Late Effects of Pelvic Radiation Therapy in the Female Patient: A Comprehensive Review

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Abstract

Radiation therapy (RT) is a valuable treatment option for gynecologic cancers, but it is also associated with acute and chronic toxicity that can greatly impact a patient's quality of life. The severity and incidence of these side effects depend on various factors, such as the site, volume of tissue within the radiation field, treatment schedule, total dose, dose per fraction, and type of RT. Gastrointestinal (GI) toxicity is the most common side effect of pelvic radiation and late toxicity can include strictures, lower GI bleeding, and fibrosis. Genitourinary complications may include hemorrhagic cystitis, urethral and ureteral strictures, urge incontinence, fistulas, vaginal stenosis, premature ovarian insufficiency, and secondary malignancies. Outside the visceral tissues, insufficiency fractures, bone marrow suppression, and skin changes are also sporadically seen. Overall, advances in RT techniques and the understanding of patient-related factors influencing toxicity have led to improvements in treatment outcomes and reduced rates of late side effects. Understanding the late side effects associated with pelvic RT is critical for developing strategies to both minimize the risk of long-term complications and improve the quality of life of patients. This review aims to summarize the late side effects associated with RT in the pelvis and the respective interventions that may help treat toxicities.

Introduction

Radiation therapy (RT) is an essential treatment option for many gynecologic cancers, prostate cancer, and gastrointestinal (GI) malignancies. It can be used as a definitive, adjuvant, or neoadjuvant therapy. Evidence-based guidelines recommend that most gynecologic cancers can benefit from RT (eg, 60% of cervical, 45% of endometrial, 35% of vulvar, 100% of vaginal, and 5% of patients with ovarian cancer).[1,2] However, RT is associated with acute and late side effects that vary depending on which pelvic organ is targeted.[3]

Acute toxicity of RT typically occurs within a few weeks of starting treatment and is caused by the death of rapidly proliferating cells in normal tissues. Subacute effects may occur 4-12 weeks after treatment and represent a prolonged recovery from acute toxicity. Late effects can take months to years after treatment to develop and may result in fibrosis, vascular injury, or other gradual changes in slowly dividing tissues. These late effects can be long-lasting and irreversible, potentially leading to end-organ damage. In rare cases, residual DNA damage from RT can even cause delayed carcinogenesis, with the development of secondary malignancy years after RT.[4]

The incidence and severity of RT side effects are influenced by multiple factors, such as the site and volume of tissue exposed, treatment schedule, total dose, dose per fraction, and type of RT. Smoking history is a significant predictor of bowel and bladder complications from treatment.[3] Patients with active collagen vascular disease,[5]

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inflammatory bowel disease,[6] and vascular disorders such as diabetes and hypertension[7,8] may also be at higher risk for RT-related toxicity. Obesity,[9] low body mass index, and White ethnicity are also independently associated with increased toxicity.[10]

Several RT options are available for the treatment of pelvic tumors, including 3D conformal radiation therapy (3D-CRT), intensity-modulated RT (IMRT), or brachytherapy (BT).[11] Technological improvements, such as dose reduction and decreased radiation fields, have decreased radiation morbidity since 1990.[12] Furthermore, modern techniques such as IMRT are associated with excellent outcomes and limited rates of toxicity.[13,14] For example, severe late side effects resulting from RT are becoming rare in early stage cervical cancer, and most radiation-related comorbidities identified on imaging scans are clinically silent.[15]

Understanding the late side effects associated with pelvic RT is critical for developing strategies to both minimize the risk of long-term complications and improve the quality of life (QOL) of patients. This review aims to summarize the late side effects associated with RT in the pelvis and the respective interventions that may help treat toxicities.

Gastrointestinal Toxicity

Gastrointestinal toxicity is the most common side effect related to pelvic RT in both acute and late phases. Acute GI symptoms typically resolve within 2-4 weeks after treatment; however, they can sometimes progress to chronic toxicity, which can lead to worsening in QOL, especially in patients receiving definitive RT.[16-18] Chronic RT side effects in the bowel can have a latency period that varies from 6 months to several years. Most of the cases resolve within 12 months; however, lower-grade toxicity or progression to a higher grade is also commonly reported.[18]

Risk Factors

Several risk factors are associated with increased risk of GI toxicity. Age (60 y or older) is associated with a higher cumulative incidence rate of serious small intestinal obstruction or perforation.[19] Diabetes, atherosclerosis, or inflammatory bowel disease are also associated with an increased risk of toxicity from RT. The frequency of side effects in patients with a history of abdominal surgery or adjuvant RT is also increased.[18-20] For example, previous hysterectomy has been shown to increase the risk of RT toxicity due to the anatomic position of bowels deeper in the pelvis with a higher likelihood of being in the radiation field.[17] Additionally, rectal bleeding may be exacerbated in patients using anticoagulants.[20]

Small Bowel Toxicities

Both the small intestine and colon are susceptible to RT toxicity delivered within the pelvis, but the small intestine is more vulnerable due to its high epithelial mitotic rate, leading to more acute side effects. The injury can lead to focal ischemia and fibrosis, with the development of ulcers, strictures, and lower GI bleeding.[11] Severe late small bowel toxicities are rare and can present with fistula, obstruction, or hemorrhage.[21]

Diarrhea and Malabsorption

The mucosal atrophy and loss of mucin-producing goblet cells associated with RT can lead to chronic diarrhea and malabsorption. For chronic diarrhea, a multidisciplinary approach is usually helpful and antidiarrheal medications are often required. Radiation therapy to the distal ileum can cause vitamin B12 deficiency in up to 20% of patients. For malabsorption, vitamin replacement may be needed. Cholestyramine can be used when bile salt malabsorption is present.[22] Dehydration or constipation can occur as a result of impaired water absorption due to colonic radiation injury.[23] Perioperative nutritional therapy is an important intervention to help with chronic malnutrition observed in patients with prolonged chronic radiation enteritis.[24]

Obstruction/Ileus

Fibrosis of the intestinal wall can lead to dysmotility and the risk of obstruction.[7] For recurrent ileus or obstruction, the best option is conservative management, when possible, but sometimes surgery is required.[25]

Radiation Proctitis

Radiation therapy can lead to vascular sclerosis, which can then cause mucosal telangiectasias or ulceration, most commonly in the rectosigmoid colon. Patients most often present with symptoms of painless hematochezia, tenesmus, or pain. A colonoscopy is typically performed to exclude malignancy, and argon plasma coagulation can be performed at that time to help with bleeding vessels.[26] For rectal proctopathy, it is extremely important to avoid constipation. Sucralfate and hydrocortisone enemas can help protect the injured mucosa.[27] Guidelines from the Multinational Association of Supportive Care in Cancer note that hyperbaric oxygen treatment (HBOT) can be helpful for mucosal injury.[28] One study

indicated that topical formalin was as effective as argon plasma coagulation for bleeding control.[29] Topical butyrate is not helpful for chronic proctitis but can be helpful for acute proctitis.[30]

Fecal Incontinence

Fecal incontinence is a rarer late side effect of pelvic RT.[31] Surgical management is not typically indicated due to wound-healing issues postradiation.[31]

Secondary Malignancy

Secondary malignancy is a potential late side effect of RT. A meta-analysis showed an increased risk for rectal cancer after RT for cervical cancer (relative risk [RR] 1.43; 95% CI, 1.18-1.72) and prostate cancer (RR, 1.36; CI, 1.10-1.67). However, no relation was seen in patients with ovarian cancer and the modality of RT did not influence the incidence of rectal cancer postpelvic RT.[32]

Dosimetric and Planning Considerations to Reduce GI Toxicity

Some RT techniques can decrease the total radiation dose delivered to the small bowel, such as IMRT when compared with 3D-CRT,[33,34] reducing the incidence of late severe GI obstruction after postoperative pelvic RT.[35] The 3-year cumulative incidence of grade 2 or higher GI adverse events after image-guided IMRT (21%) was significantly lower than that of 3D-CRT (42%) (hazard ratio, .46), with noninferior clinical efficacy.[36,37]

Chronic rectal toxicity is correlated to the volume of the rectum receiving 70 Gy or more (V70) and should be kept as low as possible.[38] Grade 2 rectal toxicity is lower with IMRT (5%-21%) compared with 3D-CRT.[39,40] Also, the Post Operative Radiation Therapy in Endometrial Carcinoma 2 Trial (PORTEC 2) demonstrated increased levels of GI symptoms and lower QOL in patients receiving postoperative external-beam radiation therapy (EBRT) compared with vaginal BT.[41,42]

The use of image guidance and/or placement of spacers prior to and during planning may also reduce the dose delivered to organs at risk (OARs) and subsequent GI toxicity.[32,43] For example, results from the prospective EMBRACE study, which utilized MRI-guided adaptive BT for cervical cancer, reported that a rectal D2cc equivalent dose in 2 Gy fraction (EQD2)3 < 65 Gy was associated with half the risk of proctitis compared with a rectal D2cc (EQD2)3 ≥ 65 Gy.[43] Hydrogel spacers are employed at some institutions to decrease dose and toxicity by placing a physical spacer to protect OARs in gynecologic and prostate cancer.[42] Pelvic RT is also often delivered with instructions for the patient to have a full bladder, which allows displacement of the bowel superior to the pelvis, reducing the risk of bowel toxicity.

Urinary Toxicity

Genitourinary late side effects usually start 1-3 years after treatment, although higher doses of radiation can prolong latency time.[44] They occur due to epithelial and microvascular changes mediated by fibrosis (lower bladder capacity and loss of compliance) and may include hemorrhagic cystitis, urethral and ureteral strictures, urinary fistulae, and secondary primary malignancies. Radiation therapy has also been linked with infertility, lower urinary tract dysfunction (urge incontinence), bladder fibrosis, and necrosis.[45] Measurable differences in QOL can persist for more than 15 years, specifically because of urinary urgency, incontinence, and limitations in daily activities due to bladder symptoms.[46]

Risk Factors

Some patient-related factors can influence radiation-related toxicity. The use of anticoagulants increases the severity of postradiation hematuria. Obesity and heavy smoking are associated with a higher risk of bladder complications following RT for cervical cancer, especially fistula formation and hemorrhagic cystitis.[3]

Bladder Ulceration

One of the most common and severe effects related to higher doses of radiation is persistent nonhealing tissue, which can lead to bladder ulceration and stone formation. However, even in the definitive treatment of cervical cancer, where higher cumulative doses to the bladder are seen due to the combination of pelvic RT combined with BT, the probability of late genitourinary (GU) grade 3 or 4 side effects (**Table 1**) is still low, at less than 3%.[47]

Hemorrhagic Cystitis

Hemorrhagic cystitis may be a potentially life-threatening complication of pelvic RT. In a study of 1784 patients treated for cervical carcinoma with BT or EBRT, the incidence of hemorrhagic cystitis was 6.5% and the mean interval to the onset of symptoms was 35 months after completing RT. However, some patients developed hemorrhagic cystitis as late as 20 years after treatment; hence, radiation-induced cystitis must be considered at any time following the completion of RT.[48]

Treatment for hemorrhagic cystitis is usually conservative because surgical intervention can precipitate toxicity given the poor vascularity and healing after radiation. Treatment

Table 1. RTOG/EORTC Late Radiation Morbidity for Pelvic Tissues[129]

TISSUE	GRADE			
	1	2	3	4
Skin	Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration
Subcutaneous tissue	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; < 10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture > 10% linear measurement	Necrosis
Mucous membrane	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucous	Marked atrophy with complete dryness	Ulceration
Small/large intestine	Mild diarrhea; mild cramping; bowel movement 5 times daily; slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement > 5 times daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/perforation fistula
Bladder	Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)	Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria	Severe frequency and dysuria; severe telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (< 150 cc)	Necrosis/contracted bladder (capacity < 100 cc); severe hemorrhagic cystitis
Bone	Asymptomatic; no growth retardation; reduced bone density	Moderate pain or tenderness; growth retardation; irregular bone sclerosis	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis/spontaneous fracture

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group.

options include hydration, blood transfusions, and bladder irrigation with clot evacuation. In severe cases, embolization can also be considered. Other options include HBOT, intravesical formalin, argon plasma coagulation, endoscopic procedures, botulinum toxin injection, or systemic therapy.[11]

Fistulas

Urethrovaginal and vesicovaginal fistulas are more common with high-dose focal radiation injury and are directly influenced by tumor invasion of GU structures before therapy. In a review of women diagnosed with stage IVA cervical cancer (invasion of the bladder or rectum), 48% developed a fistula at a median time of 2.9 months from cancer diagnosis. In this study, there was no difference between women treated with radiation alone compared with chemoradiation in the incidence of fistula formation.[49]

Hematuria and Radiation Cystitis

Sodium pentosan polysulfate has been tested for radiation-induced hematuria with promising results.[50] Symptomatic improvement with hyperbaric oxygen is reported for late radiation cystitis.[51]

Dosimetric and Planning Considerations to Reduce Toxicity

Localized dose to the bladder neck is a potential predictor of urinary incontinence, whereas weaker associations are observed between urgency and some bladder-wall parameters.[52]

Apart from the primary site of treatment, GU toxicity is also affected by total radiation dose, treatment volume, treatment modality, and treatment technique. With more typical doses of EBRT for gynecologic cancers (40-50 Gy in 1.8-2 Gy fractions), the likelihood of bladder side effects of moderate to severe intensity is low;[53] however, focal therapy with BT is associated with higher GU morbidity.[14,20] For example, the risk of late side effects with the incorporation of 3D treatment planning into BT correlates best with the dose received by bladder D2cc (EQD2)3

per EMBRACE with the complication probability for bladder D2cc (EQD2)3 of 101 Gy (EBRT + BT) being approximately 10%. More recent published data recommend a lower bladder dose constraint of D2cc (EQD2)3 ≤ 80-85 Gy, but only in the absence of bladder involvement by tumor.[37,54,55]

Gynecologic Organ Toxicity

Vagina

Toxicity to the vagina is commonly seen after RT for cervical and uterine cancer, which can lead to sexual dysfunction due to vaginal dryness, dyspareunia, and vaginal stenosis, impairing the QOL.

Risk Factors

The incidence is higher in locally advanced tumors, with more than half of the women reporting sexual dysfunction after RT.[56] Vaginal toxicity is lower when RT is applied as an adjuvant treatment with surgery compared with definitive RT alone.[57] Vaginal shortening is more common in patients with advanced age, concomitant chemotherapy, higher vaginal RT doses, and lack of vaginal dilator use compliance.[25,58-61]

Vaginal Ulceration

Full-thickness vaginal ulceration and necrosis are rare after RT and more frequently occur in patients requiring interstitial BT for vaginal cancers.[25] Necrosis is more common in the acute phase and the distal vagina has less radiation tolerance. For vaginal ulcerations, management is initially conservative. Options for vaginal mucosal injury include hydrogen peroxide douching, pentoxifylline, or HBOT.[62,63]

Fistulas

Uncommon but potential complications of pelvic RT are also rectovaginal and vesicovaginal fistulas.[49] They primarily occur in patients who require high doses of radiation to control gross disease involving the vagina or due to tumor invasion of adjacent organs. Interstitial BT may increase this risk compared with intracavitary BT.[49] Conservative management of fistulas is advised because surgical repair can precipitate complications. Like vaginal ulcerations, HBOT and pentoxifylline can be used.[62,63]

Vaginal Stenosis

The most common late vaginal side effect is vaginal stenosis, which can occur both with EBRT and BT. The incidence of vaginal stenosis varies widely between available studies, with rates between 2.5% and 88%.[61] Dyspareunia (or vaginismus) is a frequent complaint due to the shortening of vaginal length and the narrowing of the vaginal vault or the development of adhesions. It is often accompanied by mucosal pallor and telangiectasias. Vaginal stenosis can interfere with the ability to perform surveillance pelvic exams or the ability to have comfortable vaginal intercourse. Vaginal stenosis is primarily treated, and even prevented, with vaginal dilators.[64]

Dosimetric Considerations to Reduce Toxicity

The biggest risk of vaginal stenosis is the combined treatment of pelvic RT plus BT.[60,61] A planning aim of ≤ 65 Gy EQD2 (EBRT + BT dose) to the rectovaginal reference point was proposed by Kirchheiner et al to reduce the risk of vaginal stenosis.[65]

Secondary Malignancy

Gynecologic radiation-induced secondary malignancies were found to be predominantly more aggressive, poorly differentiated, and had rare histologic types compared with sporadic tumors. The management is influenced by previous radiation doses and the location of the radiation-induced secondary malignancies.[66]

Ovaries

Radiation toxicity to ovaries includes infertility or premature ovarian insufficiency (POI) (defined as menopause before 40 y of age) because ovaries are very sensitive to low doses of radiation, even with small fraction sizes.

Premature Ovarian Insufficiency

Oocytes are the most sensitive cells within the ovary, and even low doses of radiation can lead to hormonal changes, hot flashes, mood changes, and vaginal dryness.[67] POI is expected when ovaries remain within the radiation field for the treatment of adult malignancies, with age-dependent sensitivity to radiation.[67]

The dose predicted to result in POI immediately following treatment is 16.5 Gy at 20 years old and 14.3 Gy at 30 years old,[67] but even ovarian doses of 4 Gy or less have been associated with premature menopause.[68] With lower dose exposures, estrogen levels can recover between 6 and 18 months, but early menopause is still likely to occur.

Menopausal symptoms usually respond to the use of systemic or vaginal hormone replacement therapy. Some studies also show the benefits of serotonin reuptake inhibitors.

Fertility

Doses as low as 1.7-2.5 Gy have been associated with significant but temporary amenorrhea or sterility without ovulation for several years.[69] Women who desire future pregnancy should be evaluated by reproductive endocrinology before initiation of RT to discuss the options of ovarian transposition, ovarian stimulation with oocytes,

or embryo cryopreservation or ovarian tissue preservation, as clinically appropriate.

Ovarian Transposition to Preserve Ovarian Function

Laparoscopic ovarian transposition may be performed in premenopausal women < 40 years old before pelvic radiation to enhance the preservation of ovaries, but the surgeon must understand the radiation field (transposed ovaries should be at least 3 cm above the radiation field). High rates of preservation (80%-88%) have been reported, with an improved likelihood of success when both ovaries are transposed.[70,71] Transposition is only considered if the patient has a low risk that their primary malignancy will have ovarian spread.[70,71]

Uterus

Pelvic radiation is also correlated with increased rates of miscarriage, preterm labor, low birth weight, and placenta accreta due to arteriolar damage, decreased fetoplacental blood flow, and fibrosis, which decreases the uterine distension after pelvic RT.[72,73]

Skin Toxicity

A wide spectrum of injuries can arise as radiation-induced skin toxicities, highly variable in incidence, temporality, and severity.[74-76] Acute dermatitis usually resolves in 1-3 weeks. Late skin side effects can include persistent hyperpigmentation, telangiectasia, and radiation fibrosis. Irradiated skin also presents an increased risk of developing skin cancer.[77,78]

Risk Factors

Patient comorbidities such as vascular compromise (smoking history and diabetes) are associated with increased risk of skin toxicity as well as collagen vascular disease (specifically scleroderma). Obese patients develop skin toxicity more frequently due to increased apposition of skin in the groin and pannus. Immunocompromised patients and HIV-seropositive patients also develop increased toxicity from RT, although the reported literature does not correlate CD4 count with outcomes.[79-81]

Treatment-Related Factors

Factors depending on the type of treatment can also influence the development of skin toxicity. Treatment-related factors, including lower megavoltage photon beam energy, proton therapy, field size, and tangential fields, can increase the risk of skin toxicity.[82-84] Modern pelvic RT using high-energy photons (10-18 MV) and multifield arrangements are associated with skin-sparing effects. Consequently, radiation dermatitis for gynecologic cancer is usually mild. However, when the radiation target volumes are close to or involve the skin surface, the incidence of skin reactions is higher. For example, less than half of patients with endometrial cancer present with skin reactions, while almost all patients treated with RT for vulvar cancer will develop skin toxicity to some degree, and grade 3 skin reactions may become common.[82-84] If inguinal nodal basins are included in the treatment plan, the skin is exposed to higher doses of radiation and the risk of toxicity is higher.[82] Many of the cases are mild or moderate, but serious injury may also develop and result in RT break or disability.[82,85] The use of IMRT may reduce the risk of grade 3 or higher skin toxicities, minimizing skin doses outside the target volume.[74,85] Dose, fractionation, concurrent radiosensitizing systemic therapy, and re-irradiation are also important considerations[86] that may affect the risk of skin toxicity.

Treatment of Skin Toxicities

Skin hygiene and water-based creams are helpful for skin erythema or dry desquamation. Moisturizers can address dry skin.[87] Topical anesthetics can be used for the management of patient discomfort. Silvadene cream may be used to manage moist desquamation. Radiation-induced telangiectasias can be treated with laser intervention if a patient has cosmesis concerns.[26] Radiation fibrosis of the skin can be difficult to treat, but in some cases, may respond to oral pentoxifylline and vitamin E.[88] Management of chronic ulcerations includes wound care with dressing, ointment, debridement, and, if needed, a biopsy to rule out skin cancer.[89]

Bone Toxicity

Radiation therapy side effects within the bones typically occur chronically, over the course of several years. Among the most common changes are osteopenia, increased bone density (osteosclerosis), and changes in the sacroiliac joints.[90]

Pelvic Fractures

Radiation-related insufficiency fractures can develop at the pubic symphysis,[91] the pubic rami, and, most commonly, the sacrum.[92,93] The clinical presentation is usually localized pain.[94]

Risk Factors

Risk factors such as osteoporosis, kidney or vascular disease, and long-term use of steroids are associated with pathological fractures or osteonecrosis.[95-97] The risk of RT-related fractures varies based on the type of malignancy

treated. The rates are the highest for anal and cervical cancers (14% and 8%-20%, respectively).[92,94,98] For rectal cancer, the rates of pathological pelvic fractures are slightly lower, reported between 7% and 11%.[99] In patients with prostate cancer, a small retrospective series in patients primarily treated with 3D-CRT showed a pelvic fracture incidence of 6.8% over the 5 years following whole-pelvic radiation.[100] Other risk factors include older age, pre-existing osteopenia, diabetes mellitus, low body weight, and higher radiation doses (above 50 Gy).[92,101]

Diagnosing Pelvic Fractures and Other Bony Changes

Diagnosis is traditionally made with imaging, with CT showing peripheral sclerotic areas or fracture lines.[97,102] In some cases, an MRI will be warranted, with an acute fracture line showing edema (low T1, high T2).[103] Later findings will include linear sclerosis (low T1, low T2) surrounding the fracture.[103] Bone scintigraphy is also sensitive, showing the characteristic Honda sign.[94,103] It is important to rule out metastatic disease if pathological fracture is suspected, but biopsy should be carefully considered since the findings of healing bone can mimic malignancy.[104]

Prevention and Treatment of PIF

The prevention of osteoporosis is important to preserve bone mineral density. Calcium and vitamin D supplements, as well as weight-bearing exercises, can be helpful. Bisphosphonates, hormonal therapy, and calcitonin can also be used for fracture prevention.[104] The use of IMRT may also help reduce the risk of pelvic insufficiency fractures (PIFs). A systematic review and meta-analysis identified the 5-year incidence of PIFs at 15% following pelvic radiation (59% symptomatic); however, fractures were less likely with IMRT, with an incidence of 4.8%.[105] Patients can typically be managed with pain medication and rest. Pentoxifylline, alone or in combination with other therapies, can be safe and effective for fractures or osteoradionecrosis, but requires further investigation.[95,106]

Secondary Malignancy and Radionecrosis

Secondary malignancies may arise related to radiation, most commonly hematologic malignancies, and bone osteosarcomas.[107,108] Osteosarcomas may have similar features to radiation necrosis, another potential late complication from radiation. Radiation necrosis often has a long latent period and is more common than malignancy. Lack of pain generally favors necrosis alone. Globular calcification may occur in radiation necrosis and usually is not present with malignancy. Lack of progression on serial imaging also favors radiation necrosis.[109] There are several case reports regarding avascular femoral head necrosis from radiation, which is an uncommon but very serious complication that can lead to significant morbidity, especially in older patients.[97]

Hematologic/Bone Marrow Toxicity

Hematologic toxicity is responsible for the overwhelming majority of acute grade 4 radiation toxicity. Given the high replication rates, hematopoietic cells are very sensitive to lower doses of radiation.[110] The pelvis contains at least 25% of the bone marrow reserves. It has also been established that IMRT can minimize the dose of radiation to the bone marrow. Several studies suggest that this lowers the risk of hematologic complications and may improve the likelihood of completing all intended doses of chemotherapy.[107,108,111]

Follow-up with weekly blood counts is usually performed in patients with concurrent chemotherapy. If the absolute neutrophil count drops below 500/µL or platelets are less than 40,000/µL, radiation treatment is suspended. Hemoglobin levels are preferably maintained at more than 10 mg/dL, especially in patients with cervical cancer.[20]

Peripheral Nerve Toxicity

Peripheral nerve toxicity after pelvic RT is a relatively less common toxicity, with radiation-induced lumbosacral plexopathy (RILP) being the most common complication.[112]

Radiation-Induced Lumbosacral Plexopathy

Radiation-induced lumbosacral plexopathy translates into damage to the lumbosacral plexus, which includes the lumbar (L1-L4) and sacral (L5-S5) portions of the lumbar plexus, which has both motor and sensory fibers to the abdominal wall, anteromedial thigh, and leg.[113] The exact mechanism of RILP remains not fully understood, with recent investigations indicating microvascular injury followed by the development of radiation-induced fibrosis as the most accepted pathogenesis.[112,114]

Risk Factors

Several factors are linked with RILP, including larger total delivered doses (>50 Gy to the plexus), higher amounts per fraction (2.5 Gy), heterogeneous high-dose distribution, and possibly BT.[112,114,115]

Presentation and Diagnosis

The onset of RILP is slowly progressive, mostly affecting motor fibers and function. Sensory

impairments and neuropathic pain are typically developed later. Symptoms start usually unilaterally and then progress to bilateral, typically asymmetric, damage. Knee-jerk and ankle reflexes are almost always decreased.[112,114,116] RILP may develop as a very late complication from radiation, with a case report mentioning the condition 36 years after RT for cervical cancer.[117]

Radiation-induced lumbosacral plexopathy is a diagnosis of exclusion, with some other possible diagnoses including metastasis, local tumor growth, or degenerative compression of lumbosacral nerve roots. Axial imaging is valuable for diagnosis. PET scanning using F-18 fluorodeoxyglucose (FDG) can aid in diagnosing recurrent tumors,[118,119] but it has limited potential in identifying intrinsic lumbosacral plexus pathologies.[120] Other potential differential diagnoses to consider include lumbar infection and connective tissue diseases, including systemic vasculitis and polyneuropathy. Workup can also include laboratory studies, cerebrospinal fluid analysis, nerve conduction studies, and needle electromyography.[121,122]

Treatment and Prevention of RILP

Unfortunately, no curative therapy is available for RILP. The therapeutic modalities mostly target symptomatic improvement, with neuropathic pain being the most common type of pain, for which several guidelines have been published.[123,124] Tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitor antidepressants, pregabalin, and gabapentin are the most acceptable.[123] Adjuvant rehabilitation is recommended, especially neurostimulation physical therapy.[124,125] Psychotherapy can be recommended as a second-line therapy.[124] Once the motor deficit is seen, translating into severe axonal damage, recovery is rarely described.[112,114,126,127] Spontaneous recovery is less common.[128]

To prevent RILP, the optimal strategy is to avoid exceeding dose-volume constraints when radiation is delivered. This precludes damage to at-risk organs, for which state-of-the-art RT technologies (eg, volumetric-modulated arc therapy) can be used.[96]

Conclusion

Radiation therapy offers valuable treatment options for gynecologic, prostate, and GI cancers. However, it comes with the potential for acute and chronic toxicity that can significantly impact patients' QOL. The severity and occurrence of these side effects depend on several factors, including the treatment area, tissue volume in the radiation field, treatment schedule, total dose, dose per fraction, and RT type.

There are several options for the prevention and treatment of these late effects, and patients should be appropriately counseled prior to treatment and monitored during and after treatment to assess and treat late toxicities. Referrals should be made to appropriate specialists in other disciplines to help with the long-term management of radiation-induced late toxicities. Patients should also undergo routine surveillance and standard screening for other malignancies.

In conclusion, advancements in RT techniques and our understanding of patient-related factors influencing toxicity have led to improved treatment outcomes and reduced rates of late side effects. Future research should continue to focus on optimizing treatment strategies to minimize toxicity and enhance the QOL of patients undergoing pelvic RT for gynecologic cancers.

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