Cancer Imaging (2006) **6,** S131–S139
DOI: 10.1102/1470-7330.2006.9095

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FOCUS ON: TREATMENT PLANNING

Wednesday 18 October 2006, 09:30–11:00

Radiation injury: imaging findings in the chest, abdomen and pelvis after therapeutic radiation

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Abstract

Radiation may be used as adjuvant or primary therapy in a variety of tumors in the chest, abdomen and pelvis. Therapeutic radiation affects not only malignant tumors but also surrounding normal tissues. The risk of injury depends on the size, number and frequency of radiation fractions, volume of irradiated tissue, duration of treatment, and method of radiation delivery. Concomitant chemotherapy can act synergistically to produce injury. Other predisposing factors include infection, prior surgery and chronic illness like hypertension, diabetes mellitus and atherosclerosis. Radiation changes vary, based on the target organ and the time from completion of therapy. While most serious complications related to radiotherapy are relatively uncommon, given the number of patients that are treated and the relatively long latency period for development of radiation changes, follow-up imaging studies frequently have findings that should be recognized as radiation related. Familiarity with the spectrum of imaging findings after radiation injury permits differentiation from other etiologies such as recurrent malignancy. The following will discuss imaging findings that may be seen during imaging surveillance in patients with malignancy affecting the chest, abdomen and pelvis.

Keywords: *Radiation injury; imaging; chest; abdomen; pelvis.*

Introduction

In the chest, the most common tumors that are treated with radiotherapy are cancers of the breast and lung. In patients with breast cancer, the combination of lumpectomy and radiation therapy as primary treatment has become more commonplace. The standard portal used to treat the primary tumor and associated nodes include the breast, ipsilateral axilla and supraclavicular region. Only the breast is treated when disease is limited. For lung cancer, the primary tumor and associated areas of nodal drainage are irradiated.

Abdominal and pelvic tumors that are typically treated with radiation therapy include lymphoma, gastro-esophageal, and pancreatic carcinoma as well as tumors of the gastrointestinal tract, gynecologic tract and genitourinary tract. Pelvic cancer treated with radiation alone at doses of 30–70 Gy or in conjunction with other therapies include colorectal, bladder, prostate and gynecologic malignancies. Cervical cancer is generally treated with definitive radiation therapy in cases in which the primary lesion is large or has spread beyond the cervix. Standard treatment usually includes external beam therapy as well as brachytherapy. These patients are generally young and with higher long term survival rates allowing the manifestation of radiation change to be observed on serial follow-up studies. Colorectal cancers are often treated with radiation and chemotherapy, before or after surgery as neoadjuvant or adjuvant therapy respectively. Doses of approximately 50 Gy are used to decrease the incidence of local recurrence after surgery. Radiation is also used frequently in patients with bladder cancer and men with prostate cancer.

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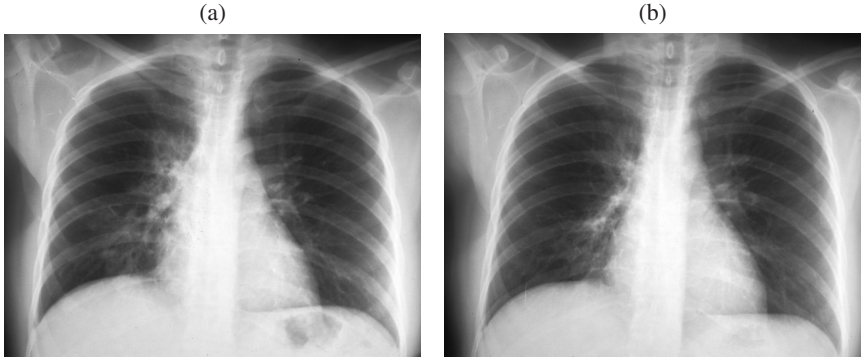


Figure 1 **A 44-year-old woman treated with radiation for right breast cancer. Chest radiographs obtained (a) 4 months and (b) 7 months after therapy, show radiation pneumonitis evolving to fibrosis.**

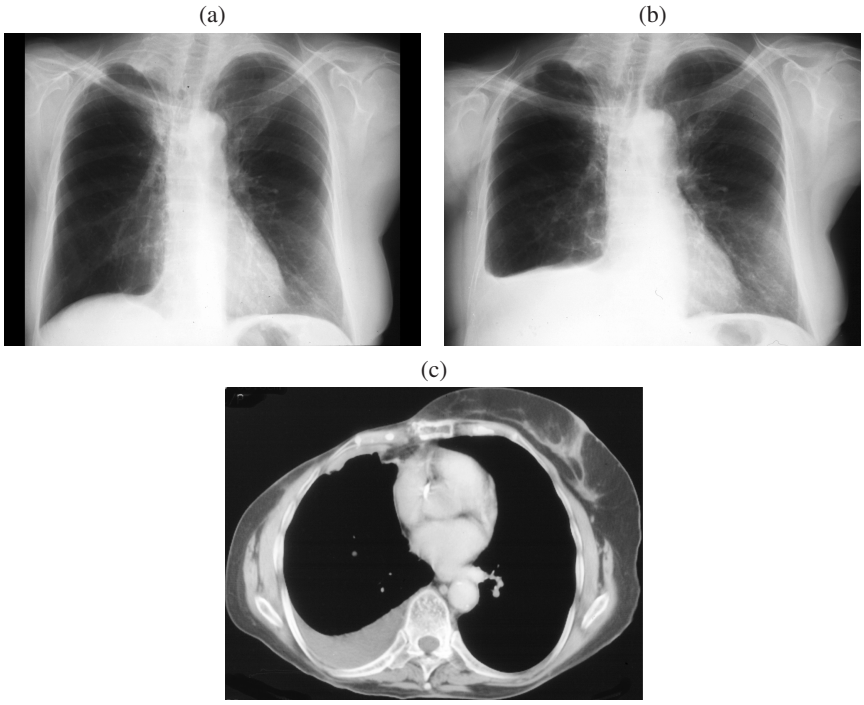


Figure 2 **A 74-year-old woman treated with radiotherapy for right breast cancer. Chest radiographs were obtained (a) 29 years and (b) 34 years after therapy was completed. CT of the chest (c) was also obtained. (b) shows development of pleural effusion and CT shows pleural thickening and an effusion that proved to be malignant mesothelioma at pleural biopsy.**

Lungs

Radiation pneumonitis and fibrosis are expected changes in the chest. Other more serious complications such as myocardial infarction, pericardial effusion, brachial plexus neuropathy, bone and soft tissue necrosis, fractures and radiation-induced malignancy may also occur[1].

Radiation induced pneumonitis typically develops approximately 6–8 weeks after treatment with doses of 30–40 Gy and is a well known early expected effect of therapy that is related to total dose and fractionation[2]. Radiation pneumonitis is most extensive 3–4 months following the end of therapy and eventually becomes radiation fibrosis (Fig. 1). Fibrosis becomes a stable finding approximately 9–12 months after therapy[3]. If changes occur after that time period, superimposed infection or recurrent tumor should be considered[3]. Concomitant chemotherapy especially with drugs that have known direct pulmonary toxicity such as bleomycin further potentiates the effects of radiotherapy. Other radiation enhancing drugs include actinomycin D, adriamycin, cyclophosphamide, mitomycin C and vincristine[4].

Radiation injury to the lungs does not follow anatomic boundaries. It has sharp, well defined areas of air space consolidation with borders that conform to the radiation portals. Less extensive radiation pneumonitis may present as patchy consolidation in the irradiated field

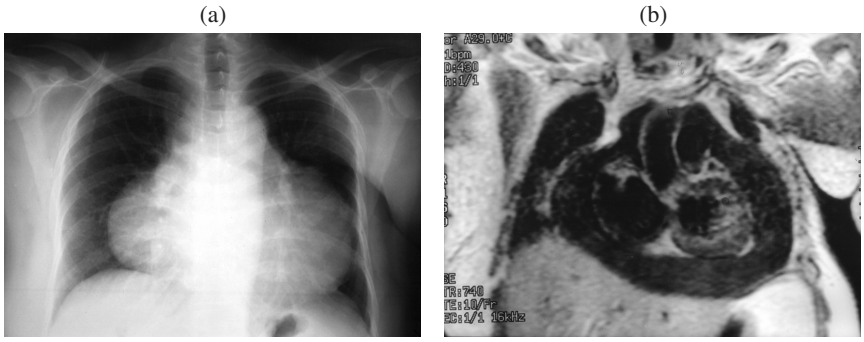


Figure 3 **A 49-year-old woman treated for right breast cancer 4 weeks earlier with radical mastectomy and approximately 50 Gy to the chest wall over 3 weeks. (a) Frontal chest radiograph shows enlargement of cardiac silhouette. (b) Cardiac MRI shows large pericardial effusion.**

and when the damage is very early or minimal in extent, manifests as indistinctness of the pulmonary vasculature. Radiation fibrosis is generally seen in all patients who received therapeutic doses of radiation. Volume loss is typical. Bronchiectatic changes may also be seen. Less obvious changes include minimal pleural thickening, slight elevation of the hila or minor fissure, slight medial retraction of pulmonary vessels, minimal tenting of elevation of a hemidiaphragm and minor blunting of cardiophrenic angles. Computed tomography (CT) demonstrates radiation injury earlier than conventional radiographs because of its greater sensitivity to minimal differences in radiographic density[5,6]. On CT, radiation change can appear as homogeneous consolidation, patchy consolidation, discrete consolidation or solid consolidation[5]. Homogeneous consolidation appears as ground glass opacity on thin section CT and occurs within 2–3 weeks of therapy. Patchy consolidation is analogous to the findings on conventional radiographs. Discrete consolidation is well demarcated but non-uniform with traction changes that likely represent fibrosis. Solid consolidation is seen at doses higher than 50 Gy and is more uniform with volume loss and bronchiectatic change. Conventional radiotherapy delivers higher doses to the surrounding tissues because of radiation attenuation. Three-dimensional conformal therapy is used to limit the amount of injury to the lung and surrounding tissues by using multiple smaller beams aimed at the tumor. This type of therapy results in injury that has different patterns: mass-like, modified conventional and scar-like[6]. Recurrent disease should be suspected in irradiated lung if there is alteration in the stable contours of radiation fibrosis, failure of contracture of an area of radiation pneumonitis or filling in of ectactic bronchi[7].

Other findings after radiotherapy include hyperlucency of the irradiated lung, spontaneous pneumothorax, pleural effusions and calcification of lymph nodes. Pleural effusions are frequently seen on CT within 6 months of therapy and are typically small, resolving spontaneously[8]. Cytologic evaluation may be necessary to exclude malignancy particularly in rapidly accumulating collections (Fig. 2).

Heart

Radiation injury to the heart can manifest in many different ways. Therapeutic radiation can cause damage to the pericardium, myocardium and vasculature of the heart. The incidence of pericardial disease is related to the dose, fraction size, volume irradiated and technique. At doses below 40 Gy, the incidence is low ranging between 2 and 6%[9,10]. Moderate sized mediastinal fields have a 1% incidence of pericardial disease that rises to 17% when the fields are larger with treatment of extensive disease[10]. Radiation pericarditis generally presents 6–9 months after therapy and the majority of cases occur within 12–18 months of therapy[11]. Both pericardial effusions and pericardial fibrosis are known to occur. Pericardial effusions can be small and incidental findings or large enough to require intervention (Fig. 3). Eccentric effusions may occur likely due to adhesions of the treated pericardium[12]. Fibrosis of the myocardium can also occur and is aggravated by the use of cardiotoxic chemotherapy with agents such as doxorubicin[13]. The incidence of myocardial infarction is higher in patients treated for left breast carcinoma than in patients treated for right breast carcinoma as would be expected with the portals used[2].

Nerves

Nerves are typically quite radio-resistant and the incidence of neural damage after irradiation is directly related to the dose. The concomitant use of chemotherapy also increases the incidence of brachial plexus neuropathy. Signs and symptoms develop approximately 10 months after therapy and may range from mild and self-limiting to severe and debilitating[14]. The brachial plexus is best seen with magnetic resonance imaging. The changes seen on MRI are decreased signal intensity of the fat in the

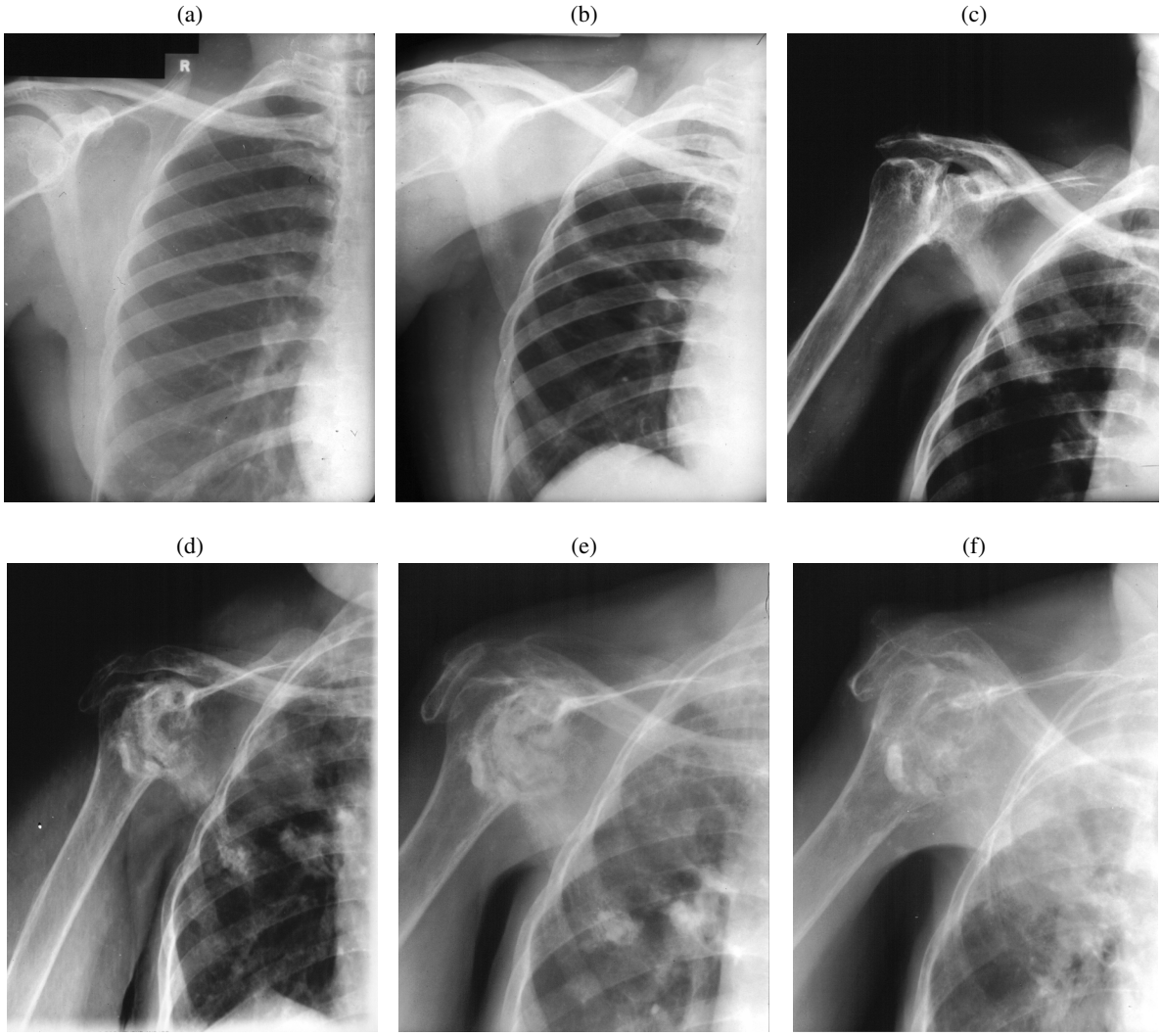


Figure 4 **A woman treated with radiotherapy for right breast cancer. Serial radiographs of the right upper chest and shoulder obtained at (a) baseline, (b) 5years, (c) 10 years, (d) 15 years, (e) 20 years, and finally (f) 35 years after therapy. There is gradual development of multiple rib fractures with abnormal healing and a neuropathic shoulder due to neurologic injury.**

axilla and supraclavicular regions most likely related to fibrosis which results in loss of clarity and distortion of the neurovascular bundle[15]. Severe injury of the brachial plexus results in motor and sensory deficits in the upper extremity causing a flail arm or neuropathic changes in the shoulder (Fig. 4). Radiation injury to the lumbosacral plexus is not common and is only seen with doses higher than 70 Gy in the pelvis[16].

Bones and soft tissues

In children, the spine may be irradiated for Wilm's tumor, neuroblastoma, Hodgkin lymphoma and acute lymphocytic leukemia with central nervous system relapse. This often results in inhibition of vertebral growth and short stature, as well as kyphoscoliosis with asymmetric irradiation. Osteitis and secondary fractures may also be observed. In adults, the spine is usually irradiated for metastatic disease. Acutely, edema and necrosis of the marrow results in increased T2-signal intensity within days[17]. Conversion to fatty marrow results in T1-hyperintensity, occurring as early as 2 weeks post therapy and completed by 6–8 weeks in 90% of patients (Fig. 5)[17].

Changes in bone after radiotherapy follow a characteristic pattern. The first conventional radiographic sign of change is demineralization and osteopenia which develops approximately 12 months after therapy is completed and may be progressive. Small lytic areas in irradiated bone may be seen and may be difficult to distinguish from metastatic disease. Spontaneous fractures, aseptic necrosis and bony resorption may also occur within the radiation field[18]. For diseases of the chest, these changes typically encompass the ribs,

clavicle and shoulder. The incidence of rib fracture after radiation therapy is approximately 1.8% and the rate of fractures is related to the radiation dose with doses greater than 50 Gy resulting in a higher incidence[18]. The addition of chemotherapy to the treatment regimen may result in an increased rate of rib fractures. More than one rib is generally involved and nonunion of fractures is not unusual (Fig. 4). Callus formation may have an atypical appearance that may simulate radiation induced sarcoma. In the pelvis, insufficiency fractures of the vertebral bodies, sacrum, and pubis can occur[19,20]. It is important to recognize the linear, low signal intensity fracture line on MRI since surrounding bone marrow edema may simulate marrow replacing tumor. In the past when ortho-voltage treatment was widely used, femoral neck fractures were more common[21]. Avascular necrosis of the hips is also a known complication of radiotherapy.

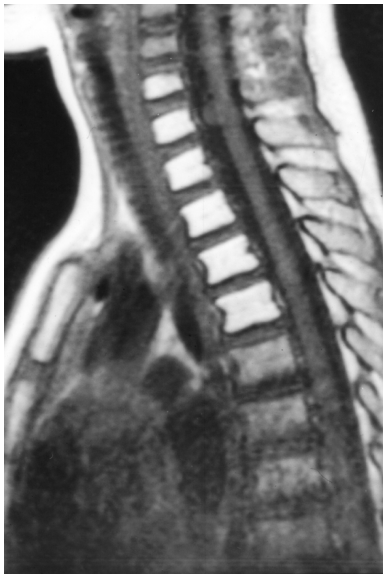


Figure 5 **Sagittal T1 weighted MRI shows fatty marrow replacement of the cervical thoracic spine from prior radiation.**

Ionizing radiation is known to be carcinogenic. An increased risk for the development of lung cancer in patients irradiated for breast carcinoma has been described, particularly in smokers[22]. Radiation-induced mesothelioma has also been described[23]. Skin changes such as atrophic ulceration and severe tissue necrosis requiring surgical resection is rare with a previously reported incidence of less than 0.5%[1]. Skin changes such as benign ulceration with or without superimposed infection can be difficult to distinguish from radiation induced soft tissue sarcoma by imaging. The incidence of sarcomas after radiotherapy is reported to be about 0.1% and the sarcomas usually occur 10 or more years after therapy[1,18,24]. Radiation induced sarcomas usually occur around the shoulder and pelvis in women because of the more frequent use of radiotherapy for breast and gynecologic cancers and the better long term survival of these patients. Radiation induced soft tissue sarcoma and sarcoma of bone may occur. Malignant fibrous histiocytoma is the most frequent histology of soft tissue sarcomas. Osteosarcoma is the histologic diagnosis that has been described most often with bony sarcomas[25–30]. The most common imaging findings are a new soft tissue mass and bony destruction. Bony destruction is seen on cross sectional imaging and production of osteoid matrix may be observed (Fig. 6). Although imaging findings are not specific, appreciation of the long latency period after radiation therapy may help suggest the diagnosis. Histologic proof of suspected malignant lesions should be obtained because the differential diagnosis would include metastases, infection and severe benign changes.

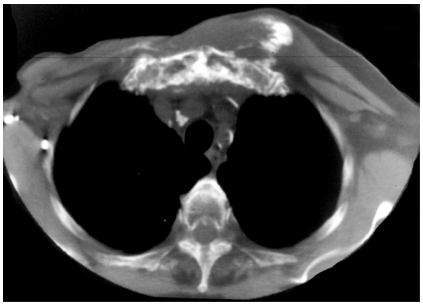


Figure 6 **An 80-year-old woman treated with radiotherapy for breast carcinoma 12 years earlier. Chest CT shows a soft tissue mass and sternal destruction with osteoid matrix that was proven to be radiation induced osteosarcoma.**

Liver, spleen and pancreas

The liver is usually included during radiation treatment to the stomach, pancreas or thoracolumbar spine. The tolerance of the whole liver is 30–35 Gy in conventional fractionation, but parts of liver can be treated with doses in excess of 70 Gy with three-dimensional radiotherapy treatment planning[31]. Radiation-induced liver disease (RILD), or radiation hepatitis, is a clinical syndrome of anicteric ascites and hepatomegaly occurring 2 weeks to 4 months after hepatic irradiation, because of venoocclusive disease[31]. The irradiated liver appears hypodense on non-contrast CT scans (Fig. 7). This CT finding can also be seen in patients who receive more than 45 Gy to a portion of the liver, regardless of whether they develop RILD. Patients are usually asymptomatic if the non-irradiated liver is healthy. The irradiated liver is hypodense with well-defined linear margins that conform to radiation portals (Fig. 8). In a fatty liver, the CT density pattern may be reversed. The irradiated area can enhance more than adjacent liver, because of increased arterial flow or delayed clearance of contrast from radiation-induced venoocclusive disease. On MR images, increased water within the irradiated liver causes T1-hypointensity and T2-hyperintensity[32].

The spleen may be irradiated to treat lymphoma, splenomegaly or hypersplenism. It is very radiosensitive

and lymphoid tissues are destroyed within hours after a dose of 4–8 Gy[33,34]. At doses of 35–40 Gy, splenic fibrosis and atrophy may result (Fig. 8). The effects of splenic irradiation are usually not clinically significant, although functional hyposplenism and fulminant pneumococcal sepsis can occur. Irradiation to the pancreas causes necrosis and fibrosis similar to chronic pancreatitis. The pancreatic acinar epithelium is more sensitive than the islet cells and the imaging features are also similar to pancreatitis[33]. Pancreatic atrophy is eventually seen (Fig. 8).

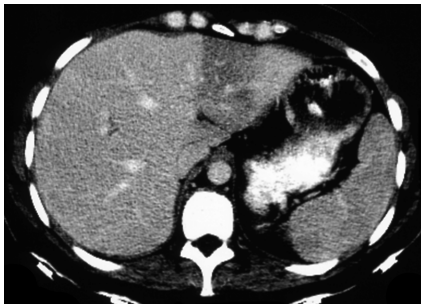


Figure 7 **CT of the abdomen shows well demarcated band of low attenuation of the left lobe of the liver after radiation to the spine for metastatic breast cancer.**

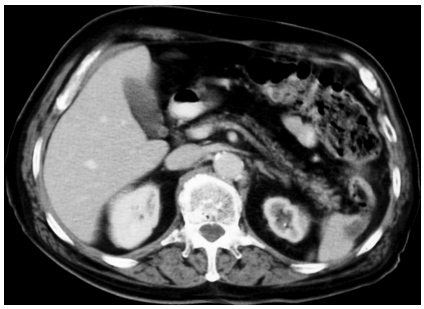


Figure 8 **CT of the abdomen shows atrophy of the spleen, pancreas and left kidney after radiation therapy 3 years earlier for gastric lymphoma.**

Kidneys and ureters

The kidney is radiosensitive and 28 Gy to both kidneys in 5 weeks or less frequently leads to renal failure[35]. A dose of 17 Gy in 5 weeks or more is better tolerated without pre-existing renal impairment. The risk of renal impairment increases with prior or concurrent chemotherapy[35]. In acute radiation nephritis, the kidney remains normal in size and shape, although glomerular damage is present histologically. Radiological changes appear months to years after treatment, ultimately resulting in atrophic poorly functioning but non-obstructed kidneys with smooth outlines (Fig. 8). Compensatory hypertrophy of the non-irradiated contralateral kidney can develop. If only a portion of the kidney is irradiated, only that portion is affected. Malignant hypertension may develop 1–10 years after renal irradiation due to renin overproduction, requiring nephrectomy relief[35].

The overall incidence of urologic complications after pelvic irradiation is reported to be approximately 21%, however, only 2.5% of such complications could be ascribed to the effects of radiation alone, since surgery and chemotherapy may have additive effects[36]. The incidence of radiation cystitis is reported to range from 3 to 12% depending on the dose to the bladder. The ureter is fairly radioresistant and radiation induced strictures are infrequent[35]. Ureteral injury, however, may not become apparent for many years after therapy. The risk of ureteral stenosis in cervical cancer is 1% at 5 years, 1.2% at 10 years, 2.2% at 10 years, and 2.5% at 20 years[37]. Continued surveillance of renal function in these patients is therefore necessary.

The prostate and seminal vesicles typically become atrophic after treatment. The peripheral zone of the prostate loses its normal T2 hyperintensity and becomes uniformly low signal on T2 weighted images[38]. Urethral strictures can occur in males in the prostatic and membranous portion of the urethra particularly after transurethral resection of the prostate[39]. In female patients, uterine atrophy can be seen in pre-menopausal women who receive therapeutic doses of radiation. T2 weighted images also show loss of zonal anatomy with uniformly low signal of the myometrium[40]. Cervical stenosis occurs rarely and can result in distension of the endometrial cavity with retained secretions. The ovaries also become atrophic and fibrotic with loss of follicular cysts.

Gastrointestinal system

While the majority of the gastrointestinal tract lies outside of the radiation fields used to treat malignancy in the chest, the esophagus may be injured and radiation-induced injury to the esophagus may be a limiting factor in therapy of thoracic neoplasms. Esophageal injury typically occurs at doses higher than 45 Gy[41]. Esophageal dysmotility is the earliest and most common finding. Mucosal changes such as edema, ulceration and fistula formation may also occur. These findings can be expected 4–12 weeks after completion of therapy. Esophageal strictures typically occur 4–8 months after therapy and usually have smooth, tapered margins. Radiation induced esophageal carcinoma is rare but has been described as occurring about 14 years after therapy is completed[42].

The stomach and duodenum may be injured after therapy to retroperitoneal structures such as the pancreas or lymphadenopathy. Radiographic findings include prepyloric and pyloric ulcers with deformity. These ulcers cannot be distinguished from benign peptic ulceration except that they may not heal. Fixed narrowing, deformity and an aperistaltic antropyloric region without ulceration

can also occur[43]. On CT, non-specific gastric wall thickening is observed, occasionally with perigastric stranding.

The small intestine is quite radiosensitive and is potentially in the treatment field for all intra-abdominal, retroperitoneal and pelvic tumors. Rapidly proliferating cells such as those in the mucosa of the small intestine are most radiosensitive and therefore at highest risk for acute injury which occurs within weeks of therapy and is rarely evaluated radiographically. The terminal ileum is more commonly injured, because it is more fixed. Acutely, small bowel dilation with edema and mucosal sloughing can occur and usually resolves[43]. The changes in the vascular and interstitial connective tissues are more insidious and the initial injury leads to progressive ischemia of the intestinal wall. Chronic bowel injury is caused by submucosal obliterative vasculitis that results in further ischemia and fibrosis[43]. Fibrotic strictures may cause small bowel obstruction. Complex fistulae are late features. Similar findings occur in the colon. Submucosal edema and fibrosis are seen at barium examinations as thickening and straightening of small-bowel folds and separation of adjacent loops. CT can directly reveal bowel wall thickening related to submucosal edema. Fluoroscopic evaluation may show single or multiple areas of stenosis and small-bowel obstruction (Fig. 9). Altered peristalsis may also be encountered. Late changes of mesenteric fibrosis result in fixation of small bowel loops with tethering, sometimes elicited only by careful spot compression during fluoroscopy. CT findings reflect fluoroscopic findings and can exclude tumor recurrence as the cause. CT is also useful in identifying extra-luminal air or contrast in fistulae and can show increased density in the mesentery.

The overall incidence of chronic radiation injury to the bowel after radiotherapy to the pelvis is about 1%–5%[43]. The most important risk factor for injury to the gastrointestinal tract is the dose of radiation given. A study of patients with prostate cancer showed that doses of more than 70 Gy raised the likelihood of rectal bleeding after therapy[44]. Radiation damage to the colon can be shown radiographically as loss of distensibility with strictures of various lengths and degrees of narrowing. Widening of the pre-sacral space may also be seen. Barium studies may show mucosal changes such as ulceration, pseudo-polypoid protrusions or contour irregularities ranging from tiny serrations to ragged margins and even circumferential lesions simulating malignancy. The possibility of radiation induced colon cancer has also been suggested[43]. The rectum is relatively radioresistant but is frequently injured because of its fixed location near organs in the pelvis that are frequently targeted for radiotherapy. The use of large-volume balloon catheters should be avoided because of the risk of perforation in patients with radiation proctitis.

Vascular injury

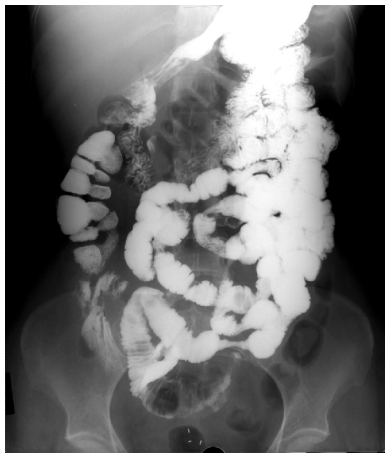
Radiation injury differs in small and large vessels. The endothelial lining of the microvasculature is the most radiosensitive portion of the vasculature and severe damage results in intracellular edema with resultant vascular occlusion[45]. Less severe damage results in telangiectasia. Arteriolar damage is frequent, and consists of myointimal proliferation indistinguishable from atherosclerosis[45]. Acute lymphocytic vasculitis affecting the media, intima and adventitia of medium sized vessels is also observed. In medium and large arteries, atheromas and fibrosis are observed less often, resulting in stenosis. Rupture of irradiated large vessels occurs mostly in the carotid arteries and less frequently in the aorta and femoral arteries[45].

Conclusion

The field of radiation oncology has evolved with advent of new techniques such as intensity modulated radiation therapy (IMRT) that may reduce the side effects of radiation on normal tissues. Compared to conventional radiation where multiple large beams pass through the body conforming to the target that needs to be treated, IMRT allows beams to be broken up into thousands of tiny pencil-thin radiation beams, each with a different intensity that enters the body from many more angles. The combined effect is to produce a high-dose volume with a sharp-dose gradient at its boundaries that can be designed into complex three-dimensional shapes, therefore complex irregular clinical target volumes can be irradiated while sparing adjacent normal tissues. Studies have shown a decrease in both acute and late bowel toxicity in patients treated to the pelvis[46]. In patients treated for prostrate cancers less rectal dose has been documented with IMRT with improved outcome[47]. However, there are potential risks to IMRT as well. One of the major risks is that the high degree of conformation with IMRT may lead to geographic misses of disease and recurrences especially for disease sites where positioning and motion play a large role or where there are significant changes in anatomy and biology during the course of radiation therapy. The consequences of a large volume of normal tissues receiving low dose radiation may increase the incidence of secondary malignancies outside the treatment fields. Some studies have suggested that IMRT may almost double the incidence of second malignancies from about 1% after conventional radiation therapy to 1.75% after IMRT for patients surviving 10 years[48]. Therefore, some institutions are evaluating the use of Proton therapy in the treatment of cancers. The physical properties of proton beams offer further improvements in dose localization over photons (X-rays) and reduce the risk of second malignancies. Protons give very low radiation dose to normal tissues while depositing high-energy radiation at carefully targeted tumors. As protons

enter the body, they deposit a minimal amount of energy to the skin or tissues between the skin and the target volume. Most of the energy is deposited in the target volume with only minimal dose passing beyond the target to normal tissues. Proton beams have been shown to give less dose bladder, rectum and bone marrow in patients with prostrate cancer[49]. They have no exit dose, which should definitely lead to decrease in secondary malignancies from radiation treatment especially in pediatric patients. This novel treatment is being further investigated at this time.

(a)



(b)

Figure 9 **A 31-year-old female treated for Ib cervical cancer 2 years earlier with 40 Gy whole pelvis and intracavitary radiation. (a) Small bowel follow-through and (b) compression spot image show narrowing and tethering of small bowel loops in the pelvis.**

In summary the use of radiation to treat primary and metastatic tumors results in damage to normal tissue that is often evident on imaging studies. Treatment techniques have continued to evolve dramatically and techniques such as IMRT and proton therapy are specifically designed to decrease dose and injury to tissues surrounding malignant tumors. However some patients treated with definitive radiation therapy over the past several decades continue to survive and present for surveillance. Evaluation of imaging studies in these patients requires an understanding of the expected changes post therapy.

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