoamenorrhea, gynecomastia, decreased libido, erectile dysfunction, and isosexual or heterosexual precocious puberty (sex steroid excess). Additional biochemical testing is recommended to exclude hormone hypersecretion (►**Table 1**).[3]

Nearly 50 to 70% patients with adrenocortical carcinoma have clinical or biochemical evidence of hormone excess. Glucocorticoids (cortisol) and sex steroids (dehydroepiandrosterone sulfate, androstenedione) are most commonly elevated; approximately 50% of patients with functional hormone excess have cosecretion of cortisol and adrenal androgens. It is rare to encounter aldosterone hypersecretion in adrenocortical carcinoma; however, mineralocorticoid effects may be mediated by excess cortisol overwhelming the 11-beta-hydroxysteroid dehydrogenase 2 enzyme or by steroid precursors with mineralocorticoid activity.[21]

Diagnostic Approach to Adrenal Masses

Computed Tomography

The CT protocol for evaluation of adrenal lesions includes unenhanced thin-section images to measure the attenuation of the lesion, followed by post contrast imaging between 60 and 90 seconds after administration of intravenous contrast and a 15-minute delayed-phase for evaluation of washout characteristics.[22]

Absolute percentage washout (APW) is calculated as

$$(\text{enhanced HU} - \text{15-min delayed HU})/(\text{enhanced HU} - \text{unenhanced HU}) \times 100\%$$

and Relative percentage washout (RPW) as

$$(\text{enhanced HU} - \text{15-min delayed HU})/(\text{enhanced HU}) \times 100\%$$

On imaging adrenocortical adenomas are well-defined, homogenous, small (<4cm) lesions with variable amounts of intracytoplasmic lipids. Lipid-rich adenomas have an attenuation value of less than or equal to 10 Hounsfield unit (HU) on unenhanced CT. Using 10-HU as the threshold has a sensitivity of 71% and specificity of 98%.[23] If the plain CT

Table 1 Hormonal evaluation of adrenal tumors/incidentalomas

Condition	Indication	Test	Interpretation
Glucocorticoid excess	All adrenal tumors	1 mg ONDST	Post-ONDST cortisol ≤1.8 μg/dL (50 nmol/L): normal 1.9-5.0 μg/dL (51–138 nmol/L): possible ACS >5.0 μg/dL (138 nmol/L): ACS
Mineralocorticoid excess	Concomitant hypertension or unexplained hypokalemia	PAC PRA/PRC	Elevated aldosterone (>10–15 ng/dL), suppressed renin (<1 ng/mL/hr) and elevated ARR (>20–30 ng/dL per ng/mL/h): positive screen for PA
Sex steroid excess	Imaging or clinical features suggestive of ACC	DHEA-S, 17-OHP, androstenedione, Te, E2	Use age and gender appropriate cutoffs to interpret
Catecholamine excess	[a]All adrenal tumors	Plasma free metanephrines or urinary fractionated metanephrines	Use age-appropriate cutoffs to interpret

Abbreviations: 17-OHP, 17-hydroxyprogesterone; ACC, adrenocortical carcinoma; ACS, autonomous cortisol secretion; ARR, aldosterone renin ratio; DHEA-S, dehydroepiandrosterone sulfate; E2, estradiol; ONDST, overnight dexamethasone suppression test; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; PRC, plasma renin concentration; Te, testosterone.
[a]May avoid in patients with clear evidence of adenoma; however, no definite evidence is available in this regard.

attenuation is more than 10HU, washout characteristics further help in characterization with lipid poor adenomas showing an absolute washout percentage of more than 60% and relative washout of more than 40%.[24]

An incidental adrenal lesion less than 1 cm does not require further evaluation as these subcentimeter nodularity or bulky adrenal glands on CT are findings of uncertain significance. Adrenal masses with characteristic benign features such as at least 50% macroscopic fat, cystic attenuation with no enhancement, hematoma or pseudocyst formation, granulomatous calcification, less than 10 HU on noncontrast CT, or signal drop in chemical shift MRI can be left alone regardless of their size.[4] Adrenal masses between 1 and 4 cm with prior imaging showing a stable lesion for more than 1 year is most likely a benign lesion. A new or enlarging lesion is concerning for malignancy. In this category of patients with no known malignancy, adrenal CT protocol is to be performed and resection should be considered based on the clinical, biochemical, and imaging features. If there is known extra-adrenal malignancy in this group of patients, positron emission tomography-computed tomography (PET-CT) is recommended and biopsy if indeterminate. For patients with no prior imaging or malignancy and if the size is 1 to 2 cm, the lesion is probably benign and a follow-up imaging at 12 months is suggested after evaluating the functional status biochemically. If the lesion is between 2 and 4 cm in size, adrenal CT protocol should be done to confirm a benign lesion. If indeterminate on CT, a follow-up imaging at 6 / 12 months should be done to establish stability. For adrenal masses more than 4 cm with no definite benign features and no history of malignancy, resection is recommended. For adrenal masses more than 4cm size with a history of malignancy, PET-CT or biopsy is recommended.[4]

Myelolipomas are well-defined lesions with fat and myeloid components. The density of the lesion depends on the proportion of these components. These lesions are characterized on CT by the presence of macroscopic fat (< -30 HU). On ultrasonography (USG) predominantly fatty lesions are hyperechoic.[1] On MRI, myelolipomas follow signal characteristics of fat, with increased signal intensity on T1-weighted (T2W) images and decreased signal on fat-saturated T2W images.

Pheochromocytoma has been described as a great mimic and has varied imaging findings. On USG, pheochromocytomas can be solid or mixed solid cystic. On unenhanced CT, almost all lesions have attenuation values more than 10 HU; rarely intracellular fat-containing pheochromocytomas can have low attenuation values of less than 10 HU. On CT, these lesions typically enhance avidly; however, they can be heterogeneous with cystic changes and can show calcification. Washout characteristics are variable and show overlap with both benign and malignant lesions. Ten percent of pheochromocytomas are malignant. Imaging cannot reliably differentiate between benign and malignant pheochromocytoma, unless there is direct local extension or distant metastases.[25,26]

Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma arise from the sympathetic nervous system with varying degrees of differentiation. Neuroblastomas are heterogeneous tumors with areas of necrosis and calcification. More than 90% have calcification. Neuroblastoma characteristically displaces adjacent organs and encases vessels. Psoas and paraspinal muscle infiltration can occur. Neural foraminal and epidural involvement can also occur which is better evaluated with MRI.[27,28] Ganglioneuroma is a benign neurogenic tumor with decreased attenuation of less than 40 HU on unenhanced CT with foci of punctate or discrete calcification. On postcontrast CT, the mass is homogeneously low in density and surrounds the vessels. USG may be required to confirm that the mass is solid. On MRI, the lesion shows low signal intensity on T1W images, heterogeneously high signal intensity on T2W images, and may show a whorled appearance.[24]

Adrenocortical carcinomas are commonly large at presentation and heterogeneous due to the presence of hemorrhage and necrosis. Intratumoral calcifications are seen in about 30% of cases. These lesions demonstrate relative washout of

less than 40% and absolute washout of less than 60% at 15 minutes. Tumor thrombus in the renal vein and inferior vena cava is common. Local invasion, regional and paraaortic lymphadenopathy and distant metastases to the lungs, liver, and bones are also common at presentation.[24] Rarely there can be focal loss of signal intensity on out-of-phase images due to foci of intracytoplasmic fat.[1]

If an adrenal lesion is indeterminate on imaging, the features favoring malignancy would include size more than 4cm, hypersecretion of multiple adrenocortical hormones, young age (<40 years), and sudden onset of new symptoms or fast progression of symptoms.[29]

Metastases have nonspecific findings on cross-sectional imaging and are more commonly bilateral. Typically demonstrating slower washout than adenomas with APW less than 60% and RPW less than 40%.[24] In patients with renal cell carcinoma and hepatocellular carcinoma, washout characteristics are similar to lipid poor adenomas and hence cannot be relied upon.[30] In patients with history of malignancy, 87% of adrenal lesions less than 3cm and 95% of lesions more than 3 cm are malignant.[31]

Magnetic Resonance Imaging

With its inherent tissue characterizing strengths, recent technological advancements and the availability of accelerated pulse sequences, MRI has become an invaluable imaging tool for the evaluation of adrenal lesions. Lack of ionizing radiation is additionally beneficial, particularly in children, young patients, or in those undergoing follow-up imaging. In clinical practice, MRI is usually considered when the findings on CT are inconclusive.

Chemical shift imaging (CSI) is the mainstay of MRI evaluation that allows the detection of intravoxel lipids typically present in adenoma. CSI should be performed as a dual-echo gradient-recalled echo sequence in which both echoes are obtained in the same breath-hold to ensure adequate coregistration of data on both in-phase and opposed-phase images. With current generation scanners, 2D and 3D CSI techniques provide comparable image quality but using 3D interpolated sequences offers technical advantage of higher spatial resolution and signal-to-noise ratio, which can potentially aid in improved characterization of smaller lesions.[32] The assessment of morphological features on MRI may aid in improving the characterization of indeterminate lesions on CT especially if contrast-enhanced CT (CECT) is contraindicated. On literature review, for lipid rich adrenal adenomas most studies have shown effectively no difference in diagnostic performance between unenhanced CT and MRI. CSI has, however, been shown to have superior performance when evaluating lipid poor adenomas with attenuation values between 10 and 30 HU at unenhanced CT. The assessment of lesions at CSI can be performed qualitatively by visual analysis or quantitatively using adrenal-to-spleen ratio (ASR) or the adrenal signal intensity index (SI-index). An ASR less than 0.71 and SI-index more than 16.5% are previously described thresholds at 1.5T that optimize the diagnosis of adrenal adenoma. When performing qualitative evaluation, the liver should not be used as a reference organ to determine any adrenal signal intensity decrease, because the liver will also show decreased signal intensity on opposed phase images when there is hepatic steatosis. Rather, muscle or spleen should be used as the internal reference organ.[33] The accuracy of both qualitative and quantitative methods is considered to be comparable in diagnosing adrenal adenoma.

Though CT is still the most commonly used modality to stage neuroblastoma, MRI is an excellent modality for the evaluation of intraspinal extension and marrow infiltration.[34,35] There is limited utility of MRI sequences other than CSI for the characterization of adrenal masses. Pheochromocytomas may show typical markedly hyperintense signal on T2W images (light bulb sign) that is considered as a characteristic feature. However, on the review of recent literature, the appearance of pheochromocytoma is reported to be quite variable and up to a third of them can be hypointense on T2W images that undermines the importance of the light bulb sign.[25,36,37] Also, adrenal cysts can also appear markedly hyperintense on T2W images mimicking the light bulb sign. Diffusion-weighted imaging to differentiate adenoma from other lesions has not shown much added value because of conflicting results and significant overlap in the quantitative apparent diffusion coefficient values. Dynamic contrast-enhanced MRI has recently shown some success in differentiating adenoma from metastasis; however, these observations need to be validated by further larger studies in the future.

Ultrasonography

USG has a limited role in the evaluation of adrenal lesions. The mass could be detected incidentally during a routine abdominal USG; however, the imaging findings are nonspecific and require further characterization by CT/MRI. Low attenuation masses like ganglioneuroma can sometimes mimic a cystic lesion on CT where USG and MRI can help to confirm the solid nature of the mass. USG is mainly used for image-guided biopsy in indeterminate lesions with equivocal imaging findings, malignant lesions that are not amenable for resection, and in select cases to confirm metastasis from an extra-adrenal malignancy.[38]

Positron Emission Tomography

Fluorine-18 fluorodeoxyglucose positron emission tomography (F-18 FDG PET-CT) combines functional and anatomic imaging and is particularly useful in the evaluation of malignant adrenal masses. Adrenocortical carcinoma shows high F-18 FDG uptake and can be used for disease staging and in recurrent disease.[39] A new tracer C-11 MTO (metomidate) is being recently developed that binds to an enzyme in the steroid synthesis that could help in determining the adrenocortical origin of tumor in the future.[40]

Radionuclide imaging in neuroendocrine tumors like pheochromocytoma and neuroblastoma is done for lesion detection, staging, treatment planning, follow-up and in select cases while considering radionuclide therapy. These tumors are characterized by increased expression of somatostatin receptors, a property that has been exploited in recent years for functional imaging. Radiolabeled somatostatin

analogues can bind to these receptors and emitted radioactivity can be imaged. Nuclear scintigraphy imaging like I-123/131 MIBG (meta-iodobenzyl guanidine) and In-111 Octreotide imaging is now largely replaced by positron emitting isotope gallium-68 (Ga-68) that is tagged to a somatostatin analogue DOTA peptide. There are three important Ga-68 DOTA peptides available for imaging that include Ga-68 DOTATOC, Ga-68 DOTA-NOC, and Ga-68 DOTA-TATE. Ga-68 DOTA peptide PET-CT has the advantage of better spatial resolution and better lesion detectability. Ga-68 DOTATATE PET has high sensitivity in detection of pheochromocytoma and was found to have higher sensitivity (95%) compared to F-18 FDG PET-CT in a meta-analysis.[41] Though mostly benign, metastatic pheochromocytoma can occur in 2 to 26% of patients.[42] In metastatic pheochromocytoma, F-18 FDG PET is preferred and has higher sensitivity in detecting metastatic lesions. This is related to tumor biology and cellular differentiation. I-123/I-131 MIBG (availability of I-123 MIBG, compared to I-131 MIBG, is limited and it is not available in India and many other countries) imaging is a cost-effective initial modality that could be used for the detection of pheochromocytoma if anatomic imaging is inconclusive, in patients with syndromic association and for mapping extra-adrenal paragangliomas. It also helps to make a decision on MIBG therapy in select patients who are not surgical candidates.[43–46] Approximately 10% of neuroblastomas have been found to be MIBG nonavid and somatostatin receptor expression has been observed in 77 to 89% of neuroblastoma cells.[47] Ga-68 DOTATATE PET-CT/FDG PET is used in staging of MIBG nonavid disease and Ga-68 DOTATATE in addition helps to assess candidates suitable for peptide receptor radionuclide therapy.[48,49]

In a patient with known extra-adrenal malignancy, F-18 FDG PET-CT helps to differentiate adrenal metastasis from an incidental benign adrenal adenoma with a high diagnostic accuracy.[50] False-negative lesions are encountered when the nodule is small in size (<10mm), lesion with hemorrhage or necrosis, and in some histological types where the primary lesion is non-FDG avid like bronchioloalveolar carcinoma. Nonmetastatic lesion in the adrenal gland that can be FDG avid includes approximately 3 to 5% of adrenal adenomas (probably related to the functional state), pheochromocytoma, adrenal hyperplasia, infection, and benign lesions like endothelial cyst with hemorrhage.[51]

Staging and Management

Staging of adrenocortical carcinoma and suspected malignant pheochromocytoma is one of the critical aspects of their management. Any management decision should be undertaken in a multidisciplinary meeting involving the endocrinologist, surgeon, radiologist, and the oncologist. After a comprehensive clinical and biochemical evaluation, CECT of chest, abdomen, and pelvis is the modality of choice for the evaluation of adrenocortical carcinoma. MRI abdomen can also be used as an alternative imaging modality. Additional imagings like PET-CT are required only in selected situations such as suspicion of brain or bone metastasis or the lesion is indeterminate on CT and MRI.[29] European Network for the Study of Adrenal Tumors staging is one of the most widely used staging systems (►**Table 2**).[39] Tumor staging, especially the presence of metastasis, is the most important prognostic factor. At the time of diagnosis, the stage of tumor, status of resection, mitotic index, cortisol level, and the general condition of the patient are taken into consideration for deciding on the management strategy and for prognostication. These will be reassessed at each follow-up to alter the management accordingly.

Table 2 ENSAT staging for ACC[29]

ENSAT stage	Definition
I	T1, N0, M0
II	T2, N0, M0
III	T1–T2, N1, M0 T3–T4, N0–N1, M0
IV	T1–T4, N0–N1, M1

Abbreviations: ACC, adrenocortical carcinoma; ENSAT, European Network for the Study of Adrenal Tumors.
T1: Tumor size ≤5 cm.
T2: Tumor size >5 cm.
T3: Infiltration into surrounding tissue.
T4: Tumor invasion into adjacent organs or venous tumor thrombus in vena cava or renal vein.
N0: No positive lymph node.
N1: Positive lymph node.
M0: No distant metastases.
M1: Presence of distant metastases.

Follow-Up Imaging

Considering the aggressive nature of adrenocortical carcinoma, a close follow-up is necessary. Most of the recurrence occurs before 5 years during follow-up. Although literature evidence is poor in this domain, it is generally recommended that follow-up imaging should be performed every 3 months for initial 2 years, 3 to 6 months for next 3 years, and annual follow-up imaging for the next 5 years. CECT of chest, abdomen, and pelvis is the modality of choice for the follow-up of these patients. Local ablative techniques such as radiofrequency ablation, cryoablation, and microwave ablation can be considered in advanced disease.

Image-Guided Interventions

Although diagnostic imaging has improved over the years in characterizing adrenal lesions noninvasively, adrenal biopsy is still considered the safe method to obtain tissue diagnosis.[38] Several recommendations suggest that adrenal biopsy is indicated only in situations where diagnostic imaging and biochemical tests are not able to provide the answer that is critical for the management of these patients.[3,38,52] The most useful indication for adrenal biopsy is to rule out metastasis in patients with an extra-adrenal malignancy.[52] Other indications are to identify an unknown primary, differentiate benign from malignant lesions, and to characterize infective lesions. Pheochromocytoma should be characterized using biochemical, morphological, and functional imaging and biopsy should only be attempted when

plasma and urine metanephrines are normal or with pharmacologic adrenergic blockade whenever performed in suspicious lesions.[2] Resectable adrenocortical tumors should be subjected to surgery rather than biopsy to avoid tumor seeding.[38] The choice of imaging guidance depends on the local expertise and the location of the tumor. USG and/or CT are most commonly used modalities to guide adrenal biopsy. USG provides real-time guidance and can provide rapid assessment of complications, whereas CT can provide better visualization for deep seated or small lesions.

Adrenal venous sampling (AVS) is an invasive but safe procedure to obtain blood samples directly from both the adrenal veins to diagnose autonomous excess production of hormones. Cannulation and subsequent sampling are relatively easier on the left side compared to the right side. The commonest indication for AVS is to evaluate primary hyperaldosteronism (older than 40 years of age) where it helps in reliably differentiating unilateral disease from bilateral disease.[53–55] The two forms of the disease have entirely different management approach: adrenalectomy for unilateral disease and treatment with mineralocorticoid receptor antagonists for bilateral disease that highlight the importance of performing AVS. Other less common indications of AVS are to evaluate cortisol excess and androgen excess.[56]

Conflict of Interest
None declared.

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Imaging Recommendations for Diagnosis, Staging, and Management of Ovarian and Fallopian Tube Cancers

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Abstract

Ovarian malignancy the third most common gynecological malignancy and is the leading cause of death in women. Non-specific clinical presentation delays the diagnosis, and they often present in the advanced stage of disease. No imaging modality is recommended for screening as there is no significant mortality reduction. Ultrasound (USG) is usually the initial modality in suspected ovarian mass. MRI is recommended for the characterization of indeterminate ovarian or adnexal mass on USG. CT abdomen and pelvis with oral and IV contrast is the recommended imaging modality in staging the disease, predicting the resectability and in selecting the patients who would benefit from neoadjuvant chemotherapy. Early ovarian cancers are staged by post-surgical histology and undergo upfront surgery. Advanced disease benefit by neoadjuvant chemotherapy and less morbidity by interval cytoreduction where image-guided biopsy is performed for histological diagnosis. Follow-up recommendations are based on tumor histology. CT/PET CT is recommended for diagnosing recurrence.

Keywords
- screening
- CT
- staging
- resectability
- cytoreduction
- follow-up
- PET CT

Introduction

Ovarian cancer is the second most common gynecological cancer worldwide and third most common in developed countries. About 95% of ovarian malignancies are epithelial origin and the rest arise from other subtypes. The two broad subtypes of epithelial ovarian cancers are type 1 that are low-grade tumors and type 2 that are aggressive tumors and most

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often present in advanced stages.[1] Though ovarian cancers are traditionally staged surgically, up to 40% of patients may be under staged at laparotomy.[2] The role of the imaging is to characterize the ovarian lesion, determine the extent, predict primary resectability or unresectability, to evaluate the response to chemotherapy and localize the recurrence.[3]

Risk Factors and Etiopathogenesis

Several theories have been postulated about the origin of ovarian cancers. According to the World Health Organization (WHO), epithelial ovarian cancers are classified into high-grade serous and low-grade serous, mucinous, endometrioid, clear cell carcinomas and malignant Brenner tumor and carcinosarcomas.[4]

High-grade serous carcinomas are postulated to arise from the fimbrial end of the fallopian tube through precursor lesions called STIC (serous tubal intraepithelial carcinoma). Low-grade serous tumors may arise from benign or borderline tumors of the ovary.

Risk factors for ovarian cancer include genetic mutations such as BRCA 1 and 2 and Lynch syndrome, nulliparity, endometriosis, obesity, and smoking.

Protective factors include use of oral contraceptive pills, breastfeeding, tubectomy, and tubal ligation.[5]

Epidemiology in India and Globally

Ovarian cancer currently ranks as the seventh most common cancer in women, worldwide. Often called a "silent killer," it has high mortality rates due to its insidious onset and lack of specific symptoms. It occurs more commonly in developed countries such as the US and Europe.[6] However, mortality rates are highest in Asian and African countries with the existing disparities in access to healthcare and affordability. In Asia, the highest ovarian cancer-related mortality rate is seen in India.[7] Carcinoma ovary is the third most common cancer in Indian women followed by breast and cervix. The cumulative risk of developing ovarian cancer between 0 and 74 years of age is about 1 in 133.[8]

Imaging Referral Guidelines

No imaging is recommended for screening for ovarian carcinoma in the general population as there was no significant reduction in mortality rates due to screening according to ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) trial.[9] Ultrasonogram (USG) with CA-125 levels may be considered for women with hereditary cancer syndromes starting at 30 to 35 years of age if they have not undergone risk-reducing salpingo-oophorectomy.[10]

USG is the initial imaging modality of choice in suspected ovarian lesions. If the lesion is suspected to be malignant on USG, staging CT abdomen and pelvis with oral and IV contrast is indicated to evaluate the extent of disease and identify patients who would benefit from neoadjuvant chemotherapy.[11,12] If the lesion is indeterminate on USG, MRI is recommended for further evaluation.[13]

FDG- PET-CT is helpful for patients with primary peritoneal carcinomatosis or elevated tumor markers with inconclusive CT findings.[14]

Serum CA-125 levels and CT are the standard tools for assessing the response to chemotherapy.[15] FDG-PET-CT is useful in early prediction of response after neoadjuvant chemotherapy due to its functional imaging.[16] In MR imaging, DWI is useful in early prediction of response by an increase in ADC values.[17]

Rising CA-125 levels, symptoms and signs of relapse after treatment prompts imaging evaluation for recurrence. CT chest, abdomen, and pelvis is the imaging modality of choice in clinically suspected/known recurrence of disease in carcinoma ovary.[14] PET-CT has similar or higher accuracy compared to CT in detecting recurrences.[18]

Clinical and Diagnostic Work-up Excluding Imaging

Women with ovarian malignancies usually have a wide range of symptoms from vague abdominal discomfort, painless abdominal distension, mass per abdomen and bowel or bladder disturbances. Rarer clinical symptoms include acute abdomen secondary to ovarian torsion, bowel obstruction, gastrointestinal bleeds, vaginal bleeds, lymphadenopathy, and paraneoplastic syndromes.

The serum tumor markers remain the easiest and sensitive screening tool, albeit non-specific. Serum levels of cancer antigen 125 (CA 125) show sensitivity of 78% and specificity of 77% for epithelial tumors. Higher sensitivity and specificity are observed in postmenopausal women, advanced stage, and higher grade.[19,20] The human epididymis protein 4 (HE 4) level may be useful in patients with low/normal CA 125. CEA and CA 19.9 are other markers that can also be elevated.

Specific tumor markers such as inhibin B alfa feto protein (AFP) and beta human chorionic gonadotropin (beta HCG) lactate dehydrogenase (LDH) are used for diagnosis and follow-up of non-epithelial tumors.

Biopsy of ovarian masses is generally not recommended as rupture and peritoneal seeding can upstage the tumor. In patients with ascites, diagnostic cytology yields vary in 30 to 70%. In women who are not eligible for surgical cytoreduction, image-guided biopsies or laparoscopic biopsy may establish diagnosis.[21–23]

Additional evaluation with upper GI endoscopy and colonoscopy should be considered for all women with clinic-radiological suspicion or elevated serum markers suggestive of gastrointestinal primary.

Irrespective of family history, these patients should be offered genetic testing that has an impact on treatment plan and choice and after treatment care.[24] Patients with epithelial carcinoma of the ovary should be offered testing for *BRCA1* or *BRCA2* mutations and for Lynch syndrome. Patients with mucinous, clear cell, endometrioid cancers are offered testing for DNA mismatch repair deficiency.

Imaging Guidelines

Screening for Ovarian Cancer

Ovarian cancer is the most common cause of cancer deaths due to gynecological malignancies. Because it presents with non-specific symptoms, it is diagnosed in the advanced stage in 58% of patients which results in a low 5-year survival rate (30%). When diagnosed early as a localized disease, the 5-year survival rate is 93%.[25] This led to the development of screening tools for ovarian cancer.

The common screening tools considered are transvaginal USG and serum CA-125 levels. Both have the disadvantage of high false-positive rates leading to unnecessary interventions. According to the randomised controlled trials on ovarian cancer screening, there was no significant reduction in mortality rates due to ovarian cancer with screening.[9,26,] Because of the negative net benefit and risk ratio, it is not recommended to screen asymptomatic high risk women.[27–29]

For high risk women, risk-reducing salpingo-oophorectomy(RRSO) is recommended at 35 to 40 years of age and upon completion of child bearing. High-risk women who have not elected RRSO, screening with transvaginal sonography and CA-125 levels, although of uncertain benefit, is recommended at the clinician's discretion starting at the age of 30 to 35 years.[8]

Diagnosis

The initial imaging modality of choice is ultrasonography in a suspected adnexal or ovarian mass (USG).[10] The International Ovarian Tumour Analysis (IOTA) and Ovarian-Adnexal Reporting and Data System (O-RADS) may be used for the characterization and risk stratification of adnexal masses.[30] If the lesion is benign, it can be followed up or no further evaluation is recommended.

If the USG findings are indicative of a lesion with high risk of malignancy, evaluation by a gyneco-oncologist along with CT of the abdomen and pelvis or CT thorax, abdomen and pelvis is recommended for staging of the disease and treatment planning.[11] In patients with indeterminate features, MRI of the abdomen and pelvis is recommended for further characterization.[11]

In the evaluation of indeterminate adnexal lesions, MRI is a superior modality than USG/CT. MRI has increased specificity compared with the USG, decreasing the number of false-positive diagnoses for malignancy and thereby avoiding unnecessary or over-extensive surgery.[31]

The Ovarian-Adnexal Reporting and Data System (O-RADS) is released by American College of Radiology for USG and MRI.[30,31] It assigns a probability of malignancy based on the imaging features of an adnexal lesion and provides information to facilitate optimal patient management and a uniform reporting system with standardized lexicons. The primary goal of the O-RADS risk stratification system is to improve communication between radiologists and referring physicians in a reproducible fashion, so that women with benign lesions or borderline tumors can avoid unnecessary or over-extensive surgery, respectively, and women with potential malignancy are promptly referred for gynecologic oncologic surgical evaluation.

The classical benign adnexal lesions on ultrasound include unilocular cyst < 10 cm with smooth inner walls and also typical dermoid cysts, typical hemorrhagic and endometriosis cysts, hydrosalpinx and paraovarian/peritoneal inclusion cysts. On MRI, typical benign feature is cysts with T2 dark/DWI dark solid components.[30,31]

High-risk features that indicates malignancy in adnexal masses on ultrasound include unilocular cyst with > 4 papillary projections, multilocular cyst with solid component with color score of 3 to 4, solid lesion with smooth outer contour with color score of 4, solid lesion with irregular outer contour and when the lesion is associated with ascites and/or peritoneal nodules. Solid tissue with high-risk time intensity curve in dynamic post contrast MRI is a high-risk feature.[30,31]

Indeterminate features of adnexal masses on ultrasound include unilocular cyst > 10 cm in size or with irregular inner walls, multilocular cyst, multilocular cyst with solid component with a color score of 1 to 2. Unilocular cyst with 1 to 3 papillary projections or solid components and solid lesion with smooth outer contour with color score of 1 to 3. High-risk features on MRI include solid components showing low-risk or intermediate-risk time intensity curve on dynamic post contrast images.[30,31]

Image-Guided Intervention for Diagnosis

In ovarian cancer patients amenable to primary cytoreductive surgery, definitive diagnosis is by surgical histopathology.

Image-guided biopsy is recommended only in patients who are not amenable for primary cytoreductive surgery. Trans-abdominal or trans-vaginal ultrasound-guided biopsy of omental, peritoneal, or adnexal mass can be done to confirm diagnosis and histopathological type of ovarian cancer before starting optimal neoadjuvant chemotherapy. If biopsy is not feasible, ascitic or pleural fluid aspiration, cystoscopy, and CA-125:CEA ratio of > 25 can be used for diagnosis.[3] In patients with pleural effusion, nature of effusion must be confirmed with pleural fluid aspiration and cytology.

Staging

Contrast-enhanced CT (CECT) of the abdomen and pelvis or CECT thorax, abdomen and pelvis is the recommended imaging for staging of ovarian cancer. CT plays an important role in the assessment of operability and for identifying lesions in regions that are difficult to resect

CT characterizes the tubo-ovarian lesion and detects the involvement of the adjacent pelvic organs such as infiltration into the uterus, rectum, and sigmoid colon, involvement of the ureter. It also detects the extension of the disease outside the pelvis with involvement of the peritoneum, omentum, mesentery, visceral organs, and lymph nodes (►**Fig.1**). The reported accuracy of CT in staging of ovarian cancer is up to 94%.[14]

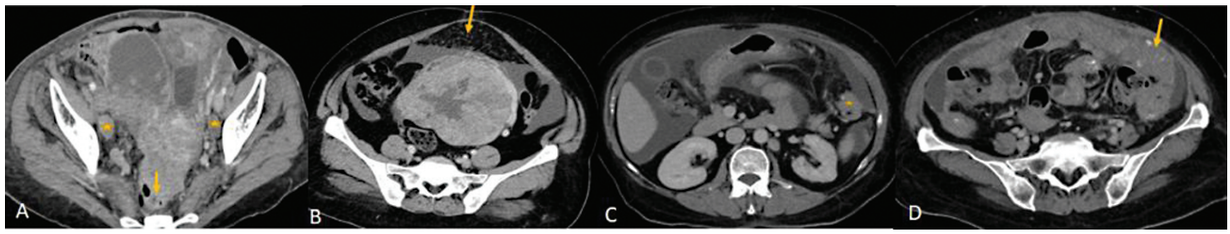

Fig. 1 (**A**) CECT of a patient with ovarian carcinoma: Lesion with irregular solid tissue in right adnexa and irregular solid lesion in left adnexa with infiltration into the anterior wall of the rectum (yellow arrow) and uterus and necrotic bilateral external iliac lymph-nodes (*). (**B-D**) Spectrum of omental involvement in advanced ovarian carcinoma along with massive ascites. (**B**) omental fat stranding and nodularity (yellow arrow), (**C**) omental deposit (*), (**D**)- omental caking(arrow).

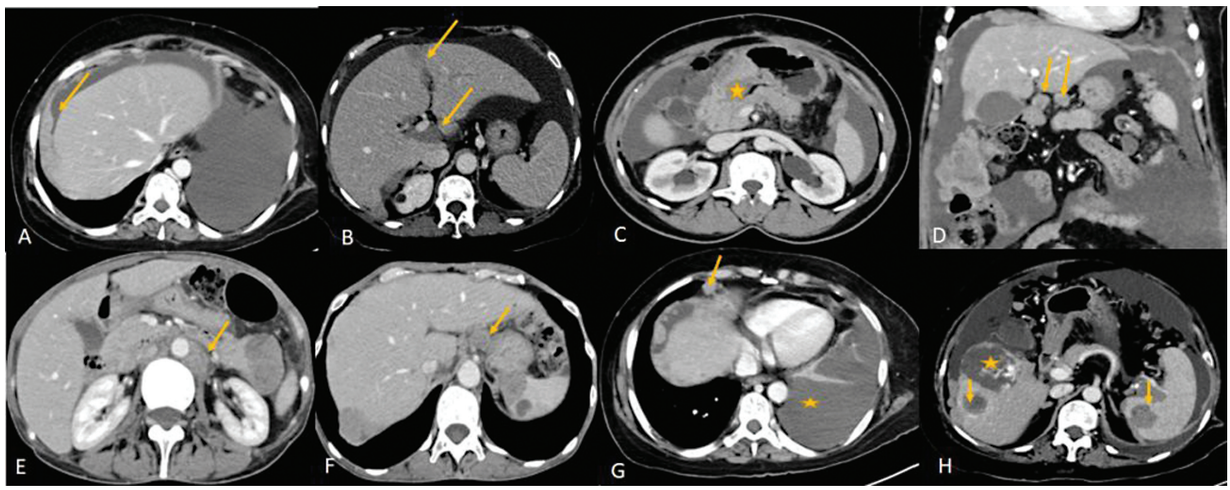

Fig. 2 (**A-E**) CECT showing some of the unfavorable sites of involvement which makes complete cytoreduction less likely. (**A**) Plaque like subdiaphragmatic disease(arrow), (**B**) intersegmental fissures of liver and porta (arrows), (**C**) Disease encasing the stomach (*), (**D**) Lesser omentum (arrows), (**E**)lymph-nodes above the level of renal hilum(arrow). (**F-H**: Metastatic disease in carcinoma ovary: **F**: Celiac lymph-node (arrow). (**G**) Anterior cardiophrenic lymph-node (arrow) and malignant left pleural effusion (*) (**H**) Liver and splenic intraparenchymal deposits (arrows), * - incidental hemangioma in liver.

Further CT detects the involvement of certain sites such as the mesenteric root, gastrosplenic ligament, lesser sac, porta hepatis, hepatic intersegmental fissures, subdiaphragmatic regions, infiltrating liver, and splenic deposits and also helps in detecting lymphadenopathy at or above the celiac axis, extraperitoneal disease, and pelvic sidewall invasion and thereby predicts non resectability (►**Fig. 2**).[14] The limitation of the CT is to detect deposits that are less than 5 mm within the peritoneum, bowel surface especially when there is no ascites.[32] For deposits that are < 5 mm, the sensitivity of CT is only 11%.[33] Positive oral and rectal contrast improves detection of visceral peritoneal deposits. CT chest can be used in cases of suspected pleural or pulmonary metastasis.

Alternatively, MRI and FDG-PET-CT may be appropriate for staging**.** MRI has equivalent accuracy to CT in staging of ovarian cancer with sensitivity of 0.88, specificity of 0.74, and accuracy of 0.84.[34] However, the limitations are that MRI is more sensitive to motion and has long duration of study compared to CT. FDG PET has a specificity as low as 54% and sensitivity of 86% in diagnosis and treatment of ovarian cancers. PET CT can be false positive in certain benign tumors such as fibroma and dermoid and in non-neoplastic conditions such as hydrosalpinx and endometriosis. However, various studies demonstrate that when combined with CT, it has a higher accuracy than FDG-PET or CT alone.[35,36] Others imaging modalities such as non-contrast CT, ultrasound of abdomen and pelvis are not recommended for staging.[14]

CT is also recommended to assess response in patients who are undergoing neoadjuvant chemotherapy before interval debulking (►**Fig. 3**).[14]

The 2014 revised FIGO staging classification is used for staging of ovarian, fallopian tube, and peritoneal malignancies.[37] In the recent FIGO 2021 staging report, there are no changes in the staging system. FIGO classification along with equivalent stages in the Union of International Cancer Control (UICC) TNM staging is given in ►**Table 1**.

Follow-up

Except for a few tumors with low malignant potential, patients are seen every 2 to 4 months in the first 2 years, then every 3 to 6 months in the next 3 years, and annually after 5 years. Follow-up is mainly with clinical examination and tumor markers for epithelial tumors. The role of imaging for routine surveillance is unclear due to poor sensitivity of imaging in picking up small volume recurrence and due to no proven positive effect on survival. Thus, imaging is indicated

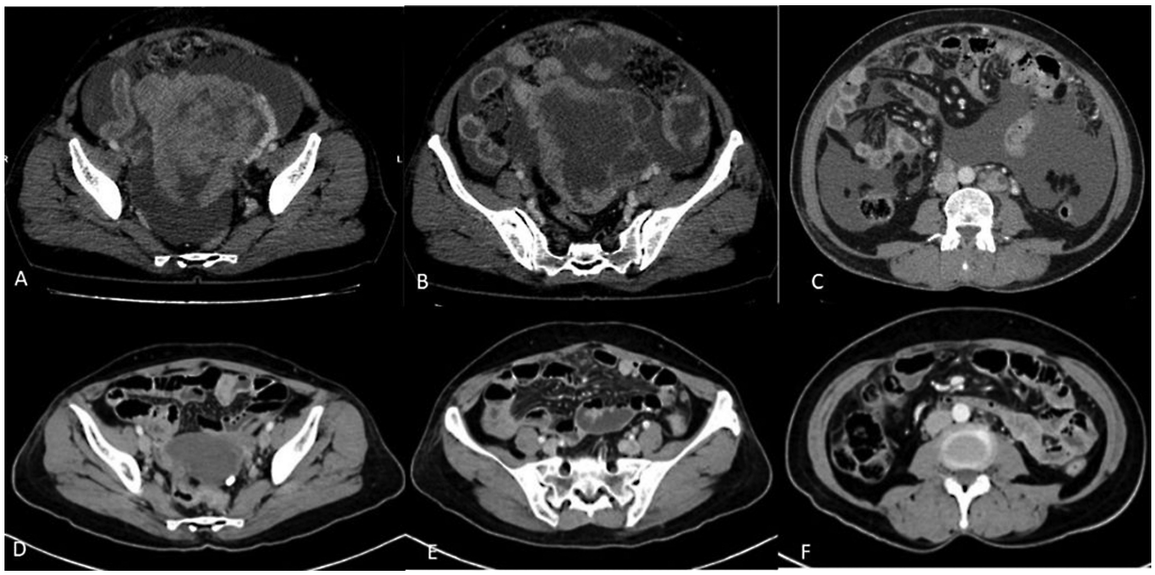

Fig. 3 (**A-F**) Role of contrast-enhanced CT in assessing the response after neoadjuvant chemotherapy. CECT images before (**A-C**) and after (**D-F**) 3 cycles of neoadjuvant chemotherapy show significant reduction in size of the primary mass lesion in the pelvis (**A and D**) and omental deposits (**B and E**) and resolution of ascites and retroperitoneal lymph-nodes (**C and F**).

Table 1 Staging of ovarian cancer (FIGO and UICC TNM staging)

UICC stage	FIGO Stage	Stage description
T1N0M0	I	The tumor is limited to the ovary (or ovaries) or fallopian tube(s).
T1aN0M0	IA	The tumor is limited to one ovary with an intact capsule or one fallopian tube. There is no tumor on the surface of the ovary or fallopian tube. No cancer cells are found in the ascitic fluid or peritoneal washings.
T1bN0M0	IB	The tumor is limited to both ovaries or fallopian tubes but not on their outer surfaces. No cancer cells are found in the ascitic fluid or peritoneal washings.
T1cN0M0	IC	The cancer is in one or both ovaries or fallopian tubes and any of the following are present: IC1: rupture and spillage of tumor during surgery IC2: capsule rupture before surgery or tumor on ovarian or fallopian tube surface IC3: tumor cells in the ascites or peritoneal washings
T2N0M0	II	Involvement of 1 or both ovaries or fallopian tubes with extension to pelvis (below pelvic brim) or primary peritoneal cancer.
T2aN0M0	IIA	Extension/implants on the uterus and/or the fallopian tubes and/ or the ovaries.
T2bN0M0	IIB	Involvement of other intraperitoneal pelvic structures
T1-3N0-1M0	III	Involvement of 1 or both ovaries or fallopian tubes, or peritoneal cancer with spread to the peritoneum outside the pelvis confirmed by cytology or histology and/or metastasis to the retroperitoneal lymph nodes
T1-2 N1M0	IIIA1	Positive retroperitoneal lymph nodes (cytologically or histologically proven) IIIA1(i) Metastasis up to 10 mm in greatest dimension IIIA1(ii) Metastasis more than 10 mm in greatest dimension
T3a2N0-1M0	IIIA2	Microscopic involvement of extra pelvic peritoneum with or without positive retroperitoneal lymph nodes
T3bN0-1M0	IIIB	Macroscopic deposits in the extra pelvic peritoneum, with largest deposit less than 2 cm in size with or without retroperitoneal lymph nodes
T3cN0-1M0	IIIC	Macroscopic deposits in the extra pelvic peritoneum with largest deposit more than 2 cm in size (includes extension of tumor to capsule of the liver and spleen without parenchymal involvement of either organ)
Any T Any N M1	IVA	Pleural effusion with positive cytology
Any T Any N M1	IVB	Parenchymal metastases to solid organs and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Table 2 Follow-up recommendations for various types of ovarian tumors and indications for imaging[3,38]

Histological type	Follow-up recommendation	Indications for imaging
Epithelial high-grade serous carcinoma of ovary, fallopian tube, and peritoneum	Once in 3 months in first year Once in 4–6 months until 5 years Annually after 5 years	Not routinely indicated. Indicated only if there are 1. symptoms and/or signs of recurrence 2. Rising CA-125 levels 3. when tumor markers or physical exam is unreliable
Low-grade serous cancers	Similar as high-grade tumors but at less frequent intervals	Same as above
Borderline tumors	Similar as high-grade tumors but at less frequent intervals	Same as above + transvaginal sonography if one ovary is preserved
Mucinous tumors	Similar as high-grade serous tumors	Similar as high-grade serous tumors
Granulosa cell tumors	Once in 6–12 months if early stage, low risk Once in 4–6 months if high risk	Reserved for patients with symptoms and signs or elevated biomarkers
Dysgerminoma	Year 1-Every 2–3 months Year 2-Every 3–4 months Year 3-Every 6 months Year 4–5-Every 6 months After 5 years-annually	Year 1-abdominal/pelvic CT (every 3–4 months) Year 2-abdominal/pelvic CT (every 6 months) Year 3-abdominal/pelvic CT (annually) Year 4–5-abdominal/pelvic CT (annually) After 5 years-as clinically indicated
Non-dysgerminoma	Year 1-Every 2 months Year 2-Every 2 months Year 3-Every 4–6 months Year 4–5-Every 6 months After 5 years-annually	Year 1-Chest/abdominal/pelvic CT (every 3–4 months) Year 2-Chest/abdominal/pelvic CT (every 4–6 months) Year 3-Abdominal/pelvic CT (every 6–12 months) Year 4–5-Abdominal/pelvic CT (every 6–12 months) After 5 years-As clinically indicated

only in patients with biochemical recurrence. Imaging is also of benefit also in patients with high clinical suspicion of recurrence but show no elevation of tumor markers.

As of now, use of other imaging modalities for follow-up is unsupported. Refer to ►**Table 2** for follow-up recommendations for tumors with various histological types.

Recurrence

CECT of the thorax, abdomen, and pelvis is the recommended imaging modality of identifying recurrence. The tumor usually recurs as peritoneal implants within the peritoneal cavity and along the surface of the visceral organs. The sensitivity and specificity of CECT ranges from 58% to 84% and 59% to 100%, respectively.[39]

MRI was comparable to CT for detecting recurrence >2 cm. However, for overall detection of recurrence, MRI had significantly lower accuracy than CT/FDG PET/PET CT.[40] The reported diagnostic accuracy of FDG-PET/CT is similar or more than the CECT in detecting recurrent ovarian tumors (►**Fig. 4**).[18,41] The sensitivity and specificity of FDG-PET/CT ranges from 95% to 97% and 80% to 100%, respectively.[18] However, these figures are predominantly from high-grade

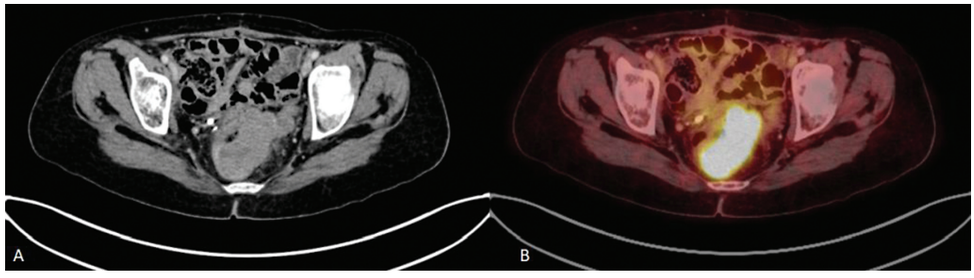

Fig. 4 (**A**, **B**) CECT and FDG PET-CT showing recurrence along the wall of the rectum in a patient with carcinoma ovary post neoadjuvant chemotherapy, interval debulking followed by adjuvant chemotherapy with elevated CA-125 levels on follow up.

Table 3 Summary of principles of management of ovarian cancer[3]

Primary treatment	Early stage (Stages I and II)	Surgery-staging laparotomy	Stage IA and IB of low-grade serous, mucinous, and grade I-endometrioid, stage IA of clear cell histology	Observation observation/chemotherapy
			All high-grade serous, grade 2,3-endometrioid stage IC and above of low-grade serous, mucinous and grade I-endometrioid stage IB and above of clear cell histology	6# adjuvant chemotherapy
	Advanced stage (stages III and IV)	Surgery–primary cytoreduction	6# adjuvant chemotherapy ± targeted therapy	
		3# NACT in select stage IIIC/IV	Surgery–interval cytoreduction	3# adjuvant CT ± targeted therapy
Treatment of relapsed disease	Platinum-refractory/resistant relapse (no response progression during or within 6 months of completion of platinum based chemotherapy)		Single-agent chemotherapy/best supportive care [paclitaxel, gemcitabine, topotecan, pegylated liposomal doxorubicin (PLD)]	
	Platinum-sensitive relapse (progression more than 6 months after completion of previous platinum chemotherapy)		Platinum based combination chemotherapy ± targeted therapy	
	Isolated serological relapse (elevation of CA-125 levels alone)		Can be observed until symptomatic/radiological evidence of relapse (decision to be individualized)	
	Long disease-free interval and localized relapse		Surgical resection of relapsed disease may be considered	

serous ovarian carcinomas. However, limiting factors such as spatial resolution, metabolic activity on or between bowel loops, and the presence of post-surgical inflammation/adhesion may reduce the diagnostic accuracy of PET/CT.[40] False-negative results are seen in mucinous adenocarcinomas and necrotic, cystic or low volume recurrence. Thus, FDG-PET/CT can be used as an adjunct when CT findings are indeterminate with persistent clinical concern.[42]

Principles of Management

Depending on the stage and extent of disease, ovarian cancer patients are managed with primary cytoreduction (removal of uterus, tubes and ovaries, omentum, peritoneal biopsy and lymph-node dissection), secondary cyto-reduction following neo-adjuvant chemotherapy, palliative intent chemotherapy, and best supportive care.

Chemotherapy may be omitted in low-grade, stage IA or IB cancers. All other stages are given four to six cycles of adjuvant chemotherapy. Fertility-sparing surgery may be an option in ovary-confined disease, if the woman wishes to consider future child-bearing options.

The principle of management in advanced stages is "optimal debulking (removal of all macroscopic disease)" followed by adjuvant chemotherapy.[43,44]

The preferred chemotherapy regimen is six cycles of paclitaxel and carboplatin. Neoadjuvant chemotherapy with interval cytoreductive surgery has become a preferred option, especially in high-volume disease.[44–46]

Targeted therapies such as bevacizumab and PARP inhibitors, have shown to improve overall or progression survival, especially in women with genetic mutations such as BRCA 1 and 2.[47,48] Hyper-thermic intraperitoneal chemotherapy (HIPEC) is also given in optimally debulked advanced stage III/IV ovarian cancers. ►**Table 3** summarizes the principles of management.

Follow-up Management and Treatment of Relapse

Clinical examination is routinely performed posttreatment and at 3 to 4 monthly intervals. Serum markers, if elevated at diagnosis, is the simplest methodology to follow-up.[49,50] The role of serial imaging posttreatment is debatable and is left to the institutional protocol.

The roles of surgical management including secondary cytoreduction, HIPEC in patients with relapsed epithelial cancers remains controversial. The management of relapsed cancers remains systemic chemotherapy and appropriate choice of PARP inhibitor and/or VEGF inhibition.

The flowchart below summarizes the imaging and management guidelines for ovarian cancer (►**Fig. 5**).

Summary of Recommendations

1. No screening tests or imaging are recommended even for high-risk patients for detection of ovarian/tubal cancers.
2. Ovarian cancers are primarily staged through primary cytoreductive surgery and the pathology is confirmed surgical histopathology.
3. Staging through imaging is best done with CT of the abdomen and pelvis with oral and IV contrast and CT

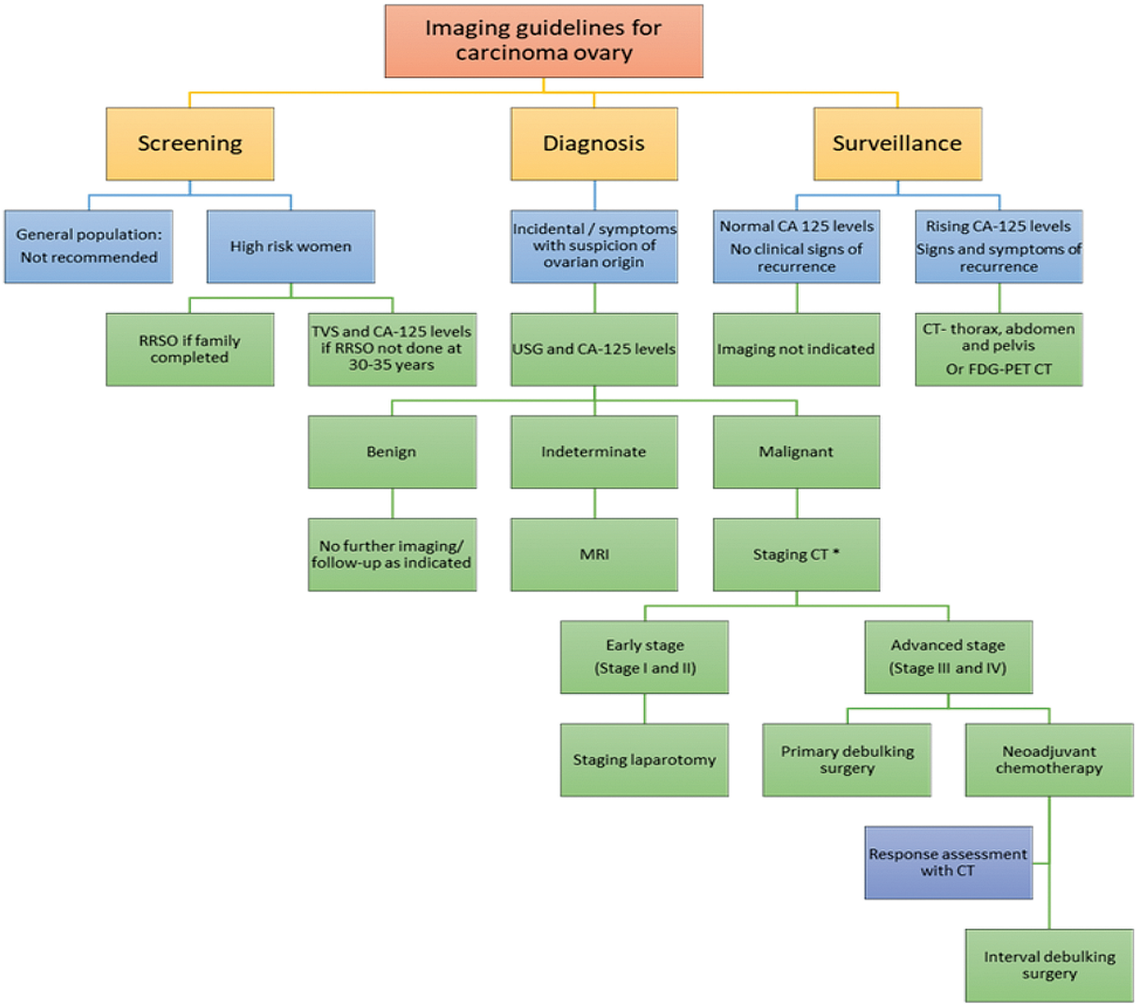

Fig. 5 Imaging guidelines for carcinoma ovary. RRSO, risk reducing salpingo-oophorectomy; TVS, transvaginal sonography. *Apart from CT, other equivalent appropriate modalities for staging include, MRI abdomen and pelvis with contrast and FDG PET-CT.

chest is a useful addition in those with pleural effusion.

4. CT abdomen and pelvis with oral and IV contrast is also used to assess the response to neoadjuvant chemotherapy before interval debulking surgery.
5. In case of suspected recurrence, contrast-enhanced CT thorax, abdomen, and pelvis with oral contrast is the imaging modality of choice. FDG PET CT may be considered when CT findings are inconclusive and there is high clinical suspicion of recurrence.

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Conflict of Interest
None declared.

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

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Abstract

Uterine cancers are classified into cancers of the corpus uteri (uterine carcinomas and carcinosarcoma) and corpus uteri (sarcomas) by the AJCC staging system (eighth edition). Endometrial carcinoma is the most common amongst these with prolonged estrogen exposure being a well-known risk factor. The FIGO staging system for endometrial carcinoma is primarily surgical and includes total hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy. Imaging is useful in the preoperative evaluation of tumor stage, especially assessment of myometrial invasion and cervical stromal extension. Dynamic contrast enhanced MRI with DWI has a high staging accuracy and is the preferred imaging modality for primary evaluation with contrast-enhanced CT abdomen being indicated for recurrent disease. PET/CT is considered superior in evaluation of lymph nodes and extra pelvic metastases.

Keywords

- dynamic contrast-enhanced MRI
- endometrial neoplasms
- gynecology and obstetrics
- leiomyosarcoma
- magnetic resonance imaging
- medical oncology
- positron emission tomography computed tomography
- radiology

Introduction

Tumors of the uterine corpus include epithelial tumors, mesenchymal tumors, mixed epithelial and mesenchymal, miscellaneous tumors (neuroendocrine or germ cell), lymphoid, myeloid and secondary tumors.[1,2] The American Joint Committee on Cancer (AJCC) staging system has classified uterine cancers into two groups: corpus uteri (uterine carcinomas and carcinosarcoma) and corpus uteri (sarcomas).[3] Out of these, endometrial cancer is the most common and is classified histologically into Type I and Type II. Definitive diagnosis is usually made through endometrial biopsy or dilatation and curettage; however, pre-operative

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radiological imaging is required to stage the disease and to tailor patient's management. The treatment comprises surgical staging and adjuvant radiotherapy and/or chemotherapy depending on the final surgico-pathological stage.

Risk Factors and Etiopathogenesis

Long-term estrogen excess (exogenous or endogenous) is postulated to have a causative effect on Type I cancers.[4] Early menarche, late menopause, nulliparity, anovulatory states (polycystic ovary syndrome) and estrogen only hormonal therapy are causes of prolonged estrogen exposure. The other risk factors include obesity, diabetes mellitus, Lynch syndrome, Cowden syndrome, tamoxifen therapy, and previous pelvic irradiation.[5] Most patients present at an early stage and are associated with a good prognosis, which depends on several factors, including the clinical stage, depth of myometrial invasion, histological grade, cell type, lymphovascular invasion, nodal status, and patient age. In contrast, Type II cancers have a worse prognosis and risk factors include Black race, older age, and lower body mass index.[4,5]

Epidemiology, Clinical Presentation in India and Global

There has been an increase in the incidence and prevalence of cancers in female population worldwide. Though breast and carcinoma cervix are the most common causes of morbidity and mortality, carcinoma of the uterine corpus continues to pose a significant concern. It is the sixth most common cancer with detection of 417,000 new cases and 97,000 deaths, as per GLOBOCAN 2020.[6] Uterine malignancies are predominantly seen in developed countries as compared with the developing countries; however, the incidence shows a rising trend in both due to an increase in the prevalence of associated risk factors such as excess body weight and diabetes. The National Cancer Registry of India showed heterogeneous distribution of cancers in India with breast and carcinoma cervix being the most common since 2012.[7] It had projected the risk of uterine corpus in 26,514 patients in 2020 with cumulative risk of 1 in 190, indicating its potential risk. GLOBOCAN 2020 showed 16,413 new cases of carcinoma uterine corpus, with 6,385 deaths, estimating its 5-year prevalence of 6.56 per 100,000 in Indian population.[6]

Imaging Referral Guidelines

Endometrial Carcinoma

Endometrial carcinoma is staged surgically according to the joint 2017 International Federation of Gynecology and Obstetrics (FIGO)/Tumour, Node, Metastasis (TNM) classification system.[3] The staging procedure includes total hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy, unless the patients desire fertility sparing surgery (and are candidates for the same). Imaging serves as an adjunct in the treatment stratification of endometrial carcinoma.[8,9] According to the NCCN guidelines,[10] the initial imaging workup varies according to the treatment offered.

For Non-Fertility Sparing treatment, pelvic contrast-enhanced magnetic resonance imaging (CEMRI) is recommended (to establish origin of tumor as endometrial versus endocervical and local disease extent evaluation).[11] In early stages (►**Fig. 1**), evaluation with transvaginal sonography can be done followed by MRI as an optional modality.[12] Chest X-ray is the baseline evaluation, to be followed by non-contrast computed tomography (NCCT) chest in case of any abnormality. CECT chest and abdomen (including pelvis) is recommended for metastatic evaluation in high-grade carcinomas (poorly differentiated endometrioid, clear cell, serous, undifferentiated carcinoma, and carcinosarcoma) and PET/CT (neck/chest/abdomen/pelvis/groin) can be done in select cases. In case of postoperative incidental finding of endometrial cancer or incompletely staged cancer with

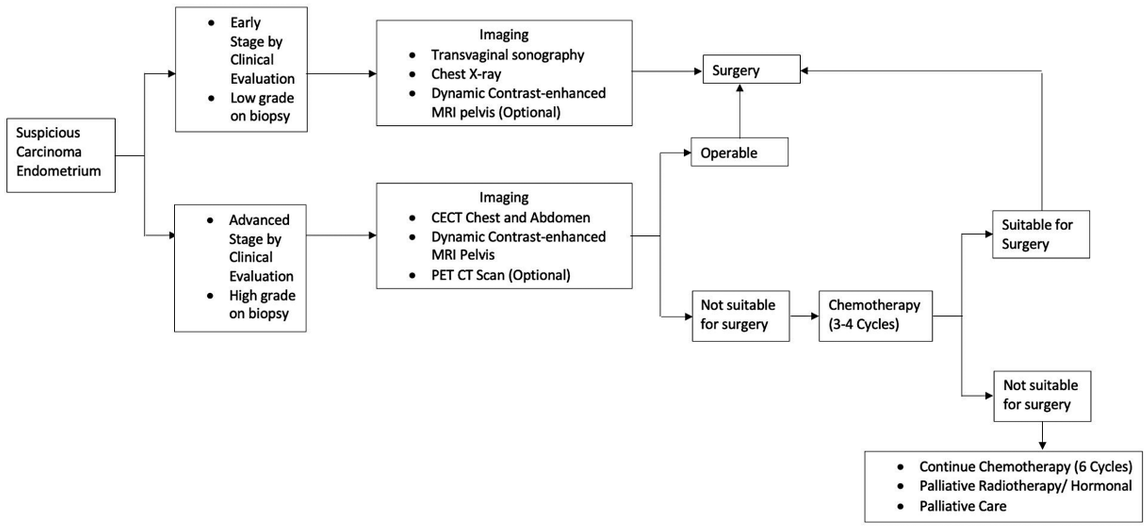

Fig. 1 Imaging referral and treatment algorithm for endometrial carcinoma.Adapted from references [10,12].

uterine risk factors (tumor > 2 cm, high-grade carcinomas, invasion > 50% myometrium, cervical stromal involvement and LVSI), CECT chest and abdomen is suggested to evaluate for metastatic disease. Additional imaging can be considered based on the clinical concern for metastases (delay in presentation or treatment, abnormal physical exam finding, abdominal or pulmonary symptoms, bulky uterine tumor and vaginal or extrauterine disease).[10,13]

For Fertility-Sparing treatment, CEMRI pelvis is preferred to exclude any myoinvasion and assess the local disease extent.[14] If MRI is contraindicated, transvaginal ultrasound pelvis can be considered. Chest X-ray is the baseline evaluation to be followed by non-contrast computed tomography (NCCT) chest in case of any abnormality. If metastasis is suspected in select patients, PET/CT (neck/chest/abdomen/pelvis/groin) is recommended. Additional imaging can be considered based on the clinical concern for metastases.[10]

Uterine Sarcoma

Uterine sarcomas may be diagnosed after total/supracervical hysterectomy (SCH) or after biopsy/myomectomy and the imaging workup varies accordingly. For the initial workup of patients with incidental finding of uterine sarcoma or incompletely resected uterus/adnexa, CEMRI abdomen and pelvis is recommended with non-contrast CT chest for metastatic disease. In cases of SCH, suspicious tumor fragmentation, myomectomy, or intraperitoneal morcellation local tumor extension and residual disease is to be evaluated with pelvic MRI. PET/CT (neck/chest/abdomen/pelvis/groin) is recommended to clarify ambiguous findings. Additional imaging can be considered based on the clinical concern for metastases (as in case of endometrial carcinoma).[10,15]

Clinical/ Diagnostic Workup Excluding Imaging

The clinical presentation is usually abnormal uterine bleeding in premenopausal women and postmenopausal bleeding in the elderly age group. A detailed history including use of hormones, tamoxifen use, diabetes mellitus, and family history is essential followed by a complete systemic and gynecological examination. Endometrial and endocervical sampling is required to make a definitive diagnosis and endocervical curettage is done before endometrial aspiration. Endometrial biopsy is done with endometrial aspiration using devices such as Pipelle or a fine Karman's cannula.[4] In women with inadequate or negative sampling and strong suspicion of malignancy, hysteroscopy and directed biopsy is advised.

The preoperative laboratory evaluation includes a complete blood count, liver and renal function tests, blood sugar, serum electrolytes serum electrolytes, viral marker and viral marker and urinalysis. In selected patients with extrauterine spread of disease (especially nodal involvement in high-risk tumors), serum levels of CA 125 maybe elevated and can be used to monitor response to therapy.[16] The serum human epididymis protein (HE4) levels are elevated in aggressive types of disease and are useful for detecting early disease recurrence.[17]

Genetic evaluation is suggested for younger patients (< 50 years), family history of uterine and colorectal malignancies and those with known related genetic syndrome.

Imaging Guidelines

Screening

Routine screening is not recommended for endometrial carcinoma because majority of the patients with endometrial cancer present with abnormal uterine bleeding and at a stage with disease confined to the uterus. In addition, there is no non-invasive test available with sufficiently high specificity and sensitivity for screening. However, in patients with Lynch syndrome, endometrial biopsy is recommended every 1 to 2 years beginning at the age of 30 to 35 years as a screening procedure.[18]

Diagnosis and Staging

Staging of endometrial carcinoma is primarily surgical and typically performed with laparoscopy.[8] The diagnosis is established by histopathological evaluation and MRI maybe done in equivocal cases to distinguish between cancers of endometrial and cervical origin. Preoperative disease assessment requires depth of myometrial invasion (MRI) and histologic type and grade (endometrial biopsy).

Transabdominal and transvaginal ultrasound are used as baseline screening modalities in patients presenting with abnormal uterine bleeding or postmenopausal bleeding. Transvaginal US has accuracies ranging from 73% to 84% in assessing myometrial invasion (►**Fig. 2**) with insufficient data about prediction of cervical extension or lymphadenopathy.[19,20]

Computed tomography (CT) has a limited role in evaluating myometrial invasion (►**Fig. 3**) and cervical extension in endometrial cancer. In comparative studies of CT with US or MRI for myometrial invasion, the accuracy of CT is reported to be 58% to 61% versus 68% to 69% for US and 88% to 89% for MRI.[21,22] In select cases, CT chest and abdomen is indicated as a part of metastatic workup.

Dynamic contrast-enhanced MRI (►**Fig. 4**) is the preferred imaging modality to evaluate myometrial invasion with high accuracy (59% to 100%), sensitivity (71% to 100%), and specificity (72% to 100%).[23] The staging accuracy ranges from 83% to 92%.[24,25]

PET CT is considered to be better in the evaluation of lymph node metastases and metabolically active nodes of any size are considered to be metastatic.[26] It is also superior in the assessment of extrapelvic disease and bone metastases.[3,27]

MRI Sequences and Imaging Protocols

Scanner: There is improved signal-to-noise ratio (SNR), spatial resolution, anatomic detail and faster scanning techniques with the use of 3 Tesla (T) scanners. The use of phase-array surface abdominopelvic coil is recommended for both 1.5 T and 3.0 T scanners.

Patient preparation: Fasting is advised for 4 hours, but water intake is encouraged before the scan. A moderately full bladder is required during the scan and the patient should be asked to void ~30 to 45 minutes before the examination.

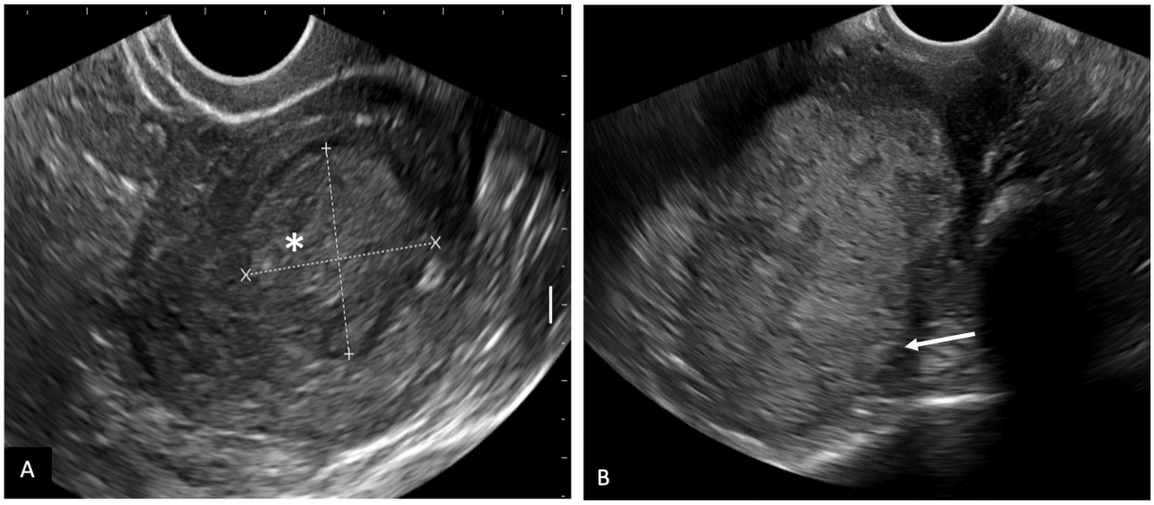

Fig. 2 **Transvaginal ultrasound in carcinoma endometrium**. **A**: A large relatively well-defined iso to hyperechoic mass lesion (*) in the endometrial cavity with < 50% myometrial invasion. **B**: An ill-defined hyperechoic mass in the endometrial cavity with > 50% invasion into myometrium (arrow).

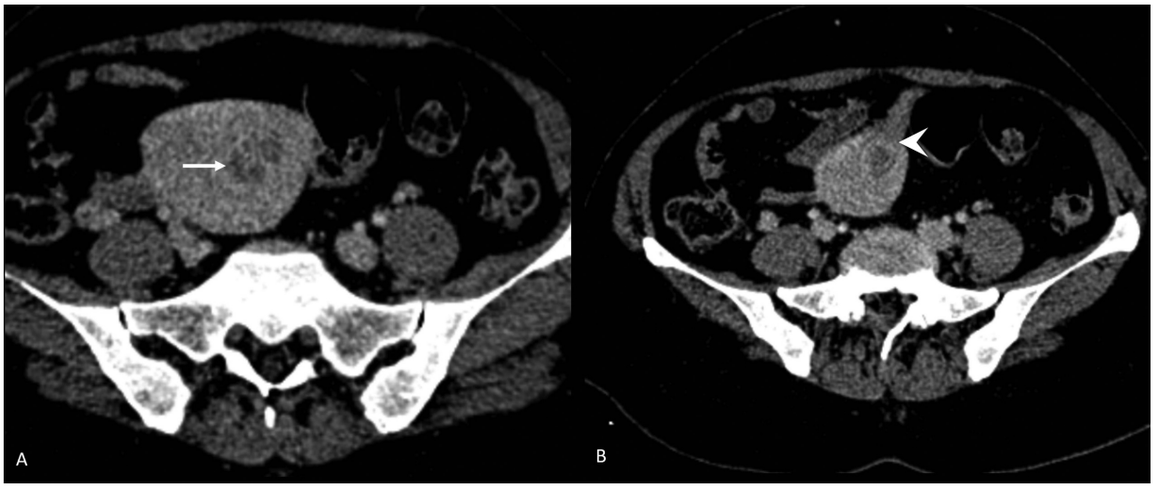

Fig. 3 **CECT abdomen in endometrial carcinoma.** Patient had pacemaker and MRI was contraindicated. An ill-defined heterogeneously enhancing lesion in the endometrial cavity (arrow in **A**) with >50% invasion into myometrium (arrowhead in **B**).

Antispasmodic drugs such as butylscopolamine (40 mg) IM/IV or glucagon IV/IM (0.5–1.0 mg) are recommended to reduce bowel motion. Vaginal opacification with ~10 mL of lignocaine 2% jelly gives optimal contrast resolution.[28]

MRI Technique and Sequences: In the pelvis, T2W FSE sequences are the mainstay of evaluation. Sequences are oriented in relation to the pelvis or dedicated to the uterine axis.[29] T2-weighted images include a small FOV (512 × 256 matrix, 24 cm FOV) sagittal T2WI of the pelvis and a small FOV T2W sequences of pelvis in the axial oblique plane perpendicular to the uterine corpus. T1W sequence of the pelvis in the axial plane is followed by diffusion-weighted imaging (DWI) in axial oblique (in sync with the axial oblique T2WI). Large FOV (256 × 256 matrix, 32 cm FOV) T1- or T2-weighted image of upper abdomen is obtained to evaluate for lymph nodes and hydronephrosis. DWI in the axial plane (large FOV) is also acquired in sync with the large FOV T2 sequence.[8] The dynamic contrast-enhanced sequences are acquired for the assessment of preservation of endometrial halo and differential enhancement of the endometrial soft tissue and the myometrium. Dynamic acquisition can be done in the sagittal plane using a three-dimensional gradient echo T1WI, fat-saturated sequence following the administration of 0.1 mmol/kg of gadolinium at 2 mL/s. Images are acquired before contrast injection and then at 25 seconds, 1 minute and 2 minutes after injection followed by a delayed sequence in the axial oblique plane 4 minutes after injection.[30]

Staging

Endometrial Carcinoma

Carcinomas are usually isointense on T1WI and hyperintense (relative to the myometrium) on T2WI. The lesion shows

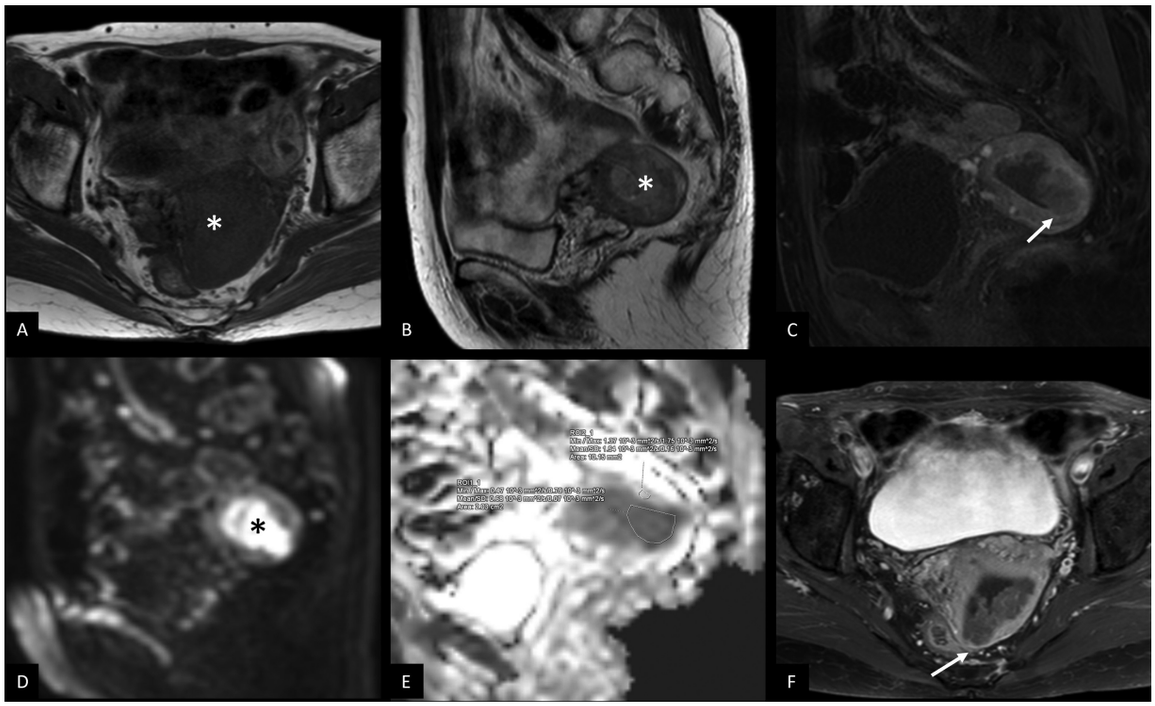

Fig. 4 **Dynamic contrast-enhanced MRI pelvis in carcinoma endometrium (stage IB).** T1 axial oblique (**A**) and T2 sagittal (**B**) show an ill-defined polypoidal mass lesion (*) in the endometrial cavity. DCE MRI (**C**) shows mild contrast enhancement of tumor and disruption of subendometrial zone of enhancement (arrow in **C**) with myometrial invasion of >50%. DWI (**D**) shows diffusion restriction (*) with low ADC value in the ADC map (**E**). Post contrast T1 axial oblique (**F**) shows myometrial invasion of >50% with intact serosal margin (arrow in F).

diffusion restriction with low mean ADC values.[31] Post-contrast administration, tumor enhances slowly and less avidly than the myometrium.

Assessment of myometrial invasion is crucial in the staging of endometrial carcinoma. Deep myometrial invasion is excluded in the presence of an intact junctional zone (JZ) along with smooth early subendometrial enhancement (25–60 seconds). Disruption of the JZ with the tumor within the outer myometrium is suggestive of myometrial invasion (> 50%). The presence of leiomyomas or adenomyosis can result in an overestimation of the depth of myometrial invasion. Deep myometrial invasion is best assessed during the equilibrium phase (2–3 minutes after contrast injection). An imaging delay of ~90 seconds is considered optimal timing for best tumor-myometrium contrast.[32] Delayed-phase images (4–5 minutes after contrast) are useful for detecting cervical stromal invasion.[30]

For extrauterine extension, T2WI should be interpreted in conjunction with the DWI. The presence of intermediate to high signal intensity tumor causing disruption of the normal low signal intensity cervical stroma is suggestive of cervical stromal invasion on T2WI.

Serosal involvement is suggested by an irregular uterine contour/disrupted low signal intensity of the uterine serosa on T2WI, and a loss of the normal edge of enhancing myometrium on DCE sequences.[8]

Tumor abutting or indenting the bladder/rectum over a significant area; tumor interrupting the low signal intensity of the bladder/rectal muscular layer or tumor invading the bladder/rectal muscular wall on T2WI is suggestive of bladder/ rectal involvement. The presence of bullous edema alone is not sufficient to label it as stage IVA disease. Adnexal deposits can be well picked up on DWI and T2WI.[30]

Lymph node involvement can be well picked up on T1WI and DWI. Morphological features such as short-axis diameter of more than 10 mm, rounded shape, loss of fatty hilum are features that help to identify suspicious lymph nodes.[33] However, there is a degree of overlap in the sizes and ADC values of benign and malignant pelvic lymph nodes.

For treatment response, the role of CEMRI and ADC values is still evolving. The commonest site for recurrence is the vagina[34] followed by pelvic and paraaortic lymph nodes. The presence of a T2 hyperintense mass with disruption of the normal low signal intensity linear configuration of the vault is suggestive of vault recurrence.

Uterine Sarcomas

The primary uterine sarcomas are leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), and adenosarcoma. Usually, the diagnosis of sarcomas is made after hysterectomy or myomectomy. The staging of LMS and ESS is different and that of adenosarcoma is the same as endometrial carcinoma. Size is an important criterion in staging though myometrial invasion in LMS and ESS is definitional.[3]

T2WI and contrast enhanced T1WI (►**Fig. 5**) are useful in assessing the size, spread into adnexa, abdominal tissues, bladder or rectum (key T descriptors). LMS are usually solid

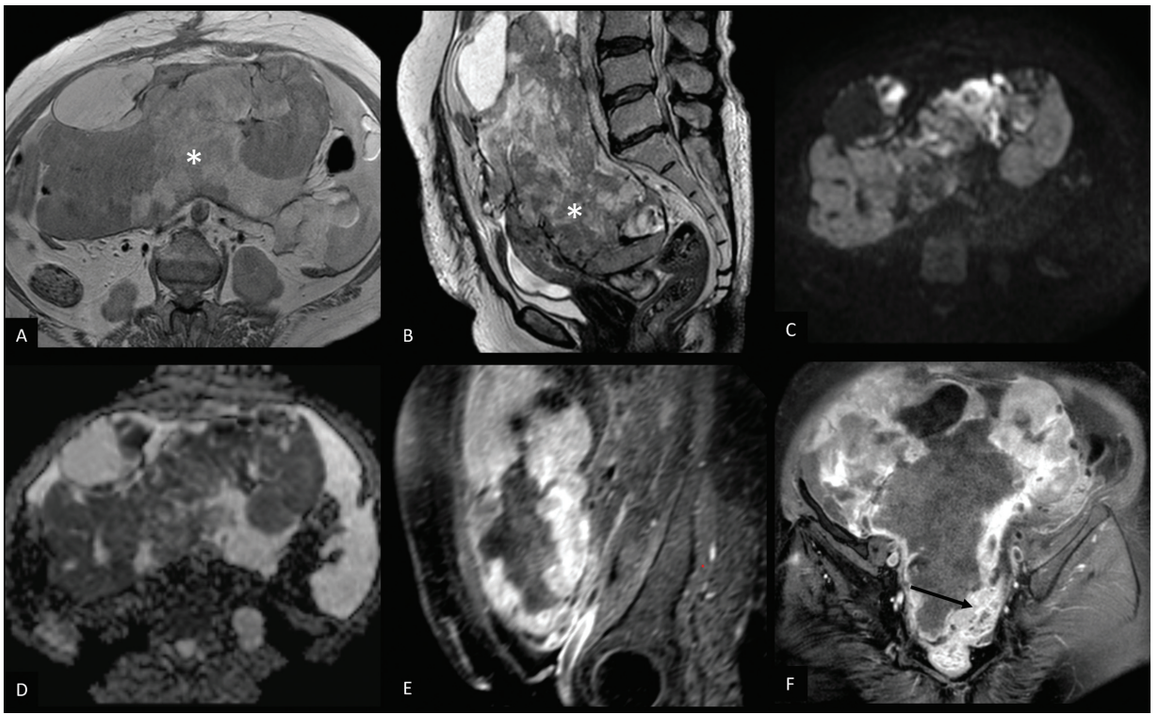

Fig. 5 Contrast enhanced MRI of leiomyosarcoma of uterus (stage IV A). T1 axial (**A**) and T2 sagittal (**B**) images show a large, ill-defined, heterogeneous lesion (*) replacing the entire uterus and involving bilateral adnexa, reaching up to the bilateral pelvic side walls. DWI (**C**) and corresponding ADC map (**D**) show areas of diffusion restriction. Post contrast sagittal (**E**) and coronal (**F**) images show heterogeneous enhancement of the mass and infiltration of the rectum (arrow in F).

masses with irregular margins, hemorrhagic T1 hyperintense areas, and intermediate to high signal on T2WI with heterogenous post contrast enhancement and diffusion restriction. ADC values in LMS range from $0.791 \pm 0.145 \times 10^{-3}$ to $1.17 \pm 0.15 \times 10^{-3}$ mm^2/s.[35]

PET CT is considered superior in evaluation of lymph nodes and extra pelvic metastases. ►**Table 1** summarizes the TNM and FIGO staging of uterine cancers including carcinoma and sarcoma.

Follow-up/Surveillance

Endometrial Carcinoma

In cases of non-fertility-sparing treatment for endometrial carcinoma, imaging is to be guided by the symptoms of the patient, risk assessment, and clinical signs of recurrent or metastatic disease (palpable mass; lymphadenopathy; vaginal tumor; and any new pulmonary, abdominal or pelvic symptoms).[36,37] Based on these symptoms, CT abdomen and/or chest CT maybe performed. Whole body PET/CT and/or CEMRI abdomen can be performed as clinically indicated in selected patients.[10,38]

In cases of fertility-sparing treatment, repeat CEMRI pelvis is preferred for patients with persistent endometrial carcinoma (6–9 months of failed medical therapy), especially if further fertility-sparing approaches are being considered.[10] Additional imaging can be considered based on the clinical concern for metastases.

In case of suspected recurrence or metastases, CT abdomen and/or chest CT is recommended with whole body PET/CT and MRI abdomen indicated in select patients.

Uterine Sarcoma

In cases of uterine sarcoma, CECT of the chest/abdomen/pelvis (or CEMRI abdomen with NCCT chest) is recommended every 3 to 6 months for the first 3 years and then every 6 to 12 months for the next 2 years. Subsequently, annual to biannual imaging can be considered for up to an additional 5 years (varies according to the stage and histology grade and can be done every 3 months). Additional imaging, including PET/CT, is based on the clinical concern for metastases.[10,39]

Principles of Management

Treatment planning should be done in multidisciplinary tumor board.[40] For the management of early-stage including high-risk cases, minimally invasive approach is preferred.[41] The steps include peritoneal wash cytology, exploration of intra-abdominal structures, type-I extra fascial hysterectomy, bilateral salpingo-oophorectomy + lymphadenectomy. More extensive procedures including radical hysterectomy are needed to take negative margins in advanced disease.[40] Decision of systematic lymphadenectomy is based on the risk of nodal involvement. In patients with low-grade endometrioid adenocarcinoma with tumor size $\leq$ 2 cm and with none or superficial myometrial invasion, the risk of nodal

Table 1 TNM and FIGO staging of malignancies of the uterine corpus (carcinoma endometrium, carcinosarcoma, leiomyosarcoma, and endometrial stromal sarcoma) [Adapted from reference[10]]

	FIGO	Carcinoma Endometrium & Carcinosarcoma	Sarcoma (Leiomyosarcoma & Endometrial stromal sarcoma)
T			
TX		Primary lesion cannot be assessed	Primary lesion cannot be assessed
T0		No evidence of primary lesion.	No evidence of primary lesion
T1	I	Lesion confined to the body of uterus including endocervical glandular involvement	Growth limited to the uterus
T1a	IA	Lesion limited to the endometrium or < 50% myometrial invasion	Size of the lesion ≤ 5 cm in greatest dimension
T1b	IB	Lesion invading ≥ 50% myometrium	Lesion > 5 cm
T2	II	Lesion invading the cervical stroma (not endocervix) but not extending beyond the uterus.	Lesion seen beyond the uterus, within the pelvis
T2a	IIA	-	Lesion involves adnexa
T2b	IIB	-	Lesion involves other pelvic tissues
T3	III	Lesion involving serosa, adnexa, vagina or parametrium	Lesion infiltrates abdominal tissues
T3a	IIIA	Direct extension or metastasis to serosa and/or adnexa	One site
T3b	IIIB	Direct extension or metastasis to vagina or parametrium	More than one site
T4	IVA	Infiltration of bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)	Lesion invades bladder or rectum
N			
NX		Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis	No regional lymph node metastasis
N0(i +)		Isolated cancer cells in regional lymph node(s), not > 0.2 mm	Isolated cancer cells in regional lymph node(s) not > 0.2 mm
N1	IIIC1	Regional lymph node metastasis in pelvic lymph nodes	Regional lymph node metastasis (FIGO IIIC)
N1mi	IIIC1	>0.2 mm to ≤ 2.0 mm in diameter (pelvic lymph nodes)	
N1a	IIIC1	> 2.0 mm in diameter (pelvic lymph nodes)	
N2	IIIC2	Regional lymph node metastasis to para-aortic lymph nodes with or without positive pelvic lymph nodes	–
N2mi	IIIC2	>0.2 mm ≤ 2.0 mm in diameter (para-aortic lymph nodes)	
N2a	IIIC2	> 2.0 mm in diameter (para-aortic lymph nodes)	
M			
M0		No distant metastasis	No distant metastasis
M1	IVB	Distant metastasis including metastasis to inguinal lymph nodes, intraperitoneal disease, liver, lung, or bone. (excludes metastasis to pelvic or para-aortic lymph nodes, uterine serosa, vagina, or adnexa).	Distant metastasis (excluding adnexa, pelvic, and abdominal tissues)

involvement is < 1% and hence, lymph node dissection can be safely omitted. While systematic pelvic and para aortic nodal dissection is done for the purpose of staging in those with intermediate-risk factors, in patients with high-risk factors, nodal dissection is recommended for therapeutic benefit too.[40,42] Sentinel node biopsy should be considered for staging if facilities are available. Infra colic omentectomy should be done for serous variants and carcinosarcoma.[40] Younger women with uterus confined well-differentiated endometrioid adenocarcinoma and no myometrial invasion may be offered fertility preserving treatment.[43] Decision for adjuvant therapy is decided using prognostic risk stratification based on predictive factors and molecular profile (►**Table 2**).[40,44,45]

Management of Recurrent Disease

Recurrent disease is difficult to treat and evidence on efficacy of available modalities is limited. The most common site is vaginal vault and for radiation naïve cases radiotherapy is preferred.[40] Advanced radiation techniques including SBRT and IMRT have shown better patient tolerance. For previously irradiated cases either surgery or systemic therapy are preferred. Pelvic recurrence is associated with relatively poor outcome and management depends on disease distribution and nature of prior therapy. For distant recurrence systemic chemotherapy is used. Several targeted therapeutic agents are investigated with promising potential. Immunotherapy has shown promising results and pembrolizumab is

Table 2 Selection criteria of adjuvant therapy. Adapted from Concin et al.[40]

Risk group	Common treatment recommendation	
Low risk	No adjuvant treatment	
Intermediate risk	Vaginal brachytherapy Consider observation if age < 60 years	
High-intermediate risk	Vaginal brachytherapy Consider EBRT, if LVSI un-equivocally positive, especially if no lymph node dissection or sentinel nodes have been performed.	
High-risk	I. EBRT, Consider VBT, if no LVSI II. Vaginal brachytherapy if grade 1–2 disease (e.g., stage II disease) III. Pelvic radiotherapy if Stage I, grade 3 LVSI un equivocally positive, Stage II IV. Stage III-combined radiotherapy and chemotherapy	**Non-endometrioid** I. Stage IA-vaginal brachytherapy after full surgical staging, II. LVSI negative Stage IB-III: combined external beam RT and chemo

recommended for MSI high tumors; pembrolizumab and lanvatinib have been found useful for microsatellite stable cases.[40,46]

Summary of Recommendations

- The FIGO staging system for endometrial carcinoma is primarily surgical and based on histopathology.
- Imaging, though not mandatory, is useful in the preoperative evaluation of tumor stage, especially assessment of myometrial invasion and cervical stromal extension.
- Dynamic contrast-enhanced MRI with DWI has high staging accuracy and is the preferred imaging modality.
- In cases of clinically suspected recurrence post treatment, PET/CT is the preferred imaging modality for the evaluation of recurrent disease.

Synoptic Reporting Formats

The reporting formats for MRI pelvis (for primary disease) and CECT abdomen (for follow-up evaluation) have been provided.

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Conflicts of Interest
None declared.

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

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Abstract

Cervical cancer is the fourth most common cancer in women globally and the second most common cancer in Indian women, more common in lower socioeconomic strata. Improvement in survival and decrease in morbidity reflect the earlier detection with screening and imaging, as well as multifactorial multimodality therapy integrating surgery, and concurrent chemoradiation therapy providing superior therapeutic benefits. Imaging plays a vital role in assessing the extent of disease and staging of cervical cancer. The appropriateness criteria of a modality are different from its availability based on infrastructure, medical facilities, and resource status. Although in an ideal situation, magnetic resonance imaging (MRI) would be of greatest value in locoregional assessment of extent of disease and fluorodeoxyglucose positron emission tomography-computed tomography for distant staging; often, an ultrasonography, chest radiograph, and bone scans are utilized, with contrast-enhanced computed tomography representing a fair superior diagnostic accuracy, and can be reported as per the RECIST 1.1 criteria. MRI is also of good utility in the assessment of residual disease, predicting response and detecting small volume recurrence. MRI offers the highest diagnostic accuracy in determining parametrial invasion and hence surgical planning; so also, MRI-guided radiation planning helps in more accurate graded radiation dose planning in radiation therapy. Stage and therapy-based surveillance imaging should be encouraged and recommended.

Keywords
- cancer
- cervical
- guidelines
- imaging
- MRI

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Introduction

Cervical cancer is the fourth most common cancer in women globally and the second most common cancer in women in India. Annual global and Indian estimates of new cases for the year 2020 were 6,04,127 and 1,23, 907, respectively.[1] It is more common in women belonging to lower socioeconomic strata and more than 85% of all cases occur in developing countries. Even in these countries, the incidence is declining that could be attributed to better lifestyle, genital hygiene, and safe sexual practices. Down-staging among the diagnosed cases and earlier stages at presentation alongwith improved treatment protocol with chemoradiation therapy have led to improved survival. Pretreatment imaging plays a critical role in staging the disease as well as planning the appropriate treatment for the patient.

Etiology and Risk Factors

Infection with high-risk human papilloma virus (HPV) is a necessary but not sufficient cause for cervical cancer, with genotypes 16 and 18 being responsible for nearly 70% of cases.[2] HPV is a common sexually transmitted infection. In more than 90% of women, infection is transient and self-limiting; while in less than 10% virus may persist. Incorporation of viral genome into the host nucleus is the key step in HPV carcinogenesis. Factors that increase acquisition and persistence of HPV are also risk factors for cervical cancer and these include infections with other sexually transmitted diseases (human immunodeficiency virus and *Chlamydia trachomatis*), tobacco use, early onset of sexual activity, multiple sexual partners, multiparity, poor nutrition, personal hygiene, and long-term use of hormonal contraceptives. A minor fraction of cases of cervical cancer is HPV independent.

Classification

►**Table 1** shows the World Health Organization fifth edition 2020; classification of cervical tumors. Squamous cell carcinoma is the most common histologic type followed by adenocarcinoma.

Table 1 World Health Organization (WHO) fifth edition, 2020; classification of tumors of female reproductive organs classifies cervical tumors

Squamous epithelial tumors	Squamous metaplasia Atrophy Condyloma acuminatum Low-grade squamous epithelial lesion Cervical intraepithelial neoplasia 1 High-grade Squamous intraepithelial neoplasia Cervical intraepithelial neoplasia 2 Cervical intraepithelial neoplasia 3 Squamous cell carcinoma, HPV-associated Squamous cell carcinoma HPV-independent
Glandular tumors and precursors	Endocervical polyp Mullerian papilloma Nabothian cyst Tunnel clusters Microglandular hyperplasia Lobular endocervical glandular hyperplasia Diffuse laminar endocervical hyperplasia Mesonephric remnants and hyperplasia Arias-Stella reaction Endocervicosis Tuboendometrioid metaplasia Ectopic prostatic tissue Adenocarcinomas of in-situ NOS Adenocarcinoma in situ, HPV-associated Adenocarcinoma in situ HPV-independent Adenocarcinoma, NOS Adenocarcinoma, HPV-associated Adenocarcinoma, HPV-independent, gastric type Adenocarcinoma, HPV-independent, clear cell type Adenocarcinoma, HPV-independent, mesonephric type Adenocarcinoma, HPV-independent, NOS Endometrioid adenocarcinoma
Other epithelial tumors	Carcinosarcoma, adenosquamous and mucoepidermoid carcinomas, adenoid basal, and unclassified carcinomas.
Mixed epithelial and mesenchymal tumors	Adenomyoma and adenosarcoma
Germ cell tumors	Germ cell tumors

Abbreviations: HPV, human papilloma virus; NOS, not otherwise specified.

Clinical Presentation and Workup

The median age at presentation of invasive cervical cancer is in the fifth decade. Early-stage disease is often asymptomatic and detected on screening. Abnormal vaginal bleeding in the form of postcoital, intermenstrual, or postmenopausal bleeding is the most common symptom. Foul smelling, blood-stained vaginal discharge is another common symptom. Constitutional symptoms, back pain, bladder or bowel habit alterations may occur in advanced stages. Rarely lower limb swelling due to deep vein thrombosis may be the presenting symptom. A detailed physical examination should include palpation of the supraclavicular and groin nodes, and liver to exclude metastatic disease. A pelvic examination including speculum, vaginal, and rectal examination is mandatory for the assessment of the cervical lesion as well as local spread to vagina, parametria, rectovaginal septum, and rectum. A punch biopsy should be performed from the visible cervical growth. Colposcopic examination and guided biopsy are required in a patient with grossly normal looking cervix but with an abnormal screening test. After confirmation of diagnosis, a comprehensive pretreatment workup should be done including hematocrit, liver and renal function tests, a chest radiograph, and an abdominopelvic imaging. An examination under anesthesia, cystoscopy, and proctoscopy are recommended only if clinically indicated.

Early detection of cervical cancer and precancer is possible by screening. Various methods available for screening include cytology, visual inspection with acetic acid and HPV DNA testing.

Imaging in Cervical Cancer

Imaging in cervical cancer is crucial for staging, to determine the extent of disease, in treatment planning and for response assessment.

Imaging findings are used as an adjunct to clinical staging.

Imaging Guidelines

The FIGO (*International Federation of Gynecology and Obstetrics*) staging system guides management protocol for cervical cancer patients and traditionally, this system was based on clinical evaluation with only limited imaging investigations. However, the most recent update on FIGO cervical cancer staging has allowed imaging findings in stage allocation. Equivalence of the TNM (*Tumor Node Metastases*) staging system maintained by the AJCC (*American Joint Committee on Cancer*) and the FIGO classification lay down common imaging and management recommendations. Version 9 update of the 8th edition AJCC TNM staging (►**Table 2**) highlights the changes of incorporation of imaging and surgical findings, elimination of lateral spread from T1a, addition of a subcategory to T1b (T1b3), and histopathology updated to reflect HPV-associated and independent carcinomas.[3] With advancements in technology of computed tomographic (CT) scan and magnetic resonance imaging (MRI), there has been enough evidence to support good accuracy and diagnostic performance of these imaging modalities in determining the extent of disease and staging. In an ideal setting, MRI serves as the modality of choice for local extent of the disease, particularly for endocervical growths that cannot be evaluated on per-speculum or per-vaginal examination. The addition of diffusion weighted imaging has further enhanced the efficacy of MRI for locoregional extension, nodal involvement, and posttherapy tumor recurrence. However, since cervical cancer is more prevalent in women from low socioeconomic strata, MRI may not be accessible and/or affordable to them. Hence, role of ultrasound (US) and CT becomes more crucial in the management algorithm. US, the most readily available modality, offers comparable performance; however, it majorly depends on the expertise and skill of the operator and thus has not been able to find its place in routine practice. Availability of CT is better than MRI with added advantage of faster acquisition of images and better patient compliance. Positron emission tomography-computed tomography (PET-CT), on the other hand, provides functional information in addition to anatomical details. Considering all these factors, the recent FIGO 2018 has recommended baseline evaluation with cross-sectional imaging for patients with carcinoma cervix, but has not outlined a particular imaging protocol and advised to utilize the available modalities as per available infrastructure,[4] attributed to limited resources in low- and middle-income countries in contrast to the incorporation of imaging evaluation at the pretreatment level in the high-income countries. The NCCN *(National Comprehensive Cancer Network)* (►**Tables 2–4**) recommends baseline evaluation with MRI for local staging and CT or PET-CT for lymph node detection and distant metastases.[5] Considering these different scenarios, the European Society of Gynecological Oncology, European Society for Therapeutic Radiotherapy and Oncology, and the European Society for Pathology put forth new guidelines in 2018 after FIGO apprised the role of imaging in its revised guidelines. The joint guidelines included imaging for staging, treatment and follow-up of cervical cancer based on combined staging by TNM and FIGO system,[6,7] putting forth MR as a mandatory early investigation modality, with an optional transvaginal/transrectal US —if a skilled radiologist is available. The integration of various modalities of imaging, pathology, and clinical examination has been highlighted in the European guidelines that can be used for staging and treatment planning for the patients.[5] Considering heterogeneity of resources in our country, the National Cancer Grid of India has categorized imaging guidelines as optimal and minimal based upon availability of imaging modality.[8] MRI has been considered as the optimal imaging modality for disease assessment in early as well as advanced stages, whereas PET-CT is considered optional. On the other hand, in resource constraint setting, a radiograph of the chest and US abdomen should at least be performed for the patients and any indeterminate/suspicious node may be evaluated with fine-needle aspiration cytology sampling.

Imaging for Diagnosis

A. US: It is often the primary investigation performed for the presenting clinical symptoms, and it may be performed per-abdomen or per-vaginum, or both; the latter depicting a superior resolution. Cervical cancer appears as a hypoechoic lesion, with its epicenter in the cervical lips. Locoregional involvement of the uterine body and parametrium can also be seen. Large, lobulated, irregular pelvic nodes and attenuated hilum are suggestive of metastatic adenopathy. Involvement of extrapelvic organs may also be seen. A larger limitation of US is its subjectivity in assessment, often resting the diagnostic acumen to the hands of the skill of the operating radiologist. The following points should be noted:

a. Epicenter and size of the lesion in three dimensions.
b. Extent of vaginal involvement
c. Involvement of parametrium, rectum or urinary bladder.
d. Pelvic lymph nodes.
e. Retroperitoneal lymph nodes.
f. Renal morphology, and comment on hydroureteronephrosis.
g. Any other incidental finding

B. MRI: Carcinoma of the cervix is usually seen as a soft tissue appearing iso to hypointense on T2-weighted (T2W; compared with the normal darker signal intensity), isointense on T1W imaging, higher signal intensity on fat saturated sequences, and restricted diffusion. An important feature often is the differential enhancement between the uninvolved cervix and myometrium compared with cervical lesion, as seen on

Table 2 AJCC TNM staging system

TNM stage	FIGO stage	Description
Tumor stage(T)		
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded)
T1a	IA	Invasive carcinoma that can be diagnosed only by microscopy with maximum depth of invasion ≤5 mm
T1a1	IA1	Measured stromal invasion ≤3 mm in depth
T1a2	IA2	Measured stromal invasion >3 mm and ≤5 mm in depth
T1b	IB	Invasive carcinoma with measured deepest invasion >5 mm (>stage IA); lesion limited to the cervix uteri with size measured by maximum tumor diameter; note: the involvement of vascular/lymphatic spaces should not change the staging, and the lateral extent of the lesion is no longer considered
T1b1	IB1	Invasive carcinoma >5 mm depth of stromal invasion and ≤2 cm in greatest dimension
T1b2	IB2	Invasive carcinoma >2 cm and ≤4 cm in greatest dimension
T1b3	IB3	Invasive carcinoma >4 cm in greatest dimension
T2	II	Carcinoma invades beyond the uterus but has not extended onto the lower one-third of the vagina or to the pelvic wall
T2a	IIA	Involvement limited to the upper two-thirds of the vagina without parametrial invasion
T2a1	IIA1	Invasive carcinoma ≤4 cm in greatest dimension
T2a2	IIA2	Invasive carcinoma >4 cm in greatest dimension
T2b	IIB	With parametrial invasion but not up to the pelvic wall
T3	III	Carcinoma involves the lower one-third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney; note: the pelvic wall is defined as the muscle, fascia, neurovascular structures, and skeletal portions of the bony pelvis; cases with no cancer-free space between the tumor and pelvic wall by rectal examination are FIGO stage III
T3a	IIIA	Carcinoma involves the lower one-third of the vagina, with no extension to the pelvic wall
T3b	IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
T4	IVA	Carcinoma has involved (biopsy-proven) the mucosa of the bladder or rectum or has spread to adjacent organs (bullous edema, as such, does not permit a case to be assigned to stage IVA)
Nodal status(N)		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) ≤0.2 mm or single cells or clusters of cells ≤200 cells in a single lymph node cross-section
N1	IIIC1	Regional lymph node metastasis to pelvic lymph nodes only
N1mi	IIIC1	Regional lymph node metastasis (>0.2 mm but ≤2.0 mm in greatest dimension) to pelvic lymph nodes
N1a	IIIC1	Regional lymph node metastasis (>2.0 mm in greatest dimension) to pelvic lymph nodes
N2	IIIC2	Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes
N2mi	IIIC2	Regional lymph node metastasis (>0.2 mm but ≤2.0 mm in greatest dimension) to para-aortic lymph nodes, with or without positive pelvic lymph nodes
N2a	IIIC2	Regional lymph node metastasis (>2.0 mm in greatest dimension) to para-aortic lymph nodes, with or without positive pelvic lymph nodes
Metastatic status (M)		
M0		No distant metastasis
cM1	IVB	Distant metastasis (includes metastasis to inguinal lymph nodes, intraperitoneal disease, lung, liver, or bone; excludes metastasis to pelvic or para-aortic lymph nodes or vagina)
pM1	IVB	Microscopic confirmation of distant metastasis (includes metastasis to inguinal lymph nodes, intraperitoneal disease, lung, liver, or bone; excludes metastasis to pelvic or para-aortic lymph nodes or vagina)

Abbreviations: AJCC, American Joint Committee on Cancer; FIGO, International Federation of Gynecology and Obstetrics.

Table 3 Principles of imaging for initial workup, the NCCN guidelines

Stage I
Nonfertility sparing
◇ Consider pelvic MRI with contrast to assess local disease extent (preferred for FIGO stage IB1–IB3)
◇ Neck/chest/abdomen/pelvis/groin PET/CT (preferred) or chest/abdomen/pelvis CT or PET/MRI for FIGO stage IB1–IB3
◇ For patients who underwent TH with incidental finding of cervical cancer, consider neck/chest/abdomen/pelvis/groin PET/CT or chest/abdomen/pelvis CT to evaluate for metastatic disease and pelvic MRI to assess pelvic residual disease
◇ Other imaging should be based on symptomatology and clinical concern for metastatic disease
Fertility sparing
◇ Pelvic MRI (preferred) to assess local disease extent and proximity of tumor to internal cervical os; perform pelvic transvaginal ultrasound if MRI is contraindicated
◇ Neck/chest/abdomen/pelvis/groin PET/CT (preferred) or chest/abdomen/pelvis CT in FIGO stage IB1–IB3
◇ Consider chest CT with or without contrast
◇ Other imaging should be based on symptomatology and clinical concern for metastatic disease
Stage II–IVA
Pelvic MRI with contrast to assess local disease extent (preferred)
Neck/chest/abdomen/pelvis/groin PET/CT (preferred) or chest/abdomen/pelvis CT to evaluate for metastatic disease
Other initial imaging should be based on symptomatology and clinical concern for metastatic disease
For patients who underwent TH with incidental finding of cervical cancer, consider neck/chest/abdomen/pelvis/groin PET/CT or chest/ abdomen/pelvis CT to evaluate for metastatic disease and pelvic MRI with contrast to assess pelvic residual disease
a. MRI and CT are performed with contrast throughout the guidelines unless contraindicated. Contrast is not required for screening chest CT
b These factors may include abnormal physical exam findings or pelvic, abdominal, or pulmonary symptoms
c These factors may include abnormal physical exam findings, bulky pelvic tumor (>4 cm), delay in presentation or treatment, and pelvic abdominal or pulmonary symptoms

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PET/CT, positron emission tomography/computed tomography; TH, total hysterectomy.

dynamic subtracted fat-saturated T1 post contrast images. Cervical cancers are usually hypoperfused compared with their endometrial counterparts. Neuroendocrine tumors, however, may show avid enhancement. Parametrial invasion is seen as a loss of distinction of the hypointense T2W signal of the cervical and vaginal outer surface junction with the bright fat containing parametrium, with spiculations, lobulations, or frank invasion (►**Fig. 1**).

Imaging for Staging

It can be divided into imaging for locoregional disease and systemic spread.

A. *Evaluation of locoregional disease:* Investigation of choice for local staging of cervical cancer is pelvic MRI. Contrast administration is optional, and when administered, a dynamic postcontrast MRI helps in better parametrial assessment, differentiating from the vascular plexus. The cervix is better evaluated when the vaginal cavity is distended by US or lignocaine jelly, opening up and outlining the patent fornices, and superior estimation of parametrial invasion. The following points should be considered while reporting MRI for cancer cervix, which help in determining stage of the lesion and management.

1. Dimensions of the lesion in orthogonal axes.
2. The site of the lesion and its extent within the confines of the cervix. Its epicenter, involvement of the fornices, the involvement of the lower uterine segment and vagina.
3. The extension of the lesion outside the confines of the uterus, for example, the parametrium on either side, involvement of the bladder, and rectum as well as the involvement of pelvic side walls.
4. Any secondary obstructive collection within the uterus due to stenosed endocervical canal.
5. Pelvic nodal disease on both sides along with sub sites. Internal, external iliac, obturator and common iliac nodes in their short axis dimension should be measured and mentioned separately. Screening abdomen is suggested, with careful analysis for the presence of supra- and infra renal-hilar retroperitoneal nodes.
6. Assessment of inguinal nodes.

B. Evaluation of systemic spread: Investigation of choice for systemic staging is CT with contrast (only portal venous phase may suffice). Both the abdomen (upper abdomen) and thorax should be covered. PET-CT has been used for both locoregional and systemic staging in clinically advanced stages. Depending on the available resources, technetium 99 m methylene diphosphonate bone scan

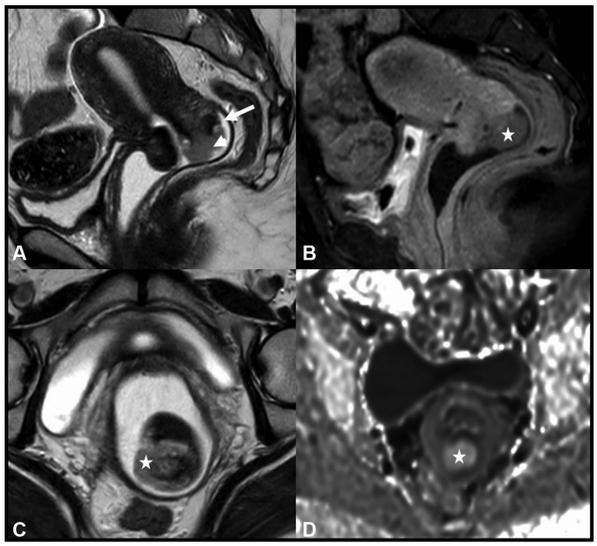

Fig. 1 A young 34-year-old lady with a history of postcoital pervaginal bleeding. Magnetic resonance imaging shows early-stage cervical lesion, pathologically proven as squamous cell carcinoma. (A) Small field of view sagittal T2-weighted image shows a polypoid exophytic lesion (marked by arrowhead) arising from the posterior lip of the cervix. Arrow shows superior delineation of the posterior vaginal forniceal space, due to intravaginal instillation of lignocaine, distending the vaginal space. In this case, the posterior fornix and vaginal wall are clearly seen as uninvolved by the disease. (B) Postcontrast imaging shows differential poor enhancement of the lesion (marked by *). (C) Small field of view axial T2-weighted image shows lignocaine jelly surrounding the cervical lips and vaginal wall, also helping in ruling out lateral parametrial invasion. (D) Diffusion weighted imaging shows restricted diffusion seen as a high signal intensity (marked by *).

may be used for detecting predominantly sclerotic skeletal metastases. Chest radiographs have been used for detecting or following up on lung metastasis as well as pleural effusion, and US may be used to rule out organ metastases or adenopathy.

The following points should be considered for systemic staging.

a. Retroperitoneal nodes, mention above or below the level of renal vein. Involvement of the major vessels by the nodes should be recorded.
b. Liver or other organ metastasis.
c. Peritoneal involvement.
d. Mediastinal adenopathy.
e. Supraclavicular nodes.
f. Kidneys and ureters for any dilatation.
g. Any pelvic arterial or venous and/or pulmonary embolus
h. Apart from the above, an attempt for locoregional assessment in terms of size, parametrial invasion, and bowel/bladder wall involvement should be made.

Fluorodeoxyglucose (FDG) PET-CT: It has been a useful tool in pre-treatment evaluation to rule out distant nodal involvement or other metastatic disease. It is essential to rule out metastases, in early-stage cancer for definitive curative therapy, and hence PET-CT is recommended by the NCCN guidelines for workup of cervical cancers clinically considered as stage IB. Metastatic workup of clinical stage IIB and III who are planned for multimodality treatment include a FDG PET-CT if available. The ability to reliably identify and characterize retroperitoneal nodal metastases may help in altering the radiotherapy (RT) field. Another nuclear medicine procedure proven to be helpful prior to surgical excision is the sentinel node scintigraphy. A radionuclide colloid, commonly Technetium (TcO4) nano colloidal filtered sulfur colloid, is injected in the peritumoral region and scan obtained. Identification of the echelon node and frozen section examination of the sentinel node helps in intraoperative decision making. Radical surgery is abandoned in favor of definitive chemoradiation if sentinel lymph node shows metastatic disease. A check-list for PET-CT should include the following:

a. Standardized uptake value of all the metabolically active lesions.
b. Bone lesions.

Imaging for Planning Therapy

Based on the locoregional extent of disease and clinical status of patient, radical surgery or definitive radiation therapy (RT) with or without concurrent chemotherapy is planned. For RT planning contouring, contrast-enhanced CT (CECT) is the primary modality of imaging. MRI and CT fusion as well as PET-CT have been used as well. An advantage of MR over CT is its better soft tissue resolution that helps in planning graded radiation doses. Hypoxic imaging also serves as a surrogate for prediction of response to RT. Traditionally, brachytherapy prescription from last many decades has been performed using anatomical surrogates that represent boundaries of medial parametrium (referred as point A, representing the crossing of ureter and uterine artery). In the last two decades, MR has also been integrated for brachytherapy treatment planning in cervix cancer.

Imaging in Prediction of Pretreatment and Post-Treatment Response

MRI is a reliable modality for the assessment of post-therapy (especially post radiation) response, with remarkable reduction in size of the lesion, cicatrizing appearance of the cervical lips; accompanied with the tumor-related isointense T2W signal intensity changing to T2 dark signal intensity as the neoplasm undergoes fibrosis and the restricted diffusion moving towards near normal facilitation. Smaller areas of residual disease may be detected by remnant areas of signal intensity lacking these features and mimicking the index lesion. MRI has also been integrated in response and outcome prediction. Tumor necrosis identified on T2W MRI is known to clearly impact outcomes after chemoradiation.[9] MR-based radiomics also allow discrimination of responders versus non responders prior to onset of chemoradiation therapy.[10] Dynamic contrast-enhanced MRI identifies hypoxic fraction and allows identification of patients who are expected to have unfavorable outcome.[11] Blood oxygen

Table 4 The NCCN guidelines for imaging on surveillance

Stage I
Nonfertility sparing
a. Imaging should be based on symptomatology and clinical concern for recurrent/metastatic disease[b]
b. For patients with FIGO stage IB3 or patients who required postoperative adjuvant radiation or chemoradiation due to high-risk factors[d]
c. Neck/chest/abdomen/pelvis/groin PET/CT[a] may be performed at 3–6 months after completion of treatment
Fertility sparing
a. Consider pelvic MRI with contrast 6 months after surgery and then yearly for 2–3 years
b. Other imaging should be based on symptomatology and clinical concern for recurrent/metastatic disease[b]
Stage II to IV
Neck/chest/abdomen/pelvis/groin PET/CT (preferred) or chest/abdomen/pelvic CT with contrast within 3–6 months of completion of therapy
Consider pelvic MRI with contrast at 3–6 months post completion of therapy
Other imaging should be based on symptomatology and clinical concern for recurrent/metastatic disease[e]
Stage IVB or recurrence
Imaging as appropriate (CT, MRI, or PET/CT) to assess response or determine further therapy
a. MRI and CT are performed with contrast throughout the guidelines unless contraindicated. Contrast is not required for screening chest CT
b. These factors may include abnormal physical exam findings or pelvic, abdominal, or pulmonary symptoms
c. Risk factors may include positive nodes, positive parametria, positive margins, or local cervical factors
d. These factors may include abnormal physical exam findings such as palpable mass or adenopathy, or new pelvic, abdominal, or pulmonary symptoms

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PET/CT, positron emission tomography/computed tomography.

level-dependent hypoxia imaging characterizes tumor biology at the cellular level.[12]

For response assessment in metastatic lymph nodes and other distant sites, either CECT or PET-CT or PET-CECT is useful. It is also imperative to note that in cervical cancer chemoradiotherapy studies, traditional radiological response evaluation has been sparingly utilized. Multiple ongoing studies especially that combine RT and drugs (targeted agents or immunotherapy) now utilize RECIST 1.1 for determining progression-free survival.[13,14] As chemoradiotherapy studies have traditionally not utilized RECIST 1.1, studies are underway within multi-institutional collaboration to understand the impact of such a transition on assessment of various disease outcome endpoints.

The NCCN guidelines recommend the use of CECT/PET-CT/MRI modality for response assessment and surveillance, varying over 6 months to 2 to 3 yearly, depending on the stage of presentation and the therapy received (►**Table 4** ►**Table 5** and ►**Table 6**).

Table 5 The NCCN guidelines on imaging for recurrence

Neck/chest/abdo/pelvis/groin PET-CT/CT
Consider pelvic MRI

Abbreviations: MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PET/CT, positron emission tomography/computed tomography.

Synoptic reporting formats have been attached for reference of the salient features essential for appropriate imaging (►**Table 7** and ►**Table 8**).

Table 6 The NCCN guidelines on imaging in small cell neuroendocrine carcinoma of the cervix

Additional workup
Neck/chest/abdomen/pelvis/groin PET/CT + brain MRI (preferred) or Chest/abdomen/pelvis CT + brain MRI
Treatment response assessment
If primary treatment is chemoradiation, then neck/chest/abdomen/pelvis/groin PET/CT ± brain MRI (preferred) or chest/abdomen/pelvis CT ± brain MRI If neoadjuvant chemotherapy is used, consider reassessment to rule out metastatic disease prior to chemoradiation and brachytherapy
Surveillance
Neck/chest/abdomen/pelvis/groin PET/CT ± brain MRI (preferred) or Chest/abdomen/pelvis CT ± brain MRI

Abbreviations: MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PET/CT, positron emission tomography/computed tomography.

Table 7 Synoptic reporting CT for cervical cancer

Protocol:	
Patient instructions:	Patient is asked to void 30 minutes prior to the scan Serum creatinine to be in check, ideally <1.2 mg/dL, above which the eGFR is calculated. If it is >30 mL/min, full dose contrast can be safely injected. If <30 mL/min, decide on IV contrast injection on case-by-case basis
Contrast agent:	Oral: 750–1,000 mL of oral positive contrast agent for delineating bowel loops, starting at ~2 hours prior to the procedure IV: At the time of scan, ~80–120 mL of nonionic contrast is injected at the rate of 2 mL/sec. Iso-osmolar contrast agent used if eGFR is on the lower side
Scan area:	Dome of diaphragm to perineum
	Usually for multidetector CT, the section collimation is 2.5 mm, the table speed is 12.5 mm per rotation, and the reconstructed section width is 3–5 mm. Section thickness: 5mm. Isotropic multiplanar postprocessing reconstruction at 1 mm interval
Reformatting and contrast adjustment:	Sagittal reformats and optimal change of windowing should also be used for assessment of findings
Interpretation	
Cervical lesion:	Size: Dimension (if lesion is well appreciated) Uterine body involved or not—If yes, its extent of involvement. Associated hydrometra / hematometra
Locoregional involvement:	Vaginal wall involvement: Uninvolved/involved (If involved, Upper two-thirds / whole) Parametrial involvement: Involved/equivocal (CT is not the ideal modality for the assessment of medial parametrial involvement) If involved, then the extent of involvement Hydroureter: Absent/present (with/without hydronephrosis) Renal function: Symmetric uptake/delayed nephrogram (Optional excretory phase may be obtained) Bowel involvement Bladder involvement
Adenopathy:	Size: Short axis dimension Morphology: round / oval; regular margins / irregular; hilum preserved / lost; homogenous / heterogenous enhancement. Site : Locoregional / Metastatic Locoregional nodal sites: Perivisceral, internal iliac, external iliac, and common iliac sites Metastatic nodal sites: Para-aortic and inguinal nodes and other distant sites
Ovaries:	Normal/suspicious
Ascites:	Present/absent
Pleural effusion:	Present/absent
Peritoneum and omentum:	Involved/not involved
Other viscera:	Liver, gall bladder, spleen, pancreas, adrenals and lung base
Metastases:	Bone/viscera
	Any other incidental benign appearing or indeterminate finding

Abbreviations: eGFR, estimated glomerular filtration rate; IV, intravenous; CT, computed tomography.

Principles of Management

Management guidelines are broadly dependent on the stage of disease, and its presence as an in-situ versus invasive component. The choice of treatment depends upon stage of the disease, patient's performance status, and preference. In patients up to FIGO stage IB2 disease (with disease confined to cervix) radical surgery is the preferred modality of treatment, although definitive RT gives equivalent survival in these patients. In stage IA disease (with microscopic invasive carcinoma with less than 5 mm depth of invasion), cervical conization or extrafascial hysterectomy with or without pelvic lymphadenectomy is recommended. For stages IB1 and IB2, more radical surgery in the form of radical hysterectomy with bilateral pelvic lymphadenectomy is considered.[15] Adjuvant RT is indicated in patients with any two intermediate risk factors including deep cervical stromal invasion, lymphovascular stromal invasion, and tumor size more than 4 cm.[16] Adjuvant chemoradiotherapy with concurrent cisplatin is recommended in patients with any high-risk features including positive surgical margins, positive lymph nodes, or parametrial involvement.[17]

Neoadjuvant chemotherapy followed by surgery is not superior to concomitant chemoradiotherapy (CTRT) in stages

Table 8 Synoptic reporting MRI for cervical cancer

Protocol	
Patient instructions:	4 hours fasting, but water intake is encouraged prior to the scan Patient is asked to void 30 minutes prior to the scan Serum creatinine to be in check, ideally <1.2 mg/dL, above which the eGFR is calculated. Contrast enhanced scan can be safely performed for eGFR >30mL/min. Antiperistaltic medication (e.g., Buscopan) is recommended
Preparation:	For optimal reporting, instillation of per-vaginum sterile jelly is necessary
Sequences:	Dedicated oblique axial small FOV high-resolution T2W sequence. Dedicated oblique sagittal small FOV 24 cm high-resolution T2W sequence. Coronal T2W sequence, optional for small versus large FOV, but small FOV is preferred Large FOV T2W image in coronal plane to include kidneys for hydronephrosis Fat-saturated sequence for lower abdomen and pelvis Axial T1W sequence for screening upper abdomen. Diffusion-weighted imaging, with b value 600–800, optional FOV, but preferably small FOV Dynamic postcontrast screening is recommended in cases of uncertain diagnosis or equivocal parametrial extension. Precontrast followed by 4 to 5 runs of postcontrast imaging. (may be avoided in obviously large infiltrating diseases of advanced stage) Multiplanar postcontrast fat sat sequence
Interpretation	
Tumor description: Morphology descriptors	Exophytic vs. endophytic Location: Anterior cervical lip /posterior cervical lip /circumferential Dimension: Percentage involvement of stroma, i.e., >50% or <50% Signal intensity description: T2W, restricted diffusion, dynamic postcontrast enhancement characteristics Circumferential cervical hypointense stromal ring: Whether intact or involved, focally or circumferentially
Locoregional extent:	Uterine body involved or not—If yes, its extent of involvement Associated hematometra/hydrometra Vaginal forniceal space: Maintained/effaced/involved Vagina: Anterior/posterior; Upper two-thirds/upto inferior aspect Parametrium: Free/stranding/involved, seen as nodular enhancing soft tissue If parametrium involved, its lateral extent Hydroureter: Absent/present, without/with hydronephrosis Bowel wall: Uninvolved/involved Bladder wall: Uninvolved/bullous edema/involved
Adenopathy:	Size: Morphology: Site: Locoregional nodal sites: Perivisceral, internal iliac, external iliac, and common iliac sites Metastatic nodal sites: Para-aortic (nodes below the renal hilum/above the renal hilum) and inguinal nodes and other distant sites
Uterus:	Endometrial thickness Any other comment
Ovaries:	Normal/suspicious
Ascites:	Present/absent
Pleural effusion:	Present/absent
Peritoneum and omentum:	Involved/not involved
Other viscera:	Liver, gall bladder, spleen, pancreas, adrenals, and lung base
Metastases:	Bone/viscera
	Any other incidental benign appearing or indeterminate finding

Abbreviations: eGFR, estimated glomerular filtration rate; FOV, field of view; MRI, magnetic resonance imaging; T1W, T1-weighted.

IB2, IIA, and IIB.[18] CTRT is the standard of care for bulky IB-IVA. Individual patient data meta-analysis from 13 trials confirmed benefit of CTRT in comparison to RT alone. Hazard ratio for overall survival (OS) and disease-free survival (DFS) was 0.81 and 0.78, respectively, which translates into absolute survival benefit of 10% in FIGO stage I/II and 3% in stage III/IVA.[19] A phase III randomized study comparing concurrent chemoradiation versus radiation alone, in patients with

stage III B disease showed improvement in both DFS (44% to 52%) and OS (46–54%) in favor of concurrent chemoradiation.[18] Thus, CTRT remains the standard of care even in stage III disease. The most commonly used chemotherapy regimen is weekly cisplatin[19] 40 mg/m^2.

Integration of MRI in last two decades facilitated development of brachytherapy "adaptive target concept" that was based on response of tumor to external radiation.[20] Integration of target concept, simultaneous development of MRI compatible brachytherapy applicators for intracavitary–interstitial implants, and accurate tumor identification at brachytherapy has led to upward of 90% local control in patients with even very advanced cervical cancer. The results of multicentric international study of MR based brachytherapy (EMBRACE) have been recently reported and represent benchmark for cervical cancer brachytherapy.[21] Further adaptations of brachytherapy dose were performed in EMBRACE II.[21] Taken together these studies have recruited more than 2,800 patients worldwide. Though these were single arm large registration studies, a recent meta-analysis of more than 5,000 patients reported close to 11% improvement in 3-year DFS with integration of MR-based brachytherapy.[22] This highlights the role of RT as curative therapy for early cervical cancer with marked improvement in DFS in advanced disease.

For patients with metastatic or recurrent disease who are not candidates for surgical resection or RT, platinum and paclitaxel with or without bevacizumab are the preferred treatment. Cisplatin-based doublets demonstrate superiority over cisplatin monotherapy in terms of response rates and PFS, whereas addition of bevacizumab to doublet shows prolongation of OS (GOG240).[23,24] Japan Clinical Oncology Group(JCOG) demonstrated noninferiority with substitution of carboplatin AUC5 for cisplatin in JCOG0505(27).[9] Addition of pembrolizumab with first-line chemotherapy with or without bevacizumab improves both PFS and OS with similar benefit between overall population and in those with programmed death ligand 1 (PD-L1) combined positive score more than 1 or more than 10.[25]

There is little evidence to suggest that treatment in second line or later line setting improves OS compared with palliation alone. Single-agent carboplatin, paclitaxel, and topotecan are the most active agents in second-line setting. In PD-L1-positive cancers, single-agent pembrolizumab has shown favorable response rates in second-line setting.

An integrated multidisciplinary oncology team working towards increasing awareness and screening, improving accuracy of imaging and multimodal therapy for management of cervical cancers, bears a positive impact towards improvement in survival and quality of life.

Summary of Recommendations

- ♢ Imaging plays a vital role in assessing the extent of disease and staging of cervical cancer.
- ♢ In clinically early-stage disease, MRI, on the basis of estimation of tumor size, cervical stromal invasion, parametrial invasion, and nodal involvement can help triage patients for surgery versus RT.
- ♢ While hypoxic imaging can predict response, MR is fairly reliable in post-RT locoregional response assessment and detect early recurrence
- ♢ CECT or PET CECT-based RECIST 1.1 may be followed for distant metastatic response assessment.
- ♢ Stage and therapy-based surveillance imaging should be recommended.

Conflict of Interest
None.

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

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Abstract

The Prostate Carcinoma Guidelines Panel have formulated these guidelines to assist medical professionals in the evidence-based management of prostate cancer. These have been formulated by a panel consisting of Indian multidisciplinary group of radiologists, uro-oncologists, urologists, radiation oncologists, medical oncologists, and pathologists. These recommendations present the best evidence available to the clinicians; however, using these recommendations will not always result in the best outcome. They aid in decision making for individual patients; however, these will never replace clinical expertise when making treatment decisions. Taking personal values and preferences or individual circumstances of patients into account is necessary for final treatment decision. Guidelines are not mandatory and should not to be referred as a legal standard of care.

Keywords

- mpMRI prostate
- prostate cancer
- prostate cancer imaging guidelines
- prostate cancer imaging recommendations
- PSMAPETCT
- PSMAPETMRI

Introduction

The Prostate Carcinoma Guidelines Panel have formulated these guidelines to assist medical professionals in the evidence-based management of prostate cancer [PCa].

These guidelines present the best evidence available to the clinicians; however, using guideline these recommendations will not always result in the best outcome. They aid in decision making for individual patients; however, these will never replace clinical expertise when making treatment decisions. Taking personal values and preferences or individual circumstances of patients into account is necessary for final treatment decision. Guidelines are not mandatory and should not to be referred as a legal standard of care.

The Guidelines Panel consists of an Indian multidisciplinary group of radiologists, uro-oncologists, urologists, radiation oncologists, medical oncologists, and pathologists.

Risk Factors and Etiopathogenesis

PCa remains the second most common cancer in men and the fifth leading cause of death around the globe.[1] It may be

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asymptomatic at the early stages and can be very slow growing which may need only active surveillance. According to the GLOBOCAN 2020 data,[1] 1,414,259 new cases of prostate cancer were reported worldwide in 2020, causing 3,75,304 deaths, with higher prevalence in developed countries.

Family history and racial/ethnic background are associated with an increase incidence PCa.

Across the globe, incidence and mortality of PCa correlate with advanced age. The mean age at the time of diagnosis approximately is 66 years in most studies. In African-American men, the incidence rates are higher than in White men, and their mortality is approximately twice as that in White men.[2]

Elevated plasma levels of prostate-specific antigen (PSA more than 4 ng/mL), a glycoprotein normally expressed by prostate tissue forms the basis of the diagnosis in most patients. However, as elevated PSA levels can also be found in men without PCa, a tissue diagnosis by biopsy remains the current standard of care to confirm cancer.

Uncertainty still exists about the relation of diet, obesity, and use of some vitamins or minerals as the cause of prostate cancer.

Epidemiology and Clinical Presentation

Significant variation is seen in the incidence of prostate cancer across the regions and populations around the globe.[1] In 2020, 1,414,259 new cases of prostate cancer were registered worldwide, representing 7.3% of all cancers in men.[3] The age-standardized rate (ASR) was the highest in Oceania (443.5 per 100,000 people) and North America (397.9) followed by Europe (328.5). As compared to these developed countries, the Asian and African countries have low incidence (185.2 and 126.8, respectively) with incidence in India up to 95.7, the lowest incidence in Niger being 66.9.

Diet modifications and physical activity are important in prostate cancer development and progression. These are mainly related to the observed worldwide and ethnic differences in the incidence rates of prostate cancer.[4–6]

Prostate cancer incidence increases with age.[1] Though only 1 in 350 men under the age of 50 years will be diagnosed with prostate cancer,[7] the incidence rate increases up to 1 in every 52 men for ages 50 to 59 years. The incidence rate reaches 60% in men over the age of 65 years.[8]

Clinical presentation: At the early stage, many patients may be asymptomatic, often with an indolent course, who need minimal or even no treatment. In symptomatic patients, the presenting symptoms are difficulty with micturition, increased frequency, and nocturia, mimicking benign prostatic hypertrophy. PCa can also present with hematuria, hematospermia, or erectile dysfunction. In advanced stages, patients may present with severe urinary symptoms such as urinary retention and with weakness, back pain, and weight loss. Bony metastases is commonly present in metastatic disease.

Clinical/Diagnostic Work-Up

Digital rectal examination (DRE): PCas are most commonly located in the peripheral zone and easily detected if the tumor volume is more than 0.2 mL. Abnormal DRE remains the first indicator for the PCa (approximately 18% of cases being detected by DRE alone[9] and is an indication of biopsy).

Prostate-specific antigen (PSA): PSA is a serum marker specific to the prostate; however, it is not specific to PCa. Hence, it can be seen elevated in other non-malignant conditions such as benign prostatic hypertrophy (BPH) and prostatitis. PSA seems a better predictor of cancer than either DRE or transrectal ultrasonography (TRUS) as an independent variable. Yet there are no standards defined for measuring PSA.[10] It is a continuous parameter, with higher levels indicating greater likelihood of PCa. However, PCa can also be seen with PSA levels below 4 ng/mL.

In addition to these variables, PSA density (the level of serum PSA divided by the prostate volume) or PSA doubling time and free/total PSA ratio can be also assessed for evaluation of the disease, in clinical settings.

Risk Stratification

Risk stratification is an integral part of PCa treatment and should be performed before starting management.

Low-risk	Gleason score $\leq$ 6, PSA $\leq$ 10 and stage T1-T2a
Intermediate-risk	Gleason score 7, PSA $>$ 10–20 and stage T2b
High-risk	Gleason score 8 to 10, PSA $>$ 20 and stage T2c

Patients are stratified in low-risk, intermediate-risk, and high-risk depending on PSA values, T stage of the disease and Gleason score.[11]

Diagnostic Evaluation

Screening and Early Detection

Screening

Systematic examination of asymptomatic men (at risk) performed by health authorities is called screening, which is aimed at the reduction of mortality as well as maintaining the quality of life in PCa patients. Aggressive screening in USA showed decreased in mortality in PCa patients.[12]

The updated Cochrane review endorsed the following points[13]: Screening is associated with an increased diagnosis of PCa, detection of more localized disease and less detection of the advanced disease. However, no cancer specific survival benefit and overall survival benefit was seen because of screening.

Where screening is considered, a single PSA test is not enough according to the results of a randomized trial of PSA testing "CAP trial"[14]. In this trial, they concluded that single PSA screening intervention detected more number of low-risk PCa cases but had no significant effect on PCa mortality after a median follow-up of 10 years.

Recommendations for screening

	Recommendation	Level of Evidence	Strength of recommendation
1.1	Do not subject men to screening with PSA without counseling them on the potential risks and benefits.	3	Strong
1.2	Offer an individualized risk-adapted strategy for early detection to a well-informed man and a life-expectancy of at least 10 to 15 years.	3	Weak
1.3	Offer early PSA testing to well-informed men at elevated risk of having PCa in men > 50 years of age, men > 45 years of age, and a family history of PCa, men of African descent > 45 years of age, men carrying *BRCA2* mutations > 40 years of age.	2a	Strong
1.4	Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of 2 years for those initially at risk in men with a PSA level of > 1 ng/mL at 40 years of age, men with a PSA level of > 2 ng/mL at 60 years of age, Postpone follow-up to 8 years in those not at risk.	3	Weak
1.5	Stop early diagnosis of PCa based on life expectancy and performance status and in men who have a life-expectancy of < 15 years are unlikely to benefit.	3	Strong

Ultrasonography and Biopsy

The transabdominal USG has no defined role in detection of PCa, which cannot characterize the prostatic lesions adequately. Transrectal USG is also not accurate in prediction of an organ-confined disease as compared to DRE. It is commonly used in guidance of prostate biopsies. Alternatively, transperineal route can also be used for biopsy. PCa detection rates are almost similar using both the routes; however, according to a few studies, transperineal route requires more extensive local anesthesia and is associated with decreased infection rates.[15] Reliability of gray-scale TRUS for detection of PCa is very low;[16] however, recent innovations in sonography techniques such as color Doppler, elastography, and contrast-enhanced USG either alone or in various combinations can give satisfactory results in PCa diagnosis. The diagnostic yield of additional biopsies performed on hypoechoic lesions is not significant.[17]

The requirement of prostate biopsy depends on the findings of PSA levels, abnormal DRE or imaging (transrectal USG/MRI). Age of patient, various comorbidities, and therapeutic implications should also be noted and discussed with the patient before the procedure to reduce unnecessary biopsies.[18,19]

Multiparametric Magnetic Resonance imaging

Multiparametric magnetic resonance imaging (mpMRI) has good sensitivity for the detection and localization of ISUP grade > 2 cancers.[20] Recent Cochrane meta-analysis that compared mpMRI to template biopsies, mpMRI had a pooled sensitivity and specificity of 0.91 and 0.37, respectively, for ISUP grade > 2 cancers.[21] Similarly, for ISUP grade > 3 cancers, mpMRI pooled sensitivity and specificity were 0.95 and 0.35, respectively. In contrast, mpMRI is less sensitive in identifying ISUP grade 1 cancer. Targeting biopsies with prior mpMRI increases the detection rates of PCa with higher ISUP grades as compared to standard systematic biopsies in both the biopsy naïve patients and repeat biopsy patients. Many centers now use a combined approach of standard systematic biopsy along with mpMRI directed biopsy (MRTBx).

Repeat biopsy after previously negative biopsy:

Indications for repeat biopsy:

- Increasing and/or persistently elevated PSA.
- Suspicious DRE, 5–30% PCa risk.
- Atypical small acinar proliferation (such as atypical glands suspicious for cancer), 31–40% PCa risk on repeat biopsy[22,23];
- Extensive (multiple biopsy sites > 3) high-grade prostatic intraepithelial neoplasia (HGPIN), approximately 30% PCa risk[23,24];
- A few atypical glands immediately adjacent to high-grade prostatic intraepithelial neoplasia (PINATYP), approximately 50% PCa risk[25];
- Intraductal carcinoma as a solitary finding, > 90% risk of associated high-volume and high grade PCa[26];
- Positive mpMRI findings.

mpMRI Protocol:

We are currently using following protocol on 1.5 T Philips MRI machine.

Sr. No.	Name of sequence	FOV (Filed of view) in mm	Slice Thickness and interslice interval (in mm)	Matrix
1	Sagittal T2W (small FOV)	200	3/0	284 × 220
2	Oblique axial T2W (small FOV)	180	3/0.3	256 × 190

(*Continued*)

Sr. No.	Name of sequence	FOV (Filed of view) in mm	Slice Thickness and interslice interval (in mm)	Matrix
3	Oblique coronal T2W (small FOV)	180	3/0.3	256 × 190
4	Axial T1W (large FOV)	363	5/1.5	406 × 296
5	Axial T2W (large FOV)	363	5/1.5	406 × 296
6	Diffusion-weighted sequence (DWI) at 0, 500, and 800	364	5/1.5	127 × 125
7	Zoom DWI at 0, 800, and 1500	180	3/0.3	64 × 62
8	Dynamic post-contrast T1W sequence (8 phases) *(small FOV)	180	4/2	64 × 64
9	Axial postcontrast fat sat T1W (large FOV)	364	5/1.5	376 × 300
10	Oblique axial postcontrast fat sat T1W (small FOV)		3/0.3	200 × 156
11	Sagittal post-contrast fat sat T1W (small FOV)		3/0.0	208 × 150
12	Coronal post-contrast fat sat T1W (small FOV)		3/0.5	208 × 152

* Dynamic T1W postcontrast sequence starts at 10 seconds from contrast injection after a mask phase, each phase is obtained 15 seconds apart.

CT SCAN

Role of CT scan in imaging of PCa is limited to nodal and metastatic staging. Although it is not advocated in detection or primary staging of PCa, a few studies show that it has some role in detection of PCas.[27]

PET CT SCAN

PET CT scan has emerged as an important staging modality for primary as well as recurrent prostate cancer. Previously, NaF was used a radiotracer that showed a high sensitivity but low specificity. Recently, tracers such as choline, fluciclovine, and especially PSMA have shown increased detection for smaller metastatic lesions that are not easily seen on CT or MR imaging.[28] Clinical implications of these occult PET/CT detected disease may be beneficial to patients. Efforts are now targeted to define their natural history and response to treatment and an overall impact of metastasis-directed therapy detected by these investigations. In comparison, with the conventional staging approach, additional lymph nodal metastases and skeletal/visceral metastases were detected in 25% and 6% of patients, respectively.[29] Thus, PSMA PET/CT is cost-effective and can be considered as a standard modality compared to conventional imaging for initial staging of men with high-risk prostate cancer.[30]

PET MRI

After promising results from the PSMA PET CT, researchers have now added MRI to PET component that provides highly accurate morphological information to the functional information of PET. The first two PSMA agents for PET imaging were 18F-DCFBC and 68Ga-PSMA-11. Two other agents with theranostic capabilities, the chelator-based PSMA-617 and the PSMA inhibitor for imaging and therapy PSMA-I&T are also now used. Some second-generation 18F-labeled PSMA legends were also introduced to overcome the high blood-pool activity and low tumor-to-background ratios of 18F-DCFBC, viz.,18F-DCFPyL, and 18F-PSMA-1007 (most recent), which has very low urine clearance. The MRI component has high soft tissue resolution, hence can be used for accurate delineation of the lesion (local staging, i.e., T staging). In contrast, the PSMA PET component has a higher value in detection of the metastatic lymph nodes and other metastatic lesions (can be used in N staging and M staging). Thus, PSMA PET-MRI overcomes the shortcomings of each modality when used singly. Because of these reasons, it has got higher sensitivity (up to 76%) as compared to mpMRI and PET, when these modalities are used alone.[31]

Recommendations for PCa detections

Recommendations for all patients

	Recommendation	Level of evidence	Strength of recommendation
2.1.1	Systematic biopsy is an acceptable approach in case mpMRI is not available.	3	Strong
	Do not use multiparametric magnetic resonance imaging (mpMRI) as an initial screening tool.	3	Strong
2.1.3.	Adhere to PI-RADS guidelines for mpMRI acquisition and interpretation and evaluate mpMRI results in multidisciplinary meetings with pathological feedback.	3	Strong
Recommendations in biopsy naïve patients			
2.2.1	2.2.1. Perform mpMRI before prostate biopsy.	1a	Strong

(*Continued*)

(*Continued*)

	Recommendation	Level of evidence	Strength of recommendation
2.2.2	2.2.2. When mpMRI is positive (PI-RADS > 3), combine targeted and systematic biopsy.	2a	Strong
2.2.3	2.2.3. When mpMRI is negative (PI-RADS < 2), and clinical suspicion of prostate cancer is low, omit biopsy based on shared decision making with the patient.	2a	Weak
Recommendations in patients with prior negative biopsy:			
2.3.1	Perform mpMRI before prostate biopsy.	1a	Strong
2.3.2	When mpMRI is positive (i.e., PI-RADS > 3), perform targeted biopsy only.	2a	Weak
2.3.3	When mpMRI is negative (i.e., PI-RADS < 2), and clinical suspicion of prostate cancer is high, perform systematic biopsy based on shared decision making with the patient.	2a	Strong

Staging: The extent of PCa is evaluated by DRE and PSA, along with mpMRI, bone scanning and CT scan.

Stage: Can be clinical (cT) or pathological (pT)T staging as per the AJCC 8th cancer staging edition.[32] Complete clinical and pathological T staging is given in ►**Table 1** in detail:

For T staging, only DRE findings are taken into account as of now. TRUS has no value in prediction of an organ-confined disease. Though mpMRI has good specificity for detection of T3 tumors, it is still not recommended for staging of the disease, in view of low sensitivity.[33] However, it can be used for planning of disease treatment.

N Stage: The regional nodes are assessed in N staging, which are defined as the nodes confined to the true pelvis (pelvic nodes below the bifurcation of the common iliac arteries). Detailed N staging in ►**Table 2**.

Abdominopelvic CT scan and MRI have been tried for nodal staging in PCa patients, which consider the size of the nodes to label them malignant (short axis more than 8 mm in the pelvic cavity and more than 10 mm outside the pelvic cavity). However, these techniques have very low sensitivity.[34] Choline PET CT also has low sensitivity.[35] According to a few studies, PSMA PET/CT has higher sensitivity for LN metastases as compared to mpMRI, abdominal contrast-enhanced CT or choline PET/CT.[36]

Various imaging modalities are used for M staging including 99mTc-Bone labelled bone scan, Fluoride PET and PET/CT, choline PET/CT, whole body MRI and PSMA PET CT, amongst these PSMA PET CT outperforms the other modalities with sensitivity (33-99%) and specificity (> 90 %).[37] Detailed M staging is shown in ►**Table 3**.

Table 1 T Staging(Clinical and Pathological)

Clinical T staging (cT):		
	Tx	Primary tumour cannot be assessed
		No evidence of primary tumour
T1		A clinically inapparent tumour that is not palpable
	T1a	Tumour incidental histologic finding in 5% or less of tissue resected
	T1b	Tumour incidental histologic finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy found in one or both sides, but not palpable
T2		Tumour is palpable and confined within the prostate
	T2a	Tumour involves one-half of one side or less
	T2b	Tumour involves more than one-half of one side but not both sides
	T2c	Tumour involves both sides
T3		Extraprostatic tumour that is not fixed or does not invade adjacent structures
	T3a	Extraprostatic extension (unilateral or bilateral)
	T3b	Tumour invades seminal vesicle(s)
T4		

Table 1 (*Continued*)

Clinical T staging (cT):		
		Tumour is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Pathological T staging(pT):		
T2		Organ confined.
T3		Extraprostatic extension.
	T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of the bladder neck
	T3b	Tumour invades seminal vesicle(s)
T4		**T4:** Tumour is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Table 2 N Staging

Nx	Regional nodes were not assessed.
N0	No positive regional nodes.
N1	Metastases in regional node(s).

Note: A node along the common iliac arteries would be considered as M1a.

Table 3 M Staging

M0		No distant metastasis.
M1		Distant metastasis
	M1a	Metastasis to non-regional lymph node(s).
	M1b	Metastasis to Bone(s).
	M1c	Other site(s) with or without bone disease e.g., lungs, liver, brain

	Recommendation	Level of evidence	Strength of recommendation
3.1	Any risk group staging: use pre-biopsy mpMRI for local staging information.	2a	Strong
3.2	Low-risk localized disease. Do not use additional imaging for staging purposes.	2a	Strong

(*Continued*)

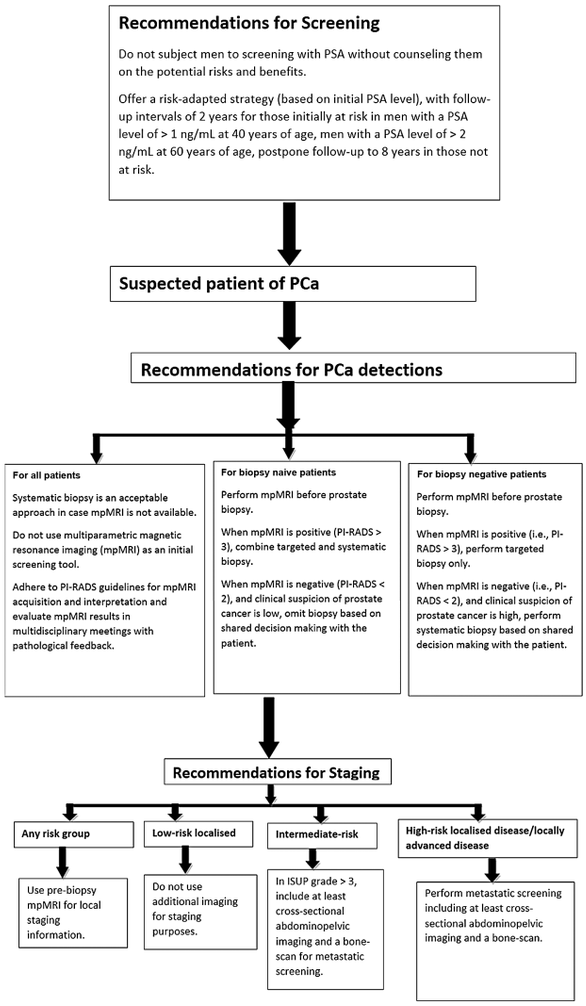
(*Continued*)

	Recommendation	Level of evidence	Strength of recommendation
3.3	Intermediate-risk disease. In ISUP grade > 3, include at least cross-sectional abdomino-pelvic imaging and a bone-scan for metastatic screening.	2a	Weak
3.4	High-risk localized disease/locally advanced disease. Perform metastatic screening including at least cross-sectional abdomino-pelvic imaging and a bone-scan.	2a	Strong

Guidelines for staging of prostate cancer:

Follow Up: Imaging techniques are not recommended in routine follow-up of localized PCa as long as the PSA is not rising. Imaging is only suggested in patients for whom the findings will affect treatment decisions, either in case of biochemical recurrence or in symptomatic patients. PSMA PET CT is better than the other modalities such as TRUS, CT scan, MRI, or choline PET CT as imaging of choice in such patients.[38]

To conclude, we can follow the flow chart for staging, diagnosis, and management of PCa



Conflict of Interest
None declared.

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Imaging Recommendations for Diagnosis, Staging, and Management of Pediatric Solid Tumors

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Abstract

Paediatric extra-cranial solid tumours are one of the common causes for paediatric malignancies. Lack of appropriate imaging at presentation, staging and for follow-up is a major challenge for paediatric solid tumours. We have reviewed the paediatric solid tumour imaging protocols suggested by the major oncological societies/groups around the world (mainly the SIOP – Society International Pediatric Oncology, and the COG – Children's Oncology Group). We have adapted some of those protocols to develop imaging recommendations for the diagnosis, staging and management of extra-cranial solid tumours based on the treatment protocols followed in India.

Keywords
- hepatoblastoma
- imaging guidelines
- neuroblastoma
- pediatric oncology
- pediatric solid tumors
- Wilm's tumor

Childhood cancer accounts for nearly 1% of all cancers diagnosed worldwide across all age groups.[1,2] Great improvement has been made in the last few decades in the treatment of childhood cancers, achieving successful treatment in up to 80% of cases.[1] This dramatic success is a result of decades of collaborative effort by various study groups across the globe. Collaborative consensus guidelines have been developed by these groups for imaging and management of pediatric tumors.

This article aims to provide imaging guidelines for the common pediatric extracranial solid tumors based on the recommendations of various pediatric groups across the world and treatment protocols followed in India.

Clinical Presentation

Pediatric tumors present with nonspecific symptoms and requires high index of suspicion to investigate for the possibility of cancer. Pediatric abdominal malignancies present most commonly as abdominal distension or a palpable abdominal mass. It may be an incidentally detected mass or present with abdominal pain, hematuria, features of

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bowel or bladder obstruction, or may present with constitutional symptoms such as fatigue, loss of appetite or fever. Renal and suprarenal tumors may present with hypertension or paraneoplastic symptoms such as opsoclonus-myoclonus.[3,4] Occasionally, they may present with precocious puberty/virilization, more so in adreno-cortical carcinomas, and rarely in hepatoblastoma and germ cell tumors.[5]

Soft tissue tumors may present with swelling or bone pain. Spinal extension of the tumor like in neuroblastoma or germ cell tumors may cause focal neurological deficits or bowel/bladder related symptoms.

Imaging Guidelines for Pediatric Abdominal Masses

Ultrasound

Ultrasound is the ideal screening tool in cases of suspected abdominal mass in children as there is no ionizing radiation or sedation involved.

Role of ultrasound is to confirm the presence of mass and determine its organ of origin. Further investigations would be based on the ultrasound findings (►**Fig. 1**).

Relook ultrasound after cross sectional study, along with Doppler might be useful to evaluate subtle vascular invasion or thrombosis in cases of doubt, e.g., tumor thrombus in hepatoblastoma or Wilm's tumor. It is a problem solving tool in cases of complex findings on cross-sectional imaging, e.g., suspected focal lesions in hepatoblastomas and lesions in contralateral kidney in cases of Wilm's tumor. In cases of suspected tumor rupture, ultrasound has a role in evaluating the tumor margin integrity and detecting echoes in the abdominal free fluid. USG-guided biopsy of solid pediatric tumors is a widely acceptable technique and again avoids unnecessary radiation (compared with CT scan).

Magnetic Resonance Imaging

MRI is the modality of choice for pediatric abdominal masses.[6] It provides better soft tissue contrast and does not expose to any ionizing radiation. However, sedation risk should be considered against radiation risk and CT scan can be performed for cases with contraindication to MRI or difficult anesthesia or no availability.[7] MRI field strength of 1.5 to 3 T and acquisition with the smallest suitable coil (e.g., head coil or flexible phased-array body coil) is recommended with breath holding and gated sequences. Study may be performed under sedation or general anesthesia if needed, depending on the age and weight of child.

CT Scan

A contrast-enhanced CT scan for hepatic or renal masses is the alternative imaging modality to MRI as per institute preference, or if MRI is contraindicated or anesthesia is not available. Care should be taken to use the lowest possible

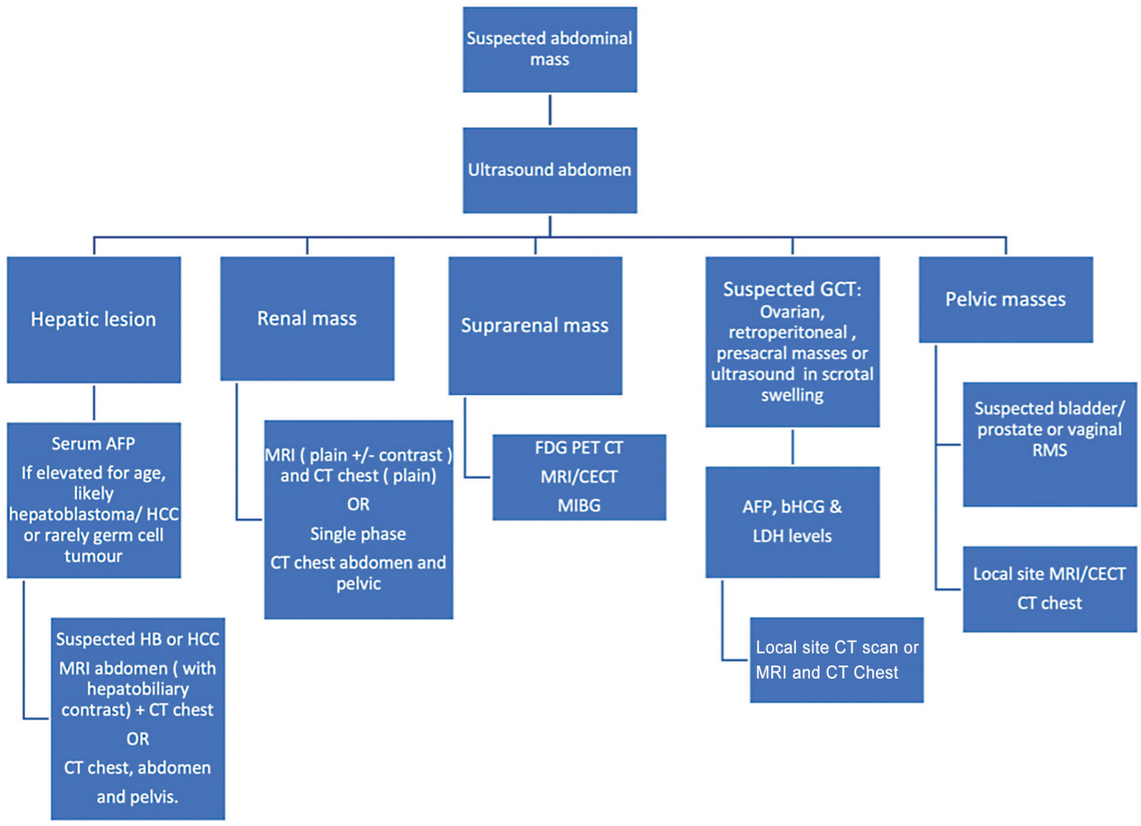

Fig. 1 Diagnostic pathways based on ultrasound findings.

radiation dose with adequate image quality. Single-phase imaging is recommended if sufficient to provide necessary information. Just a non-contrast CT scan is usually avoided. The imaging protocols are further tailored as per the organ of origin of the mass and will be discussed subsequently.

A CT chest is a mandatory diagnostic procedure for all patients of liver and renal masses and protocol is described in the respective sections.

Pediatric Liver Tumors

Pediatric liver tumors are rare and ~two-thirds of them are malignant, hepatoblastoma being the most common, (~37%) followed by hepatocellular carcinoma (HCC; 21%), and sarcoma (8%).[8] Benign tumors such as hemangioma, hemangioendothelioma, focal nodular hyperplasia, and mesenchymal hamartomas form the rest of the spectrum.

Risk Factors, Etiopathogenesis, and Clinical Presentation

Hepatoblastoma are mostly sporadic, but may be associated with genetic abnormalities and familial cancer syndromes, such as the Beckwith–Wiedemann syndrome and familial adenomatous polyposis.[9] Premature birth and very low birth weight are known to be associated with increased incidence of hepatoblastoma.[10]

The most common presenting symptom is abdominal distension or a palpable abdominal mass. It may be associated with non-specific symptoms such as abdominal discomfort, fatigue, and loss of appetite, and the child may appear pale due to anemia, especially in HCC and liver sarcomas

Imaging Guidelines for Pediatric Liver Lesions

Ultrasonography

USG is the ideal screening modality for suspected liver mass/abdominal lump.[6,11]

Contrast-enhanced USG can be performed for the initial assessment of lesion to help classify as benign or malignant. USG may be useful to evaluate hepatic veins, IVC, portal vein, and focal liver lesions and for suspected cases of tumor rupture.

Magnetic Resonance Imaging

Both MRI and CECT are the modality of choice for pediatric liver masses such as hepatoblastoma and HCC.

Respiratory gated sequences should be used. Unlike adults, breath holding is usually not possible for hepatoblastoma evaluation as these scans are generally performed under sedation or GA. The recommended MRI sequences are presented in ►**Table 1**.

MRI with contrast is also the modality of choice for post chemotherapy response evaluation, detection of metastatic liver lesions in non-hepatic primary tumor and in the follow up of patient with resected tumor.

CT Scan

Contrast-enhanced CT scan is the alternative imaging modality of choice as per the institute preference, or if there is contraindication for MRI, anesthesia is not available for MRI or separate anesthesia is needed for CT chest and MRI.

A single-sequence baseline CECT abdomen can be performed that includes both arterial and venous phases (►**Table 2**). Alternatively, dual-phase CT with late arterial phase for abdomen and portal-venous phase for the

Table 1 Imaging recommendations for pediatric abdominal tumors

MRI sequence	Plane	Thickness	Sequence coverage
T2 STIR	Coronal	5 mm	Above diaphragm to below iliac crests
T1 TSE FS	Coronal	2 mm	Above diaphragm to below iliac crests
T1 TSE FS	Axial	2 mm	Above diaphragm to below iliac crests
T2W volume sequence (SPACE/VISTA)	Coronal	0.9 mm–1.1 mm	Above diaphragm to below iliac crests
T2W STIR	Axial	5 mm	To include area of interest
T1W IP and OP	Axial	5 mm	To include area of interest
DWI/ADC (b = 0,100,500,1000)	Axial	6 mm	To include area of interest
Post-contrast			
T1W FS immediate (VIBE)	Axial	2 mm	Above diaphragm to below iliac crests
T1W FS 30 s arterial (VIBE)	Axial	2 mm	Above diaphragm to below iliac crests
T1W FS 60 s venous (VIBE)	Axial	2 mm	Above diaphragm to below iliac crests
T1W FS 2 min (VIBE)	Axial	2 mm	Above diaphragm to below iliac crests
T1W FS 5 min (VIBE)	Axial	2 mm	Above diaphragm to below iliac crests
T1W FS 10 min (VIBE)	Axial	2 mm	Above diaphragm to below iliac crests
T1W TSE FS	Axial	5 mm	Above diaphragm to below iliac crests
T1W FS 20 min (VIBE)	Coronal	2 mm	Above diaphragm to below iliac crests
T1W FS 25 min (vibe)	Axial	2 mm	Above diaphragm to below iliac crests

Note: Please note the number of slices, field of view, and TR/TE for the sequences will be variable depending on if it is a young child/old child

Table 2 Single phase CECT abdomen protocol for pediatric abdominal tumors

Imaging recommendation	Protocol	Contrast dose	Reconstructions
CT Abdomen ± Chest	-To include lung apices to lesser trochanter -Inject two-thirds of contrast bolus @ 0.5 mL per sec and one-third @ 1 mL per second -Scan after 10 seconds post injection Slice thickness – 0.6 mm Increment – 0.6 mm Pitch – 0	2 mL/kg (dose recommendations for Iohexol 300)*	Lung window: - Axial 1 mm - Cor 3 mm - Sag 3 mm Soft tissue window (chest and abdomen): - Axial 1 mm - Cor 3 mm - Sag 3 mm Bone window: - Cor 2 mm - Sag 2 mm

*Contrast type and dose used can be variable as per local department policies.

abdomen and pelvis should be performed in the evaluation of suspected hepatoblastoma. A triphasic CT with an additional delayed phase can be performed for suspected HCC. A CT scan of the chest is recommended in all patients of hepatoblastoma for the evaluation of lung metastasis.

Intervention

Recommendations for biopsy: Serum α fetoprotein (AFP) level is the most important clinical tumor marker for hepatoblastoma and is elevated in 90% of cases. Biopsy is not mandatory in cases with elevated serum AFP levels, and when imaging features are in favor of hepatoblastoma. In cases with uncertain diagnosis, low AFP levels or age of the patient < 6 month or > 3 years, a biopsy can be performed after a multidisciplinary discussion.

Reporting

The PRETEXT staging system should be used as a consensus classification for pre-treatment extent of pediatric liver tumors. Each PRETEXT annotation factor should be evaluated during reporting as the presence of any of the annotation factors upgrades the tumor from standard risk to high risk and can change the chemotherapy regime. The imaging reassessed after chemotherapy should be classified using the POST-TEXT staging system.[11] The future liver remnant (FLR) should be considered before surgery to avoid decompensation in the post-operative period.

Management

Hepatoblastoma: The tumor should be classified as high risk or standard risk based on the risk stratification system followed by the institution. Upfront surgery can be performed in cases such as PRETEXT 1 and small PRETEXT 2 tumors. Neoadjuvant chemotherapy is needed in cases with high tumor burden followed by complete surgical resection.

Liver transplant is indicated in the PRETEXT IV multifocal/-solitary POST-TEXT IV/portal vein involvement/all three hepatic veins involved/central hepatoblastomas with insufficient tumor regression/unsuccessful resection/recurrence cases.[12]

HCC: Only 20% of pediatric HCC are upfront resectable. Patients with upfront unresectable HCC are treated with neoadjuvant chemotherapy on the same lines as hepatoblastoma and reassessed for surgery.

Pediatric Renal Tumors

Introduction and Epidemiology

Wilm's tumor is by far the most common renal tumor of childhood, comprising up to 90% of all renal masses in children.[13] Children between the age of 1 and 5 years are the most commonly affected, and the peak incidence is at 3 years. Wilm's tumor is extremely uncommon after the age of 15 years. Bilateral Wilm's tumor are seen in up to 5 to 8% of patients.[14]

Risk Factors, Etiopathogenesis, and Clinical Presentation

Majority of the Wilms tumor are sporadic, but 10% may be associated with genetic abnormalities such as aniridia, genito-urinary defects, hemihypertrophy or syndromes such as WAGR (Wilm's tumor, aniridia, genito-urinary abnormalities and mental retardation/intellectual disability) syndrome, Denys–Drash syndrome, and Beckwith-Wiedemann. Mutation of the Wilms Tumor 1 gene (*WT1*), on the short arm of chromosome 11 (11p13) are associated with congenital anomalies.[15]

Imaging Guidelines for Pediatric Renal Lesion

USG is usually the first imaging modality that confirms the renal origin of the suspected abdominal mass. Cross-sectional imaging (CT/MRI) is needed for further characterization and determination of the extent as well as for local staging (►**Supplementary Table S1,** available online only). Evaluating the other kidney is of paramount importance as it upstages the disease and also rules out congenital anomalies that affect the management. USG Doppler in addition to cross-sectional imaging may help in the evaluation of IVC and renal vein thrombus.

Cross-sectional study for further evaluation (►**Supplementary Table S1,** available online only). As per the institute, preference could be

1. MRI of the abdomen with CT scan of the chest
   OR
2. Contrast-enhanced CT scan of the chest, abdomen, and pelvis

MRI Abdomen

Contrast MRI of the abdomen is preferred on a MRI field strength of 1.5 or 3 Tesla. Recommended MRI sequences (check the general abdominal MRI protocol) are large FOV STIR coronal and axial sequences for an overview of the abdomen. T2 non-fat saturated high-resolution sequence for both the kidneys, the name for it differs between different vendors (SPACE/VISTA). Pre-contrast axial T1W sequence. Diffusion-weighted images should be included with at least three b-values (b = 0, b = 500, and b = 1000). Post contrast sequences should include multiple contrast phases to cover arterial, venous, and delayed phases. MRI is the modality of choice to identify nephrogenic rests, which are better appreciated on post contrast images in the background of enhancing parenchyma and also seen well on DWI as areas of restricted diffusion.

CT Scan

CT scan of the abdomen and pelvis is still the preferred modality in many institutes. A single post contrast acquisition in the portal-venous phase should be performed for tumor assessment. CT scan of the chest is also mandatory. A plain CT chest is sufficient if MRI of the abdomen is performed; however, contrast CT chest is recommended if an IVC tumor thrombus is suspected. However, if contrast-enhanced CT scan of the abdomen and pelvis is the cross-sectional diagnostic procedure performed, a contrast-enhanced CT chest should be performed in the same setting.

Management of Pediatric Renal Tumors

The management of pediatric malignant renal masses and timing of surgery varies in different groups. In India, the renal tumor size is usually large at presentation. A customized approach is recommended based on the baseline imaging considering the risk of rupture or incomplete resection if upfront surgery is performed as described in ►**Fig. 2**.[16] Biopsy is recommended before starting chemotherapy if upfront surgery is not possible.

Radical nephroureterectomy and lymph node sampling is the surgical procedure of choice[17] Clearance of the thrombus, if present, is performed and either cavotomy or partial cavectomy may be required depending on the extent of tumor thrombus.[18] As Wilm's tumor is highly chemo-sensitive, post-operative chemotherapy is recommended for every patient, and the dosage regimen is decided based on the histology and tumor stage (►**Supplementary Table S2**, available online only). Except for stage 1 and 2 tumors with favorable histology, post-operative radiotherapy is indicated for primary tumor bed and metastatic disease.[16,19]

Upfront surgery is contraindicated in bilateral renal disease and in cases with solitary or horseshoe kidney.[16,20] For patients with bilateral Wilm's tumors, neoadjuvant chemotherapy is initiated, followed by delayed surgery in the form of bilateral partial nephrectomy or total nephrectomy on the worse side and partial nephrectomy on the opposite side. Patients with tumor spillage/rupture, or

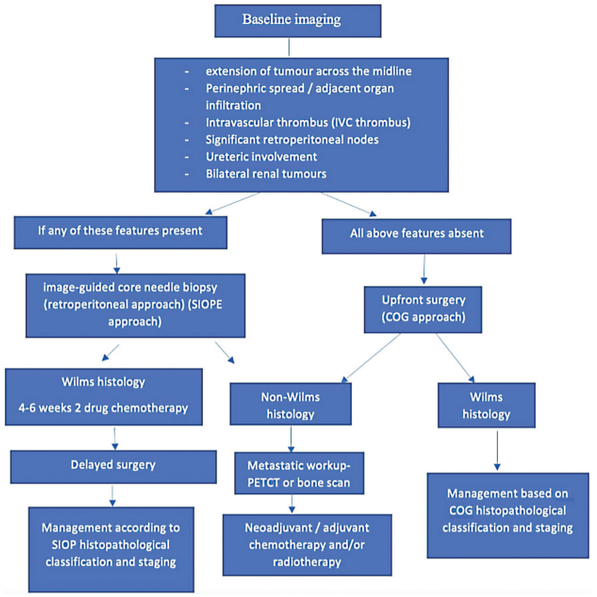

Fig. 2 Guidelines for the imaging and management of pediatric renal tumors.

regional lymph node metastasis are upstaged to stage III, and should receive abdominal radiotherapy and appropriate chemotherapy.[19,21]

Follow-up of patients: Done with USG of the abdomen and pelvis along with chest radiograph (►**Supplementary Table S2**, available online only).[11]

Extracranial Germ Cell Tumors (Pediatric)

Malignant germ cell tumors (GCT) account for 3% of pediatric cancer with bimodal age distribution.[22,23] Sites are divided as intracranial or extracranial, the later as gonadal and extragonadal. The extragonadal sites comprise sacrococcygeal, mediastinal, retroperitoneal, and other para-axial locations. Histologically, the germ cell tumors are classified as germinoma (dysgerminoma and seminoma), and non-germinomatous tumors such as endodermal sinus (yolk sac tumor), embryonal carcinoma and choriocarcinoma, or mixed type where more than one histology co-exist.

Risk Factors, Etiopathogenesis, and Clinical Presentation

Cryptorchidism and gonadal dysgenesis are associated with an increased risk of the development of gonadal GCT.[24] Some GCTs are more frequently seen with sex-linked chromosomal disorders; mediastinal GCT in Klinefelter's syndrome, germinomas in Turner's syndrome, and Swyer's syndrome.

Clinical features are variable and the presentation depends on the site of the extracranial GCT.[24] Sacrococcygeal GCT usually present as an external palpable mass in perinatal period. Testicular GCT may present as a painless swelling. Ovarian and abdominal or retroperitoneal GCT present with gradual abdominal distension and discomfort. Rarely ovarian GCT may present as acute abdomen due to torsion, rupture, or intralesional hemorrhage. Mediastinal GCT causes

symptoms due to mass effects such as airway compression, superior vena cava obstruction, or heart failure.

Diagnostic Work-up of Germ Cell Tumors

Tumor markers important for the diagnosis of GCT are α fetoprotein (aFP) secreted by yolk sac tumors and β human chorionic gonadotropin (b-hCG) secreted by choriocarcinoma. LDH is a non-specific marker of tumor burden.[25] The imaging recommended at baseline and for follow-up is summarized in ►**Supplementary Table S3**, available online only.

USG

USG is the modality of choice for the evaluation of suspected testicular pathology. Trans-scrotal USG using a linear high-frequency probe has more than 90% sensitivity and specificity in detection of testicular malignancies. In adjunct to gray scale and color Doppler, elastography provides an added value.[26] USG is usually the initial imaging modality for abdominal and pelvic GCT.

Cross-sectional Imaging

Primary site evaluation can be performed with CT scan or MRI based on the site involved and local institutional policy.

CT Scan

Contrast-enhanced single venous phase CT scan of the chest, abdomen, and pelvis is suggested for initial staging of abdominal GCT.[25,27] It is a sensitive modality for assessing retroperitoneal nodes. Noncontrast CT scan of the chest is recommended for the evaluation of lung metastasis

MRI Scan

MRI is used as an adjunct tool to USG, in cases of testicular mass with diagnostic dilemma on ultrasound. MRI abdomen and pelvis may be used instead of CT for both baseline evaluation and post treatment reassessment. MRI may particularly be used for initial workup in patients with deranged renal profile or in cases with suspicious intraspinal extension.

Contrast CT or MRI of the head should be performed if brain metastasis is suspected and in all patients with metastatic choriocarcinoma.

Recommendations for Biopsy: Biopsy is performed if AFP is not elevated and neoadjuvant chemotherapy is planned. Biopsy is not recommended for upfront resection or in testicular tumors where high orchidectomy is planned. Biopsy is performed when tumor markers are normal and/or there is a clinicoradiological mismatch.[27]

Management

A multi-modality customized strategy is needed for the treatment of GCT depending on the site, stage, and tumor biology. The COG staging for testicular, ovarian, and extragonadal germ cell tumors is recommended. GCTs are stratified into low-, intermediate-, and high-risk categories.

Surgery is the mainstay of management and first treatment option if feasible. A biopsy with neoadjuvant chemotherapy is otherwise recommended.

Neuroblastoma

Neuroblastoma (NB) is a neuroectodermal tumor arising from the sympathetic ganglion cells and is the commonest extracranial solid tumor in children.[28] This tumor commonly arises in the adrenal gland and can also occur at multiple locations including the extraadrenal abdomen, thorax, neck, and pelvis along the course of sympathetic nervous system.[29] Patients usually present with symptoms caused due to its mass effect on the surrounding organs, mostly presenting as a large abdominal mass.

Imaging Guidelines and Principles of Management

The treatment and outcome of NB are dependent on risk assessment and stage of the disease. The international Neuroblastoma Risk Group (INRG) task force puts forth a preoperative staging called International Neuroblastoma Risk Group Staging System (INRGSS), which is dependent on cross-sectional imaging (CECT or MRI) of the tumor site using Imaging defined risk factors (IDRF) (►**Supplementary Tables S4** and **S5**, available online only). A metastatic workup includes an iodine-labeled MIBG scan (radionuclide 123/124 or 131 iodine is used; however, in India, only 131 iodine is available) to look for sites of metastatic disease, especially bone lesions, a bone marrow biopsy, and aspirate for marrow disease.[29,30] The IDRFs on cross-sectional imaging help categorize the patients into L1 (non-infiltrative/operable tumor) or L2 (infiltrative or disease-encasing important structures) (►**Supplementary Table S6**, available online only).[29] Combining the outcome of these tests with other pathological and molecular criteria, and age of the patient help make decisions for management plan.

Data are emerging for the potential role of FDG PET-CT in the evaluation of neuroblastoma. In the Indian set-up, due to the unavailability of I-123 for MIBG scans, I-131 MIBG is performed. For the MIBG non-avid NB lesions, PET-CT is preferred modality for metastatic work-up. The utility of PET-CT for all NB patients work-up is debatable as there are some studies that have shown higher sensitivity of PET-CT compared with I-123 MIBG scans for stage 1 or 2 disease, but MIBG has performed better for higher stages of NB.[31]

Patients are treated with surgery alone in L1, low-risk disease or initially with chemotherapy followed by surgery, which could be a complete resection or an incomplete resection in patients with intermediate risk disease (patients having an unfavorable histology or infantile age group with metastasis receiving additional cycles of chemotherapy). Patients with high-risk neuroblastoma undergo bone marrow transplant after initial intensive chemotherapy and

surgery followed by radiotherapy and administration of differentiation agents and immunotherapy if available.

MRI/CT and MIBG scan along with bone marrow biopsy are done pre-surgically to look for residual disease, as this may alter the management of the disease.

Rhabdomyosarcoma

Introduction

Rhabdomyosarcoma (RMS) is the most common childhood soft tissue sarcoma and accounts for 3 to 5% of all pediatric malignancies. It is the third most common soft tissue tumor in children after neuroblastoma and Wilm's tumor.[32] RMS in children has two main histological subtypes, embryonal and alveolar. Further refinement of prognosis has occurred over the years with the incorporation of molecular fusion status for PAX 3/7-FOXO1 with fusion-positive tumors faring worse than fusion-negative ones. The embryonal type (nearly 75% of RMS cases), which is mostly fusion negative, is more common in younger children (<10 years of age), has better prognosis, and occurs in the head and neck region, followed by genitourinary tract and retroperitoneum. The alveolar variant, which is usually fusion positive, is the more aggressive type (~16% of RMS cases) and commonly occurs in the trunk and extremities.

Risk Factors and Etiopathogenesis and Clinical Presentation

There are no clear risk factors for RMS. Higher risk of developing RMS has been shown in children who have the following rare, inherited conditions: Li-Fraumeni syndrome, Beckwith–Wiedemann syndrome, neurofibromatosis, DICER 1, cardio-facio-cutaneous syndrome, Costello syndrome.[33]

There are no clear signs or symptoms for RMS and the presentation is largely dependent on the location of the lesion. RMS is known to have metastasis at presentation in 15 to 20% of cases, and the common sites for metastasis are lungs, bone marrow, bones, and distant lymph nodes.[34] Tumor biopsy is routinely performed as part of the main tumor work-up and at least one bone marrow aspirate and trephine performed for evaluating bone marrow involvement. The metastatic work-up includes lymph node biopsy, bilateral bone marrow aspirates, and CSF examination when LN, bone marrow, or neurological metastasis is suspected.

The RMS cases are risk stratified into low-risk, intermediate-risk, high-risk or very high-risk category based on age, tumor size, regional nodal status, tumor site, histology, PAX-FOX01 status, and Intergroup Rhabdomyosarcoma Study (IRS) post-surgical stage. Treatment for RMS cases is multimodality and in low/intermediate risk categories, the approach is chemotherapy in combination with radiotherapy and/or surgery with additional maintenance chemotherapy in high risk cases. Localized radiotherapy for metastatic disease can be used. In spite of recent advancements, multicenter trials and significantly improved treatment protocols, the 5-year overall survival for pediatric RMS stands at 75% for cases with localized disease, dropping to just 30% for cases with metastatic disease.[35,36]

Imaging Guidelines

Imaging the primary tumor should include loco-regional lymph node sites and also cover the regional extent of the tumor including the neuro-vascular structures. Evaluation for metastasis should include chest CT scan and bone scan or PET-CT for complete staging. Complete imaging and staging should be performed before biopsy is performed. All the imaging should be planned and reported by a pediatric radiologist with oncology experience and a nuclear medicine physician for hybrid imaging. Imaging reports should clearly describe the lesion location, size, lesion characteristics, extent and status of surrounding structures including regional lymph nodes.

MRI

MRI is the imaging modality of choice for both initial imaging of the tumor and subsequent follow-up examinations (►**Table 3**). The MRI protocol should include DWI/ADC and post-contrast imaging. Lesions with diffusion restriction and lower ADC values have shown to correlate with poor outcome and higher incidence of recurrence.[37] Post-contrast

Table 3 MRI imaging protocol recommendations for pediatric rhabdomyosarcoma

MRI sequence	Plane	Thickness	Sequence coverage
T2 STIR	Sag	5 mm	Pelvic lesion only (below liver to symphysis pubis)
T1 TSE	Axial	5 mm	Above diaphragm to below symphysis pubis
T1 TSE FS	Axial	2 mm	Above diaphragm to below symphysis pubis
T2W volume sequence (SPACE/VISTA)	Coronal	0.9 mm–1.1 mm	Above diaphragm to below symphysis pubis
T2W STIR	Axial	5 mm	To include area of interest
DWI/ADC (b = 0,100,500,1000)	Axial	6 mm	To include area of interest
Post-contrast			
T1W FS (VIBE) 1	Axial	2 mm	Above diaphragm to below symphysis pubis
T1W FS (VIBE)	Coronal/Sag	2 mm	Above diaphragm to below symphysis pubis
T1W FS (VIBE) 2	Axial	2 mm	Above diaphragm to below symphysis pubis

Note: Please note, the number of slices, field of view and TR/TE for the sequences will be variable depending on if it is a young child/old child.

tumor enhancement helps to map tumor response and also study neurovascular spread (for head and neck RMS). The MRI field of view should include areas of loco-regional lymph nodes.

CT Scan

Only in circumstances where MRI cannot be performed for the primary tumor site, a contrast CT scan (ideally single phase) should be done (►**Table 2**). A single-phase contrast CT scan is sufficient to evaluate both the soft tissue and bones. Intravenous contrast medium should be given at a dose of 2 mL/kg patient body weight followed by saline bolus, and images should be acquired at 65 to 70 seconds post-injection. CT can be done in addition to MRI to evaluate for skull base involvement or to look for bone erosions. Metastatic work-up should include a good inspiratory phase chest CT scan with 1 mm thin lung window reconstructions (non-contrast scan to be done when paired with PET-CT).

PET-CT/PET-MRI

A hybrid nuclear scan is mandatory for complete RMS staging before commencing treatment. Smaller lesions, nodal metastasis, and bone metastasis are better seen on PET-CT/PET-MRI compared with conventional scans. A modified Deauville score can be used to for visual assessment of suspicious lymph nodes comparing the activity with background activity in the adjacent normal tissue. Lymph nodes < 10 mm are considered non-pathological and > 15 mm are pathological. Lymph nodes < 15 mm with FDG activity should be considered suspicious. Although not validated, PERCIST (PET response criteria in solid tumors) can be used for quantitative measurements using standardized uptake values (SUV).[38] In future, whole body MRI with DWI/ADC sequence can prove to be a promising alternative to PET scans; however, it is still a subject of research and widespread adaptability for pediatric MRI protocols.

Response Assessment

Timing

The current EBM guidelines[39] and the EpSSG protocols use multidrug chemotherapy. Induction chemotherapy is combined with radiotherapy and/or surgery with additional maintenance therapy extending for 6 months to 24 months depending on randomized group for high-risk and very high-risk groups (according to early results from the ongoing FaR-RMS trial). The timing for follow-up imaging is summarized in ►**Supplementary Table S7**, available online only adapted from the EpSSG, ESPR oncology taskforce and CWS recommendations.[37] The IRS-IV trial recommendations by the intergroup Rhabdomyosarcoma Study Group (IRSG) are widely followed. They recommend neoadjuvant chemotherapy, response assessment at 10 to 12 weeks, and local treatment with surgery if possible and radiotherapy to the primary as well as to the metastasis depending on the site.[40,41]

Retinoblastoma

Retinoblastoma is the most prevalent intraocular tumor in children and represents ~2.5 to 4% of all pediatric cancers.[42,43] According to the National Cancer Registry program, the pooled crude incidence rate of retinoblastoma in 0 to 14 age group is 3.5 per million and the pooled age standardized incidence rate is ~4.4 per million.[44] The disease is curable if confined to the globe.

Types, Risk Factors, Etiopathogenesis, and Clinical Presentation

Retinoblastoma clinically presents in two distinct forms:

(1) Bilateral form (25% cases)-Caused by germline mutations of the *RB1* gene, localized on chromosome 13q14, and presents as congenital disease or early in life by 1 year. It could be hereditary or occur de novo.[43]
(2) Unilateral form (75% cases)-Random *Rb* gene mutation is the causative factor for most unilateral forms; however, 10% of cases are due to germline mutation. The mean age of presentation is ~2 years.[43]
(3) Trilateral retinoblastoma-Bilateral retinoblastoma with an asynchronous intracranial tumor, usually in the pineal region (pineoblastoma) and rarely in the suprasellar or parasellar location.

Clinical presentation: The common presentation is leukocoria. Other presentations are squint, nystagmus, change in visual status or loss of vision, and proptosis in extraocular disease. Advanced presentations with proptosis and bone marrow and CNS involvement are more commonly seen in developing countries.

Guidelines for Retinoblastoma Evaluation

Diagnosis is established by an ophthalmologist following examination under anesthesia and intratumoral calcifications detected in the lesion (usually by ultrasound).

Clinical examination:

1. Ocular examination in the clinic: For visual acuity assessment, anterior segment and posterior segment examination.
2. Examination under general anesthesia (EUA): for detailed evaluation including tumor laterality, number, location, size and vitreous/subretinal seedings. Anterior segment is also evaluated using a hand held slit lamp. Intraocular pressure is recorded using a tonometer.

Ultrasound

B-scan is performed using a 7.5 to 10 MHz high-frequency linear probe. Study can be performed without anesthesia or under sedation. Color Doppler may assist in differentiating tumor from echogenic effusions and persistent hyperplastic primary vitreous. Ultrasound is user dependent and this is the major disadvantage in response assessment.

Table 4 MRI imaging protocol for retinoblastoma

MRI sequence	Plane	Thickness	Sequence coverage
Essential sequences			
T2 W FSE/TSE (TE ≥ 120 ms) Fat-saturated	Axial	≤ 2 mm	Both orbits
T1 W TSE/FSE	Axial	≤ 2 mm	Both orbits
T2W TSE/FSE	Sagittal oblique	≤ 2 mm	Both orbits
T2W fat-saturated/STIR	Coronal	≤ 2 mm	Both orbits
Post contrast (PC)			
PC T1W SE FS/nonFS	Axial	≤ 2 mm	Both orbits
PC T1W SE FS/nonFS	Coronal	≤ 2 mm	Both orbits
PC T1W 2D or (3D GRE ≤ 1 mm)	Axial	≤ 3 mm	Brain
Optional sequences			
3D T2W (CISS/SPACE/FIESTA/ DRIVE)	Axial	<1 mm isotropic voxel	Both orbits
PC whole brain T1W 3D MPR	Axial	<1 mm	
PC whole Spine T1W	Sagittal	<3 mm	Required if there is optic nerve meningeal sheath involvement

Magnetic Resonance Imaging

High-resolution MRI of the orbit and screening of the brain is the examination of choice for pre-treatment assessment of the tumor (►**Table 4**). It detects the extent of disease (mainly involvement of the optic nerve and extra-scleral disease), its size, presence of meningeal spread, or associated intracranial primitive neuroectodermal tumor (trilateral retinoblastoma).

MRI field strength of 3 Tesla with head coil or 1.5 with dedicated orbit/small surface coil is recommended. Study should be performed under sedation or general anesthesia (GA) to obtain high-resolution images without eye movements.

To obtain high spatial resolution images, section thickness of ≤ 2 mm and in-plane pixel size of ≤ 0.5 × 0.5 mm is recommended. The image in axial and sagittal oblique plane should be aligned with the distal 1 cm end of the optic nerve (just posterior to the lamina cribrosa).

CT scan: CT is not a preferred modality due to the risk of ionizing radiation especially in cases with germline mutation. It can be used as an optional modality to detect calcification if there is diagnostic dilemma or MRI is not available.

Staging: CSF and bone marrow studies should be performed in extraocular disease/ optic nerve involvement.

Management and Follow-up Imaging (F/U)

Management and F/U imaging is based on staging.[45]

Intra-ocular Retinoblastoma Grouping/Staging

Group A: Small tumors (<3 mm) confined to the retina and located at least 3 mm from foveola and 1.5 mm from optic nerve

Group B: All tumors confined to retina and not in group A; subretinal fluid < 3 mm from tumor base

Group C: Local vitreous or subretinal seeding (<3 mm from tumor)

Group D: Diffuse vitreous or subretinal seeding (>3 mm from tumor)

Group E: Presence of at least one of the poor prognosis factors (anterior segment/ciliary body involvement; tumor involving > two-thirds of the globe; iris neo-vascularization; glaucoma; opaque media from hemorrhage; phthisis bulbi; aseptic orbital cellulitis due to tumor necrosis)

Treatment Guidelines for Retinoblastoma

For bilateral Rb, systemic therapy along with focal treatment (trans-scleral cryotherapy, diode laser transpupillary thermotherapy) is the initial treatment. In case of poor or inadequate response, targeted chemotherapy such as intra-arterial chemotherapy and/or intravitreal chemotherapy is utilized.

For unilateral intraocular Rb, enucleation is the choice in Group E tumors. Intraarterial chemotherapy (ophthalmic artery chemo-infusion) is preferred, especially for group D and select group E eyes. Intravitreal chemotherapy is delivered in persistent vitreous seeds. Intravenous chemotherapy is administered in Groups C and D and in select Group E eyes (if buphthalmos is present) where upfront intra-arterial

therapy is unavailable. Patients who have upfront enucleation also receive chemotherapy if histopathological risk factors are present in the resected specimens.

Extraocular disease is treated with chemotherapy, surgery (enucleation/exenteration) based on the response and radiotherapy. Patients with bone marrow involvement require high-dose chemotherapy with stem cell rescue for cure.

Imaging wise, in case of both unilateral and bilateral Rb, an ocular USG, MRI, and EUA is recommended at baseline.[19] Follow-up is done with USG and EUA, and for extra-ocular disease, MRI is also performed.

Note

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Conflict of Interest

None declared.

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