



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

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Abstract

Keywords

- ▶ AI
- ▶ BMT
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- ▶ iTNM
- ▶ oncology
- ▶ Lactation
- ▶ pregnancy

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.

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, breast 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 AI¹⁷ 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 (<i>bidimensional; surface area</i>)	Sum of longest diameters of target lesions (<i>unidimensional</i>)	Sum of longest diameters of nonnodal target lesions and short axis of nodal target lesions (<i>unidimensional</i>)
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 tuberculosis; 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

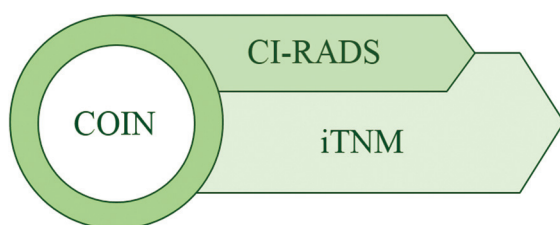
We also propose the formation of COIN, a Comprehensive Onco-Imaging Network, an alliance that will coordinate the expertise and leadership of oncoradiologists in order to form a coalition for the exchange of valuable information which will eventually augment the practice of oncoimaging. The objectives 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	Indication	Common findings	modality
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 thrombotic 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 to 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 2019 Impacting 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 fetus⁴⁶; 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/cm² 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 hypercoagulopathy. 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 al⁵² 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 accidentally 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 Gynecologists⁶³:

- 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.

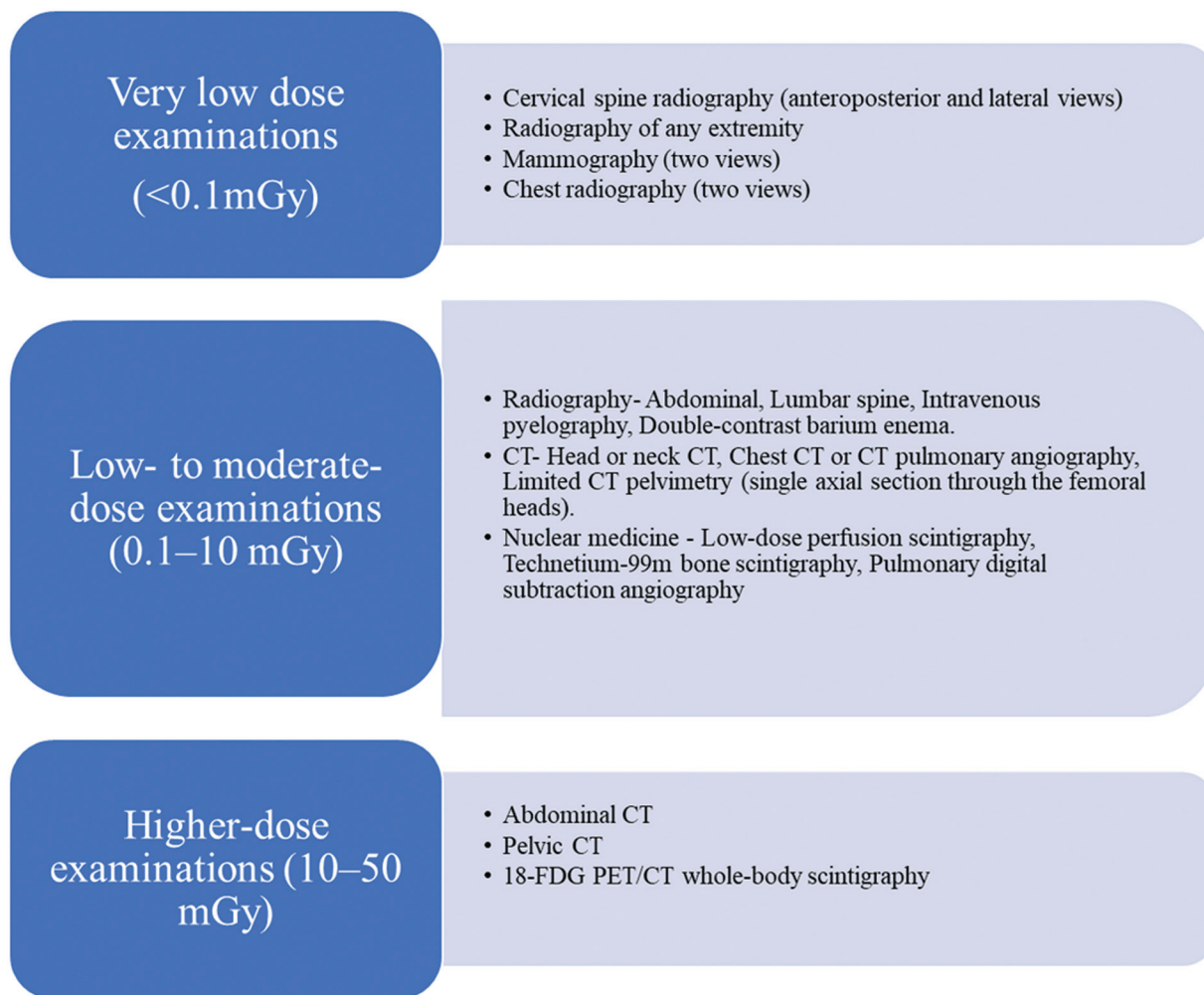


Fig. 1 Radiation doses associated with common radiologic examinations.

- 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) non-malignant 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	<i>Preengraftment phase</i> -Fungal infection -Diffuse alveolar hemorrhage -Pulmonary edema -Engraftment syndrome <i>Early posttransplantation phase</i> -Cytomegalovirus infection -Pneumocystis jiroveci pneumonia -Idiopathic pneumonia syndrome <i>Late posttransplantation phase</i> -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 system (CNS) complications	-CNS infections -Intraaxial hematomas
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	<ul style="list-style-type: none"> • In suspected Engraftment Syndrome and pulmonary edema. • Postline placement to identify the position and to evaluate any complications such as a pneumothorax.
CT Chest	<ul style="list-style-type: none"> • 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 venoocclusive disease.
USG abdomen	<ul style="list-style-type: none"> • In suspected sinusoidal obstruction syndrome, Budd–Chiari syndrome, neutropenic colitis, pyelonephritis, and hemorrhagic cystitis.
CT abdomen with contrast	<ul style="list-style-type: none"> • In suspected acute GVHD and infection. • In suspected PTLD and chronic GVHD (late posttransplant period).
CT brain	<ul style="list-style-type: none"> • In suspected intracranial hemorrhages, PRES, and infection. • I.V. Contrast study is recommended for imaging in infection.
MRI Brain	<ul style="list-style-type: none"> • 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 country⁸⁰ 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 tissue⁹¹ 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 (≤ 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.

- 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 risk⁹⁵ 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 ≥ 55 to 77 years, ≥ 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 (≤ 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 ≥ 50 years and ≥ 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 ≤ 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 ≤ 45 years, history of second breast cancer at any age, triple-negative breast cancer at age ≤ 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 months 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 ≥ 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 (≤ 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 programmed.^{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 anonym-

ization 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.

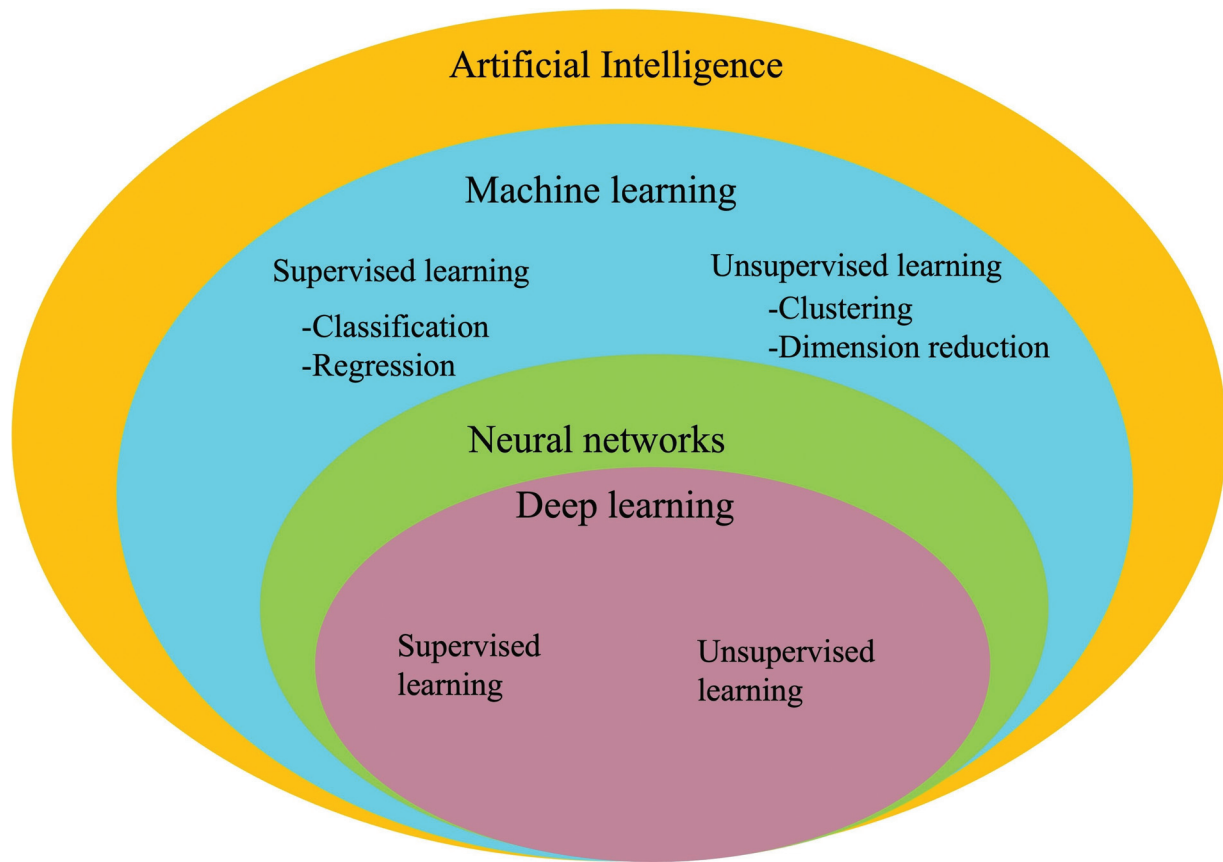


Fig. 2 Relationship between artificial intelligence, machine learning (ML), neural network, and deep learning (DL).

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.

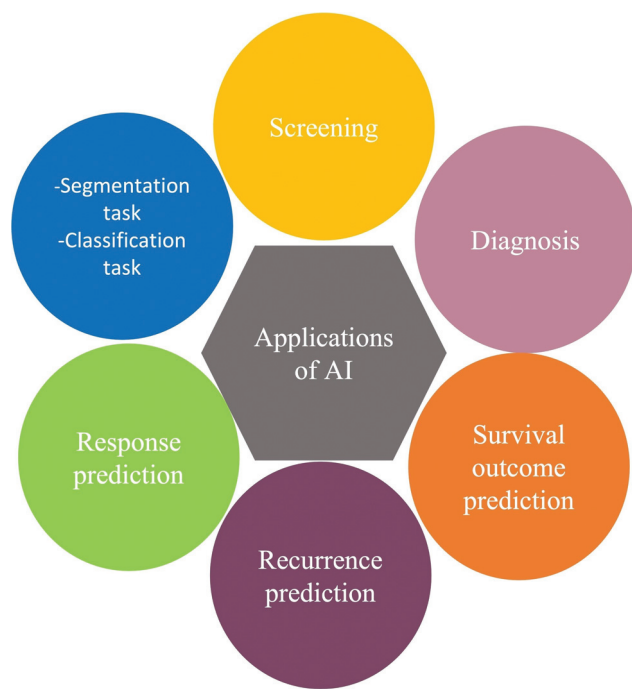


Fig. 3 Applications of artificial intelligence in oncological imaging.

- **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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None declared.

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