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

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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.

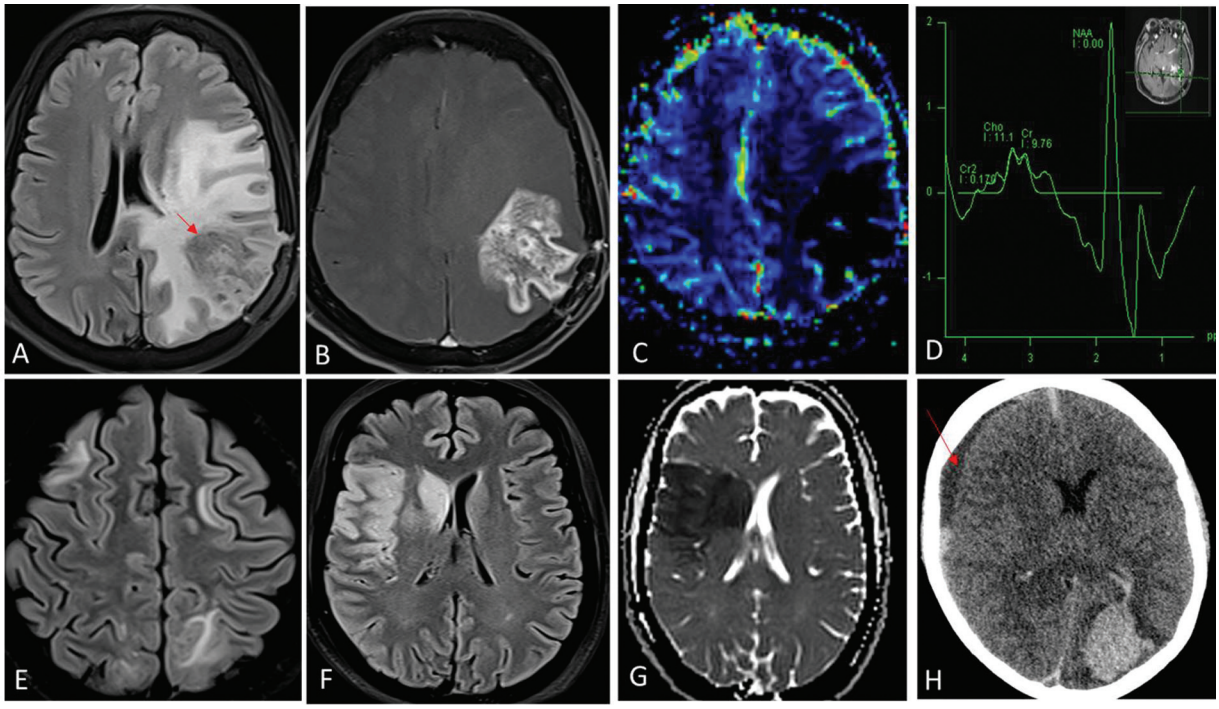

Fig. 1 Radiation necrosis (**A**–**D**). One-year postradiation and temozolomide therapy for left temporal lobe glioblastoma. Fluid-attenuated inversion recovery (FLAIR) shows intermediate-hypointense signal areas (red arrow in **A**) in the left parietal lobe with surrounding disproportionate white 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

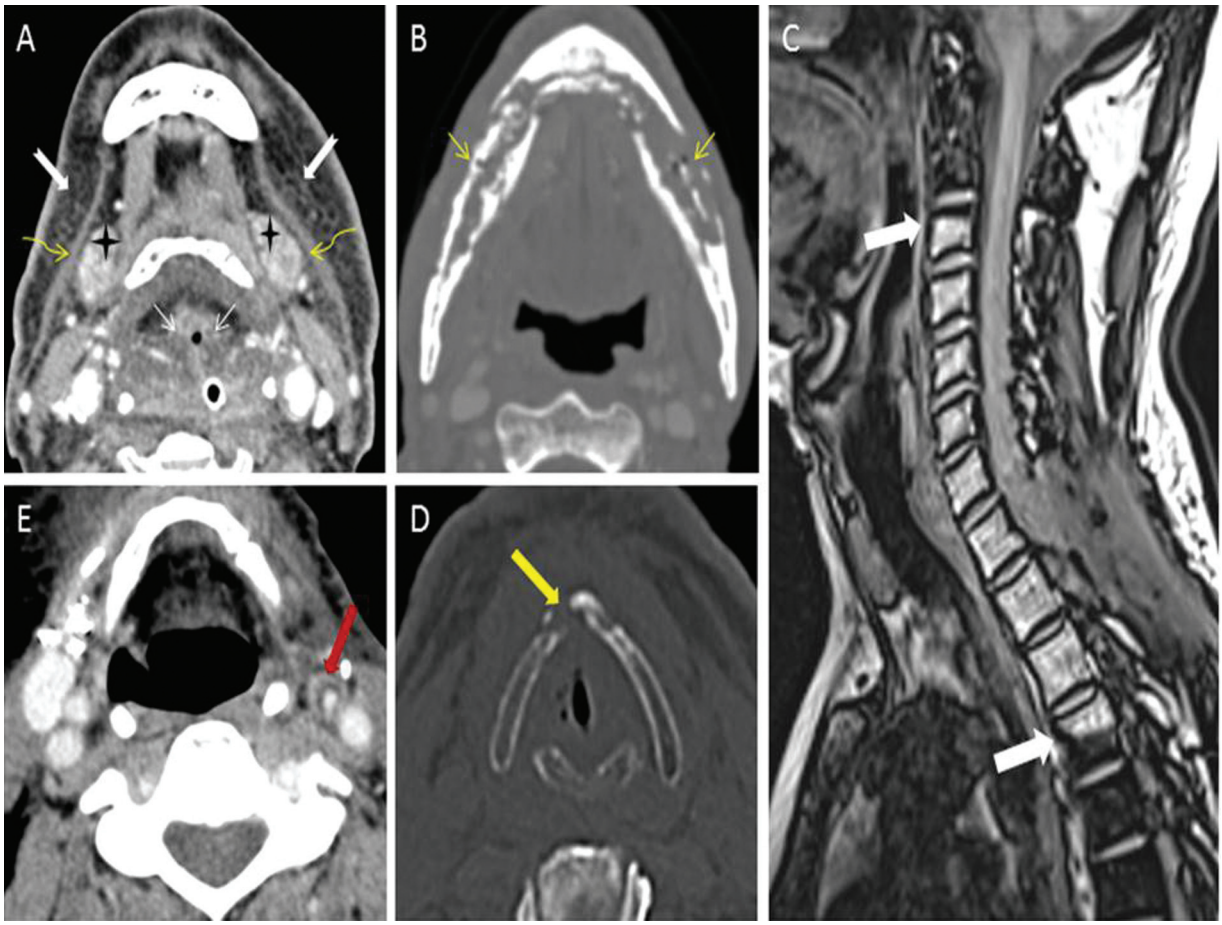

Fig. 2 (**A**) Expected radiotherapy (RT)-related soft tissue changes. Axial contrast-enhanced computed tomography (CT) image in soft tissue window shows diffuse bilateral symmetrical subcutaneous fat reticulations (notched white arrows), thickened bilateral platysma muscles (curved yellow arrows), increased 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.

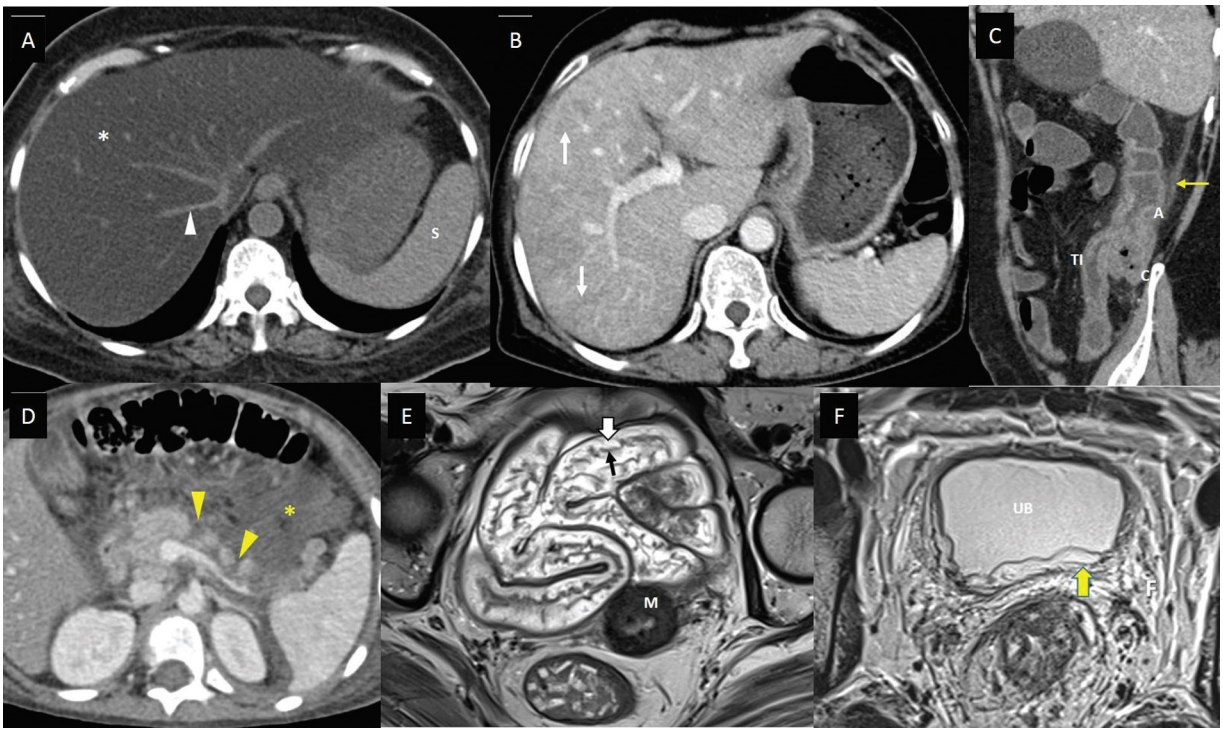

Fig. 3 Imaging features of abdominal complications of cancer therapy. (**A**) A 53-year-old suffering from acute lymphoblastic leukemia, on treatment with steroids and L-asparaginase, presented with mild abdominal pain and hyperbilirubinemia. Axial noncontrast computed tomography (CT) scan shows markedly 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 1 or 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.

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