Introduction

Radiation therapy has been an effective therapeutic modality in the management of both benign and malignant tumors for over a century. The science and technology surrounding the delivery of this targeted treatment has significantly improved our ability to not only control tumors, but to also minimize the untoward complications of irradiating normal tissues. Advances in radiation and surgical techniques have significantly decreased the incidence of debilitating lymphedema (LE); however, this side effect will continue to occur in all patients who undergo surgery and/or radiation therapy on lymphatic-rich tissues. In this article, we will briefly review the pathophysiology of radiation-induced LE and discuss some of the more common radiation treatment techniques and indications employed in the management of breast, gynecologic and prostate cancers.

Etiology of Radiation-Induced Lymphedema

Radiation causes acute and chronic effects in most soft tissue sub-types. These effects are mediated by a complex process involving hormonal and oxidative changes within the tissue microenvironment. These changes persist for years, leading to apoptosis, production of free radicals, and changes in gene expression. This causes increased fibrosis, and de-creased vascular/lymphatic vessel organization and function. \(^1\) LE occurs as a result of the late effects on the lymphatic vessels and soft tissues, which cause obstruction and mechanical dysfunction due to radiation and surgical changes. If these effects are allowed to progress, they can lead to chronic dermal congestion, fibrosis, decreased limb mobility, pain and paresthesias.

Radiation late-effects are dependent on multiple factors, including: radiation dose, volume of irradiated tissue, and the histologic components of the tissue irradiated. \(^1\) The variability in these factors makes the development of generalized statements, regarding radiation side effects, a more complicated matter.

Radiation therapy is most commonly delivered using a small daily dose, called a fraction of radiation, 5-days per week for 1-8 weeks. This as well as the total or cumulative dose is dependent on the indication, site of disease, disease type and the patient’s performance status. Late tissue effects are more likely to develop when larger daily doses and/or higher total doses are delivered. This is due to the fact that irradiated soft tissues are less able to repair the ionizing effects of larger daily doses and/or larger total doses.

The amount of tissue volume irradiated is also an important factor in the development of both acute and late effects. Even small increases in the size of the radiation field can potentially lead to a greater than expected degree of soft tissue side effects because volume increases exponentially. As larger amounts of tissue are irradiated, the degree of vascular and lymphatic injury/dysfunction, obstruction and parenchymal inflammation increases. Over time, these injuries can overwhelm the endogenous repair mechanisms and collateral vasculature of the affected tissues leading to fibrosis and/or edema.

Lymph node bearing areas to include inguinal, axillary and pelvic lymph nodes are frequently irradiated during the treatment of many cancers. There are certain high-risk indications when the regional lymphatics need to be treated with both surgery and radiation therapy. Individually, these interventions create lymphatic obstruction/disruption; however, clinically evident LE may not occur. This incidence increases dramatically when these areas are subjected to both therapeutic modalities.

Radiation Therapy in the Management of Breast Cancer

Adjuvant breast irradiation is almost always recommended following any...
breast conserving surgery. The breast can either be radiated with whole breast irradiation (WBI) or partial breast irradiation (PBI) techniques. The tissue at risk for local recurrence of breast cancer is the entire anatomic extent of the breast. This extends superiorly to the clavicle, inferiorly to approximately 2cm below the inframammary fold, laterally to the mid-axillary line, and medially to the mid-sternum. The standard of care for treating breast cancer after breast conserving surgery is WBI, which includes all ipsilateral tissues within these boundaries. Radiation can be delivered with external beam radiation therapy (EBRT) using a linear accelerator and/or through implantable, temporarily placed radiation sources known as brachytherapy.

The vast majority of patients who receive WBI are treated with EBRT. This technique requires a course of treatment, frequently 6-7 weeks long of daily treatment, 5 times per week. The planning for EBRT begins with a session called a simulation, where the radiation oncologist physically marks the borders of the breast on the patient. The patient then undergoes a CT scan of the chest so that the tissue at risk for local recurrence of breast cancer is treated. The planning for EBRT begins with a session called a simulation, where the radiation oncologist physically marks the borders of the breast on the patient. The patient then undergoes a CT scan of the chest so that the tissue at risk for local recurrence of breast cancer is treated. The planning for EBRT begins with a session called a simulation, where the radiation oncologist physically marks the borders of the breast on the patient. The patient then undergoes a CT scan of the chest so that the tissue at risk for local recurrence of breast cancer is treated. The planning for EBRT begins with a session called a simulation, where the radiation oncologist physically marks the borders of the breast on the patient. The patient then undergoes a CT scan of the chest so that the tissue at risk for local recurrence of breast cancer is treated. The planning for EBRT begins with a session called a simulation, where the radiation oncologist physically marks the borders of the breast on the patient. The patient then undergoes a CT scan of the chest so that the tissue at risk for local recurrence of breast cancer is treated. The planning for EBRT begins with a session called a simulation, where the radiation oncologist physically marks the borders of the breast on the patient. The patient then undergoes a CT scan of the chest so that the tissue at risk for local recurrence of breast cancer is treated.

During the treatment, the patients will not feel or sense the radiation, and they will usually not begin to experience any side-effects until 2-3 weeks into treatment. Many patients will develop mild fatigue, skin redness/hyper-pigmentation, and increased breast sensitivity as the course of treatment progresses. In some patients, the skin will develop dry or moist desquamation by the end of treatment. These effects are self-limiting and usually resolve within weeks-to-months after the completion of therapy.

The regional lymphatics in the axilla, supraclavicular fossa and internal mammary chain are only irradiated in specific circumstances when there is an increased risk of lymph node involvement or recurrence. Patients who have non-invasive breast cancer are not prescribed radiation to these regional lymphatics, as the risk of lymphatic spread is very uncommon. Invasive breast cancer is treated more aggressively due to the increased risk of lymphatic spread.

A sentinel lymph node biopsy (SLNB) is a procedure where a radioactive and/or blue dye is injected into the breast tumor or cavity and is allowed to migrate to the first echelon node(s), called the sentinel node. If the patient has a SLNB and no metastatic cancer is found, the patient will not require any further lymphatic surgery or lymphatic radiation. If however, the sentinel node is positive for cancer, the patient will require a more extensive axillary lymph node dissection (ALND). This procedure has a higher incidence of upper extremity LE than SLNB, and thus is no longer recommended as the first-line surgery in the absence of clinically involved axillary nodes.

Although there are no long-term, randomized-controlled-outcome data comparing WBI versus PBI, many patients with small (<3cm), low-intermediate grade breast cancers are currently being offered PBI. The rationale for PBI is that the greatest risk of a localized recurrence is within 1-2 cm of the tumor bed. PBI can be delivered either using EBRT or brachytherapy. In PBI, only the tumor bed cavity and the immediately adjacent tissues are treated.

Brachytherapy can be done with either implanted catheters or a balloon implant, which is placed into the tumor cavity. Patients are then either admitted for 4-5 days, in a radiation-shielded room, while the dose is delivered or they are treated as an outpatient, using a daily radiation delivery system. The clear advantage of using brachytherapy is the convenience for the patient. The patient undergoes radiation for 4-5 days as compared to the 6-7 week EBRT course. Prospective, non-randomized data demonstrate that, in well-selected patients, this technique offers excellent local control (>95%) and cosmetic outcome.

Following mastectomy, some patients will be offered radiation therapy to the chest wall, scar and/or regional lymphatics. This is almost exclusively done using EBRT, for 6-7 weeks. The regional lymphatics are irradiated based on the same criteria as in the above-mentioned sections on breast conserving treatment.

LE is a common side effect of breast and/or regional nodal irradiation. The incidence of ipsilateral upper extremity LE increases with combined surgery and radiation to the regional lymphatics. The occurrence of LE after a SLNB alone is 2.6–3.0%. With this patient population, the tumor location in the upper outer quadrant was identified as a risk factor for the development of LE. If an ALND is performed alone, the incidence rate of LE rises. It has been reported that after a level I/II ALND the incidence of LE of the upper arm was 14%, 12% in the forearm, and 16% in the hand utilizing a diagnostic scale of a circumference difference greater than 5%. The incidence rate of upper extremity LE after an ALND and/or radiation therapy ranges from 6.0–33.5%.

Although no randomized data have been published, there is a suggestion from the available literature that breast edema occurs much more commonly after WBI as compared with PBI. Breast LE following WBI ranges from 8 to 25% in patients who undergo a limited ALND. In a recent study, the use of whole breast intensity modulated radiation therapy...
(IMRT) has been shown to possibly decrease the risk of chronic breast edema from 30% down to 3% as compared with the conventional WBI techniques. A three-year median follow-up after lumpectomy and PBI using EBRT found a zero percent rate of breast edema. While reports on a four-year median follow up of patients undergoing lumpectomy and PBI using intraoperative electron beam therapy found a 2% (1 out of 47 patients) rate of breast edema.

Breast LE is an often-overlooked area of breast cancer treatment-related side effects. Breast edema occurs in 6–48% of patients after receiving surgery and radiation therapy for breast cancer. The incidence rate of breast lymphedema after a lumpectomy alone is 6%. This rate drastically increases with nodal dissection and radiation therapy. The incidence of breast lymphedema after a sentinel lymph node biopsy and radiation therapy is 23%; with an axillary lymph node dissection and radiation therapy is 35% in node negative patients; and 48% in node positive patients.

**Radiation Therapy in the Management of Gynecologic Malignancies**

**Cervical cancer.**

Radiation is commonly used as a definitive or adjunctive treatment in patients with cervical cancer. In addition to the cervix, uterus and paracervical tissues, the regional lymphatics are often included. These consist of paracervical, pelvic sidewall/obturateur and external iliac nodes (and para-aortic nodes in more advanced disease.) Total abdominal hysterectomy (TAH), with or without a pelvic lymph node dissection (PLND), is the most common surgical procedure for the earliest stages of invasive cervical cancer. As the disease becomes more extensive, a radical hysterectomy (RH) is recommended. Adjuvant radiation therapy is offered in cases when there is an increased risk of recurrence after surgery (i.e. large and/or deeply invasive tumors, lymphovascular space invasion, positive surgical margin, involved lymph nodes and parametrium.) This generally involves a 5-week course of EBRT, with or without chemotherapy, to the tumor bed and pelvic lymphatics. Definitive radiation is often recommended when there is higher probability of requiring adjuvant radiation therapy after surgery. Studies have demonstrated a greater incidence of complications and side-effects from combined surgery and radiation to the pelvis than either modality alone. A single therapeutic modality is therefore preferable. In cases where definitive radiation is recommended, EBRT and brachytherapy are commonly employed. Generally, 5-weeks of EBRT are delivered to the tumor, surrounding tissues and lymphatics. This is then followed by a series of brachytherapy sessions comprised of either one or two inpatient treatments, or 1-2 weeks of multiple outpatient treatments.

The EBRT technique is delivered using either opposing anterior/posterior beams or anterior/posterior and lateral beams. Some groups are using an EBRT technique, called intensity modulated radiation therapy (IMRT), to deliver highly conformal doses of radiation to the areas at risk. IMRT uses a complex computer treatment planning system that employs multiple non-opposing beams to “paint” defined radiation doses throughout the target volume. This technique seems to reduce the unintended side effects of radiation doses to non-target tissues such as small bowel, bladder, and rectum.

Acute radiation-related side effects often occur within the first 2-4 weeks of treatment, and may include: fatigue, skin redness, loose stools, urinary frequency and dysuria. Late effects manifest months to years after treatment, and may include: vaginal dryness and shortening, dyspareunia, radiation proctitis or cystitis, sacral plexopathy, changes in bowel function, and lower extremity lymphedema.

The incidence in lower extremity LE following surgery and radiation therapy in the treatment of cervical cancer ranged from 21-49%. In a retrospective study of early-stage cervical carcinoma treated with pre-operative radiotherapy and radical hysterectomy, LE occurred during the first year in 21% of the patients. In another retrospective study, cervical cancer patients were treated with radical surgery and post-operative radiation therapy with 31% of patients presenting with lower extremity LE. Patients being followed over a ten year period after undergoing radical hysterectomy followed by postoperative radiotherapy for carcinoma of the uterine cervix presented with LE at an incidence rate of 42% at five years, and 49% at ten years.

**Endometrial cancer.**

Most cases of endometrial cancer are treated with surgery alone (TAH/BSO +/- pelvic and para-aortic lymph node sampling.) However, when the risk of pelvic nodal involvement or vaginal cuff recurrence exceeds 5-10%, adjuvant radiation therapy may be recommended. The pelvic nodes are treated using a 5-week EBRT course. As with cervical cancer, some groups are using IMRT instead of the conventional opposed field radiation. The vaginal cuff (apex of the vagina) is treated using a series of outpatient brachytherapy sessions or a single inpatient session.

When EBRT is used, the acute radiation-related side effects are similar to those mentioned above for cervical cancer. The use of vaginal cuff brachy-therapy alone can lead to the development of acute radiation side effects, but skin redness does not occur because no external radiation beams traverse the skin. Fatigue, genitourinary and gastrointestinal symptoms may be more common.
testinal side effects are less frequent due to the very short range of the brachytherapy radiation dose. Late effects from EBRT may include: vaginal dryness and shortening, dyspareunia, radiation proctitis or cystitis, changes in bowel function, and lower extremity LE. A retrospective review of 517 endometrial cancer patients undergoing surgery and postoperative radiotherapy reported LE of the lower extremity as a complication in 11% of all cases. Vaginal cuff brachytherapy-alone can cause late vaginal cuff fibrosis, vaginal shortening, dryness and dyspareunia; rarely, vaginal cuff necrosis can occur.

**Vulvar cancer.**

EBRT is commonly the definitive therapeutic modality in the management of invasive vulvar cancer. The inguinal lymph nodes are the primary echelon drainage from tumors of this region and are often treated in this disease. Patients may undergo a superficial inguinal LND and/or radiation to these lymphatics. Typically, radiation is delivered with a combination of opposing anterior and posterior beams; however non-co-planar (IMRT) beams may be used instead.

The acute effects of radiation usually occur within the first 2-3 weeks of treatment, and often include: skin redness, desquamation, dysuria, urinary frequency, loose stools, and proctitis. The late effects often manifest months to years later and include: vaginal dryness, dyspareunia, vaginal and anal stenosis (from soft tissue fibrosis), rectal urgency and other bowel movement changes. Both radiation and lymph node dissection can individually cause lower extremity LE, but the combination of the two substantially increases this risk. A retrospective review of patients undergoing bilateral groin irradiation for vulvar cancer revealed a LE incidence rate of 6%, as compared to 12% of patients undergoing bilateral or unilateral inguinofemoral dissection.27

**Radiation Therapy in the Management of Prostate Cancer**

Prostate cancer is commonly treated with either surgery (prostatectomy +/- pelvic LND) or radiation therapy (EBRT or brachytherapy.) Choice of treatment is based on a variety of factors, including: age, performance status, stage of disease, tumor grade, and prostate-specific antigen (PSA). In both management approaches of radiation or surgery, the entire prostate is treated or removed.

Radiation therapy targets the prostate only and not the lymphatics when the risk of lymph node involvement is less than 15%, whereas the pelvic lymphatics are often included when the risk exceeds 15%. The radiation fields are commonly delivered from multiple beam angles, using the non-coplanar IMRT technique. IMRT allows a higher dose to be delivered to the prostate (+/- pelvic LNs), while minimizing the dose received by the adjacent non-target tissues such as small bowel, rectum, bladder, and femurs. In circumstances where the patient either has a positive surgical margin and/or a rising postoperative PSA, adjuvant radiation therapy to the prostate bed is frequently recommended. The lymphatics are generally not intentionally treated in these circumstances.

The incidence of post irradiation lymphedema was found to be strongly dependent on the extent of dissection performed to include biopsy only, limited/diagnostic dissection, or complete/therapeutic dissection.28 Patients undergoing limited/diagnostic dissection followed by pelvic irradiation have a 25-30% risk of developing lymphedema; versus a 66% risk in patients undergoing complete/therapeutic dissection followed by pelvic irradiation.28

**Conclusion**

Radiation-induced LE is an untoward complication of treatment to the lymphatics as part of the management of many common malignancies. This article briefly reviewed some of the indications, techniques and side effects of radiation therapy as they pertain to a few of the more frequently encountered oncologic tumors.

All patients undergoing surgery and/or radiation therapy for the treatment of these cancers are at risk for the development of secondary LE. Pretreatment patient evaluation and education regarding LE risk reduction practices should be performed. If lymphedema does develop, CDT is a viable therapy for the treatment and maintenance of the condition.

**REFERENCES**


