10/09/18

Chapter IX: Acute Radiation Effects: Organ Specific Organs Dose and Species Differences
Section h: Rectum – Bladder – Prostate
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Acute radiation effects on pelvic organs are well known to radiation oncologists, medical oncologists, and persons caring for cancer patients being treated for diseases of the pelvic organs. By understanding the toxicity of irradiation to pelvic organs, as observed in clinical radiotherapy, the reader can apply this knowledge to understanding radioisotope concentration in the bladder or partial body irradiation effects on the pelvis (for example, a total body exposure where the lower abdomen and pelvis is exposed while the rest of the body is shielded) during a radiation accident or radiation terrorist event.

Most patients receive a combination of external beam radiotherapy and brachytherapy (Defined as implantation of ionizing irradiation emitting sources into the organs themselves – or radiation from the inside out.). Gynecological Oncology patients treated for cancer of the cervix, endometrium, vulva, or vagina are at risk for acute radiation side effects very similar to male patients being treated for cancer of the prostate. In all patient groups receiving radiotherapy to the pelvis, there are bladder and rectal complications that can cause serious concern and risks must be minimized.

The general principles of radiation oncology apply to analysis of acute side effects for all pelvic organs, namely, total radiation dose, fraction size, and overall treatment time. Sophisticated treatment planning techniques became available in the 1990s, with the advent of 3-dimensional conformal radiotherapy treatment planning (1-2). During this same decade, the expansion of proton radiotherapy services (3) made available treatment planning techniques to conform radiation beam to target volume structures with even more normal tissue sparing. The use of Intensity Modulated Radiotherapy (IMRT) for photon/x-ray radiotherapy facilitated treatment planning volumes very similar to those shown for proton radiotherapy (4). Clinical investigators analyzing the side effects from radiotherapy and using each of these "modern" external beam treatment modalities have appropriately placed increased emphasis on analysis of late effects. These analyses point to the increased cure rate for patients presenting with cancer of the pelvic organs and recent publications have focused on long-term follow-up (5-6, 23).

Finally, for brachytherapy techniques, low dose rate radium and Cesium implants to the pelvic organs have been largely replaced by high dose rate (HDR) brachytherapy techniques, which are uncommon (7). Using HDR brachytherapy sources are not left in the patient with prolonged hospitalizations (50 hours or more). Rather, there is use of after-loading techniques, such that HDR brachytherapy sources including Iridium are periodically delivered through catheters placed into the target organ for short intervals of minutes to one hour, and then removed allowing patients to return to hospital rooms, or and in many cases remain ambulatory. The lack of need for 50 hours bedrest reduces the risk of thrombosis (blood clots).

This chapter will summarize acute radiation side effects from ionizing irradiation to pelvic organs and define methods for study of mechanisms.

Acute Radiation Effects on the Bladder

The bladder represents the pelvic organ with the greatest capacity for change in anatomic position and volume over time. Depending on fluid intake by the patient, kidney functions, the bladder expansion capacity may be significant. The bladder tissue is moved by expansion

superiorly when filled with urine and moves outside a radiotherapy treatment volume. For example, treating a patient to a target volume that focuses on the prostrate low in the pelvis can be achieved with reduced bladder toxicity by keeping the bladder full, and thus, a significant portion of the bladder will be out of the radiation field. In contrast, bladder emptying before radiotherapy of bladder cancer would be managed to produce the opposite effects. There would be a requirement to reduce the volume of the target organ, the bladder, and confine it within a small treatment target-volume low in the pelvis. A key principle in bladder cancer radiotherapy is to minimize external beam dose to organs in the transit volume including small intestine, rectum, prostate (in males), uterus, and ovaries (in females), and, of course, the surface area/volume of skin in the radiotherapy treatment field.

Radiotherapy techniques for the management of bladder cancer have changed significantly over the past several decades. The current standard Platinum compounds in chemotherapy of bladder cancer, as well as, Taxol, Etoposide, and other relatively new (and toxic) chemotherapy agents have facilitated reduction of bladder cancer volume for radiotherapy. Treatment of suspected positive or at-risk pelvic lymph nodes can be achieved with reduced radiotherapy dose to both nodes and the bladder if these "new" chemotherapy drugs are used (9). Early chemotherapy approaches included installation into the bladder of chemotherapy drugs such as Thiotepa (10). However, this therapeutic approach was limited to patients with superficial cancers of the transitional cell epithelium in the bladder, and could not be widely applied to tumors with a relatively large volume (10). Another change in management of bladder cancer in recent decades has been attention to new surgical techniques, which may remove a portion of the bladder(not a complete cystectomy) during the diagnosis and staging procedure (11). Brachytherapy techniques utilizing implantation of radium or Cesium needles as: ionizing radiation emitting sources were pioneered in the 1970s (11). These surgical techniques have been largely replaced by new external beam radiotherapy techniques. However, concern in radiotherapy of bladder cancer, also found in the radiotherapy approach to other pelvic organs, is the dose to the rectum (9). In all treatment decisions, careful attention to treatment planning is a major principle.

Radiotherapy doses of 50 Gy delivered in conventional fraction of 1.8 Gy to 2.0 Gy per fraction over 5-6 weeks are commonly used in patients, who are candidates for treatment of bladder cancer (9). The volume of tissue in the field is minimized by having patients void urine prior to each radiotherapy fraction (9). Finally, brachytherapy using high dose rate after-loading techniques can minimize the external beam dose and reduce the size of the normal tissue transit volumes thus reducing overall dose to normal tissues.

Common side effects of bladder cancer radiotherapy including: inflammation of the urethra, producing burning on urination, proctitis resulting from inflammation of the rectum, leading to painful bowel movements, and radiation dermatitis primarily in the inguinal folds of skin in the treatment volume (9).

Radiotherapy of bladder cancer in women also necessitates attention to treatment planning to minimize radiotherapy dose to the vulva and vagina by optimally reducing the risk of radiation dermatitis in these anatomic sites (9).

Acute Side Effects of Ionizing Irradiation to the Rectum

There has been a significant change in the management of both rectal cancer and anal cancer since the 1990s.

Combination chemotherapy regimens including: 5-Fluorouracil and Mitomycin-C (12) are highly effective for both local control and managing regional pelvic lymph nodes in patients with anal cancer. Combined modality treatments including: radiation and new chemotherapy drugs (12) have obviated the need for whole pelvis irradiation and in many cases, eliminated the need for brachytherapy of anal cancer (13). Surgical techniques have minimized the need for extensive resection, because of the advances in chemotherapy and the requirement for lower radiation doses.

As with female patients presenting with vulvar cancer, aggressive lymph node dissection for staging of inguinal lymph nodes and regional pelvic lymph nodes in anal cancer patients has been largely replaced by PET scanning (Positron Emission Tomography), which can identify positive nodes and allow staging without the need for aggressive surgical exploration (12). Anal cancer like vulvar cancer is commonly of squamous cell in morphology (12). Lymphatic drainage follows the similar routes in both disease categories (13-14).

Rectal cancer, defined as a primary tumor above the dentate line (anatomic separation between the squamous epithelium of the anus, and the glandular epithelium of the rectum, defines the diagnosis and the potential radiotherapy target volume. Rectal cancers are more commonly adenocarcinoma (12) and share a histology common to patients with colon cancer. In fact, patients are often categorized as having colorectal carcinoma (12). Improvements in chemotherapy have dictated a change in treatment patterns and protocols for rectal cancer. The common use of Irinotecan (CPT-11) combined with 5-Fluorouracil has been widely applied in the management of patients with colon and rectal cancer (15). PET scanning facilitates staging and decision making without the need for surgical exploration in all patients. For example, if there are widespread PET positive lymph nodes identified, this can be followed by sampling or confirmation of one or more positive areas to diagnose advanced stage. In contrast, those patients, who present with a localized node-negative rectal cancer, may require full pelvic exploration and biopsy of lymph nodes. Clinical pathways and staging determine whether patients may require whole pelvis radiotherapy or can be managed by localized excision and brachytherapy.

Patients, who require external beam radiotherapy of rectal cancer necessitate concern for radiotherapy side effects to the bladder and skin folds in the pelvis. The situation is somewhat the opposite of that described above for bladder cancer patients. High dose radiotherapy to the bladder is accompanied by concern for side effects to the rectum. In contrast, high dose radiotherapy to the rectum is accompanied by concern for acute side effects to the bladder (15). The general principles of reducing total dose in pelvic radiotherapy apply for patients with primary cancers in these pelvic treatment volumes. It is the external beam dose, which causes most severe side effects (15). Radiation dose can be minimized by reducing the treatment volume, and dose per fraction. Readers should consult the chapters in this web-based textbook dealing with basic principles of radiobiology in cancer patient management to understand the

importance of reducing total volume and fraction size for these patients, who require 5 or 6 weeks of external beam radiotherapy.

Patients, who require management of rectal cancer, and are often treated with external beam radiotherapy to a relatively small volume of the pelvis, with or without brachytherapy, are at primary risk for late rectal stricture caused by fibrosis. Decades of experience in managing patients with rectal carcinoma has provided guidelines for which patients require diverting colostomy to allow tissues in the pelvis to heal before re-anastomosis (reattachment) of the proximal and distal margins of resection. Other patients with large bulky cancers may require a permanent colostomy.

Acute Side Effects of Radiotherapy to the Prostate

Treatment options for patients with prostate cancer have changed significantly over the past several decades. While there has always been a controversy over whether patients should receive prostatectomy or radical radiotherapy, there is now a third option. Physicians stive to increase the number of patients, who can be managed by surveillance (observation) rather than either interventional modality. The widespread use of PSA (prostate specific antigen), as a biomarker for cancer, is a serum assay. It has allowed both early diagnosis of prostate cancer, but also has provided controversy over what level of PSA constitutes a requirement for further intervention including biopsy and operative staging. Treatment protocols categorize patients by PSA level, but also the kinetics of increase in PSA levels over time. Patients, who are thought to have prostate cancer may be diagnosed independent of PSA level by digital rectal exam in which a nodule or abnormality in the prostate is detected by careful examination through the anterior rectal usually then have ultrasound guided biopsy of these nodules. The so-called use of "blind" biopsies (not directed to a palpable node) of all four lobes of the prostate have also been widely used to diagnose prostate cancer.

After biopsy, physicians use a staging system based on the morphology of cells in the biopsy. The nucleus may have a pleomorphic structure in the specimen examined under the microscope. The cell structure has led to the Gleason scoring system in which the diagnostic pathology is reported with a score and then referred to as the Gleason-grade (17). A combination of the Gleason-grade and the PSA level (or kinetics) leads physicians to recommend a decision of whether to give the patient the option of radiotherapy, prostatectomy, or surveillance, which means regular follow-up visits

The change in philosophy has been guided by analysis of long-term outcome with men feeling that as high as 95% of patients with a diagnosis of prostate cancers do not die of this illness. Indolent disease can be safely managed by surveillance, particularly in elderly patients (18). The diagnosis of metastatic disease by PET scanning to identify regional lymph nodes in the pelvis, but also distant metastasis, which are commonly found in men with a relatively high Gleason and PSA score, often lead to decisions to apply androgen deprivation technique (which limits the growth of prostate cancer) or immediate use of chemotherapy. Patients with a large prostate that is obstructing urine flow may require surgical intervention or external beam radiotherapy (17). There is great controversy over the best management approach to patients with "so-called"

intermediate grade compared to high grade prostate cancer. Patients must take an active role in deciding which treatment modality to use or to adopt a program of surveillance (18).

Surgical techniques for prostatectomy have definitely improved with the common use of "nerve sparing" prostatectomy that allows the preservation of potency in men electing surgical prostatectomy (19), a change that has been a great advance in the surgical management, and replaces radical prostatectomy.

Radiotherapy techniques have also improved in the past 20 years allowing men to have the decision as to whether to elect brachytherapy techniques with implantation of Gadolinium or Radio-Iodine seeds directly into the prostate, or to have HDR (High Dose Rate) brachytherapy as described above for patients with gynecologic cancer or bladder cancer, to have external beam radiotherapy or a combination of modalities. There has been great interest in the past several decades for use of proton radiotherapy for patients with prostate cancer owing to the superior dose distribution and minimal radiation exposure to organs in the transit volume (20).

The major side effects of prostate cancer radiotherapy include: cystitis, and proctitis. The prostate sits in the pelvis between the bladder and the rectum, and the attempt to minimize dose to these tissues is paramount. As is the case with description above of preparing the patient for radiotherapy of bladder cancer, (empty bladder) and attention to the reverse therapeutic management is recommended for patients getting external beam radiotherapy for prostate cancer (full bladder). The bladder volume should be expanded out of the lower pelvis, as much as possible. Patients are urged to consume significant volumes of liquid prior to radiotherapy, and are imaged prior to external beam treatment (16). Daily documentation of the extension of the bladder outside the lower pelvic radiotherapy volume is done to minimize bladder dose. Patients treated for prostate cancer by external beam radiotherapy, who have a full bladder, suffer less severe cystitis and late radiation fibrosis of the bladder.

New techniques of placement of silicone or other reabsorbable gel into the space between the prostate and the anterior rectal wall allow dose reduction to the rectum, and, thereby, minimize the acute side effect of proctitis and late side effect of rectal stricture (21).

Management of Acute Side Effects of Irradiation to the Prostate, Bladder, Rectum, and Other Pelvic Structures

Acute radiation proctitis, prostatitis, cystitis, as well as acute radiation damage to mucus membranes of the vagina and squamous tissues in the inguinal folds, as well as vulva, rely upon basic principles of management of acute radiation side effects in all tissues and organs. Readers should consult the chapters on mechanism of radiation damage from single fraction and fractionated irradiation. Single fraction irradiation damage is also relevant to the main purpose of this textbook, namely, radiation counter-terrorism and design of radiation countermeasures to reduce side effects of acute radiation exposure.

In the clinical setting of radiation side effects, patients are managed by immobilization of tissues, and application of non-steroidal anti-inflammatory agents when possible. Pain from radiation proctitis, prostatitis, and cystitis can be managed by general analgesics, and if necessary, for

severe pain, use of narcotics (22). Tissue healing from radiation damage is best facilitated by placing the tissue at rest and allowing healing. In a setting of combined injury, which in the clinical arena means radiotherapy post-operatively or pre-operatively, represents an added complication. Patients with an acute irradiation reaction in pelvic organs in the pre-operative setting usually have a delay in surgical procedure until tissues suffering irradiation damage have been allowed to heal (23).

The administration of steroids in cases of acute irradiation reaction should be carried out cautiously with concern that prolonged weaning from steroids may take weeks to months. Since acute reactions may be suppressed by steroids, they also can recur after steroid withdrawal. In the case of placing tissues at rest for patients with proctitis, a diverting colostomy may be necessary to allow healing. The rectal tissues are stretched or aggravated by movement of fecal material, thus the need for a colostomy. Readers should consult the other chapters in this web-based textbook on irradiation damage to thoracic and volumes in the head and neck to gain more information on the availability of locally applied radiation mitigator compounds and ways to minimize irradiation damage.

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