6. RADIATION COMPLICATIONS OF THE PELVIS

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INTRODUCTION

Radiation is used with or without chemotherapy to treat malignancies in the pelvis that occur in gynecologic, genitourinary, and gastrointestinal organs. One of the most sensitive organs in the pelvis can be the small bowel which is discussed in a separate chapter (upper GI). Radiation can cause functional effects on other organs including the rectum, anus, bone and bone marrow, bladder, urethra, ureter, vulva, vagina, uterus, ovaries, testicles, and sexual organs. This chapter will discuss the pathologic and clinical effects that can result during treatment and shortly thereafter. Long-term sequelae can be seen at variable intervals following radiation. Prevention and management issues will be discussed.

A. COMPLICATIONS RELATED TO GI EFFECTS

A1. Rectum

Pathogenesis

The mucosa of the large intestine is composed of a single layer of epithelial cells which rest upon a basement membrane that lies on the lamina propria. These epithelial cells are predominantly mucin-producing goblet cells, with interspersed absorptive cells. Their undifferentiated progenitor cells, located in the bases of the crypts of Lieberkuhn, have a turnover rate of 4–8 days. Both the rates of regeneration and maturation of these cells and the rate of repair of non-lethally injured cells determine the tolerance dose for radiation treatment.[1,2]

Early injury at the cellular level is characterized by mucosal cell loss, acute inflammation, eosinophilic crypt abscesses, and endothelial swelling in the arterioles can be seen following radiation to the rectum.[3] A thickened and edematous lamina propria with patchy fibroblastic proliferation and decreased mitotic rate within the mucosa are seen.[4] At doses of 10 Gy mucosal production is decreased and mitosis of the crypt cells is decreased.[3] At 50 Gy doses (administered in 20 fractions over 1 month) in addition to mucosal cell injury and crypt shortening, infiltration of inflammatory cells occurs,[5] accompanied by the accumulation of eosinophils and the degranulation of mast cells. The pathogenesis of the early lesions depends on injury to the mucosal cells, enhanced by ischemia due to endothelial cell injury and fibrin–platelet thrombi accumulation. Cytokines secreted by the endothelial cells such as tumor necrosis factor α and transforming growth factor β contribute significantly to the development of the early injury.[6] For example, tumor necrosis factor α contributes to repression of thrombomodulin which is usually induced by irradiation; this leads to an increase of thrombin which in turn activates such injurious pathways as the activation of proteases, fibrin deposition, etc. Recently, it was found in an experimental mouse model that radiation-induced crypt damage can be minimized by avoidance of endothelial cell apoptosis either by basic fibroblast growth factor (bFGF) administration or by deletion of the sphingomyelinase gene.[7] Expression and activity of the tumor suppressor gene p53 are also of major importance in preventing mitotic catastrophe in irradiated epithelial cells,[8] while over-expression of the transcription factor NF-κB may also serve a radioprotective role.

The development of delayed tissue injury starts to be apparent as early as at 6 months posttreatment and may gradually worsen. This delayed colorectal injury is a result of lesions in the slowly responding cells of connective tissues and blood vessels.[6] The pathogenesis of the delayed injury is a result of the development of fibrosis in the stroma and in the blood vessels, causing ischemia. On the other hand, there is a belief that fibrosis may be initially caused by ischemia due to vascular deficiency,[9] or, alternatively, by fibroblast dysfunction.[10] Fibrogenic induction by cytokines mentioned above in regard to early injury can result in protracted and/or irreversible gene expression changes (e.g., thrombomodulin expression can be repressed for years posttreatment) and tissue remodeling—fibrin deposition and collagen accumulation. Therefore, late changes include subsequent fibrosis of connective tissue and endarteritis of the arterioles.[11] This fibrosis can lead to relative ischemia, and mucosal capillaries that attempt to compensate for this develop telangiectasia with friable vessels that are prone to bleeding.[12] More severe ischemia can lead to ulceration, perforation fistula, or abscess formation.

Clinical Aspects

Radiation fields may include the entire rectum as when treating patients with external beam for adjuvant radiation following resection of rectal cancer. Treatment may also include a combination of external radiation and brachytherapy resulting in high doses of radiation to a more localized area as when treating for intact cervical cancer. The last decade has seen increasing interest in limiting the volume of rectum exposed to radiation,

particularly when treating for non-rectal cancers, as when treating with conformal beams shaped around the prostate or with prostate brachytherapy alone. Common observations among all these treatments have included the correlation of higher doses and increased volumes of rectum being directly proportional to chronic complications.

Acute symptoms of the rectum can be seen early in the course of radiation therapy for cancers in the pelvic region. Symptoms usually begin following 20 Gy of standard fractionation. Early symptoms may include tenesmus, bleeding, and diarrhea. One report that documented acute rectal symptoms demonstrated acute grade 2 rectal complications in 18% of prostate cancer patients at a mean dose of 38 Gy. Patients without diarrhea had a mean rectal volume receiving a dose of at least 70 Gy–8.5 cm^3. Patients with grade 2 diarrhea had a volume of 16.5 cm^3.[13] Although radiobiological doctrine has been that acute symptoms are caused by an unrelated mechanism to late symptoms, other authors have suggested that late complications may be related to the development of acute complications.[14] O'Brien et al. found that the presence of acute proctitis was the only factor to predict any of the late rectal symptoms of urgency, frequency, and diarrhea.[15]

Late pathological changes result in rectal tissue ischemia, leading to mucosal friability, bleeding, ulcers, strictures, and fistulae. Patients typically present with painless rectal bleeding. Other symptoms include evacuation difficulties, frequent elimination, fecal incontinence, and urgency which may also develop from alterations in anorectal function as discussed in the section on anal complications. At sigmoidoscopy, a spectrum of mucosal changes can be seen including mucosal pallor or erythema, prominent telangiectasia, friability, or fistulae.[16] The onset of radiation proctitis is typically 12–18 months following treatment. Patient-related factors that may increase the risk of proctitis include hypertension, diabetes, and cerebrovascular disease that can all affect the vascular supply in the radiated field.

A recent report correlated the dose–volume histograms (DVH) of the rectum to the probability of rectal bleeding following radiation in a group of men treated with either conventional or conformal radiation for prostate cancer.[17] The analysis of relative DVH of the rectal wall (with and without the anal region) showed a significant ($P < 0.01$) relationship between the irradiated volume and the probability of rectal blood loss within 3 years for dose levels between 25 and 60 Gy. Similarly, another report showed that the average percent volume DVH for the rectal wall of patients with bleeding was significantly higher than those of patients without bleeding[18] (Figures 1 and 2). One report compared a group of men treated with MRI-guided brachytherapy alone or with supplemental external beam radiation.[19] The addition of external beam radiation increased the incidence of grade 3 rectal bleeding from 8% to 30% ($P = 0.0001$).

Treatment for cervical cancer includes EBRT with brachytherapy. A rectal point is chosen for dose calculations based on ICRU guidelines.[20] Cumulative dose to this rectal point of >75 Gy with low dose rate brachytherapy using tandem and ovoids has been demonstrated to increase the risk of serious late rectal sequelae.[21] There did not seem to be a dose threshold for less severe complications. Patients treated with cylinders or line

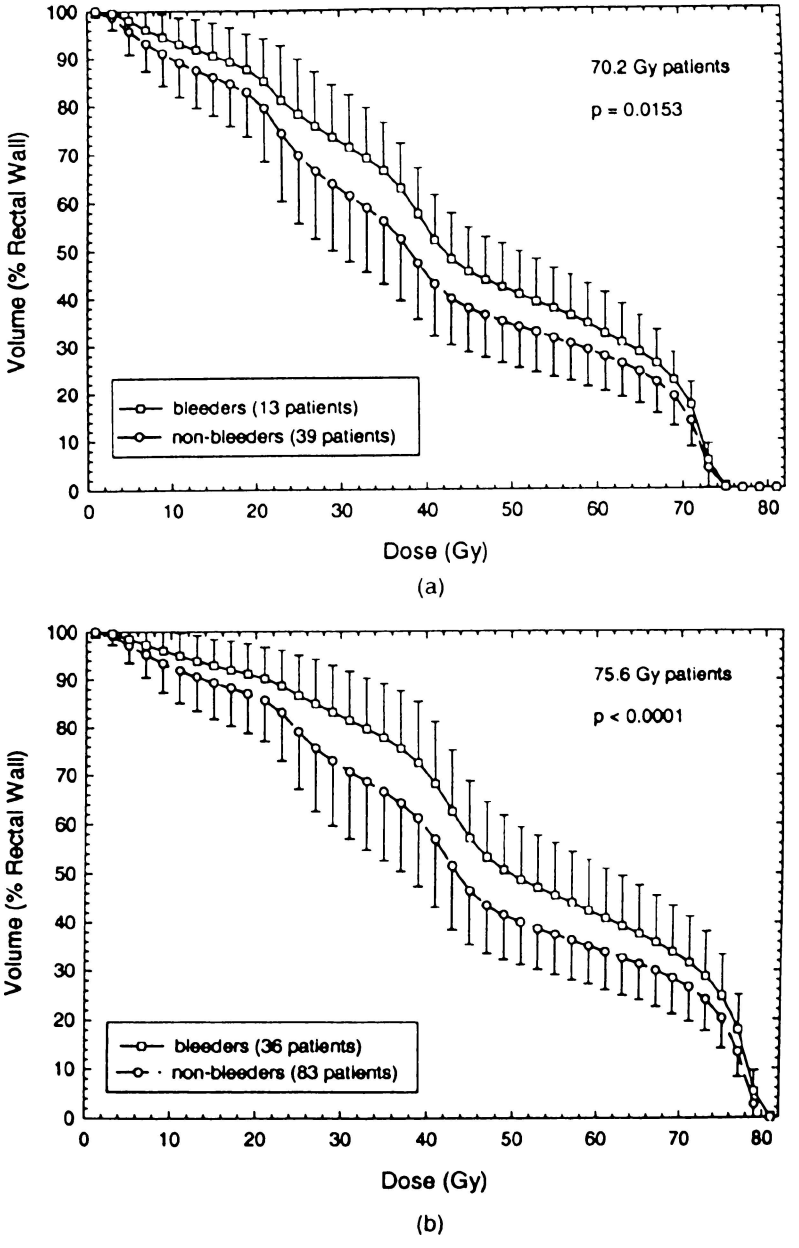
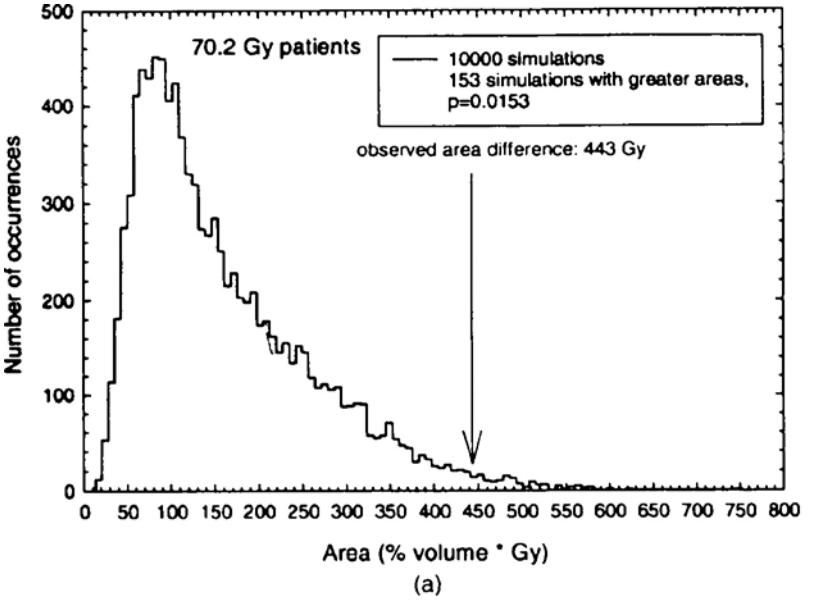


Figure 1. These two figures represent the average percent volume DVHs for patients with and without bleeding. The solid curves with squares show the results for patients with bleeding, the dashed curves with circles show the results for patients without bleeding. Reproduced with permission from Elsevier.[18]



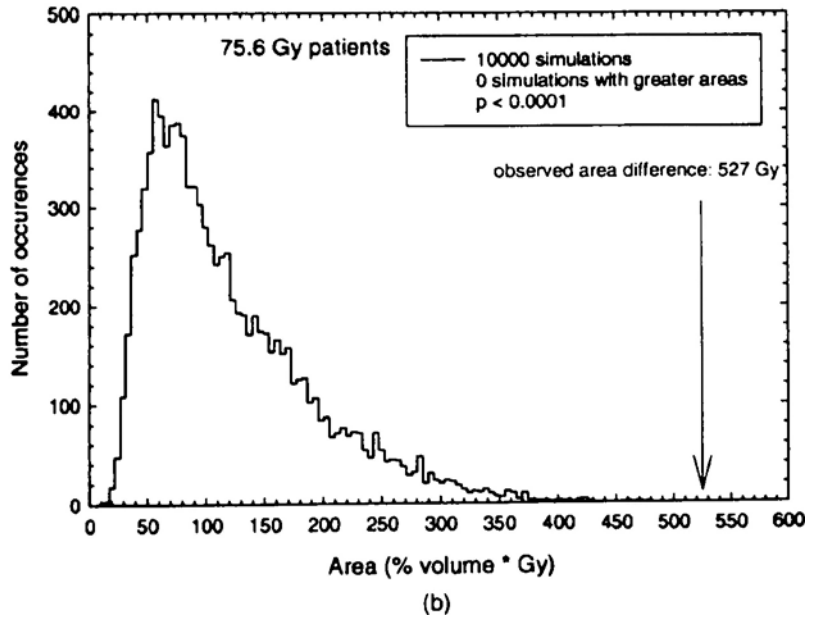


Figure 2. The distributions of the 10,000 simulated differences in area between the average histograms for bleeding and non-bleeding patients with simulated outcomes. The vertical arrows show the observed values of the area differences in the data.[18]

sources that would treat a larger volume of rectum had an increased risk of moderate to severe sequelae.[21] Typically, cumulative doses to the ICRU rectal point are limited to 65–70 Gy from tandem and ovoids. There is no indication that concurrent chemotherapy increases the risk of late rectal complications. Following treatment for cervix cancer with chemotherapy and radiation or radiation alone, grades 3–5 rectal complications occurred in 9% of patients in both the groups.[22] High dose rate brachytherapy requires careful fractionation in order not to increase the risk of rectal complications.[23] In order to stay within the same biologically effective dose range, dose to the rectal point should be limited to 60–70% of the prescribed dose to Point A.

Management

Acute symptoms of urgency and tenesmus can be treated with an antispasmodic such as Lomotil or Imodium. Pain is treated systemically with a narcotic or non-narcotic preparation titrated to the patient's level of discomfort.

Chronic radiation proctitis typically includes bleeding, stricture formation, and/or fistula. Biopsy of mucosal changes should be discouraged if they occur in an area that likely received a high dose of radiation such as the anterior rectal wall. Biopsy may cause persistent inflammation, decrease healing, and precipitate fistula formation. Interventions include low residue diets and pain control. The patient's hematocrit should be monitored so that transfusion can be given as indicated. Some patients will have sequelae that resolve in a few months with little intervention, while other patients will have a longer course that may involve 1–2 years of rectal bleeding. Non-surgical therapies include steroid enemas or Proctofoam with cortisone which is used to decrease inflammation. Mesalazine can be used as an enema, delayed absorbing capsule, or rectal suppository. This agent works as an anti-inflammatory agent directly on the bowel mucosa. Bleeding from telangiectasias has been treated with thermal coagulation or formalin application. Oral and rectal administrations of sucralfate have been described as a method of preventing proctitis. Sucralfate is an aluminum hydroxide complex of sulfated sucrose which has been used to heal ulcers in the esophagus. It is postulated to reduce the extent of microvascular injury. One study that compared rectal sucralfate to a combination of oral sulfasalazine and rectal steroids demonstrated clinical improvement in 16/17 patients compared to 8/15 patients in the steroid group. No endoscopic improvement was noted between the two groups and follow-up in this study was only for 4 weeks.[24] Another prospective study of rectal sucralfate described a benefit in 3 patients for a minimum of 3 years.[25] It can be seen that there is no report that demonstrates a superior approach for individual patients. Patients have variable presentations and degrees of sequelae. Most reports in the literature represent small single institutional experiences with incomplete follow-up. Quality-of-life data is limited.

Surgical treatment can be used if there is a failure of medical treatment, obstruction caused by a stricture, or other serious complications such as perforation, abscess, or fistula. Surgical options include diversion without resection, resection without anastomosis, and resection with anastomosis. Because of the high morbidity and mortality in these patients the simplest operation is preferred by most surgeons.[26]

A2. Anus

Pathogenesis

Mucosa above the anal orifice is made of stratified squamous epithelial cells which show a rapid turnover and hence are very radiosensitive; this mucosa is involved in the pathology of the early radiation injury in this region. Creation of microvascular thrombi also contributes to early injury. Injury sustained by muscle, stromal, and vascular cells which respond slowly to irradiation are the cause of the delayed anal radiation injury. The pathogenesis of the late injury is linked with injury of fibroblasts and miofibroblasts, leading to the development of severe fibrosis.[6] Histologically, pelvic irradiation has been found to result in damage to the myenteric plexus of the internal anal sphincter of patients with rectal cancer and these alterations seemed to be time-dependent. A trend toward increased collagen deposition following irradiation has also been observed.[27]

Tolerance dose of the normal tissue is considered to be a little above 65 Gy. When external beam therapy is given alone, doses of 60–65 Gy are prescribed, close to the tolerance dose in 1.8–2 Gy fractions over 6–7 weeks.[28]

Acute grade 3 toxicity with 2-Gy fractions is 40%, while it is 75% with 2.5-Gy fractions. Late radiation-related complications are observed in 15% of the patients, and are more common when fractions higher than 2 Gy are used.[29]

Clinical Aspects

Radiation effects on anorectal function have been increasingly recognized. Acute effects on the anus include epithelial discomfort which may be aggravated by radiation-induced diarrhea. Epithelial effects follow a sequential progression from erythema to desquamation. Shallow erosions and ulcerations can develop which can lead to tenesmus. Direct radiation to the anus can result in severe acute reactions that are exacerbated with the use of chemotherapy.

Injury to the anal sphincter complex after pelvic radiotherapy has been reported. There is limited information available on sphincter continence following radiation with or without chemotherapy for anal carcinoma. Evaluation of the sphincter is complicated by the fact that the sphincter may have been damaged by the disease process itself. The reported rates of colostomy following EBRT for complications range from 0% to 7%.[29–31] Strictures of the anus or ulceration are the most commonly reported reasons for intervention. Actual data reporting subjective and objective measurements of function are limited. One report found complete continence in 56%, liquid soiling in 26%, solid soiling in 17%, and complete incontinence in 6% of colostomy free survivors of anal cancer.[32] Manometry measurements on these patients demonstrated that both resting pressures and maximum squeeze pressures were decreased.

There have been inconsistent outcomes of anorectal studies after pelvic radiotherapy not directed to the anus. The most common changes include decreased resting anal canal pressures and decreased rectal volumes which are consistent with fibrosis.[33] The reported effects have been conflicting because of the mixture of retrospective and prospective investigations, different radiotherapeutic regimens, as well as the variance in pretreatment sphincter function, rectal capacity, and bowel activity. In addition, the

intra- and inter-individual reproducibility of anorectal manometry values, even under standard conditions in healthy volunteers, is low.[34]

A recent report from Yeoh et al. evaluated 35 patients following radiation for prostate carcinoma.[35] One year following EBRT, 56% of patients had an increase in frequency of defecation while 26% reported incontinence. Objective measurements made 1 year after radiation revealed that volumes of rectal distension associated with perception of the stimulus and desire to defecate were lower compared with baseline volumes, reflecting a heightened rectal sensitivity in the patients.[35] This may cause symptoms of urgency that cause patients to limit their activities in order to remain near a bathroom.[36] A similar study involving a group of patients with cervical cancer demonstrated that 33% of patients had late symptoms related to anorectal dysfunction.[37]

Management

If direct radiation to the anus is not necessary as in prostate cancer, cervix cancer, or rectal cancer, it may be possible to exclude at least a portion of the anus from the treatment fields. This requires marking the sphincter with a radio opaque marker or identifying it at CT simulation. Blocking this region from high dose radiation may decrease acute and chronic complications.

If it is necessary to include the anus in the treatment field, aggressive skin care is very important. In addition, a planned treatment break may actually shorten the overall treatment time by improving the tolerance of the proposed regimen. Therapeutic interventions usually include antidiarrheal medications such as loperamide or codeine. Care of the skin includes cleansing with gentle cleansers. Application of aloe, gentian violet, and/or lidocaine can help manage symptoms.

Biopsy of the anus following high dose radiation can result in non-healing ulceration. Avoidance of this procedure is preferred but if a non-healing ulceration develops, conservative management is generally used initially. This involves stool softeners, sitz baths, and wound care. There have been reports of the use of hyperbaric oxygen in the management of these complications.[38] There are limited therapeutic interventions for incontinence with the primary treatment being colostomy.

B. GU EFFECTS

B1. Bladder

Pathogenesis

The urinary bladder and ureters are covered by urothelium—mucosa made of transitional epithelium of several layers of cells (from 3–4 in full to 5–7 in the empty bladder). These cells are replenished by undifferentiated basal cells that divide so slowly that their mitotic index cannot be measured.[39] The surface layer of urothelium is made of large polyploid cells connected by tight junctions and covered by a monomolecular film of sulfonated polysaccharides or glycosaminoglycan that serves the need for internal impermeability of the bladder.

Following radiation treatment, the initial injury to bladder is mild, and the early response linked with the urothelium occurs at 6–12 months. Therefore, mucosal cell injury (loss of the surface layer of epithelial cells, resulting in the loss of bladder impermeability) becomes evident approximately at the same time when the late response occurs, caused by injury of stroma and blood vessels.[6] Radiotherapy results in urothelial cell enlargement, multinucleation, and vacuolization, although nuclear to cytoplasmic ratios remain low.[40] Enlarged nuclei may have large nucleoli, but degenerative nuclear features are usually present. A reactive, tumor-like epithelial proliferation associated with hemorrhage, fibrin deposits, fibroid vascular changes, and multinucleated stromal cells is seen in chronic cases. The adjacent tissue is hemorrhagic with deposits of fibrin and, deeper within the stroma, mesenchymal cells are often large and multinucleated.[41] The transitional epithelium becomes thin and numerous dilated submucosal capillaries create a telangiectatic appearance. Bladder contracture can develop with muscle fiber replacement.[42] This late phase of radiation cystitis can occur months to years after ionizing radiation.

Clinical Aspects

Radiation effects on the bladder have been documented following treatment for various pelvic malignancies including cervical cancers, prostate cancers, and bladder cancers. In these instances, however, the function of the bladder may have been impaired by the disease itself and separating radiation effects from disease effects may be difficult. Also, dose to the bladder can vary with treatment to encompass a substantial portion of the organ with external beam RT as in bladder cancer or for high dose delivered to a small volume of the bladder as in cervical or prostate cancer where at least a portion of the treatment may be delivered with brachytherapy.

Acute sequelae during radiation commonly include frequency and dysuria. These symptoms typically occur following more than 20 Gy to the bladder with conventional fractionation. Following completion of radiation, resolution of symptoms is seen in 2–3 weeks.

The tolerance doses (TD 5/5) for the whole bladder have been estimated to be 65 Gy. The tolerance increases if only two-thirds of the bladder is treated to 80 Gy.[43] Another analysis of bladder complications demonstrates that complication rates appear to be dependent on both the whole bladder dose (i.e., from external beam radiation) and the maximum bladder dose (i.e., from brachytherapy)[44] (Table 1). Long-term sequelae include persistent dysuria, severe pain, contracted bladder, vesicovaginal fistula, and varying degrees of hematuria. Median onset of late complications after radiation is 13–20 months.[44]

Lajer et al. followed 177 consecutive patients treated for cervical cancer prospectively and documented subjective and objective urologic morbidity at regular follow-up intervals.[45] Doses to the bladder were 46 Gy in 2-Gy fractions with additional dose delivered to at least part of the bladder from brachytherapy. The cumulative incidence of morbidity was found to increase throughout the study period until the 48-month follow-up interval. The 5-year incidences of severe morbidity were 5%, moderate morbidity

Table 1. Bladder complication summary in patients with or without chemotherapy.[44]

Disease treated	Approximate dose to ≥ 50% of the bladder (Gy)	Approximate maximum bladder dose (Gy)	Approximate clinical complication rate (%)
Prostate	40	60–65	5
Bladder	50–65	50–65	6–20[†]
Cervix	40	65–75	5–10
	40	≥80	10–20
Rectal	40–50	40–50	0

*These results are in patients treated with or without chemotherapy.
[†]Many of these symptoms may be due to the cancer.

27%, and mild morbidity was 25%. A subsequent study evaluated 36 patients who were treated with curative intent with radiotherapy for cervical cancer.[46] Urodynamic examinations were performed on admission and at regular intervals after RT. Detrusor instability and frequent small voiding did develop in 15–20% of patients during follow-up. However, there was no control group for comparison which would have helped to control for an unknown incidence of urologic morbidity which exists in the general population.[47] Hemorrhagic cystitis can occur from 6 months to 10 years following pelvic irradiation.[48] Levenback et al. reported a 6.5% incidence seen in 1784 patients treated with radiotherapy for stage IB cervical cancer.[49] Patients treated for cervical cancer with combined external beam radiation and brachytherapy have a 5–10% incidence of radiation cystitis with doses of 75 Gy to the bladder but the incidence increases with higher doses.[50] Recent reports using conformal radiation to the prostate have reported the incidence of moderate to severe hematuria in a range of 3–5%.[51] Notably, bladder complications may be less dose-dependent than rectal complications as seen in Table 2.

Management

Patients with mild to moderate urinary frequency may be treated symptomatically. Phenazopyridine hydrochloride is frequently used to relieve these symptoms. It acts as an analgesic on the bladder mucosa. Oxybutynin chloride is an antispasmodic that relaxes the bladder smooth muscle and may relieve the symptoms of frequency and

Table 2. Distribution of patients by late complication grade according to dose. Data presented as the percentage of patients, with the number in parentheses.[51]

Group	Grade 0	Grade 1	Grade 2	Grade 3	p*
Rectal complications					
70-Gy arm	53 (78)	36 (53)	11 (16)	1 (1)	
78-Gy arm	46 (69)	28 (42)	19 (28)	7 (10)	0.006
Bladder complications					
70-Gy arm	72 (106)	20 (29)	7 (11)	1 (2)	
78-Gy arm	66 (98)	22 (32)	10 (15)	3 (4)	0.63

urgency. Pharmaceuticals used to increase bladder outlet resistance include ephedrine hydrochloride, pseudoephedrine hydrochloride, and phenylpropanolamine.

The primary treatment modality for hematuria is bladder irrigation. Intravesical treatments with silver nitrate, prostaglandins, or formalin have also been used. More serious interventions can include embolization of the hypogastric arteries or urinary diversion and cystectomy. Treatment with hyperbaric oxygen has also been tried with some success. One report of 62 patients demonstrated complete resolution or marked improvement in 86% of the treated patients.[52] Another study with 40 patients treated with HBO demonstrated good response in 30 (75%) patients. Failure of the treatment was seen only in patients with very severe hemorrhagic cystitis.[53]

B2. Urethra

Clinical Aspects

Urethral injury usually consists of stricture formation. For patients undergoing radiation to the prostate, most reports have documented increased risk of stricture in patients who have had prior transurethral resections of the prostate. Following therapeutic doses of radiation ranging from 60 to 70 Gy, patients with prior TURP demonstrated stricture rates of 6–16% compared to patients without prior TURP who had stricture rates ranging from 0% to 5%.[54]

Incontinence can also result following radiation to the urethra. Following radiation to the prostate, incontinence rates have been reported as 1–2%.[55] Patients who have had a transurethral prostate resection may have an increased risk of incontinence. One study reported incontinence in 5.4% of patients who had a TURP compared to 1% of patients who had not.[45] Incontinence following pelvic radiation in women is poorly documented. Following radiation for cervical cancer, Parkin et al. reported that 45% of women responding to a mailed questionnaire complained of incontinence.[56] Pourquier et al. documented that 11% of urinary complications were incontinence.[57] Most modern series do not report incontinence as a frequent complication. It is the author's experience that women who are treated with interstitial brachytherapy to the periurethral area have frequent incontinence following treatment which might be attributed to the high doses of radiation to the sphincter that probably result in fibrosis. Incontinence following radiation and chemotherapy for bladder cancer has been described. Of 71 patients with intact bladders, a questionnaire showed that flow symptoms occurred in 6%, urgency in 15%, and control problems in 19%. Of all women 11% wore pads. Urodynamic studies demonstrated incontinence in 2 out of 32 patients.[58]

Unfortunately, the mechanism of incontinence is poorly understood. Many variables can affect incontinence in addition to damage to the urethral sphincter including age, prior childbearing history, weight, comorbid medical conditions, bladder irritability, and pelvic floor weakening. Urodynamics may be done on patients who suffer from incontinence symptoms to better define the source of the problem.

Management

Intervention needs to be tailored to the individual patient.

B3. Ureter

Clinical Aspects

Acute effects from radiation on the ureters are not clinically observed in patients. The most frequent cause of ureteral injury after treatment for cancer is a progressive disease. However, ureteral damage including stenoses, necrosis, and reflux from radiation has been described.[59] This complication is typically seen in patients treated with external RT and brachytherapy for cervical cancer. In one series, the majority of ureteral complications were seen with marked signs of radiation cystitis as well.[59] The mean latency time between RT and the manifestation of severe ureteral complications was 19.4 years with a range of 0.5–41.5 years. Two other reports documented the incidence of ureteral stricture. One report had an actual incidence of 1.5%,[60] while the second had an actuarial estimate of 1.2% at 10 years and 2.5% at 20 years.[61] Because the occurrence is rare, correlation with factors that increase the frequency of the damage is difficult. The use of a midline block during external beam,[61] deviation of the uterine tandem,[62] combination of radical surgery and RT which may further compromise the vascular supply of tissue,[63] and transvaginal radiation[61] have all been implicated as factors responsible for increasing the risk of stricture. There are no dose response data for development of this complication.

Management

Management of ureteral stenosis is individualized. An increased index of suspicion is necessary for physicians following these patients since ureteral injury may not be manifested for many years. Mild stenosis may be treated by placement of a ureteral stent. Reimplantation of the ureters with an ureteroneocystostomy or ureteroileocystotomy was successful in 5 out of 8 patients in one series.[61] Other procedures to divert the urinary stream may be used including placement of ileal conduits. Nephrectomy may be required with recurrent urinary tract infections and a non-functional kidney.

B4. Lymphatics

Pathogenesis

The lymphatics of the lower extremity can be disrupted by either surgery or radiation to the groin or pelvis. Evaluation of patients with lymphangiography following radiotherapy demonstrates obstruction of the lymphatics with extravasation of the radiopaque material from the lymphatics.[64] Microscopic examination of lymph nodes following radiation has demonstrated thickening of the fibrous capsule and a decrease in the number of lymphocytes and reticulum cells with sparse germinal centers.[64]

Clinical Aspects

Certainly, in patients who have both surgery and radiation the incidence of lymphedema is usually increased.[65] Lymphedema is underreported in the literature and may only be called to the attention of the physician once the patient has difficulty finding shoes or pants that fit or pain with standing or ambulation. Lymphedema causes effects on mobility, self-image, finances, and appearance. Edema may be unilateral or bilateral. It

can occur in as short a time as 3 months following treatment and may be mild or severe. Cellulitis or infection in the extremity may precipitate the occurrence of lymphedema. Edema usually begins as soft and pitting but may progress to become hard and brawny.

One recent series documented edema following hysterectomy with or without adjuvant radiation. The incidence of lymphedema of the leg was 11% which was similar in the surgery alone group.[65] Another study retrospectively investigated the prevalence of leg edema in gynecologic survivors. The diagnosis of lower limb lymphedema was made in 18% of the total sample: 53% of these were diagnosed within 3 months of treatment, 18% within 6 months, 13% within 12 months, and the remaining 16% up to 5 years following treatment.[66] Women most at risk for developing lower extremity lymphedema were those who had treatment for vulvar cancer with removal of lymph nodes and adjuvant radiotherapy. In this group, the prevalence was 47%. It is important for all health care providers to include care and assessment of the legs particularly during the immediate pre- and postoperative period. Another report of patients treated with surgery and radiation for cervical cancer found patients (41%) had a unilateral increase in volume of 5% or more in one leg compared with 15 healthy controls in whom the difference between limbs did not exceed 4%.[67] Of the 54 patients, 15 (28%) had a slight swelling (>5% volume increase); 3 (6%) had moderate swelling (>10% volume increase); and 4 (7%) had severe swelling (>15% volume increase), which was interpreted as treatment-induced lymphedema. Twelve (22%) of the patients had lymphoedema that was severe enough to cause symptoms.

Management

Management includes patient education of the causes and conditions that may exacerbate their edema. No optimal management exists for treatment of this problem. Precautions regarding skin care, avoidance of trauma, and checking for signs of infection in the leg or foot should be discussed. Compression should be offered as soon as edema becomes apparent. Early treatment is more likely to result in successful management. Compression hose, wrapping the leg, and static compression devices have been used. Some patients have been taught self-massage, while others have professionally administered lymphatic massage. Once edema develops, it will be a lifelong situation with which the patient will have to coexist.

B5. Skin-Vulva

Pathogenesis

The vulva is covered by stratified squamous epithelium, overlying connective tissue with elastic fibers, mucus-forming glands, sweat and sebaceous glands. The clitoris has a cavernous vascular structure.[68]

Radiation induces early vulvar lesions including gross erythema and edema. Basal epithelial cells die due to injury or endothelial cell injury leading to microvascular occlusions. Late injury includes loss of vulvar hair, depigmentation, atrophy of the epithelium, and fibrotic induration.[69]

Clinical Aspects

The skin over the pelvis has a similar tolerance to radiation of skin elsewhere in the body. However, the vulvar tissues are very sensitive to radiation. Even mild erythema can cause significant symptoms for the patient. Generally, erythema occurs around 20 Gy with routine fractionation and can progress to moist desquamation fairly quickly after that. Because of the anatomy certain structures in the vulva can self-bolus and cause early reactions. Because of the early and painful reactions induced by vulvar radiation, many treatment regimens for the anus and/or vulva have a planned treatment break included to improve the acute tolerance of the treatment. As a matter of fact, acute reaction, moist desquamation, is expected in 100% of the patients, while late effects such as fibrosis and telangiectasia occur in 37% of the patients treated with 45–70 Gy; however, these effects are minimized when dose is fractionated at 1.65–1.7 Gy.[69,70]

Management

Good skin hygiene with cleansers will improve the skin tolerance. Utilizing Aquaphor and aloe products will moisturize the skin and improve re-epithelization. The overuse of sitz baths is discouraged because excess moisture will soften the skin and make it more likely to macerate. Areas of moist desquamation may be painted with Gentian Violet that works as an antibacterial agent and a skin barrier to moisture. The use of topical 2% lidocaine gel may enable less discomfort if used prior to urinating or defecating.

Following completion of radiation, the skin of the vulva can become atrophic and thin. Telangiectasias can occur and cause bleeding with minor trauma. Soft tissue necrosis can result and may require lengthy healing times. In order to minimize long-term radiation complications to the pelvis, radiation fractionation schemes have used doses per fraction of less than 180 cGy/fraction.

B6. Vagina

Pathogenesis

The lining of the vagina is made of stratified squamous epithelium over a connective tissue lamina propria and longitudinal muscle fibers and elastic fibers.[68] Radiosensitivity of the squamous epithelium is significant and early vaginal injury is marked by acute epithelial denudation with endothelial injury that may lead to thrombosis, edema, and smooth muscle necrosis. Delayed injury involves severe fibrosis that may obliterate portions of the muscle and vasculature potentially resulting in vaginal stenosis and ulceration.[6]

Clinical Aspects

Vaginal mucosa is reasonably tolerant to radiation. An irradiation tolerance level of the proximal vagina was suggested by Hintz in 1980.[71] None of the patients treated to a maximum dose of 140 Gy developed severe complications or necrosis of the upper vagina. The distal vagina (introitus) and posterior wall are more sensitive to radiation. Hintz suggested doses to the distal vagina not to be greater than 98 Gy. A recent report of 274 patients with cervical carcinoma treated from 1987 to 1997 led to an estimated

TD 5/5 of 175 Gy for combined external and brachytherapy.[72] Serious complications include mucosal necrosis or fistula formation. Less serious complications included vaginal stenosis or shortening, formation of telangiectasia (which can lead to bleeding) or thinning of the vaginal mucosa, and dryness. One study documented a decrease in vaginal length following treatment with intracavitary radiation[73] for patients with cervical or endometrial cancer. Shortening occurred with a mean value of 1.5 cm compared to pretreatment values. Another study of patients who were asked to document changes 1 year following radiation reported that 48% of patients felt their vaginal dimensions were decreased following radiation for cervical cancer.[74]

Management

Treatment issues for vaginal toxicity depend on the level of suspicion for a recurrence. If soft tissue necrosis is observed, symptomatic management with antibiotics, estrogen cream, and gentle irrigation may heal the area. Overzealous biopsy may contribute to the formation of a fistula. But biopsy may be necessary if recurrent tumor is suspected. The strategy for prevention of vaginal stenosis or shortening has been to encourage sexual intercourse or use of vaginal dilators. Estrogen cream or systemic estrogen may also aid in the rejuvenation of cells and increase the elasticity of the vagina. Early intervention is necessary because once shortening and stenosis occur it is difficult if not impossible to reverse. It has been suggested that psychoeducational intervention may increase the compliance rate of some patients for vaginal dilatation and may reduce the sexual fears of many patients.[75] No optimal approach to vaginal dilatation is recognized. Recommendations range from every day dilatation to twice weekly. Appropriate frequency and satisfactory outcome probably depend on the patient's age, surgical procedure, radiation dose, tumor stage, and motivation. Hopefully, investigation will yield more information regarding this topic in the future.

B7. Ovaries

Pathogenesis

Radiation to the ovaries can damage oocytes and result in premature menopause because of ovarian failure of estrogen production. Primary germ cells, oocytes, are surrounded by a single layer of granulosal cells embedded in the stroma to form ovaries. Enlargement of oocytes and the proliferation of granulosal cells into Graafian follicles occur monthly during the reproductive period of life, as well as proliferation of stromal cells in the cortex. After menopause, arteries and veins develop endarteritis oblitrans and ovaries are partially atrophied. A single layer of cells (germinal epithelium) from which oocytes originated covers mature ovaries.[6]

Oocytes undergo meiosis and are relatively radioresistant (single dose LD50 is 4 Gy); however, proliferating granulosal cells are very radiosensitive and their demise leaves oocytes without support and Graafian follicles cannot be formed. Therefore, a total dose of 24 Gy (fractionated in 2-Gy single doses) leads to ablation of ovaries due to the loss of granulosa cells.[76] Early radiation injury then comprises of necrotic changes in proliferating granulosa cells, while other early changes include microvascular thrombi

and endothelial cell swelling.[76] Nevertheless, if the dose is sufficiently low, the primordial follicles with non-dividing cells may survive and later develop normally. Late radiation effects include atrophy and fibrosis, with thick walled and hyaline arterioles and venules.[6] The effects on the ovary are dependent on the age of the patient and total dose to the ovary. Low doses of radiation (4–7 Gy in 1–4 fractions) can result in permanent menopause in women over 40 years of age.[77] However, permanent sterility in young women may not result until a total dose of 20 Gy is given.

Management

Radiation-induced ovarian dysfunction should be considered following not only direct pelvic radiation, but also irradiation from inverted Y fields of Hodgkin's disease treatment or craniospinal irradiation. Estrogen replacement may be given to the patient if desired.

B8. Uterus

Pathogenesis

The uterus has four smooth muscle layers creating the myometrium, and is covered with peritoneum and connective tissue adventia. The lamina propria has specialized connective tissue cells, and the endometrium is made of columnar epithelium. The lower uterus and cervix at the vaginal surface are covered by stratified squamous epithelium. The cervical channel is covered by columnar mucus-forming glands. After menopause the blood vessels develop endarteritis oblitrans.[68]

The endometrial glands and stroma (lamina propria) are proliferating only when stimulated by estrogen (and are therefore most radiosensitive at that stage). Henceforth, early radiation injury of uterus is not dramatic. At 6–8 weeks post-intracavity irradiation, cells of the endometrium and stroma are often enlarged and have bizarre nuclei, the stroma is infiltrated by leukocytes, and fibrosis develops in all tissue layers. Delayed injury resembles the postmenopausal uterus, and post-intracavity radiation endometrium and adjacent myometrium show hyaline collagen scars (though fewer deep lesions than post-external beam therapy).[16]

When HDR intracavity brachytherapy was used for intrauterine therapy in four 8.5-Gy doses, not more than 4.6% patients experience severe complications at 5 years.[78] External beam therapy if used without brachytherapy is prescribed near to the tolerance dose, as total external beam dose of 45–50 Gy; in combination with brachytherapy it is used usually at 20–40 Gy.[28]

Radiation to the uterus can result in impaired uterine growth and blood flow that lead to early pregnancy loss and premature labor if pregnancy is achieved.[79] Uterine volume correlates with the age at which radiation was received. Radiation at a young age results in decreased volume. One study examined women who had received total body irradiation (14.4 Gy). Four of 6 women with ovarian failure had reduced uterine volume, undetectable blood supply, and absent endometrium at baseline assessment. After 3 months of sex steroid replacement treatment, uterine blood supply and endometrial response were not significantly different from controls. Uterine volume improved but remained significantly smaller than controls.[80] Another study of patients treated with

low radiation doses to the uterus for benign disease examined 1817 women treated with intrauterine radium for uterine bleeding. The radiation dose to the uterus was at least 24 Gy. Three hundred and eleven patients were less than 40 years of age. Nineteen patients became pregnant with 33 conceptions but only 6 live births resulted.[81]

In the cervix, delayed injury may include the presence of atrophic squamous epithelial cells often with such nuclei as to suggest dysplasia.[6]

B9. Testicles

Pathogenesis

The walls of the seminiferous tubules are made of a basement membrane over lamina propria containing fibromyocytes and elastic fibers. Inside the tubules are postmitotic Sertoli cells surrounded by spermatogonia A, spermatogonia B, primary and secondary spermatocytes, spermatids, and spermazoa. In the stroma are blood and lymphatic vessels and nerves, and cells of different types: fibroblasts, macrophages, mast cells, and Leydig cells.[82]

Of these cells, in the postpuberty testis, spermatogonia B and then spermatocytes are the most radiosensitive, followed by non-dividing spermatogonia A, with postmitotic cells—spermatids and spermazoa being least sensitive. The Sertoli and Leydig cells are comparatively radioresistant, surviving doses causing sterility. In the prepubescent testis, Sertoli cells are the dominant cell type in seminiferous tubules, are still dividing, and are therefore radiosensitive.[6] Therefore in prepuberal boys, irradiation can cause hormonal imbalance and arrested entry into puberty.[83]

Death of spermatogonia B and spermatocytes can be caused by cGy doses of irradiation, and follows an apoptotic pattern of cell death. This is accompanied by gene induction of apoptosis-regulating genes such as p53 and myc, and cytokines such as tumor necrosis factor alpha.[84] Due to the fact that spermatogonia B are recruited from the pool of less radiosensitive spermatogonia A, fractionated radiation may cause a more severe oligospermia. A high dose of radiation, such as 30 Gy, causes significant cell death of most cell types in testis, including Leydig cells, resulting in a decrease in testosterone.[85] A late effect of irradiation is testicular atrophy, and this could probably be best attributed to ischemia, by extrapolation from other tissues.[6]

Clinical Aspects

The testis is one of the most radiosensitive tissues in the body with a radiation dose as low as 15 cGy causing a significant depression in the sperm count.[77] The testis may be directly in the radiation field or receive scatter dose from a nearby field. Irradiation of the testis during radiation usually involves fractionated doses that may cause more stem cell killing than single-dose treatments.

Low doses of radiation kill spermatogonia which are differentiating into spermatocytes. Therefore, low doses of radiation deplete the stem cells of these developing sperm which result in decreased sperm production during the first 50–60 days after irradiation. Temporary oligo- or azoospermia result. Complete recovery takes place within 9–18 months after less than 1 Gy, 30 months for 2–3 Gy, and 5 or more years after

4–6 Gy.[77] One study of 11 cancer patients who received 118–223 cGy delivered in 24–35 fractions demonstrated temporary aspermia in all patients beginning about 3 months after RT.[86] Recovery of spermatogenesis was first noted between 10 and 18 months in 5 patients. Another group of patients who received fractionated doses of 19–178 cGy to the remaining testis following unilateral orchiectomy had azoospermia in 10–14 patients who received over 65 CGy to the testis. Sperm reappeared in the semen with 30–80 weeks after the start of treatment.[87]

Direct testicular irradiation of 24 Gy results in ablation of the germinal epithelium (responsible for sperm development) and Leydig cell function (responsible for testosterone) is seriously affected in most patients. Tsatsoulis et al. evaluated Leydig and Sertoli cell function in 18 men who had undergone unilateral orchidectomy for a testicular seminoma followed by 30 Gy in 20 fractions.[88] The median testosterone level was significantly less than in normal controls and 6 men had levels below the normal adult male range. Leydig cell damage was suggested by the decreased testosterone/LH ratio. Similarly, 10 of 12 boys demonstrated Leydig cell dysfunction 1–8 years after testicular irradiation (24 Gy) for acute lymphoblastic leukemia.[89] Lower doses of 3–9 Gy received as a scatter dose to the testes in childhood in fractionated doses resulted in oligo- or azoospermia many years later. LH and testosterone levels were normal indicating normal Leydig cell function. Also, another report demonstrated that low doses of testicular irradiation (12–15 Gy) did not result in abnormal pubertal development in 12 of 13 boys, although 7 boys who were tested demonstrated azoospermia.[90]

Management

Androgen replacement therapy to enable normal puberal development and future sexual function is required for patients with deficient testosterone production.

B10. Sexual Function

Women

Sexual function in women following radiation has been poorly evaluated. Most studies focus on vaginal stenosis because it can be quantitated. However, measurement of vaginal anatomy may not correlate well with overall sexual function.[91] Other factors including dyspareunia, bleeding or concern of bleeding, and lubrication changes can also occur.[92]

Jensen et al. evaluate 118 patients following radiation with a self-assessment questionnaire. Approximately 85% had low or no sexual interest, 35% had moderate to severe lack of lubrication, 55% had mild to severe dyspareunia, and 30% were dissatisfied with their sexual life.[74]

Emotional distress after a cancer diagnosis and treatment can certainly cause disruption in sexual function. Radiation following surgery has the potential for causing more sexual dysfunction than radiation alone.[93]

Management

Intervention strategies have focused on vaginal dilatation. Robinson et al. found increased compliance with the use of vaginal dilators and reduction of sexual fears in women following careful counseling about potential sexual difficulties and suggestions

on alternate sexual practices in addition to careful instruction in the use of a vaginal dilator.[75] Use of topical or systemic estrogens may decrease vaginal irritation and improve lubrication. However, hormone replacement therapy may not be an option for many patients who have hormone-sensitive tumors or other contraindications.

It is obvious that sexual dysfunction affects a high proportion of women receiving radiation to the pelvis. Counseling of patients and their partners regarding potential problems that may affect sexual function following RT should help patients to understand anatomic changes and allay fears. More information is needed regarding intervention strategies for dealing with various issues.

Men

Erectile dysfunction is a common sequela following curative local treatment for early-stage carcinoma of the prostate. Most reports focus on erectile function although additional symptoms that affect sexual function can develop after either prostate brachytherapy or external beam radiation to that area of the body. Reported symptoms after brachytherapy have included hematospermia, pain at orgasm, and alteration in the intensity of orgasm.[94] After EBRT symptoms have included a lack of ejaculation in 2–56% of patients, dissatisfaction with sex life in 25–60%, decreased libido in 8–53%, and decreased sexual desire in 12–58%.[94]

The etiology of erectile dysfunction has been attributed to changes in the arteriolar system supplying the corporal muscles. Goldstein et al. documented abnormal vascularity by penile Doppler ultrasonography in all patients who had altered erectile function after EBRT.[95] Similarly, Zelefsky and Eid documented abnormal distensibility of the cavernosal arteries in patients with erectile dysfunction.[96] Merrick et al. found no significant difference in the mean dose to the neurovascular bundles between potent and impotent men following brachytherapy.[97] Approximately 50% of patients develop erectile dysfunction within 5 years of prostate radiation. Factors related to the likelihood of this occurrence include pretreatment potency, patient age, use of supplemental external beam irradiation, radiation dose to the prostate, radiation dose to the bulb of the penis, time since radiotherapy, and diabetes mellitus.[97] Radiation dose to the bulb of the penis seems to correlate with the risk of erectile dysfunction after EBRT and after BT.[98,99] In the past, men who received brachytherapy for treatment have been believed to have improved potency rates than patients treated with EBRT. However, selection bias can favor these patients who may have a lower age, better performance status, and more motivation to maintain potency.[100] Another study investigated the erectile function and satisfaction of men treated for prostate cancer with 3D conformal radiation or transperineal prostate brachytherapy.[101] This report of 128 men suggested that either treatment had a similar impact on erectile function and overall satisfaction. Another report of 201 men treated with MRI-guided brachytherapy with or without external beam irradiation found that all patients (82–93%) experienced some degree of erectile dysfunction compared with baseline function within 4 years after therapy.[19]

Management

When sildenafil citrate was used at least two-thirds of patients reported rates of erectile function comparable to or superior to baseline function.[102] Intracavernosal injection of

prostaglandins can also be effective. Vacuum pumps and penile prosthesis can be used. There is no doubt that better understanding of quality-of-life issues that may lead to sexual counseling have the potential to improve sexual function. Radiation strategies that limit radiation dose to the bulb of the penis may also improve sexual outcomes.[103]

B11. Bone Effects

Pathogenesis

Radiation can affect the microvasculature of the mature bone. This injury causes decreased blood supply to the periosteum which compromises osteoblastic function and can result in an insufficiency fracture (IF). Insufficiency fractures of bone occur as a result of physiological stress on bones with deficient elastic resistance. Irradiation can damage osteoblasts, osteocytes, and osteoclasts and leave an acellular matrix that appears radiographically normal. Such radiation-induced atrophy reduces the number of functional and structural components of a tissue. These two processes can result in clinically and radiographically significant bone atrophy. In addition, previously irradiated atrophic bone is at risk for fracture, second malignancy, or infection, leading to true necrosis.[104] Resulting injuries include atraumatic femoral neck fracture, and osteonecrosis of the femoral head or of the acetabulum.

When bone marrow is irradiated, permanent ablation or hypoplasia can occur. This was demonstrated by failure of bone marrow to regenerate in-field after 30–40 Gy mantle irradiation for Hodgkin's disease.[105] However, marrow recovery has been demonstrated to occur over extended periods depending on the volume irradiated.[106] Irreversible injury after greater than 50 Gy is a consequence of irreparable damage to the microvasculature manifested by irreversible bone marrow fibrosis.

Clinical Aspects

Insufficiency fractures have been described in postmenopausal women with osteoporosis, in patients treated with high doses of corticosteroids, and in patients following radiation exposure. Osseous complications are usually considered uncommon after radiation with megavoltage radiation because of decreased absorption in bone compared to lower energy machines of the past. However, they are important to recognize because the differential diagnosis includes pelvic bone metastases.

In a retrospective study of scintigrams of 80 patients, Abe et al. reported that asymptomatic IF was found in 34% of postmenopausal patients treated with adjuvant postoperative radiation for endometrial cancer.[107] The incidence of symptomatic pelvic fractures in several series of women treated for gynecologic malignancies ranges from 1.7% to 6% following doses of 46–50 Gy to the whole pelvis.[108–112] At least one report suggested increased incidence of IF in women receiving brachytherapy in addition to EBRT.[109] Pain in the pelvic area is the initial complaint of patients. The average time to onset of symptoms is usually 11–12 months after radiation therapy. CT scans can reveal radiological findings of IF, although MRI is currently the most sensitive modality for detecting these lesions. Radionuclide bone scans reliably and non-invasively screen for bony abnormalities in the pelvis and elsewhere. Increased radionuclide uptake at the fracture site is informative, and a characteristic H-shaped pattern of uptake across the sacrum

and sacroiliac joints often corresponds to horizontal and vertical fractures.[113] Most IF is multiple and the most common location for them is in the sacrum and pubic bones.

Femoral head/acetabular damage. The tolerance doses for the femoral head have been estimated to be 52 Gy for the TD 5/5 and 65 Gy for the TD 50/5.[42] One review from Mallinckrodt reported that the cumulative actuarial incidence of femoral neck fracture was 11% at 5 years and 15% at 10 years for patients who were treated APPA to the pelvis with 18 MV photons.[114] No fracture occurred below doses of 42 Gy. Multivariate analysis demonstrated that independent prognostic variables for increasing the risk included cigarette use and radiographic evidence of osteoporosis.

Bone marrow sequelae. The bone marrow is one of the most radiosensitive organs in the pelvis. Approximately 40% of the total body bone marrow reserve lies within the pelvic bones as seen in Figure 3.[115] Hematologic toxicity can be seen acutely during radiation and exposure to radiation can result in long-term myelotoxicity. The radiation dose, dose rate, and volume all affect the acute response of the bone marrow to therapy. When small bone marrow volumes are irradiated, bone marrow in unexposed areas of the body responds by increasing its population of progenitor cells meeting the demands for hematopoiesis. Therefore, acute effects are not seen unless a substantial portion of the marrow is exposed. With exposure to large bone marrow volumes, neutropenia occurs in 2–3 weeks followed by thrombocytopenia and then anemia in 2–3 months.[114] This is represented in Figure 4. The majority of chemotherapeutic agents affect the bone marrow in a similar way. Therefore, the combination of the two modalities can be additive. Many patients receiving radiation are now treated with either sequential or concomitant systemic chemotherapy and myelotoxicity can be a significant problem.

Management

Biopsy is not recommended because of the risk of trauma-inducing radiation necrosis and also because of the low diagnostic efficiency. Histologic changes of hemorrhage, fibrosis, necrotic bone fragments, trabecular bone, and cartilage growth can result in misinterpretation by the pathologist.[109] Treatment of these lesions is usually conservative with pain management, rehabilitation exercises, and restriction of weight bearing. Most series report improvement and complete resolution in symptoms by 6–12 months.

Treatment for bone fractures following radiation has included Provera, Premarin, calcium supplements, and pamidronate. One report reported a trend toward earlier healing with drug treatment.[119]

Treatment planning in the pelvis should consider the volume of the boney pelvis that is included in the radiation field. Techniques that reduce the bone volume and avoid high dose areas in the bone should help to keep IF at a minimum level.

The management of patients with bone marrow toxicity can be divided into those that are supportive and those that are preventative. Growth factor administration is now a common supportive measure in patients with white cell deficiencies. Erythropoietin is now approved for use in patients with depressed hemoglobin levels. Transfusion is typically reserved for patients with hemoglobin levels below 8 g/dL or those that are symptomatic from low levels with the goal of ameliorating physiologic responses more quickly. Erythropoietin is typically used if hemoglobin levels are below 12 g/dL in order to improve tolerance to therapy[118] or improve "cancer-related fatigue" symptoms.[119]

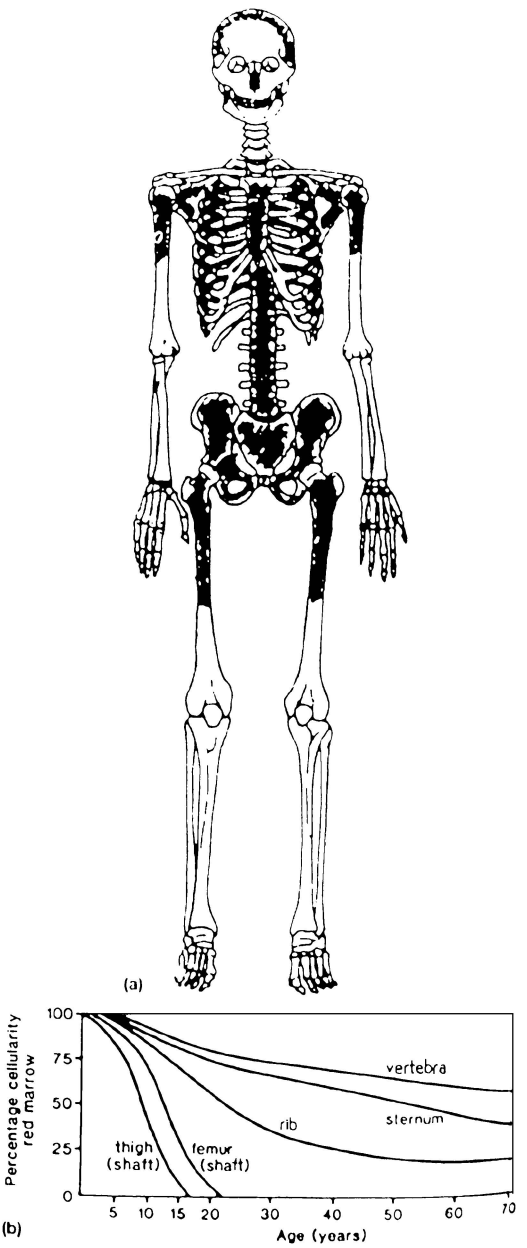


Figure 3. Bone marrow distribution in adult humans as determined by autopsy finding: active areas are shaded. The relative amount of red bone marrow in difference anatomic sites as a function of age.[114]

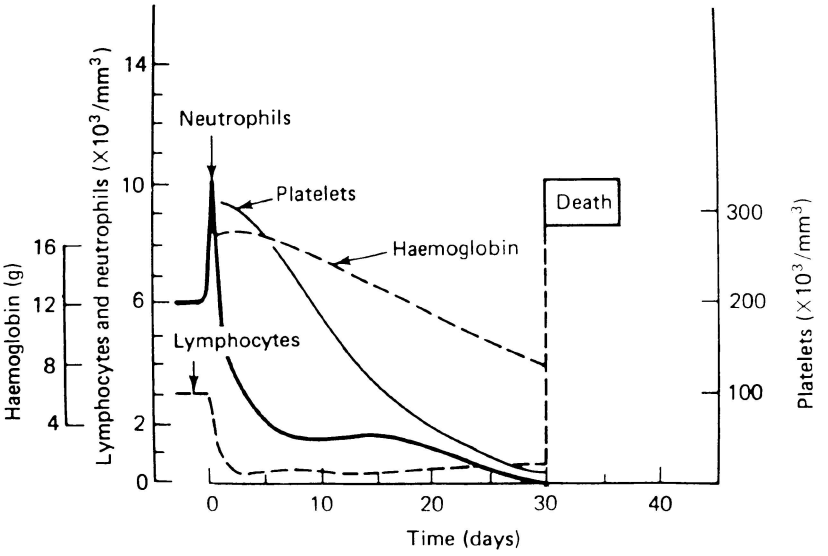


Figure 4. Temporal sequence of changes in numbers of neutrophils, platelets, and lymphocytes, and hemoglobin after lethal total body irradiation.[114]

There is increased interest in prevention of bone marrow toxicity using bone marrow sparing techniques with intensity-modulated radiation therapy. Brixey et al. evaluated 36 patients with uterine or cervical cancer who received treatment with IM-WPRT and compared them to 88 patients treated to the same target volume and total dose with conventional four-field WPRT as seen in Table 3.[120] The comparison of pelvic BM dose–volume histograms revealed that IM-WPRT planning resulted in significantly less BM volume being irradiated compared with WPRT planning, particularly within the iliac crests as seen in Figure 5. Administration of chemotherapy was held more often in the WPRT group and patients treated with chemotherapy and WPRT experienced more acute WBC toxicity. This report suggests that IMRT may be important for bone marrow sparing when pelvic radiation is required and may improve the tolerance for treatment that combines radiation with systemic chemotherapy.

Table 3. Comparison of doses to iliac crest bone marrow irradiated between whole pelvic radiation and intensity-modulated radiation.[120]

Dose (Gy)	WPRT (% vol)	IM-WPRT (% vol)	*p*
10	94.9	97.3	0.007
20	88.8	78.1	<0.001
30	54.9	52.9	0.167
40	42.4	26.2	<0.001
45	32.1	15.1	<0.001
50	0	0.46	0.012

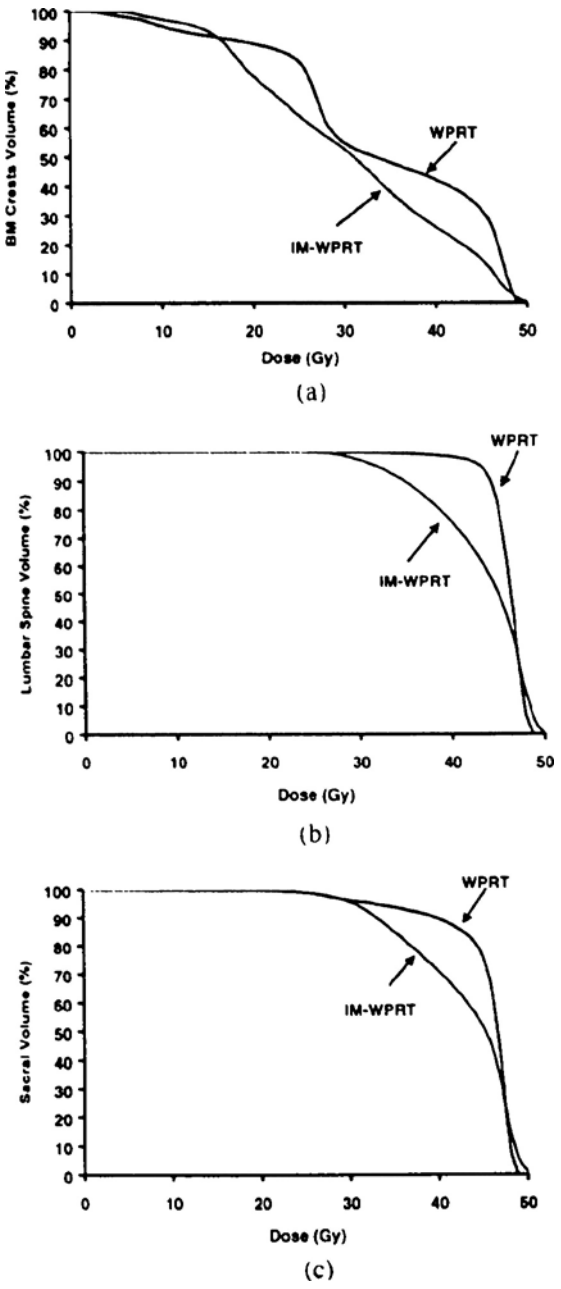


Figure 5. Comparison of the average bone marrow dose–volume histograms of 10 patients with treatment planned using both conventional whole pelvic radiation therapy and intensity-modulated pelvic radiation therapy.[120]

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