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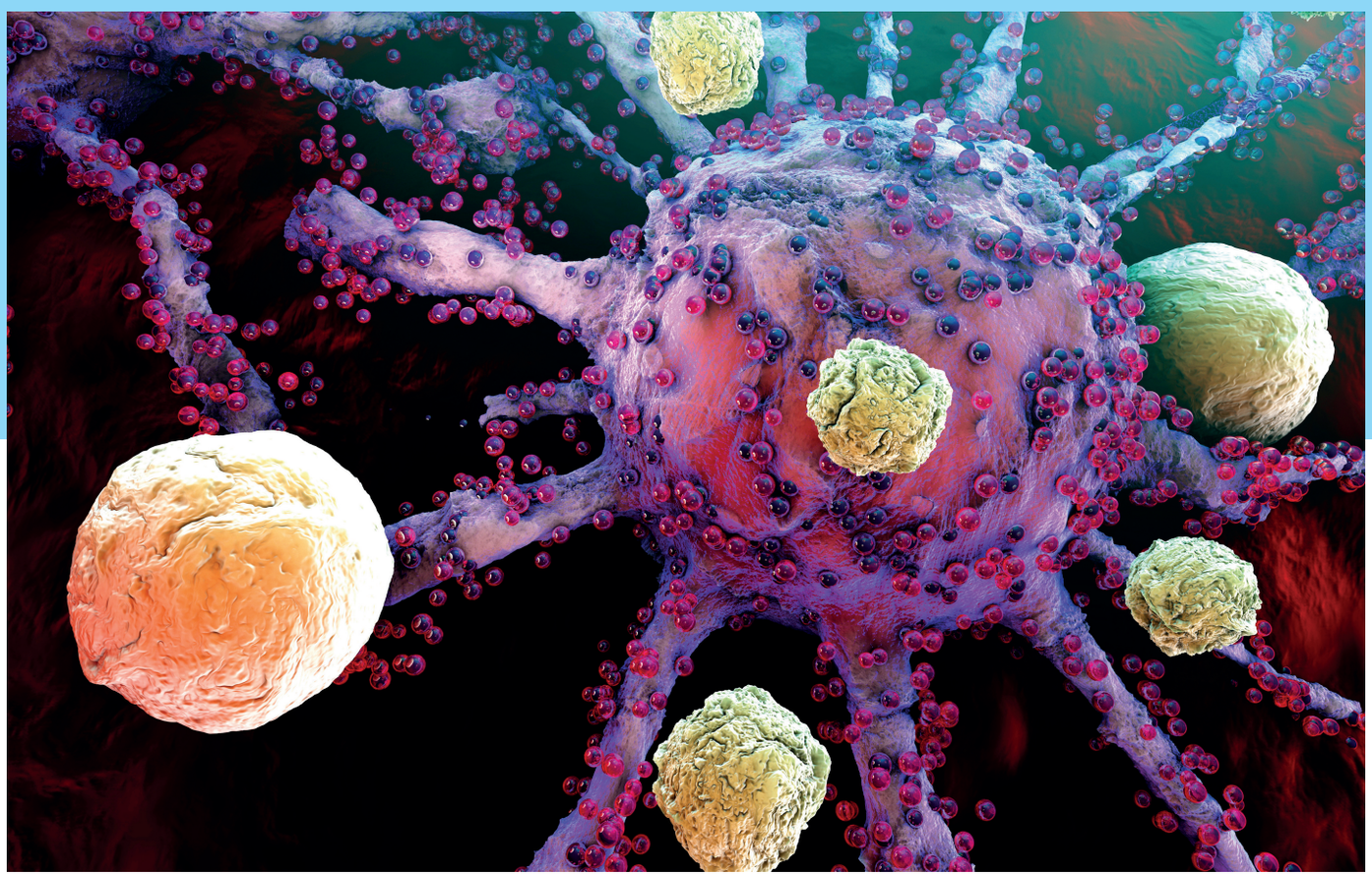

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1. Spigel, David R., et al. "Five-year survival outcomes from the PACIFIC trial: Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer." Journal of Clinical Oncology 40.12 (2022): 1301.
2. Paz-Ares, L., et al. "Durvalumab, with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

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Imaging Recommendations for Diagnosis, Staging, and Management of Hereditary Malignancies

Jinita Majithia[1] Abhishek Mahajan[2] Richa Vaish[3] Gagan Prakash[4] Saket Patwardhan[1] Rajiv Sarin[5]

[1] Department of Radiodiagnosis, Tata Memorial Hospital, Mumbai, Maharashtra, India
[2] Department of Radiology, The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, United Kingdom
[3] Department of Head and Neck Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India
[4] Department of Uro-Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India
[5] Department of Radiation Oncology and In-Charge Cancer Genetics, Tata Memorial Hospital and Advanced Centre for Treatment Research and Education in Cancer (ACTREC), Mumbai, Maharashtra, India

Address for correspondence Jinita Majithia, MBBS, DNB, Department of Radiodiagnosis, Tata Memorial Hospital, Mumbai, Maharashtra 400012, India (e-mail: jinita_10@hotmail.com).

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Abstract

Hereditary cancer syndromes, characterized by genetically distinct neoplasms developing in specific organs in more than one family members, predispose an individual to early onset of distinct site-specific tumors. Early age of onset, multiorgan involvement, multiple and bilateral tumors, advanced disease at presentation, and aggressive tumor histology are few characteristic features of hereditary cancer syndromes. A multidisciplinary approach to hereditary cancers has led to a paradigm shift in the field of preventive oncology and precision medicine. Imaging plays a pivotal role in the screening, testing, and follow-up of individuals and their first- and second-degree relatives with hereditary cancers. In fact, a radiologist is often the first to apprise the clinician about the possibility of an underlying hereditary cancer syndrome based on pathognomonic imaging findings. This article focuses on the imaging spectrum of few common hereditary cancer syndromes with specific mention of the imaging features of associated common and uncommon tumors in each syndrome. The screening and surveillance recommendations for each condition with specific management approaches, in contrast to sporadic cases, have also been described.

Keywords
- hereditary cancer syndromes
- radiogenomics
- cancer
- surveillance guidelines

Introduction

Hereditary cancer syndromes (HCSs) are syndromes characterized by genetically distinct neoplasms developing in specific organs in more than one family members,[1,2] predisposing an individual to early onset of distinct site-specific tumors. A radiologist is often the first to apprise the clinician about the possibility of an underlying HCSs based on pathognomonic imaging findings, leading to genetic testing of the individual and their relatives as a part of preventive oncology. Radiogenomics is a term coined in recent years that describes the relationship between imaging features of a lesion and the underlying genetic or molecular abnormality, which aides in approach to diagnosis, guiding therapeutic

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strategies, assessment of treatment response, and prognostication.[3]

Most of the HCSs have an autosomal dominant pattern of inheritance and comprise up to 5 to 10% of the overall worldwide cancer burden.[1,2] Among the Indian population, there is paucity of data on the incidence of hereditary cancers. The mortality rates are possibly higher in India, attributed to different lifestyles, delayed introduction of screening programs, and socioeconomic limitation to treatment access.[4] The lack of knowledge and access to accurate information as well as the social taboo and stigma associated with cancers in India leads to under-reporting and contributes to the skewed incidence.[5]

The different genetic mechanisms that play a role in the etiopathogenesis of HCSs include inactivation of tumor suppressor genes or reactivation of proto-oncogenes or abnormalities in the DNA repair genes.[6] Predisposition to certain malignancies and the therapeutic response are determined by the interaction of these genetic mutations with environmental factors called gene–environment interaction.[7] Early age of onset, multiorgan involvement, multiple and bilateral tumors, advanced disease at presentation, and aggressive tumor histology are characteristic of HCSs. A fundamental change in the approach to treatment of hereditary cancers and a paradigm shift to preventive oncology is proof that a multidisciplinary approach with collaboration of clinical, radiological, and pathological specialties with genetic research is a promising step toward precision medicine. The common and uncommon tumors observed in few commonly encountered HCS and their associated mutations have been summarized in ►**Table 1**. Several childhood cancers are also associated with germline and somatic mutations in cancer predisposition genes. The Society for Pediatric Oncology and Hematology established a CPS (cancer predisposition syndrome) working group that summarized a comprehensive review of childhood CPS and provided clinical and diagnostic recommendations for cancer prevention, surveillance, treatment, and follow-up.[8] Few of the common ones are summarized in ►**Table 2**.

A comprehensive and standardized guideline structure for screening and management of individuals with suspicion of HCSs is essential. The imaging recommendations for diagnosis and screening of few common HCSs are discussed below.

Hereditary Breast and Ovarian Cancer Syndrome

The most common cancers associated with hereditary breast and ovarian cancer syndrome (HBOCS) are breast and ovarian cancer, as its name suggests. The cumulative cancer risk identified is 55 to 70% for breast cancer and 40 to 45% for ovarian cancer in *BRCA1* carriers and 40 to 70% for breast cancer and 15 to 20% for ovarian cancer in *BRCA2* carriers.[9,10]

The median age at diagnosis for breast cancer is 40 years, compared with 61 years in the general population[11] with a 3% risk of developing breast cancer before the age of 30 years.[12] *BRCA*-associated breast cancers are usually high grade and poorly differentiated with poorer prognosis. They have a higher growth rate with shorter lead time resulting in more interval cancers.[13] Bilateral cancers are more common in *BRCA* carriers with an approximately 63% risk of developing a second primary in the contralateral breast.[13,14] More than 80% of *BRCA*-associated cancers are invasive-ductal type, commonly triple negative (negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2), with a higher than usual incidence of medullary cancers seen in *BRCA1* carriers.[11] Higher risk of male breast cancer is also observed in *BRCA* carriers.[15]

Breast density is the single most important quantifiable risk factor that can be rapidly and reliably identified and assessed on mammography. The distribution of breast density in *BRCA1* and *BRCA2* mutation carriers is similar to that in noncarriers; however, higher breast densities in carriers is associated with an increased risk of breast cancer, with relative risk being similar to that in the general population.[16] Mammographic breast density data has yielded good risk prediction accuracy.[17] *BRCA*-associated breast cancers usually have benign appearing features, that is, oval well-defined lesions with circumscribed margins on mammogram and ultrasound. Microcalcifications are rarely seen in *BRCA1* cancers but seen in up to 40% cases of *BRCA2* cancers, similar to sporadic cases. It is optional for women between 40 and 45 years, who are at average risk of breast cancer, to undergo screening mammography, whereas those between 45 and 54 years are strongly recommended to undergo annual mammograms. Those above 55 years can switch to mammograms every other year. Women at high risk, including those with high lifetime risk of breast cancer ($>$ 20%), *BRCA* or *TP53* mutation carriers, first-degree relative with *BRCA* mutation (with no genetic testing for themselves), and those who have taken radiotherapy to chest wall between 10 and 30 years of age, are recommended to have annual breast magnetic resonance imaging (MRI) with mammograms starting from 30 years of age. Several randomized controlled trials and comparative reviews have studied the advantage of MRI versus mammography for surveillance in high-risk women. Wernli et al found no significant difference in the sensitivity of the surveillance MRI compared with mammography.[18] However, a randomized controlled trial in women at high risk of familial cancer by Saadtmand et al concluded that MRI was advantageous for early-stage cancer detection and decreased the overall breast cancer-related mortality albeit at the cost of high false-positive rate[19] and increased biopsy rates.[18,20]

BRCA1-associated ovarian cancers manifest in the fourth or fifth decade of life, 5 to 10 years earlier than sporadic cases, and are usually high grade.[21] Imaging morphology is similar to sporadic cases, that is, heterogeneously enhancing solid masses with areas of hemorrhage, necrosis, and papillary projections. More than 90% cases are serous adenocarcinomas, most commonly arising from the fimbriated ends of the fallopian tubes.[21] They are more sensitive to platinum agents and poly (adenosine 5′-diphosphate–ribose) polymerase inhibitors than sporadic cancers.[22] Survival rate of *BRCA2*-associated ovarian cancers is known to be better

Table 1 Common and uncommon tumors in hereditary cancer syndromes

HCSs	Genes Involved	Chromosome	Associated tumors		Benign findings
			Common	Uncommon	
Hereditary breast and ovarian cancer syndrome	*BRCA1* and *BRCA2*	17q21 and 13q13	Breast cancer, ovarian cancer	Primary Fallopian tube serous carcinoma, primary peritoneal serous carcinoma, prostate cancer, pancreatic adenocarcinoma and colon cancer	–
Li-Fraumeni syndrome	*TP53*	17q13.1	Soft tissue sarcoma, osteosarcomas, breast cancer, brain tumors (choroid plexus carcinomas and gliomas)	Adrenocortical carcinomas, leukemia, gastrointestinal tumors	–
Cowden syndrome	*PTEN*		Breast cancer, thyroid cancer	Papillary RCC, endometrial and colorectal cancers	
von Hippel-Lindau disease (VHL)	VHL	3q25	Cerebellar/spinal cord hemangioblastomas, retinal capillary hemangioblastoma, clear cell RCCs, pheochromocytomas and pancreatic neuroendocrine tumors	Endolymphatic sac tumors, epididymal and broad ligament cystadenomas	Pancreatic and renal cysts
Familial adenomatous polyposis	*APC*	5q21	Colorectal cancer	Duodenal or periampullary cancer, desmoid tumor, osteoma, papillary thyroid cancer, hepatoblastoma, brain tumor	Congenital hypertrophy of the retinal pigment epithelium, dental abnormalities
Lynch syndrome (HNPCC)	*MLH1, MSH2, MSH6* and *PMS2*	3p21, 2p16, 2p16 and 7p22	Colorectal cancer, endometrial cancer	Ovarian cancer, urothelial cancer, small bowel, stomach and pancreas cancer	
Tuberous sclerosis	*TSC1* and / or *TSC2*	9q34, encodes hamartin and / or 16p13, encodes tuberin	Subependymal giant cell astrocytomas	Renal angiomyolipomas, cardiac rhabdomyomas, RCC	Cortical tubers, subependymal nodules, white matter abnormalities, renal cysts, lymphangioleiomyomatosis
Multiple endocrine neoplasia (MEN) 1 or Werner's syndrome	*MEN1*	11q13	Parathyroid adenoma	Thymic carcinoid, bronchial carcinoid, adrenocortical tumors, pheochromocytoma	Bronchopulmonary and thymic cysts, lipoma, meningioma, angiofibroma, collagenoma
			Enteropancreatic tumor		
			• Gastrinoma (40%)		
			• Insulinoma (10%)		
			• Nonfunctioning		
			• Ppoma (20–55%)		
			Pituitary adenoma		
			• Prolactinoma (65%)		
			• Somatotropinoma (25%)		

(*Continued*)

Table 1 (*Continued*)

HCSs	Genes Involved	Chromosome	Associated tumors		Benign findings
			Common	Uncommon	
Multiple endocrine neoplasia (MEN) 2A or Sipple's syndrome	*RET*	10q11	Medullary thyroid cancer, pheochromocytoma, pituitary adenoma	–	Cutaneous lichen amyloidosis, Hirschsprung disease
Multiple endocrine neoplasia (MEN) 2B or 3	*RET*	10q11	Medullary thyroid cancer, pheochromocytoma,	Mucosal neuromas, diffuse ganglioneuromatosis of the gastroenteric mucosa	Marfanoid habitus, medullated corneal nerve fibers, megacolon
Neurofibromatosis (NF1) or von Recklinghausen disease	*NF1*	17q11.2	Optic gliomas, pheochromocytomas	–	Cutaneous neurofibromas, Lisch nodules (pigmented iris hamartomas), Café-au-lait spots
NF2	*NF2*	22q12	Bilateral vestibular schwannomas, meningioma, ependymomas	–	Juvenile cataracts

Abbreviations: HCSs, hereditary cancer syndromes; HNPCC,–; RCC, renal cell carcinoma;

(52%) than *BRCA1*-associated (44%) and sporadic (36%) cancers.[23]

Periodic testing of CA-125 and annual transvaginal ultrasounds are recommended for surveillance of women with familial risk of ovarian cancer. However, many clinical trials including the National Comprehensive Cancer Network guidelines emphasize that they are ineffective in tumor detection and have no substantial influence on survival.[24,25] Thus, currently no screening regimen has proven to be effective in reducing mortality in *BRCA*-associated ovarian cancers. Risk-reducing salpingo-oophorectomy for prevention of occult neoplasia is the only proven mortality-reducing intervention for women more than 35 years age.[26]

Imaging and clinical screening recommendations in *BRCA* carriers are depicted in ►**Fig. 1**.

Li-Fraumeni Syndrome

Two criteria exist for diagnosis of Li-Fraumeni syndrome (LFS), the classic and Chompret criteria, summarized in ►**Fig. 2**, the latter having a higher sensitivity (82–95%) and specificity (47–58%).[27] The lifetime risk of developing cancer with *TP53* mutation is nearly 100% for females and 73% for males.[28] The incidence of tumors in LFS is 27 and 16% for soft tissue sarcomas (most common: rhabdomyosarcoma) and osteosarcomas, 60% for breast cancer, 13% for brain and adrenocortical cancers, and 4% for leukemias, respectively.[27,29] Although radiation-induced cancers are rare in the normal population (accounting for less than 5% of all treatment-related cancers), individuals with LFS have increased susceptibility to DNA-damaging effects of ionizing radiation.[30] They are at high risk of developing secondary malignancies in a previously radiated field, with an incidence of 30% and a median time for the development of 10.7 years.[27] In cancer patients testing for *TP53* variants, surgical and ablative therapeutic measures are the preferred first-line treatment while advocating the use of non-genotoxic chemotherapeutic agents and avoiding radiotherapy when possible.[31] However, a recent study done by Hendrickson et al did find that the rate of a subsequent malignancy was not significantly different between LFS patients who received radiation compared with those who did not. In fact, none of the subsequent malignancies in patients receiving radiation could be confidently classified as radiation-associated malignancy and were merely considered as disease recurrence.[32]

Previously, studies have evaluated the use of 2-deoxy-2-[fluorine-18]fluoro- D-glucose integrated with computed tomography (18F-FDG-PET/CT) as a screening tool for LFS; however, increased susceptibility to adverse effects of ionizing radiation negates routine use.[33] Whole body MRI (WB-MRI) now plays a pivotal role in surveillance of high-risk individuals. A meta-analysis done by Ballinger et al in 2017 estimated the cancer detection rate of WB-MRI as 7% with a false-positive rate of 43%, stating that WB-MRI offers clinical utility in the baseline clinical risk management.[34] A study done by Villani et al proved that screening with WB-MRI, in adults and children with LFS, detected all

Table 2 Childhood cancer predisposition syndromes

Predisposition group	Genes involved	Associated cancers
Ataxia telangiectasia	*ATM*	Leukemia
		Lymphoma
Bloom syndrome	*BLM*	Leukemia
		Lymphoma
Constitutional mismatch repair-deficiency syndrome (CMMR-D)	*MLH1, MSH2, MSH6, PMS2*	Pediatric brain tumors
		Colorectal cancers
		ALL, AML, lymphoma
		Early onset GI and GU tumors
Fanconi anemia	*FANCA, C, D1, D2, E, F, G, I, J, L, M, RAD51C, SLX4/BTBD12, FANCAB*	Leukemia (MDS, AML)
		Squamous cell carcinoma
		Wilms tumor
		Gynecological tumors
		Brain tumors
Wiskott-Aldrich syndrome (WAS)	*WAS*	Diffuse large B cell lymphoma
		Non-Hodgkin's lymphoma of larynx
		Cerebellar astrocytoma
		Kaposi sarcoma
		Smooth muscle tumors
Wilms-Aniridia-GU-anomaly-retardation (WAGR) syndrome	*WT1*	Wilms tumor
		Gonadoblastoma
Denys-Drash syndrome (DDS)	*WT1* (dominant)	Wilms tumor
		Gonadoblastoma
Beckwith-Wiedemann syndrome (BWS)	*p57, H19, LIT1, ICR1, CDKN1C, NSD1*	Wilms tumor
		Hepatoblastoma
		Adrenal carcinoma
		Rhabdomyosarcoma
Familial pleuropulmonary blastoma tumor predisposition syndrome	*DICER1*	Pleuropulmonary blastoma
		Cystic nephroma
		Sertoli-Leydig cell tumors
		Rhabdomyosarcoma
		Supratentorial primitive neuroectodermal tumor
		Intraocular medulloepithelioma
Nevoid basal cell carcinoma syndrome (NBCCS)/Gorlin syndrome	*PTCH1, 2, SUFU*	Basal cell carcinoma
		Desmoplastic medulloblastoma
		Ovarian fibromas
Familial retinoblastoma syndrome (RB)	*RB1*	Retinoblastoma
		Osteosarcoma
		Melanoma
		Glioma
Rhabdoid tumor predisposition syndrome	*SMARCB1/INI1*	Rhabdoid tumor
		Medulloblastoma
		Choroid plexus tumor
		Schwannoma

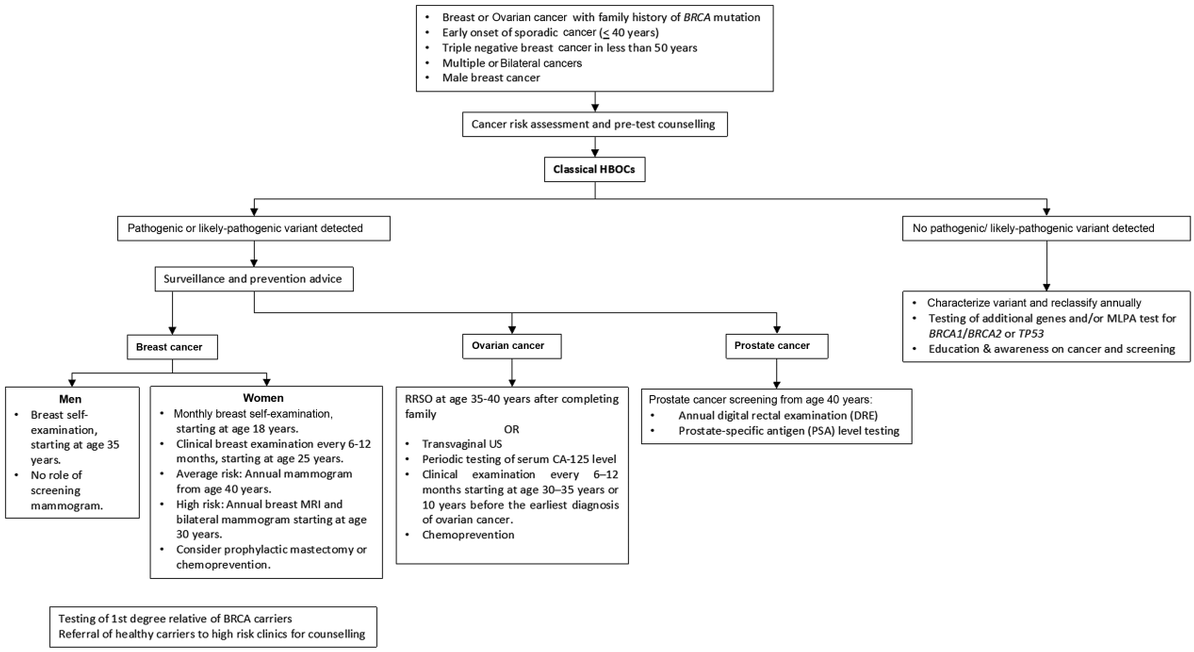


Fig. 1 Imaging and clinical screening recommendations in *BRCA* carriers. CT, computed tomography; HBOCS, hereditary breast and ovarian cancer syndrome; MRI, magnetic resonance imaging; RRSO, risk-reducing salpingo-oophorectomy.

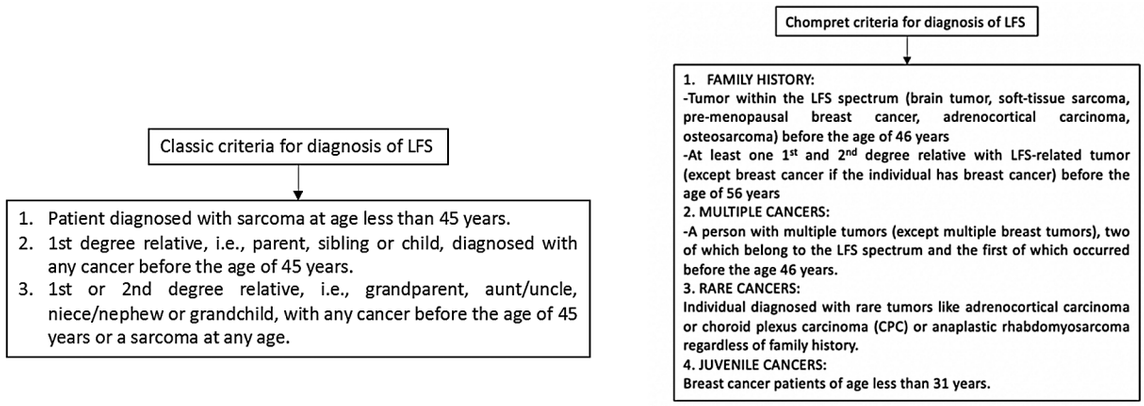
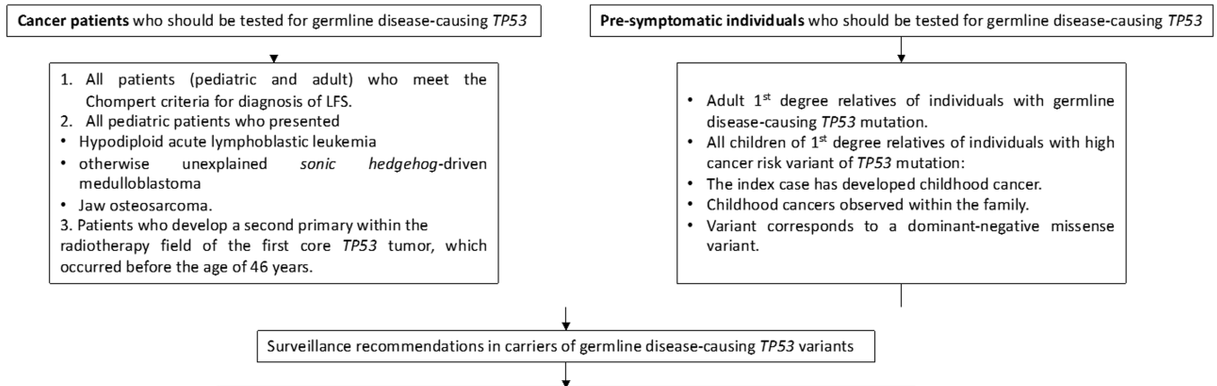


Fig. 2 Classic and Chompret criteria for diagnosis of Li-Fraumeni syndrome (LFS).

tumors in asymptomatic individuals with a 3-year survival rate of 100%, as opposed to 23% in persons who did not undergo surveillance.[35] The cancer detection rate in children with WB-MRI, however, may be lower than adults.[36] Image sequences include coronal T1 and short tau inversion recovery with axial diffusion-weighted images (DWI). Contrast administration is not routinely recommended.

Screening for breast cancers in LFS is done with annual breast MRI. Diagnostic imaging may include mammography but is reserved for older women and is not recommended for young women as the sensitivity of mammography is significantly lower in dense breasts of young women. Breast cancers are usually intraductal type and appear as irregular spiculated solid masses on imaging. Malignant phyllodes is also frequently associated with LFS appearing as a large heterogeneous mass with cystic and necrotic areas of degeneration and marked peripheral and internal vascularity on ultrasound. Women with LFS who develop breast cancer are advised to have bilateral mastectomy rather than lumpectomy to reduce the risk of developing a second primary breast cancer. Also, administration of radiotherapy post lumpectomy is also a challenge since it carries a risk of developing cancer in the radiation field. There is no known elevated risk of male breast cancer.

Almost 50% patients with choroid plexus carcinoma are associated with *TP53* alteration.[37] Gliomas like astrocytoma, oligodendroglioma and glioblastoma multiforme are other common brain tumors occurring in LFS. All these have typical features on imaging similar to their sporadic counterparts. Atypical presentation like leptomeningeal spread or involvement of the posterior fossa are encountered.[38]



Examination	Periodicity	Age to start	Age to end
Clinical Examination: Children: Specific attention to signs of virilization or early puberty and blood pressure measurement.	Every 6 months	Birth	Until 18 years
Adults: Who received radiotherapy, occurrence of basal cell carcinomas within the radiotherapy field	Annually	18 years	-
Whole-Body MRI without gadolinium enhancement	Annually	Birth	-
Brain MRI	Annually	Birth	Until 18 years
Breast MRI	Annually	18-20 years	Until 65 years
Abdominal ultrasound	Every 6 months	Birth	Until 18 years
Colonoscopy	Every 2-5 years	18 years	-
Urine Steroids	Every 6 months	18 years	Until 18 years
Complete Blood Count	Annually	-	-

Fig. 3 Surveillance recommendations in carriers of germline disease-causing *TP53* variants. LFS, Li-Fraumeni syndrome; MRI, magnetic resonance imaging.

Pediatric patients with adrenocortical cancer almost always have *TP53* mutations, appearing as large heterogeneously enhancing masses with metastasis to lungs, liver and lymph nodes on cross-sectional imaging. Screening abdominal ultrasounds are usually sufficient; however, MRI is more sensitive for smaller lesions.

Surveillance recommendations in carriers of germline disease-causing *TP53* variants is depicted in ►**Fig. 3**.[39]

von Hippel-Lindau Disease

von Hippel-Lindau Disease (VHL) is characterized by the development of vascular tumors due to inactivation of *VHL* gene that leads to upregulation of somatic and vascular growth factors, including vascular endothelial growth factor (VEGF). Renal, central nervous system, and pancreas are the most commonly involved organ systems.

The most common malignancy associated with VHL is renal cell carcinoma (RCC). Early diagnosis of RCC is imperative as they are known to be multiple, prone to relapse, and also the most common cause of death. Diagnosis as well as screening for RCCs utilizes the renal imaging protocol on CT (with unenhanced, cortico-medullary, nephrogenic, and excretory phases) which is the gold standard for depiction of characteristic vascular lesions showing arterial enhancement and venous wash out. MRI is increasingly preferred over CT for imaging in VHL owing to the absence of ionizing radiation, superior evaluation of smaller lesions, improved detection of intratumoral lipid, and hemorrhage and safer use with renal impairment. A recent study by Farhadi et al in 2020 correlated the relationship between apparent diffusion coefficient (ADC) and the growth rates of RCC for predicting the volume doubling time (VDT); ADC bearing a negative relationship with growth rate and positive relationship with VDT, thus, establishing the use of DWI in identifying RCCs with higher growth rates.[40] Imaging also plays an important role in targeted intervention. Percutaneous focal ablation, like CT-guided radio frequency ablation (RFA) and cryoablation, is the preferred treatment for RCCs in VHL as it significantly improves the cancer-free survival,[41] especially for smaller (< 3 cm) and multiple tumors. Nephrectomy is not recommended; however, for tumors larger than 3 cm, nephron-sparing surgery may be performed.[41] Some prefer to use a cutoff of 4 cm for surgery as this may help delay the surgery time.[42]

About 70% cases of VHL exhibit hemangioblastomas in the central nervous system, usually multiple with a high rate of recurrence, seen with decreasing frequency in the cerebellum (52%), spinal cord (cervical or thoracic) (44%), and brain stem (18%).[43] On MRI, intense hypervascular enhancement of mural nodule is seen with tumor-related cysts showing nonenhancing walls. Calcification is characteristically absent. Spinal MRI screening for spinal hemangioblastomas is mandatory in the presence of cerebellar hemangioblastoma as they usually coexist. Retinal hemangioblastomas are found in 70% of cases over the age of 60 years. Diagnostic workup includes ophthalmoscopy and fluorescein angiography, the role of imaging being limited. MRI may depict a

hypervascular retinal nodule with or without retinal detachment.

There are two subtypes of VHL, depending on the absence (type 1) and presence (type 2) of pheochromocytoma. VHL exhibits a distinct pattern of plasma catecholamine excess, almost exclusively norepinephrine production, as compared with combination of metanephrine and normetanephrine in MEN2 or NF1.[44] On cross-sectional imaging, pheochromocytomas show avid early arterial enhancement with venous washout. Calcification as well as areas of necrosis and hemorrhage may be seen. Radionuclide meta-iodobenzylguanidine (MIBG) scan can be used for tumor localization as well as detection of occult metastasis. Recent studies have showed that the diagnostic accuracy of WB-MRI is comparable to that of MIBG.[45]

Endolymphatic sac tumors are associated with VHL in mere 20% cases; however, bilateral occurrence is pathognomic and can be detected on contrast-enhanced MRI of the brain and internal auditory meatus.

Pancreatic serous cystadenomas and neuroendocrine tumors (NET) are also common, with the latter harboring a malignant potential and detected in up to 15% patients with VHL.[46] Serous cystadenomas have the typical appearance of "cluster of small cysts" with a central scar identified on cross-sectional imaging. They require no treatment unless symptomatic. NETs have the typical early arterial enhancement and venous washout like other hypervascular NET on cross-sectional imaging and are seen most commonly in the head and uncinate process of pancreas. Endoscopic ultrasound with or without contrast has a significant role in the diagnosis, intervention (tissue sampling and/or targeted ablation) and surveillance of NETs in VHL.[47] MRI has increased sensitivity over CT and the use of DWI has significantly improved the sensitivity of tumor detection, comparable to PET/CT wherein low ADC values suggest higher grade tumor.[47 68]Ga-DOTATATE PET/CT is useful for the depiction of small NETs, whereas ^{18}F-FDG-PET/CT has increased sensitivity for higher grade tumors.[47]

Tumor-to-tumor metastasis is a peculiar phenomenon associated with VHL and refers to the spread of malignant cells from RCC, NET, and pheochromocytoma to existent hemangioblastomas, which act as a host for metastases,[48] suspected with sudden change in size of hemangioblastomas.

Systemic chemotherapeutic treatment in few VHL patients with inoperable or previously treated lesions is recommended, like VEGF-receptor inhibitor and fibroblast growth factor inhibitor.

Summary of individuals who should be tested for *VHL* mutation is given in ►**Fig. 4**.

VHL alliance suggested surveillance guidelines have been tabulated in ►**Fig. 5**.[49–51]

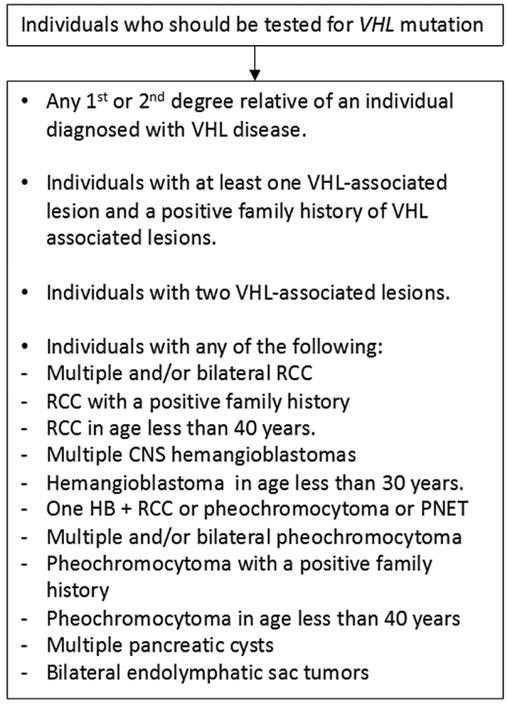


Fig. 4 Individuals who should be tested for *VHL* mutation. CNS, central nervous system; Hb, hemoglobin; PNET,—; RCC, renal cell carcinoma; VHL, von Hippel-Lindau disease.

Multiple Endocrine Neoplasia Syndrome

Multiple endocrine neoplasia (MEN) syndrome is a group of autosomal dominant cancer syndromes characterized by the simultaneous presence of neoplasms in two or more endocrine organs.[52] There are two types: MEN 1 (Wermer's syndrome) and MEN2. MEN1 affects all age groups without any gender predilection with a prevalence of 2/100,000.[53] MEN2 has a prevalence of 1/200,000 live births.[54] The associated abnormalities in MEN syndromes have been summarized in ►**Fig. 6**.

MEN1

MEN1 constitutes many endocrine and nonendocrine tumors; however, approximately one-third of deaths in MEN1 are caused by endocrine malignancies. The crux of the management lies in early diagnosis and intervention that lead to improved outcome and decreased morbidity. Recommendations suggest performing genetic testing in individuals with significant family history or when the clinical presentation is suggestive of MEN1, supplemented with regular biochemical screening and cross-sectional imaging in patients who harbor the mutation.[55]

Parathyroid adenomas are the most common tumors in MEN1 (100% cases), presenting with elevated parathormone and hypercalcemia, usually before the age of 20 to 25 years. On ultrasound, which is usually the first investigation, they appear as nodular hypoechoic masses with increased vascularity. Asymmetric uptake and retention on delayed images of ^{99m}Tc-sestamibi nuclear scintigraphy are pathognomic. The sensitivity and positive predictive values of ultrasound and nuclear scintigraphy are similar. Increased sensitivity of four-dimensional CT is observed especially with smaller lesions and multigland involvement.[56] Dynamic MRI is superior to CT for demonstrating the hypervascular nature of

VHL Alliance suggested active surveillance guidelines

	At birth	At 1-4 years	At 5-15 years	At more than 16 years	During pregnancy
Clinical Examination (Neurological evaluation, Ophthalmic examination and Hearing test)	+	Annual	Annual	Annual	-
Biochemical Tests (Plasma metanephrine or 24-hour urinary metanephrine levels)	-	-	Annual	Annual	+
Abdominal Ultrasound	-	-	Annual; starting from 8 years of age	Annual	-
Abdominal MRI	-	-	If biochemical abnormalities found	Every 1-2 years	-
MRI of brain and internal auditory canal	-	-	Every 2-3 years	Annual	+
MRI of whole spine	-	-	-	Every 2-3 years	+

Fig. 5 VHL alliance suggested surveillance guidelines. MRI, magnetic resonance imaging; VHL, von Hippel-Lindau disease.

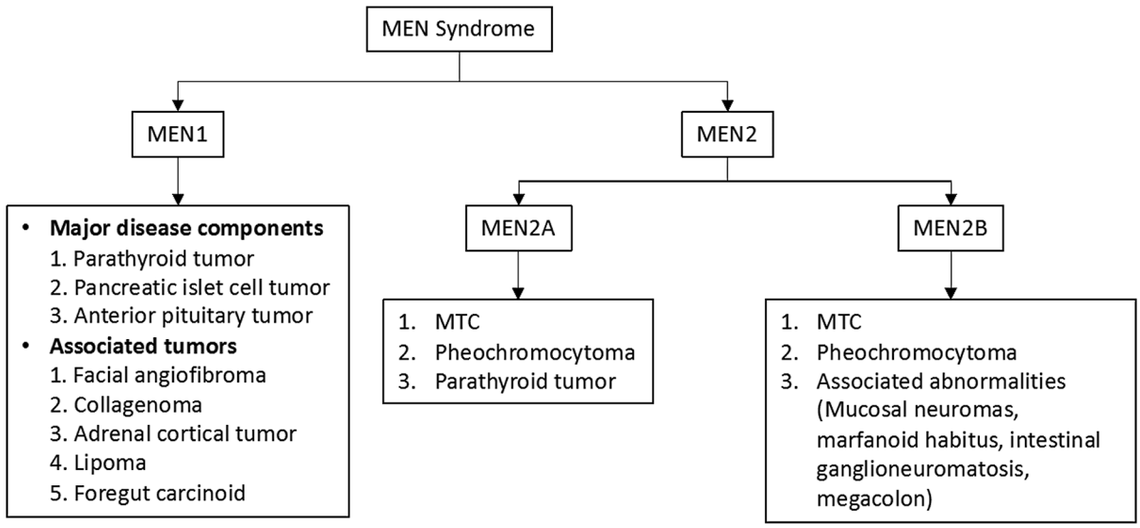


Fig. 6 Associated abnormalities with MEN syndromes. MEN, multiple endocrine neoplasia syndrome; MTC, medullary thyroid cancer.

parathyroid adenomas. Contrast–time curve generation allows quantitative analysis of the perfusion parameters of parathyroid adenomas and reveals a faster time-to-peak, higher peak enhancement, and faster wash in washout compared with cervical lymph nodes or thyroid, thus improving the diagnostic accuracy.[57] Hyperparathyroidism is treated with surgery, usually entailing excision of three and a half gland (subtotal parathyroidectomy) in cases where all the four glands are affected.

Enteropancreatic NET, seen in 30 to 70% cases, is a cause of significant morbidity and mortality in MEN1 syndrome as most of them are functional, however, with a lesser malignant potential. Transabdominal ultrasound is usually the first investigation performed. Endoscopic ultrasound has a higher sensitivity (100%) and specificity (95%), but is invasive and depends on operator efficiency. Cross-sectional imaging is most widely performed for diagnosis and staging. Most common are gastrinomas, frequently occurring in the duodenum, and tend to be multiple. Patients are usually offered non-surgical treatment except for cases with secretory tumors, pancreatic origin and size more than 2 cm. Patients with insulinoma, VIPoma, and glucagonoma are offered surgery.[58]

A high incidence of anterior pituitary tumors is observed in women with MEN1 (30–40%).[59] They are usually microadenomas (two-third cases) and best visualized on MRI, as small hypointense lesions on T1. Dynamic post-contrast sequence acquisition is essential for their depiction. ^{68}Ga-DOTATATE PET/CT can identify functioning and nonfunctioning pituitary adenomas, although it is most useful in

detecting residual normal pituitary tissue after adenomectomy and for diagnosis of recurrence of functioning adenomas.[60] Treatment remains similar to sporadic cases.

Screening protocol for MEN1 is depicted in ►**Fig. 7**.[61]

MEN2

MEN2A (Sipple's syndrome) is more common and MEN2B is less common but more aggressive. All the variants of MEN2 show high penetrance of medullary thyroid cancer (MTC), seen in 90 to 95% cases. Ultrasound should be performed for all patients with MTC as the initial evaluation. MTC appears as a solid markedly hypoechoic nodule with increased vascularity. Microcalcification may be seen. Metastasis to central and lateral compartment cervical nodes and mediastinal nodes with pulmonary and hepatic metastasis should be looked for. American Thyroid Association 2015 recommends contrast-enhanced CT scan of the neck and chest, triple-phase contrast-enhanced CT of the liver, axial MRI, and bone scintigraphy in cases with extensive neck disease or high calcitonin (>500 pg/dL) to rule out distant metastasis[55] in MTC cases. Recently, European Association of Nuclear Medicine guidelines 2020 recommended use of ^{18}F-FDOPA PET/CT (6–18F-fluoro-L-3,4-dihydroxyphenylalanine) in persistent MTC. Use of ^{18}F-FDG-PET/CT is limited to aggressive variants, while ^{68}Ga-somatostatin analogs PET/CT is suboptimal.[62] Surgery is the best form of prevention as well as cure for MTC with regular postoperative monitoring of serum calcitonin to detect recurrence. Early thyroidectomy may lower the mortality from hereditary MTC to less than 5%[63] with a more aggressive neck dissection for successful cure.

There may be an association of benign or malignant pheochromocytomas in MEN2 syndrome. Therefore, once the germline *RET* mutation is confirmed, it is important to rule out the presence of a pheochromocytoma. If cross-sectional imaging is nondiagnostic or depicts a unilateral disease, functional imaging like MIBG is suggested that has a higher sensitivity (87–90%). The screening for pheochromocytomas should be started in childhood, age of onset varying according to the risk category of mutation. Screening consists of measuring free plasma and 24-hour urine metanephrine and nor-metanephrine supplemented with cross sectional imaging if these levels are high. In cases with synchronous presentation of MTC and pheochromocytoma, pheochromocytoma should be treated first, followed by MTC.[64] Adrenalectomy is the treatment of choice following adrenal blockade.

Individuals who should be tested for MEN1

- Patients less than 35 years with hyperparathyroidism
- Patients with two or more endocrine organ tumors
- First-degree relatives with MEN1

Tumor	Age for initiation (years)	Biochemical marker	Imaging Modality
Parathyroid	8	Calcium, PTH	None
Gastrinoma	20	Gastrin (± gastric pH)	None
Insulinoma	5	Fasting glucose, insulin	None
Other pancreatic NET	<10	Chromogranin-A; pancreatic polypeptide, glucagon, VIP	MRI, CT, or EUS (Annual)
Anterior pituitary	5	Prolactin, IGF-I	MRI (every 3 yrs)
Adrenal	<10	When symptoms or signs of functioning tumor and/or tumor >1 cm identified on imaging	MRI or CT (Annual with pancreatic imaging)
Thymic and bronchial carcinoid	15	None	CT or MRI (every 1–2 years)

Fig. 7 Guidelines for screening protocol for MEN1 syndrome. CT, computed tomography; EUS, endoscopic ultrasound; IGF-1, insulin-like growth factor-1; MRI, magnetic resonance imaging; , MEN1, multiple endocrine neoplasia 1; NET, neuroendocrine tumor; PTH - Parathormone;, VIP - Vasoactive Intestinal Peptide.

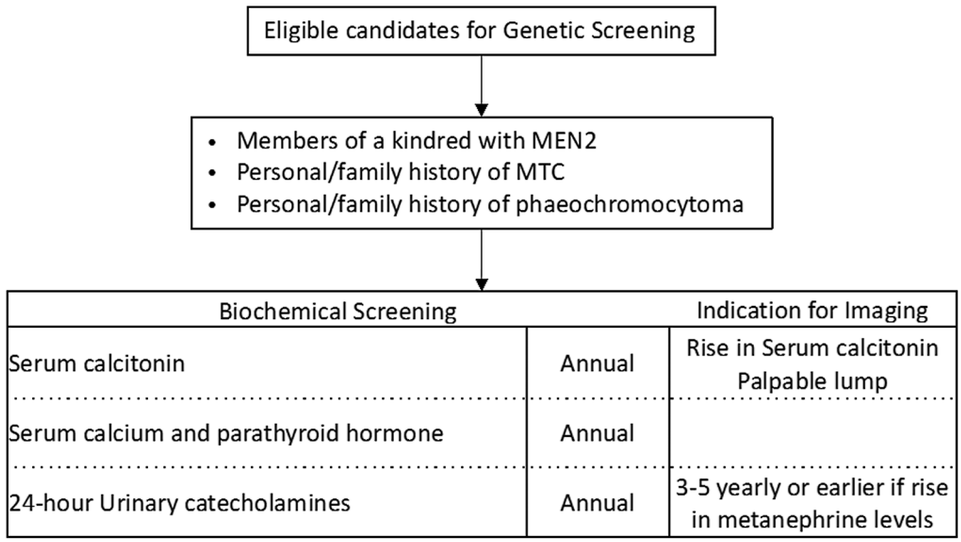


Fig. 8 Guidelines for screening protocol for MEN2 syndrome. MEN2, multiple endocrine neoplasia 2; MTC, medullary thyroid cancer.

Parathyroid tumors are seen in MEN2A and require investigations similar to MEN1 syndrome. Hyperparathyroidism does not develop in MEN2B, and thus screening is not required.

Guidelines for biochemical and radiological screening in individuals at high risk of developing MEN2 are depicted in ►**Fig. 8**.[61]

Tuberous Sclerosis

Tuberous sclerosis (TSC) is a neurocutaneous syndrome. The classic clinical triad for diagnosis includes facial adenoma sebaceum, epilepsy, and mental retardation, seen in 30 to 40% cases. The clinical diagnosis of TSC is divided into major and minor features summarized in ►**Fig. 9**.

The most common intracranial manifestation of TSC is cortical tubers or hamartomas, seen in 95% cases. On CT, they are hypodense areas of gyral widening. Calcification may be seen with progression. On MRI, they are T1 hypointense and T2 hyperintense with contrast enhancement in 10% cases. Microstructural changes in the tubers are detected by diffusion tensor imaging.[65] Occasionally, a cyst-like appearance may be seen on MRI following evolution of cortical tubers. These are associated with more severe epilepsy phenotypes. Cortical tubers associated with refractory epilepsy often require surgery. Pulsed arterial spin-labeled technique helps in quantifying perfusion characteristics of cortical tubers. Hyperperfused lesions are associated with increased frequency of seizures.[66] Preoperative evaluation with ^{18}F-FDG-PET/MRI for TSC has emerged as an indispensable noninvasive method to select the tubers as surgical candidates in refractory epilepsy.[67] Evaluating the involvement of perituberal cortex on MRI is essential for defining the extent of resection.[68]

Subependymal nodules are also common and appear isointense on T1 and iso- to hyperintense on T2 more and are more prone to calcification than cortical tubers. Radial migration lines are the most common white matter abnormality identified in TSC.

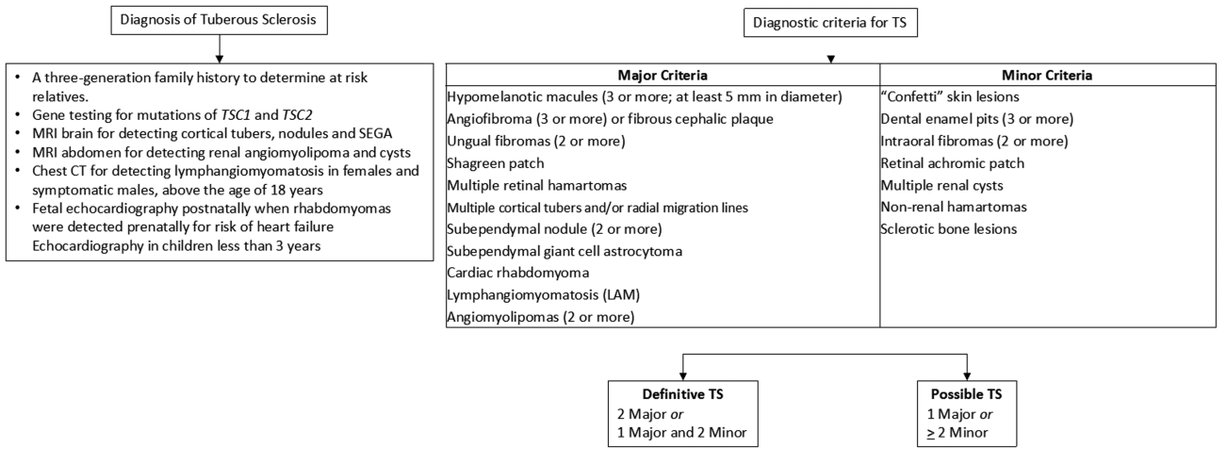


Fig. 9 Clinical features for diagnosis of TSC. CT, computed tomography; SEGA, subependymal giant cell astrocytoma; TSC, tuberous sclerosis.

Updated TSC Surveillance and Management Recommendations (2021)

Procedure	For Newly diagnosed / Suspected TS	For individuals diagnosed with TS
BRAIN		
Brain MRI with and without gadolinium	Yes	Every 1-3 years up to age 25; periodically as adults if SEGAs present in childhood
EEG	Yes; if abnormal, follow-up with 24-hour video EEG	Routine EEG determined by clinical need
TSC associated neuropsychiatric disroder (TAND)	Yes	Annual
SKIN EYES AND TEETH		
Complete eye exam with dilated fundoscopy	Yes	Annual
Skin Examination	Yes	Annual
Dental Examination	Yes	Every 6 months
HEART		
Fetal echocardiography	If rhabdomyomas identified in prenatal ultrasound	-
Echocardiogram	Yes	Every 1-3 years if rhabdomyoma present in asymptomatic children; more frequently in symptomatic individuals
ECG	Yes	Every 3-5 years; more frequently if symptomatic
KIDNEYS		
Blood Pressure	Yes	Annual
Abdominal MRI	Yes	Every 1-3 years
GFR test	Yes	Annual
LUNGS		
Clinical screening for LAM symptoms	Yes	At each visit
Pulmonary function test and 6-min walking test	In all females age 18 or older; in adult males only if symptomatic	Annual if lung cysts detected on CT
CT chest	In females 18 years and older; in adult males only if symptomatic	Every 2-3 years if lung cysts detected on CT; otherwise every 5-10 years
GENETIC		
Counselling and Consultation	Obtain 3-generation family history	Genetic testing of *TSC1/TSC2* and counselling if not done previously in individuals of reproductive age

Fig. 10 The updated International Tuberous Sclerosis Complex Consensus Group recommendations for surveillance and management. CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalography; GFR, growth factor receptor; LAM, lymphangioleiomyomatosis; MRI, magnetic resonance imaging; SEGA, subependymal giant cell astrocytoma; TSC, tuberous sclerosis.

Subependymal giant cell astrocytoma (SEGA) is defined as a lesion more than 1 cm in size at the caudothalamic groove or a subependymal lesion showing serial growth.[69] It is the most common central nervous system tumor in TSC, seen in 10 to 15% cases. It presents in late childhood and remains asymptomatic unless complicated with hydrocephalus. On MRI, they are hypo- to isointense compared with cortex on T1 and heterogeneously iso- to hyperintense on T2, most of them showing contrast enhancement. Early surgical resection is the standard treatment. Medical management with mechanistic target of rapamycin (mTOR) inhibitors is currently indicated for patients with symptomatic SEGA that are not amendable to surgery.[70]

Lymphangioleiomyomatosis (LAM) is characterized by multiple thin-walled cysts scattered in lungs. Strong female preponderance is noted with symptoms developing in the middle age. TSC association is seen in approximately 15% cases of LAM. Solitary or multiple cardiac rhabdomyomas are seen in approximately 60% of children, but only 20% of adults, and are usually asymptomatic. On MRI, they are well-defined

masses on the ventricular septum, isointense to myocardium on T1, and hyperintense on T2. Although surgical excision is the mainstay of treatment, mTOR inhibitors can be used as a temporary treatment for symptomatic cardiac rhabdomyomas in TSC, especially in high risk and inoperable cases.[71]

About 20% case of renal angiomyolipoma (AML) are associated with TSC. Presence of fat within AML can be demonstrated on CT, but best appreciated on T1 in- and opposed-phase images. Evaluation of lipid-poor AMLs can be a challenging and needs differentiation from RCC that is not uncommon in TSC. Multifocal and bilateral AMLs pose a challenge for surgical management, and thus RFA or cryoablation techniques are employed, especially for smaller tumors. mTOR inhibitors are used preoperatively that cause a significant reduction in size of lesions (38–95%) and reduce the risk of recurrence.[72]

The International Tuberous Sclerosis Complex Consensus Group reviewed the 2013 surveillance and management recommendations and published updated guidelines in 2021.[73] They have been summarized in ►**Fig. 10**.

Conclusion

Identification and diagnosis of hereditary syndromes and genetic predisposition syndromes require an integrated approach of clinical evaluation, genetic testing, and radiological screening and surveillance. Surveillance recommendations have been developed for different HCSs over years based on the spectrum of associated cancers with the aim of prevention and early diagnosis. National and international collaboration to build cancer registries will be crucial for an evidenced-based and targeted approach to genetically predisposed individuals.

Conflict of Interest
None declared.

References

1 Rutman AM, Kuo MD. Radiogenomics: creating a link between molecular diagnostics and diagnostic imaging. Eur J Radiol 2009; 70(02):232–241
2 Garber JE, Offit K. Hereditary cancer predisposition syndromes. J Clin Oncol 2005;23(02):276–292
3 Nagy R, Sweet K, Eng C. Highly penetrant hereditary cancer syndromes. Oncogene 2004;23(38):6445–6470
4 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65(02): 87–108
5 Rajkumar T, Soumittra N, Vidubala E, et al. Organization and running of the first comprehensive hereditary cancer clinic in India. Hered Cancer Clin Pract 2005;3(04):165–170
6 Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. Nat Med 2004;10(08):789–799
7 European Society of Radiology (ESR) Medical imaging in personalised medicine: a white paper of the research committee of the European Society of Radiology (ESR). Insights Imaging 2015;6 (02):141–155
8 Kuhlen M, Borkhardt A. Cancer susceptibility syndromes in children in the area of broad clinical use of massive parallel sequencing. Eur J Pediatr 2015;174(08):987–997
9 Kuchenbaecker KB, Hopper JL, Barnes DR, et al; BRCA1 and BRCA2 Cohort Consortium. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 2017;317(23):2402–2416
10 Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003;72(05):1117–1130
11 Mavaddat N, Barrowdale D, Andrulis IL, et al; HEBON. ; EMBRACE. ; GEMO Study Collaborators. ; kConFab Investigators. ; SWE-BRCA Collaborators. ; Consortium of Investigators of Modifiers of BRCA1/2. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). Cancer Epidemiol Biomarkers Prev 2012;21(01):134–147
12 Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DEBreast Cancer Linkage Consortium. Risks of cancer in BRCA1-mutation carriers. Lancet 1994;343(8899):692–695
13 Chen Y, Thompson W, Semenciw R, Mao Y. Epidemiology of contralateral breast cancer. Cancer Epidemiol Biomarkers Prev 1999;8(10):855–861
14 Graeser MK, Engel C, Rhiem K, et al. Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2009;27 (35):5887–5892
15 Tai YC, Domchek S, Parmigiani G, Chen S. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 2007; 99(23):1811–1814
16 Mitchell G, Antoniou AC, Warren R, et al. Mammographic density and breast cancer risk in BRCA1 and BRCA2 mutation carriers. Cancer Res 2006;66(03):1866–1872
17 Tice JA, Cummings SR, Ziv E, Kerlikowske K. Mammographic breast density and the Gail model for breast cancer risk prediction in a screening population. Breast Cancer Res Treat 2005;94(02): 115–122
18 Wernli KJ, Ichikawa L, Kerlikowske K, et al. Surveillance breast MRI and mammography: comparison in women with a personal history of breast cancer. Radiology 2019;292(02):311–318
19 Saadatmand S, Geuzinge HA, et al. FaMRIsc study group. MRI versus mammography for breast cancer screening in women with familial risk (FaMRIsc): a multicentre, randomized, controlled trial. Lancet Oncol 2019;20(08):1136–1147
20 Raikhlin A, Curpen B, Warner E, Betel C, Wright B, Jong R. Breast MRI as an adjunct to mammography for breast cancer screening in high-risk patients: retrospective review. AJR Am J Roentgenol 2015;204(04):889–897 Erratum in: AJR Am J Roentgenol. 2015 May;204(5):1137
21 Girolimetti G, Perrone AM, Santini D, et al. BRCA-associated ovarian cancer: from molecular genetics to risk management. BioMed Res Int 2014;2014:787143
22 Swisher EM, Sakai W, Karlan BY, Wurz K, Urban N, Taniguchi T. Secondary BRCA1 mutations in BRCA1-mutated ovarian carcinomas with platinum resistance. Cancer Res 2008;68(08): 2581–2586
23 Bolton KL, Chenevix-Trench G, Goh C, et al; EMBRACE. ; kConFab Investigators. ; Cancer Genome Atlas Research Network. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. JAMA 2012;307(04): 382–390
24 Evans DG, Gaarenstroom KN, Stirling D, et al. Screening for familial ovarian cancer: poor survival of BRCA1/2 related cancers. J Med Genet 2009;46(09):593–597
25 Stirling D, Evans DG, Pichert G, et al. Screening for familial ovarian cancer: failure of current protocols to detect ovarian cancer at an early stage according to the international Federation of gynecology and obstetrics system. J Clin Oncol 2005;23(24):5588–5596
26 Toss A, Molinaro E, Sammarini M, et al. Hereditary ovarian cancers: state of the art. Minerva Med 2019;110(04):301–319

27 Bougeard G, Renaux-Petel M, Flaman JM, et al. Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. J Clin Oncol 2015;33(21):2345–2352
28 Chompret A, Brugières L, Ronsin M, et al. P53 germline mutations in childhood cancers and cancer risk for carrier individuals. Br J Cancer 2000;82(12):1932–1937
29 Bougeard G, Sesboüé R, Baert-Desurmont S, et al; French LFS working group. Molecular basis of the Li-Fraumeni syndrome: an update from the French LFS families. J Med Genet 2008;45(08): 535–538
30 Hendrickson PG, Luo Y, Kohlmann W, Schiffman J, Maese L, Bishop AJ, Lloyd S, Kokeny KE, Hitchcock YJ, Poppe MM, Gaffney DK, Tao R. Radiation therapy and secondary malignancy in Li-Fraumeni syndrome: A hereditary cancer registry study. Cancer Med 2020. Nov;9(21):7954–7963 Doi: 10.1002/cam4.3427
31 Villani A, Shore A, Wasserman JD, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. Lancet Oncol 2016;17(09):1295–1305
32 Hendrickson PG, Luo Y, Kohlmann W, et al. Radiation therapy and secondary malignancy in Li-Fraumeni syndrome: a hereditary cancer registry study. Cancer Med 2020;9(21):7954–7963
33 Nogueira ST, Lima EN, Nóbrega AF, et al. 18F-FDG PET-CT for surveillance of Brazilian patients with Li-Fraumeni syndrome. Front Oncol 2015;5:38
34 Ballinger ML, Best A, Mai PL, et al. Baseline surveillance in li-fraumeni syndrome using whole-body magnetic resonance imaging: a meta-analysis. JAMA Oncol 2017;3(12):1634–1639
35 Villani A, Tabori U, Schiffman J, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study. Lancet Oncol 2011; 12(06):559–567
36 O'Neill AF, Voss SD, Jagannathan JP, et al. Screening with whole-body magnetic resonance imaging in pediatric subjects with Li-Fraumeni syndrome: a single institution pilot study. Pediatr Blood Cancer 2018;65(02):e26822
37 Tabori U, Shlien A, Baskin B, et al. TP53 alterations determine clinical subgroups and survival of patients with choroid plexus tumors. J Clin Oncol 2010;28(12):1995–2001
38 Orr BA, Clay MR, Pinto EM, Kesserwan C. An update on the central nervous system manifestations of Li-Fraumeni syndrome. Acta Neuropathol 2020;139(04):669–687
39 Frebourg T, Bajalica Lagercrantz S, Oliveira C, Magenheim R, Evans DGEuropean Reference Network GENTURIS. Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes. Eur J Hum Genet 2020;28(10):1379–1386
40 Farhadi F, Nikpanah M, Paschall AK, et al. Clear cell renal cell carcinoma growth correlates with baseline diffusion-weighted MRI in Von Hippel-Lindau disease. Radiology 2020;295(03):583–590
41 Ganeshan D, Menias CO, Pickhardt PJ, et al. Tumors in von Hippel-Lindau syndrome: from head to toe-comprehensive state-of-the-art review. Radiographics 2018;38(03):849–866
42 Jilg CA, Neumann HP, Gläsker S, et al. Nephron sparing surgery in von Hippel-Lindau associated renal cell carcinoma; clinicopathological long-term follow-up. Fam Cancer 2012;11(03):387–394
43 Filling-Katz MR, Choyke PL, Oldfield E, et al. Central nervous system involvement in Von Hippel-Lindau disease. Neurology 1991;41(01):41–46
44 Eisenhofer G, Lenders JW, Timmers H, et al. Measurements of plasma methoxytyramine, normetanephrine, and metanephrine as discriminators of different hereditary forms of pheochromocytoma. Clin Chem 2011;57(03):411–420
45 Mori H, Wakabayashi H, Saito S, et al. Comparison of detectability between WB-MRI and MIBG images in patients with metastatic pheochromocytoma and paraganglioma. J Nucl Med 2021; 62:1111
46 Charlesworth M, Verbeke CS, Falk GA, Walsh M, Smith AM, Morris-Stiff G. Pancreatic lesions in von Hippel-Lindau disease? A systematic review and meta-synthesis of the literature. J Gastrointest Surg 2012;16(07):1422–1428
47 Khanna L, Prasad SR, Sunnapwar A, et al. Pancreatic neuroendocrine neoplasms: 2020 update on pathologic and imaging findings and classification. Radiographics 2020;40(05): 1240–1262
48 Schmid S, Gillessen S, Binet I, et al. Management of von Hippel-Lindau disease: an interdisciplinary review. Oncol Res Treat 2014; 37(12):761–771
49 Binderup ML, Bisgaard ML, Harbud V, et al; Danish vHL Coordination Group. Von Hippel-Lindau disease (vHL). National clinical guideline for diagnosis and surveillance in Denmark. 3rd edition. Dan Med J 2013;60(12):B4763
50 Kruizinga RC, Sluiter WJ, de Vries EG, et al. Calculating optimal surveillance for detection of von Hippel-Lindau-related manifestations. Endocr Relat Cancer 2013;21(01):63–71
51 VHL Family Alliance. The VHL handbook: what you need to know about VHL—a reference handbook for people with von Hippel-Lindau disease, their families, and support personnel. 2020. https://www.vhl.org/care-treatment/resources/
52 Thakker RV. Multiple endocrine neoplasia type 1 (MEN1) and type 4 (MEN4). Mol Cell Endocrinol 2014;386(1-2):2–15
53 Kamilaris CDC, Stratakis CA. Multiple Endocrine Neoplasia Type 1 (MEN1): An Update and the Significance of Early Genetic and Clinical Diagnosis. Front Endocrinol (Lausanne) 2019. Jun11: 10:339. Doi: 10.3389/fendo.2019.00339
54 Moline J, Eng C. Multiple endocrine neoplasia type 2: an overview. Genet Med 2011;13(09):755–764
55 Wells SA Jr, Asa SL, Dralle H, et al; American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 2015;25(06):567–610
56 Eichhorn-Wharry LI, Carlin AM, Talpos GB. Mild hypercalcemia: an indication to select 4-dimensional computed tomography scan for preoperative localization of parathyroid adenomas. Am J Surg 2011;201(03):334–338, discussion 338
57 Nael K, Hur J, Bauer A, et al. Dynamic 4D MRI for characterization of parathyroid adenomas: multi- parametric analysis. AJNR Am J Neuroradiol 2015;36(11):2147–2152
58 Niederle B, Selberherr A, Bartsch DK, et al. Multiple endocrine neoplasia type 1 and the pancreas: diagnosis and treatment of functioning and non-functioning pancreatic and duodenal neuroendocrine neoplasia within the MEN1 syndrome - an International Consensus Statement. Neuroendocrinology 2021;111(07): 609–630
59 Grajo JR, Paspulati RM, Sahani DV, Kambadakone A. Multiple endocrine neoplasia syndromes: a comprehensive imaging review. Radiol Clin North Am 2016;54(03):441–451
60 Iglesias P, Cardona J, Díez JJ. The pituitary in nuclear medicine imaging. Eur J Intern Med 2019;68:6–12
61 Scarsbrook AF, Thakker RV, Wass JAH, et al. Multiple endocrine neoplasia: spectrum of radiologic appearances and discussion of a multitechnique imaging approach. Radiographics 2006;26:433–451
62 Castinetti F, Taïeb D. Positron emission tomography imaging in medullary thyroid carcinoma: time for reappraisal? Thyroid 2021;31(02):151–155
63 Gagel RF, Tashjian AH Jr, Cummings T, et al. The clinical outcome of prospective screening for multiple endocrine neoplasia type 2a. An 18-year experience. N Engl J Med 1988;318(08):478–484
64 de Laat JM, van Leeuwaarde RS, Valk GD. The importance of an early and accurate MEN1 diagnosis. Front Endocrinol (Lausanne) 2018;9:533
65 Peters JM, Prohl AK, Tomas-Fernandez XK, et al. Tubers are neither static nor discrete: evidence from serial diffusion tensor imaging. Neurology 2015;85(18):1536–1545
66 Pollock JM, Whitlow CT, Tan H, Kraft RA, Burdette JH, Maldjian JA. Pulsed arterial spin-labeled MR imaging evaluation of tuberous sclerosis. AJNR Am J Neuroradiol 2009;30(04):815–820

67 Liu S, Cai Y, Rong R, et al. Tuberous sclerosis complex (TSC) with epilepsy on ^{18}F-FDG simultaneous PET/MR. Eur J Nucl Med Mol Imaging 2020;47(10):2471–2472
68 Ruppe V, Dilsiz P, Reiss CS, et al. Developmental brain abnormalities in tuberous sclerosis complex: a comparative tissue analysis of cortical tubers and perituberal cortex. Epilepsia 2014;55(04): 539–550
69 Roth J, Roach ES, Bartels U, et al. Subependymal giant cell astrocytoma: diagnosis, screening, and treatment. Recommendations from the International Tuberous Sclerosis Complex Consensus Conference 2012. Pediatr Neurol 2013;49(06):439–444
70 Jóźwiak S, Nabbout R, Curatolo Pparticipants of the TSC Consensus Meeting for SEGA and Epilepsy Management. Management of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC): Clinical recommendations. Eur J Paediatr Neurol 2013;17(04):348–352
71 Sugalska M, Tomik A, Jóźwiak S, Werner B. Treatment of cardiac rhabdomyomas with mTOR inhibitors in children with tuberous sclerosis complex-a systematic review. Int J Environ Res Public Health 2021;18(09):4907
72 Staehler M, Sauter M, Helck A, et al. Nephron-sparing resection of angiomyolipoma after sirolimus pretreatment in patients with tuberous sclerosis. Int Urol Nephrol 2012;44(06):1657–1661
73 Northrup H, Aronow ME, Bebin EM, et al; International Tuberous Sclerosis Complex Consensus Group. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Pediatr Neurol 2021; 123:50–66

Imaging Recommendations for Diagnosis, Staging, and Management of Hematological Malignancies

Amrita Guha[1]

[1] Department of Radio-diagnosis, Tata Memorial Hospital, Mumbai, Maharashtra, India

Address for correspondence Amrita Guha, MD, DNB, Department of Radio-diagnosis, Tata Memorial Hospital, Mumbai, Maharashtra 400012, India (e-mail: amritaguha85@gmail.com).

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Abstract

The NIC defines hematological cancers as those that begin in blood forming tissues such as bone marrow or cells of the immune system and these broadly include three groups: leukemias, lymphomas, and myelomas. The role of imaging is also fundamentally different between the three main groups of hematological malignancies. While imaging is the main tool for staging as well as treatment response assessment in lymphoma, it represents one of several key criteria for the diagnosis and follow-up of myeloma; whereas in leukemia, imaging has a role to play in the detection and management of treatment-related complications which is a crucial part of post-transplant treatment.

Keywords
- hematology
- medical oncology
- radiology

Introduction

The NIC defines hematological cancers as those that begin in blood forming tissue such as bone marrow or cells of the immune system and these broadly include three groups leukemias, lymphomas, and myelomas.[1] The role of imaging is also fundamentally different between the three main groups of hematological malignancies. While imaging is the main tool for staging as well as treatment response assessment in lymphoma,[2,3] it represents one of several key criteria for the diagnosis and follow-up of myeloma[4]; whereas in leukemia, imaging has a role to play in the detection and management of treatment-related complications which is a crucial part of post-transplant treatment.

In myeloma, whole-body magnetic resonance imaging (WB-MRI) is recognized as a highly sensitive test for the assessment of myeloma, and is also endorsed by clinical guidelines, especially for detection and staging. In lymphoma, WB-MRI is presently not recommended, and merely serves as an alternative technique to the current standard imaging, Flourine-**18** fluorodeoxyglucose positron emission tomography/computed tomography ([18F]FDG-PET/CT), especially in pediatric patients.[5]

Even for lymphomas with variable FDG avidity, such as extranodal mucosa-associated lymphoid tissue lymphoma (MALT), contrast-enhanced CT, but not WB-MRI, is presently recommended, despite the high sensitivity of diffusion-weighted MRI and its ability to capture treatment response that has been reported in the literature.[5] In leukemia, neither MRI nor any other cross-sectional imaging test (including PET) is currently recommended outside of clinical trials.[5]

Epidemiology, Clinical Presentation in India and Global

Almost all of these cancers occur almost a decade earlier in India compared with the West. Possible reasons proposed have included the demographics of the Indian population (largely younger), increased incidence of chronic infections and antigenic stimulation, genetics, and socioeconomic status. The average ASR for multiple myeloma (MM) is 0.1 to 1.9 in India, and around 2.8 to 3.9 in the US, with similar figures for Hodgkin's lymphoma (HL).[6] Incidence of leukemias is between 2.4 and 4.6 per 100,000 when compared with 9.6 to 11 in Canada.[6]

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Imaging Guidelines

Lymphomas

PET-CT is recommended for the routine staging of FDG-avid, nodal lymphomas (essentially all histologies except chronic lymphocytic leukemia/small lymphocytic lymphoma (-CLL/SLL), lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia, mycosis fungoides, and marginal zone non-Hodgkin's lymphomas (NHLs), unless there is a suspicion of aggressive transformation) as the gold standard.[7]

CT scan is preferred in the other lymphomas. A chest X-ray is no longer required in lymphoma staging because it less accurate than CT.[8] Moreover, CT identifies more hilar nodes and may better discriminate between a single large nodal mass and an aggregate of individual nodes.[3]

Definition of bulky disease: A single nodal mass, in contrast to multiple smaller nodes, of 10 cm or greater than a third of the transthoracic diameter at any level of thoracic vertebrae as determined by CT is retained as the definition of bulky disease for HL.[9] A chest X-ray is not required to determine bulk because of its high concordance with CT.[8] However, a variety of sizes have been suggested for NHL[10] with limited evidence suggesting 6 cm as best for follicular lymphoma15 and 6 to 10 cm in the rituximab era for diffuse large-B-cell lymphoma (DLBCL).[11] However, none of the proposed sizes have been validated in the current therapeutic era. Therefore, the recommendation for HL and NHL is to record the longest measurement by CT scan, with the term X no longer necessary.[3]

If a PET-CT is performed, a bone marrow aspirate/biopsy is no longer required for the routine evaluation of patients with HL. In DLBCL, PET-CT is also more sensitive than bone marrow biopsy (BMB) but has been reported to miss low-volume diffuse involvement of 10 to 20% of the marrow.[12] If the scan is negative, a BMB is indicated to identify involvement by discordant histology if relevant for a clinical trial or patient management.[13]

Response Assessment

Lugano's criteria are used for response assessment as summarized in ►**Table 1**.[18] End-of-treatment assessment is more accurate with PET-CT, especially for patients with radiologic (CT) CRu or partial response (PR) in HL, DLBCL, and follicular lymphoma.[3] PET-CT-based criteria eliminate CRu and improve the prognostic value of PR. In early- and advanced-stage patients with HL, a negative predictive value of 95 to 100% and a positive predictive value of more than 90% have been reported.[14,15] In aggressive NHL, studies have reported a negative predictive value of 80 to 100%, but a lower positive predictive value, ranging from 50 to 100%.[16]

A CT-based response is preferred for histologies with low or variable FDG avidity and in regions of the world where PET-CT is unavailable. However, in the absence of a PET-CT scan, a mass that has decreased in size but persists is considered at best a PR in the absence of a biopsy documenting the absence of lymphoma, and the former term CRu is not to be considered.7

Summary of response and follow-up strategies as per the IWG, NCCN, and ESMO criteria are as follows[3]:

1) PET-CT should be used for response assessment in FDG-avid histologies, using the 5-point scale; CT is preferred for low or variable FDG avidity.
2) A complete metabolic response even with a persistent mass is considered a complete remission.
3) A PR requires a decrease by more than 50% in the sum of the product of the perpendicular diameters of up to six representative nodes or extranodal lesions.
4) Progressive disease by CT criteria only requires an increase in the PPDs of a single node by more than or equal to 50%.
5) Surveillance scans after remission are discouraged, especially for DLBCL and HL, although a repeat study may be considered after an equivocal finding after treatment.
6) Judicious use of follow-up scans may be considered in indolent lymphomas with residual intra-abdominal or retroperitoneal disease.

PET-CT is used for staging and response assessment of lymphomas, during treatment (interim PET) and for remission assessment at the end of treatment.[7] MRI is the modality of choice for suspected central nervous system lymphoma.

Mantle-cell lymphoma is routinely FDG avid; limited data suggest that the sensitivity and specificity of identifying bowel involvement is low and should not replace other investigative measures.

The standard response criteria currently in use for lymphoma are the Lugano criteria which are based on [18F]FDG-PET or bidimensional tumor measurements on computerized tomography scans. These differ from the RECIST criteria used in solid tumors, which use unidimensional measurements.

Imaging Guidelines of Leukemias

PET imaging is considered investigational and experimental for all indications in acute lymphoblastic leukemia, acute myeloid leukemia, and chronic myeloid leukemia. Routine advanced imaging is not indicated in the evaluation and management of chronic myeloid leukemias, myelodysplastic syndromes, or myeloproliferative disorders in the absence of specific localizing clinical symptoms or clearance for hematopoietic stem cell transplantation.[17]

CLL/SLL: PET imaging is not indicated in the evaluation of CLL/SLL except for suspected Richter's transformation.

Suspected transformation (Richter's) from a low-grade lymphoma to a more aggressive type is based on one or more of the following: New B symptoms, rapidly growing lymph nodes, development of extranodal disease, a significant recent rise in LDH above normal range- A PETCT may be advisable in such cases.[18]

Imaging Guidelines for Post-Hematopoietic Stem Cell Transplantation (HSCT)

Selected patients of leukemias/lymphomas are offered HSCT and imaging plays a very important role in surveillance of these patients.

Table 1 Lugano response criteria for PET-CT follow-up in lymphomas[28]

Modality	Complete response	Partial response	Stable disease	Progressive disease
CT	Lymph modes $\leq$ 1.5 cm in Ldi Complete disappearance of radiologic evidence of disease	Single lesion: $\downarrow \geq$ 50% in PPD Multiple lesions: $\downarrow \geq$ 50% in SPD of up to six lymph nodes or extranodal sites	$\downarrow \leq$ 50% in SPD of up to six lymph nodes or extranodal sites (no criteria for progressive disease are met)	1) New lymphadenopathy or $\uparrow$; single node must be abnormal with: a) Ldi $>$ 1.5 cm and b) PPD $\geq$ 50% and c) Ldi or Sdi $\uparrow$ 0.5 cm if $\leq$ 2.0 cm and $\uparrow$ 1.0 cm if $>$ 2.0 cm
				2) $\uparrow$ splenic volume: a) with prior splenomegaly: $\uparrow >$ 50% of its prior $\uparrow$ beyond baseline b) without prior splenomegaly: $\uparrow >$ 2.0 cm c) New or recurrent splenomegaly
				3)New or Larger non measured lesions
				4) Recurrent previously resolved lesions
				5) New extranodal lesion $>$ 1.0 cm in any axis (new lesions $<$ 1.0 cm in any axis are included if attributable to lymphoma)
FDG-PET-CT	Scores 1, 2, 3 in nodal or extra nodal sites with or without a residual mass	Scores 4 or 5 with $\downarrow$ uptake compared with baseline and residual mass(es)	Scores 4 or 5 with no obvious change in FDG uptake	Scores 4 or 5 any lesion with $\uparrow$ uptake from baseline and /or new FDG-avid foci

Abbreviations: FDG-PET-CT, fluorodeoxyglucose positron emission tomography/computed tomography; LDi,—; PPD,—; SPD,—.

Pretransplant Imaging in HSCT: This imaging generally takes place within 30 days prior to transplant, and involves a reassessment of the patient's disease status as well as infectious disease clearance. CT of the sinuses, neck, chest, and/or abdomen/pelvis is recommended. Nuclear renal function study to ensure adequate renal function and echocardiogram are routinely indicated to ensure adequate cardiac function to proceed with the transplant.

Post-transplant Imaging in HSCT: There are many common complications from HSCT, including infection, graft versus host disease, hepatic sinusoidal obstruction syndrome, restrictive lung disease, among others. These can be classified into early (less than 30 days) and delayed (more than 100 days) complications.

These patients often require several CT chest scans in the post-transplant period due to their susceptibility to infection (most commonly lung). At the very least, scans for disease response generally takes place at day 30 and day 100 post-transplant. CT chest without contrast is indicated for patients with bronchiolitis obliterans with organizing pneumonia, a delayed post-transplant complication for surveillance and evaluation of acute changes.

Imaging Guidelines of Myelomas

Plasma cell disorders range from the spectrum of the mostly benign monoclonal gammopathy of unknown significance to the intermediate smoldering multiple myeloma to the frankly malignant MM.[19] Imaging of bone lesions forms a major stay in the diagnosis and management of MM. The CRAB criteria: Hyper***c***alcemia, ***R***enal insufficiency, ***A***naemia and ***B***one lesions—at least one or more bone lesions on X-Ray/CT/PET-CT—form the four pillars upon which a diagnosis is made in patients with clonal bone marrow plasma cells more than 10%.[19]

At least one well-defined lytic lesion of diameter greater than 5mm is necessary to satisfy the bony lesion category of CRAB lesions.[4] Advances in cross-sectional imaging have led the IMWG to form newer guidelines with the definition of myeloma-defining events) in which at least two or more focal lesions in the marrow of size greater than 5 mm can be used to make the diagnosis, in the absence of focal lytic lesions on X-ray or CT.[4] Newer advanced sequences like diffusion-weighted imaging with background suppression (DWIBS) have also helped to increase sensitivity and specificity of bony lesion detection; however, their inclusion into a formal role as defining criteria is awaited pending further research.

Imaging Guidelines

For screening and diagnosis:

1) X-ray is not to be used unless it is the only modality available. Similarly, there is no role of technetium scans.[20]
2) Whole-body low-dose CT (WBLDCT) is the ideal screening tool. It is the scan with arms over the head (to reduce beam hardening artifacts on vertebrae if arms are placed on the side of the body).[21] Even one focal lesion of size greater than 5 mm is sufficient for diagnosis.[22]
3) In clinically suspected MM patients who are screening negative on WBLDT, WBMRI is strongly advised.[23] Conventional T1 sequences pick up marrow infiltration and diffusion-weighted imaging has been shown to be the single most sensitive sequence.[22]
4) Imaging of bone marrow is the opposite of imaging findings elsewhere in the body: Normal bone marrow shows restricted diffusion with low apparent diffusion coefficient (ADC) values, whereas disease (-metastases/myeloma) leads to a facilitated diffusion with a progressive increase in ADC values. ADCs of normal bone marrow is very low (range, $0.2–0.5 \times 10^{-3}$ mm^2/sec), whereas a value greater than 0.597×10^{-3} mm^2/s showed 96% sensitivity and 100% specificity for MM.[24]
5) DWIBS**:** It is a free-breathing sequence wherein multiple thin slice axial sections of the whole body are acquired. It relies on the relatively unchanged "incoherent" motion within a voxel during respiration where the "coherent" motion is affected. It is the incoherent motion of the water molecules that determines diffusivity. This

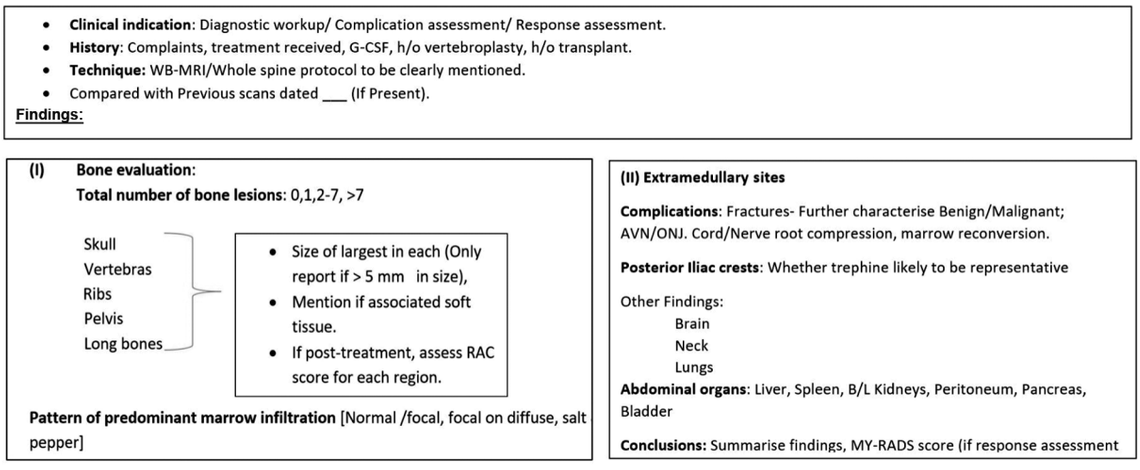

Fig. 1 Structured reporting format of myelomas.[27] AVN,—; G-CSF,—; MY-RADS, Myeloma Response Assessment and Diagnosis System; ONJ,—; RAC,—; WB-MRI, whole body magnetic resonance imaging.

sequence is commonly acquired in the coronal plane and short tau inversion recovery sequence is the commonly employed pre-pulse fat saturating sequence that is combined with DWIBS to achieve uniform fat suppression.[25] B values generally range from 800 to 1000 seconds mm^2.

For post-treatment assessment: 18 FDG-PET-CT is the gold standard for assessing post-treatment response. Complete suppression of FDG avidity on post-therapy scans confers increased overall survival and serves as a good prognostic marker.[26]

Structured Reporting System

In an effort to promote standardization and diminish variations in the acquisition, interpretation, and reporting of whole-body MRI in myeloma and allow response assessment, the IMWG and NICE UK group together developed the Myeloma Response Assessment and Diagnosis System (MY-RADS).[27] A sample of the reporting template is described below (►**Fig. 1**).

Disclaimer

This article is not an original paper and is only a compilation of imaging guidelines from various sources, which have been cited appropriately.

Conflict of Interest

None declared.

References

1 Definition of hematologic cancer - NCI Dictionary of Cancer Terms - National Cancer Institute. Accessed December 21, 2022, at: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/hematologic-cancer

2 Younes A, Hilden P, Coiffier B, et al. International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). Ann Oncol 2017;28(07):1436–1447

3 Cheson BD, Fisher RI, Barrington SF, et al; Alliance, Australasian Leukaemia and Lymphoma Group Eastern Cooperative Oncology Group European Mantle Cell Lymphoma Consortium Italian Lymphoma Foundation European Organisation for Research Treatment of Cancer/Dutch Hemato-Oncology Group Grupo Español de Médula Ósea German High-Grade Lymphoma Study Group German Hodgkin's Study Group Japanese Lymphorra Study Group Lymphoma Study Association NCIC Clinical Trials Group Nordic Lymphoma Study Group Southwest Oncology Group United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32(27):3059–3068

4 Chantry A, Kazmi M, Barrington S, et al; British Society for Haematology Guidelines. Guidelines for the use of imaging in the management of patients with myeloma. Br J Haematol 2017;178(03):380–393

5 Mayerhoefer ME, Archibald SJ, Messiou C, Staudenherz A, Berzaczy D, Schöder H. MRI and PET/MRI in hematologic malignancies. J Magn Reson Imaging 2020;51(05):1325–1335

6 Bhutani M, Vora A, Kumar L, Kochupillai V. Lympho-hemopoietic malignancies in India. Med Oncol 2002;19(03):141–150

7 Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 2014;32(27):3048–3058

8 Bradley AJ, Carrington BM, Lawrance JAL, Ryder WDJ, Radford JA. Assessment and significance of mediastinal bulk in Hodgkin's disease: comparison between computed tomography and chest radiography. *Citeseer*. 17:2493–2498. Accessed December 21, 2022, at: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.982.5563&rep=rep1&type=pdf

9 Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7(11):1630–1636

10 Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol 2009;27(27):4555–4562

11 Pfreundschuh M, Ho A, Cavallin-Stahl E oncology MW-T lancet, 2008 undefined. Prognostic significance of maximum tumour (bulk) diameter in young patients with good-prognosis diffuse large-B-cell lymphoma treated with CHOP-like. *Elsevier*. Accessed December 21, 2022, at: https://www.sciencedirect.com/science/article/pii/S1470204508700780

12 Pelosi E, Penna D, Douroukas A, et al. MB-TQJ, 2010 undefined. Bone marrow disease detection with FDG-PET/CT and bone marrow biopsy during the staging of malignant lymphoma: results from a large multicentre study. *europepmc.org*. Accessed December 21, 2022, at: https://europepmc.org/article/med/21150862

13 Paone G, Itti E, Haioun C, et al. Bone marrow involvement in diffuse large B-cell lymphoma: correlation between FDG-PET uptake and type of cellular infiltrate. Eur J Nucl Med Mol Imaging 2009;36(05):745–750

14 Cerci JJ, Pracchia LF, Linardi CCG, et al. 18F-FDG PET after 2 cycles of ABVD predicts event-free survival in early and advanced Hodgkin lymphoma. J Nucl Med 2010;51(09):1337–1343

15 Engert A, Haverkamp H, Kobe C, et al; German Hodgkin Study Group Swiss Group for Clinical Cancer Research Arbeitsgemeinschaft Medikamentöse Tumortherapie. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. Lancet 2012;379(9828):1791–1799

16 Mikhaeel NG, Timothy AR, Hain SF, O'Doherty MJ. 18-FDG-PET for the assessment of residual masses on CT following treatment of lymphomas. Ann Oncol 2000;11(Suppl 1):147–150

17 Conte MJ, Bowen DA, Wiseman GA, et al. Use of positron emission tomography-computed tomography in the management of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. Leuk Lymphoma 2014;55(09):2079–2084

18 Mauro FR, Chauvie S, Paoloni F, et al. Diagnostic and prognostic role of PET/CT in patients with chronic lymphocytic leukemia and progressive disease. Leukemia 2015;29(06):1360–1365

19 Guha A, Vijan A, Agarwal U, et al. Imaging for plasma cell dyscrasias: what, when, and how? Front Oncol 2022;12:825394. Doi: 10.3389/FONC.2022.825394

20 Hillengass J, Usmani S, Rajkumar SV, et al. International Myeloma Working Group consensus recommendations on imaging in monoclonal plasma cell disorders. Lancet Oncol 2019;20(06):e302–e312

21 Ormond Filho AG, Carneiro BC, Pastore D, et al. Whole-body imaging of multiple myeloma: diagnostic criteria. Radiographics 2019;39(04):1077–1097

22 Lecouvet FE. Whole-body MR imaging: musculoskeletal applications. Radiology 2016;279(02):345–365

23 Rajkumar S, Dimopoulos M, Palumbo A oncology JB-T lancet, 2014 undefined. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Elsevier*. Accessed December 21, 2022, at: https://www.sciencedirect.com/science/article/pii/S1470204514704425

24 Koutoulidis V, Fontara S, Terpos E, et al. Quantitative diffusion-weighted imaging of the bone marrow: an adjunct tool for the diagnosis of a diffuse MR imaging pattern in patients with multiple myeloma. Radiology 2017;282(02):484–493
25 Bergstrom DJ, Kotb R, Louzada ML, Sutherland HJ, Tavoularis S, Venner CPMyeloma Canada Research Network Consensus Guideline Consortium. Consensus guidelines on the diagnosis of multiple myeloma and related disorders: recommendations of the myeloma Canada research network consensus guideline consortium. Clin Lymphoma Myeloma Leuk 2020;20(07):e352–e367
26 Nanni C. PET/CT with standard non-FDG tracers in multiple myeloma. Mol Imaging Mult Myeloma 2019;93–97;. Doi: 10.1007/978-3-030-19019-4_7
27 Messiou C, Hillengass J, Delorme S, et al. Guidelines for acquisition, interpretation, and reporting of whole-body MRI in myeloma: myeloma response assessment and diagnosis system (MY-RADS). Radiology 2019;291(01):5–13
28 Van Heertum RL, Scarimbolo R, Wolodzko JG, et al. Lugano 2014 criteria for assessing FDG-PET/CT in lymphoma: an operational approach for clinical trials. Drug Des Devel Ther 2017;11:1719–1728

Imaging Recommendations for Positron Emission Tomography (PET) in Oncology

Arvind K. Chaturvedi[1] Abhishek Mahajan[2] Saugata Sen[3] Shivakumar S. Swamy[4] Diva Shah[5] Nivedita Chakrabarty[6]

[1] Department of Radiology, Rajiv Gandhi Cancer Institute, New Delhi, India
[2] Department of Radiodiagnosis, The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, United Kingdom
[3] Department of Radiology and Imaging Sciences Tata Medical Center, Kolkata, West Bengal, India
[4] Department of Radiology, HCG, Bangalore, Karnataka, India
[5] Department of Radiodiagnosis, HCG Cancer Centre, Ahmedabad, Gujarat, India
[6] Department of Radiodiagnosis, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, Maharashtra, India

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

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Abstract

Cancer is one of the leading causes of morbidity and mortality. Imaging studies are central to the initial staging and follow-up management of cancers. In the past, oncologists have largely relied on anatomical imaging for staging, restaging, and therapy monitoring. The introduction of positron emission tomography-computed tomography (PET-CT) and its availability has transformed the practice of cancer imaging. PET-CT is an imaging technique that provides complementary information to imaging by CT or magnetic resonance imaging alone as it incorporates functional imaging to the anatomic information. It actually embeds tumor biology on the anatomical image. There are significant contributions of the CT component in adding value to the strength of PET-CT. PET-CT is useful for initial staging of cancers. It is particularly useful in detection of distant metastases, in assessing response to therapy and in detection of recurrence. Its utility in restaging and follow-up of cancers is now well established. Its role varies across different primary cancer sites. To cover the role of PET-CT in all cancer types is neither the intention nor feasible in a single article. In this article, an attempt will be made to highlight the generic concepts of PET-CT imaging and its role in primary staging and post-therapy follow-up across some common malignancies. Its pitfalls and limitations will also be discussed.

Keywords
- imaging
- oncology
- PET-CT

Principles of PET-CT Scanning

Cancer cells proliferate and grow by rapidly metabolizing glucose to lactate. Increased glucose uptake in cancer cells is the key to positron emission tomography-computed tomography (PET-CT) imaging.[1,2] However, you need to identify a glucose analogue that will follow the same metabolic pathways as glucose but will render itself to be detected by imaging. The glucose analogue 18F-fluoro-2-deoxyglucose (FDG) is the most widely used PET-CT radiopharmaceutical

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in clinical routine. Its uptake and trapping in cancer cells can be picked up by a PET-CT scanner as it is unstable. It is an isotope that emits positrons. The positrons are positively charged and readily combined with a freely available negatively charged electron. When the positron and electron collide, they both disappear. This process is called annihilation and it ends in releasing the gamma rays that are detected by a PET-CT scanner.

Availability and Indications for PET-CT

When it comes to high-end imaging studies, particularly PET-CT there are significant global inequities. The availability and cost of PET-CT remain a major issue. The logistics for transport of FDG is another bottleneck as it has a half-life of 110 minutes and needs a cyclotron for its production. Within India most PET-CT scanners are clustered in big cities with hardly any visible availability in tier-2 and tier-3 cities. While an affording patient in a big city has easy and quick access to PET-CT, a needy patient in a remote area may never get one. The referring physicians are over enthusiastic and quick to order a PET-CT regardless of the evidence in a particular situation. Since there are no strict guidelines in India, we often find indiscriminate use or misuse of PET-CT. As most patients pay out of pocket, there is hardly any audit or control by a regulatory body. It is estimated that 20% of PET-CT scans ordered in India are not in line with evidence-based practice.

In the United States, insurance coverage for PET-CT was driven by evidence-based data. The Center for Medicare and Medicaid Services authorized coverage for different cancers over a period of time based on evidence.[3] Their strategy has been coverage with evidence development. As of now most cancers are covered for reimbursement. However, it is not covered for screening. Initially the terminology used for initial scan was for "diagnosis and staging." For subsequent scan, the terminology was for "restaging and monitoring response to treatment." The current terminology is PET-CT for initial treatment strategy and PET-CT for subsequent treatment strategy. The cancers that are now covered are colorectal, esophagus, head and neck (T3,T3 tumors or bulky nodes), lymphoma, non-small cell lung cancer (NSCLC), ovary, brain, cervix (except for initial treatment strategy), small cell lung cancer (SCLC), soft tissue sarcoma, pancreas, testes, prostate (not for initial treatment strategy), thyroid, breast (for distant metastases), melanoma, myeloma, and other solid tumors in a specific situation. However, there is a limit on the number of PET-CT scans that can be covered for subsequent management after completion of initial anticancer therapy. The total number of PET-CT scans to guide subsequent treatment strategy cannot exceed three.

Preparation before PET-CT Scan

Adequate hydration is recommended as it would ensure reduced FDG concentration in the urine.[4] This will minimize artifacts. Consumption of 1 L of water prior to FDG injection is helpful. Oral contrast agent is usually not given even for a diagnostic CT scan.

Glucose containing parenteral nutrition and intravenous fluids should be stopped 4 hours before the FDG injection. After the injection of FDG, the patient should remain seated or recumbent and silent. Remaining silent will minimize FDG uptake in laryngeal muscles. The patient should be kept warm to minimize FDG agglomeration in brown fat. Patients must avoid any exercise or physical activity for minimum 24 hours prior to the PET-CT examination. Patients should empty the bladder immediately before the study to minimize urinary bladder activity. The patient should not move during the examination which will take approximately 20 to 40 minutes.

Serum glucose level prior to FDG administration should be checked. For FDG-PET-CT study, plasma glucose level has to be below 11 mmol/L (~200 mg/dL). Levels equal to or higher than 11 mmol/L (~200 mg/dL) requires rescheduling of PET-CT.

Breast Cancer

PET-CT is not recommended for routine staging of early-stage breast cancer. National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology, Spanish Society of Medical Oncology, and the National Institute for Care Excellence, UK, do not recommend PET-CT in females having early-stage (I or II) breast cancer or even in those with operable stage III breast cancer.[5] However, there are situations where a PET- CT can pick up distant metastases in the bone, soft tissues, or elsewhere thereby changing the initial management strategy, which can happen in locally advanced breast cancer, breast cancer with extensive axillary lymphadenopathy, and triple negative breast cancers. Therefore, it appears reasonable to evaluate such cases with PET-CT which is superior to CT or magnetic resonance imaging (MRI) for detecting distant metastases.

Head and Neck Cancers

The prevalence of head and neck cancers is high in India.

The usual malignancies in the head and neck region are as follows:

1. Head and neck squamous cell carcinoma (HNSCC).
2. Thyroid cancer, mainly papillary cancer.
3. Nasopharyngeal cancer (NPC)
4. Lymphoma (systemic or confined to the neck glands)
5. Minor salivary gland cancers
6. Rhabdomyosarcoma
7. Retinoblastoma

Unless otherwise stated, this part of the article mainly deals with HNSCC.

Imaging for the malignancies in the head and neck is required for:

a. Primary staging
b. Radiotherapy planning
c. Treatment response and post-treatment follow-up

A. Primary staging
   Tumor-node-metastasis (TNM) staging guidelines, NCCN, and American Society of Clinical Oncology (ASCO) have all advocated the use of contrast-enhanced CT (CECT) or MRI in the primary staging of HNSCC.[6] This is in contrast to lymphoma, where a pre-therapy, interim, and post therapy 18F-FDG-PET-CT (PET-CT) is recommended.
   Indications of PET-CT in staging of malignancies in the head and neck are limited. NCCN advocates CECT or contrast-enhanced MRI (CEMRI) for the initial staging of both the primary site and for nodal staging. In case of failure of detection of primary on cross-sectional imaging, PET-CT may be used. PET-CT may also be used to guide biopsy and interventions for proper and better sampling especially in the nodes.
   For nodal disease too, cross-sectional imagings (CECT, CEMRI) are proposed. When nodal disease reaches midline and a surgical approach is contemplated, PET-CT may be used to assess the contralateral neck.[7] Again, when there is high nodal burden and chances of distant metastasis is high, PET-CT may be considered.
   In HNSCC, if the primary is advanced (T3 or T4 stage) or there is a large neck nodal burden, PET-CT may be considered to exclude distant metastasis.
   In NPC, PET-CT may be considered for whole body staging when there are nodes below the level of cricoid cartilage or when the nodes are larger than 6 cm. Again, in thyroid cancers, nodes in the retropharyngeal region mandate exclusion of distant metastasis, which may be performed by PET-CT.
B. Radiotherapy planning
   PET-CT guided planning for radiotherapy has been used in head and neck cancer. It has proven superior to CT-based planning in delineating tumor volume, especially in post-surgery neck. There is a high negative predictive value of PET-CT for neck nodes and this helps in planning radiotherapy as well, both in upfront treatment and in post-surgical subjects.
C. Treatment response and post-treatment follow-up

CECT or CEMRI is usually performed for follow-up after local and or systemic therapy. In case of locoregionally advanced disease, PET-CT may be performed for follow-up. PET-CT should be done minimum 3 to 6 months after radiation therapy as there may be high false-positives if done within 3 months.

PET-CT is the initial imaging modality of choice if residual disease is suspected after definitive radiotherapy and where surgery is contemplated.

For lymphoma, as discussed, PET-CT is the best choice in primary staging, interim, follow-up as well as post-therapy imaging.

Pitfalls

Tuberculous nodes are FDG avid and may cause confusion in a patient with known malignancy undergoing a staging scan. Many patients develop infection after chemotherapy and again false-positive findings on PET-CT cause confusions. PET-CTs performed within 3 to 6 months of surgery or radiotherapy are prone to false-positive findings due to post treatment inflammation.

Recommendation for India

In India, the constraints of widespread use of PET-CT are expense and availability of scanners and cyclotrons for generation of the isotope. The scan being an outpatient procedure is not covered by insurance and is, hence, an out-of-pocket expense. Almost all tier-2 cities are devoid of scanner and it is only of late that all aircrafts are being allowed to carry isotopes. One must also consider the guidelines that clearly have no significant role of use of this scan in first-line staging of all patients as well as for follow-up.

In HNSCC, PET-CT for routine evaluation is justified only if residual/recurrent disease post-radiotherapy is suspected and surgery is being contemplated. Assessment of response at least 12 weeks after chemoradiation may be helpful in avoiding unnecessary neck dissection. Cervical lymph node metastases with unknown primary are another reasonable indication for doing a PET-CT.[7] It provides value in initial staging of stage III and IV HNSCC. It is not recommended for routine surveillance after 6 months of completion of therapy.

Colorectal Cancer

Colorectal cancer (CRC) ranks third in males and second in females among most common cancers and is responsible for 10% of all tumor types globally. In India, colon and rectal cancers are 9th and 10th most common cancers in males respectively. As far as females in India are concerned, colon cancer ranks 9th, while rectal cancer does not figure in the list of top 10 cancers.[8] In the last decade, mortality rate of CRC has significantly reduced due to advancement in imaging technology and optimization of surgical, neoadjuvant and palliative therapies. Adenocarcinoma is most common cancer affecting colon or rectum, while other less common cancers of colon include gastrointestinal stromal tumors lymphoma, carcinoid, neuroendocrine, and squamous cell carcinoma.[9] Certain hereditary syndromes like familial adenomatosis polyposis, lynch syndrome, and Peutz-Jeghers syndrome are associated with colonic polyp or cancers and genetic testing has significant role in such patients.

Coloscopy remains the gold standard for primary evaluation of CRCs. It gives a benefit to simultaneous biopsy from the lesion and in same sitting also gives an opportunity for therapeutic polypectomy for small size polyps. Alternative method includes virtual CT colonoscopy and it is recommended as screening tool in an asymptomatic patient by American Cancer Society. Imaging in CRCs has significantly evolved over the time and it has established central role in screening to surveillance of CRC. Various modalities range from barium enema, multi-detector computed tomography (MDCT), MRI to the development of novel tracers, and fusion technologies (PET-CT). PET-CT has evolving role in CRC.

Role of PET-CT in Screening

Many colon cancers develop from preexisting colonic polyps or adenoma and also associated with many hereditary polyposis syndromes. Screening tool should be safe, accurate, easily available, and cost-effective. Normal lymphoid tissue in colon may cause focal or diffuse physiological uptake, and in the same way, inflammatory conditions like ulcerative colitis and diverticulitis can cause focal uptake on FDG-PET-CT; thus, PET becomes least suitable modality for screening of colon cancer or premalignant conditions like polyposis. FDG-PET should not be used as a routine screening or initial staging of CRC patients.

PET-CT in Diagnosis and Primary Staging

Entire tumor removal and regional lymphadenectomy carry the best prognosis for CRC.

PET-CT is suboptimal for T-staging of the primary tumor due to limited spatial resolution and failure to differentiate layers of colon and rectum.

Due to better visualization of anatomic details, transrectal ultrasound and MRI are excellent for T-staging of rectal cancers. MRI is the most reproducible method for T staging of rectal cancers and for tumors of the anal canal. Post-contrast MDCT is standard of imaging investigations for cancers of colon cranial to the peritoneal reflection.

Accurate staging also requires nodal staging and evaluation of distant metastasis accurately.

PET-CT is invaluable for differentiating benign from malignant nodes at a distant location from the primary tumor owing to the metabolic activity. However, small nodes in the proximity to the primary tumor can evade detection owing to FDG uptake of the primary tumor. PET-CT also has limitations in detection of nodal metastasis from mucinous CRC as it does not show significant uptake, small size nodes appear false-negative; while associated inflammatory conditions give false-positive in normal size or in enlarged nodes.[10]

FDG-PET has increased sensitivity than CT for identifying liver metastasis and mild peritoneal and omental disease. FDG-PET shows highest accuracy of up to 98% in identification of hepatic metastases. Early detection of hepatic metastasis in colorectal carcinoma provides opportunity of neoadjuvant chemotherapy followed by liver resection. FDG-PET, due to its superiority in identifying extrahepatic metastatic sites, also helps in management decision making as the treatment plan then changes from localized treatment to systemic chemotherapy.

PET-CT in Restaging, Recurrence, and Surveillance in CRC

Colon cancer recurs in a different pattern as compared with the rectal cancer. Rectal cancers recur more locally than colon cancers. For suspected recurrence due to clinical symptoms or rising tumor marker levels, PET has an established role for recurrence detection. FDG-PET is also superior in response evaluation post-radiotherapy, chemoradiation, or local ablative treatment.

On post-treatment scan for response assessment, PET-CT provides useful information on presence of viable tumor, distinguishes disease from fibrosis/scar, and also helps in prognostication. PET-CT also add benefits in rectal cancer patients who develop local recurrence following chemoradiations. PET-CT plays an important role in surgical planning of patients who develop recurrence in the form of operable hepatic or pulmonary metastasis. Although PET-CT is an optimal method for restaging and monitoring treatment response following chemoradiation, many issues like lack of standardization for optimal timing of imaging, universal criteria for response evaluation, and cost-effectiveness offer challenges. In India, MDCT is still most commonly used modality for surveillance and therapeutic monitoring.

PET-CT in Radiation Therapy Planning for CRC

PET-CT guided planning for radiotherapy has been used for CRC patients. Radiation portal field size can be reduced without omitting macroscopic disease in the vicinity of primary tumor by using PET-CT for radiotherapy planning. PET-defined gross tumor volume (GTV) is invaluable for planning the boost volume for adjuvant radiation therapy post-rectal tumor resection.

The development of PET-CT has a considerable impact in decision making and intention to treat from curative to palliative in locally advanced CRCs. However, major limitations of PET-CT include technical, economical, and logistic challenges, as well as lack of robust evidence for standardization and formal guidance for PET-CT protocols in staging, restaging, and surveillance at present. Future implications of development of PET-CT as standard imaging tool for evaluation of CRC will depend upon newer PET-CT machines with radiation dose reduction, better spatial resolution, latest cost-effective isotopes having increased specificity, and more importantly oncologist and cancer imaging specialist jointly working on patient management.

Current Recommendations

- PET-CT scan is not recommended as a standard screening tool for CRCs or for the evaluation of premalignant conditions.[10]
- For staging, PET-CT is not routinely used, unless initial CT study suggestive of hepatic metastasis or when there is diagnostic dilemma for hepatic or extrahepatic metastases on CT scan or on MRI. MRI is standard imaging tool for staging of rectal cancers and MDCT for colon cancer.
- PET-CT scan is not routinely indicated for restaging after nonsurgical treatment of metastatic CRC, unless curative resection is considered.
- PET-CT scans are recommended for staging/restaging in surgical resection of hepatic or pulmonary metastasis.

Pitfalls and Challenges of PET-CT Scanning

Lack of standardization across institutions
Mucinous and other non-FDG-avid tumors

Cyclotron and costs
Nonspecific inflammation
Radiation.

PET-CT in Lung Cancer

Role of PET-CT in the management of lung cancer has immensely increased in recent times.[11–14] Amalgamation of functional and anatomic information has allowed PET-CT to look into various aspects of lung cancer, allowing more precise disease staging and providing helpful data during the characterization of indeterminate pulmonary nodules. Moreover, increased accuracy of PET-CT over conventional modalities in certain situations has made PET-CT an invaluable noninvasive modality for the investigation of lung cancer.

Common indications for PET-CT with regard to pulmonary nodules or masses are as follows;

- For TNM staging of the mediastinum and screening for metastases that might not be detected by CT alone;
- For radiotherapy planning; and
- For restaging lung cancer patients following treatment.

In addition, PET-CT can provide some information on the histopathological type of lung mass. PET-CT is useful for staging and restaging of disease, detecting recurrent or residual disease, assessing response to therapy, and for prognostication. Prior studies evaluating preoperative maximum standardized uptake value have shown that lepidic predominant adenocarcinoma and other well-differentiated tumors have less FDG-avidity than squamous cell carcinomas.[15] Ninety percent of all lung cancer cases are NSCLC on histological analysis.

As per the NCCN imaging appropriateness criteria, FDG-PET-CT covering skull base to knees or whole-body FDG-PET-CT is recommended for stage I to stage IV NSCLC.[13,16] As per the NCCN guidelines, distant disease detected on PET-CT requires histopathologic or other imaging confirmation, and FDG uptake detected in mediastinal nodes requires histopathologic confirmation. Incidental lung nodule more than 8 mm requires FDG-PET-CT for evaluation as per the NCCN guidelines.

Standardized uptake value more than that of the baseline mediastinal blood pool is considered as a positive PET result. False-negative results of PET can be seen in small nodules, generally less than 8 to 10 mm in diameter (T1a), mucinous adenocarcinomas with a relatively small number of cells, and low-grade malignancies such as carcinoma in situ (Tis) and minimally invasive adenocarcinoma [T1a(mi)]. Occult metastases detected on FDG-PET-CT in locally advanced NSCLC can help to reduce the frequency of futile thoracotomies.

The rates of progression-free survival and overall survival are dismal ($p < 0.001$) in upstaged disease with PET-CT. There is no recommendation to use bone scintigraphy for staging NSCLC. FDG-PET-CT can better differentiate tumor from postobstructive atelectasis than CT, the distinction essential for local tumor staging, deciding biopsy site, planning radiation therapy, and evaluation of treatment response. Studies have shown increased FDG uptake in areas of atelectasis as compared with normal lung, and reduced FDG uptake as compared with tumor tissue. Gross tumor volume assessed using PET tends to be smaller than CT-measured tumor volume in 13 to 17% of patients. Disadvantage of FDG-PET-CT lies in the evaluation of chest wall invasion owing to blooming artifact.

Conclusion

PET has high accuracy in detecting lymph nodal as well as extrathoracic metastases.[15] As per the NCCN guidelines, FDG-PET-CT covering skull base to knees or whole-body FDG-PET-CT is recommended for stage I to stage IV NSCLC.[14] Imaging specialists should be aware of the advantages and disadvantages of FDG-PET-CT in staging.

Summary and Conclusions

Emergence and availability of PET-CT have transformed the way we stage and manage cancers. It has a proven role for staging of most cancers, assessing response to therapy, and in follow-up. Guidelines for the use of PET-CT in oncology vary across countries and across institutions. In the light of clinical judgement if the possibility of metastatic disease is high and it will entail a change in management, then advising a PET-CT appears reasonable regardless of the guidelines. If use of PET-CT for detection results in change of management, then it is justified. More often the change in management is from a more aggressive treatment strategy to a less aggressive one, thereby saving costs and unnecessary intervention.

Conflict of Interest
None declared.

References

1 Kapoor V, McCook BM, Torok FS. An introduction to PET-CT imaging. Radiographics 2004;24(02):523–543
2 Czernin J, Allen-Auerbach M, Nathanson D, Herrmann K. PET/CT in oncology: current status and perspectives. Curr Radiol Rep 2013; 1(03):177–190
3 National Oncologic PET Registry (NOPR). Accessed December 11, 2022, at: https://clinicaltrials.gov/ct2/show/NCT00868582
4 Boellaard R, Delgado-Bolton R, Oyen WJ, et al; European Association of Nuclear Medicine (EANM) FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging 2015;42(02):328–354
5 Caresia Aroztegui AP, García Vicente AM, Alvarez Ruiz S, et al; Oncology Task Force of the Spanish Society of Nuclear Medicine and Molecular Imaging. 18F-FDG PET/CT in breast cancer: evidence-based recommendations in initial staging. Tumour Biol 2017;39(10):1010428317728285. Doi: 10.1177/1010428317728285
6 National Comprehensive Cancer Network (NCCN). Accessed December 11, 2022, at: http://www.nccn.org/
7 Goel R, Moore W, Sumer B, Khan S, Sher D, Subramaniam RM. Clinical practice in PET/CT for the management of head and neck squamous cell cancer. AJR Am J Roentgenol 2017;209(02):289–303
8 Sirohi B, Shrikhande SV, Perakath B, et al. Indian Council of Medical Research consensus document for the management of colorectal cancer. Indian J Med Paediatr Oncol 2014;35(03):192–196
9 Van Cutsem E, Verheul HM, Flamen P, et al. Imaging in colorectal cancer: progress and challenges for the clinicians. Cancers (Basel) 2016;8(09):81

10 Vikram R, Iyer RB. PET/CT imaging in the diagnosis, staging, and follow-up of colorectal cancer. Cancer Imaging 2008;8 Spec No A (Spec Iss A):S46–S51
11 Shreve P, Faasse T. Role of positron emission tomography-computed tomography in pulmonary neoplasms. Radiol Clin North Am 2013;51(05):767–779
12 Cuaron J, Dunphy M, Rimner A. Role of FDG-PET scans in staging, response assessment, and follow-up care for non-small cell lung cancer. Front Oncol 2013;2:208
13 Takeuchi S, Khiewvan B, Fox PSet al. Impact of initial PET/CT staging in terms of clinical stage, management plan, and prognosis in 592 patients with non-small-cell lung cancer. Eur J Nucl Med Mol Imaging 2014;41(05):906–914
14 National Comprehensive Cancer Network. NCCN Imaging Appropriate Use Criteria (NCCN imaging AUC™). USA: National Comprehensive Cancer Network; 2016
15 Vansteenkiste JF, Stroobants SG, De Leyn PR, et al. Lymph node staging in non-small-cell lung cancer with FDG-PET scan: a prospective study on 690 lymph node stations from 68 patients. J Clin Oncol 1998;16(06):2142–2149 Crossref, Medline, Google Scholar
16 Greenspan BS. Role of PET/CT for precision medicine in lung cancer: perspective of the Society of Nuclear Medicine and Molecular Imaging. Transl Lung Cancer Res 2017;6(06): 617–620 Crossref, Medline, Google Scholar

Imaging Recommendations for Theranostic PET-CT in Oncology

Rahul V. Parghane[1,2] Abhishek Mahajan[3] Nivedita Chakrabarty[4] Sandip Basu[1,2]

[1] Radiation Medicine Centre, Bhabha Atomic Research Centre, Tata Memorial Hospital Annexe, Parel, Mumbai, Maharashtra, India
[2] Homi Bhabha National Institute, Mumbai, Maharashtra, India
[3] Department of Radiodiagnosis, The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, United Kingdom
[4] Department of Radiodiagnosis, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, Maharashtra, India

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

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Abstract

We in this article have presented a review of the guideline recommendations on theranostic positron emission tomography-computed tomography (PET-CT) imaging which will be helpful to assist practitioners in providing appropriate patient care. Multiple guidelines by different societies and medical associations provide standards for diagnosis, imaging, and treatment of cancer patients. They have generated a number of recommendations related to ^{68}Ga-DOTATATE and ^{68}Ga-PSMA-11 PET-CT, which are the classical examples of theranostic PET-CT imaging in current practice.

Keywords

- theranostics
- PET-CT
- ^{68}Ga-DOTATATE PET-CT
- ^{68}Ga-PSMA-11 PET-CT
- FAPI PET-CT
- neuroendocrine tumors
- prostate cancer
- PRRT

Introduction

The term "theranostics" is fusion of two words diagnostics and therapeutics in which diagnostic and therapeutic tools related to the same specific molecular targets are coupled. In essence, theranostics integrates diagnostic modality for the detection of a molecular target for which a specific therapy is intended. Although the term theranostics is reportedly new and probably first used by John Funkhouser in 1998 for the development of a test for monitoring the efficacy of a new anticoagulant drug, the concept behind "theranostics" is not and had been applied to imaging and treatment of thyroid diseases for more than 80 years and revisited over the years.[1,2]

In nuclear medicine, the theranostic system includes use of two identical or very closely related radiopharmaceuticals for diagnosis and therapeutic purpose. The tumor-specific substrates, receptor ligands, transporter, or cell surface proteins can serve as target for development of theranostic couples when labeled with specific radionuclides for imaging or therapy purpose as mentioned in ►**Table 1**. Theranostics has been used in nuclear medicine over past eight decades. Radioiodine is a prime example of a classic theranostic agent with use of same radioisotope ^{131}I for same molecular target of sodium iodide symporter for imaging and therapeutics in patients with differentiated thyroid carcinoma.

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Table 1 Theranostic pairs commonly used in clinical practice

Diagnostic agents	Therapeutic agents	Molecular/ Cellular target	Function of target	Oncological conditions
^{68}Ga-DOTATOC ^{68}Ga-DOTATATE ^{68}Ga- DOTANOC	^{177}Lu-DOTATATE ^{90}Y-DOTATATE ^{225}Ac-DOTATATE	SSTR	Cell-surface receptor	Well-differentiated neuroendocrine tumors
^{68}Ga-PSMA-11 ^{68}Ga-PSMA-617 ^{68}Ga-PSMA-I&T	^{177}Lu-PSMA-617 ^{225}Ac-PSMA-617	PSMA	Cell-surface protein	Metastatic castration-resistant prostate cancer
^{68}Ga-FAPI-04 and FAPI-derivatives	^{90}Y, ^{177}Lu or ^{153}Sm-labeled FAPI-derivatives	FAP	Stroma of cancer-cell surface of activated fibroblasts	Various types of cancers-sarcomas, breast esophageal, lung, pancreatic, prostate cancers, etc.

Abbreviations: FAPI, fibroblast activation protein inhibitor; PSMA, prostate-specific membrane antigen; SSTR, somatostatin receptor.

Recent advancement in molecular biology and radiochemistry has led to introduction of newer theranostic agents for neuroendocrine tumors (NET) and prostate cancer (PC) in nuclear medicine. These agents used combination of two different radioisotopes (each one emitting different types of radiation: electromagnetic radiation for imaging and particulate irradiations for therapy) lined to the specific molecules that utilized same cellular structure, biologic process and also same target for imaging and therapy intent are called theranostic pairs as shown in ►**Table 1**. The main concept behind theranostics is "We treat what we see and we see what we treated."[3] For this purpose, molecular imaging plays a cornerstone role for determining target lesions, quantification, and prognostication of disease process in individual patients. Over the past two decades, imaging technology evolved tremendously with emergence of hybrid imaging in nuclear medicine such as positron emission tomography-computed tomography (PET-CT) examinations. The hybrid PET-CT imaging is a double-edged sword with improved cutting-edge imaging technology on one side and cost and radiation exposure on another side. Hence, there is requirement for recommendation and appropriate use criteria on clinical use of hybrid PET-CT imaging and these are formulated by multidisciplinary panels and presented in various guidelines. We reviewed the guidelines for clinical use of theranostic PET-CT imaging in oncological conditions and compiled and presented in this article.

^{68}Ga-labeled Somatostatin Analogs for PET-CT Imaging

Somatostatin is a naturally occurring hormone that acts by binding to somatostatin receptors (SSTR) and these receptors are over-expressed in most of NETs. SSTR is a target for therapy in NET over last three decades. In initial years of peptide receptor radionuclide therapy (PRRT) procedures, ^{111}In-pentetreotide (imaging by using gamma camera based scintigraphy and therapy with help of Auger electrons) was used as theranostic agent in metastatic NET cases.[4–6] The emergence of hybrid PET-CT imaging and development of newer radiopharmaceuticals based on ^{68}Ga-labeled somatostatin analog (^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{68}Ga- DOTANOC) was a game changer and led to upgradation of imaging in NET,[7] as PET-CT imaging with ^{68}Ga-labeled somatostatin analog has several advantages, including improved radiation dosimetry, measurement of lesional activity by using semiquantitative PET-based analysis, higher spatial resolution with better sensitivity and specificity compared to scintigraphy, and conventional imaging.[8,9]

On June 1, 2016, U.S. Food and Drug Administration approved ^{68}Ga-DOTATATE PET-CT imaging as a diagnostic tool for the detection of location and extent of tumor in NET patients.[10] This led to inclusion of ^{68}Ga-labeled somatostatin analog PET-CT scans in many guidelines.[11–13]

European Association of Nuclear Medicine (EANM) Recommendations

Recently, the procedure guideline given by EANM on PET-CT study with ^{68}Ga-labeled somatostatin analogs has been revised and updated.[14] They provided the clinical indication of ^{68}Ga-labeled somatostatin analogue PET-CT imaging in NET as follows:

i. To detect and localize primary site (diagnosis of NET).
ii. To determine extent of local and metastatic disease (staging of NET).
iii. To detect residual, recurrent, or progressive disease (restaging of NET).
iv. To determine SSTR status and select patients with metastatic disease for PRRT based upon SSTR status (management and prognosis of NET).
v. To determine therapy response (surgery, radiotherapy, chemotherapy or PRRT).

They recommended discontinuation of somatostatin analogue therapy prior to ^{68}Ga-labeled somatostatin analog PET-CT scan for 1 day for short-lived molecules and 3 to 4 weeks for long-acting somatostatin analogue therapy to avoid possible SSTR blockade. They also recommended use of ^{68}Ga-labeled somatostatin analog PET-CT scan for determining primary site in metastatic NET case of an unknown primary with no evidence of a primary disease on conventional imaging and cited use of ^{68}Ga-labeled somatostatin analogue PET-CT scan for characterization of a bronchial

mass suspicious of bronchial NET, when other diagnostic modalities are inconclusive.[15–29]

ESMO Recommendations

The ESMO provided guidelines for diagnosis, treatment, and follow-up of patients with gastroenteropancreatic NET. They recommended use of ^{68}Ga-labeled somatostatin analog PET-CT scan for tumor staging, preoperative imaging, and restaging in NET patients. They also mentioned if PET not available, somatostatin receptor scintigraphy (SRS) may be used as less sensitive imaging modality as compared to PET-CT examination. They recommended the use of PRRT as second-line therapy in patients with midgut and pancreatic NET who fulfil general requirements for PRRT. One important prerequisite for PRRT is high-grade SSTR expression (Krenning 3/4) in lesions, which is assessed by using ^{68}Ga-labeled somatostatin analogue PET-CT scan before PRRT in these NET patients. They cited lifelong follow-up in treated NET patients, which included clinical symptom evaluation, biochemical parameters analysis, conventional, and SSTR imaging. Hence, they recommended use of ^{68}Ga-labeled somatostatin analog PET-CT scan in follow-up of SSTR expressing NET patients at the interval of 12 to 36 months.[30]

European Neuroendocrine Tumor Society (ENETS) Recommendations

The European Neuroendocrine Tumor Society (ENETS) provided consensus guidelines on radiological, nuclear medicine, and hybrid imaging with standards of care in NET patients. Similar to ESMO guidelines, they also recommended use of ^{68}Ga-labeled somatostatin analog PET-CT scan for tumor staging, preoperative imaging, and restaging in NET patients. They also mentioned high sensitivity of ^{68}Ga-labeled somatostatin analog PET-CT imaging for the detection of lymph node metastases, bone metastases, liver metastases, small peritoneal lesions, and primary site of small-intestinal NET as compared with conventional imaging modalities.[31]

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) version 4.2021 to January 2022 mentioned appropriateness of SSTR imaging by using ^{68}Ga-labeled somatostatin analogue PET-CT or PET- magnetic resonance imaging (MRI) for assessment of distant disease and SSTR status in NET patients. They mentioned that SSTR imaging is particularly important for evaluation of benefit from SSTR-directed therapies. They also mentioned that whenever possible PET-CT or PET-MRI should be performed in combination of contrast-enhanced CT or MRI imaging in order to minimize total numbers of imaging studies.[32]

North American Neuroendocrine Tumor Society and Other Societies

Representatives from various societies assembled under auspices of an autonomous workgroup to develop appropriate use criteria for SSTR-PET imaging (^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE) in patients with well-differentiated NET (grade 1 and grade 2). They evaluated 12 clinical scenarios. Out of these, nine were recommended as appropriate use criteria:

i. Initial staging of NET after the histological confirmation
ii. Detection of primary site in known metastatic NET
iii. Selection NET patients for PRRT
iv. Staging of NET prior to plan surgery
v. Evaluation of a mass suggestive of NET not amenable to endoscopic or percutaneous biopsy
vi. Monitoring of NET
vii. Evaluation of patients with biochemical evidence and symptoms of a NET without evidence of it on conventional imaging and or prior histological diagnosis
viii. Restaging of NET patients with symptomatic or biochemical progressive disease but without progressive disease on conventional imaging
ix. Conventional imaging showing new indeterminate lesion but having unclear progressive disease in NETs

They mentioned that SSTR-based PET demonstrated better sensitivity and specificity than conventional imaging and ^{111}In-pentetreotide. They also cited that, SSTR-based PET is clearly preferred in initial diagnosis, selecting patients for PRRT, and localizing of unknown primaries in known metastatic NETs.[13]

Prostate-Specific Membrane Antigen PET-CT Imaging

The PC over-expresses the prostate-specific membrane antigen (PSMA), a transmembrane glycoprotein, present on cell membrane. Over-expression of PSMA is associated with higher grade tumor, metastatic castration-resistant tumor, and tumor aggressiveness in PC. The PSMA is an excellent target for theranostics in PC, as it is internalized after binding to the ligand, leading to high detection rate and better lesion to background uptake ratio for imaging purpose and inducing direct DNA damage with less risk of nonspecific radiation for therapeutic purpose. The ^{68}Ga-PSMA-11, ^{68}Ga-PSMA-617, and ^{68}Ga-PSMA-I&T are developed as PET tracer in PC imaging. There is no data available for direct comparison of these different ligands. Most of published clinical work and clinical practices in nuclear medicine used ^{68}Ga-PSMA-11 PET-CT imaging in PC and translated into ^{177}Lu-PSMA-617 and ^{225}Ac-PSMA-617 agents for therapeutic purposes.[33–42] Various clinical guidelines given by the medical societies (namely urological, oncological, nuclear medicine, and radiation oncology societies) have recommended use of ^{68}Ga-PSMA PET-CT imaging in PC.

Society of Nuclear Medicine and Molecular Imaging and European Association of Nuclear Medicine

The Society of Nuclear Medicine and Molecular Imaging and EANM jointly provided procedure guidelines[43] for the

recommendation, performance, interpretation, and reporting of PSMA PET-CT imaging in PC as follows:

i. To detect tumor lesions in the presence of biochemical recurrence of PC (especially low serum prostate-specific antigen [PSA] values between 0.2 and 10 ng/mL).
ii. For primary staging of PC with high-risk disease before surgical or external beam radiation planning.
iii. For staging prior and during PSMA-based radionuclide therapy.
iv. To do molecular targeted biopsy in high suspicion case of PC with prior negative biopsy.
v. To monitor response of systemic therapy in metastatic PC.

American Society of Clinical Oncology (ASCO) Recommendations:

The ASCO provided evidence and expert recommendations for optimal use of imaging in advanced PC. They mentioned use of either conventional imaging (defined as CT, bone scan, and prostate MRI) and/or next generation imaging (PET, PET-CT, PET-MRI, whole-body MRI) in advanced PC according to the clinical scenario. They recommended use of PET-CT for added clinical benefits and clarification in high-risk/very high-risk localized PC with negative or equivocal finding on conventional imaging. Another clinical scenario in which PSMA-based PET-CT imaging is recommended by ASCO is rising serum PSA level after prostatectomy or radiotherapy with negative conventional imaging in men for whom salvage local or regional therapy is contemplated. ASCO also recommended use of PET-CT imaging in hormone-sensitive metastatic PC at initial diagnosis or after initial treatment. For metastatic castration-resistant prostate cancer (CRPC) with serum PSA progression, they mentioned that use of next-generation imaging (PET, PET-CT, PET-MRI, whole-body MRI) for this cohort is unclear in view of a paucity of prospective data. However, they mentioned that use of next-generation imaging (PET, PET-CT, PET-MRI, whole-body MRI) could be contemplated, especially in the setting of a clinical trial.[44]

European Association of Urology, European Society of Urogenital Radiology, and Other Societies (The EAU-EANM-ESTRO-ESUR-ISUP-SIOG), in their guidelines on PC, recommended use of PSMA-based PET-CT imaging for staging in PC with high-risk localized disease/locally advanced disease and for the management of PC with persistent/recurrence serum PSA level after radical prostatectomy (serum PSA level $>$ 0.2 ng/mL) or radiotherapy in which the result of PSMA PET-CT imaging will influence subsequent treatment decisions. This guideline also recommended use of ^{177}Lu-PSMA-617 therapy in metastatic CRPC patients, which are showing high expression of PSMA (exceeding uptake in lesion over liver) on PSMA PET-CT scan.[45,46]

NCCN Recommendations

The NCCN version 3.2022-January 2022 mentioned that ^{68}Ga-PSMA-11 PET-CT imaging can be considered as an alternate to standard imaging of bone and soft tissue for initial staging, detection of lesions in biochemically recurrent disease, and as workup for progressive disease in bone and soft tissue. They cited that ^{68}Ga-PSMA-11 PET-CT imaging has increased sensitivity and specificity for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at initial staging and biochemical recurrence. Therefore, the panel of NCCN does not feel that conventional imaging is a necessary prerequisite to PSMA PET-CT. To reduce false-positive rate of PSMA PET-CT in PC, use of radiographic or histological confirmation is recommended by NCCN.[47]

^{68}Ga-Fibroblast Activation Protein Inhibitors PET-CT Imaging

The fibroblast activation protein (FAP) is a serine proteinase and highly expressed on cell surface of activated fibroblasts but absent in resting fibroblasts. Over-expression of FAP is related in wound healing, fibrotic processes, and stroma of many malignancies. The FAP-associated fibroblasts are found in more than 90% of epithelial tumors on histopathological studies. The cancer-associated fibroblasts with extracellular fibrosis contributed up to 90% of gross tumor mass, leaving original tumor cells in minority. Hence, FAP is a potential target for theranostic in a large variety of cancers.[48]

The University Hospital Heidelberg group recently developed a series of quinoline-based FAP inhibitors (FAPI) based on clinical and preclinical research.[49] They labeled these FAPI compounds with diagnostic and therapeutic radioisotopes via chelator DOTA. For diagnostic purposes, they labeled FAPI-01, FAPI-02, FAPI-04, FAPI-21, and FAPI-46 with ^{68}Ga. Kratochwil et al demonstrated that ^{68}Ga-FAPI-04 PET-CT imaging is capable to visualize tumor lesions in 28 different types of cancer with high sensitivity and image quality. They cited that ^{68}Ga-FAPI-04 PET-CT imaging showed overall intense tracer uptake with high-contrast images in various types of cancers, such as sarcomas, cholangio-carcinoma, esophageal, breast, lung, hepatocellular, colorectal, head-neck, ovarian, pancreatic, and PCs, etc., and use of ^{68}Ga-FAPI-04 PET-CT imaging led to non-invasive tumor characterization, tumor staging, and radio-ligand therapy pre-evaluation for theranostic purpose.[50]

The ^{90}Y, ^{177}Lu, or ^{153}Sm-labeled FAPI-derivatives (FAPI-46, DOTA.SA.FAPI, and FAPI-04) were used as therapeutic agents on compassionate ground in treating breast cancer, sarcoma, and pancreatic cancer patients in various case reports and a few studies. Case report and studies cited that FAPI-derivatives therapies were well tolerated and showed signs of clinical responses, such as stable disease or tumor lesion shrinkage as well as reduction in clinical symptoms.[51–53]

Guideline for FAPI PET-CT Imaging

There is paucity of FAPI PET-CT imaging data in literature. Hence, role of FAPI PET-CT scan in cancer imaging and management required further exploration in larger prospective trials before coming to any conclusion on clinical use of

these imaging agents. Radiolabeled FAPI as theranostic agents is under development and still in its infancy but showed promising results in preliminary reports and expected to enter clinical trials in near future. Therefore, at present no guidelines on FAPI PET-CT imaging exist in the literature.

Advantages of Theranostic PET over Conventional Imaging in PC and NET

►**Supplementary Table S1** (in supplement) shows the comparison of CECT, FDG-PET-CT, MRI, and PSMA PET-CT for PC.[54–60] As shown in ►**Table 1**, PSMA PET-CT is superior to the conventional imaging modalities for the localization of primary lesion, staging, and detection of relapse. Besides, PSMA PET-CT also gives lower radiation exposure when compared to CECT and FDG-PET-CT. ►**Supplementary Table S2** (in supplement) shows the comparison of CECT, FDG-PET-CT, MRI, and ^{68}Ga- DOTATOC PET-CT for NET.[61–65] Similarly, ^{68}Ga-DOTATOC PET-CT appears to be better for the localization of primary lesion, staging, and response evaluation. Also, radiation exposure with ^{68}Ga-DOTATOC PET-CT is lower than CECT and FDG-PET-CT.

Indian Experience on ^{68}Ga-DOTA-NOC/TATE and ^{68}Ga-PSMA PET-CT

There has been substantial use of both ^{68}Ga-labeled somatostatin analogs and ^{68}Ga-PSMA PET-CT imaging for varied applications in a wide variety of tumors, though no Indian guideline exists on the clinical use of these diagnostic modalities. Naswa et al conducted a prospective study on comparison of ^{68}Ga-DOTANOC PET-CT and conventional imaging in NETs. They found superior sensitivity and specificity of ^{68}Ga-DOTANOC PET-CT imaging over conventional imaging in detecting primary site and metastatic disease, with significant change in the management of NETs after use of ^{68}Ga-DOTANOC PET-CT imaging.[66] In our experience, ^{68}Ga-labeled somatostatin analogs PET-CT have outperformed over conventional imaging both for staging and restaging of NETs.[67–77] Sampathirao and Basu studied 51 patients with CUP-NETs with ^{68}Ga-DOTATATE PET-CT: unknown primary was detected in 31 of 51 patients (resulting in sensitivity of 60.78%), while overall lesion detection sensitivity was 96.87%. Tumor heterogeneity exists in NET, hence ^{68}Ga-labeled somatostatin analogs PET-CT in combination of ^{18}F-FDG-PET-CT (dual tracer PET-CT) have evolved as an important functional imaging approach over Ki-67 labelling index for deciding treatment strategies in metastatic and inoperable NETs (PRRT vs. chemo-PRRT). In neoadjuvant setting, cross-sectional imaging modality, such as triphasic CECT, is superior for identifying involvement of major abdominal blood vessels by tumor over noncontrast PET-CT imaging. The whole body ^{68}Ga-labeled somatostatin receptor-based PET-CT is more valuable imaging modality over conventional imaging for response evaluation and surveillance in NETs. Theranostic ^{68}Ga-labeled somatostatin analogs PET-CT is an excellent imaging modality for deciding PRRT in clinical conditions beyond NETs such as metastatic/inoperable medullary thyroid carcinoma, metastatic/inoperable paraganglioma/pheochromocytoma, noniodine concentrating metastatic differentiated thyroid carcinoma, Merkel cell carcinoma, meningioma, and recurrent/inoperable phosphaturic mesenchymal tumor.[67–77] Jain et al prospectively evaluated diagnostic accuracy of ^{68}Ga-PSMA PET-CT imaging in PC. They found that ^{68}Ga-PSMA PET-CT imaging significantly improved detection rate of PC by using a SUVmax cutoff value in patients with raised PSA between 4 and 20 ng/mL or abnormal digital rectal examination findings.[78] Kallur et al evaluated the clinical utility of ^{68}Ga-PSMA PET-CT imaging in 262 patients of PC.[79] In our experience, ^{68}Ga-PSMA PET-CT imaging is better imaging modality in detection of primary, staging, restaging, response evaluation, and prognostication of PC patients.[79,80]

Theranostic ^{68}Ga-Labeled SSTR-Based PET-CT imaging in Pediatric Population

At present no guideline exists for ^{68}Ga-labeled somatostatin analogs PET-CT imaging in pediatric group. As such, available literature for clinical use of theranostic ^{68}Ga-labeled somatostatin analogs PET-CT imaging in pediatric group is limited in view of low prevalence and rare incidence of NETs in this group. Most studies suggest ^{68}Ga-labeled somatostatin analogs PET-CT imaging should be considered as first-line imaging modality in pediatric NETs. Goel et al evaluated role of ^{68}Ga-DOTATATE PET-CT in 30 pediatric NET patients and they found that ^{68}Ga-DOTATATE PET-CT was superior imaging technique over conventional imaging for detecting bone metastases.[81] Jha et al found that better lesion detection rate of ^{68}Ga-DOTATATE PET-CT in pediatric group of pheochromocytomas.[82] Well-differentiated neuroblastoma has high expression of SSTR2, resulting in better sensitivity of ^{68}Ga-labeled somatostatin analogs for lesion detection as compared to ^{123}I-MIBG imaging. But still there are no current guidelines on ^{68}Ga-labeled somatostatin-based PET-CT imaging in view of scarcity of data in pediatric population. Overall, ^{68}Ga-labeled somatostatin analogue PET-CT imaging in pediatric group showed number of advantages over conventional imaging such as low radiation exposure, fast clearance time, simple preparation, few pharmacological interactions, higher prognostic value, and identifying individuals for PRRT.[83]

Conclusion

Theranostic approach in oncological condition requires integration of therapeutic and diagnostic modality for targeting specific molecule, which can be labeled with radiopharmaceuticals for imaging or therapeutic purpose. Theranostic PET-CT imaging is helpful for diagnosis, finding status of target molecule in the tumor cells, and determining extension of disease that helps in clinical decision-making and design of effective treatment plan. Other advantages of theranostic PET-CT imaging include assessment of biologic behavior and tumoral heterogeneity, prognostification of disease, and predicting response and toxicities of therapies.

This guideline review on theranostic PET-CT imaging thus summarizes the perspectives expressed in multiple guidelines on various receptor-based PET-CT imaging by different societies, discussing upon their clinical use, in order to achieve the goal of best management of cancer patients with reduced expenditure and avoiding potentially unnecessary treatments and interventions.

Authors' Contributions

Rahul V. Parghane was involved in conceptualization, designing, definition of intellectual content, literature search, manuscript preparation, manuscript editing, and manuscript review. Abhishek Mahajan contributed to conceptualization, designing, manuscript editing, and manuscript review. Nivedita Chakrabarty edited and reviewed the manuscript. Sandip Basu contributed to conceptualization, designing, definition of intellectual content, manuscript editing, and manuscript review.

Ethical Committee Clearance

Not required as patient data not revealed.

Conflict of Interest

None declared.

Reference

1 Kelkar SS, Reineke TM. Theranostics: combining imaging and therapy. Bioconjug Chem 2011;22(10):1879–1903
2 DeNardo GL, DeNardo SJ. Concepts, consequences, and implications of theranosis. Semin Nucl Med 2012;42(03):147–150
3 Turner JH. Recent advances in theranostics and challenges for the future. Br J Radiol 2018;91(1091):20170893
4 Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008;9(01):61–72
5 Krenning EP, Kwekkeboom DJ, Bakker WH, et al. Somatostatin receptor scintigraphy with [111In-DTPA-D-Phe1]- and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. Eur J Nucl Med 1993;20(08):716–731
6 Krenning EP, Bakker WH, Breeman WA, et al. Localisation of endocrine-related tumours with radioiodinated analogue of somatostatin. Lancet 1989;1(8632):242–244
7 Hofmann M, Maecke H, Börner R, et al. Biokinetics and imaging with the somatostatin receptor PET radioligand (68)Ga-DOTA-TOC: preliminary data. Eur J Nucl Med 2001;28(12):1751–1757
8 Singh S, Poon R, Wong R, Metser U. 68Ga PET imaging in patients with neuroendocrine tumors: a systematic review and meta-analysis. Clin Nucl Med 2018;43(11):802–810
9 Levine R, Krenning EP. Clinical history of the theranostic radionuclide approach to neuroendocrine tumors and other types of cancer: historical review based on an interview of Eric P. Krenning by Rachel Levine. J Nucl Med 2017;58(Suppl 2):3S–9S
10 Raj N, Reidy-Lagunes D. The Role of 68Ga-DOTATATE positron emission tomography/computed tomography in well-differentiated neuroendocrine tumors: a case-based approach illustrates potential benefits and challenges. Pancreas 2018;47(01):1–5
11 Öberg K, Knigge U, Kwekkeboom D, Perren AESMO Guidelines Working Group. Neuroendocrine gastro-enteropancreatic tumors: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23(suppl7):124–130
12 Shah MH, Goldner WS, Halfdanarson TR, et al. NCCN guidelines insights: neuroendocrine and adrenal tumors, Version 2.2018. J Natl Compr Canc Netw 2018;16(06):693–702
13 Hope TA, Bergsland EK, Bozkurt MF, et al. Appropriate use criteria for somatostatin receptor PET imaging in neuroendocrine tumors. J Nucl Med 2018;59(01):66–74
14 Bozkurt MF, Virgolini I, Balogova S, et al. Guideline for PET/CT imaging of neuroendocrine neoplasms with ^{68}Ga-DOTA-conjugated somatostatin receptor targeting peptides and ^{18}F-DOPA. Eur J Nucl Med Mol Imaging 2017;44(09):1588–1601
15 Campana D, Ambrosini V, Pezzilli R, et al. Standardized uptake values of (68)Ga-DOTANOC PET: a promising prognostic tool in neuroendocrine tumors. J Nucl Med 2010;51(03):353–359
16 Conry BG, Papathanasiou ND, Prakash V, et al. Comparison of (68)Ga-DOTATATE and (18)F-fluorodeoxyglucose PET/CT in the detection of recurrent medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging 2010;37(01):49–57
17 Kayani I, Bomanji JB, Groves A, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using 68Ga-DOTATATE (DOTA-DPhe1,Tyr3-octreotate) and 18F-FDG. Cancer 2008;112(11):2447–2455
18 Ambrosini V, Tomassetti P, Castellucci P, et al. Comparison between 68Ga-DOTA-NOC and 18F-DOPA PET for the detection of gastro-entero-pancreatic and lung neuro-endocrine tumours. Eur J Nucl Med Mol Imaging 2008;35(08):1431–1438
19 Fanti S, Ambrosini V, Tomassetti P, et al. Evaluation of unusual neuroendocrine tumours by means of 68Ga-DOTA-NOC PET. Biomed Pharmacother 2008;62(10):667–671
20 Kayani I, Conry BG, Groves AM, et al. A comparison of 68Ga-DOTATATE and 18F-FDG PET/CT in pulmonary neuroendocrine tumors. J Nucl Med 2009;50(12):1927–1932
21 Ambrosini V, Castellucci P, Rubello D, et al. 68Ga-DOTA-NOC: a new PET tracer for evaluating patients with bronchial carcinoid. Nucl Med Commun 2009;30(04):281–286
22 Schartinger VH, Dudás J, Decristoforo C, et al. ^{68}Ga-DOTA^{0}-Tyr^{3}-octreotide positron emission tomography in head and neck squamous cell carcinoma. Eur J Nucl Med Mol Imaging 2013;40(09):1365–1372
23 Kauhanen S, Seppänen M, Minn H, et al. Fluorine-18-L-dihydroxyphenylalanine (18F-DOPA) positron emission tomography as a tool to localize an insulinoma or beta-cell hyperplasia in adult patients. J Clin Endocrinol Metab 2007;92(04):1237–1244
24 Traub-Weidinger T, Putzer D, von Guggenberg E, et al. Multiparametric PET imaging in thyroid malignancy characterizing tumour heterogeneity: somatostatin receptors and glucose metabolism. Eur J Nucl Med Mol Imaging 2015;42(13):1995–2001
25 Prasad V, Ambrosini V, Hommann M, Hoersch D, Fanti S, Baum RP. Detection of unknown primary neuroendocrine tumours (CUP-NET) using (68)Ga-DOTA-NOC receptor PET/CT. Eur J Nucl Med Mol Imaging 2010;37(01):67–77
26 Putzer D, Gabriel M, Henninger B, et al. Bone metastases in patients with neuroendocrine tumor: 68Ga-DOTA-Tyr3-octreotide PET in comparison to CT and bone scintigraphy. J Nucl Med 2009;50(08):1214–1221
27 Ambrosini V, Nanni C, Zompatori M, et al. (68)Ga-DOTA-NOC PET/CT in comparison with CT for the detection of bone metastasis in patients with neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2010;37(04):722–727
28 Ugur O, Kothari PJ, Finn RD, et al. Ga-66 labeled somatostatin analogue DOTA-DPhe1-Tyr3-octreotide as a potential agent for positron emission tomography imaging and receptor mediated internal radiotherapy of somatostatin receptor positive tumors. Nucl Med Biol 2002;29(02):147–157
29 Gabriel M, Oberauer A, Dobrozemsky G, et al. 68Ga-DOTA-Tyr3-octreotide PET for assessing response to somatostatin-receptor-mediated radionuclide therapy. J Nucl Med 2009;50(09):1427–1434
30 Pavel M, Öberg K, Falconi M, et al; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Gastroenteropancreatic neuroendocrine neoplasms: ESMO clinical practice

guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31(07):844–860
31 Sundin A, Arnold R, Baudin E, et al; Antibes Consensus Conference participants. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological, nuclear medicine & hybrid imaging. Neuroendocrinology 2017;105(03):212–244
32 Shah MH, Goldner WS, Benson AB, et al. Neuroendocrine and adrenal tumors, Version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2021;19(07):839–868
33 Barbosa FG, Queiroz MA, Nunes RF, et al. Revisiting prostate cancer recurrence with PSMA PET: atlas of typical and atypical patterns of spread. Radiographics 2019;39(01):186–212
34 Scher HI, Fizazi K, Saad F, et al; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367(13):1187–1197
35 Kratochwil C, Giesel FL, Eder M, et al. [^{177}Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. Eur J Nucl Med Mol Imaging 2015;42(06): 987–988
36 Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging 2015;42(02):197–209
37 Hofman MS, Hicks RJ, Maurer T, Eiber M. Prostate-specific membrane antigen PET: clinical utility in prostate cancer, normal patterns, pearls, and pitfalls. Radiographics 2018;38(01): 200–217
38 Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid ^{68}Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. J Nucl Med 2015;56 (05):668–674
39 Rauscher I, Maurer T, Fendler WP, Sommer WH, Schwaiger M, Eiber M. (68)Ga-PSMA ligand PET/CT in patients with prostate cancer: how we review and report. Cancer Imaging 2016;16(01): 14
40 Ballas LK, de Castro Abreu AL, Quinn DI. What medical, urologic, and radiation oncologists want from molecular imaging of prostate cancer. J Nucl Med 2016;57(Suppl 3):6S–12S
41 Fendler WP, Rahbar K, Herrmann K, Kratochwil C, Eiber M. 177Lu-PSMA radioligand therapy for prostate cancer. J Nucl Med 2017;58 (08):1196–1200
42 Emmett L, Willowson K, Violet J, Shin J, Blanksby A, Lee J. Lutetium ^{177} PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. J Med Radiat Sci 2017;64(01):52–60
43 Fendler WP, Eiber M, Beheshti M, et al. ^{68}Ga-PSMA PET/CT: joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging 2017;44(06): 1014–1024
44 Trabulsi EJ, Rumble RB, Jadvar H, et al. Optimum imaging strategies for advanced prostate cancer: ASCO guideline. J Clin Oncol 2020;38(17):1963–1996
45 Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2021;79(02):243–262
46 Cornford P, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Part II-2020 update: treatment of relapsing and metastatic prostate cancer. Eur Urol 2021;79(02):263–282
47 NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY Prostate cancer version 3.2022-January 2022. Accessed December 12, 2022, at: https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
48 Jiang GM, Xu W, Du J, et al. The application of the fibroblast activation protein α-targeted immunotherapy strategy. Oncotarget 2016;7(22):33472–33482
49 Lindner T, Loktev A, Altmann A, et al. Development of quinoline-based theranostic ligands for the targeting of fibroblast activation protein. J Nucl Med 2018;59(09):1415–1422
50 Kratochwil C, Flechsig P, Lindner T, et al. ^{68}Ga-FAPI PET/CT: tracer uptake in 28 different kinds of cancer. J Nucl Med 2019;60(06): 801–805
51 Ballal S, Yadav MP, Kramer V, et al. A theranostic approach of [^{68}Ga]Ga-DOTA.SA.FAPi PET/CT-guided [^{177}Lu]Lu-DOTA.SA.FAPi radionuclide therapy in an end-stage breast cancer patient: new frontier in targeted radionuclide therapy. Eur J Nucl Med Mol Imaging 2021;48(03):942–944
52 Ferdinandus J, Costa PF, Kessler L, et al. Initial clinical experience with ^{90}Y-FAPI-46 radioligand therapy for advanced stage solid tumors: a case series of nine patients. J Nucl Med 2022;63(05): 727–734
53 Kratochwil C, Giesel FL, Rathke H, et al. [^{153}Sm]Samarium-labeled FAPI-46 radioligand therapy in a patient with lung metastases of a sarcoma. Eur J Nucl Med Mol Imaging 2021;48(09):3011–3013
54 Regmi SK, Sathianathen N, Stout TE, Konety BR. MRI/PET Imaging in elevated PSA and localized prostate cancer: a narrative review. Transl Androl Urol 2021;10(07):3117–3129
55 Liu F, Dong J, Shen Y, et al. Comparison of PET/CT and MRI in the diagnosis of bone metastasis in prostate cancer patients: a network analysis of diagnostic studies. Front Oncol 2021;11:736654
56 Kichloo A, Amir R, Aljadah M, et al. FDG-PET versus PSMA-PET: a patient with prostate cancer. J Investig Med High Impact Case Rep 2020;8:2324709620941313
57 Tsechelidis I, Vrachimis A. PSMA PET in Imaging Prostate Cancer. Front Oncol 2022;12:831429
58 Smith-Bindman R, Lipson J, Marcus R, et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. Arch Intern Med 2009;169(22):2078–2086
59 Kwon HW, Kim JP, Lee HJ, et al. Radiation dose from whole-body F-18 fluorodeoxyglucose positron emission tomography/computed tomography: Nationwide Survey in Korea. J Korean Med Sci 2016; 31 Suppl 1(Suppl 1):S69–S74
60 Waller J, Flavell R, Heath CL. High accuracy of PSMA PET in initial staging of high-risk prostate cancer. Radiol Imaging Cancer 2020; 2(04):e204025
61 Maxwell JE, Howe JR. Imaging in neuroendocrine tumors: an update for the clinician. Int J Endocr Oncol 2015;2(02):159–168
62 Gamal GH. The utility of 18F-FDG PET/CT in the diagnosis, staging of non-functioning pancreatic neuroendocrine tumors. Egypt J Radiol Nucl Med 2021;52(01):234
63 Schraml C, Schwenzer NF, Sperling O, et al. Staging of neuroendocrine tumours: comparison of [^{68}Ga]DOTATOC multiphase PET/CT and whole-body MRI. Cancer Imaging 2013;13(01):63–72
64 Garcia-Carbonero R, Garcia-Figueiras R, Carmona-Bayonas A, et al; Spanish Cooperative Group of Neuroendocrine Tumors (GETNE) Imaging approaches to assess the therapeutic response of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): current perspectives and future trends of an exciting field in development. Cancer Metastasis Rev 2015;34(04):823–842
65 Accessed December 12, 2022, at: https://clinicaltrials.gov/ProvidedDocs/28/NCT03136328/Prot_SAP_000.pdf
66 Naswa N, Sharma P, Kumar A, et al. Gallium-68-DOTA-NOC PET/CT of patients with gastroenteropancreatic neuroendocrine tumors: a prospective single-center study. AJR Am J Roentgenol 2011;197 (05):1221–1228
67 Thapa P, Ranade R, Ostwal V, Shrikhande SV, Goel M, Basu S. Performance of 177Lu-DOTATATE-based peptide receptor radionuclide therapy in metastatic gastroenteropancreatic neuroendocrine tumor: a multiparametric response evaluation correlating with primary tumor site, tumor proliferation index, and dual tracer imaging characteristics. Nucl Med Commun 2016; 37(10):1030–1037

68 Sampathirao N, Basu S. MIB-1 index-stratified assessment of dual-tracer PET/CT with ^{68}Ga-DOTATATE and ^{18}F-FDG and multimodality anatomic imaging in metastatic neuroendocrine tumors of unknown primary in a PRRT workup setting. J Nucl Med Technol 2017;45(01):34–41

69 Basu S, Sirohi B, Shrikhande SV. Dual tracer imaging approach in assessing tumor biology and heterogeneity in neuroendocrine tumors: its correlation with tumor proliferation index and possible multifaceted implications for personalized clinical management decisions, with focus on PRRT. Eur J Nucl Med Mol Imaging 2014;41(08):1492–1496

70 Basu S, Chakraborty S, Parghane RV, et al. One decade of 'Bench-to-Bedside' peptide receptor radionuclide therapy with indigenous [^{177}Lu]Lu-DOTATATE obtained through 'Direct' neutron activation route: lessons learnt including practice evolution in an Indian setting. Am J Nucl Med Mol Imaging 2020;10(04):178–211

71 Basu S, Parghane RV, Kamaldeep, Chakrabarty S. Peptide receptor radionuclide therapy of neuroendocrine tumors. Semin Nucl Med 2020;50(05):447–464

72 Parghane RV, Talole S, Basu S. Prevalence of hitherto unknown brain meningioma detected on ^{68}Ga-DOTATATE positron-emission tomography/computed tomography in patients with metastatic neuroendocrine tumor and exploring potential of ^{177}Lu-DOTATATE peptide receptor radionuclide therapy as single-shot treatment approach targeting both tumors. World J Nucl Med 2019;18(02):160–170

73 Parghane RV, Talole S, Basu S. ^{131}I-MIBG negative progressive symptomatic metastatic paraganglioma: response and outcome with ^{177}Lu-DOTATATE peptide receptor radionuclide therapy. Ann Nucl Med 2021;35(01):92–101

74 Parghane RV, Ostwal V, Ramaswamy A, et al. Long-term outcome of "Sandwich" chemo-PRRT: a novel treatment strategy for metastatic neuroendocrine tumors with both FDG- and SSTR-avid aggressive disease. Eur J Nucl Med Mol Imaging 2021;48(03):913–923

75 Parghane RV, Naik C, Talole S, et al. Clinical utility of ^{177} Lu-DOTATATE PRRT in somatostatin receptor-positive metastatic medullary carcinoma of thyroid patients with assessment of efficacy, survival analysis, prognostic variables, and toxicity. Head Neck 2020;42(03):401–416

76 Basu S, Parghane RV, Naik C. Clinical efficacy of ^{177}Lu-DOTATATE peptide receptor radionuclide therapy in thyroglobulin-elevated negative iodine scintigraphy: a "not-so-promising" result compared to GEP-NETs. World J Nucl Med 2020;19(03):205–210

77 Parghane RV, Bhandare M, Chaudhari V, et al. Surgical feasibility, determinants, and overall efficacy of neoadjuvant ^{177}Lu-DOTATATE PRRT for locally advanced unresectable gastroenteropancreatic neuroendocrine tumors. J Nucl Med 2021;62(11):1558–1563

78 Jain H, Sood R, Faridi MS, Goel H, Sharma U. Role of 68Ga-PSMA-PET/CT for the detection of primary prostate cancer prior to biopsy: a prospective study. Cent European J Urol 2021;74(03):315–320

79 Kallur KG, Ramachandra PG, Rajkumar K, et al. Clinical utility of Gallium-68 PSMA PET/CT scan for prostate cancer. Indian J Nucl Med 2017;32(02):110–117

80 Suman S, Parghane RV, Joshi A, et al. Therapeutic efficacy, prognostic variables and clinical outcome of ^{177}Lu-PSMA-617 PRLT in progressive mCRPC following multiple lines of treatment: prognostic implications of high FDG uptake on dual tracer PET-CT vis-à-vis Gleason score in such cohort. Br J Radiol 2019;92(1104):20190380

81 Goel R, Shukla J, Bansal D, et al. (68)Ga-DOTATATE positron emission tomography/computed tomography scan in the detection of bone metastases in pediatric neuroendocrine tumors. Indian J Nucl Med 2014;29(01):13–17

82 Jha A, Ling A, Millo C, et al. Superiority of ^{68}Ga-DOTATATE over ^{18}F-FDG and anatomic imaging in the detection of succinate dehydrogenase mutation (SDHx)-related pheochromocytoma and paraganglioma in the pediatric population. Eur J Nucl Med Mol Imaging 2018;45(05):787–797

83 Maaz AUR, O'Doherty J, Djekidel M. ^{68}Ga-DOTATATE PET/CT for neuroblastoma staging: utility for clinical use. J Nucl Med Technol 2021;49(03):265–268

Imaging Recommendations for Diagnosis, Staging and Management of Treatment-Related Complications in Cancer

Sumit Mukhopadhyay[1] Saugata Sen[1] Priya Ghosh[1] Anisha Gehani[1] Anurima Patra[1] Aditi Chandra[1] Argha Chatterjee[1] Dayananda Lingegowda[1] Bharat Gupta[1] Meenu Gupta[2] Prakash Venugopal[3] Amrita Chakraborty[4] Ketul K. Pathak[5] Pradipta Kumar Mishra[6] Jeevitesh Khoda[7]

[1] Department of Radiology and Imaging Sciences, Tata Medical Center, Kolkata, West Bengal, India
[2] Department of Radiology & Imaging, Medanta Hospital, Lucknow, Uttar Pradesh, India
[3] Department of Radiology and Imaging, Sri Ramakrishna Hospital, Coimbatore, Tamil Nadu, India
[4] Department of Radiology and Imaging, HCG EKO Cancer Center, Kolkata, West Bengal, India
[5] Department of Radiology, Institute of Kidney Diseases and Research Center - Institute of Transplant Sciences, Ahmedabad, Gujarat, India
[6] Department of Radiodiagnosis, Acharya Harihar Regional Cancer Center, Cuttack, Odisha, India
[7] Department of Radiology and Interventional Oncology Services, Rajiv Gandhi Cancer Institute and Research Center, India

Address for correspondence Sumit Mukhopadhyay, MD, Department of Radiology and Imaging Sciences, Tata Medical Center, Kolkata, West Bengal 700160, India
(e-mail: sumitmukhopadhyayrad@gmail.com).

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Abstract

Precision medicine is becoming increasingly common in oncology, with treatments tailored to individual patients and cancer. By integrating these underlying concepts of health care, chemotherapy and radiotherapy can be tailored to improve safety and efficacy. On the other hand, oncology treatment regimens may result in local and systemic changes and complications depending on the type of treatment. For the proper and prompt management of cancer patients, it is essential to interpret this posttreatment imaging correctly. This article aims at guiding treating physicians to be able to distinguish complications from expected posttreatment changes.

Keywords
- complications
- oncology
- radiology
- review

Introduction

Precision medicine is becoming increasingly common in oncology, with treatments tailored to individual patients and cancer.[1] By integrating these underlying concepts of health care, chemotherapy and radiotherapy (RT) can be tailored to improve safety and efficacy.[2] On the other hand, oncology treatment regimens may result in local and systemic changes and complications depending on the type of treatment.[3] For the proper and prompt management of cancer patients, it is essential to interpret this posttreatment imaging correctly. This article aims at guiding treating physicians to be able to distinguish complications from expected posttreatment changes.

Etiopathogenesis and Risk Factors

Chemotherapy and radiation therapy impairs mucosal immunity. Stem cell transplantations and some chemotherapy agents result in neutropenia. These factors and other factors such as graft versus host disease, and the use of immunomodulatory agents increase the risk of infections in cancer patients during treatment.

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Acute effects of RT are mainly on organs having rapid cell turnover, such as skin or mucosal surfaces. On the other hand, chronic or late complications of RT, such as fibrosis, perforation, or fistula formation, are a result of microvascular injury or direct parenchymal damage.[4]

Risk factors for treatment related complications are:

- Local extent and histology of the primary neoplasm.
- Preoperative chemotherapy and/or RT.
- Type of radiation therapy.
- Radiation dose, duration, and fractionation.
- Size of the field of irradiation.
- Concurrent use of chemotherapy.
- Comorbid medical conditions.
- Poor nutritional status.

Epidemiology, Clinical Presentation

Around 650,000 cancer patients receive systemic therapy or RT in the United States each year, while 180,000 receive both. The number of emergency department visits associated with cancer treatment outpaced visits related to overall health care. The most implicated cancers were lung (20.0%), breast (13.2%), and non-Hodgkin lymphoma (9.7%).

The most common complications in patients with hematologic malignancies were neutropenia (15.0%), sepsis (11.6%), and anemia (11.5%). In the case of solid tumor malignancies, the most frequent complications are sepsis (7.4%), neutropenia (7.3%), and anemia (6.7%).

Among the other common presentations, dehydration was among the most common complications associated with head and neck, colon, and esophageal cancers. Intestinal obstruction was commonly seen in gynecologic (ovary, uterus, and cervix) and gastrointestinal (GI) (colorectal and anal canal) cancers. GI hemorrhage was most commonly seen in prostate cancer. Congestive cardiac failure was commonly seen in breast cancer and non-Hodgkin lymphoma. Pneumonia was associated with lung cancer and multiple myeloma while acute kidney injury (AKI) was most commonly associated with urinary bladder cancer.[5]

Imaging Referral Guidelines

National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO), and American Society of Clinical Oncology (ASCO) clinical guidelines are available for the management of immunotherapy-related toxicities[6] and cancer-related infections.[7] These guidelines have also mentioned the management of treatment-related complications according to symptoms.

No consensus guidelines exist on the frequency and modality of routine posttreatment imaging in the asymptomatic patient. In the case of signs and symptoms or the presence of worrisome features on clinical examinations, imaging protocol may be tailored to answer specific clinical questions.

Most of the literature on imaging of complications of cancer therapy predominantly uses computed tomography (CT) and magnetic resonance imaging (MRI).

American College of Radiology (ACR) provided guidelines for the choice of imaging based on clinical presentation in the form of ACR appropriateness criteria. No specific guidelines are available on imaging of posttreatment complications in cancer.

National Cancer Grid (NCG) of India has formulated guidelines for palliative care of cancer but does not recommend imaging referral.[8] NCG, however, mentions the use of CT scans in cases where corrective measures are feasible and justifiable.[9]

Clinical/Diagnostic Workup (Other than Imaging)

Complications of systemic anticancer treatment are class-specific (i.e., agent-specific). A sepsis workup should be done if there is fever and/or cytopenia for localized or systemic features of inflammations (like intra-abdominal collection, pyelonephritis, etc.). Hypokalemia or paralytic ileus should be a differential diagnosis of intestinal obstruction. For suspected lung infection, sputum and blood culture sensitivity with Gram stain and/or bronchoalveolar lavage (BAL) is helpful. Opportunistic and atypical infection should be ruled out by organism-specific polymerase chain reaction test from BAL and/or nasopharyngeal swab. Many tyrosine kinase inhibitors cause lung injury which is a diagnosis of exclusion sometimes with a classical clinical presentation with radiological findings. There is no specific diagnostic test other than a rapid response to steroid and drug withdrawal and infrequent reappearance on rechallenge.

For meningeal enhancement, cerebrospinal fluid cytology, cell count, biochemistry, and/or microbiological culture should be performed before labeling as carcinomatous meningitis in a clinical context. For immune checkpoint inhibitor (ICI)-induced systemic complications, organ-specific diagnostic guidelines exist (NCCN, ESMO, and ASCO guidelines) and infection should be ruled out before giving high-dose steroids for immune-related adverse events (irAE). Blood-borne viral infection (i.e., hepatitis B, hepatitis C, human immunodeficiency virus) and Koch's should be ruled out before giving immunosuppressants like infliximab for the treatment of steroid-refractory irAE.

Imaging Guidelines

Screening

Currently, there is no evidence to support screening for complications that may develop as a result of treatment of cancers in the general population except for when they present with symptoms.

Diagnosis

Central Nervous System (►Table 1 and 2, ►Fig. 1)

To establish the diagnosis of radiation (treatment)-related neurological complications, imaging is the first-line and most crucial investigation.[10] It also helps to rule out differential diagnosis such as metastases, tumor progression, hemorrhage, infarcts, and infections. MRI brain with

Table 1 Central and peripheral nervous system complications by chemotherapy and immunomodulatory drugs

CNS complication	Symptoms	Agents	Diagnostic assessment
Acute and chronic encephalopathy	Reduced attention, confusion, reduced alertness, hallucinations	Ifosfamide, carmustine, cisplatin, cytarabine, fluorouracil, rituximab, alemtuzumab, brentuximab, blinatumomab	MRI
PRES	Headache, confusion visual changes, and seizures	Bevacizumab, ipilimumab, rituximab, sirolimus, sorafenib, sunitinib, tacrolimus, cisplatin, vincristine, cyclophosphamide, methotrexate, bortezomib, sorafenib, rituximab, tacrolimus	MRI
Hemorrhage	Seizures, confusion, focal neurological deficits	Bevacizumab, imatinib, TKIs, sirolimus, temsirolimus, everolimus, ridaforolimus	CT or MRI
Thromboembolic infarcts	Focal neurological deficits	Ipilimumab, bevacizumab, cisplatin, 5-fluorouracil, gemcitabine, bleomycin	MRI (with DWI), cardiac assessment
Venous sinus thrombosis	Focal neurological deficits, seizures	L-asparaginase	MRI with MR venogram
Cerebellar syndrome	Dizziness, ataxia	Cytarabine, capecitabine, bortezomib, rituximab, trastuzumab, cytosine arabinoside, 5-fluorouracil, and vincristine	MRI
Hypophysitis	Fatigue and headache, hormonal imbalance	Ipilimumab, nivolumab, pembrolizumab, atezolizumab	MRI
Myasthenia gravis	Fluctuating muscle weakness, ptosis, double vision, dysphagia, dysarthria, facial muscle weakness	Immune checkpoint inhibitors	No imaging
Peripheral neuropathy		Immune checkpoint inhibitors	MRI brain or spine (exclude CVA, structural cause)
Guillain–Barre syndrome	Ascending, progressive muscle weakness, shortness of breath, facial weakness, numbness and tingling in the feet or hands, burning, stabbing, or shooting pain in affected areas, loss of balance, and coordination	Immune checkpoint inhibitors	No imaging
Transverse myelitis		Immune checkpoint inhibitors	MRI brain and spine
Encephalitis	Confusion, altered mental status, altered behavior, headache, seizures, weakness, and gait instability	Immune checkpoint inhibitors	MRI
Aseptic meningitis	Headache, photophobia, neck stiffness, nausea or vomiting, and occasionally fever	Immune checkpoint inhibitors	MRI

Abbreviations: CNS, central nervous system; CT, computed tomography; CVA, cerebrovascular accident; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; PRES, posterior reversible encephalopathy syndrome; TKI, tyrosine kinase inhibitor.

intravenous contrast is the modality of choice. CT can be useful for quick assessment of raised intracranial tension, calcifications, acute hemorrhage, venous sinus thrombosis, or infarcts.

MRI angiogram with susceptibility-weighted imaging is preferred for evaluation of radiation-induced vascular injuries such as vascular narrowing or stenosis, capillary telangiectasia, cavernous malformations, microhemorrhages, and infarcts. CT can be useful for the detection of basal ganglia calcification associated with mineralizing microangiopathy.[11]

If patients with glioma are treated with RT and concurrent temozolomide after surgical resection, they become susceptible to radiation-related brain parenchymal damage, resulting in pseudoprogression and radiation necrosis.[12] The

Table 2 Clinical features of common CNS Complications and initial Imaging Recommendation

CNS complication	Symptoms	Diagnostic assessment
Leukoencephalopathy	Gait difficulties with frequent falls, cognitive impairment, and incontinence	MRI
Radiation Necrosis	Headaches, short-term memory impairment, and focal seizures	MRI with DWI, spectroscopy, and perfusion
Cerebrovascular complications (infarcts, hemorrhage, SMART)	Focal neurological deficits	MR angiogram > CT angiogram
Secondary CNS tumors	Seizures, focal deficits, symptoms due to lobe involved	MRI with contrast

Abbreviations: CNS, central nervous system; CT, computed tomography; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; SMART, stroke-like migraine after radiation therapy.

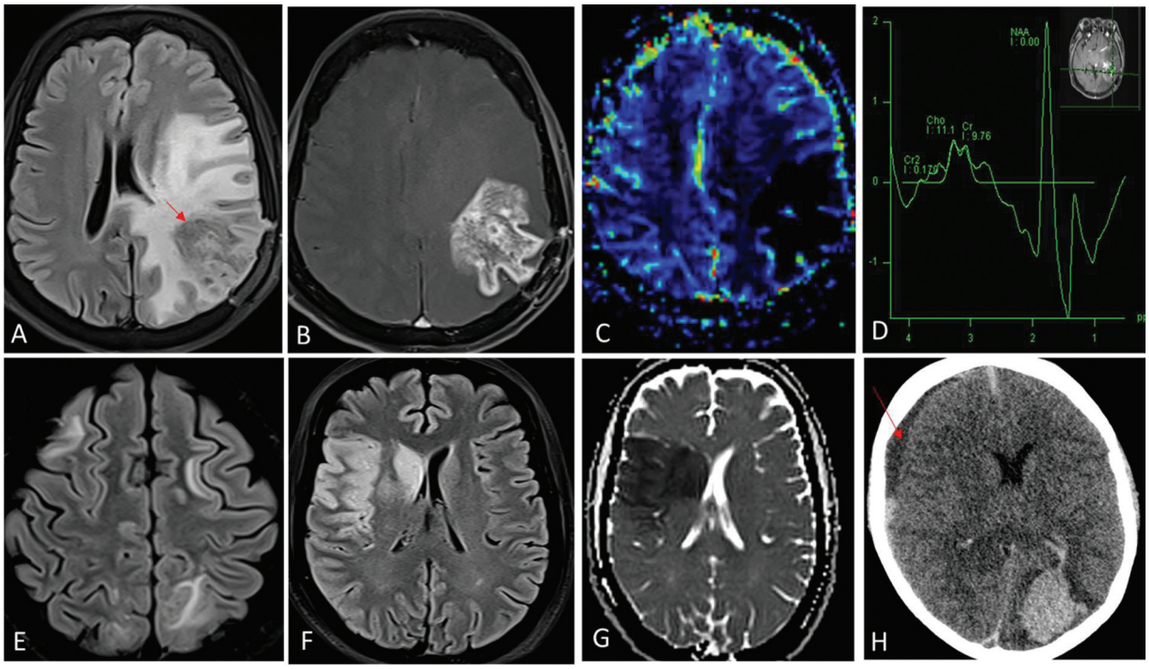

Fig. 1 Radiation necrosis (**A**–**D**). One-year postradiation and temozolomide therapy for left temporal lobe glioblastoma. Fluid-attenuated inversion recovery (FLAIR) shows intermediate-hypointense signal areas (red arrow in **A**) in the left parietal lobe with surrounding disproportionate white matter edema. Contrast image (**B**) shows irregular and nodular enhancement (Swiss-cheese pattern) and relative cerebral blood volume (rCBV) perfusion (**C**) did not show any increased perfusion. Presence of lipid-lactate peak in the corresponding area on magnetic resonance (MR) spectroscopy (**D**) represents necrosis. These imaging features are typical for radiation-induced injury. Absence of increased choline:NAA ratios (**D**) further helps exclude tumor progression. Posterior reversible encephalopathy syndrome (PRES) (**E**). Bilaterally asymmetrical FLAIR hyperintensity in frontoparietal white matter suggestive of vasogenic edema. Acute arterial infarcts (**F** and **G**). FLAIR hyperintense areas (**F**) in right frontoparietal cortex and right basal ganglia due to cytotoxic edema, showing restriction on the corresponding diffusion-weighted image (**G**) are suggestive of watershed territory infarcts. Intracerebral hematoma (**H**). Acute hematoma in left occipital lobe appears hyperdense on noncontrast computed tomography (CT). There is an intraventricular extension of bleed into the left lateral ventricle. Subdural hematoma is noted along right cerebral convexity as well (red arrow in **H**). Chemotherapeutic agents are common inciting factors for PRES, cerebral hematoma, and arterial infarcts.

imaging modality of choice for radiation-related brain parenchymal injury is MRI with spectroscopy and perfusion. It helps to discriminate viable tumors from radiation necrosis/pseudoprogression.[13] Imaging guidelines are similar for radiation-induced necrosis associated with brain metastases following radiation therapy.[14–16]

MRI brain is the modality of choice for evaluation of chemotherapy-related neurotoxicity.[17] However, most drugs produce similar and nonspecific imaging patterns. The diagnosis can be established by resolution of MRI findings in post-drug cessation follow-up imaging. Few drugs have characteristic imaging findings and require additional MRI sequences to suggest the diagnosis. Areas of symmetrical diffusion restriction in white matter on diffusion-weighted imaging are most sensitive for detection of acute methotrexate toxicity post-intrathecal route of drug administration.[18] L-asparaginase cause venous sinus thrombosis which can be easily picked up on MRI with MR venography.

Table 3 Imaging Recommendation for evaluation of complications in the Head and Neck region

Complications	Imaging recommendation of choice
Radiation-induced brain necrosis	MRI with IV contrast MR diffusion MR perfusion MR spectroscopy
Brachial plexopathy	MRI with or without IV contrast
Spinal/Cranial nerve abnormality	MRI with IV contrast CT with/without IV contrast
Dental caries	No imaging needed Clinical evaluation OPG (may be done)
Trismus	MRI T-M joints with or without IV contrast
Radiation-induced lung injury/fibrosis	HRCT thorax
Radiation-induced bone and cartilage necrosis	CT with IV contrast MRI with IV contrast
Radiation-induced vascular changes	CT angiogram Conventional angiogram
Radiation-induced secondary neoplasms	MRI with IV contrast CT with IV contrast

Abbreviations: CT, computed tomography; HRCT, high-resolution computed tomography scan; IV, intravenous; MRI, magnetic resonance imaging; OPG, orthopantomogram; T-M, temporomandibular.

Immunotherapeutic agents can cause autoimmune hypophysitis. MRI with pituitary sequences should be advised in this situation.

Head and Neck (►**Table 3**, ►**Fig. 2**)

CT and MRI are the key cross-sectional imaging modalities that play a complementary role to each other in the diagnosis of treatment complications (►**Table 3**). CT is useful to pick up gas bubbles adjacent to necrosed cartilages that clinch the diagnosis of chondronecrosis.[19]

CT is complementary to MRI to assess bony destruction and remodeling and is thus useful to identify the pattern of bony involvement in osteoradionecrosis.

Contrast-enhanced CT/conventional angiography are required for the diagnosis of vascular complications such as pseudoaneurysms, vascular thrombosis, and carotid blowouts.

MRI is useful in select cases of treated oral cavity, nasopharyngeal, skull base, and sinonasal tumors. In the presence of brachial plexopathy, high-resolution T2-weighted images and short tau inversion recovery images are helpful for diagnosis.

Additional MRI perfusion, diffusion, and spectroscopy sequences are needed to differentiate other causes from radiation-induced brain necrosis affecting the temporal lobes after radiation therapy to nasopharyngeal cancers.[20]

Thorax

*Lungs (►**Table 4**)*

Medication-induced pulmonary injury is usually suspected owing to the temporal association of symptoms with the initiation of medication.[4,21] Patient presentations range from asymptomatic individuals to severely symptomatic patients with dyspnea, cough, wheezing, and fever.

The United States National Cancer Institute Common Terminology Criteria for Adverse Events provides a classification system for stratifying the severity of "pneumonitis." This nomenclature ranges from asymptomatic (grade 1, radiologic abnormalities only) to fatal (grade 5).[22]

In grade 1 (usually asymptomatic patients) a baseline chest radiograph suffices.

For other grades (2–5), appearance of any new respiratory symptoms requires prompt investigation. All patients presenting with pulmonary symptoms should be assessed by[23] high-resolution CT scan (without intravenous contrast material) using multiplanar reformation and volumetric expiratory acquisition.[24]

Symptoms of radiation-induced lung injury (RILI) include cough, low-grade fever, and dyspnea. These symptoms typically develop between 4 and 12 weeks following treatment.

The severity of radiation pneumonitis is graded based on the clinical presentation. The grading system (scale of 1 to 5) commonly used is the Radiation Therapy Oncology Group system:

CT thorax is the modality of choice and depicts the radiation changes before it is evident at radiography. Acute RILI changes are usually detected with CT scan by 4 weeks after the completion of RT.[25]

*Cardiac (►**Table 5**)*

Certain cancer treatments can damage the heart and the cardiovascular system and cause congestive heart failure, ischemia, hypertension, hypotension, and arrhythmias.[26]

Currently, posttreatment cardiac evaluation is most often performed with echocardiography which is the first line of imaging.[27] Previous history of cancer and cancer therapy are associated with increased coronary artery calcium scores. These patients often undergo chest CT scan for oncologic

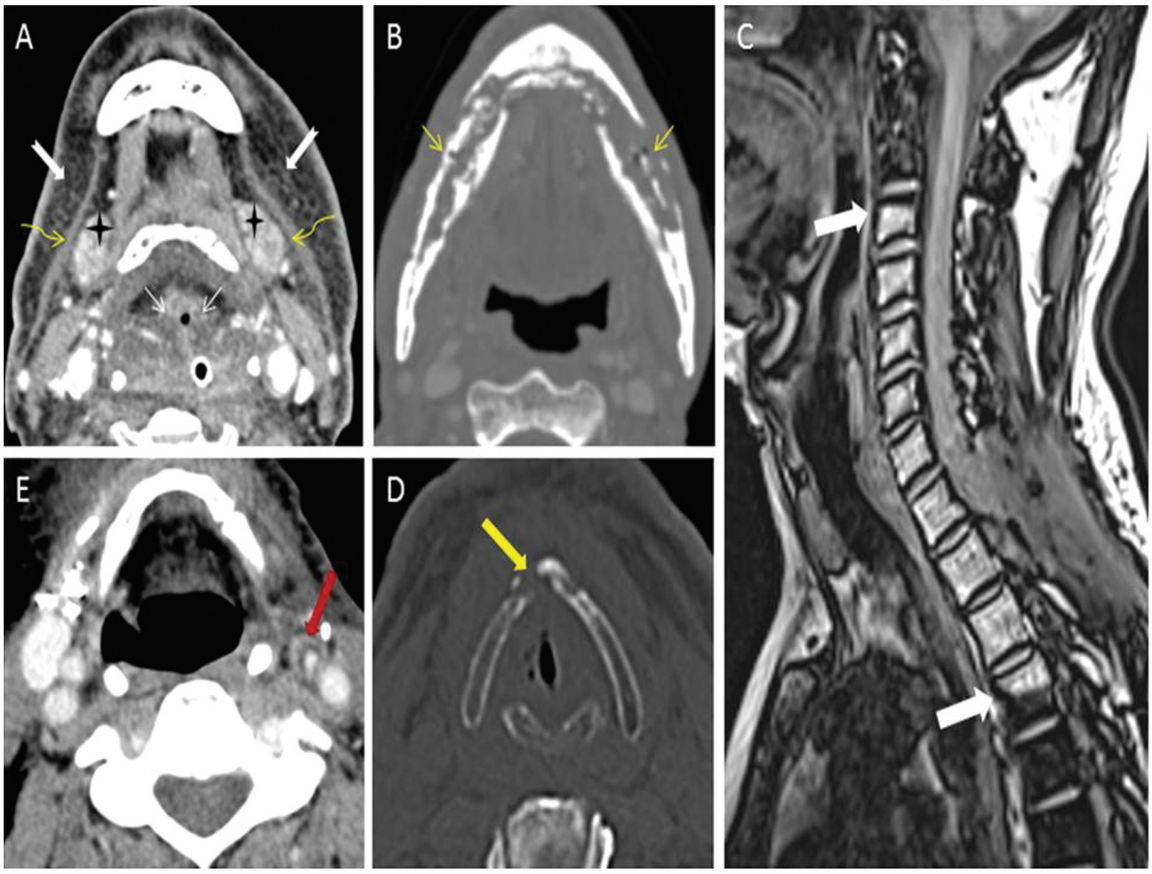

Fig. 2 (**A**) Expected radiotherapy (RT)-related soft tissue changes. Axial contrast-enhanced computed tomography (CT) image in soft tissue window shows diffuse bilateral symmetrical subcutaneous fat reticulations (notched white arrows), thickened bilateral platysma muscles (curved yellow arrows), increased enhancement of bilateral submandibular glands (black stars), and edema of hypopharyngeal structure (thin straight white arrows). (**B**) Radiation-induced osteonecrosis. Axial contrast-enhanced CT image in bone window shows bizarre lysis, fragmentation, and sclerosis of the mandible (thin straight yellow arrows). Absence of expansile soft tissue at site of bone destruction rules out the possibility of recurrence. (**C**) Radiation-induced fatty marrow conversion. Sagittal Dixon T1-weighted fat magnetic resonance (MR) image shows conversion to fatty marrow from C3-D4 vertebrae with sharp margins at mid-C2 and mid-D4 levels (thick white arrows) corresponding with the radiation portal. (**D**) Radiation-induced chondronecrosis. Axial noncontrast-enhanced CT image in bone window kernel shows lysis of thyroid cartilage (thick yellow arrow) with air foci in the vicinity of the right vocal cord. (**E**) Radiation-induced atherosclerosis. Axial contrast-enhanced CT image in soft tissue window shows fatty atherosclerotic mural changes in the left external carotid artery (thick red arrow) causing luminal stenosis.

Table 4 Imaging recommendation for treatment related complications involving the Respiratory System

Clinical presentation	Complications	Implicated therapy	Imaging recommendation
Dyspnea, cough, wheezing, and fever	MIPI (medication-induced pulmonary injury)	Cytotoxic chemotherapy TKI Immunotherapy	CT (HRCT) scan without contrast
Cough, low-grade fever, and dyspnea	RILI (radiation-induced lung injury)	Radiation therapy	CT (HRCT) scan without contrast

Abbreviations: CT, computed tomography; HRCT, high-resolution computed tomography scan; TKI, tyrosine kinase inhibitor.

surveillance. It is important to note the presence and degree of coronary artery calcifications during these routine scans. Coronary CT is the imaging of choice for coronary artery disease characterization.[28]

Late sequelae of high-dose chest RT can cause constrictive pericarditis and valve stenosis.

CT scan or MRI can be used for evaluation of these entities.

Cardiac MRI is the noninvasive gold standard for morpho-functional myocardial characterization, thereby improving the detection of cardiotoxicity over conventional functional assessment. Nevertheless, the routine use of cardiac MRI is not currently recommended.[27,29]

Table 5 Imaging Recommendation for treatment related complications involving Cardiovascular System

Implicated therapy	Complication	Imaging recommendation
RT	Coronary artery disease	Coronary CT
RT	Valvular disease	Echocardiography/coronary CT/cardiac MRI
RT/Immunotherapy	Pericarditis	Echocardiography/coronary CT/cardiac MRI
RT/ChT	Cardiomyopathy	Echocardiography/cardiac MRI
ChT/Immunotherapy	Myocarditis	Echocardiography/cardiac MRI

Abbreviations: ChT, chemotherapy; CT, computed tomography; MRI, magnetic resonance imaging; RT, radiotherapy.

Other Thoracic Organs

For evaluation of pleura, pericardium, thymus, great vessels, and lymph nodes both CT and MRI can be used. CT scan is the modality of choice and is used more frequently. MRI is used as a problem solving tool.[25]

Abdomen (►Table 6, ►Fig. 3)

Liver injury symptoms include fatigue, right upper quadrant pain, nausea, vomiting, jaundice, abdominal swelling, and skin rashes. The different mechanisms of action of chemotherapy and RT may result in a broad spectrum of pathological and radiological hepatic injuries. These include acute or chronic hepatitis, steatosis, fibrosis, pseudocirrhosis, sinusoidal changes, and nodular hyperplasia. Ultrasonography (USG) is performed initially to rule out metastases, hemorrhage, and obstructive causes of jaundice. It may also detect ascites and gallbladder wall thickening (bystander effect). Either CT or MRI can be used for further characterization of liver involvement. MRI is more accurate in diagnosing steatosis/steatohepatitis, sinusoidal obstruction syndrome, and focal nodular hyperplasia-like nodules.[30–32]

For treatment-related oral mucosal and gingival ulceration, chemotherapy- and RT-induced nausea and vomiting (unless alternative causes are suspected, such as brain metastases or bowel obstruction), and uncomplicated mild diarrhea no imaging is needed.

For patients presenting with moderate or severe diarrhea, abdominopelvic CT scan with intravenous contrast needs to be done if complications such as enteritis, toxic megacolon, or abscess are suspected.[6] CT enterography may be performed in subacute or chronic situations.

Patients with suspected bowel obstruction (which may be due to complications of therapy such as stricture, adhesions, enteritis, and colitis) should undergo a supine abdominal radiograph as the initial investigation. Abdominopelvic CT scan with intravenous contrast would be needed to further localize and demonstrate the cause of obstruction. Subacute cases may be investigated with oral contrast fluoroscopy, small bowel follow-through or enema studies, CT, or MR enterography.

Patients with dysphagia, retrosternal pain, and odynophagia, that is, suspected esophagitis, endoscopy would be needed. Fluoroscopic examination (contrast swallow studies) may be done in subacute presentation. For suspected esophageal stricture, fibrosis, or fistula, fluoroscopy examination and/or CT scan with oral and intravenous contrast would be needed.

If a patient presents with upper abdominal pain, epigastric tenderness, and vomiting, radiation-induced gastritis or gastric/duodenal ulceration would be a possible cause, for which endoscopy would be diagnostic and no imaging would be required.

Table 6 Treatment related complications involving the Abdomen and Pelvis - Clinical presentation and initial Imaging Recommendation

Clinical presentation	Possible causes	Implicated therapy	Imaging recommendations
Oral mucosal and gingival ulceration	Mucositis (Therapy-related or Candida)	Cytotoxic chemotherapy agents Allogeneic HSCT recipients with GVHD	Usually no imaging recommended
Retrosternal pain Dysphagia Odynophagia	Esophagitis (due to mucositis or infective causes: Candida, HSV, bacterial, CMV, Aspergillus) Esophageal stricture/fibrosis/fistula	Radiation therapy Cytotoxic chemotherapy agents Myelosuppressants (neutropenia, mucositis)	Usually no imaging recommended (endoscopy needed) Fluoroscopy may be done, especially in chronic presentation CT scan with oral contrast: for fistula/stricture demonstration
Upper abdominal pain, epigastric tenderness, vomiting	Gastritis Gastric/duodenal ulcerations	Radiation therapy	Usually no imaging recommended (endoscopy needed)

Table 6 (*Continued*)

Clinical presentation	Possible causes	Implicated therapy	Imaging recommendations
Upper abdominal pain, epigastric tenderness, vomiting, raised serum amylase, lipase	Acute pancreatitis	Cytarabine L-asparaginase ATRA Immunotherapy agents Gemcitabine Cytarabine	CECT abdomen
Incidental rise in serum amylase lipase	–	Sunitinib, sorafenib	Usually no imaging recommended
Acute abdominal pain (and tenderness) Fever Nausea Vomiting Diarrhea (sometimes bloody)	Colitis/enterocolitis (neutropenic, *Clostridioides difficile*, GVHD, CMV, ischemic) Cholecystitis Appendicitis	Myelosuppressants + Cytotoxic chemotherapy (esp. in acute leukemias, taxanes in solid tumors) (neutropenia, mucositis)	CECT abdomen: for diagnosis, extent, complications (appendicitis, abscess, perforation)
Perianal swelling, pain, erythema	Anorectal cellulitis, fistula, abscess (usually polymicrobial: Enterobacteria, anaerobes, enterococci, *Pseudomonas aeruginosa*)	Cytotoxic chemotherapy	Consider CECT pelvis: for extent, drainable collections
Diarrhea (acute) Malabsorption (chronic)	Enteritis (therapy related or infective)	Cytotoxic chemotherapy Radiation therapy (ileitis)	Consider CECT/CT enterography in nonresolving or chronic cases
Constipation with/without abdominal distension, vomiting	Small/large bowel strictures, fistula, adhesions leading to acute/subacute obstruction Ileus	Radiation therapy Vinca alkaloids	Abdominal radiograph Fluoroscopy in subacute cases CECT abdomen
Fever, burning micturition, hematuria, pyuria	Urinary tract infections	Myelosuppressants Genitourinary procedures/ instrumentation	Ultrasonography of urinary tract
Rising urea, creatinine	Renal failure (AKI: acute, CKD: chronic)	Chemotherapy agents	Ultrasonography of urinary tract MRI may be done for early detection of AKI
Hematuria, frequency of micturition, burning micturition	Hemorrhagic cystitis	Cytotoxic agents (especially cyclophosphamide) Viral (in immunocompromised): BK virus, adenovirus, CMV Radiation therapy	Cystoscopy in refractory cases For severe/doubtful cases: CT urogram/ MR urogram/USG urinary tract/retrograde pyelogram (if CT scan with IV contrast is contraindicated)
Lower abdominal pain, distension in females Urinary incontinence Leakage of urine/stool through vagina	Cervical stenosis Hematometra/pyometra Vesicovaginal fistula Rectovaginal/rectovesical fistula	Radiation therapy (in pelvic cancers)	Ultrasonography MRI pelvis/fistulogram CECT pelvis with delayed phase/rectal contrast
Difficulty in micturition (usually males)	Urethral stricture	Radiation therapy	Retrograde cystourethrography, voiding cystourethrography
Females: amenorrhea, menstrual irregularities Males: features of hypogonadism, reduced sperm counts	Gonadal dysfunction	Cytotoxic chemotherapy Radiation therapy	In addition to hormonal evaluation, ultrasonography of the pelvis/testes

Abbreviations: AKI, acute kidney injury; ATRA, all-trans retinoic acid; CECT, contrast-enhanced computed tomography; CKD, chronic kidney disease; CMV, cytomegalovirus; CT, computed tomography; GVHD, graft versus host disease; HSCT, hematopoietic stem cell transplant; HSV, herpes simplex virus; IV, intravenous; MRI, magnetic resonance imaging; USG, ultrasonography.

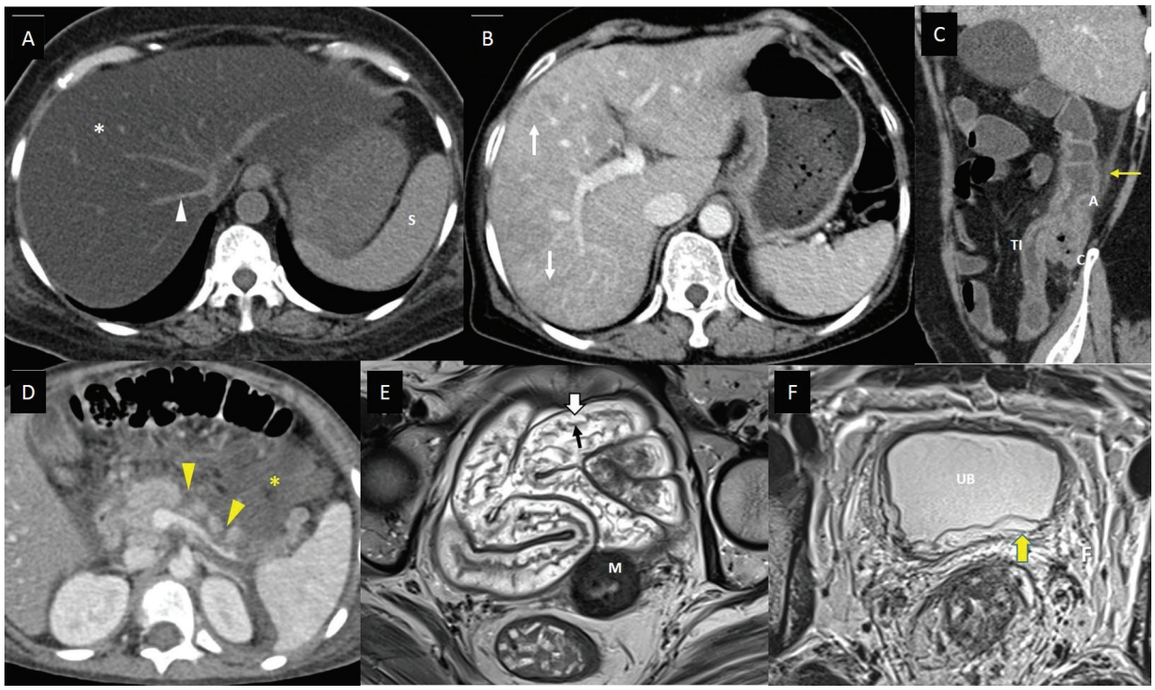

Fig. 3 Imaging features of abdominal complications of cancer therapy. (**A**) A 53-year-old suffering from acute lymphoblastic leukemia, on treatment with steroids and L-asparaginase, presented with mild abdominal pain and hyperbilirubinemia. Axial noncontrast computed tomography (CT) scan shows markedly reduced density of the entire hepatic parenchyma (white asterisk), suggesting fatty liver. The vessels (white arrowhead) and spleen (S) appear hyperdense to hepatic parenchyma in this noncontrast phase of CT scan due to diffuse fatty infiltration. (**B**) A 61-year-old lady with metastatic carcinoma stomach, on treatment with oxaliplatin. Axial CT scan of the abdomen with intravenous (IV) contrast done after few cycles of chemotherapy shows heterogeneous enhancement of the hepatic parenchyma with linear hypodensitites (white arrows), which is new compared to the baseline CT scan done 3 months back, suggesting oxaliplatin-induced sinusoidal obstruction syndrome. (**C**) A 48-year-old man with lung adenocarcinoma, treated with pembrolizumab and carboplatin, presented to the emergency department (ED) complaining of abdominal pain, multiple episodes of diarrhea, and vomiting 6 days after a chemotherapy cycle. Sagittal CT scan of the abdomen with IV contrast shows thickened and edematous wall of ascending colon (A), caecum (C), and terminal ileum (TI), with surrounding fat stranding (yellow arrow), and maintained mural stratification. The patient was found to be severely neutropenic, and these imaging findings along with the clinical presentation, suggested neutropenic enterocolitis/typhlitis. (**D**) A 6-year-old boy suffering from acute lymphoblastic leukemia, on treatment regimen containing L-asparaginase, presented to the ED with acute abdominal pain and vomiting. He was found to be hypotensive and serum amylase and lipase were raised. Axial CT scan of the abdomen with IV contrast shows nonenhancing areas within the pancreatic parenchyma indicating necrosis (yellow arrowheads), and collection in peripancreatic region containing foci of fat (yellow asterisk). The features suggest acute necrotizing pancreatitis with peripancreatic fat necrosis. (**E**) A 47-year-old lady receiving radiation therapy for carcinoma of the cervix uteri, underwent response assessment magnetic resonance imaging (MRI) after 20 fractions along with cisplatin. Axial T2-weighted MR image shows submucosal edema as hyperintense signals (white block arrow) deep to the hypointense mucosal layer (black arrow), and maintained mural stratification, involving pelvic small bowel loops, indicating radiation-induced enteritis. The tumor with posttreatment changes is seen involving the cervix (M). (**F**) A 32-year-old man with rectal adenocarcinoma, underwent a response assessment MRI after neoadjuvant chemoradiotherapy. He complained of mild lower urinary tract symptoms. Axial T2-weighted MR image shows edematous wall of urinary bladder (UB), with hyperintense signals involving the submucosa and muscularis (yellow block arrow), and surrounding edematous pelvic fat (F). The features suggested radiation-induced cystitis.

In case these symptoms are associated with raised serum amylase and lipase, acute pancreatitis is suspected, and an abdominopelvic CT scan with intravenous contrast is indicated. If the scan is normal, magnetic resonance cholangiopancreatography may be considered.

Neutropenic patients presenting with acute abdominal pain, fever, vomiting, and diarrhea, would be suspected to have infective or noninfective colitis/enterocolitis. USG would be recommended as an initial investigation and abdominopelvic CT scan with intravenous contrast would be indicated.

For patients with suspected urinary tract infection presenting with fever, burning micturition, hematuria, and/or pyuria, USG would be the initial imaging. Patients on cytotoxic chemotherapy (such as cyclophosphamide) or RT presenting with hematuria, hemorrhagic cystitis can be due to the therapy or viral infections. Cystoscopy and urinary tract imaging is indicated in refractory and severe cases. If renal function allows, CT urogram is done, otherwise, MR urogram and renal USG may be performed.[33] Patients with rising urea and creatinine would be suspected to have AKI or chronic kidney disease in appropriate setting. Usually, USG is performed. MRI may be done to evaluate the kidney and other organs.

If female patients on pelvic radiation therapy present with lower abdominal pain and distension, cervical stenosis with hematometra or pyometra is a possibility. USG would be the initial investigation of choice. MRI of the pelvis would

Table 7 Imaging recommendation for evaluation of complications involving Bones and Soft tissues

Clinical presentation	Imaging recommendation
Back pain with or without radiculopathy[1]	Radiograph of spine CT without IV contrast MRI without IV contrast
New onset soft tissue swelling[2]	Ultrasound of area of interest If nondiagnostic; CT or MRI of area of interest with IV contrast
Osteonecrosis[3]	MRI of area of interest without IV contrast CT of area of interest without IV contrast
Vertebral compression fractures[4]	MRI spine of area of interest without and with IV contrast
Patients receiving estrogen therapy or ADT with increased risk for osteoporosis related fractures	BMD measurement/DEXA every 2 years or more frequently depending upon age and risk factors[5] BMD measurement/DEXA and risk monitoring every 1- to 2-year interval[6] Baseline DEXA followed by DEXA scan at 1 year to assess risk and response[7]

Abbreviations: ADT, androgen deprivation therapy; BMD, bone mineral density; CT, computed tomography; DEXA, dual energy X-ray absorptiometry; IV, intravenous; MRI, magnetic resonance imaging.

demonstrate the cause better. Patients presenting with urinary incontinence, urine, or stool discharge through vagina would be suspected to have fistulas, and fluoroscopic examination with relevant contrast is the initial investigation. CT scan of the pelvis with intravenous contrast (delayed phase images) or with rectal contrast will delineate the communication better. MRI of the pelvis or MR fisulogram may demonstrate some fistulous communications better. In patients who present with difficulty in micturition following radiation therapy, urethral strictures are suspected and retrograde cystourethrography/voiding cystourethrography are required imaging modalities for diagnosis.

Bones and Soft Tissues (►Table 7)
The imaging recommendations are given in ►**Table 7**.[34–36]

Follow-Up and Surveillance
Women who were exposed to thoracic irradiation as an adolescent should undergo routine follow-up screening (with adjunctive breast MRI) sooner than usually recommended. Mammographic screening is recommended annually by the Society of Breast Imaging, ACR, and NCCN beginning 8 to 10 years after the radiation exposure.[37,38]

For patients undergoing combined chemotherapy and radiation therapy, imaging monitoring of left ventricular ejection function has been recommended at 2-year intervals.[39] Echocardiography is typically used. In patients who are found to have decreased systolic function, the next step should be cardiac MRI.[40]

There exists no other substantial role for surveillance to detect treatment-related complications.

Principles of Management

Most of the grade 1or grade 2 systemic anticancer drug-related and RT toxicity is manageable with supportive care without altering the recommended dose and frequency. For any grade 3 or grade 4 toxicity every effort should be made to find out any identifiable underlying factor(s) contributing to such toxicity (like uncontrolled comorbidity, poor nutritional status, etc.). Any correctable cause should be addressed accordingly. Majority of the time dose reduction is recommended in case of grade 3/4 toxicity. Prophylactic hematopoietic growth factor should be used liberally whenever indicated to reduce the incidence of febrile neutropenia. Permanent interruption is required in majority of grade 4 and few grade 3 toxicities. Patient counseling, home remedies, early identification, and treatment of toxicities are very important and effective strategy to maintain treatment compliance. For ICI-induced irAE, well-recommended and well-studied organ-specific guidelines exist (ASCO and ESMO guidelines). No dose reduction is recommended or permitted for any ICI-related irAE. Initial antibiotics cover and ruling out underlying or associated infection is recommended for any immunosuppressive therapy to treat irAE. Imaging is required to differentiate treatment complications from infection and tumor recurrence.

Summary of Recommendations

- There are no consensus guidelines regarding the frequency and modality of routine posttreatment imaging in an asymptomatic patient.
- In the case of equivocal signs and symptoms or presence of worrisome features on clinical examinations and other laboratory tests, imaging protocol may be tailored to answer specific clinical questions.
- Most imaging guidelines advocate the use of MRI and CT scan in complementary roles.

Conflict of Interest
None declared.

References

1 Badalamenti G, Messina C, De Luca I, Musso E, Casarin A, Incorvaia L. Soft tissue sarcomas in the precision medicine era: new advances in clinical practice and future perspectives. Radiol Med (Torino) 2019;124(04):259–265

2 Kucha N, Soni TP, Jakhotia N, et al. A prospective, comparative analysis of acute toxicity profile between three-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT) in locally advanced head and neck cancer patients. Cancer Treat Res Commun 2020;25:100223
3 Ngo D, Jia JB, Green CS, Gulati AT, Lall C. Cancer therapy related complications in the liver, pancreas, and biliary system: an imaging perspective. Insights Imaging 2015;6(06):665–677
4 Stone JB, DeAngelis LM. Cancer-treatment-induced neurotoxicity–focus on newer treatments. Nat Rev Clin Oncol 2016;13(02): 92–105
5 Jairam V, Lee V, Park HS, et al. Treatment-related complications of systemic therapy and radiotherapy. JAMA Oncol 2019;5(07): 1028–1035
6 Thompson JA, Schneider BJ, Brahmer J, et al. Management of Immunotherapy-Related Toxicities, Version 1.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2022;20 (04):387–405. Doi: 10.6004/jnccn.2022.0020
7 Baden LR, Swaminathan S, Angarone M, et al. Prevention and Treatment of Cancer-Related Infections, Version 2.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2016;14(07):882–913. Doi: 10.6004/jnccn.2016.0093
8 NCG palliative care guidelines 2021 [Internet]. NCG; 2021. Accessed April 1, 2022, at: https://tmc.gov.in/ncg/index.php/guidelines/palliative-care-guidelines
9 NCG. Approach to managing malignant bowel obstruction [Internet]. NCG Guidelines for palliative care. 2021. Accessed April 1, 2022, at: https://tmc.gov.in/ncg/images/Approach%20to%20managing%20Malignant%20Bowel%20Obstruction.pdf
10 Kanda T, Wakabayashi Y, Zeng F, et al. Imaging findings in radiation therapy complications of the central nervous system. Jpn J Radiol 2018;36(09):519–527
11 Albano D, Benenati M, Bruno A, et al; Young SIRM Working Group. Imaging side effects and complications of chemotherapy and radiation therapy: a pictorial review from head to toe. Insights Imaging 2021;12(01):76
12 Kessler AT, Bhatt AA. Brain tumour post-treatment imaging and treatment-related complications. Insights Imaging 2018;9(06): 1057–1075
13 Shah R, Vattoth S, Jacob R, et al. Radiation necrosis in the brain: imaging features and differentiation from tumor recurrence. Radiographics 2012;32(05):1343–1359
14 Leao DJ, Craig PG, Godoy LF, Leite CC, Policeni B. Response assessment in neuro-oncology criteria for gliomas: practical approach using conventional and advanced techniques. AJNR Am J Neuroradiol 2020;41(01):10–20
15 Chukwueke UN, Wen PY. Use of the Response Assessment in Neuro-Oncology (RANO) criteria in clinical trials and clinical practice. CNS Oncol 2019;8(01):CNS28
16 Linhares P, Carvalho B, Figueiredo R, Reis RM, Vaz R. Early pseudoprogression following chemoradiotherapy in glioblastoma patients: the value of RANO evaluation. J Oncol 2013; 2013:690585
17 Dietrich J, Klein JP. Imaging of cancer therapy–induced central nervous system toxicity. Neurol Clin [Internet]. 2014. Accessed December 13, 2022, at: https://www.neurologic.theclinics.com/article/S0733-8619(13)00087-X/abstract
18 Sindhwani G, Arora M, Thakker VD, Jain A. MRI in chemotherapy induced leukoencephalopathy: report of two cases and radiologist's perspective. J Clin Diagn Res 2017;11(07):TD08–TD09
19 Glastonbury CM, Parker EE, Hoang JK. The postradiation neck: evaluating response to treatment and recognizing complications. AJR Am J Roentgenol 2010;195(02):W164-71
20 Gehani A, Sen S, Chatterjee S, Mukhopadhyay S. Imaging features of postradiotherapy changes in head and neck cancers. Indian J Radiol Imaging 2021;31(03):661–669
21 Nishino M, Ramaiya NH, Awad MM, et al. PD-1 inhibitor-related pneumonitis in advanced cancer patients: radiographic patterns and clinical course. Clin Cancer Res 2016;22(24):6051–6060
22 Terbuch A, Tiu C, Candilejo IM, et al. Radiological patterns of drug-induced interstitial lung disease (DILD) in early-phase oncology clinical trials. Clin Cancer Res 2020;26(18):4805–4813
23 Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012;30(21):2691–2697
24 Lee H, Lee HY, Sun J-M, et al. Transient asymptomatic pulmonary opacities during osimertinib treatment and its clinical implication. J Thorac Oncol 2018;13(08):1106–1112
25 Benveniste MF, Gomez D, Carter BW, et al. Recognizing radiation therapy-related complications in the chest. Radiographics 2019; 39(02):344–366
26 Yeh ETH, Tong AT, Lenihan DJ, et al. Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. Circulation 2004;109(25):3122–3131
27 Čelutkienė J, Pudil R, López-Fernández T, et al. Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC). Eur J Heart Fail 2020;22(09):1504–1524
28 Whitlock MC, Yeboah J, Burke GL, Chen H, Klepin HD, Hundley WG. Cancer and its association with the development of coronary artery calcification: an assessment from the multi-ethnic study of atherosclerosis. J Am Heart Assoc 2015;4(11):e002533
29 Wang DY, Salem J-E, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. JAMA Oncol 2018;4(12):1721–1728
30 Gatti M, Calandri M, Bergamasco L, et al. Characterization of the arterial enhancement pattern of focal liver lesions by multiple arterial phase magnetic resonance imaging: comparison between hepatocellular carcinoma and focal nodular hyperplasia. Radiol Med (Torino) 2020;125(04):348–355
31 Vernuccio F, Godfrey D, Meyer M, et al. Local tumor control and patient outcome using stereotactic body radiation therapy for hepatocellular carcinoma: iRECIST as a potential substitute for traditional criteria. AJR Am J Roentgenol 2019;213(06): 1232–1239
32 Hennedige TP, Hallinan JTPD, Leung FP, et al. Comparison of magnetic resonance elastography and diffusion-weighted imaging for differentiating benign and malignant liver lesions. Eur Radiol 2016;26(02):398–406
33 UpToDate [Internet]. Accessed April 1, 2022, at: https://www.uptodate.com/contents/chemotherapy-and-radiation-related-hemorrhagic-cystitis-in-cancer-patients
34 Hutchins TA, Peckham M, Shah LM, et al; Expert Panel on Neurological Imaging. ACR Appropriateness Criteria® low back pain: 2021 update. J Am Coll Radiol 2021;18(11S, Supplement): S361–S379
35 Kransdorf MJ, Murphey MD, Wessell DE, et al; Expert Panel on Musculoskeletal Imaging. ACR Appropriateness Criteria® soft-tissue masses. J Am Coll Radiol 2018;15(5S):S189–S197
36 Shah LM, Jennings JW, Kirsch CFE, et al; Expert Panels on Neurological Imaging, Interventional Radiology, and Musculoskeletal Imaging. ACR Appropriateness Criteria® management of vertebral compression fractures. J Am Coll Radiol 2018;15(11S): S347–S364
37 Lee CH, Dershaw DD, Kopans D, et al. Breast cancer screening with imaging: recommendations from the Society of Breast Imaging and the ACR on the use of mammography, breast MRI, breast ultrasound, and other technologies for the detection of clinically occult breast cancer. J Am Coll Radiol 2010;7(01): 18–27

38 Bevers TB, Anderson BO, Bonaccio E, et al; National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: breast cancer screening and diagnosis. J Natl Compr Canc Netw 2009;7(10):1060–1096
39 Johnson CB, Sulpher J, Stadnick E. Evaluation, prevention and management of cancer therapy-induced cardiotoxicity: a contemporary approach for clinicians. Curr Opin Cardiol 2015;30 (02):197–204
40 Huang H, Nijjar PS, Misialek JR, et al. Accuracy of left ventricular ejection fraction by contemporary multiple gated acquisition scanning in patients with cancer: comparison with cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2017;19(01):34

Imaging Recommendations for Image-Guided Biopsy in Oncology

Kunal B. Gala[1,2] Daksh Chandra[1,2] Nitin Sudhakar Shetty[1,2] Ujjwal Agarwal[1,2] Harshit Bansal[1,2] Md Shariq[3] Himanshu A. Pendse[4] Amit Janu[1,2] Rupesh Mandava[5] Suyash S. Kulkarni[1,2]

[1] Department of Radio-Diagnosis, Tata Memorial Hospital, Tata Memorial Centre, Mumbai, India
[2] Department of Radiology, Homi Bhabha National University (HBNI), Mumbai, India
[3] Department of Radiology, Queens Hospital, Romford, United Kingdom
[4] Department of Radiology, Royal Perth Hospital, Australia
[5] Department of Radiology, KIIMS Hospital, Hyderabad, India

Address for correspondence Suyash S. Kulkarni, DMRD, DNB, Interventional Radiology, Department of Radio-Diagnosis, Room No 71, Tata Memorial Hospital, Tata Memorial Centre, Parel, Mumbai, India (e-mail: suyashkulkarnitmh@gmail.com).

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Abstract

The percutaneous needle biopsy (PNB) is the initial step for obtaining the diagnosis and it helps in treatment. It aids in primary diagnosis, tumor staging, or ruling out infective etiology. It is a safe and successful minimally invasive method compared to open biopsies. PNB is defined as the placement and insertion of a needle into a suspected lesion or organ with the intent of retrieving tissue or cells for diagnosis. It can fine needle aspiration cytology or core needle biopsy. The patient needs to be counseled regarding the procedure and detailed history, including anticoagulant history needs to be taken. The SIR consensus guidelines have divided biopsies into low-risk procedures with a bleeding risk of $< 1.5\%$ and high-risk procedures $> 1.5\%$. There are advancements in needle design (e.g., echogenic tip while performing ultrasound-guided needle biopsy) and image-guidance technology (ultrasound quality, multi-slice CT scan) that improved these procedures safety and efficacy. There are different types of needles available such as coaxial, aspiration needles, Murphy's bone biopsy needle, which depends on the tissue which needs to be sampled or the organ to be biopsied. Various different types of biopsy guns, such as semi-automatic, automatic, or manual are available. The newer technology such as fusion and navigation biopsies helps in better characterizing and localization of the lesion, improving the yield of the biopsy. Open and excisional biopsies have a higher mortality and morbidity rate than percutaneous biopsies, they are reserved for cases where the image-guided method has failed to provide the diagnostic yield. Sample collection must be done under a sterile container in formaline or microbiological examination. Regular analysis and rad-path correlation are key to success and improving diagnostic yield. This abstract provides an overview of the existing biopsy literature.

Keywords
- diagnostic accuracy
- complication
- core-needle biopsy (CNB)
- oncologic imaging
- percutaneous biopsy

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Introduction

Percutaneous needle biopsy is an integral part of cancer diagnosis and treatment. It is the first step in achieving the diagnosis.[1] It helps in tumor staging because it provides pathologic confirmation of metastasis. Percutaneous image biopsy-guided biopsies are minimally invasive, safe, and effective procedures.[2] The safety and efficacy of these treatments have increased due to advancements in needle design (e.g., echogenic tip while doing ultrasound-guided needle biopsy) and image-guidance technologies.[3] Open and excisional biopsies are reserved for selected cases where the image-guided procedure has failed to give the diagnostic yield because it is more mortality and morbidity than percutaneous biopsy. This document provides an overall review of the current literature on biopsy.[4]

Indications

Following are scenarios where biopsy is recommended- ►**Table 1**

A) Diagnosis of pulmonary nodules-computed tomography (CT) is the preferred image guidance modality. Ideally, the most vertical (perpendicuar) path is selected, which avoids bullae, interlobar fissures, and large vessels[5] (►**Fig. 1A–C**).

Table 1 Indications of performing a percutaneous biopsy

1. To establish the diagnosis of the benign or malignant nature of the lesion.
2. To obtain tissue for microbiological analyses in suspected or known infections in the post-treatment setting.
3. To classify a malignancy and perform immunohistochemistry (IHC) on the sample and obtain molecular analysis for the targeted.
4. To stage a patient with suspected malignant tumors elsewhere.[3]

Contraindication

Absolute-
- Difficult location,
- Irreversible coagulopathy and
- Refusal to Consent.

Relative
- Unco-operative patient (can be done under general anasthesia),
- Significant co-morbidities (e.g., respiratory or hemodynamic instability),
- Pregnancy (especially if ionizing radiation is present, can be done ultrasound-guided.)[4]

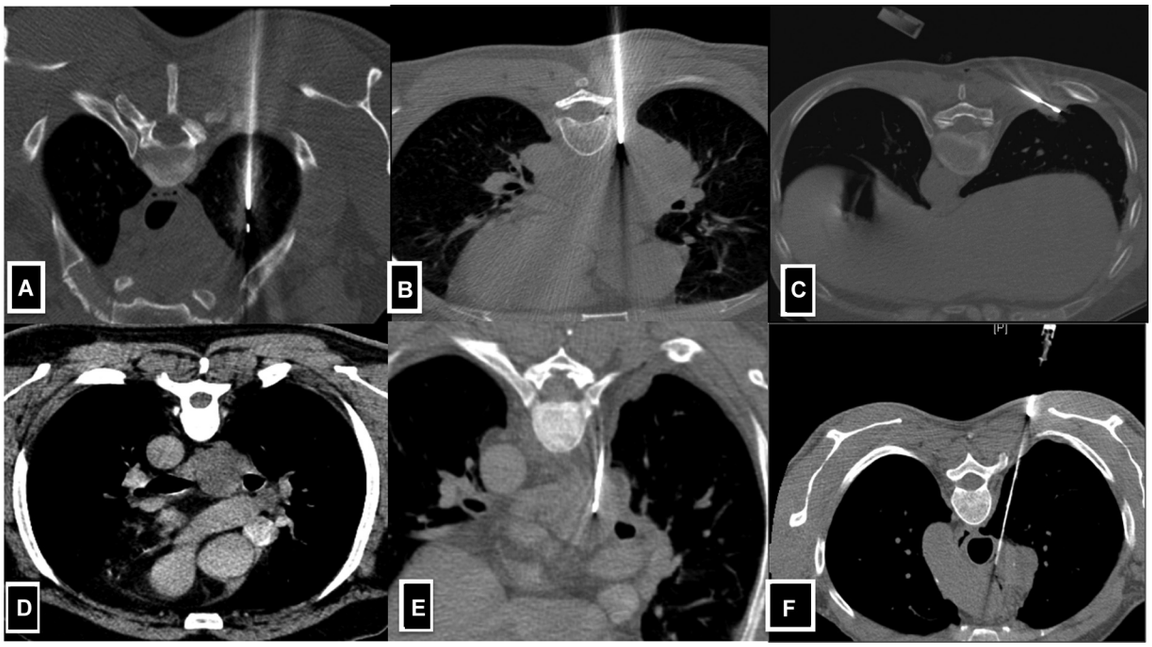

Fig. 1 (A–F) Axial CT images demonstrate lung and mediastinal lesion biopsy technique.
A-Solitary lesion in the right upper lobe posterior approach taken where the needle is perpendicular to the lesion.
B-Large lung mass in the right lower lobe posterior approach taken for biopsy.
C-Small lesion located in the subpleural location of the right lower lobe, tangential approach taken to obtain the larger length of the core.
D & E-CECT reveals subcarinal lymph node in k/c/o carcinoma of the lung. Extrapleural posterior approach was taken with hydro dissection of the parietal and visceral pleural and a biopsy of the mediastinal lymph node was done.

B) Mediastinal lesions-CT-guided direct mediastinal or extrapleural approach is generally preferred over a transpulmonary approach to avoid pleural transgression and thereby decrease the risk of pneumothorax and pulmonary haemorrhage.[6] Ultrasonographic (USG) guidance can be used for large mediastinal lesions, which are in contact with the chest wall and are easily visualised (►**Fig. 1D–F**).

C) Abdominal and pelvic lesions-Soft-tissue masses involving the peritoneum, omentum, retroperitoneal nodes, and mesenteric lymph nodes are amenable to percutaneous biopsies under USG or CT guidance depending on size and location. Liver biopsies are done under USG guidance; however, CT guidance can be preferred when there is difficulty in visualizing lesions such as under the dome of the diaphragm. In certain cases, a combination of modalities can be used where both USG and CT scan can be used for lesions near para cardiac location[7] or navigation/fusion techniques with USG guidance can be done (►**Fig. 2**).

D) Musculoskeletal tumors-Soft tissue masses can be easily targeted on USG; however, CT guidance is recommended for lesions limited to bone. The needle path and approach need to be discussed with the orthopaedic oncosurgeon because an inappropriately performed biopsy will lead to contamination of the compartment, wider excision during surgery, a wider area of irradiation, and difficulty in flap reconstruction of the defect.

E) Spinal lesions-The biopsy of vertebral lesions depends on the location of the lesion within the vertebra and the level of vertebra. It can be transpedicular, parapedicular, transforaminal, and para laminar for lumbar and thoracic vertebrae. It can be an anterolateral, posterolateral, posterior, and anterior transoral approach under fluoroscopy or CT guidance for the cervical vertebra, depending on the location of the lesion[8] (►**Fig. 3**).

F) Head and neck lesions-Deep seated head and neck biopsies are most commonly performed under CT guidance. Various approaches such as subzygomatic, retromandibular, paramaxillary and submastoid, transoral and posterior approaches are commonly used.[9] In contrast, the biopsies of superficial organs such as lymph node, submental, parotid glands, and thyroid gland lesions are done under USG guidance (►**Fig. 4**).

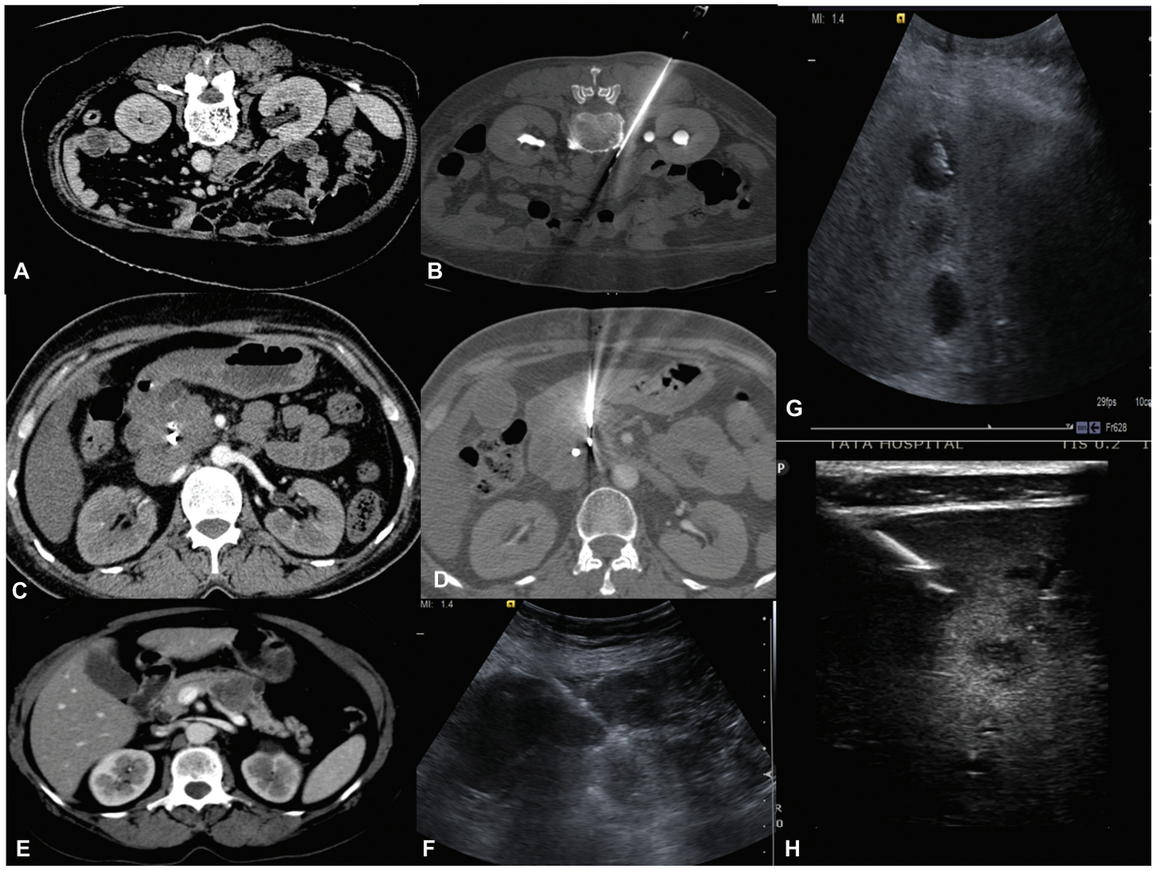

Fig. 2 (A–B) Left Paraspinal approach for biopsy of the aortocaval lymph node.
(C–D) CECT reveals pancreatic head mass where biopsy is performed via transgastric approach.
(E–F) CECT reveals pancreatic body mass, USG guided biopsy of pancreatic mass with compression of bowel loops.
(G–H) USG guided liver lesions biopsy traversing normal liver parenchyma. H-Lesions appreciated by using high-frequency probe.

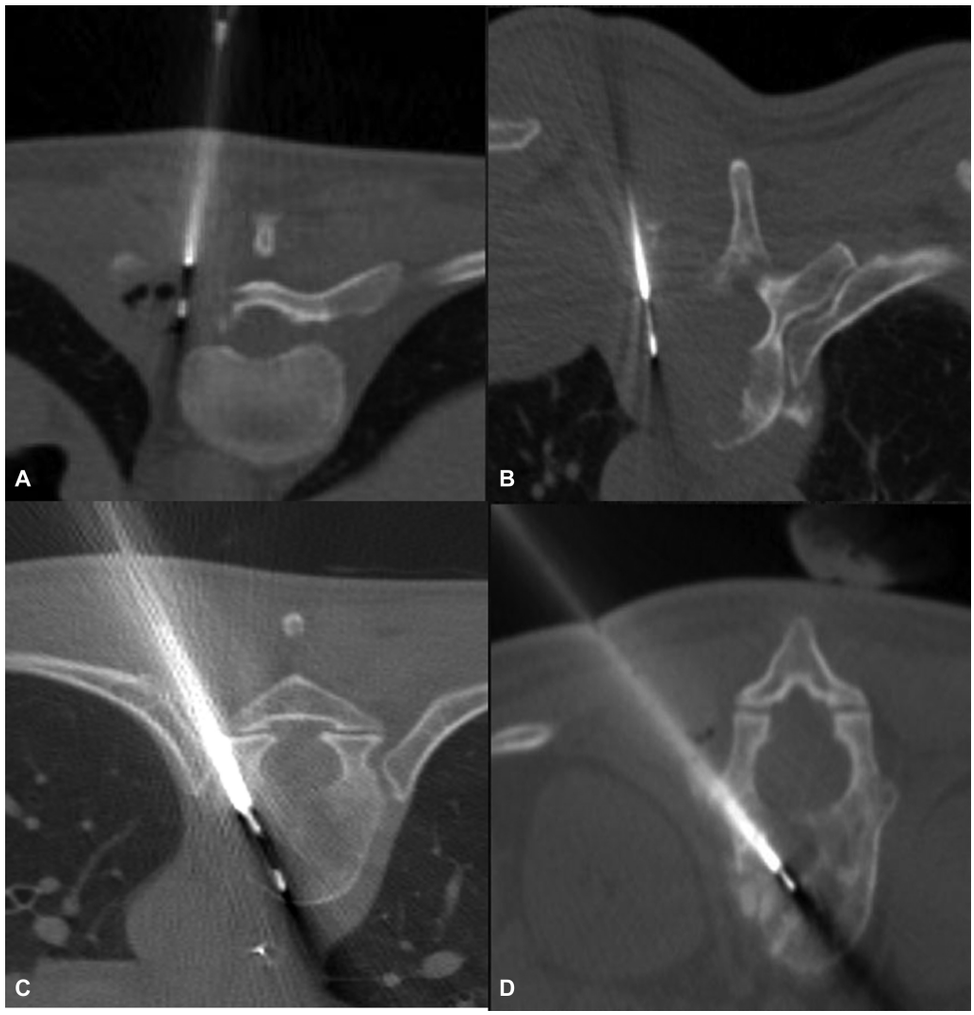

Fig. 3 (A and B) Axial CT images demonstrate vertebral lesion biopsy by parapedicular technique. (C and D) Axial CT images demonstrate vertebral lesion biopsy by transpedicular technique.

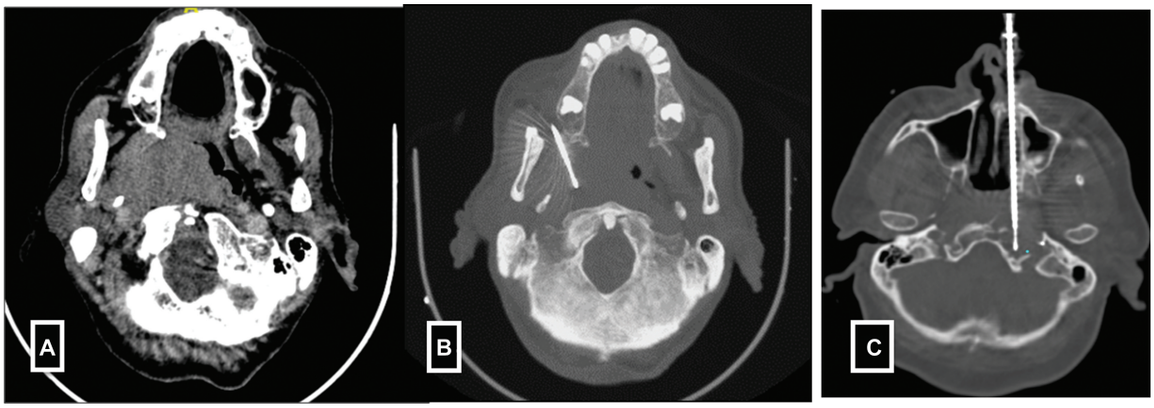

Fig. 4 (A-B) Paramaxiiary approach for parapharyngeal mass biopsy. (C) Trans nasal approach for petrous mass biopsy.

Definitions

According to the Cardiovascular and Interventional Radiological Society of Europe (CIRSE), the definition of percutaneous needle biopsy (PNB) is "The placement or insertion of a needle into a suspected lesion or organ for the intent of retrieving tissue or cells for diagnosis." Imaging techniques used as a guide for PNB are ultrasound, fluoroscopy,

computed tomography, positron emission tomography CT (PET-CT) and magnetic resonance imaging (MRI). The imaging technology used is determined by nature, location of the lesion, the patient's compliance, availability of the technique, and preference of the operators. Fine-needle aspiration cytology (FNAC) and core biopsy (CB) are two types of PNB. FNAC is a technique that involves using a thin, hollow needle (18–25 gauge) to collect cells for cytological evaluation by aspiration. FNAC is used to prove metastasis or where the lesion is difficult to biopsy due to the vicinity of a critical structure such as a major blood vessel, bowel or any major organ. CB is the extraction of a portion of tissue for the histological assessment using a hollow needle (9–20 gauge) with a cutting and capturing device.[4,10]

The technical success of PNB is defined as the procurement of sufficient samples to establish the diagnosis. Clinical success is defined as a patient's outcome depending on the biopsy result. According to the protocol, clinical success guides the clinician for appropriate surgical or medical management.[4]

Patient Information and Consent

Prior to doing a biopsy, the patient's detailed medical history, anticoagulant history, clinical examination, laboratory data such as complete blood count and coagulation profile need to be done except for superficial cases, i.e., low-risk case (Category 1-according to CIRSE). Pre-procedural cross-section images need to be available for procedural planning, such as choosing the best imaging guidance (with or without contrast injection to delineate the lesion better), the patient's position, access routes, needle type and trajectory, and the number of samples to be collected. Following institutional protocols, informed consent should be sought directly by the interventionist doing the procedure. The indications, procedure details, complications, and alternative options must be appropriately discussed with patients. The need for prophylactic antibiotics (transrectal biopsies), peri-procedural drugs, such as anesthesia and pain medication that may be required and post-procedure medications must be explained.[11,12]

Contraindications and Precautions

Antiplatelet/anticoagulation drugs should be stopped before the procedure, especially for biopsies with a moderate or high risk of bleeding. Evaluation of coagulation status and discontinuing anticoagulation medications before the procedure as per the Society of Interventional Radiology (SIR) guidelines. The SIR consensus guidelines have divided biopsies into low-risk procedures with a bleeding risk of $< 1.5\%$ and high-risk procedures $>1.5\%$. Superficial biopsies and transjugular liver biopsies are categorized as low-risk, while solid organ and deep non-organ biopsies are categorized as high risk for bleeding. The SIR guidelines recommend the correction of the International Normalized Ratio (INR) to 2.0 to 3.0 for low-bleeding-risk procedures and 1.5 to 1.8 for high-bleeding risk procedures. Platelet transfusion should be considered if the platelet count is $< 20 \times 10^9$/L or $< 50\ 10^9$/L for low and high bleeding risk procedures, respectively. It is recommended to withhold the antiplatelet or anticoagulant medications for 3 to 5 days before high-bleeding risk biopsies (►**Table 2**).[13]

Technique/Protocol/Image Acquisition

A careful review of the cross-sectional/functional images needs to be done. The preferred imaging modality is chosen, and the biopsy trajectory is planned. Patients should be fasting for 4 to 6 hours before the procedure when sedation or deep anesthesia is needed, especially for children (below 15 years) and individuals who are apprehensive or have lesions in a critical location. Peripheral venous access (18–20 Gauge) should be obtained in all patients before the procedure and vitals need to be monitored pre-procedure, intra procedure, and at least 2 hours after the procedure. On the biopsy day, the checklist must be filled before the biopsy.[4]

Patient Positioning and Preparation

The patient is positioned depending on the lesion location, modality used, and easy access route to the lesion avoiding the major neurovascular structures, lung fissure and bullae, bowel etc. The patient should be in a comfortable and stable position for the procedure. The target route must be as short as possible; however, in certain specific situations, a longer route is advised, such as in subcapsular liver or lung lesions. A longer track with intervening normal liver parenchyma in the liver reduces the risk of hemoperitoneum due to the tamponade effect; similarly, in subpleural lesions, a longer oblique intraparenchymal needle path helps in the easy maneuvering of the needle and increases technical success.[14] In some situations, intravenous contrast media injection (including the contrast-enhanced US, e.g., for isoechoic liver or renal tumors) is required to visualize the target lesion before biopsy and visualize the vital structures. All biopsies are done in free-breathing techniques, rarely in a difficult location such as lung bases; it should be done in the end-expiratory phase as the lesion position will be relatively more stable.[15]

Table 2 Pre- Biopsy checklist

1. Check blood parameters (hemoglobin, platelet count, PT/INR, viral markers)
2. Confirm the patient's identity and the procedure to be performed.
3. If a contrast agent needs to be administered, the renal function test should be evaluated and safety assured after ruling out any history of allergy to such materials.
4. Any use of anticoagulation needs to be reconfirmed to avoid inadvertent complications.
5. Informed consent needs to be taken after explaining the risks and benefits of the procedure in detail.

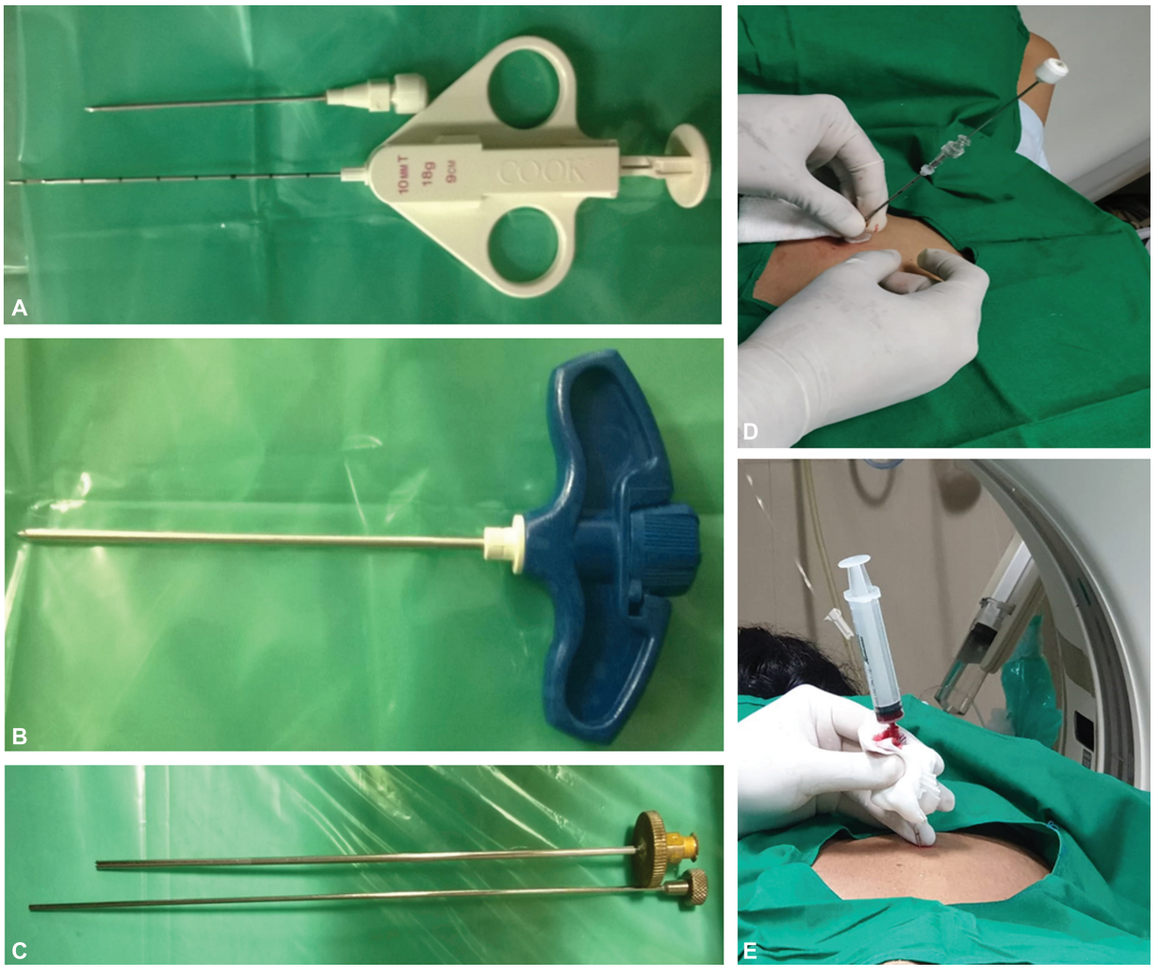

Fig. 5 (A) Coaxial biopsy system showing biopsy needle and gun. (B-C) Murphy's needle and ackerman's used for bone biopsy. (D-E) Post biopsy clot embolisation of biopsy tract in lung biopsy.

Techniques

Coaxial technique-A guide needle, larger than the biopsy needle (typically 9–19G), is advanced under image guidance, reaching the edge of the target. The inner stylet is removed, the biopsy gun is introduced into the lesion, and multiple specimens are taken with a single puncture. This may prevent tumor cells from seeding along the needle tract by re-inserting the inner stylet of the coaxial needle before the removal compared to the non-coaxial method. The coaxial technique reduces procedural time and procedure-related pain (by reducing repeated punctures) and also decreases the rate of complications (►**Fig. 5**).

Hydro-dissection is a technique where 0.9% saline solution facilitates image-guided biopsies by displacing important mobile structures (such as bowel, neurovascular bundle, etc.) away from the needle trajectory[16] (►**Table 3**).

Table 3 Different biopsy techniques

1. Hydrodissection in subcarinal nodes biopsy. 2. Curve needle technique in mediastinal biopsy and abdominal lesions. 3. Inspiration and expiration for small pulmonary nodules and liver lesions. 4. Lateral decubitus in adrenal biopsy and lung biopsy. 5. Artificial pleural effusion and pneumothorax with the help of a spinal needle.
Different types if biopsy guns available. 1. Automatic 2. Semi-automatic **3.** Vacuum-assisted
Different types of Biopsy needles available. 1. Coaxial 2. Aspiration needles 3. Murphy's bone biopsy needle 4. Steerable needles

Image Analysis and Interpretation

A percutaneous needle biopsy can be performed under the US, CT, fluoroscopy, MR, fluoro-CT, cone-beam CT or PET-CT guidance. The advantages and disadvantages of the most frequently used image guidance techniques are summarized in ►**Table 4**.

The selected imaging modality should allow the following:

Table 4 The advantages and disadvantages of the most frequently used image guidance techniques

	USG	CT/Fluoroscopy	MRI
Advantages	Real-time imaging is available. Portability present. Availability. No radiation exposure, feasible for pregnant patients. Less procedure time. Less cost as no need to give contrast.	Visualization of deep lesions is limited in obese patients.	Near real time with specific sequences Excellent visualization of deep lesions. No radiation exposure.
Disadvantages	Visualization of deep lesions is limited in obese patients, however it can be overcome with the upcoming fusion biopsy technique.	Real-time imaging only possible with CT fluoroscopy. Portability is an issue. Availability is an issue since the cost is more. Radiation exposure is an issue. More procedure time. More cost	Portability is an issue. Availability is an issue since the cost is more. More procedure time. Maximum cost.

- Proper visualization of the target lesion and all the adjacent relevant anatomy.
- Adequate visualization of biopsy equipment used during the procedure.
- Comfortable patient positioning and operator's maneuvers.
- Prompt and adequate evaluation and management of possible complications (e.g., pneumothorax).
- Limited ionizing radiation exposure (particularly in children and young patients).

The new software has become available to facilitate needle insertion and target visualization during a biopsy under challenging lesions that allows fusing images obtained from different modalities, such as CT, MR or PET-CT with real-time USG or fluoroscopy. Special optical or electromagnetic navigation systems are required for performing biopsies using this technique.[17]

USG guidance-The needle can be inserted parallel or perpendicular to the transducer with the freehand or hand-guided technique. The tip needs to be visualized during needle insertion as an echogenic complex. Multiple punctures of the liver/renal capsule should be avoided to avoid the risk of bleeding. TRUS (trans-rectal)/TVUS (trans-vaginal) route can be used to biopsy prostate, vaginal/cervical vault lesions, and other deep-seated pelvic lesions (►**Fig. 6**).[18]

CT guidance-The biopsy planning is done on the axial scans and needs to be confirmed on the multiplanar reformatted images. The path length and angle are measured on the CT scan. The skin access point is marked using a radiopaque marker or a radiopaque grid positioned on the patient before the preliminary CT. A low-dose CT scan (reduced kVp and mAs) can be performed to reduce the overall dose of radiation[19] (►**Table 4**).

Sample collection-

All biopsy samples need to be collected in formalin for histopathology. If the imaging finding is for infection additional sample needs to be collected for culture and sensitivity and if tuberculosis is suspected for gene expert.[20]

Complications

The complication needs to be anticipated early and appropriate treatment needs to be done. All emergency drugs should be available within the department and the operating physician needs to know about these drugs.

The most common complication is bleeding and significant bleeding after PNB is rare. It is approximately 0.5% of all cases.[21] The biopsy tract must be plugged with a gelatin sponge, coils, or glue if the bleeding is from the coaxial needle. This can also be done as prophylactic in cases where it is a high risk, as in highly vascularized tumors or highly vascularized organs such as the spleen. The majority of complications occur within 4 to 6 hours following the biopsy.

Analgesics (typically, paracetamol, or NSAIDs) are prescribed if the pain is present.

Perforation of organ–can be there if any transgression of the bowel is there. Most of the time, conservative management will settle, but one should look for any signs of peritonitis.[22]

Pneumothorax is one of the most common complications of lung biopsy; however, only progressive, moderate, or tension pneumothorax needs catheter placement. One can use 1 to 3 mL of saline or autologous blood clot to seal the needle tract in lung biopsy can also be performed to reduce the risk of pneumothorax.[23]

Quality Control

The physician performing the PNB always strives to achieve 100% success and 0% complication. However, it is challenging to achieve these results, so SIR has come out with quality-improving guidelines to determine an optimal success rate threshold for percutaneous biopsy.[2] The numerous factors will influence the procedure's ultimate success. These factors include the number of samples taken, the magnitude of the target abnormality, the organ system in which the biopsy is conducted, the presence of an onsite cytopathologist, the pathology staff's experience, the imaging technology available, and the operating physician's competency.

There should be a regular audit of the PNB and these need to be looked at carefully to keep on improving. Another thing is to have regular meetings with pathology colleagues to improve the overall accuracy of the biopsy and have a good rad-path correlation.

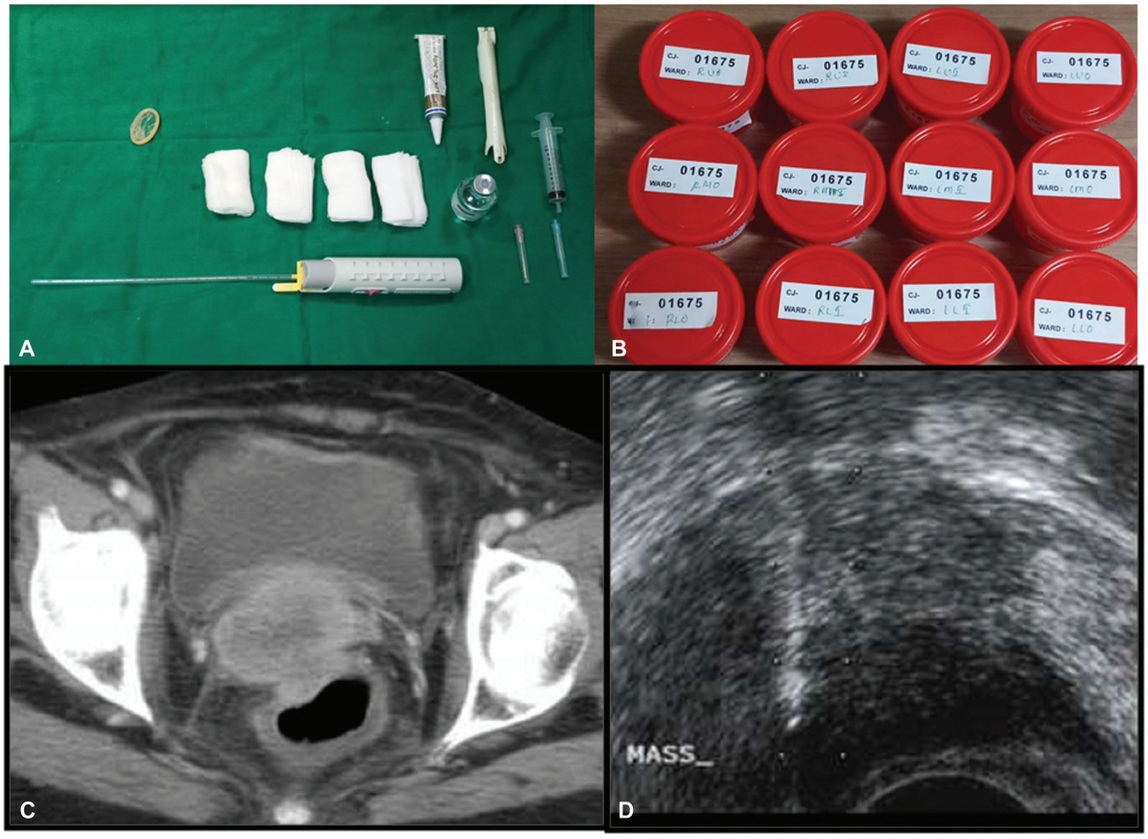

Fig. 6 (A-B) Instrumentation used in TRUS guided biopsy and 12 containers for 12 core biopsy of the prostate. (C-D) Axial CT shows an ill-defined cervical mass sampled through TRUS guided approach.

Regulatory Issues

The overall reported diagnostic technical success rate of PNB is 70 to 96%; however, it varies greatly depending on the size and location of the target, the benign or malignant nature of the lesion, the number of samples obtained, the availability of an onsite cytopathologist, the experience of the Irs and pathologists, and the availability of equipment. PNB's clinical success can be defined as the procedure's utility in improving patient care assessed by biopsy results, including quality of life (QoF).[24,25] The selection of patients for targeted or immune-targeted therapy and recruitment into clinical trials can be a positive outcome of PNB in the era of customized cancer care.

Summary

- Complete blood count and coagulation profile are recommended in all patients scheduled for a biopsy except for superficial low-risk biopsies (Category 1).
- General anesthesia is recommended for pediatric patients.
- Antibiotic prophylaxis is recommended only in immunosuppressed patients, infective cases, or transgression of the bowel, as in transrectal biopsies.
- A longer route is recommended in the subcapsular liver or subcapsular lung lesions.
- Major complications occur within 4 to 6 hours after biopsy and bleeding is the most common complication.
- Analysis of biopsy and rad-path correlation needs to be done.

Note

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

Conflict of Interest

None declared.

References

1 Gupta S, Madoff DC. Image-guided percutaneous needle biopsy in cancer diagnosis and staging. Tech Vasc Interv Radiol 2007;10 (02):88–101
2 Cardella JF, Bakal CW, Bertino RE, et al; Society of Interventional Radiology Standards of Practice Committee. Quality improvement guidelines for image-guided percutaneous biopsy in adults. J Vasc Interv Radiol 2003;14(9 Pt 2):S227–S230
3 Schiavon LHO, Tyng CJ, Travesso DJ, Rocha RD, Schiavon ACSA, Bitencourt AGV. Computed tomography-guided percutaneous biopsy of abdominal lesions: indications, techniques, results, and complications. Radiol Bras 2018;51(03):141–146
4 Veltri A, Bargellini I, Giorgi L, Almeida PA, Akhan O. CIRSE guidelines on percutaneous needle biopsy (PNB). Cardiovascular and Interventional Radiology 2017;40(10):1501–1513

5 Gutierrez A, Abtin F, Suh RD. Percutaneous transthoracic lung biopsy. In percutaneous image-guided biopsy. New York, NY: Springer; 2014:141–166
6 Gupta S, Seaberg K, Wallace MJ, et al. Imaging-guided percutaneous biopsy of mediastinal lesions: different approaches and anatomic considerations. Radiographics 2005;25(03):763–786, discussion 786–788
7 Shankar S, van Sonnenberg E, Silverman SG, Tuncali K. Interventional radiology procedures in the liver. Biopsy, drainage, and ablation. Clin Liver Dis 2002;6(01):91–118
8 Heyer CM, Al-Hadari A, Mueller KM, Stachon A, Nicolas V. Effectiveness of CT-guided percutaneous biopsies of the spine: an analysis of 202 examinations. Acad Radiol 2008;15(07):901–911
9 Wu EH, Chen YL, Wu YM, Huang YT, Wong HF, Ng SH. CT-guided core needle biopsy of deep suprahyoid head and neck lesions. Korean J Radiol 2013;14(02):299–306
10 Tam AL, Lim HJ, Wistuba II, et al. Image-guided biopsy in the era of personalized cancer care: proceedings from the society of interventional radiology research consensus panel. J Vasc Interv Radiol 2016;27(01):8–19
11 Lorentzen T, Nolsøe CP, Ewertsen C, et al; EFSUMB. EFSUMB Guidelines on Interventional Ultrasound (INVUS), part I–general aspects (long version). Ultraschall Med 2015;36(05):E1–E14
12 Sato S, Mishiro T, Miyake T, et al. Prophylactic administration of antibiotics unnecessary following ultrasound-guided biopsy and ablation therapy for liver tumors: open-labeled randomized prospective study. Hepatol Res 2009;39(01):40–46
13 Patel IJ, Rahim S, Davidson JC, et al. Society of Interventional Radiology Consensus Guidelines for the Periprocedural Management of Thrombotic and Bleeding Risk in Patients Undergoing Percutaneous Image-Guided Interventions-part II: recommendations: endorsed by the Canadian Association for Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe. J Vasc Interv Radiol 2019;30(08):1168–1184. e1. Doi: 10.1016/j.jvir.2019.04.017
14 Gupta S, Wallace MJ, Cardella JF, Kundu S, Miller DL, Rose SCSociety of Interventional Radiology Standards of Practice Committee. Quality improvement guidelines for percutaneous needle biopsy. J Vasc Interv Radiol 2010;21(07):969–975
15 Wu CC, Maher MM, Shepard JA. CT-guided percutaneous needle biopsy of the chest: preprocedural evaluation and technique. Am J Roentgenol 2011;196(05):W511-4
16 Tyng CJ, Bitencourt AG, Martins EB, Pinto PN, Chojniak R. Technical note: CT-guided paravertebral adrenal biopsy using hydrodissection–a safe and technically easy approach. Br J Radiol 2012; 85(1015):e339–e342
17 Grasso RF, Faiella E, Luppi G, et al. Percutaneous lung biopsy: comparison between an augmented reality CT navigation system and standard CT-guided technique. Int J CARS 2013;8(05): 837–848
18 Rosati A, Gueli Alletti S, Capozzi VA, et al. Role of ultrasound in the detection of recurrent ovarian cancer: a review of the literature. Gland Surg 2020;9(04):1092–1101
19 Sodickson A, Weiss M. Effects of patient size on radiation dose reduction and image quality in low-kVp CT pulmonary angiography performed with reduced IV contrast dose. Emerg Radiol 2012; 19(05):437–445
20 Du J, Huang Z, Luo Q, et al. Rapid diagnosis of pleural tuberculosis by Xpert MTB/RIF assay using pleural biopsy and pleural fluid specimens. J Res Med Sci 2015;20(01):26–31
21 Atwell TD, Smith RL, Hesley GK, et al. Incidence of bleeding after 15,181 percutaneous biopsies and the role of aspirin. Am J Roentgenol 2010;194(03):784–789
22 Loeb S, Vellekoop A, Ahmed HU, et al. Systematic review of complications of prostate biopsy. Eur Urol 2013;64(06): 876–892
23 Lang EK, Ghavami R, Schreiner VC, Archibald S, Ramirez J. Autologous blood clot seal to prevent pneumothorax at CT-guided lung biopsy. Radiology 2000;216(01):93–96
24 Burke DRSociety of Interventional Radiology Standards of Practice Committee. Quality improvement guidelines for percutaneous transhepatic cholangiography and biliary drainage. J Vasc Interv Radiol 2003;14:243–246
25 Adiga S, Athreya S. Safety, efficacy, and feasibility of an ultra-low dose radiation protocol for CT-guided percutaneous needle biopsy of pulmonary lesions: initial experience. Clin Radiol 2014;69 (07):709–714

Imaging Recommendations for Molecular Imaging

Sikandar Shaikh[1]

[1] Department of Radiodiagnosis, Shadan Institute of Medical Sciences, Hyderabad, Telangana, India

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Address for correspondence Sikandar Shaikh, DMRD, DNB, MNAMS, EDiR, FICR, Department of Radiodiagnosis, Shadan Institute of Medical Sciences, Hyderabad, Telangana 500072, India (e-mail: idrsikandar@gmail.com).

Abstract

In vivo molecular imaging is having a great potential that will have an impact on the medicine by detecting diseases in early stages like screening, identifying extent of disease, selecting disease- and patient-specific therapeutic treatment which will be the hallmark of the personalized medicine, for directed targeted therapy, and also for measuring molecular-specific effects of treatment. Currently, most commonly used molecular modalities are positron emission tomography- or single-photon emission computed tomography-based techniques.

Keywords

► molecular imaging

With the many ongoing preclinical research related to the novel molecular targets of different diseases which can be identified by using the more advanced and multifunctional contrast agents will be useful for the molecular targets that are developed along with new technologies and instrumentation for multimodality molecular imaging. Contrast-enhanced molecular ultrasound with molecularly-targeted contrast microbubbles is explored as a clinically translatable molecular imaging strategy for screening, diagnosing, and monitoring diseases at the molecular level. Optical imaging with fluorescent molecular probes and ultrasound imaging with molecularly-targeted microbubbles are attractive strategies since they provide real-time imaging, are relatively inexpensive, produce images with high spatial resolution, and do not involve exposure to ionizing similarly along the irradiation. Raman spectroscopy/microscopy has also emerged as the most potential molecular optical imaging strategy for ultrasensitive detection of multiple biomolecules/biochemicals in both in vivo and ex vivo versatility. Photoacoustic imaging is a hybrid of optical and ultrasound modalities involving optically excitable molecularly-targeted contrast agents and quantitative detection of resulting oscillatory contrast agent movement with ultrasound. Current preclinical findings and advances in instrumentation such as endoscopes and microcatheters suggest that these molecular imaging modalities have numerous clinical applications and will be translated into clinical use in the near future.

Molecular imaging is defined as the ability to visualize and quantitatively measure the function of biological and cellular processes in vivo.[1,2] As the anatomical imaging is well established imaging modality and plays a major role in medical imaging for the diagnosis, surgical guidance/follow-up, and monitoring response to the treatment, the field of molecular imaging is evolving and promises the significant improvement in the specificity, sensitivity, and quantitation not only for the screening and the early diagnosis, which is focused and having the personalized management and therapy, but also for the earlier treatment follow-up. The biggest advantage of in vivo molecular imaging is its ability to evaluate and characterize the pathologies of various diseases at the tissue level without any invasive techniques like biopsies or surgical procedures. This information will be able to help in the concept of the personalized treatment and planning. The one of the classical recent advances is the treatment of breast cancer by the combinations of various chemotherapeutic drugs that will be targeting the epidermal growth factor receptor types I and 2 (EGFR and HER2/neu), mammalian target of rapamycin, estrogen receptor, and/or histone deacetylase, and here the best strategy is dependent on the molecular profile of the tumor (e.g., HER2/neu-targeted therapy is only effective in HER2-positive breast cancers).[3] Thus, the in vivo molecular imaging is being used for the identification and quantification of the various molecular markers profile (e.g., EGFR, HER2) of the tumor. This is possible by noninvasive techniques where the need of the

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biopsy and time associated with pathological characterization are different. This concept of the personalized medicine will be used for the best care for patients having the advanced stage of the cancers and with poor prognosis. The risk of exposure to various side effects of therapy will be impacting the quality of the life.

The various preclinical applications in the advances in molecular imaging contrast agents will have the capability for the different multiplex nano- and/or microparticles with several entities: (1) Here, the use of the molecule for the different targeting to the specific tissues/the different disease marker like the binding ligands; (2) the different molecules will be used for the detection of the agent having the different imaging modalities; and, (3) the direct attachment of the various systems like the Doxel, is the liposome encapsulation of doxorubicin, which is the cytotoxic drug used for the inhibition of the DNA replication and for the targeted delivery of a therapeutic drug in the region of the interest. For example, Blanco et al[4] showed the direct attachment of the chemotherapy drug, Doxorubicin, to a superparamagnetic iron oxide nanoparticle, which is then encapsulated in liposomes coated with RGD peptides; and these particles have the property to attach to the tumor angiogenic vessels which have the high levels of $\alpha_V\beta_3$-integrins like the protein receptors that help in binding the different RGD peptides. These will be of help for the better localization of these magnetic particles by using magnetic resonance imaging (MRI).

In addition, the molecular imaging can measure the response to therapy more precisely and early. The tumor response to chemotherapy is being done by response evaluation criteria in solid tumors criteria, where the different anatomical imaging methods like computed tomography or MRI by using the tumor size, tumor volume in post-therapy settings, and time lapse after the management reflect the total tumor volumetric changes for the accurate reflection of therapeutic efficacy for various treatment options.[5] Thus, the molecular imaging can improve the therapeutic monitoring by direct effect of a drug at an earlier time point before the various morphological–anatomical changes that can become visible on imaging. The different modalities of the molecular imaging are having different protocols based on the systems, techniques, and the combined modalities.

Molecular Imaging has revolutionized the imaging concepts at the molecular level with better, faster, and more precise evaluation in the concept of the precision medicine.

Conflict of Interest
None declared.

References

1 Mankoff DA. A definition of molecular imaging. J Nucl Med 2007; 48(06):18N–21N [PubMed] [Google Scholar]
2 Peterson TE, Manning HC. Molecular imaging: 18F-FDG PET and a whole lot more. J Nucl Med Technol 2009;37(03):151–161 [PMC free article] [PubMed] [Google Scholar]
3 Wong ST. Emerging treatment combinations: integrating therapy into clinical practice. Am J Health Syst Pharm 2009;66(23, Suppl 6):S9–S14 [PubMe d] [Google Scholar]
4 Blanco E, Kessinger CW, Sumer BD, Gao J. Multifunctional micellar nanomedicine for cancer therapy. Exp Biol Med (Maywood) 2009; 234(02):123–131 [PMC free article] [PubMed] [Google Scholar]
5 Desar IM, van Herpen CM, van Laarhoven HW, Barentsz JO, Oyen WJ, van der Graaf WT. Beyond RECIST: molecular and functional imaging techniques for evaluation of response to targeted therapy. Cancer Treat Rev 2009;35(04):309–321 [PubMed] [Google Scholar]

Prognostic Significance of Various Clinicopathologic Parameters and BRAF V600E Mutation in Papillary Thyroid Microcarcinoma—An Observational Study

Sobiya Mahnaz Ayesha[1] Monalisa Hui[1] Shantveer G. Uppin[1] Megha Shantveer Uppin[1] Shubhranshu Jena[2] Rajsekhar Shanthappa Patil[2] Ranganath Ratnagiri[2] Tara Roshni Paul[1]

[1] Department of Pathology, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad, Telangana, India
[2] Department of Surgical Oncology, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad, Telangana, India

Address for correspondence Shantveer G Uppin, MD, Department of Pathology, 5th floor, Millennium Block, NIMS, Punjagutta, Hyderabad, Telangana, 500082, India (e-mail: drsguppin@yahoo.co.in).

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Abstract

Introduction A specific subset of papillary microcarcinoma of thyroid (PMC) can metastasize regionally and to distant organs, and thus, have a significant effect on the overall survival of the patient cohort.

Objectives We aim to analyze the prognostic significance of various clinicopathologic parameters including *BRAF*^{V600E} mutation by immunohistochemistry in PMC, in order to identify the subset of cases with aggressive behavior.

Materials and Methods Data regarding the PMC cases was retrieved retrospectively from medical records. The clinicopathologic factors like age, tumor size, focality, capsular invasion, histologic subtype, lymphovascular invasion, perithyroidal fat invasion (PTFI), lymph node (LN) metastasis, and distant metastasis were studied in depth. Tissue microarray was constructed to perform immunohistochemistry with CK19 and *BRAF*^{V600E}. Information regarding overall survival (OS) and development of metastasis, if any, was noted. Chi-squared test was performed to know the association between various factors. To determine odds ratio, logistic regression was done. Survival analysis was done using Kaplan–Meier and Cox-regression analysis.

Results PMC was diagnosed in 48 patients (M:F = 1:2.4), between 22 and 70 years of age (median = 46.5 years). Chi-squared test showed significant association of fibrosis with tumor size more than or equal to 0.5 cm, infiltrative borders, PTFI, and LN metastasis. Tumor size was also associated with infiltrative borders; and LN metastasis with PTFI. *BRAF*^{V600E} positivity showed significant association with histologic pattern, PTFI and distant metastasis. On logistic regression, tumor size showed significantly increased odds ratio with presence of fibrosis and infiltrative borders. Presence of fibrosis also showed significant association with infiltrative borders and LN metastasis. BRAF^{V600E} had significantly increased odds ratio with histologic pattern, both on univariate and multivariate logistic regression. Kaplan–Meier analysis revealed

Keywords
- thyroid
- papillary microcarcinoma
- prognosis
- BRAF^{V600E}
- lymph node metastasis

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significantly reduced OS with presence of LN metastases (p-value = 0.050, log-rank test). Cox-regression did not yield a significant hazard ratio for the various factors studied.

Conclusion This study shows association of LN metastasis with intratumoral fibrosis, PTFI and reduced OS. Intratumoral fibrosis was also associated with tumor size more than 5mm, infiltrative borders and PTFI. Increasing tumor size and infiltrative borders also showed an association. In addition, *BRAF*^{V600E} positivity was found to be associated with histologic pattern, PTFI and distant metastasis.

Introduction

Papillary microcarcinoma (PMC) is defined as papillary thyroid carcinoma (PTC) of size $\leq$1 cm.[1] Most of them are diagnosed incidentally in thyroidectomy or autopsy specimens. Advances in imaging modalities (including PET/CT, done both for screening purposes and for surveillance of other known malignancy) have led to increased early detection of small thyroid nodules.[2,3] Many of these either remain clinically silent for the entire lifetime or have excellent long-term outcome. However, a proportion of cases metastasize to cervical lymph nodes (LNs) and distant sites. Various factors like multifocality, tumor size more than 5mm, LN metastasis and extrathyroid extension (ETE) have been found to predict the risk of recurrence.[4–7] Identification of a subset of patients with aggressive behavior is important to stratify patients for implementation of radical therapeutic approach similar to classical PTC.

The frequency of *BRAF*^{V600E} mutation in PTC ranges from 60 to 80% and is associated with high risk clinicopathological features. Similar incidences have also been noted in PMC accounting for 37.5% to 74% of cases and are associated with aggressive features despite their small size.[8–10]

There are not many studies on PMC in Indian literature till date.[11–15] In this article, we have analyzed the prognostic significance of various clinicopathologic parameters including *BRAF*^{V600E} mutation by immunohistochemistry (IHC) in PMC.

Materials and Methods

This is a retrospective study of cases diagnosed as PMC in our institute, from January 2014 to May 2020 (n = 48). The demographic and clinical data were retrieved form histopathology requisition forms and medical records. The inclusion criterion was thyroidectomy specimens diagnosed as PMC on routine histopathology. And exclusion criteria were tumor size exceeding 1 cm and concurrent presence of other malignancy (e.g., follicular/oncocytic carcinoma).

The hematoxylin and eosin (H&E)-stained histopathology sections of these cases were reviewed by three pathologists to confirm the original diagnosis and to also document various histopathological parameters like tumor size, focality, capsular invasion, histologic subtype, lymphovascular invasion, perithyroidal fat invasion (PTFI), and stage of the tumor. The pathological changes in the adjacent thyroid (including both neoplastic and non-neoplastic entities) were also analyzed.

Immunohistochemistry

For performing IHC, a tissue array block was constructed by extracting tumor tissue from formalin fixed paraffin embedded blocks of the cases using manual Quick-Ray needle. Of the total 48 cases, paraffin blocks of only 37 patients were available for constructing the tissue microarray and performing subsequent IHC. After initial review of H&E-stained slides, the tumor areas were marked and tissues were extracted from corresponding area on the paraffin block using 5mm tip of Quick Ray needle. The extracted tissues were then transferred to a recipient block. One or two cores were extracted per case depending on the availability of tumor tissue and each array block held 14 tumor tissue cores. Four micron sections were cut from these tissue array blocks and IHC with CK19 (Clone EP72, Pleasanton, California, USA) and *BRAF*^{V600E} (Clone VE1, Ventana Hoffmann La -Roche Ltd., Switzerland) antibodies was performed on fully automated immunostainer ('Ventana GX' with 'Ventana Benchmark GX, Hoffmann La - Roche Ltd, Switzerland'). The IHC results for these two antibodies performed on tissue microarray slides were analyzed. In addition, results of CK19 IHC wherever performed at time of initial diagnosis were also reviewed.

Follow-up details were noted where ever available. Information regarding overall survival, persistence of disease, and development of recurrence/metastasis if any was also noted.

Statistical Analysis

The nominal data was compared using ratios. Continuous numerical data was studied using median. Percentages were used for both nominal and ordinal data. Chi-squared test was performed to find out the association between factors like tumor size, focality, histopathological variant, infiltrative margins, fibrosis, PTFI, LN metastasis, distant metastasis, and *BRAF*^{V600E} positivity. To determine odds ratio, univariate and multivariate logistic regression was done. Kaplan–Meier survival analysis was done to compare time to death between various prognostically significant groups. Cox-regression analysis (univariate and multivariate) was done to know the association of survival time with covariates and to calculate the hazard ratios for each variable. These were done using Statistical Package for the Social Sciences (SPSS) software version 29.

Ethics

Ethics approval was obtained from the NIMS institutional ethics committee (approval letter no.EC/NIMS/2809/2021, dated 28.08.2021). Waiver of informed consent was obtained due to the retrospective nature of the study. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional) and with the Helsinki declaration of 1964, as reviewed in 2013.

Results

Of the total 1,088 thyroidectomy specimens received during study period, 32.4% (353) had malignant tumors. Of these, 58.6% (207) were PTCs and 14.4% (51) PMCs. Among the PMC cases, three cases were excluded as they had a history of concurrent malignancy like follicular carcinoma, oncocytic (Hurthle cell) carcinoma and mucoepidermoid carcinoma.

Demographic and Clinical Findings

The remaining 48 patients diagnosed with PMC included 29.2% (14) men and 70.8% (34) women (M:F = 1:2.4) aged between 22 and 70 years (median, 46.5 years). Of these, only 22.9% (11) presented with palpable solitary nodule in thyroid. In 43.7% (21) patients, tumors were incidentally detected either at ultrasonography of neck (14.6%,7 cases) or thyroidectomies for other causes (multinodular goiter—27%, 13 cases; Grave's with compressive symptoms—2%, 1 case). The remaining 33.3% (16) patients presented with metastasis in cervical LN (20.8%,10 cases) and distant sites (12.5%,6 cases). In the later cases, PMCs were detected in subsequent thyroidectomies.

Surgical Management

The surgical management in these patients included hemithyroidectomy in 29.2% (14), subtotal thyroidectomy in 20.8% (10), near total thyroidectomy in 6.25% (3), and total thyroidectomy in 43.75% (21). Concurrent neck LN dissection was done in 39.6% (19) of these patients. Three patients who had initial hemithyroidectomy subsequently underwent completion thyroidectomy.

Pathological Findings (►Fig. 1, ►Table 1)

Though majority were unifocal/solitary tumors, a significant number were multifocal tumors (2–6 in number). Hence, a total of 81 tumor foci were detected in 48 patients. The size of the tumors ranged from less than 1 mm to 10 mm with median size of 5mm. Most of the tumors were right sided, unencapsulated with near equal distribution of tumors having circumscribed and infiltrative borders. On histology, follicular variant was the most common type followed by classical variant. Variation in architectural pattern between different foci of multicentric tumors was noted in some cases. Though none of our cases showed any evidence of either lymphovascular invasion or ETE, PTFI by the tumor was noted in 8.3% (4) cases.

LN metastases were detected in 62.5% (15/24) patients with LN dissection. In 26% (4/15) of these patients, there was discordance between architectural pattern of tumor in thyroid and LN metastases. In these four cases, the tumor showed follicular pattern in the thyroid, whereas the LN metastases showed classic papillary pattern. There was another case where the primary tumor in thyroid showed predominant classic pattern with about 30% tall cell area, whereas the LN metastasis had completely tall cell pattern.

The common findings in adjacent thyroid included lymphocytic thyroiditis, Hashimoto's thyroiditis, and adenomatous goiter. Concurrent oncocytic (Hurthle cell) adenoma was detected in 4.2% (2) cases. Details of selected gross and microscopic findings of the cases are provided in ►**Table 1**.

Normal parathyroid glands were found in thyroidectomy specimen in 20.8% (10) cases (14.6%, [7] cases showed one and 6.25%, [3] cases showed two glands) and ectopic thymic tissue in neck node dissection of 2% (1) cases.

The distant metastases noted in 12.5% (6) patients affected scalp, gluteal region, mandible, sternum, sacroiliac bone, and mediastinum.

IHC Findings (►Fig. 2)

Of the 77% (37) cases included in tissue array block, IHC findings of only 73% (35) cases could be evaluated due to tissue loss in two cases. In addition, there were four cases in which IHC results of CK19 performed at the time of original diagnosis were available for review. Thus, final results of IHC analysis are derived from 81.25% (39) cases for CK19 and 73% (35) cases for $BRAF^{V600E}$. CK 19 was positive in all (100%, 39/39) and $BRAF^{V600E}$ in 54.3% (19/35) cases tested.

Follow-Up

Follow-up details were available in 68.75% (33) cases and the follow-up period ranged from 2 to 54 months (mean, 23.3 months). Five (10.4%) patients received radioactive iodine therapy following surgery. During follow-up, 9% (3/33) patients developed metastases to brain (3%, 1), lung (3%, 1), and LN (3%, 1) at 5 months, 6 months, and 39 months after initial surgery, respectively. During the follow-up period, 9% (3/33) patients died at 2, 18, and 54 months after initial surgery. One of the deceased was a patient who had brain metastasis at follow-up and died at 18 months after initial surgery.

Statistical Analysis

The chi-squared test showed significant association between presence of fibrosis and tumor size more than or equal to 0.5 cm, infiltrative borders, PTFI and LN metastasis. Apart from presence of fibrosis, tumor size more than or equal to 0.5 cm was found to be associated with infiltrative borders. LN metastasis also showed association with PTFI. $BRAF^{V600E}$ positivity showed significant association with histologic pattern, PTFI and distant metastasis. (►**Table 2**)

The logistic regression analysis was done with those clinicopathological parameters that were found to have significant association on chi-squared test (shown in ►**Supplementary Table S1**). The odds ratio for tumor size more than or equal to 0.5 cm was significantly increased with

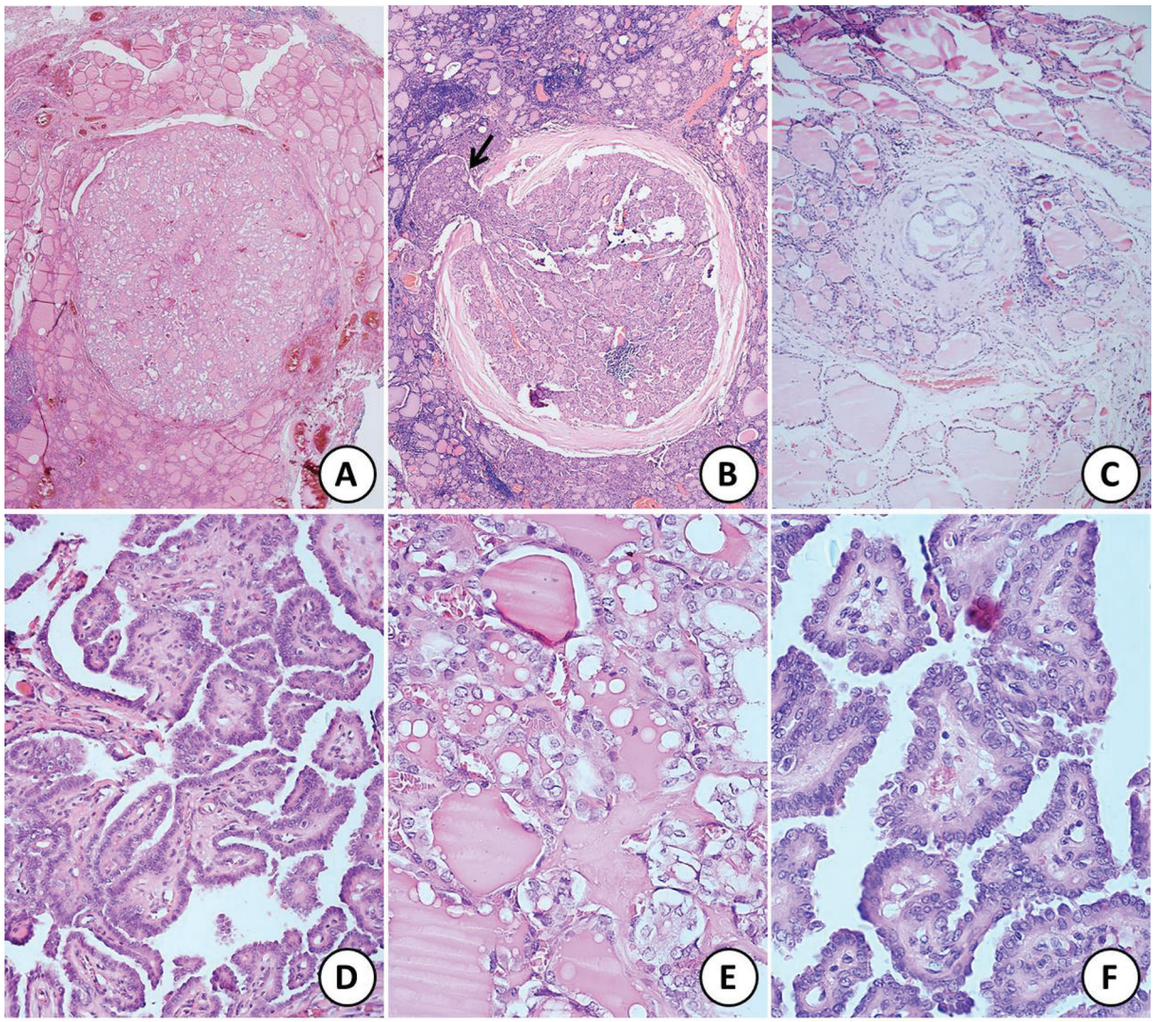

Fig. 1 Sections of papillary microcarcinoma of thyroid showing **(A)** unencapsulated tumor, **(B)** encapsulated tumor with focal capsular breach and extracapsular extension (black arrow), and **(C)** very tiny focus of tumor comprising only a few follicles. All the three above tumors show follicular pattern of growth (hematoxylin and eosin [H&E]; Ax20, Bx40, Cx100). **(D)** Papillary microcarcinoma with classical papillary pattern of growth (H&E; x200). **(E) and (F)** Higher magnification to highlight the nuclear features of clearing, grooves, intranuclear inclusions, and overlapping (H&E; Dx400, Ex400).

presence of fibrosis and infiltrative borders (odds ratio = 4.333 and 5.320; *p*-value= 0.045 and 0.010, respectively). However, multivariate regression did not show statistically significant association between these factors.

Presence of fibrosis had significantly increased odds ratio (positive association) with infiltrative borders, presence of LN metastasis and tumor size more than or equal to 0.5 cm on univariate logistic regression. However, on multivariate analysis only infiltrative borders showed significant association with presence of fibrosis. PTFI did not show any significant association on logistic regression.

Logistic regression of $BRAF^{V600E}$ versus other factors was also not statistically significant, except with histological patterns. The classic variant showed significant positive association with BRAF positivity, as compared to the follicular variant, on both univariate and multivariate regression (odds ratio= 5.042 and 5.405, *p*-value= 0.037 and 0.050, respectively). In addition, on multinomial logistic regression the follicular and classic variants showed significantly increased odds ratio with BRAF positivity, as compared to the diffuse sclerosing variant (as depicted in ►**Supplementary Table S1**).

Kaplan–Meier survival analysis revealed significantly reduced overall survival (OS) with the presence of LN metastases with a *p*-value of 0.050 (log-rank test) (►**Supplementary Fig. S1**). However, the comparison between the other parameters was not statistically significant. The 5-year follow-up period was not reached for LN metastasis; hence an estimate of survival at 5-years is not possible. One-year and two-year survival rates were 100 and 50% for cases with presence of LN metastasis.

The univariate and multivariate Cox-regression analysis did not yield a significant hazard ratio for the various factors studied.

Discussion

PTC accounts for 70 to 90% of well-differentiated thyroid malignancies and PMC comprises nearly 30% of all diagnosed

Table 1 Gross and microscopic features of PMC cases

Feature		No of cases
Focality	Unifocal (1) Multifocal (2–6)	30 18
Location	Right lobe Left lobe Isthmus Bilateral lobes Isthmus+ right lobe	23 14 5 5 1
Capsule (no. of foci = 81)	Encapsulated: With capsular invasion Without capsular invasion Unencapsulated: Circumscribed Infiltrative	12 3/12 9/12 69 36/69 33/69
Histologic variant (no. of foci = 81)	Follicular variant Classic variant Tall cell variant Diffuse sclerosing variant	50 28 2 1
Adjacent thyroid	Calcification Psammoma bodies Fibrosis/ sclerosis Stromal hyaline Lymphocytic thyroiditis Hashimoto thyroiditis Adenomatous goiter Oncocytic (Hurthle cell) adenoma	7 1 6/10 1 12 10 9 2
Lymph node dissection (*n* = 24)	Involved Size of largest metastatic deposit Extranodal extension	15/24 15–60 mm 3/24
TNM stage	T1a N1a N1b M1	48 1 14 6

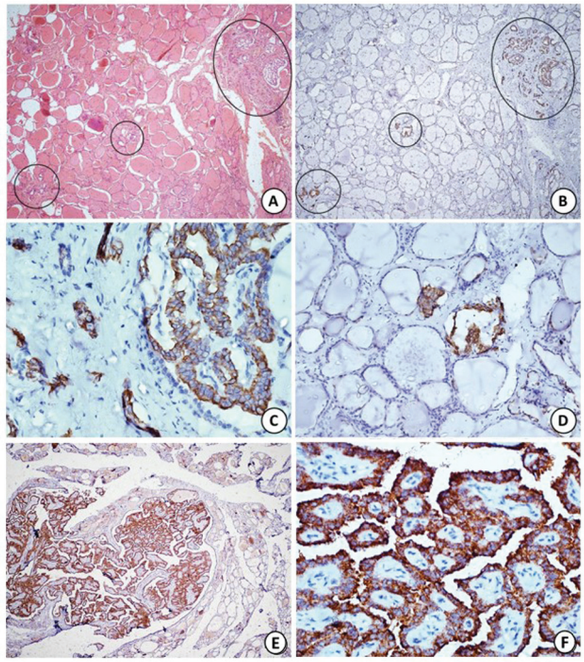

Fig. 2 (A) Section shows multicentric papillary microcarcinoma involving three distinct foci (black circles), two of which are very tiny comprising of only few follicles (hematoxylin and eosin [H&E]; x40). **(B)** Immunohistochemistry (IHC) with CK19 highlights all the foci of papillary microcarcinoma (black circles) including the tiny ones. **(C, D)** Higher magnification shows strong cytoplasmic staining in tumor cells with CK19 (HRP-Polymer; Bx40, Cx400, Dx200). **(E, F)** Diffuse strong cytoplasmic staining with $BRAF^{V600E}$ on IHC (Ex40; FX400).

PTC.[16] In the present study, majority of the thyroid malignancies were PTC of which 19.76% were categorized as PMC. The clinical significance of PMC is not clear. Though majority of PMCs have an indolent course and excellent prognosis, some are associated with recurrence and distant metastasis with fatal outcome.[9,17,18] This study was done with the goal of identifying association of various clinicopathologic factors including the $BRAF^{V600E}$ IHC with the risk of aggressive disease in PMC. The various clinicopathological factors including the rate of recurrence are comparable to other studies as shown in ►**Table 3**.

Though the median age and gender distribution of the cases in the present study were similar to other studies, the median diameter of the tumor varied considerably.[4,11,19] Multifocality was seen in 37.5% cases similar to Park et al and John et al.[11,19] Various studies have reported the incidence of ETE ranging from 3.9 to 52.2%.[4,11,19] The American Joint Committee on Cancer (AJCC) 8th edition does not consider microscopic ETE that is not grossly evident.[20] PTFI is no longer considered as ETE. As the definition of ETE has changed recently, only 8.3% cases showed minimal ETE/PTFI that cannot be classified as T3b tumors. Similar to other studies LN metastasis was noted in one-third of the cases.[4,19] The rate of recurrence occurring in tumor bed, cervical LNs, or at distant sites in the present study was slightly higher than other studies (9 vs. 2.4-6%).[4,11,19] However the reported range of recurrence rate in PMC is lower compared to conventional PTC.[1]

The present study revealed association of LN metastasis with fibrosis and PTFI similar to Neimeier et al.[21] Unlike the latter, there was no significant association of $BRAF^{V600E}$ mutation with LN metastasis in this study. Similar observations were noted in few other studies as well.[22,23] Studies have shown contradictory results regarding the association of LN metastasis with tumor size more than 5mm.[16,24,25] The present study did not show any correlation. We also found presence of LN metastasis to be associated with significantly reduced OS on Kaplan–Meier analysis (►**Supplementary Fig. S1**). The minimal ETE/PTFI was found to be associated with presence of fibrosis, LN metastasis and $BRAF^{V600E}$ positivity on chi-squared analysis. However, the odds ratio was not statistically significant with any of the clinicopathologic parameter. This highlights the importance of the change made in AJCC 8th edition, wherein PTFI is no longer considered a criterion in T staging.

A meta-analysis has shown association of $BRAF^{V600E}$ mutation with the histological subtype, ETE, and advanced

Table 2 Association of clinicopathological factors with size, presence of fibrosis, LN metastasis, and BRAFV600E IHC status

Characteristic	Size (cm)			Fibrosis			LN metastasis			BRAF		
	<0.5	≥0.5	*p*-Value	Pre	abs	*p*-Value	pre	abs	*p*-Value	pos	neg	*p*-Value
n	19	29		16	32		15	33		19	16	
Age≥ 45 y	9	20	0.135	11	18	0.404	10	19	0.551	12	10	0.968
Size ≥ 0.5 cm	–	–	–	13	16	0.037	11	18	0.217	12	12	0.452
Multifocality	7	11	0.939	5	13	0.527	8	10	0.127	8	6	0.782
Infilt borders	5	19	0.007	14	10	<0.001	9	15	0.350	11	7	0.404
Fibrosis	3	13	0.037	–	–	–	9	7	0.009	8	6	0.782
PTFI	1	3	0.533	4	0	0.002	4	0	0.001	4	0	0.021
LN mets	4	11	0.217	9	6	0.009	–	–	–	8	4	0.288
Distant mets	2	4	0.738	1	5	0.355	2	4	0.907	1	5	0.037
Death	1	2	0.822	1	2	0.909	2	1	0.133	1	1	0.900
BRAF positive	7	12	0.452	8	11	0.782	8	11	0.288	–	–	–
Pattern: Follicular Classic Tall cell Diff scl	 12 7 0 0	 13 13 2 1	0.269	 8 6 1 1	 17 14 1 0	0.465	 10 4 1 0	 15 16 1 1	0.364	 6 11 2 0	 11 4 0 1	0.032

Abbreviations: pos, positive; neg, negative; pre, present; abs, absent; IHC, immunohistochemistry; LN, lymph node; mets, metastasis; Infilt, infiltrative; PTFI, perithyroidal fat invasion; scl, sclerosing.

clinical stage suggesting a poor outcome in PMC similar to PTC.[26] The present study showed association of *BRAF*^{V600E} with histologic pattern, PTFI and distant metastasis (as shown in ►**Table 2** and ►**Supplementary Table S1**). Choi et al and Fakhruddin et al did not find any statistically significant association between *BRAF*^{V600E} mutation and other clinicopathologic factors.[22,23] On the contrary, Virk et al found *BRAF*^{V600E} mutation associated with LN metastasis, infiltrative borders, fibrosis, ETE, and classic nuclear features of papillary carcinoma.[27] Another study suggested that tumors greater than 5mm and a subset of patients with *BRAF*^{V600E} mutation may develop highly aggressive PMCs. The authors also noted increased frequency of recurrence with ETE, LN metastases, and type of surgical procedure. There was neither any association with *BRAF*^{V600E} mutation on multivariate analysis nor any change in outcome of *BRAF*^{V600E} mutated patients on aggressive treatment.[28] Mercante et al found aggressive tumor behavior in cases showing capsular invasion without ETE and advised radical treatment in them.[29]

There was an association of increasing size with presence of fibrosis and infiltrative borders in our study. A similar observation was made by Miccoli et al.[25] Presence of fibrosis also showed significantly increased odd's ratio with infiltrative borders on univariate and multivariate logistic regression. Tumor-associated stromal reaction, like desmoplasia, fibrosis, or sclerosis were more frequent in *BRAF*^{V600E} -mutated tumors, but stromal calcification and psammoma bodies were not, according to Virk et al.[27] Karkuzhali et al

Table 3 Comparison of the various clinicopathological parameters with other studies

	Current study	Park et al[19]	Shi et al[4]	John et al[11]
Male: Female	14:34 (1:2.4)	42: 237 (1:5.6)	21:230 (1:10.9)	18:59 (1:3)
Median age, years	46.5 ± 15	46.5 ± 11.6	42.9 ± 10.1[b]	44.54 ± 10.5[b]
Median diameter, cm	0.5 ± 0.6	0.81 ± 0.67	0.11 ± 0.07[b]	0.41[b]
Multifocality (%)	18/48 (37.5)	50/122 (41.0)	12/251 (4.8)	34/77 (43.4)
Extrathyroidal invasion (%)	4/48(8.3)[a]	145/278 (52.2)	25/251 (10)	3/77 (3.9)
LN metastasis (%)	15/48 (31.3)	97/278 (34.9)	84/251 (33.5)	11/77 (14.2)
Thyroiditis (%)	22/48 (45.8)	10/87 (11.5)	40/251 (15.9)[c]	8/77 (10.4)
Recurrent or persistent (%)	3/33 (9)[d]	6/98 (6.1)	6/251 (2.4)	2/77 (2.6)
Mean follow-up duration, months	23.3 ± 17.85	53.4	45.4 ± 3.5	20

Abbreviations: IQR, interquartile range; LN, lymph node; SD, standard deviation.
Median values are accompanied by the IQR and means by the SD.
[a], Perithyroidal fat invasion; [b]these are mean values; [c], includes only Hashimoto's thyroiditis; [d] follow-up details were available in 33 cases only.

also found increased stromal changes like calcification with increasing tumor size.[15]

Certain histomorphologic patterns like tall cell variant of PMC have been found to be associated with poor prognosis.[8] However, none showed statistically significant outcome on survival analysis in this study.

We found that CK19 is a highly sensitive marker for PTC including PMC and can help detect even minute tumor foci that can be easily overlooked on routine H&E sections.

The limitations of current study include relatively small number of cases studied, lack of molecular analysis for $BRAF^{V600E}$ mutation, and short follow-up time. Larger studies with longer follow-up period and adjunct molecular testing would be helpful.

Conclusion

Despite these limitations, significant conclusions that can be drawn from present study are association of LN metastasis with intratumoral fibrosis, PTFI and reduced OS. Intratumoral fibrosis was also associated with tumor size more than 5mm, infiltrative borders, and PTFI. Increasing tumor size and infiltrative borders also showed an association. In addition, $BRAF^{V600E}$ positivity was found to be associated with histologic pattern, PTFI and distant metastasis.

Authors' Contributions

Sobiya Mahnaz Ayesha contributed to designing, definition of intellectual content; literature search, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, editing and review; Monalisa Hui helped in designing, definition of intellectual content; literature search, experimental studies, data analysis, statistical analysis, manuscript preparation, editing and review; Shantveer G Uppin helped in conceptualization, designing, definition of intellectual content, literature search, experimental studies, data analysis, statistical analysis, manuscript preparation, editing and review; Megha Shantveer Uppin and Tara Roshni Paul helped in definition of intellectual content, manuscript preparation, editing, and review; Shubhranshu Jena, Rajsekhar Shanthappa Patil, and Ranganath Ratnagiri contributed to definition of intellectual content, clinical studies, manuscript preparation, editing, and review. Shantveer G Uppin has provided guarantee.

Conflict of Interest

None declared.

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None.

References

1 Rosai J, Albores Saavedra J, Asioli S, et al. Papillary thyroid carcinoma. In: Lloyd RV, Osamura RY, Kloppel G, Rosai J, eds. WHO Classification of Tumors of Endocrine Organs. 4th edition. Lyon: IARC; 2017:81–91
2 Corn S, Mitmaker E, Tabah R, Ciarallo A, How J. Incidental thyroid uptake on PET scanning: epidemiology, clinical significance, and management challenge. J Cancer Metastasis Treat 2021;7:41
3 Nishimori H, Tabah R, Hickeson M, How J. Incidental thyroid "PETomas": clinical significance and novel description of the self-resolving variant of focal FDG-PET thyroid uptake. Can J Surg 2011;54(02):83–88
4 Shi C, Guo Y, Lv Y, et al. Clinicopathological features and prognosis of papillary thyroid microcarcinoma for surgery and relationships with the BRAFV600E mutational status and expression of angiogenic factors. PLoS One 2016;11(12):e0167414
5 Cooper DS, Doherty GM, Haugen BR, et al; American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19(11):1167–1214 [published correction appears in Thyroid. 2010 Jun;20 (6):674–5]
6 Leboulleux S, Tuttle RM, Pacini F, Schlumberger M. Papillary thyroid microcarcinoma: time to shift from surgery to active surveillance? Lancet Diabetes Endocrinol 2016;4(11):933–942
7 Kluijfhout WP, Pasternak JD, Kwon JS, et al. Microscopic positive tumor margin does not increase the risk of recurrence in patients with T1-T2 well-differentiated thyroid cancer. Ann Surg Oncol 2016;23(05):1446–1451
8 Bernstein J, Virk RK, Hui P, et al. Tall cell variant of papillary thyroid microcarcinoma: clinicopathologic features with BRAF (V600E) mutational analysis. Thyroid 2013;23(12):1525–1531
9 Lee X, Gao M, Ji Y, et al. Analysis of differential BRAF(V600E) mutational status in high aggressive papillary thyroid microcarcinoma. Ann Surg Oncol 2009;16(02):240–245
10 Marchetti I, Iervasi G, Mazzanti CM, et al. Detection of the BRAF (V600E) mutation in fine needle aspiration cytology of thyroid papillary microcarcinoma cells selected by manual macrodissection: an easy tool to improve the preoperative diagnosis. Thyroid 2012;22(03):292–298
11 John AM, Jacob PM, Oommen R, Nair S, Nair A, Rajaratnam S. Our experience with papillary thyroid microcancer. Indian J Endocrinol Metab 2014;18(03):410–413
12 Fonseca D, Murthy SS, Tagore R, et al. BRAF status in the variants of papillary thyroid carcinoma. Int J Head Neck Pathol. 2018; 1:41–47
13 Tagore KR, Ramineni Asok Kumar S. Unusual presentation of papillary microcarcinoma of thyroid as thigh mass. Case Rep Pathol 2011;2011:651701
14 Nimmagadda A, Krishna Mohan VS, Manthri R, Kalawat TC. Unusual metastases in papillary microcarcinoma of thyroid. Indian J Nucl Med 2019;34(01):32–34
15 Karkuzhali P, Yogambal M, Kumar M. An Indian tertiary care hospital scenario of papillary carcinoma of thyroid. J Clin Diagn Res 2017;11(06):EC26–EC29
16 Chow SM, Law SC, Chan JK, Au SK, Yau S, Lau WH. Papillary microcarcinoma of the thyroid-prognostic significance of lymph node metastasis and multifocality. Cancer 2003;98(01):31–40
17 Lin KD, Lin JD, Huang HS, Jeng LB, Ho YS. Skull metastasis with brain invasion from thyroid papillary microcarcinoma. J Formos Med Assoc 1997;96(04):280–282
18 Liou MJ, Lin JD, Chung MH, Liau CT, Hsueh C. Renal metastasis from papillary thyroid microcarcinoma. Acta Otolaryngol 2005; 125(04):438–442
19 Park YJ, Kim YA, Lee YJ, et al. Papillary microcarcinoma in comparison with larger papillary thyroid carcinoma in BRAF (V600E) mutation, clinicopathological features, and immunohistochemical findings. Head Neck 2010;32(01):38–45
20 Tran B, Roshan D, Abraham E, et al. An analysis of the American Joint Committee on Cancer 8th Edition T Staging System for Papillary Thyroid Carcinoma. J Clin Endocrinol Metab 2018;103 (06):2199–2206

21 Niemeier LA, Kuffner Akatsu H, Song C, et al. A combined molecular-pathologic score improves risk stratification of thyroid papillary microcarcinoma. Cancer 2012;118(08): 2069–2077
22 Choi SY, Park H, Kang MK, et al. The relationship between the BRAF(V600E) mutation in papillary thyroid microcarcinoma and clinicopathologic factors. World J Surg Oncol 2013; 11:291
23 Fakhruddin N, Jabbour M, Novy M, et al. BRAF and NRAS mutations in papillary thyroid carcinoma and concordance in BRAF mutations between primary and corresponding lymph node metastases. Sci Rep 2017;7(01):4666
24 Friguglietti CU, Dutenhefner SE, Brandão LG, Kulcsar MA. Classification of papillary thyroid microcarcinoma according to size and fine-needle aspiration cytology: behavior and therapeutic implications. Head Neck 2011;33(05):696–701
25 Miccoli P, Minuto MN, Ugolini C, et al. Intrathyroidal differentiated thyroid carcinoma: tumor size-based surgical concepts. World J Surg 2007;31(05):888–894
26 Lee JH, Lee ES, Kim YS. Clinicopathologic significance of BRAF V600E mutation in papillary carcinomas of the thyroid: a meta-analysis. Cancer 2007;110(01):38–46
27 Virk RK, Van Dyke AL, Finkelstein A, et al. BRAFV600E mutation in papillary thyroid microcarcinoma: a genotype-phenotype correlation. Mod Pathol 2013;26(01):62–70
28 Zheng X, Wei S, Han Y, et al. Papillary microcarcinoma of the thyroid: clinical characteristics and BRAF(V600E) mutational status of 977 cases. Ann Surg Oncol 2013;20(07):2266–2273
29 Mercante G, Frasoldati A, Pedroni C, et al. Prognostic factors affecting neck lymph node recurrence and distant metastasis in papillary microcarcinoma of the thyroid: results of a study in 445 patients. Thyroid 2009;19(07):707–716

The "Blast" Behind Jerky Eyes

Jasmine Singh[1] Shivani Randev[1] Chandrika Azad[1] Harkirat Kaur[2] Vishal Guglani[1]

[1] Department of Pediatrics, Government Medical College and Hospital, Sector 32, Chandigarh, India
[2] Department of Radiodiagnosis, Government Medical College and Hospital, Sector 32, Chandigarh, India

Address for correspondence Chandrika Azad, MD, Department of Pediatrics, Government Medical College and Hospital, Sector 32, Chandigarh, 160036, India (e-mail: chandrika_azad@yahoo.co.in).

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Abstract

Opsoclonus is defined as hyperkinetic, omnidirectional, spontaneous, and involuntary chaotic eye movements. Opsoclonus-myoclonus-ataxia syndrome is addressed by many names including "dancing eyes-dancing feet syndrome," "Kinsbourne syndrome," and "infantile polymyoclonia." The early accounts of the clinical syndrome date back to 1962 when Marcel Kinsbourne described six cases of this phenotype. However, it was not until 1968 the association with occult neuroblastoma was first reported. We report the video of a 1-year-old boy who presented with this syndrome for a duration of 3 months. He was diagnosed to have an abdominal neuroblastoma and was treated with resection of the tumor and administration of intramuscular adrenocorticotropic hormone. He showed complete resolution of symptoms. The syndrome is difficult to recognize and might be confused with seizures, tremors, or chorea; hence, it is important that residents learnt to recognize this syndrome and look for an underlying tumor actively.

Keywords
- neuroblastoma
- paraneoplastic syndrome
- opsoclonus-myoclonus-ataxia syndrome

Case Description

A 1-year-old boy presented with complaints of regression of milestones and tremulousness of neck for a duration of 3 months. He was born out of nonconsanguineous marriage at term with an uneventful perinatal period. The neurodevelopment was normal (sitting without support, speaking bisyllables and having stranger anxiety) till 8 months of age. After this age, he gradually lost milestones and now he was unable to speak any words or sit even with support. As per parents, the child was excessively irritable and slept for very short durations. On examination, vitals were stable, no significant pallor, icterus, neurocutaneous markers, apparent congenital malformation, abnormal odor, or organomegaly were noted. There were opsoclonus movements of eyes in all directions of gaze; these movements also persisted during sleep. The truncal instability was there along with intermittent jerky movements of neck and limbs. No cranial nerve palsy, tone abnormality or focal neurological deficit was noted (►**Video 1**). Rest of the systemic examination was normal.

Video 1

Video of the child showing opsoclonus movement of eyes in all direction with tremulousness of head. Online content including video sequences viewable at: https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0043-1761264.

In view of the clinical picture, the possibility of opsoclonus-myoclonus-ataxia syndrome (OMAS) was considered. The electroencephalography revealed no evidence of seizure activity. Magnetic resonance imaging of brain was grossly normal. Chest X-ray and ultrasound abdomen showed no mass. Cerebrospinal fluid analysis revealed acellular fluid

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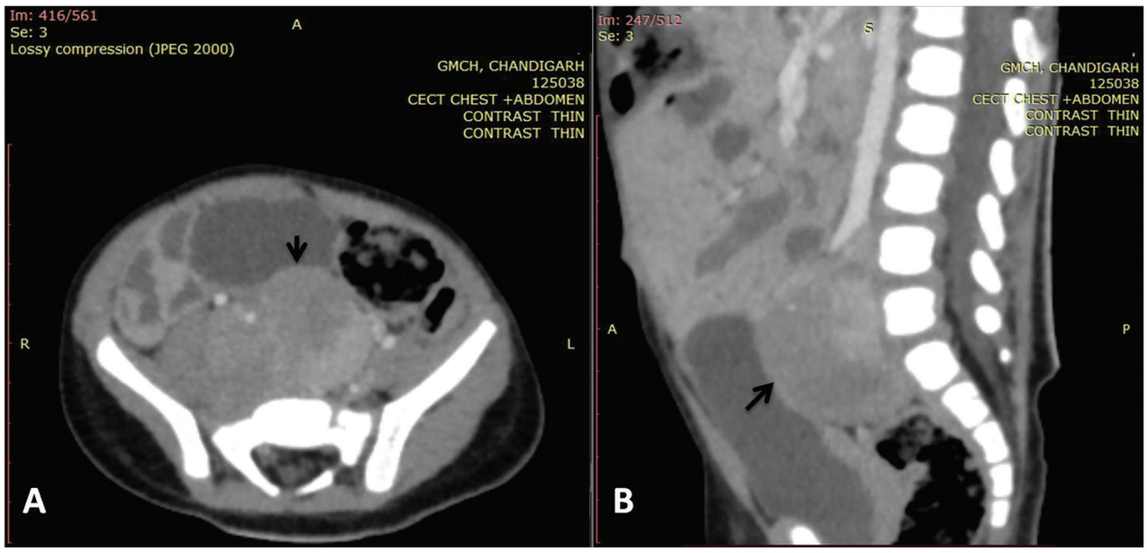

Fig. 1 (A) Axial and (B) sagittal image of contrast-enhanced computed tomogram of abdomen showing well-defined heterogeneously enhancing mass lesion (black arrows) in the retroperitoneum, in the midline and on the right side, extending cranially from the level of aortic bifurcation and caudally into the rectovesical pouch in the pelvis till S2-S3 vertebral level displacing the right iliac vessels anterolaterally.

with sugar and protein of 70 and 20 mg/dL, respectively. Contrast-enhanced computed tomography (CECT) of abdomen revealed a large heterogeneously enhancing lesion measuring $2.5 \times 3.1 \times 4.5$ cm in the retroperitoneum involving organ of Zuckerkandl (►**Fig. 1A** and **B**). This was followed by a fluorine 18 fluorodeoxyglucose single-photon emission computerized tomography that showed increased tracer uptake (maximum standardized uptake value: 6.9, $4.6 \times 2.6 \times 4.8$ cm) in the retroperitoneal soft tissue mass implicating somatostatin receptor expressing retroperitoneal soft tissue mass. Due to financial constraints, urine catecholamine metabolites were not assessed.

The patient was referred to higher center for further management. The mass was surgically excised. The histopathology of excised mass was suggestive of ganglioneuroblastoma, intermixed subtype. Child was started on pulsed dexamethasone (20 mg/m^2/day in two divided doses for 3 consecutive days every month), intramuscular adrenocorticotropic hormone (ACTH), and monthly intravenous immunoglobulin (IVIG) (1–2 g/kg every 4 weeks for 12 months). IV cyclophosphamide (25 mg/kg) was given at 4 weekly intervals for three doses. In view of partial response at 3 months, therapy was escalated to rituximab (375 mg/m^2/dose once a week for 4 doses). Child is currently asymptomatic and has regained regressed milestones. At 18 months follow-up, child has neither experienced recurrence of symptoms nor shown any evidence of tumor on repeat imaging.

Discussion

The early accounts of clinical syndrome of OMAS date back to 1962 when Marcel Kinsbourne described six cases of this phenotype. However, it was not until 1968 the association with occult neuroblastoma was first reported. Studies in India have demonstrated that this entity contributes to 7% children presenting with movement disorders.[1,2] The syndrome might be confused with seizures, tremors, or chorea. In most of the cases, the etiology is paraneoplastic. However, parainfectious etiology has also been seen. Around 50% of pediatric cases of OMAS are accounted for by an underlying neuroblastoma, whereas only 2 to 3% of neuroblastomas present with this paraneoplastic syndrome.[3,4] The pathophysiology of this disorder remains an enigma. There have been speculations about damage to omnipause cells in the nucleus raphe interpositus of pons and disinhibition of fastigial nucleus in cerebellum.[5] The diagnosis is primarily clinical, but the search for the underlying cause needs to be extensive and thorough with CECT chest, abdomen, and pelvis actively looking for a tumor. Neuroblastoma is the most common underlying tumor (73%) that is followed by ganglioneuroblastoma (22%) and ganglioneuroma (4%) in that order.[6] The management strategy is two pronged: management of underlying tumor and immunotherapy for OMAS. The tumor is treated with resection and/or chemotherapy depending upon risk stratification. As for the paraneoplastic manifestation, either an aggressive upfront approach or gradual escalation approach may be followed. All regimens involve the use of steroids (prednisolone, ACTH, or dexamethasone pulses), IVIG, cyclophosphamide, and rituximab. Resistant cases might require plasmapheresis.[7] OMAS-associated neuroblastic tumors have shown favorable outcomes when compared with those without OMAS.[3] It has been seen that with an increase in the pre-treatment duration, the prognosis worsens and the risk of long-term neurological sequelae increases.[4] Thus, early diagnosis and management are important to improve prognosis. Also, it is noteworthy that patients in OMAS in whom no tumor is localized after adequate investigation, the search for tumor must be repeated at 6 months as small sized tumors might be missed in the initial screening.

Funding
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Conflict of Interest
None declared.

Informed Consent
A written informed consent was taken from the parents of the child.

References

1 Goraya JS. Acute movement disorders in children: experience from a developing country. J Child Neurol 2015;30(04):406–411
2 Neurological sequelae of the dancing eye syndrome - PubMed [Internet]. [cited 2021 Mar 19]. Accessed January 8, 2023, at: https://pubmed.ncbi.nlm.nih.gov/8929735/
3 Sahu JK, Prasad K. The opsoclonus–myoclonus syndrome. Pract Neurol 2011;11(03):160–166
4 Galstyan A, Wilbur C, Selby K, Hukin J. Opsoclonus-myoclonus syndrome: a new era of improved prognosis? Pediatr Neurol 2017;72:65–69
5 Pranzatelli MR. The neurobiology of the opsoclonus-myoclonus syndrome. Clin Neuropharmacol 1992;15(03): 186–228
6 Pranzatelli MR, Tate ED, McGee NR. Demographic, clinical, and immunologic features of 389 children with opsoclonus-myoclonus syndrome: a cross-sectional study. Front Neurol 2017; 8:468https://www.frontiersin.org/articles/10.3389/fneur.2017.00468 cited 2022Oct26 [Internet]
7 Rossor T, Yeh EA, Khakoo Y, et al; OMS Study Group. Diagnosis and management of opsoclonus-myoclonus-ataxia syndrome in children: an international perspective. Neurol Neuroimmunol Neuroinflamm 2022;9(03):e1153. Doi: 10.1212/NXI.0000000000001153

Case Report of a Glioma Patient with Homozygous Missense Amino Acid Substitution in *KDR* Gene

Kalyan Ram Uppaluri[1] Himavanth Reddy Kambalachenu[1] Hima Jyothi Challa[1] Saadvik Raghuram Y.[2] Deepak Sharma[1] Ramya Gadicherla[1] Srinivas Ketavath[1] Kalyani Palasamudram[1] Sri Manjari K.[1]

[1] GenepoweRx, Suit #2B, Plot No. 240, Nirvana, Road No. 36, Jawahar Colony, Jubilee Hills, Hyderabad, Telangana, India
[2] Medicover Cancer Institute, Madhapur, Hyderabad, Telangana, India

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Address for correspondence Kalyan Ram Uppaluri, MD, GenepoweRx, Suit #2B, Plot No. 240, Nirvana, Road No. 36, Jawahar Colony, Jubilee Hills, Hyderabad 500033, Telangana, India (e-mail: kalyan@khdreamlife.com).

Abstract

Gliomas are the most commonly seen cancers of the central nervous system with a variable genetic predisposition. Here, we report a homozygous missense variant in the *KDR* gene in a patient with recurrent glioma. The 35-year-old male patient was diagnosed with stage IV glioma with a recurrence after 10 years from a low-grade stage two glioma. The patient underwent a repeat right craniotomy and ventriculo-peritoneal shunt placement. Biopsy of the lesion showed areas of necrosis with microvascular proliferation and multinucleated tumor cells. An in-depth analysis of NGS data comprising a multigene panel of 351 genes (Agilent Cancer Core Panel) found a homozygous missense variant in exon 25 of the *KDR* gene that resulted in a substitution of an amino acid glutamine for arginine at codon 1118. The *KDR* gene or VEGF2 receptor is a type III receptor tyrosine kinase of the *VEGF* gene involved in angiogenesis. We hypothesize that the variation in the *KDR* gene may have a role in the patient's transition from grade II to grade IV glioma. While the clinical relevance of this mutation is not clear, screening mutations in the protein tyrosine and serine/threonine kinase domain of the KDR will provide critical insights into the development and progression of glioma in the pediatric and adult populations.

Keywords
- glioma
- Protein Kinase
- KDR

Introduction

Gliomas are the most frequent neoplasms of the central nervous system (CNS) originating from glial cells in older adults (mean age of 65 years). They are diffusely infiltrative tumors that affect the surrounding brain tissue. Glioblastoma multiforme is the most malignant type of glioma, while pilocytic astrocytoma is the least. Based on the histopathological analysis, gliomas are graded into four types (I–IV). The first type, Grade I glioma, is easily curable as it is usually benign. The second type, Grade II glioma, also called lower grade glioma (LGG), is often encountered in young adults. LGG is characterized by seizures and lesions in the temporal, frontal, or insular lobes. Most glioma cases detected belong to Grade III or Grade IV. In the United States, there are six cases of gliomas diagnosed per 100,000 people every year.[1] In India, 1 to 4 brain tumors per 100,000 cases occur. Glioblastoma multiforme (GBM) accounts for 18% of all primary brain tumors and 45.9% of all glioma tumors (data from Population-based Cancer Registry, GCRI). Thus, overall, the epidemiological data on GBM tumors indicates that the incidence of this malignancy is increasing in India.[2] Genetic factors, along with environmental influence, are known to cause gliomas. LGG in a young adult

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may be more genetic in etiology. As more genetic studies are being done, several new genetic biomarkers are found to be associated with specific cancers. We report a case of recurrent gliomas, with increasing severity, in a young individual found to have a germline mutation in the *KDR* gene.

Case Report

A 35-year-old man with recurrent glioma was diagnosed with LGG in 2013, for which he underwent right-sided craniotomy and radiation therapy. This time he came in with aggressive secondary GBM, likely originating from the previous LGG. The patient presented with symptoms of generalized seizures and ECOG (Eastern Cooperative Oncology Group) performance status of level 3. Magnetic resonance imaging (MRI) brain showed right frontal craniotomy changes, including meningocele, along with new lesions in the right frontal lobe. The patient underwent a repeat right craniotomy and ventriculoperitoneal shunt placement. Biopsy of the lesion showed areas of necrosis with microvascular proliferation and multinucleated tumor cells. The patient was diagnosed as *IDH* mutated, *ATRX* mutated, GBM WHO grade IV. The patient was started on antiepileptics. He was also started on the chemotherapy agent Lomustine.

The attending physician sought tumor profiling and multigene panel testing to aid in drug decision-making of Foods and Drug Administration (FDA)-approved therapeutic molecules for approved biomarkers because the genetic factor was assumed to be linked to carcinogenesis. They investigated the correlation between non-routinely assessed oncogenes from a panel of 351 genes (Agilent Cancer Core Panel; **►Supplementary Table S1**, available online only>) and clinical, morphological, and molecular features to isolate gene variants, which might hold a diagnostic or prognostic significance and potential relevance for treatment. The DNA was extracted from FFPE blocks using the MN NucleoSpin DNA FFPE XS kit, followed by NGS Library preparation using SureSelect XT HS2 DNA system, a hybrid capture-based technology that includes 351 genes and subjected to paired-end sequencing on Illumina Novoseq 6000 platform. A total of 9.5 GB of raw data were generated, followed by the quality screening of raw FASTQ files, adapter trimming, mapping of raw data to the hg38 reference genome and generation of Sam/Bam files. VCF file was generated using the GATK 4.2.2 pipeline. Annotation of VCF file was using Ensembl VEP and Oncotator.

Results of Gene Panel test: Variant analysis in the targeted genes found a homozygous missense variant in exon 25 of the *KDR* gene (chr4:55089425C > T; NM_002253.4) (**►Fig. 1**). The single nucleotide substitution of C > T results in an amino acid substitution of glutamine for arginine at codon 1118 (c.3353G > A; p.Arg1118Gln) (**►Fig. 2**). The observed *KDR* gene variant lies in the protein tyrosine and serine/threonine kinase domain of the KDR protein. Though there are no proven clinical studies yet, and *in silico* analysis of the *KDR* gene variant p.Arg1118Gln was found to be probably damaging by PolyPhen-2 (HumVar and HumDiv) and deleterious by SIFT.

Discussion

The *KDR* gene encodes a kinase insert domain receptor, also known as VEGFR2,[3] which is a type III receptor tyrosine kinase of the *VEGF* gene involved in angiogenesis.[4] Angiogenesis plays an essential role in the transition from early stages of cancer to metastasis or stage IV. Strategies or medications that block VEGF-KDR signaling successfully inhibit experimental tumor growth, as this is the foremost signaling step required for the

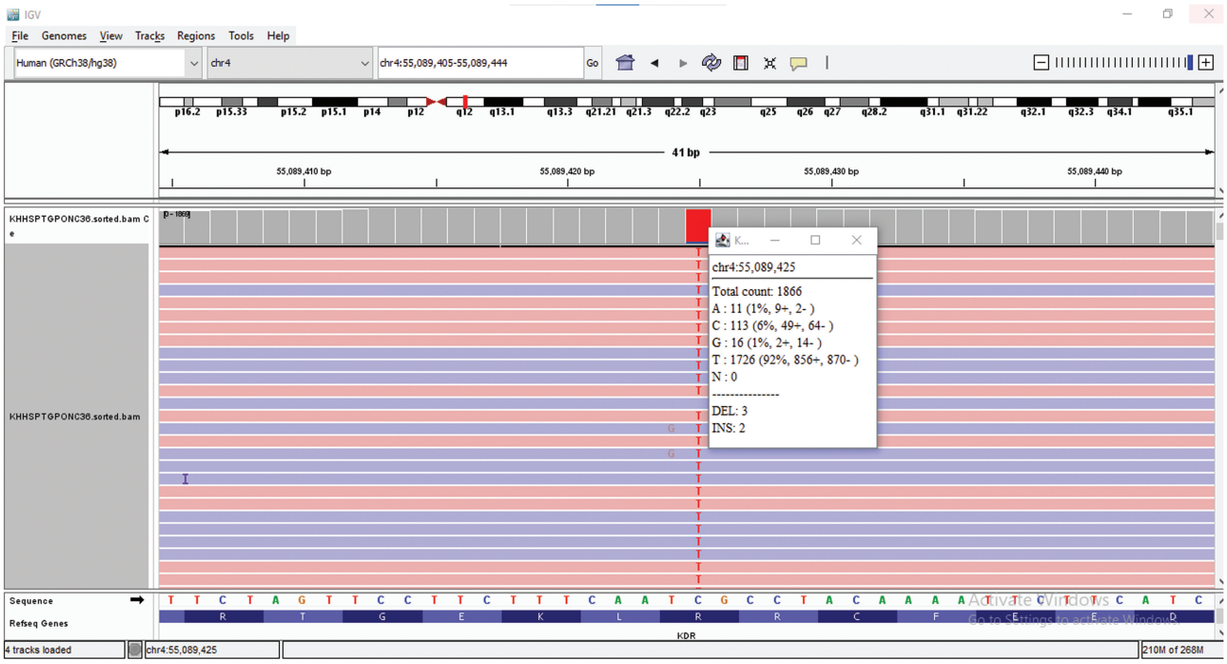

Fig. 1 KDR Gene Variant in IGV.

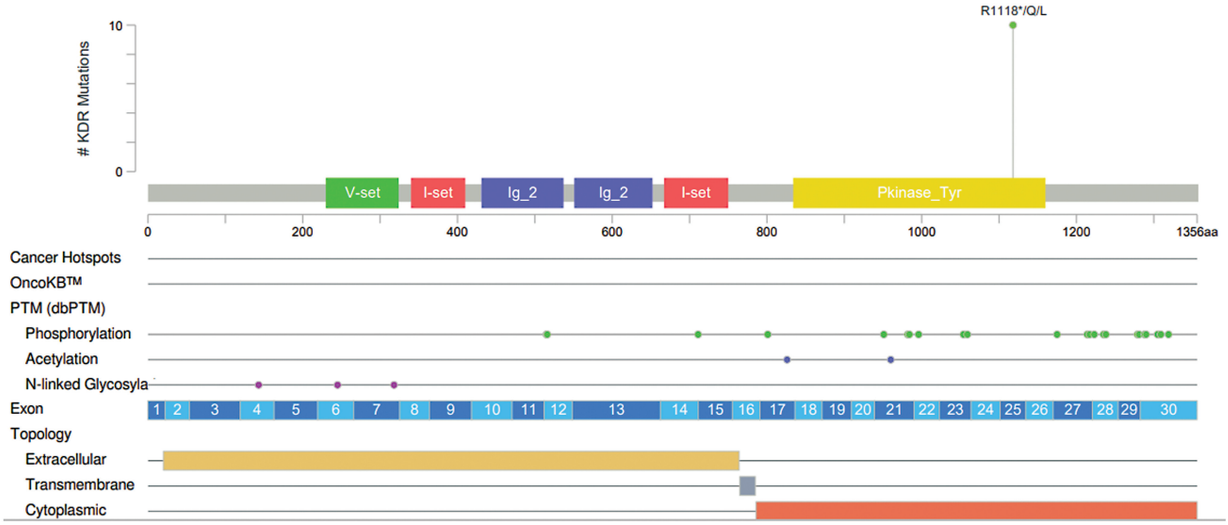

Fig. 2 Location of KDR Gene Variant (p.Arg1118Gln) (1).

proliferating tumor endothelium.[5] It is well known that many FDA-approved drugs targeting the *KDR* gene (including apatinib, cabozantinib, pazopanib, and sorafenib) have been applied to treat renal, gastric, colorectal, and other cancers.[6–9] A clinical trial in a Chinese cohort is going on to treat recurrent glioblastoma with apatinib.[10]

Association of *KDR* gene Mutations in Glioma

Mutations in the *KDR* gene have been reported in different cancer types, predominantly in melanoma and non-melanomatic skin cancers (►**Supplementary Fig. S1**, available online only). The p.Arg1118Gln variant in heterozygous conditions has previously been reported in glioblastoma, rectal adenocarcinoma, uterine endometrioid cancer, and colon adenocarcinoma (Resource: cBioportal).[11,12] Two different mutations affecting the codon 1118 (p.Arg1118Ter and p.Arg1118Leu) have previously been reported in patients with glioblastoma multiforme, sarcoma, uterine endometrioid carcinoma, lung, and colon adenocarcinoma (The AACR Project GENIE Consortium, 2017).[13] KDR p.Arg1118Ter variant is present in 0.02% of AACR GENIE cases and comprised colon adenocarcinoma, endometrial endometrioid adenocarcinoma, lung adenocarcinoma, and sarcoma and astrocytoma.[14–16]

The limitation of this case report is that the targeted therapy associated with the *KDR* gene in gliomas is under clinical trials only. Though the detected variant was with a very high variant allele fraction, Sanger validation in paired tumor-normal specimens may strengthen the authenticity of zygosity. Hence, the present information helps facilitate further exploration of functional analyses of *KDR* mutations in gliomas.

Conclusion

This is the first report of the *KDR* gene variant in a homozygous state reported in a patient diagnosed with glioma. Screening mutations in protein tyrosine and serine/threonine kinase domain of the KDR will provide critical insights into the development and progression of glioma in the pediatric and adult populations. Screening for germline mutations in pediatric cases, it is strongly recommended to conduct additional testing with paired tumour-normal specimens. Because GBM, the most aggressive type of glioma, is a vascular tumor, the *KDR* gene associated with VEGF is probably implicated in tumor growth. Therefore, in young GBM patients with germline *KDR* mutations, it might be prudent to give a trial of anti-vascular drugs along with the conventional treatment regimen.

Authors' Contributions
All authors have contributed and approved the manuscript.

Patient consent
The authors certify that they have obtained all appropriate patient consent forms

Statement of Ethics
This retrospective review of patient data did not require ethical approval under local guidelines. Written informed consent was obtained from the patient to publish this case report.

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Conflicts of Interest
None declared.

References

1 Ostrom QT, Gittleman H, Stetson L, Virk SM, Barnholtz-Sloan JS. Epidemiology of gliomas. Cancer Treat Res 2015;163:1–14
2 Trivedi T, Panchal K, Bhalala N, Trivedi P. Prognostic significance of STAT3 gene expression in patients with glioblastoma tumors: a study from Western India. J Egypt Natl Canc Inst 2022;34(01):30

3 Zehir A, Benayed R, Shah RH, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med 2017;23(06):703–713
4 Biterge-Sut B. A comprehensive analysis of the angiogenesis-related genes in glioblastoma multiforme vs. brain lower grade glioma. Arq Neuropsiquiatr 2020;78(01):34–38
5 Banerjee K, Núñez FJ, Haase S, et al. Current Approaches for Glioma Gene Therapy and Virotherapy. Front Mol Neurosci 2021;14:621831
6 Geng R, Song L, Li J, Zhao L. The safety of apatinib for the treatment of gastric cancer. Expert Opin Drug Saf 2018;17(11):1145–1150
7 Cochin V, Gross-Goupil M, Ravaud A, Godbert Y, Le Moulec S. [Cabozantinib: Mechanism of action, efficacy and indications]. . [Cabozantinib: Mechanism of action, efficacy and indications]Bull Cancer 2017;104(05):393–401
8 Noguerido A, Mulet-Margalef N, Matos I, et al. The safety of ramucirumab for the treatment of colorectal cancer. Expert Opin Drug Saf 2018;17(09):945–951
9 Choi YJ, Kim HS, Park SH, et al. Phase II study of Dovitinib in patients with castration-resistant prostate cancer (KCSG-GU11-05). Cancer Res Treat 2018;50(04):1252–1259
10 Glioblastoma Response Prediction to Apatinib. Accessed Jan 30, 2023, at: https://clinicaltrials.gov/ct2/show/NCT04814329?term=Glioblastoma&cond=KDR+gene&draw=2&rank=1
11 Cerami E, Gao J, Dogrusoz U, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. [published correction appears in Cancer Discov 2012;2:960]Cancer Discov 2012;2(05):401–404
12 Gao J, Aksoy BA, Dogrusoz U, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 2013;6(269):pl1
13 AACR Project GENIE Consortium. AACR Project GENIE: powering precision medicine through an international consortium. Cancer Discov 2017;7(08):818–831
14 Killela PJ, Pirozzi CJ, Reitman ZJ, et al. The genetic landscape of anaplastic astrocytoma. Oncotarget 2014;5(06):1452–1457
15 Sun S, Li X, Qu B, Xie K, Li J, Miao J. Association of the VEGFR2 single nucleotide polymorphism rs2305948 with glioma risk. Medicine (Baltimore) 2022;101(01):e28454
16 Jonsson P, Lin AL, Young RJ, et al. Genomic correlates of disease progression and treatment response in prospectively characterized gliomas. Clin Cancer Res 2019;25(18):5537–5547

Protean Neuroophthalmic Presentations of Common Childhood Malignancies—A Report of Two Cases

Pritam Singha Roy[1] Richa Jain[1] Anmol Bhatia[2] Nabhajit Mallik[3] Narender Kumar[3]

[1] Pediatric Hematology-Oncology Unit, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India
[2] Department of Radiodiagnosis and Imaging, Postgraduate Institute of Medical Education and Research, Chandigarh, India
[3] Department Hematology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Address for correspondence Richa Jain, DM, Pediatric Hematology-Oncology Unit, Department of Pediatrics, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India (e-mail: docrichajain@gmail.com).

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Abstract

Common pediatric malignancies often surprise clinicians with unusual presentations. In this narrative, we report two patients with common childhood cancer having unique neuroophthalmic characteristics. In the first case, we have a child with a common childhood solid tumor presenting with blindness without proptosis, while the second case is of a child with a common hematological malignancy presenting with unilateral proptosis without visual impairment. The report highlights that common childhood cancers may present with neuroophthalmic symptoms on rare occasions, creating a diagnostic conundrum.

Keywords
- blindness
- leukemia
- marrow
- neuroblastoma
- proptosis

neuroophthalmic symptoms Introduction

Childhood malignancies may present with nonspecific and overlapping clinical features, making it difficult to differentiate them from each other clinically. They often puzzle clinicians and pose interesting diagnostic challenges.[1–7] We describe two unique neuroophthalmological presentations of common childhood malignancies in this report.

Case 1

A 6-year-old boy presented with a 2-week history of headache and painless, progressive binocular vision loss. There was a preceding history of intermittent fever for 2 months, nocturnal bone pains, and recent-onset anemia, requiring a transfusion. He had severe bilateral visual impairment at presentation, with only the perception of light present. There was no obvious proptosis or raccoon eye. Fundoscopy revealed bilateral blurring of disk margins without optic atrophy. Severe pallor, generalized bony tenderness, and hepatomegaly were present on examination. Sutural diastasis was noted at sagittal and coronal sutures. The constellation of clinical presentation and the examination findings raised suspicion of acute leukemia or metastatic neuroblastoma.

Skull radiograph revealed remarkable sutural diastasis (►**Fig. 1A**). A contrast-enhanced magnetic resonance imaging (CE-MRI) of the brain and orbit unveiled multiple intracranial, extradural collections over bilateral frontoparietal and occipital areas (►**Fig. 1B**). Soft-tissue depositions over the orbital apices causing bilateral optic nerve compression were also evident, explaining the binocular blindness. A bone marrow (BM) aspiration and bilateral trephine demonstrated clusters of small, round, blue tumor cells (►**Fig. 1C**), with immunohistochemistry indicating a positivity for neuron-specific enolase, CD 56, and CD 81 (►**Fig. 1D**), confirming the presence of metastatic neuroblastoma in the BM. Computed

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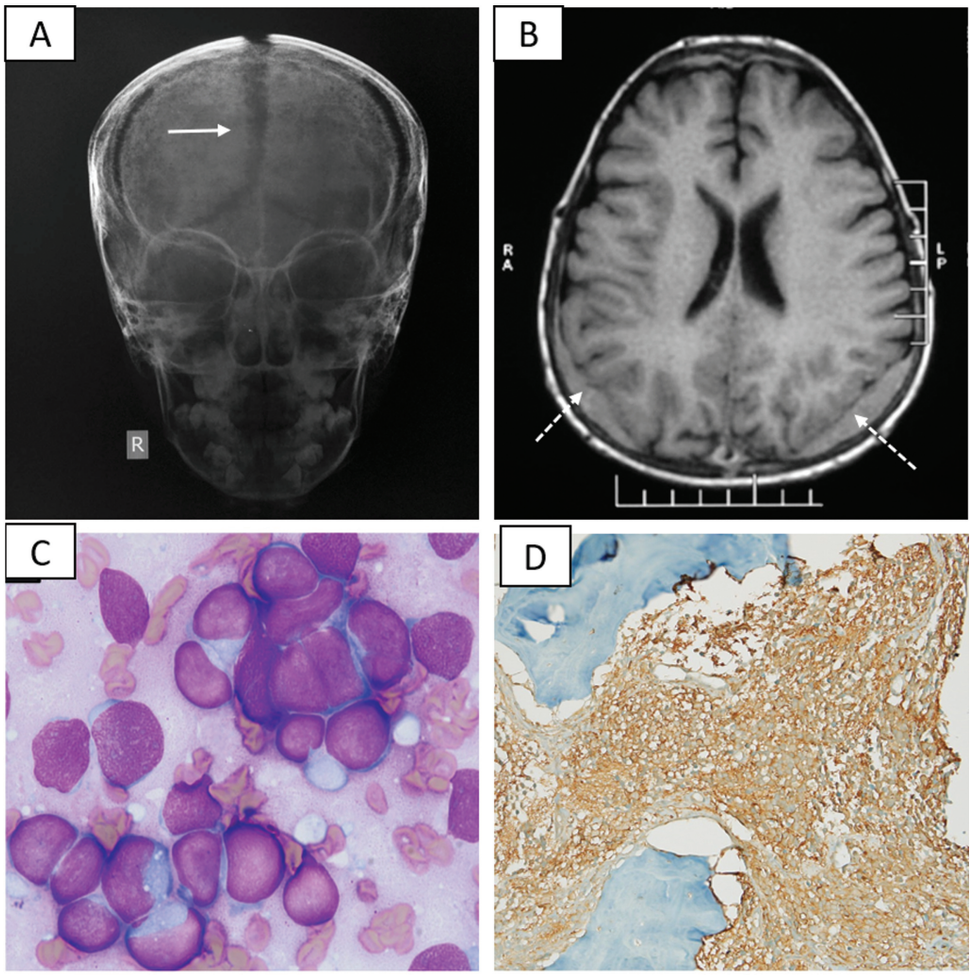

Fig. 1 (**A**) Antero-posterior view of the skull radiograph showing remarkable sutural diastasis (*white arrow*), (**B**) axial section of T1-weighted MRI of the brain illustrating extradural soft tissue deposits along bilateral parieto-occipital regions (*white dotted arrows*), (**C**) bone marrow aspirate smear showing infiltration by blastoid atypical cells, and (**D**) immunohistochemistry demonstrating positivity for neuronspecific enolase

tomography and a DOTATATE positron emission tomography scan were done for staging, showing a left suprarenal mass (size: 15 × 12 mm), with extensive metastasis to bones, BM, and cranial meninges over fronto–parieto–occipital regions. Treatment for high-risk neuroblastoma was initiated with the rapid COJEC protocol.[8,9] There was an improvement in the systemic symptoms. However, the vision loss did not recover. A reassessment was performed after eight cycles of induction chemotherapy, demonstrating extensive BM disease. After a detailed discussion with the family, a decision to proceed with palliative care was taken.

Case 2

A 3-year-old boy presented with proptosis involving the left eye for 1 month without pain, visual impairment, or systemic symptoms. Physical examination was unremarkable, except for nonaxial proptosis with esotropia and periocular fullness in the left eye (►**Fig. 2A**). A CE-MRI of the brain and orbit was performed and demonstrated a homogeneously enhancing soft tissue mass involving the basisphenoid with extension into the left orbit (►**Fig. 2B**). Dura-based, multifocal, nodular, enhancing soft-tissue deposits along the left frontoparietal convexity were also apparent. Clinicoradiological possibilities of metastatic neuroblastoma and parameningeal rhabdomyosarcoma were considered. Abdominal ultrasonography and chest radiograph were normal. The tumor was at a difficult site to access for a biopsy. While a complete blood count was normal at the baseline, a repeat evaluation after 7 days revealed evolving cytopenias with a hemoglobin of 95 g/L, total leukocyte count of 4.17×10^9 /L, differential leukocyte count of polymorphs: 23%, lymphocytes: 60%, monocytes: 16%, and a platelet count of 165×10^9 /L. Subsequent BM aspiration revealed findings consistent with acute leukemia (►**Fig. 2C**). Flow cytometry confirmed the presence of T cell acute lymphoblastic leukemia (ALL). Cerebrospinal fluid was paucicellular (three cells/μL), and cytospin did not detect leukemic infiltration. However, the child was considered "central nervous system (CNS)-positive" due to the MRI findings suggestive of leptomeningeal carcinomatosis. Induction chemotherapy was initiated for high-risk T cell ALL as per the Indian Childhood Collaborative Leukaemia

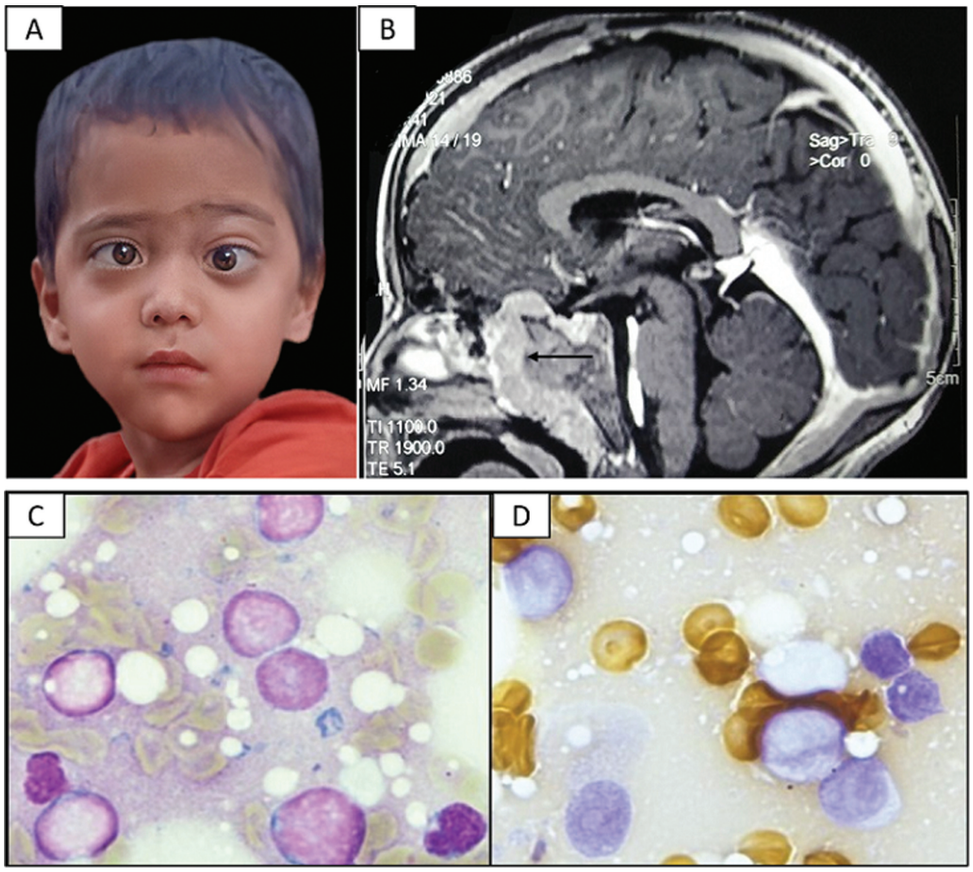

Fig. 2 (**A**) Proptosis of the left eye, (**B**) sagittal section of T1-weighted CE-MRI of brain illustrating enhancing sheet of soft tissue at the basisphenoid with extension to the orbit (*black arrow*), (**C**) bone marrow aspirate smear showing blasts (May–Grunwald–Giemsa stain; 1,000x), (**D**) the blast cells were MPO negative (myeloperoxidase stain; 1,000x). CE-MRI, contrast-enhanced magnetic resonance imaging.

Group protocol.[10] The proptosis resolved 2 weeks into treatment. Reassessment by BM, MRI brain, and 18-fluorodeoxyglucose-positron emission tomography confirmed remission at the end of consolidation. The child will subsequently receive CNS radiotherapy as a part of the treatment protocol.

Discussion

Childhood cancers can have protean presentations. Extracranial malignancies may infiltrate the brain or the orbit and may be the initial manifestation of the disease.[11–16] The unique presenting features of the cases in the current report are binocular painless visual loss in the absence of proptosis or raccoon's eye in a child with metastatic neuroblastoma, unilateral proptosis being the sole manifestation of T cell ALL in a young boy.

While malignancy was correctly suspected in both cases, the initial possibilities that were considered were different from the final diagnosis. Tissue diagnosis was rendered difficult due to the CNS location of the mass lesions, with BM aspiration and trephine clinching the diagnosis.

Orbital involvement is frequent in patients with metastatic neuroblastoma; raccoon's eye and proptosis are well-recognized manifestations. However, a presentation with visual loss without proptosis, as seen in case 2, is a rarity. ►**Table 1** summarizes the limited reports of orbital metastasis of neuroblastoma presenting with blindness without proptosis.[11–13,17,18] Treatment modalities to salvage vision have included steroids, decompressive surgery, and initiation of chemotherapy to treat the primary disease. The vision remained compromised in the majority of the reported cases, and the role of either steroids or surgery in salvaging the vision is not clear. Orbital metastasis of neuroblastoma confers a poor outcome, partially explained by a higher association with MYCN amplification.[19–21]

Proptosis due to orbital involvement by ALL is not considered a CNS-positive disease. A summary of selected reports of childhood ALL with proptosis is presented in ►**Table 2**.[22–26] Notably, three of six cases, including the current one, had associated intracranial or optic nerve involvement, translating to CNS positivity. Proptosis may be the presenting manifestation of precursor B- or T-lineage ALL affecting infants, children, or adolescents. Orbital infiltration is more frequently unilateral, with bilateral involvement being quite uncommon. Visual impairment has been reported infrequently with proptosis. The oncological outcome of these patients does not differ from the patients who do not have orbital involvement.[22–26]

Table 1 Selected reports of patients with neuroblastoma presenting with blindness without proptosis

S No.	Author, year of publication, country	Number of patients	Age	Duration of blindness; visual acuity at diagnosis	Site of optic nerve compression by metastatic tumor	Treatment	Visual outcome; final acuity	Oncologic outcome
1.	Roy et al[17], 2021, India	1	3 y and 9 mo	2 wk; perception of light only	Optic canal; bilateral	High-dose dexamethasone, rapid COJEC chemotherapy	No improvement	On therapy
2.	Sivakumar et al [18], 2006, USA	1	4 y	2 wk; 20/200	Optic canal; bilateral	Not included	Not included	Not included
3.	McGirt et al[11], 2005, USA	1	33 mo	4 d; no perception of light	Optic foramen; bilateral	High-dose methylprednisolone, decompressive surgery	Partial improvement; finger counting, recognizing faces and printed book characters	Not included
4.	Lau et al[12], 2004, USA	1	2 y	Several days; no perception of light	Intracranial course; bilateral	High-dose steroid	Partial improvement; right eye-20/400 , left eye-hand movements	In clinical remission
5.	Varma et al[13], 2003, United Kingdom	1	2.5 y	3 wk; hand movement perceived	Orbital apices; bilateral	Pulse methylprednisolone	Right eye-partial improvement; 6/60, left eye-no improvement	Not included
6.	Current report	1	6 y	2 wk; no perception of light	Orbital apices; bilateral	Rapid COJEC chemotherapy	No improvement	Refractory disease

Table 2 Selected reports of childhood acute lymphoblastic leukemia presenting with proptosis

S No.	Author, year of publication, Country	Number of the patient(s)	Age	Ophthalmic features	Radiology	Oncologic diagnosis	Mode of diagnosis	Outcome
1.	Wang et al[22], 2020, China	1	4 y	Unilateral proptosis	Orbital extraconal mass	Hypodiploid B-cell ALL	Bone marrow study	Well on therapy
2.	Sathitsamitphong et al[23], 2019, Thailand	1	3 y	Unilateral proptosis	Orbital mass with intracranial extension	B-cell ALL	Bone marrow study	In remission; on therapy
3.	Sivaperumal et al[24], 2018, India	1	5 y	Bilateral proptosis	Not included	B-cell ALL	Bone marrow study	In remission; on therapy
4.	Ramamoorthy et al[25], 2016, India	1	4 y	Unilateral proptosis	Retrobulbar mass with intracranial extension	B-cell ALL	Biopsy from the orbital mass and bone marrow study	Well on therapy
5.	Thakker et al[26], 2006, India	1	8 mo	Right eye tearing, lid swelling, proptosis	Large, homogeneous orbital mass causing axial displacement of the globe and expansion of the orbit	B-cell ALL	Bone marrow study	Alive and well 14 mo posttreatment
6.	Current report	1	3 y	Unilateral proptosis	Mass over basisphenoid with extension into the left orbit	T-cell ALL	Bone marrow study	Doing well on therapy

Conclusion

Common childhood malignancies may manifest with myriad neuroophthalmic manifestations, and a high index of suspicion is required to reach the correct diagnosis.

Declaration of Patient Consent

The authors certify that they have obtained consent from the parents for the publication of images and clinical information of the child in the journal. The parents understand that the child's name and initials will not be published and due efforts will be made to conceal the identity.

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None.

Conflict of Interest

None declared.

References

1 Gökçe M, Aytaç S, Ünal Ş, Altan İ, Gümrük F, Çetin M. Acute megakaryoblastic leukemia with t(1;22) mimicking neuroblastoma in an infant. Turk J Haematol 2015;32(01):64–67
2 Kawasaki Y, Makimoto M, Nomura K, et al. Neonatal acute megakaryoblastic leukemia mimicking congenital neuroblastoma. Clin Case Rep 2015;3(03):145–149
3 Wang YM, Mo JQ, Kuo DJ, Wong V. *MLL* rearranged acute lymphoblastic leukaemia presenting as a maxillary sinus mass with a discordant immunophenotypic profile from the bone marrow. BMJ Case Rep 2019;12(02):e227400
4 Ünal Ş, Kuşkonmaz B, Balcı YI, et al. An unusual presentation of pediatric acute lymphoblastic leukemia with parotid gland involvement and dactylitis. Turk J Haematol 2010;27(02): 117–119
5 Sadawaite S, Jijina F, Nair CK, Seth S, Ghosh K. An unusual presentation of pediatric acute lymphoblastic leukemia. Indian J Hematol Blood Transfus 2008;24(02):59–62
6 Gallagher BL, Vibhakar R, Kao S, Cooper CS. Bilateral testicular masses: an unusual presentation of neuroblastoma. Urology 2006;68(03):672.e15–672.e17
7 Mittal D, Mandelia A, Bajpai M, Agarwala S. Adrenal neuroblastoma with metastatic mandibular mass: an unusual presentation. J Cancer Res Ther 2015;11(03):645
8 Ladenstein R, Pötschger U, Valteau-Couanet D, et al. Interleukin 2 with anti-GD2 antibody ch14.18/CHO (dinutuximab beta) in patients with high-risk neuroblastoma (HR-NBL1/SIOPEN): a multicentre, randomised, phase 3 trial. Lancet Oncol 2018;19 (12):1617–1629
9 Jain R, Hans R, Totadri S, et al. Autologous stem cell transplant for high-risk neuroblastoma: achieving cure with low-cost adaptations. Pediatr Blood Cancer 2020;67(06):e28273
10 Das N, Banavali S, Bakhshi S, et al. Protocol for ICiCLe-ALL-14 (InPOG-ALL-15-01): a prospective, risk stratified, randomised, multicentre, open label, controlled therapeutic trial for newly diagnosed childhood acute lymphoblastic leukaemia in India. Trials 2022;23(01):102
11 McGirt MJ, Cowan JA Jr, Gala V, Garton HJ, Muraszko KM, Thompson BG. Surgical reversal of prolonged blindness from a metastatic neuroblastoma. Childs Nerv Syst 2005;21(07):583–586
12 Lau JJC, Trobe JD, Ruiz RE, et al. Metastatic neuroblastoma presenting with binocular blindness from intracranial compression of the optic nerves. J Neuroophthalmol 2004;24(02):119–124
13 Varma D, George N, Livingston J, Negi A, Willshaw HE. Acute visual loss as an early manifestation of metastatic neuroblastoma. Eye (Lond) 2003;17(02):250–252
14 Belgaumi AF, Kauffman WM, Jenkins JJ, et al. Blindness in children with neuroblastoma. Cancer 1997;80(10):1997–2004
15 Taylor CW, Taylor RE, Kinsey SE. Leukemic infiltration of the orbit: report of three cases and literature review. Pediatr Hematol Oncol 2005;22(05):415–422
16 Bidar M, Wilson MW, Laquis SJ, et al. Clinical and imaging characteristics of orbital leukemic tumors. Ophthal Plast Reconstr Surg 2007;23(02):87–93
17 Roy PS, Chhabra P, Jain R, Gupta P, Sodhi KS, Bansal D. Metastatic, bilateral adrenal neuroblastoma presenting with blindness without proptosis. J Pediatr Hematol Oncol 2021;43(08):e1250–e1252
18 Sivakumar S, Poulik J, Sivaswamy L. Monocular blindness as presentation manifestation of neuroblastoma. Neurohospitalist 2016;6(01):41
19 Smith SJ, Diehl NN, Smith BD, Mohney BG. Incidence, ocular manifestations, and survival in children with neuroblastoma: a population-based study. Am J Ophthalmol 2010;149(04): 677–682.e2
20 Harreld JH, Bratton EM, Federico SM, et al. Orbital metastasis is associated with decreased survival in stage M neuroblastoma. Pediatr Blood Cancer 2016;63(04):627–633
21 DuBois SG, Kalika Y, Lukens JN, et al. Metastatic sites in stage IV and IVS neuroblastoma correlate with age, tumor biology, and survival. J Pediatr Hematol Oncol 1999;21(03):181–189
22 Wang L, Ashraf DC, Kinde B, Ohgami RS, Kumar J, Kersten RC. Hypodiploid B-lymphoblastic leukemia presenting as an isolated orbital mass prior to systemic involvement: a case report and review of the literature. Diagnostics (Basel) 2020;11(01):25
23 Sathitsamitphong L, Natesirinilkul R, Choeyprasert W, Charoenkwan P. Unusual presentation with orbital mass in a child with precursor B-cell acute lymphoblastic leukemia. Case Rep Hematol 2019;2019:8264689
24 Sivaperumal PR, Latha SM, Narayani S, Scott J. Bilateral proptosis in a child: a rare presentation of acute lymphoblastic leukemia. J Ophthalmic Vis Res 2018;13(04):511–513
25 Ramamoorthy J, Jain R, Trehan A, Saxena AK, Ahluwalia J. Orbital mass in a child with acute lymphoblastic leukemia: a case report and review of the literature. J Pediatr Hematol Oncol 2016;38(08): 646–648
26 Thakker MM, Rubin PAD, Chang E. Pre-B-cell acute lymphoblastic leukemia presenting as an orbital mass in an 8-month-old. Ophthalmology 2006;113(02):343–346

Radiation Recall Dermatitis in Breast Cancer Patient after Trastuzumab: A Case Report with Review of Literature

Rohit Avinash Vadgaonkar[1] Pradeep Ventrapati[2] Ankita Mehta[1] Anupurva Dutta[3]

[1] Department of Radiation Oncology, Breast Cancer Management Group, Homi Bhabha Cancer Hospital and Research Centre, Visakhapatnam, Andhra Pradesh, India
[2] Department of Medical Oncology, Breast Cancer Management Group, Homi Bhabha Cancer Hospital and Research Centre, Visakhapatnam, Andhra Pradesh, India
[3] Department of Pathology, Breast Cancer Management Group, Homi Bhabha Cancer Hospital and Research Centre, Visakhapatnam, Andhra Pradesh, India

Address for correspondence Rohit Vadgaonkar, MD, Department of Radiation Oncology, Breast cancer management group, Homi Bhabha Cancer Hospital and Research Centre, APIIC Plot, Aganampudi village, National Highway No.5, Visakhapatnam 530053, Andhra Pradesh, India (e-mail: dr.ravad@gmail.com).

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Abstract

Radiation recall dermatitis (RRD) is an extremely rare phenomenon. A variety of factors such as antineoplastic agents, pharmaceutical agents, physical and environmental factors have been proposed to be the underlying cause of RRD. Only a handful cases have been reported till date, where trastuzumab is sought to be the triggering agent. The presentation of RRD varies from mild erythematous to extensive confluent dermatitis, resolving over a period of 1 to 2 weeks with conservative management. Most of the patients tend to tolerate rechallenge well without showing reappearance. We hereby describe a lady with breast cancer having RRD following administration of trastuzumab. She developed reaction 28 days post-radiotherapy and managed conservatively. Furthermore, she was rechallenged with the same dose, that she tolerated very well, without any reappearance. Hence, an acquaintance of the clinicians to this rare entity is essential for timely diagnosis and appropriate management.

Keywords
- radiation recall dermatitis
- trastuzumab
- radiation recall phenomenon

Introduction

Radiation recall is an ill-defined inflammatory phenomenon characterized by reactions triggered by exposure to a certain agent in the previously irradiated region.[1] It is triggered by post-radiation exposure to certain offending agents including antineoplastic and other pharmacological agents, physical and environmental factors.[1–3] Radiation recall dermatitis (RRD) is the most common manifestation of radiation recall phenomenon.[3] The first documented evidence of RRD was reported long back in 1959 by D'Angio et al.[4] Presently more than hundred cases have been reported in the form of either isolated case reports or small case series. The estimated incidence of RRD is around 6 to 8%.[1–3]

We report a case of RRD in breast cancer patient triggered by trastuzumab along with a review of literature of similar cases. A literature review was done for all published case reports or case series in English language on RRD with trastuzumab using the keywords "radiation recall dermatitis," "trastuzumab," and "radiation recall phenomenon."

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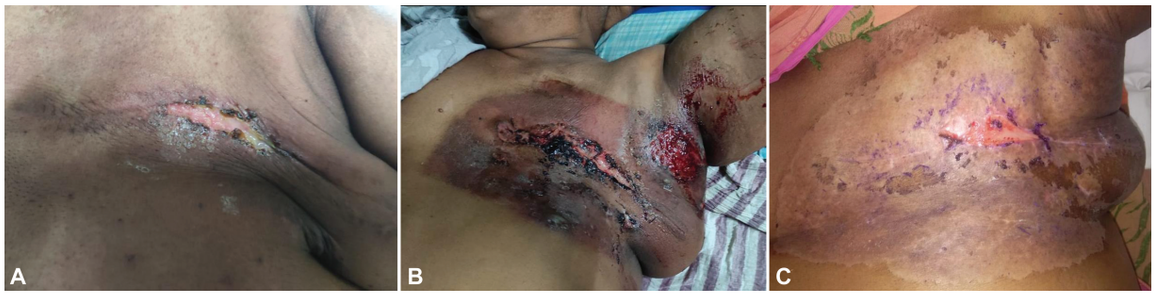

Fig. 1 (**A**) Area of moist desquamation, 7 days post-LRRT. (**B**) Radiation recall dermatitis (RRD), 14 days post-trastuzumab, 28 days post-LRRT. Reaction was well demarcating radiation chest wall portals. (**C**) Near complete resolution of RRD with small persistent area of moist desquamation along the scar, 42 days post-LRRT. LRRT, locoregional radiotherapy.

Case Report

A 59-year-old postmenopausal hypertensive lady without any significant family history or any history of allergy evaluated for a 5×4 cm lump in the left breast and a 1×1 mobile axillary lymph node in June 2021. Histopathology confirmed it as invasive breast carcinoma, no special type, grade 3, hormone receptor positive (estrogen receptor: Allred score—8, progesterone receptor: Allred score— 7) and Her 2 Neu positive on immuno-histochemistry. Staging 18F-fluorodeoxyglucose positron emission tomography/computed tomography scan depicted a soft tissue lesion of 49×42 mm in upper inner quadrant with a small satellite nodule in lower outer quadrant along with axillary lymph nodes without any distant metastases. She received three cycles of multiagent neoadjuvant chemotherapy consisting TCH regimen (docetaxel 75 mg/m^2, carboplatin area under the curve 6, and trastuzumab loading dose of 6 mg/kg followed by 4 mg/kg) that led to partial clinicoradiological partial response. She underwent modified radical mastectomy 4 weeks after completion of chemotherapy. The final histopathology report revealed a unifocal tumor of maximum size of 2 cm with 1 out of 38 dissected lymph nodes was positive without extranodal extension (stage- ypT1c ypN1a). Later, she received adjuvant chemotherapy with three more cycles of TCH. Further, she was started on three weekly maintenance trastuzumab along with anastrozole.

Four weeks post-adjuvant TCH and one week after seventh cycle of trastuzumab, she received locoregional radiotherapy (LRRT) targeting left chest wall (CW) and left supraclavicle fossa (SCF). LRRT was delivered using 6 MV photons to a total dose of 40 Gy in 15 fractions over a period of 3 weeks via bitangential portals for CW and a single anterior portal for SCF radiation. The entire treatment was performed by deep inspiratory breath hold technique and a 5 mm thick bolus was placed throughout the course of radiation over the CW for adequate coverage of the skin. Maximum dose (D max) to the planning target volume (PTV) was 107.2% and volume receiving 105% (V105%) was 11.6 cc; all the other dosimetric parameters for PTV and organs at risk were within the predefined limits.[5] She tolerated LRRT well and at the end of LRRT, she had radiation therapy oncology group (RTOG) grade 1 dermatitis and grade 1 esophagitis at the completion of radiation that were well managed with topical steroid creams and anesthetic antacid gel. In the last week of LRRT, she received her eighth cycle of trastuzumab without any undue toxicity. After 1 week of completion of LRRT, she presented with focal moist desquamation along the scar over the CW (►**Fig. 1A**) for which she was prescribed placental extract gel. Two weeks later, ninth cycle of trastuzumab was given (14 days post-LRRT).

In the subsequent week, she had progressive worsening of dermatitis and after 2 weeks (28 days post-LRRT), she landed up with worsening RTOG grade 3 dermatitis. Intense dermatitis in the form of ulceration, small areas of hemorrhage, was noted over the entire CW (►**Fig. 1B**). However, the reaction was restricted within the LRRT portals and no reaction was observed outside the irradiated region, leading to the diagnosis of RRD. She was managed with topical 1% gentian violet (GV) application along with analgesics. There were no signs or evidence or any superadded infection. Surprisingly, no reaction was observed over the site of SCF irradiation. High-resolution computed tomography chest ruled out underlying recall pneumonitis. Gradually over a period of 3 weeks (42 days post-LRRT), the reaction showed significant improvement with near complete resolution with a persistent small area of moist desquamation along the scar that healed completely in next 2 weeks (►**Fig. 1C**). After 40 days from ninth cycle (54 days post-LRRT), she was rechallenged with the same dose of trastuzumab, without any reappearance of recall reaction.

Discussion

RRD is a well-known entity but largely under-reported.[1] Most of the reported cases are with chemotherapy agents,[2,6,7] followed by some non-neoplastic agents,[8,9] physical agents,[3,10] and other pharmaceutics.[11,12] However, only a few case reports highlight this reaction following targeted therapies[13] including trastuzumab.[13–19] The overexpression of the HER2 is observed in 20 to 30% of primary breast cancers[20] and trastuzumab is a recombinant humanized immunoglobulin G1 monoclonal antibody against HER2, indicated for the management of both primary breast cancer and metastatic disease.[20] The most serious and/or common adverse reactions reported with trastuzumab usage are cardiac dysfunction, infusion-related reactions, neutropenia, and pulmonary adverse reactions.[20] Although dermatitis

with severity ranging from mild-to-moderate has been reported with the use trastuzumab,[20,21] radiation recall is extremely rare and all documented cases have developed reaction to the irradiated skin (RRD),[13–19] with only a single reported case of radiation recall pneumonitis[17] till date.

All cases depicting RRD triggered by trastuzumab[13–19] are summarized in ►**Table 1**. Average duration between radiotherapy (RT) and occurrence of RRD was noted to be 135 days (range: 29–283 days). The triggering cycle of trastuzumab for development of RRD and the cumulative doses at the occurrence of RRD are highly variable in the literature. Moreover, the development of RRD does not seem to be related to RT tolerance as most of the patients developed RRD despite a good tolerance. The RT dose fractionation and target volumes also do not seem to have any corelation with the incidence or intensity of RRD, as majority of these cases are reported with hypofractionated LRRT. However, Alsabbak et al have observed the reaction all over the treated region of breast but with an increased intensity over the area of RT boost region.[14]

Anupama et al have reported an identical incidence of RRD to the present case.[19] In her case, the reaction was occurred 28 days post-LRRT and it was limited to CW region only. We have noticed the reaction only in the irradiated CW and SCF did not show any recall reaction. Such incidences of discriminated RRD have also been reported previously[22] However, exact pathophysiology of these type of reactions is not yet been described in the literature.[1] Various postulated hypotheses include depletion or changes in performance of irradiated stem cells,[1,23] idiosyncratic reaction to triggering agents,[2] vascular endothelial damage,[2] altered immunological responses, and upregulation of specific enzymes that activate prodrug locally in previously irradiated region.[2,24] It has also been postulated that cumulative DNA damage along with oxidative stress may play a role in RRD.[2] Also, histopathological confirmation is not required unless clinical scenario leads to a high suspicion of recurrence.[23] Histological features show changes identical to radiation dermatitis consisting epidermal dysplasia, necrosis of keratinocytes, ballooning degeneration, increased mitotic figures, and inflammatory infiltrates.[23]

Most reported incidences of RRD are of mild-to-moderate grade and rarely lead to life-threatening reactions.[2,6] Also, in our review of literature, all cases of RRD triggered by trastuzumab were of mild-to-moderate intensity and well managed with oral antihistamines, local steroid, or antibiotic cream. No standard set of guidelines exist for the management of these reactions.[2,6] However, discontinuation of triggering agent or delaying further exposure proposed to be the most important measure.[2,6,25] Decision for the symptomatic management with topical moisturizers, steroidal creams, and other anti-inflammatory agents should be individualized on the bases of severity of reaction.[2,6,25] In the present case, alongside analgesics, we have used topical 1% GV. Antifungal and antiseptic properties of topical GV have been used to manage radiation dermatitis and burnt cases traditionally.[26] Most of these cases have shown a near complete resolution within 2 to 7 days, but an intermittent pain may persist for a longer duration. Rechallenging the same triggering agent in most of the instances does not lead

Table 1 Reported incidences of RRD triggered by trastuzumab

Sr. No.	Author	Patient characteristics	Radiotherapy details	Triggering agent	Description of RRD	Treatment and outcome	Rechallenge
1.	Shrimali et al, 2009[16]	A 71-year-old female with breast cancer, history of allergies: NR	45Gy in 20# to CW and SCF, at conclusion she had erythematous dermatitis	Trastuzumab (dose: NS) every 3 weeks with anastrozole (1mg/day), started 42 days after RT	Mild, asymptomatic erythematous RRD noticed 3 weeks after first cycle (62 days after RT)	Intravenous hydrocortisone and oral paracetamol. Complete resolution of RRD (duration: NS)	Yes, under steroid coverage with same dose, without reappearance
2.	Chung et al, 2009[18]	A 41-year-old female with breast cancer, history of eczema, allergic rhinitis, and contact dermatitis to numerous allergens	42.5Gy in 16# to WB and 10 Gy TBB and 37.5Gy in 16# to SCF, IMN, and axilla. Post-RT she had brisk erythema and moist desquamation over inframammary fold	Trastuzumab (513.28 mg) IV every 3 weeks, started 28 days after RT	Mild, painful, swollen, erythematous RRD, 3 days after 12th cycle (283 days post-RT)	Nil. Brisk erythema resolved spontaneously within 2 days, pain persisted for ~14 days	Yes, without reappearance
3.	Moon et al, 2013[15]	A 55-year-old female with breast cancer, no past history of allergies	45Gy in 25# to WB, SCF and IMN, axilla with TBB 9Gy in 5#. At conclusion she had erythematous dermatitis	Trastuzumab (6mg/kg) every 3 weeks, 45 days after RT	Mild, erythematous RRD, noticed 9 days after fifth cycle (159 days post-RT)	Nil. Resolved completely in 7 days	Yes, same dose, without reappearance
4.	Alsabbak et al, 2013[14]	A 47-year-old female with breast cancer, history of allergies: NR	50 Gy in25# to CW and 14Gy in 7# boost to area of positive margins by 9 MeV electrons with 1 cm bolus. At conclusion she had erythematous dermatitis with a small area of desquamation	Trastuzumab (dose: NS) every 3 weeks, continued during RT	Mild, erythematous RRD 2 weeks after third cycle (56 days post-RT). RRD was most prominent in the area of boost	Benadryl and topical steroid. Complete resolution of RRD (duration: NS)	Yes, after 3 weeks. No reappearance

(*Continued*)

Table 1 (*Continued*)

Sr. No.	Author	Patient characteristics	Radiotherapy details	Triggering agent	Description of RRD	Treatment and outcome	Rechallenge
5.	Levy et al, 2013[13]	Age: NS, female with breast cancer, history of allergy: NR	50Gy in 25#, Site: NS	Trastuzumab (dose: NS), started 25 weeks after RT	Severity of RRD: NS, developed in 2 weeks after exposure (189 days post-RT)	NS	NS
6.	Lee et al, 2014[17]	A 55-year-old female with fibroadenoma of breast with axillary metastases, history of allergy: NR	50.4Gy in 20# to WB	Trastuzumab (dose: NS) every 3 weeks, started 10 days after RT	Mild, erythematous RRD and edematous plaques, developed 24 weeks after RT (168 days post-RT) along with radiation recall pneumonitis	Prednisolone, 30mg, Improvement in 2 weeks	NS
7.	Anupama et al 2018[19]	A 56-year-old female with breast cancer, past history of allergies: No	40 Gy/15# to CW and SCF, at conclusion: mild erythematous dermatitis	Trastuzumab (450mg) every 4 weeks, started 4 weeks after RT	Mild-to-moderate, painful, swollen and erythematous, maculopapular RRD with discoloration, next day of first cycle (29 days post-RT)	Topical betamethasone cream, erythema reduced in 2 days but pain persisted for 2 weeks	Yes, after 4 weeks, no reappearance

Abbreviations: CW: chest wall, IMN: internal mammary nodes, IV: intravenous, NR: not reported, NS: not specified, RRD: radiation recall dermatitis, RT: radiotherapy, SCF: supra-clavicular fossa, TBB: tumor bed boost, WB: whole breast, #: number of fractions

to reappearance of RRD.[1,2,6] However, for oncological benefit, continuation of offending agents with added protective measures and under careful surveillance even during reaction has also been reported and it may not worsen the reaction further.[1,2,6]

Hence, though the incidence of radiation recall is rare, its diagnosis is likely to be made more frequently in modern oncology practice and oncologists should be aware of this phenomenon. A robust systematic review with inclusion of all reported cases and case series to characterize this unpredictable clinical phenomenon will add immense knowledge for the management and prognosis of radiation recall and hence, it is highly recommended.

Conclusion

In the current multidisciplinary era of cancer management, oncologists should be aware of radiation recall phenomenon with trastuzumab so as to aid for a timely diagnosis and intervention. Moreover, until the exact pathophysiological mechanism and predictors radiation recall is understood, oncologists should report such cases encountered in their day-to-day practice.

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Conflict of Interest
None declared.

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References

1 Azria D, Magné N, Zouhair A, et al. Radiation recall: a well recognized but neglected phenomenon. Cancer Treat Rev 2005; 31(07):555–570
2 Burris HA III, Hurtig J. Radiation recall with anticancer agents. Oncologist 2010;15(11):1227–1237
3 Camidge R, Price A. Characterizing the phenomenon of radiation recall dermatitis. Radiother Oncol 2001;59(03):237–245http://www.ncbi.nlm.nih.gov/pubmed/11369064
4 D'Angio GJ, Farber S, Maddock CL. Potentiation of x-ray effects by actinomycin D. Radiology 1959;73(02):175–177
5 Bentzen SM, Agrawal RK, Aird EG, et al; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol 2008;9(04):331–341
6 Ben-Yosef H. Radiation recall dermatitis. Lancet 1996;348 (9037):1321http://www.ncbi.nlm.nih.gov/pubmed/8909413
7 Guarneri C, Guarneri B. Radiation recall dermatitis. CMAJ 2010; 182(03):E150–E150
8 Cho S, Breedlove JJ, Gunning ST. Radiation recall reaction induced by levofloxacin. J Drugs Dermatol 2008;7(01):64–67http://www.ncbi.nlm.nih.gov/pubmed/18246700
9 Jain S, Agarwal J, Laskar S, Gupta T, Shrivastava S. Radiation recall dermatitis with gatifloxacin: a review of literature. J Med Imaging Radiat Oncol 2008;52(02):191–193
10 Le Scodan R, Wyplosz B, Couchon S, Housset M, Laccourreye O. UV-light induced radiation recall dermatitis after a

chemoradiotherapy organ preservation protocol. Eur Arch Otorhinolaryngol 2007;264(09):1099–1102
11 Ng AWY, Wong FCS, Tung SYS K ONimesulide–a new trigger of radiation recall reaction. Clin Oncol (R Coll Radiol) 2007;19(05): 364–365
12 Marchand A, Georgin-Mège M, Cellier P, Martin L, Avenel-Audran M, Le Corre Y. Exemestane-induced radiation recall dermatitis and morbilliform rash. J Dermatol 2016;43(05):575–576
13 Levy A, Hollebecque A, Bourgier C, et al. Targeted therapy-induced radiation recall. Eur J Cancer 2013;49(07):1662–1668
14 Alsabbak H, Aljuboori Z, Spierer M, Klein P. The association of adjuvant trastuzumab (Herceptin) with radiation recall dermatitis: a case study. J Cancer Sci Ther 2013;05(12):. Doi: 10.4172/1948-5956.1000236
15 Moon D, Koo JS, Suh C-O, Yoon CY, Bae J, Lee S. Radiation recall dermatitis induced by trastuzumab. Breast Cancer 2016;23(01): 159–163
16 Shrimali RK, McPhail NJ, Correa PD, Fraser J, Rizwanullah M. Trastuzumab-induced radiation recall dermatitis–first reported case. Clin Oncol (R Coll Radiol) 2009;21(08):634–635
17 Lee HE, Jeong NJ, Lee Y, et al. Radiation recall dermatitis and pneumonitis induced by trastuzumab (Herceptin®). Int J Dermatol 2014;53(03):e159–e160http://www.ncbi.nlm.nih.gov/pubmed/24716200
18 Chung C, Stuart D, Keyes M. Radiation recall reaction induced by adjuvant trastuzumab (Herceptin). Case Rep Med 2009; 2009:307894. Doi: 10.1155/2009/307894
19 Anupama C, Vinayak V, Anuradha H, Maka V. Trastuzumab induced radiation recall dermatitis: an interesting case. Int J Basic Clin Pharmacol 2018;7(12):2465–2467
20 Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344(11): 783–792
21 Corbin KS, Breen WG, Strauss JB. Radiation dermatitis in patients treated with concurrent trastuzumab emtansine (T-DM1). Clin Transl Radiat Oncol 2020;24:99–101
22 Jeter MD, Jänne PA, Brooks S, et al. Gemcitabine-induced radiation recall. Int J Radiat Oncol Biol Phys 2002;53(02): 394–400
23 Smith KJ, Germain M, Skelton H. Histopathologic features seen with radiation recall or enhancement eruptions. J Cutan Med Surg 2002;6(06):535–540
24 Saif MW, Black G, Johnson M, Russo S, Diasio R. Radiation recall phenomenon secondary to capecitabine: possible role of thymidine phosphorylase. Cancer Chemother Pharmacol 2006;58(06): 771–775
25 Hird AE, Wilson J, Symons S, Sinclair E, Davis M, Chow E. Radiation recall dermatitis: case report and review of the literature. Curr Oncol 2008;15(01):53–62http://www.ncbi.nlm.nih.gov/pubmed/18317586
26 Khanna NR, Kumar DP, Laskar SG, Laskar S. Radiation dermatitis: an overview. Indian J Burns 2013;21(01):24. Doi: 10.4103/0971-653X.121877

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yogeshkembhavi1@gmail.com | +91 99675 94597