Radiation Therapy for Pelvic Malignancy and its Consequences

Eli D. Ehrenpreis
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Springer

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Eli D. Ehrenpreis
This book is dedicated to my wife Ana and my children Benjamin, Jamie and Joseph, who are my constant source of love and inspiration. I also want to thank the Keyser Family Fund for their generous support of my academic ventures.
William Small Jr.
This book is dedicated to my father, William Small. He instilled in me a work ethic and sense of purpose that continues to inspire me to this day. To my family, my wife Julie and daughters Christina and Rebecca, I could not do what I do without your love, support and sacrifice. Finally, to all the patients that have allowed me to have the privilege of being their doctor, I am honored and humbled by your courage and trust. My hope is that someday this book is not needed because we have eliminated cancer.
Robert Marsh
This book is dedicated to each and every patient who has had to experience the trauma of a cancer diagnosis. Your courage and humor in the face of this unwanted and unexpected intruder, is a daily source of encouragement to all of us who work in this field

Foreword

The theme of pelvic radiation is generally described in the context of a textbook of colorectal surgery or a textbook of gastroenterology. In most instances it is not even addressed in a separate chapter but is included in the chapter describing the treatment of rectal carcinoma. The same coverage of the theme is noted in gynecology and urology textbooks. The fascinating and innovative method of educating the reader about these subjects in this book is highly commendable. The editors have managed to create 16 separate chapters describing the methods of application, indications for, and potential hazards of, radiation therapy in an interdisciplinary method. They have amassed world-renowned experts from the fields of urology, gynecology, colorectal and general surgery, gastroenterology, and radiation oncology. They have deftly melded the subject matter to provide for the reader a comprehensive compendium of all of the relevant themes both common to and specific to each of these subject areas. I am very impressed with the result and accordingly highly commend this textbook to all practitioners who use radiation therapy to treat their patients. I am confident that this textbook is the first of its kind and may well set the benchmark for a new type of interdisciplinary treatise.

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Preface

Radiation therapy, used alone or in combination with chemotherapeutic agents and/or surgery, is a standard approach to the treatment of a variety of pelvic malignancies. These treatments, along with earlier diagnosis from improved imaging modalities and increased disease awareness, have resulted in higher documented survival rates in patients with cervical, ovarian, prostate, rectal, and bladder cancers, regardless of the stage of disease at the time of diagnosis. As long-term survival and cure has become a reality for patients, including those with advanced pelvic cancers, survivors are faced with the challenge of living with the untoward consequences of their medical and surgical treatments. There have been many advances in the delivery of radiation therapy, including computer-aided dosimetric analysis, intensity modulated radiation therapy (IMRT), brachytherapy, megavoltage equipment, radioprotective techniques and compounds, alternative dosage regimen and image guided therapy—just to name a few. Nonetheless, a significant proportion of patients receiving treatment for pelvic malignancies may yet sustain acute, and sometimes chronic injuries of surrounding pelvic organs. Radiation-induced organ damage may be compounded by the aftermath of aggressive surgery, leaving reduced rectal, bladder, or vaginal capacities, and by toxic effects of chemotherapy, including neurologic and vascular damage. In the modern era of multimodality therapy, pelvic toxicities that occur when radiation therapy is used in combination with other therapies, either before, during or after radiotherapy, should be referred to as *treatment-related*, as opposed to simply *radiation-induced* toxicity.

In general, chronic radiation (or treatment related) injury may result in dysfunction of the bladder and bowel. Sexual dysfunction, infertility, and early menopause are also anticipated in patients receiving radiation therapy for ovarian, cervical, endometrial, and vaginal cancers. Less-commonly encountered problems in patients receiving radiation therapy include pelvic and sacral insufficiency fractures and lumbosacral plexopathy. Unfortunately, patients often suffer in silence with pelvic organ injuries rather than report embarrassing symptoms to their physicians and other healthcare providers. The small body of published research

in the medical literature clearly demonstrates that symptoms of treatment-related injury and other negative outcomes in patients with pelvic malignancies have profound effects on quality of life.

There is an extant body of literature on treatment-related injury and other consequences occurring after therapy for pelvic malignancies. However, information on this topic has generally been compartmentalized to the specific organ system in which symptoms occur. Thus, studies of female sexual dysfunction following radiation therapy are published in the gynecologic literature; clinical trials for radiation proctopathy are found in gastroenterology journals, while studies on the effects of these treatments on bladder function are relegated to urologic texts. The opportunity to combine the efforts of an internationally recognized group of specialists on these conditions to provide a single reference on the entire spectrum of treatment-related pelvic injury was the impetus for the creation of this book.

Our book provides a review of the clinical use of radiation therapy for gynecologic, urologic, and gastrointestinal cancers. It then follows with a summary of clinical and pathologic findings seen with acute and chronic treatment-induced pelvic injuries. Diagnostic modalities and potential treatments are featured. In addition, a thoughtful chapter on female sexual function and quality of life after treatment for pelvic malignancies is included—a subject that is just beginning to be explored. In combining these topics into one volume, this book is intended to promote an overall appreciation and improved understanding of the complex issues affecting patients undergoing treatment for pelvic malignancies. It is the sincere wish of its authors and editors that this knowledge, in turn, will produce a meaningful improvement in the clinical management and general well being of this complex group of patients.

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Part I
Role of Pelvic Radiation

The Role of Radiation Therapy in the Treatment of Malignant Gynecological Tumors

1

Tamer Refaat and William Small Jr.

Introduction

Radiation therapy is an essential treatment modality incorporated in the management of various gynecological malignancies. In this chapter, we will present in detail the role of radiation therapy in endometrial cancer, being the most common gynecological tumor, and cervical cancer and highlight the role of radiation in ovarian, vulvar and vaginal cancers.

Endometrial Cancer

Uterine cancer is the most common gynecologic malignancy, with over 52,000 new cases and almost 8600 deaths in 2013 [1]. Radiation therapy plays an essential role in the management of this long-time well-known surgically managed disease. At least 46 % of all patients with endometrial carcinoma should be considered for treatment with radiation at some point in their treatment course [2]. High cure rates in adenocarcinoma of the endometrium have been reported in series combining surgery with some form of radiation. Radiation therapy is the sole effective treatment modality for inoperable patients due to morbid obesity or medical comorbidities [3]. Radiation has also been used as an adjunct to surgery for uterine sarcomas.

Radiation Alone for Medically Inoperative Adenocarcinoma

In early stage adenocarcinoma of the endometrium, surgery with or without radiation is the generally accepted mainstay of therapy, however, many patients with endometrial cancer present with medical conditions in which surgery is contraindicated. In these patients, radiation becomes the only curative option. Brachytherapy alone or in combination with external-beam radiation therapy (EBRT) has been used. The overall 5-year survival rates for patients in whom radiation is used alone are 40–60 % [4–15], whereas, the survival rate for patients undergoing surgery with or without radiation is significantly higher [16, 17]. Although direct comparison of survival is difficult because of intercurrent deaths in the radiation-alone group, pelvic failure rates also tend to be higher in patients treated with radia-

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tion alone [4–15]. Rose and associates [16] used a case-control study to compare treatment results in patients who received primary radiation therapy vs. surgery. They noted no statistical difference in survival.

Radiation can be delivered with a combination of EBRT and intracavitary irradiation or with intracavitary irradiation alone. Kupelian and associates [5] reported a series of patients treated primarily with intracavitary irradiation. They noted a 14% 5-year uterine recurrence rate and an extrauterine pelvic recurrence rate of only 2%. Other series have also reported high local failure rates [6–8, 13]. The series reported by Rouanet and colleagues [6] noted a 24.2% 5-year local failure rate even though all patients received EBRT. Grigsby and coworkers [9] noted a reduced pelvic failure with the addition of EBRT to intracavitary irradiation. In their group of 49 patients treated with both intracavitary and high-dose EBRT, the 5-year survival was 85.4%. These results were updated in 1995 to include a total of 101 patients. Overall 5- and 10-year survival rates were 66 and 38%, respectively. Disease-free survival (DFS) rates at 5 and 10 years were 84 and 82%, respectively. Seventy-two of the 101 patients were treated with a combination of external beam and implant. In this study, the reported DFS is higher than the overall survival most probably because intercurrent deaths were censored from the DFS calculation [10]. Patanaphan and associates [11] also noted an increased survival rate in patients who received combined EBRT and intracavitary irradiation (67%) compared with patients who received intracavitary irradiation alone (57%).

High-dose-rate (HDR) brachytherapy in medically inoperable patients has not been as widely studied as low-dose-rate (LDR) brachytherapy. The largest series to date was reported by Knocke and associates [15]. In this study, 280 patients were analyzed, with the majority being clinically stage I and treated with HDR alone. Overall 5- and 10-year survival rates were 52.7 and 27.7%, respectively. Local control rates at 5 and 10 years were 75.4 and 70%, respectively. A report from Canada of 27 patients with clinical stage I and stage II disease noted a 15% pelvic failure rate and an 11% rate of late, serious complications [12]. Nguyen and Petereit [14] reported on 36 patients with clinical stage I disease treated with HDR alone. They noted an excellent uterine control rate of 88%, although this was associated with a significant complication rate. Modifications in technique have reduced the complication rate. Coon and colleagues [18] reported 10-year result with using Rotte "Y" applicator for HDR brachytherapy in 49 patients with medically inoperable endometrial cancer. Five patients had acute grade 1 or 2 toxicity and four patients had late grade 2 or 3 toxicity. The 3- and 5-year actuarial cause-specific survival rates were 93 and 87%, respectively. Overall survival rates were 83 and 42% at 3 and 5 years, respectively. Olson et al. [19] examined the dosimetric and clinical outcomes of using three-dimensional (3D) computed tomography (CT)-guided treatment planning for HDR brachytherapy in a series of 27 inoperable stage I endometrial cancer patients who received HDR brachytherapy using a tandem and cylinder applicator. Twenty-three patients received EBRT. For EBRT and HDR brachytherapy plans, the median HDR brachytherapy dose was 22 Gy with 4–5 fractions while for HDR brachytherapy-only plans, the median HDRB dose was 35 Gy with 5 fractions. The median clinical target volume (CTV) was 83 cc. The median CTV D90 was 88.6% of the prescription dose (PD). They concluded that 3D treatment planning better accounts for irregular CTV shape and provides dose reduction to organs at risk, in comparison to the point-based dosimetry that overestimated the CTV dose. Reportedly, all patients in their series completed treatment with no grade 3 toxicities; there were three local failures [19].

In conclusion, primary radiation therapy in medically unresectable endometrial cancer produces good pelvic control and disease-specific survival. The treatment techniques vary, but intracavitary irradiation is the mainstay of treatment with some series advocating the addition of EBRT for some or most of the patients.

Table 1.1 Gynecologic Oncology Group Protocol No. 33: Recurrence related to grade and myometrial invasion; surgery alone with negative risk factors

	No invasion	Inner third	Middle third	Outer third
Grade 1	0/55	5/61 (8%) (2P, 1V)	0/4	
Grade 2	0/17	2/41 (5%)	1/7 (14%) (1V)	1/2 (50%) (1V)
Grade 3	1/5 (20%)	2/7 (29%) (1V)	1/1 (100%) (1P)	

P pelvic failure, *V* vaginal failure

Patterns of Recurrence Without Radiation Therapy

When deciding on whether or when to use radiation therapy as an adjunct to hysterectomy, physicians are required to have knowledge of the patterns of failure with surgery alone. Between 1977 and 1983, the Gynecologic Oncology Group (GOG) entered 1180 patients into a prospective study (Protocol No. 33) of early stage disease; the goal of the study was to relate surgical-pathologic parameters and postoperative treatment to recurrence-free interval and recurrence site. Table 1.1 relates recurrence to grade and depth of myometrial invasion in patients with no risk factors who were treated with surgery alone. Risk factors included positive nodes, adnexal spread, capillary space involvement, isthmus/cervix involvement, positive cytology, and gross disease outside the uterus. The site of recurrence is given when available. These data show that in patients with grade 1 or 2 disease and no myometrial involvement, the risk of recurrence with surgery alone is low and adjuvant radiation therapy probably is not indicated. However, despite negative risk factors, patients with high-grade or deep myometrial invasion are at significant risk for recurrence [17].

Similarly, Eifel and associates [20] reported a recurrence rate of 0.8% (1/127) in patients with non-invasive tumors treated with surgery alone. This recurrence occurred in a patient with an initial grade 1 endometrial carcinoma in whom an anaplastic carcinoma of the pelvic sidewall developed, which the authors believed to be a second primary; it was, however, scored as a recurrence. Price and colleagues [21] also studied the pattern of recurrence in patients with stage I disease treated with surgery alone. They noted a vaginal recurrence rate of 4.4, 5.7, and 13.6% for well, intermediate, and anaplastic histology, respectively. In the same group, the incidence of recurrence was 3.7% with no myometrial invasion, 4.7% with superficial invasion, and 15.1% with deep myometrial invasion.

Patients with pathologic stage II disease treated with hysterectomy alone are at a higher risk of recurrence than those whose disease is classified as pathologic stage I. The GOG study noted recurrence in seven of 29 patients (four pelvic, one vaginal) treated with surgery alone. Therefore, in this group of patients, the local recurrence rate was approximately 20% in those who did not receive radiation therapy [17]. In a review by Fanning and coworkers, [22] no patient with stage IIA (based on the old staging system) disease treated with surgery alone had a recurrence compared to five of six patients with stage IIB disease. Other investigators have noted that in patients with stage II disease, histologic grade and depth of invasion remain important prognostic variables [23–25]. Therefore, recurrence rates in patients with stage IIA disease probably are influenced greatly by other known prognostic variables.

Lympho-vascular space invasion has also been noted to be a risk factor for recurrence. Tsuruchi and associates [26] noted a recurrence rate of 30.7% in clinical stage I and stage II patients with lympho-vascular space invasion vs. 3.2% in patients who had no invasion. Other authors have noted similar increased recurrence rates [27, 28]. Age is also a prognostic factor for survival. Younger women tend to have a better prognosis than older women. For instance, the GOG reported survival rates of 96.3% for patients ≤50 years old, 87.3% for patients 51–60 years old, 78% for patients 61–70 years old, 70.7% for patents

71–80 years old, and 53.6% for patients older than 80 [29]. As a general guideline, for every 1-year increase in age, the risk of recurrence increases by 7% [30]. Patients with stage III disease represent a highly variable group. Patients with extrauterine spread limited to the peritoneal fluid, or adnexa, or both, generally have more favorable outcomes compared to patients with other intra-abdominal metastases. In the GOG study of patients with stage IIIA disease who were treated with surgery alone, the recurrence rate was 0% (0/2) for adnexal involvement and 7% (1/14) for positive cytology. This compares with a recurrence rate of 50% in patients with positive pelvic nodes (stage IIIC) [17].

Lymph node metastasis is the most important prognostic factor in clinical early-stage endometrial cancer. Of patients with cT1 disease, 10% will have pelvic and 6% will have paraaortic lymph node metastases [17]. Patients with lymph node metastases have an almost six times higher risk of developing recurrent cancer than patients without lymph node metastases. One study showed a recurrence rate of 48% for patients with positive lymph nodes, including 45% with positive pelvic nodes and 64% with positive aortic nodes, compared to 8% for patients with negative nodes. The 5-year DFS rate for patients with lymph node metastases was 54% compared with 90% for patients without lymph node metastases [30].

Peritoneal relapse accounts for almost 25% of all recurrences in a study by Mariani et al. that included 599 patients with both stage IV disease and stage I–III disease. Any two of four independent factors (nonendometrioid histology, positive peritoneal cytology, cervical stromal invasion and lymph node metastases) were identified as predictors for peritoneal failure [31]. The recurrence rates for papillary serous histology, even when confined to the uterus, range from 50 to 85%, with upper abdominal recurrences predominating [20, 32–38]. The histologic feature of papillary architecture alone does not appear to increase the recurrence rate [35, 36], although some authors have suggested that this presents some increased risk [39, 40]. In patients with papillary serous histology, adjuvant radiation therapy would need to address the whole abdomen and is discussed later. Clear cell carcinoma has also been noted to have a higher recurrence rate [33, 41, 42].

The Role of Radiation in Operable Clinical Stage I Endometrial Adenocarcinoma

There have been numerous single-institution reviews and a few prospective, randomly assigned trials addressing the role of adjuvant irradiation, most of these reports based on the old FIGO (International Federation of Gynecology and Obstetrics) staging system that included stages IC, IIA and IIB. The uterine neoplasm staging system has been updated by FIGO and American Joint Committee on Cancer (AJCC) in 2010 and according to the new staging system, stage I now includes stage IA—that is tumor invades less than half of the myometrium, and stage IB—that is tumor invades one half or more of the myometrium. These changes were made because the survival rates of different stages in the previous staging system were similar [43, 44]. When combined with surgery, radiation can be given either before or after surgery. Advocates of preoperative irradiation state that the benefits include irradiating the tumor with an intact blood supply with a possible reduction in subsequent distant metastases and a questionable decreased risk of radiation side effects. Postoperative irradiation has the advantage of prior staging to help determine the need for irradiation and the areas at risk.

Aalders and coworkers [43] published a trial of 540 clinical stage I patients randomly assigned to postoperative vaginal irradiation with or without additional EBRT. The patients who received additional EBRT had a pelvic/vaginal recurrence rate of 1.9 vs. 6.9% in patients who were not given additional irradiation. No survival advantage was seen with EBRT. With additional evaluation, the authors concluded that patients with grade 3 disease who had more than half myometrial invasion benefited significantly from additional EBRT. The authors also recommended irradiation in cases of vascular invasion, given the poor prognosis shown in these lesions. Piver and

associates [44] reported their results from a prospective, randomly assigned trial in clinical stage I patients comparing hysterectomy alone vs. preoperative uterine irradiation or postoperative vaginal irradiation. They noted more vaginal recurrences in patients who had received a hysterectomy alone (7.5%) than in patients treated before surgery (4.5%); none of the patients treated after surgery had a vaginal or pelvic recurrence.

In multiple, nonrandomly assigned reviews, authors have attempted to define the role of radiation in stage I disease. Piver and colleagues [45] reported their results from a prospective trial using postoperative vaginal irradiation in patients with grade 1/2 disease who had invasion of less than 50% and no other evidence of disease. Patients with grade 3 disease or deep myometrial invasion received postoperative EBRT (group II). No patient in group I had a recurrence, and only one patient in group II had a pelvic recurrence. Grigsby and associates [46] reported the results of a study of 858 clinical stage I patients, most of whom received preoperative intracavitary irradiation. Patients with deep myometrial invasion received EBRT. Only 1% of these patients had an isolated pelvic recurrence, and 3% had pelvic and distant recurrences. Nori and coworkers, [47] using vaginal and selected EBRT either before or after surgery, noted a significant reduction in recurrences and improvements in survival compared with those of historical control subjects who had received surgery alone. Similarly, excellent pelvic and vaginal control rates have been noted in multiple series combining surgery and radiation [48–54]. A survey of American gynecologic oncologists was undertaken to analyze surgical staging and its effect on adjuvant treatment recommendations in stage I endometrial carcinoma. For patients without lymph node metastasis, the majority of gynecologic oncologists recommended radiation for patients with grade 3 lesions or deep invasion or both. The recommendations for grade 1 and grade 2 lesions and lesions that are not deeply invasive were more variable [54].

To define the role of radiation therapy in intermediate-risk endometrial adenocarcinoma, the GOG performed a prospective, randomly assigned trial (GOG-99). All patients received complete surgical staging and were found to have stage IB, IC (corresponding to IA, IB in the updated FIGO staging), or II (occult) disease. The patients were randomly assigned to no additional therapy or 50.4 Gy of whole-pelvic radiation therapy. A total of 390 eligible patients were randomly assigned. The estimated 2-year, progression-free interval was 88% in the nontreated group vs. 96% in the radiation therapy group ($p=0.004$). There were 17 pelvic/vaginal recurrences in the nontreated group vs. three in the radiation therapy group (two patients who refused radiation therapy). The estimated 3-year survival was 89% in the no-additional-therapy group vs. 96% in the radiation therapy group ($p=0.09$). The 5-year survival rates, 92 vs. 86%, though not significant, favored the radiation group. An unplanned subset analysis was conducted in an attempt to define a group of patients with increased risk of recurrence. This group, based on prognostic factors including high grade, advanced age, deep myometrial invasion, or lymphovascular space involvement was defined as high-intermediate risk (HIR). The 2-year cumulative incidence of recurrence was 26% in the observation group vs. 6% in the radiation group [55]. Results of a randomly assigned study from the Netherlands (PORTEC trial) were reported by Creutzberg and associates [56]. In this trial, patients were randomly assigned to pelvic radiation therapy (46 Gy at 2 Gy/fraction) vs. no further therapy. Eligibility criteria included any adenocarcinoma including papillary-serous and clear cell, postoperative FIGO stage I, grade 1 with deep (greater than 50%) myometrial invasion, grade 2 with any invasion, and grade 3 with superficial (less than 50%) invasion. Peritoneal cytology was recommended but not required. In all 714 patients were entered and evaluable. The majority of patients were histologically adenocarcinoma. Approximately one-third of patients were FIGO stage IB, grade 2. There were six grade 3 complications and one grade 4 complication in the radiation therapy group vs. one grade 3 complication in the surgery-alone patients. Five-year locoregional recurrences were noted in 14% of the untreated patients vs. 4% in the radiation

therapy patients ($p<0.001$). Overall 5-year survival was 85% in the control group vs. 81% in the radiation therapy group ($p=0.37$). Following subsequent central pathology review, there was a substantial shift from grade 1 to grade 2 lesions that would not have been eligible for inclusion in the study. Exclusion of these cases from analysis yielded essentially unchanged results, with 10-year recurrence rates of 5% for the radiation therapy group and 17% for the control group ($p<0.001$), and 10-year overall survival rates of 65 and 70%, respectively. Additionally, a subset analysis was conducted on patients with at least two of three risk factors (grade 3 lesions, outer 50% myometrial invasion, and age ≥60 years) who were found to have increased risks of locoregional relapse. The 10-year rates of locoregional recurrence in this high-risk group were 4.6% in the radiation therapy group and 23.1% in the control group [57]. Fifteen years follow-up update was released where 426 patients were still alive at the analysis date with median follow-up of 13.3 years. The 15-year actuarial locoregional recurrence rates were 6% for patients who received EBRT compared to 15.5% for those who did not ($P<0.0001$), however, the difference in 15-year overall survival was not statistically significant (52 vs. 60%, $p=0.14$). A trend towards increased second primary cancer was noted (22% for EBRT vs. 16% $p=0.1$). Multivariate analysis confirmed the relevance and importance of risk stratification for treatment selection, with high-risk patients as the best candidates to receive postoperative adjuvant radiation therapy [58]. The two randomly assigned studies, GOG-99 and the Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC) trial from the Netherlands, both seem to support the ability of radiation therapy to improve locoregional control in early stage endometrial cancer. This benefit is seen despite the inclusion of relatively lower-risk patients with stage IB disease. The GOG trial also notes a strong trend to an improved survival. The significantly improved locoregional control demonstrated by adjuvant radiation therapy in the PORTEC-1 trial was achieved primarily by a reduction in vaginal recurrence as compared to the control arm [17]. Vaginal brachytherapy (VBT) alone has been shown in many single-institution nonrandomized trials to result in a low rate of recurrence in properly selected patients [59–65].

The ASTEC and EN.5 trials were randomized trials in which 905 patients were randomized to adjuvant pelvic EBRT (40–46 Gy in 20–25 fractions) or no adjuvant EBRT. Thus far, the data have only been presented in oral presentation format at the ASCO 2007 annual meeting. VBT could be used regardless of the external beam randomization and was delivered as 4 Gy in two fractions (HDR) or 15 Gy via LDR. Treatment centers were required to decide in advance whether they would offer brachytherapy to all patients or to no patients. Brachytherapy was given to 52% of patients in each arm. Morbidity was 56% in the EBRT arm compared to 24% in the no-EBRT arm. At a median follow-up of 46 months, the 5-year hazard ratio (HR) for radiation therapy for overall survival was 1.01 ($p=0.98$). The 5-year HR for radiation therapy for disease-specific survival was 1.17. The HR for an isolated pelvic or vaginal recurrence was 0.53 for the group receiving EBRT. There is a small but significant decrease in pelvic recurrence with pelvic EBRT [66].

The PORTEC-2 was designed to compare postoperative EBRT to postoperative VBT in 427 patients with high-intermediate risk endometrial cancer. For this trial, HIR was defined as (1) age≥60 and stage IC grade 1–2, (2) age≥60 and stage IB grade 3, or (3) any age and stage IIA grade 1–2, or grade 3 with <50% myometrial invasion. At a median follow-up of 36 months, 3-year actuarial rates of vaginal relapse were 0.9% in the VBT arm and 1.9% in the EBRT arm ($p=0.97$). The 5-year rates of vaginal recurrence were 1.8% (95% confidence interval [CI] 0.6–5.9) for VBT and 1.6% (0.5–4.9) for EBRT (HR 0.78, 95% CI 0.17–3.49; $p=0.74$). Five-year rates of locoregional relapse (vaginal or pelvic recurrence, or both) were 5.1% (2.8–9.6) for VBT and 2.1% (0.8–5.8) for EBRT (HR 2.08, 0.71–6.09; $p=0.17$). 1.5% (0.5–4.5) vs. 0.5% (0.1–3.4) of patients presented with isolated pelvic recurrence (HR 3.10, 0.32–29.9; $p=0.30$), and rates of distant metastases were similar (8.3% (5.1–13.4) vs 5.7% (3.3–9.9); HR 1.32,

0.63–2.74; $p=0.46$). There was no difference in overall (84.8% (95% CI 79.3–90.3) vs 79.6% (71.2–88.0); HR 1.17, 0.69–1.98; $p=0.57$) or DFS (82.7% (76.9–88.6) vs 78.1% (69.7–86.5); HR 1.09, 0.66–1.78; $p=0.74$). Rates of acute grade 1–2 gastrointestinal toxicity were significantly lower in the VBT group than in the EBRT group at completion of radiotherapy (12.6% (27/215) vs 53.8% (112/208)). The authors concluded that VBT should be the treatment of choice for patients with high-intermediate risk of recurrence [67, 68].

Stage II Disease

Treatment of stage II disease ranges from radiation therapy alone to radical hysterectomy to a combination of surgery and radiation. Treatment of patients with stage II disease with radiation alone has generally resulted in much lower control and survival rates than when radiation and surgery have been combined [69]. In addition, patients with cervical disease detected before surgery have been noted to have a worse prognosis than those patients with occult disease [69]. Patients presenting with clinical stage II disease have commonly been treated with preoperative irradiation followed by extrafascial hysterectomy. The 5-year survival rates in patients who have received a combination of preoperative EBRT, intracavitary irradiation, and hysterectomy range from 69 to 88% [70–75]. The local control rates in these series are excellent. Grigsby and colleagues [73] noted an 8.9% overall pelvic failure rate. Bruckman and associates [71] noted no isolated pelvic failures and an overall pelvic failure rate of only 5%.

Radical hysterectomy alone has also been advocated as the treatment of choice by some authors. Boente and coworkers [76] noted a lower recurrence rate and complication rate in patients undergoing radical hysterectomy compared with patients treated with radiation therapy and extrafascial hysterectomy. Arguments against radical hysterectomy have included the observation that many patients with endometrial cancer are elderly or obese and thus have significant comorbidities. In addition, if the decision to add EBRT is made after surgery, a higher complication rate can be expected. Given the high false-positive rates of endocervical curettage, radical hysterectomy should probably be considered only in cases that include gross cervical involvement. Parthasarathy et al. reviewed data of 3664 endometrioid carcinoma patients in stages IC (corresponding to IB in current staging system) and II from the National Cancer Institute database who were diagnosed and treated between 1998 and 2001. One thousand one hundred and seventy-five patients among them received adjuvant radiotherapy; their 5-year survival rate was 89.9% compared with 87.8% in those who did not receive radiation and that was statistically significant ($P=0.04$). Furthermore, there was improvement in disease-specific survival rate in stage II patients among those who received radiation therapy (86.5% compared to 81.9%; $P=0.02$). The benefit of radiation was more notable in patients with grade 3 disease and in those 70 years or older [77]. A treatment approach that has gained favor in patients with stage II disease is initial extrafascial hysterectomy with lymph node sampling and cytology followed by irradiation. This approach has resulted in patient survival rates comparable to those seen in patients who received preoperative irradiation and has also resulted in excellent pelvic control rates [25, 78, 79].

Stage III Disease and Stage IVA Disease

Stage III or stage IVA disease can be separated into *clinical* and *pathologic*. Multiple series have noted an increased recurrence rate when irradiation alone is used [80–82]. Patients with pathologic stage III disease have a better prognosis compared to patients with clinical stage III disease [83, 84]. The role of radiation in stage III/IVA disease needs to be individualized for the extent of disease in each particular patient. In postoperative patients with positive pelvic lymph nodes, adnexal disease, serosal or parametrial spread, vaginal metastasis, or bladder/rectal invasion, pelvic irradiation with or with-

out a vaginal-cuff boost should be considered. Using this algorithm, most series report 5-year survival rates of approximately 40–50% in patients with pathologic stage III disease [81, 82]. Local control is accomplished in the majority of patients. In certain situations, there may be a role for extended-field and whole-abdominal irradiation (WAI).

Extended-Field Irradiation

The use of extended-field irradiation is limited to patients at high risk for extrapelvic recurrence. The clearest indication appears to be in patients who have evidence of para-aortic lymph node metastases as the only evidence of disease outside the pelvis. Extended-field irradiation refers to irradiating the pelvis, the common iliac, and the para-aortic lymph nodes. Potish and associates [85] reported their results in irradiating 40 women, all of whom had evidence of para-aortic lymph node metastasis. They reported a 47% 5-year survival in surgically staged patients, with only one severe complication. These results compare to a 10% 5-year survival in previous series that did not use extended-field irradiation [86]. Rose and colleagues [87] compared 17 patients who received extended-field irradiation to nine who did not. The survival in the extended-field irradiation group was 53% compared to 12% in the non-irradiated group, despite one treatment-related death in the former group.

Whole-Abdominal Irradiation

The role of WAI in endometrial carcinoma remains controversial. Whole-abdominal irradiation has been used in a variety of patients ranging from those who received adjunctive therapy for high-risk surgical stage I disease [88] to those with intraperitoneal metastatic disease [89]. Whole-abdominal irradiation is used when there is a risk of intra-abdominal spread that may be impacted by treatment. A number of authors have advocated the use of WAI in treating surgical stage III patients. Gibbons and coworkers [88] noted a 57.8% 7-year DFS in patients with surgical stage III disease who were treated with WAI. Potish and associates [90] also noted an excellent 5-year relapse-free survival of 90% in patients with adnexal metastases or positive peritoneal cytology compared to zero in patients with macroscopic spread of cancer beyond the adnexa. The Gibbons article noted that three of a total of 27 patients treated with WAI had significant long-term bowel toxicity [88]. The Potish article noted that only one of 27 patients had significant long-term bowel toxicity, although these investigators used a lower dose of WAI [89].

Loeffler and colleagues [91] reported the Joint Center experience with the use of WAI in 16 patients. They concluded that patients with extensive extrauterine involvement, and sarcomas, did not appear to benefit from WAI and that it may have reduced intra-abdominal recurrence in only a small subset of patients. Smith and associates, [92] in an update of the Stanford experience, noted a 3-year DFS rate of 79% with an overall survival rate of 89% in patients with stage III or IV endometrial adenocarcinoma.

Chemotherapy

A phase II study was conducted by the Radiation Therapy Oncology Group (RTOG 9708) combining adjuvant pelvic radiation therapy with concomitant chemotherapy followed by chemotherapy in grade 2 or 3 endometrial adenocarcinoma with either >50% myometrial invasion, cervical stromal invasion, or pelvic-confined extra-uterine disease. Forty-six patients were enrolled with a median follow-up time of 4.3 years. Chronic toxicity was grade 1 in 16%, grade 2 in 41%, grade 3 in 16%, and grade 4 in 5%. Overall survival and DFS were 85 and 81%, respectively. The 4-year pelvic, regional, and distant recurrence rates were 2, 2, and 19%, respectively. There were no recurrences in patients with stage IC, IIA, or IIB disease. While patients with extrauterine stage III disease demonstrated a pattern of distant recurrence, this trial illustrates the potential of combined therapy in the postoperative treatment for patients with disease confined to the uterus

[93]. A randomized phase III study in early stage high-risk endometrial cancer patients compared adjuvant radiation therapy with or without chemotherapy (NSGO-EC-9501/EORTC 55991). Eligible patients had surgical stage I, II, IIA (with positive peritoneal cytology only), or IIIC (positive pelvic lymph nodes only) and qualified for adjuvant therapy based on risk of micrometastatic disease. Radiation therapy consisted of EBRT to 44 Gy with or without a VBT boost. The HR for progression-free survival was 0.58 in favor of combined therapy ($p=0.046$), which translated into an estimated 7% absolute difference in progression-free survival from 75 to 82% [94]. The GOG 122 trial randomized patients between whole-abdominal radiation therapy and chemotherapy with cisplatin and doxorubicin. A total of 396 patients with stage III or IV endometrial cancer were randomized to receive WAI (30 Gy in 20 fractions, with a 15 Gy boost) or chemotherapy with cisplatin and doxorubicin every 3 weeks for seven cycles, followed by one cycle of cisplatin. With a median follow-up of 74 months, the HR for progession of disease was 0.74 favoring the chemotherapy arm. The stage-adjusted death HR was 0.68, also favoring the chemotherapy group [3]. Mundt and coworkers [95] reported recurrence rates in 43 patients with stage I–IV endometrial cancer who received adjuvant chemotherapy alone. A recurrence rate of 67.4% was seen, with a 3-year actuarial pelvic recurrence rate of 48.1%. Thirty-one per cent of recurrent patients recurred in the pelvis alone. Given these results, adjuvant chemotherapy protocols in endometrial cancer should probably continue to incorporate locoregional radiation therapy.

Uterine Papillary Serous Carcinoma

As discussed previously, patients with uterine papillary serous carcinoma have a higher recurrence rate compared to those with other uterine adenocarcinomas; there is also a preponderance of upper abdominal failures in these patients [20, 32, 38]. This has led a number of investigators to attempt more aggressive adjuvant radiation therapy, including WAI. Published reports of studies using WAI in patients with uterine papillary serous carcinoma suggest a reduction in recurrence rates in early stage disease. Mallipeddi and associates [95] reported the use of whole-abdominal radiation on ten patients with uterine papillary serous carcinoma, five of whom were alive at follow-up. This study noted long-term control in patients with superficial myometrial invasion, with or without positive cytology, who received optimal radiation. As in a previous report, [96] vaginal recurrences were lower with a vaginal-cuff boost. Gibbons and coworkers [88] noted a 60% long-term recurrence-free survival in a group of patients who received WAI therapy. The 5-year actuarial survival in patients treated with whole-abdominal radiation therapy was 86% [97]. This is in contrast to the low 3-year survival in GOG-94 [98, 99]. Chemotherapy is also frequently used as an adjuvant therapy for papillary serous cancer. Table 1.2 reviews various series using whole-abdominal radiation.

Techniques of Radiation Therapy

Radiation can be delivered by means of external sources (EBRT), implanted irradiation (brachytherapy), or radioactive fluid. This section discusses EBRT and brachytherapy. Radioactive fluid instillation is occasionally done intraperitoneally most commonly as adjuvant therapy in ovarian cancer and rarely in patients with positive peritoneal cytology. Some work has been done using P37 in patients with endometrial carcinoma with positive cytology [101]; this work is not discussed further, however, because data are somewhat limited.

EBRT is used to irradiate areas thought to be at risk for disease recurrence, including the whole pelvis, the whole pelvis plus the para-aortic nodal region, and the whole abdomen. EBRT is produced by cobalt machines, linear accelerators, or with charged particle cyclotrons (i.e., protons). As the energy of radiation increases, the beam penetration also increases, making it possible to limit the peripheral radiation needed for delivery of a desired dose at depth. Because the pelvis has a relatively thick separation, higher en-

Table 1.2 Clinical results of whole-abdominal radiation

Reference	No. of patients	% Serous histology	Survival (%)	Recurrence rate (%)	Follow-up (median months)
Mallipeddi et al. [100]	10	100	60	50	64
Frank et al. [96]	9	100	55	67	25
Greer and Hamberger [89]	31		63[a] (5 year)	19	>24
Gibbons et al. [88]	56	18	64 (7 year)	36	45
Loeffler et al. [91]	16		50 (1.5 year)	62.5	17
Small et al. [97]	30	47	86 (5 year)	23	27
Potish et al. [90]	27	0	71	25	NS
Smith et al. [92]	48	NS	77 (3 year)	40	37 (mean)

NS not significant

[a] For patients with residual disease <2 cm ($n=27$)

ergy beams are preferred. There are limited data regarding charged particle therapy and this form of therapy is beyond the scope of this chapter.

Whole-abdominal irradiation is used to irradiate the entire abdominal contents. With modern radiation machines, this usually can be accomplished with a single setup, treating with an anterior and posterior field. The total whole-abdominal dosage is usually limited to 2000–3000 cGy in fractions of 100–150 cGy per treatment. Vital organs may need to be shielded to limit the radiation dose. The kidneys should be shielded to limit the dose to approximately 1800 cGy; liver shielding should also be considered if the dose exceeds 2500 cGy. Whole-abdominal irradiation in endometrial cancer is usually followed by a boost to the pelvis, preceded in many situations by a para-aortic nodal boost.

Treatment of the para-aortic nodes can be accomplished with either separate fields matched to the pelvic field or in continuity with pelvic radiation fields. We prefer to use a single field to avoid problems of matching. The para-aortic nodes can be treated with a two- or four-field technique, generally to a total dosage of 4500 cGy at 180 cGy per fraction. If a two-field technique is used, care must be taken to ensure that the dose to the spinal cord is limited to less than 4500 cGy. If a four-field technique is used, the location of the kidneys must be verified to avoid exceeding kidney tolerance.

Whole-pelvic irradiation can be accomplished by either a two- or four-field technique using 3D conformal radiation therapy, with intensity-modulated radiation therapy or Tomotherapy. To avoid excessive maximal dosages, the two-field technique should be used only with high-energy beams. The two-field technique uses opposed anterior and posterior fields. The upper border of the field is generally placed at the L4-5 or L5-S1 interspace. If there is no disease extension into the vagina, the lower border should encompass one-half to two-thirds of the vagina. The lateral borders should be placed approximately 1.5 cm lateral to the bony pelvic rim. A marker should always be placed to indicate the location of the vaginal cuff/cervix or the most distal aspect of tumor extension. The *four-field technique* allows lateral shielding of structures that cannot be shielded in the anteroposterior field. In the four-field technique, the upper- and lower-field borders are identical to those in the two-field technique. The anterior border of the lateral field is placed at or anterior to the anterior pubic symphysis. The posterior border is placed at the S2-3 interspace unless tumor extension necessitates larger fields. With 3D conformal radiation therapy, currently the standard of care for radiation therapy, the CTV, defined as the area that is at risk for harboring microscopic metastatic disease, is outlined on a CT scan. Normal tissues, such as bladder, rectum, large intestine, and small intestine, are also outlined in the same manner. Anteroposterior,

posteroanterior, and lateral field borders are defined to include the CTV while sparing as much normal tissue as possible. A dose volume histogram, or DVH, can then be created to define the amount of normal tissue receiving a certain critical dose if felt to be clinically important.

Pelvic radiation therapy technique is extremely important in treatment outcomes, especially in reducing short-term and long-term toxicity [102]. Barium should be given at the time of simulation to document the position of the small bowel [103]. Attempts to reduce the small bowel in the radiation field include placing the patient in the prone position with a full bladder with or without abdominal compression. Patients should always be treated with a full bladder to move as much of the small bowel as possible out of the pelvic field. The total pelvic radiation therapy dosage typically is 45–50 Gy for adjuvant therapy.

Intensity-modulated radiation therapy (IMRT) is a radiation technique, which is currently increasingly used for treatment of gynecologic malignancies including endometrial cancer especially in adjuvant settings to minimize gastrointestinal complications. This technique allows for decreased radiation doses to critical structures such as bone marrow or small bowel while continuing to treat the tumor to the same dose. Several small trials have showed an improved toxicity profile with IMRT [104−106]. A recently closed trial, RTOG 0418, was designed to assess the utility, efficacy, side effects, and control and survival rates when IMRT is used for postoperative endometrial and cervical cancer.

Brachytherapy refers to the placement of a radioactive source in or near the desired treatment volume. This allows a higher local radiation dose and spares surrounding normal tissues. The two main forms of deliver of brachytherapy are the LDR and the HDR techniques. The LDR technique uses isotopes that deliver radiation with a dose rate of approximately 40–100 cGy/h to the prescribed target. HDR brachytherapy, which delivers approximately 200 cGy/min, can be performed on an outpatient basis. There is a significant biologic difference between LDR and HDR brachytherapy: HDR delivery has a higher "effective" radiation dose for the same nominal LDR dose. Therefore, the delivered HDR doses must be adjusted lower to give the same effective LDR treatment. Pulsed Dose Rate (PDR) brachytherapy attempts to eliminate the unfavorable radiobiology of the High Dose Rate Brachytherapy while maintaining the ability to optimize finely the dose distribution and eliminate the personnel exposure to radiation. Biologically, since each fraction comes before the complete repair of the sublethal cellular damage, the tissue experiences the radiation as almost continuous, mimicking LDR brachytherapy. Although, this approach incorporates the biological advantage of Low Dose Rate brachytherapy and the optimization advantage of the High Dose Rate brachytherapy, it also has many disadvantages including inpatient treatments, lack of applicator stabilization, and possibility of mechanical failure. PDR brachytherapy presents opportunities to potentially improve brachytherapy, but it also come with detriments. Although PDR has prospered in Europe and Asia, unfortunately in the USA it has floundered because the Nuclear Regulatory Commission (NRC) requires that a physicist and/or radiation oncologist be present throughout the treatment, which is almost impossible to accomplish in a long treatment schedule in a hospital setting [107]. The isotopes used in LDR treatment typically include cesium-137 or radium-226. Radium-226 has fallen out of favor because of radiation safety issues. Cesium-137 has a half-life of 30 years, allowing reuse of a source over a long period, although periodic calibration to allow for decay is necessary. HDR and PDR treatments typically use an iridium-192 source that needs frequent recalibration and replacement. Iridium-192 can also be used as an LDR isotope. Typically, in most gynecologic applications of brachytherapy, the sources of radiation are left in place temporarily and then removed. This is the case in most LDR applications and all HDR applications. Permanent LDR brachytherapy procedures have a limited use in gynecologic malignancies and are not discussed further. The sources of radiation are, in almost every case, afterloaded into a hollow radiation carrier. This permits some planning before determining the strength of radioactive isotope to use

and significantly reduces radiation exposure during placement. The carriers used for afterloading can be divided roughly into those used to treat the intact uterus and those used after surgery. The uterus may be treated with a tandem alone, as is done in treating cervical cancer. Treating the uterus with a tandem alone may underdose the thicker sections of the myometrium. The use of duel-curved tandems or three tandem applicators, as noted above, has been shown to have good outcome data for toxicity, recurrence, and survival for unresectable disease [18]. Heyman [108] originally described using multiple radium capsules packed into the uterus to stretch and thin the wall to improve the dose distribution. Simon and Silverstone [109] later developed afterloading capsules to decrease radiation exposure during placement.

Brachytherapy dose is defined either in terms of actual dosage delivered or in terms of total milligram-hours, which is simply derived by multiplying the total milligrams of equivalent radium by the total number of hours of the implant. The doses of radiation used when delivered before surgery with planned hysterectomy typically range from 2500 to 4000 mg-h to the uterus using a tandem or Simon–Heyman capsules and colpostats to deliver 1900–2000 mg-h (6000–6500 cGy vaginal surface dose) to the upper vagina. In some patients, 50 Gy of postoperative EBRT is added, with the whole-pelvic dosage limited to approximately 2000 cGy by the addition of a midline shield. When definitive radiation is delivered without planned hysterectomy, uterine milligram-hours range from 3000 to 10,000, depending on whether EBRT is also delivered [4–9]. Although not commonly reported, the point A dose (i.e., the dose defined as 2 cm superior and 2 cm lateral to the external os) is approximately 7500–8500 cGy [4, 6]. HDR is generally delivered in a fractionated manner, with an attempt to deliver biologically equivalent dose to the traditional LDR implants.

Posthysterectomy VBT is generally delivered with a vaginal cylinder or with ovoids. The dose delivered with low-dose brachytherapy alone tends to be prescribed at the vaginal surface. Doses range from 6000 to 7000 cGy [43, 48, 49]. The use of postoperative high-dose brachytherapy is becoming more common, allowing outpatient treatment. A common dose schedule is 2100 cGy divided into three fractions of 700 cGy and prescribed to 0.5 cm from the vaginal mucosal surface [47]. There is quite a bit of variation in the dose schedule for high dose rate radiation amongst radiation oncologists [110]. The ideal timing of postoperative radiation therapy is not known. There is support for initiating postoperative irradiation within 6 weeks after surgery. A higher local failure rate was seen with a delay of longer than 6 weeks [111]. Given the time needed to initiate treatment planning, patients for whom postoperative irradiation is being considered should be referred immediately to the radiation oncologist to prevent nonmedical delays in the initiation of therapy. The need for a vaginal-cuff boost after postoperative EBRT recently has been questioned by a number of investigators [111, 112]. Numerous large studies have consistently used vaginal-cuff boosts with excellent long-term results [46, 47]. In addition, at least one nonrandomly assigned review noted improved local control with the addition of a vaginal-cuff boost to postoperative EBRT [113]. The number of absolute vaginal-cuff recurrences prevented by a vaginal-cuff boost is probably small. Most institutions utilize HDR vaginal-cuff boosts and have used a 600 cGy vaginal surface dose for two to three fractions. Other institutions deliver a higher total vaginal mucosal dose and limit the mid-pelvis external dose by using a midline shield [46].

Recurrent Disease

Locoregionally recurrent endometrial cancer can be cured with radiation therapy, even when resection is a reasonable option but may be less desirable because of potential surgical complications owing to common comorbidities among uterine carcinoma patients such as obesity, hypertension, and others. Results tend to be best in patients with vaginal-cuff recurrences and without previous irradiation. Curran and colleagues [114] reported on 55 patients with isolated vaginal re-

currences who were treated with definitive irradiation. Patients with vaginal mucosal recurrence had a 3-year actuarial survival and a local control rate of 85 and 100%, respectively. This compared with a 13% 3-year actuarial survival and a 0% local control rate in patients with sidewall involvement at the time of recurrence. The 5-year survival rate overall was 48% in patients who did not receive previous irradiation compared to 16% in patients who were receiving their second course of radiation therapy. Other authors have seen similar results [115−120]. The PORTEC trial also noted a 3-year survival of 69% after vaginal recurrence compared to 13% after pelvic or distant relapse [56]. Other prognostic factors noted included histologic type of recurrence, [117] time to recurrence, [116], and tumor size [120]. Site of recurrence is also to be considered: data from the PORTEC trial demonstrated that the 3-year survival rate among women with pelvic recurrence was only 8% compared to 73% for women with isolated vaginal recurrence. In this update, treatment of vaginal relapse was effective with 89% complete response and 5-year survival rate of 65%. The survival rate was similar for patients with pelvic recurrence to those with distant metastases [121]. The exact technique used in salvage irradiation needs to be individualized for each patient. Generally, a combination of EBRT and brachytherapy should be used. Because the normal anatomic barrier of the uterus does not confine recurrent disease, EBRT to sterilize nonpalpable disease should probably always be part of the planned therapy.

Uterine Sarcomas

Uterine sarcomas tend to behave in a more malignant fashion than do endometrial cancers. The three most common histologic variants of uterine sarcomas are endometrial stromal sarcoma (ESS), leiomyosarcoma (LMS), and carcinosarcoma. As in endometrial adenocarcinomas, surgery is the preferred primary therapy in uterine sarcomas. A number of institutions have reviewed their experience in patients who have received adjuvant radiation and compared the results to patients who underwent surgery alone. The data are presented in some series as uterine sarcomas, and in others the histologies are divided among carcinosarcoma, LMS, and ESS. Given the selective use of radiation in these trials, a bias towards irradiating patients with poor prognostic features would be expected. Despite this bias, there is significant evidence to support the use of adjuvant radiation in many patients. There seems to be a general consensus that postoperative radiation therapy improves local control in carcinosarcomas. Some reviews support an improvement in survival, while others do not [122−129].

A randomized trial was recently reported in which 224 patients who underwent total abdominal hysterectomy bilateral salpingo oophorectomy (TAH-BSO) and were randomized to adjuvant EBRT (50.4 Gy in 28 fractions) or no further therapy. Results showed improved locoregional control with adjuvant EBRT ($p=0.004$), but did not show an improved overall survival or progression-free survival [130].

LMSs tend to have a higher propensity for distant metastasis, and it would, therefore, follow that local adjuvant treatments may have less of an influence on survival. There is evidence in some series for an improvement in local control with the addition of adjuvant radiation [131, 132]. Hornback and coworkers [133], conversely, reviewing the use of radiation in GOG-20, did not find a difference in first recurrence rates with the use of adjuvant radiation in LMS, although an improvement in pelvic control was seen in the mixed mesodermal sarcomas. There is less support regarding improvement in survival. At least one institution noted no improvement in survival with adjuvant radiation when treating LMSs with low mitotic activity [134].

A GOG phase III study [135] examined the postoperative efficacy of postoperative WAI with 1 Gy BID or 1.5 Gy daily to a total dose of 30 Gy compared to adjuvant cisplatin, ifofsamide, and mesna (CIM). The study focused on patients with carcinosarcoma and included all stages of disease. In all, 232 patients were randomized with 43% of the patients being stage I–II, and 45% stage III. There were a total of 112 recurrences, with 60 occurring in the WAI group and

52 in the CIM group. There were no significant differences in the number or site of recurrences. However, there were slightly more vaginal recurrences with CIM and slightly more abdominal recurrences with WAI. There was no significant survival difference.

ESSs have traditionally been divided into low grade and high grade. The National Comprehensive Cancer Network (NCCN) guidelines have modified the classification of ESSs, so that the group previously referred to as high-grade ESSs is now known as high-grade undifferentiated sarcomas, and the group previously referred to as low-grade ESSs is now known simply as ESS. Patients with low-grade ESS tend to have a favorable prognosis, and there is little evidence that in early stage disease, adjuvant radiation would offer a benefit [136]. There is evidence that adjuvant radiation may improve local control in patients with high-grade ESS [122, 128] and possibly survival [128, 137].

In a series of patients with ESS reported by Weitmann and associates [138], a 93.8% 5-year local control rate was seen in patients who received surgery and radiation therapy, with the majority of patients having high-grade disease. The actuarial overall survival at 10 years was 52.8%.

A number of publications have looked at uterine sarcomas without dividing the patients into separate histologic categories. A report by the Grup Oncologic Catala-Occita reviewed their experience in 103 patients with uterine sarcomas. A local control and survival advantage was seen with adjuvant radiation [139]. The Curie Institute also reported on uterine sarcomas and found an improvement in local control with the addition of radiation in high-grade tumors [140].

Given the overall rarity of uterine sarcoma, the above discussion basically focuses on earlier stage disease. The use of adjuvant radiation in advanced disease is based on even more limited data and extrapolations from endometrial adenocarcinoma results. There is a need for open dialogue between patient and physician, and also for further studies investigating the role of multimodality therapy.

Conclusion

Radiation plays a prominent role in the treatment of uterine tumors. Its most common role is in the adjuvant setting after hysterectomy. There may also be a role for adjuvant irradiation in some uterine sarcomas. When applied properly, radiation can contribute to tumor control with acceptable rates of serious complications.

Cervical Cancer

Cervical cancer is a major cause of morbidity and mortality worldwide, with an estimated incidence of over 11,000 new cases in the USA alone and much higher incidence in developing nations [141]. It is the third most common gynecologic malignancy and cause of death among gynecologic cancers in the USA [1].

Bulky Stage IB and IIA Disease

Women with bulky stages IB2 and IIA cervical cancer have a higher local failure rate and worse survival than those with smaller volume disease. Surgery as a sole treatment modality results in as high as 30% relapse rate [142, 143]. Unfortunately, we still lack strong predictive molecular biomarkers that would most likely identify those at higher risk for relapse and provide this patient category with some benefit from individualized targeted therapies. Grag et al. suggested that pretreatment nuclear expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-**k**B) might be associated with a poor outcome for cervical cancer patients treated with chemoradiation [144]. The optimal management strategies of women with primary tumors measuring $\geq$4 cm in diameter include: (1) primary chemoradiotherapy, (2) neoadjuvant chemotherapy, followed by radical hysterectomy with or without subsequent chemoradiotherapy, or (3) primary radical hysterectomy and lymphadenectomy followed by tailored RT with concomitant chemotherapy.

Concurrent Chemoradiation

Historically, Primary radiotherapy (RT) has usually been the treatment of choice for women with bulky stage IB2 and IIA2 cervical cancer. In a review of 1352 patients with stage IB disease treated with RT alone at the M. D. Anderson Cancer Center and followed for a median of 12.2 years, rates of central and pelvic tumor control and disease-specific survival for tumors < 5 cm were 99, 97, and 88 %, respectively, and for tumors between 5 and 7.9 cm were 93, 84, and 69 %, respectively [145]. However, among the 66 patients with tumor size > 8 cm, outcomes were less favorable (central and pelvic control and disease-specific survival rates were 69, 57, and 40 %, respectively). Furthermore, for patients with tumors in the 5–7.9 cm category, outcomes were significantly better for those with exophytic as compared to endocervical morphology (disease-specific survival 76 vs. 66 %, respectively). If primary RT is utilized, concomitant cisplatin during RT provides additional benefit over RT alone [146, 147]. Much of the data supporting chemoradiotherapy over radiotherapy alone come from trials conducted in the setting of locally advanced disease. Thus, when definitive RT is chosen, cisplatin-based chemoradiotherapy rather than RT alone is indicated. Timely completion of RT is essential for good outcomes, whether chemotherapy is used or not [148−152]. The importance of time to complete RT to overall outcomes was illustrated in a series of 1224 women with cervical cancer treated with definitive RT for stage IB–III disease [148]. Treatment courses extending beyond 9 weeks resulted in significantly higher rates of pelvic failure and poorer disease-specific survival at 10 years as compared to those whose treatment was administered over a shorter time period. Similar findings were noted in a pattern of care study involving 837 women undergoing RT for stages I–III cervical cancer [149]. As compared to a total treatment time of 6 weeks or less, those treated over 10 weeks or more had significantly higher rates of 4-year in-field recurrence (20 vs. 4 %, respectively). These data are retrospective rather than from prospective trials, and it is possible that longer treatment duration may be a surrogate for the presence of unfavorable tumor or patient characteristics. Nevertheless, in general, RT should be completed within 56 days, if at all possible. From a radiobiologic standpoint, it is likely that similar considerations apply to patients undergoing chemoradiotherapy, as well.

Many of these bulky tumors extend laterally beyond the tumoricidal isodose curve of the brachytherapy application; further, they may contain hypoxic central areas, which do not respond well to RT. These observations provide the rationale for some to recommend an extrafascial hysterectomy following chemoradiotherapy, since approximately one-half of these specimens harbor residual disease, even if concomitant chemotherapy is administered [153, 154]. While many studies find that pelvic recurrence rates are lower than expected (2–5 vs. 15–20 %) in women who have postradiotherapy hysterectomy, the impact of surgery on extrapelvic recurrence and survival is less well established [155−159]. A randomized study comparing RT with and without extrafascial hysterectomy in 256 women with bulky IB2 disease showed a lower local recurrence rate in the surgery arm (14 vs. 27 %), but the difference was not statistically significant [159]. Unfortunately, the study was hampered by the delivery of suboptimal doses in the RT alone arm (87 % received 78–80 Gy) with 51 % receiving RT over a protracted treatment period (> 60 days). Furthermore, concurrent chemotherapy was not administered. Despite the difference in local disease control, survival was similar in both groups. It has been suggested that the presence of residual local disease on cervical biopsies performed under anesthesia 8–10 weeks after the completion of chemoradiotherapy may serve to identify those women who may benefit from hysterectomy [160].

Neoadjuvant Chemotherapy Followed by Surgery

This is an acceptable treatment approach in communities with limited access to radiation therapy facilities in women with tumors, which would not otherwise be considered surgically resectable.

Cisplatin-based chemotherapy is the mainstay in treatment; cervical squamous cell carcinoma is known to be a cisplatin-chemosensitive cancer. A prospective trial directly compared surgery (followed by adjuvant RT) with or without neoadjuvant chemotherapy (three courses of cisplatin 50 mg/m^2, vincristine 1 mg/m^2, and bleomycin 25 mg/m^2 on days 1–3, at 10-day intervals) in 205 women with stage IB disease >2 cm in diameter. Sixty-one patients in the study group and 56 in the control group had bulky stage IB tumors. Neoadjuvant chemotherapy was associated with a 90% objective response rate, a higher likelihood of resectability with negative margins (100 vs. 85%), and a significant decrease in the rate of pelvic failure, but only a trend towards better survival (82 vs. 77%) [161]. Other studies either did not show any significant advantage for the neoadjuvant approach [162−164], or utilized suboptimal treatment in the control arm (RT instead of concurrent chemoradiation) [165].

However, a Cochrane meta-analysis of six trials enrolling 1036 women demonstrated statistically significant progression-free survival (HR 0.76, 95% CI 0.62–0.94) in favor of neoadjuvant chemotherapy. However, this did not result in significant overall survival benefit, or decrease in local or distant recurrence. Furthermore, the analysis included significantly dissimilar clinical trials [166]. A phase III trial in patients receiving paclitaxel plus cisplatin and ifosfamide as compared to cisplatin and ifosfamide alone (48 vs. 23%), showed significantly higher, optimal response rates, defined as surgical specimen residual disease with <3 mm of stromal invasion, in the three-drug arm, but yet overall survival was not significantly different [167].

Primary Surgery

The advantage of this approach includes accurate pathological determination of the extent of the disease and subsequent individualized tailored adjuvant therapy, and the potential for resection of bulky metastatic lymph nodes, which may improve prognosis [168, 169]. In a large study comparing patients with stage IB1 and IB2 cervical cancers managed by primary radical hysterectomy, the prognosis of stage IB cervical cancer was best determined by lymphovascular space invasion and depth of invasion, not tumor size as staging criteria would suggest [170]. These factors are best determined pathologically after radical hysterectomy. For the subset of patients for whom radical hysterectomy is the sole treatment required, treatment time is shortened and acute and late radiation sequelas are avoided. Primary radical hysterectomy will also avoid the difficulties of determining if there is viable tumor left after completion of primary chemoradiation. Also, the potential for preservation of ovarian function in young women (although this is frequently not successful) and for prevention of radiation-associated vaginal stenosis, may be an important advantage of primary surgical management. A primary surgical approach is mandatory in the setting of an undiagnosed coexistent pelvic mass, or anatomic alterations that make optimal RT difficult. It might also be beneficial in patients with acute or chronic pelvic inflammatory disease which is a relative contraindication to concurrent chemoradiation [171]. Furthermore, if patients are poorly compliant with Radiation Therapy or if expert Radiation Therapy or a Brachytherapy facility is not available, primary radical hysterectomy should be performed.

Primary Surgery vs. Chemoradiation

This is an unpopular approach for treatment of bulky cervical cancer because most of the patients will still require postoperative RT or concurrent chemoradiation [172]. It might also result in higher morbidity and mortality in this patient subset [173−175]. In an RTOG trial of 367 women with stage IB or IIA cervical cancer randomly assigned to pelvic or pelvic plus paraaortic RT, the estimated cumulative incidence of grade 4 and 5 complications was 11% in women who had postoperative RT vs. only 2% in those who received RT alone [176]. However, with the current advances in surgical technique, there has been a significant decline in the rates of postoperative morbidity. GOG 92 trial randomly as-

signed 277 patients with intermediate-risk factors to pelvic RT vs. no further therapy following radical abdominal hysterectomy [177]. The rates of grade 3 or 4 complications involving the gastrointestinal and urogenital tracts in the RT group were 2.3 and 3.1% vs. 0 and 1.4%, respectively. Similarly, in GOG 109, a randomized trial of adjuvant RT vs. chemoradiation following radical hysterectomy in 243 patients with high risk factors, rates of posttreatment small bowel obstruction in the chemoradiation and RT alone groups were 3 and 2%, respectively [178]. However, neither of these trials specifically enrolled patients with stage IB2 cancers.

Locally Advanced (Stage IIB, III, IVA) Disease

Definitive concurrent cisplatin-based chemoradiation therapy is the standard of care in locally advanced cervical cancer; however, a majority of those with recurrences have a poor prognosis despite improving salvage therapies [179–183]. Nodal involvement, particularly of para-aortic nodes, is the most important adverse prognostic factor, reducing survival by one-half. However, while the presence of lymph node metastases does not change the FIGO staging of cervical cancer, it significantly impacts the prognosis of these patients [179, 184]. Decades ago, it was thought that the lymphatic spread of cervical cancer advances in an orderly fashion, starting at the obturator lymph nodes and then progressing to the common iliac nodes, and the para-aortic nodes [185]. However, the implementation and utilization of the sentinel lymph node mapping technique clearly showed that not only any pelvic lymph node but also para-aortic lymph nodes might be the first site of metastases [186, 187]. Bader et al. [188] reported the variable pattern of first site of lymph node metastases in 619 invasive cervical cancer patients. Of 61 patients with one positive lymph node (10%), the external iliac (43%) and obturator (26%) regions and the parametrium (21%) were the most commonly involved pelvic lymph node sites with solitary metastases, and isolated metastases were reported to common iliac (7%), presacral (1%), and para-aortic nodes (1%). Of 59 patients with two positive lymph nodes (10%) at any location, patients had one parametrial and one pelvic node involved (32%), two ipsilateral positive nodes (31%), one positive lymph node on both sides of the pelvis (27%), and two positive nodes within the parametrium (10%) [188]. Several studies have shown that advanced FIGO stage, and increased depth of invasion increase the risk of lymph node metastases [189–191].

Controversies exist regarding nodal staging. Some institutions implement pretreatment staging lymphadenectomy as a standard institutional protocol while others rely mainly on imaging studies. Institutions where staging lymphadenectomy is a routine practice believe that CT and magnetic resonance imaging (MRI) are poor approaches in detecting small volume metastatic disease (<1 cm), and doubt the specificity of [18] F-fluorodeoxyglucose positron emission tomography (PET) scanning [192]. One hundred eighty-four patients with stages IB2–IVA cervical cancer reported by Leblanc et al. underwent pretreatment laparoscopic staging procedures, including transperitoneal abdomino-pelvic exploration and extraperitoneal bilateral infrarenal para-aortic lymph node dissection. Twenty-four per cent of women with clinical stages IB2 and IIA cervical cancer were found to have positive para-aortic lymph node metastases that resulted in extending their radiation field, while sparing 75% with stages IIB–IVA disease overtreatment. The authors confirmed the superiority of laparoscopic staging lymphadenectomy compared to CT or MRI in identifying patients with para-aortic lymph node metastases [192]. Utilization of laparoscopic lymphadenectomy resulted in improved staging lymphadenectomy-induced adverse events vs. the open extraperitoneal approach [193–196]. Other studies reported possible survival advantage of lymphadenectomy especially in patients with bulky nodal disease [197, 198].

As the only gynecologic malignancy that is still staged clinically, it should be noted that the accuracy of cervical cancer staging is only 60%, with most errors related to undiagnosed lymph

node metastases [199]. The sensitivity, specificity, positive predictive value, and negative predictive value of CT were only 34, 96, 60 and 91 % [200, 201]. Other reports showed the limitations of CT and MRI in diagnosing any microscopic lymph node metastases and reported 20–50 % failure in detecting macroscopic lymph node metastases. However, while PET scanning provided a better detection rate, its sensitivity did not exceed 86 % [202−208]. A GOG study evaluated the treatment outcomes of cervical cancer patients who had negative para-aortic lymph nodes identified by surgical staging vs. radiographic clinical staging prior to definitive chemoradiation. The analysis included patients who participated in 1 of 3 phase III GOG trials (GOG 85, GOG 120, and GOG 165). All patients had FIGO stage IIB–IVA disease without evidence of para-aortic lymph node metastases and received definitive cisplatin-based chemoradiation. The study included 555 patients who underwent surgical staging and 130 patients who underwent radiographic evaluation. Stage III and IV patients who underwent surgical staging had better 4-year progression-free survival (48.9 vs 36.3 %) and overall survival (54.3 vs 40 %). In multivariate analysis, the radiologic only staging was associated independently with a poorer prognosis compared with the surgical staging (for disease progression: HR, 1.35, 95 % [95 % CI], 1.01–1.81; for death: HR, 1.46, 95 % CI, 1.08–1.99). The study concluded that surgical staging might provide better prognosis [199].

Elective para-aortic radiation therapy in locally advanced cervical cancer patients who did not undergo surgical staging has been investigated in a number of controlled randomized clinical trials. RTOG randomly assigned 337 stage IIB cervical cancer patients to pelvic radiation therapy with or without 45 Gy to the para-aortic region and the 10-year cumulative incidence of death due to cervical cancer was estimated as significantly higher in the pelvic-only arm ($P=0.01$). There was statistical significant 10-year overall survival difference in favor of the extended-field radiation therapy arm (55 vs 44 %, $P=0.02$) but no difference regarding the DFS (40 vs 42 %). A higher percentage of local failures were salvaged on the extended-field arm compared with the pelvic-only arm (25 vs 8 %). This study also reported a trend, that was not statistically significant, for higher cumulative incidence of grade 4 and 5 toxicities among patients receiving extended field (8 %, 6 %) vs. pelvis only (4 %, 1 %) radiation therapy ($p=0.06$, 0.24), respectively. Patients with a history of abdominal surgery prior to the extended-field radiation therapy had higher incidence of grade 4 and 5 complications (11 vs 2 %) [176]. Of 441 cervical cancer patients with either stage I and IIB disease with proximal vaginal and/or parametrial involvement and positive pelvic LNs either on lymphangiogram or at surgery, or stage III regardless of pelvic node status on lymphangiogram randomized in an European Organisation for Research and Treatment of Cancer (EORTC) study to whole-pelvis radiation therapy with or without extended field to include the para-aortic lymph nodes (45 Gy). The study did not show any statistical significant advantage for the extended-field approach; however, the study was criticized for the relatively inferior 4-year DFS (51 %). The authors noted statistically significant higher incidence of para-aortic metastases and distant metastases without tumor at pelvic sites among patients who did not receive para-aortic region radiation, but this did not result in any DFS or overall survival advantage [209]. RTOG 90-01 randomized 403 patients with locally advanced cervical cancer and clinically negative para-aortic LNs to extended-field radiation therapy (EFRT) vs. concurrent chemoradiation. All patients received LDR brachytherapy boost. At a median follow-up of 43 months, the 5 year OS was 73 vs. 58 % ($P=0.0004$), and DFS was 67 vs. 40 % ($P<0.001$) in favor of the concurrent chemoradiation. Furthermore, significantly less distant metastases ($P<0.001$) and locoregional recurrences ($P<0.001$) events were reported among patients receiving concurrent chemoradiation. There was no significant difference regarding the treatment-induced adverse events in both arms [181]. Updated results at a median follow-up of 6.6 years for the 228 surviving patients showed statistical significance DFS advantage among patients receiving concurrent chemoradiation (all stages) and OS stages IB–IIB disease with a trend for higher OS in stages III and IVA

disease [180]. Currently, standard whole-pelvis chemoradiation is a standard of care among such patients with clinically negative para-aortic lymph nodes; however, a randomized controlled trial comparing extended-field chemoradiation vs. whole-pelvis chemoradiation in such patients would be worthwhile.

Many studies have investigated the efficacy and toxicity profile of EFRT in patients with proven para-aortic nodal metastases. Early studies demonstrated unacceptable rates of treatment-induced adverse events when utilizing EFRT concurrently with chemotherapy. Of 29 cervical cancer patients with biopsy-proven para-aortic nodal metastases who received hyperfractinated EFRT (1.2 Gy per fraction, twice daily) concurrent with 2–3 cycles every 3 weeks cisplatin-based chemotherapy and boosted by brachytherapy, 25 patients (86%) completed the treatment course. Acute grades 3 and 4 chemotherapy-induced adverse events were 48 and 28%, and radiation induced were 21 and 28%, respectively. One patient died of grade 5 adverse events during the treatment course [210]. Updated results showed that the grade 3 and 4 late toxicity were 7 and 17%. The 2- and 4-year OS were 46 and 29%, and the probability of disease failure at any site was 46, 60, and 63% at 1, 2, and 3 year, respectively. The authors concluded that the hyperfractionated EFRT with concurrent chemotherapy resulted in unacceptable toxicity but no advantage regarding patient's survival or tumor control when compared to the standard fractionation [211].

A phase 2 RTOG trial that included cervical cancer patients with para-aortic or high common iliac nodes randomized to receive EFRT with concurrent weekly cisplatin and brachytherapy boost vs. same treatment plus amifostine aimed at reducing radiation-induced toxicity. Arm 1 included 26 patients who did not receive amifostine; the acute and late grade 3/4 toxicity rates were 81 and 40%, respectively, and the estimated DFS and OS at 18 months are 46 and 60%, respectively [212]. Arm 2 with amifostine included 15 patients after exclusions for ineligibility or withdrawing consents; the acute and late grade 3/4 toxicities were 87 and 20%, respectively, and the estimated median survival was 34.8 months [213]. Similarly, a GOG study included 86 cervical cancer patients with para-aortic nodal metastases assigned to receive EFRT with concomitant cisplatin-based chemotherapy and brachytherapy boost. Acute grade 3–4 toxicities were gastrointestinal (18.6%) and hematologic (15.1%). The 3-year OS and PFI rate were 39 and 34%, respectively [214].

Recently, IMRT has been increasingly utilized, aiming to improve the toxicity profile of EFRT in high-risk patients, limit the radiation dose to OARs (gastrointestinal (GI) and genitourinary (GU) tracts), and safely permit escalation of the radiation doses to involved pelvic and para-aortic lymph nodes beyond 55 Gy [105, 215–218]. Of 22 cervical cancer patients who received extended-field IMRT concurrently with chemotherapy, none of the patients experienced acute or subacute grade 3 or 4 GI or GU toxicity [217]. Another study included thirty-six patients with Stage IB2-IVA cervical cancer treated with extended-field IMRT with concurrent chemotherapy showed acute grade ≥ 3 GI, GU, and myelotoxicity of 1, 1, and 10 patients, respectively and late (2 year) grade ≥ 3 toxicity in 10% of the patients. The 2-year actuarial locoregional control, DFS, and OS were 80, 51, and 65% respectively [218]. Marnitz et al. compared IMRT delivered by helical tomotherapy (HT) compared to conventional IMRT concurrent with chemotherapy, and found that HT significantly improved the target comformity, homogeneity and OAR sparing. However, more evidence is required before adopting this approach [219]. A dosimetric comparison of IMRT, passive scattering proton therapy (PSPT), and intensity-modulated proton therapy (IMPT) to the para-aortic (PA) nodal region in advanced gynecological malignancies. All plans created included IMRT to pelvis nodes with either PSPT or IMPT to para-aortic nodes with optimization aimed to deliver 50.4 Gy. Both PSPT and IMPT resulted in statistically significant decrease in doses to OARs; namely, small and large intestines and kidneys while maintain appropriate coverage to the planning target volume. However, this looks like a promising data, clinical studies are required to provide enough evidence to adopt such therapy [220].

Radiation Therapy Techniques

External Beam Radiation Therapy

Historically, EBRT to the pelvis was based on the bony landmarks that included the entire pelvis. This approach minimized any geographical miss but meanwhile it resulted in high incidence of treatment-induced adverse events due to the involvement of the organs at risk within the radiation field. Two-dimensional, fluoroscopic radiographs assisted the planning. The whole pelvis was usually treated with 6–15 MV of X-ray via anterior and posterior parallel fields or box fields. After an EBRT dose of 44–50 Gy in 22–28 fractions over 4.5–5.5 weeks, and patients with locally advanced disease were boosted to 54–60 Gy, with central shielding [221].

With the advancement in RT and the development of CT based treatment planning, 3D conformal radiation therapy (3DCRT) has replaced the two-dimensional approach and became a standard of care almost everywhere. This approach decreased the treatment-induced adverse events and provided better coverage of the target volumes. MRI, or PET images can be fused with the CT simulation images for better localization of the tumor and more conformal coverage to avoid any possible marginal miss. The implementation of the IMRT technology further reduced the organs at risk of treatment toxicity [222–227]. Furthermore, this did not result in higher rates of in-field failures [222, 223, 227]. Guidelines on CTV definitions for a number of tumor sites including the postoperative gynecological setting have been published [228, 229]. Still, the volumes for definitive radiation therapy for cervical cancer patients varies [222, 223, 225, 226, 230]. The higher likelihood of organ motion, tumor regression, and change in the cervix topography oblige radiation oncologists to take great caution when applying tight treatment fields [231–237].

Brachytherapy

Generally, radiation therapy for cervical cancer consists of a combination of external whole-pelvic irradiation and intracavitary irradiation. The aim is to eradicate cancer in the primary tumor site, parametrial tissue, and regional lymph nodes [238]. EBRT is given initially to decrease the bulk of the tumor, providing a better geometric anatomy and allowing optimal dose delivery in intracavitary brachytherapy therapy. Brachytherapy is employed by means of uterine tandem and vaginal ovoids or ring to provide a high-radiation dose to the cervical tumor after it is partially shrunken by EBRT. The application of brachytherapy in cervical cancer patients has been proven to reduce the rate of local failure and to improve the survival rate compared with EBRT alone; 78 vs. 53% for local control [239] and 43–87% vs. 21.0–60.5% for survival [240–242]. A recent Surveillance, Epidemiology, and End Results study highlighted the importance of brachytherapy in cervix cancer management. The study that was published in 2013 included over 7000 cervical cancer patients and utilized the Surveillance, Epidemiology, and End Results database using a matched cohort analysis of patients treated between 2000 and 2009. Brachytherapy used resulted in higher cancer-specific survival rates (64 vs. 52%), and 4-year overall survival (58 vs. 46%). Unfortunately, this study also reported a decreased utilization rate of brachytherapy between 1998 and 2009 from 83 to 58%, respectively. This decrease in use was seen regardless of stage and histologic type [243].

LDR brachytherapy has long been used [242], but immobilization and hospitalization of patients and exposure of medical personnel to radiation have been by-products of the increasing popularity of the HDR technique in the recent years [244, 245]. It remains difficult to compare the superiority of the two methods due to poor methodology in reporting complications and loss of a large number of patients to follow-up in most studies. In a study of approximately 2000 patients, Lorvidhaya et al. [246] reported similar survival and complications at each disease stage in patients undergoing HDR and LDR brachytherapy. Still, conventional HDR brachytherapy complications, such as rectovaginal fistula, vesicovaginal fistula, ureteral stricture, and vaginal necrosis and stenosis are worrisome to many practitioners. Conventional high-dose radiation therapy for bulky tumors certainly results in a

high rate of complications, such as rectovaginal fistula, vesicovaginal fistula, stricture ureter, and vaginal necrosis and stenosis [247].

Brachytherapy can be delivered with LDR, HDR, or PDR systems. LDR brachytherapy was the first modality to be traditionally used utilizing Cesium-137 based on an initial assumption of a radiobiological advantage over HDR brachytherapy [248, 249], presumably due to enhanced repair of normal tissues following LDR brachytherapy. HDR brachytherapy utilizing Iridium-192 has come into favor in many institutions because of many practical advantages that include remote after-loading that minimizes radiation exposure, use in an out-patient setting that might result in reduced cost [250], potentially better tolerance and a superior toxicity profile [251, 252], and superior treatment-plan optimization [253]. Most reports have shown similar treatment outcomes and treatment-induced adverse events in both LDR and HDR brachytherapy [244–246, 254–256]. PDR brachytherapy is theoretically considered to hold some radiobiological advantages over high dose rate (HDR) brachytherapy as each fraction comes before the complete repair of the sub-lethal cellular damage of the subsequent fraction, the tissue perceives the radiation as almost continuous, mimicking low-dose–rate (LDR) brachytherapy. Furthermore, PDR maintains the fine optimization of the dose distribution to the target volume (TV) and protect the personnel involved in the treatment from the risk of radiation exposure. Therefore, PDR hold the radiobiological advantages of LDR and the fine planning and radiation protection advantages of HDR. Although, this approach incorporates the biological advantage of LDR brachytherapy and the optimization advantage of the HDR brachytherapy, it also has many disadvantages including inpatient treatments, lack of applicator stabilization, and possibility of mechanical failure. In summary, PDR brachytherapy presents opportunities to potentially improve brachytherapy, but it also comes with detriments. Although PDR has prospered in Europe and Asia, unfortunately in the USA it has floundered because the NRC requires that a physicist and/or radiation oncologist be present throughout the treatment, which is almost impossible to accomplish in a long-treatment schedule in a hospital setting [251, 257]. Notably, many French radiation oncology centers favor the LDR and relatively recently the PDR, believing in the biological advantages of LDR and PDR and the possibility of optimizing treatment plans by controlling the source stepping time in each dwell position [258, 259].

Historically, most radiation oncologists prescribed their treatment to ICRU38 point A. However, this is an empiric point and does not reflect the dose to the tumor, because the tumor itself is not imaged and the tumor topography is very variable. This long term used point "A" that was introduced more than 50 years ago with no access to 3D imaging is a good representation of "an average extension" of the tumor/cervix, we endorse the volume-based individualized brachytherapy planning based on tumor topography and recommend the trend of prescription to HR-CTV as MRI-based image-guided brachytherapy (IGBT) facilitates a higher degree of adaptation and individualization. The International Commission on Radiation Units and Measurements (ICRU) Report 38 for dose specification of gynecologic brachytherapy [247] recommended that reference points such as Point A not to be used because, "such points are located in a region where the dose gradient is high and any inaccuracy in the determination of the distance results in large uncertainties in the absorbed doses evaluated at those points." In order to find other alternatives for dose prescription before the implementation of IGBT guidelines published by The Groupe Européen de Curiethérapie and the European Society for Radiotherapy and Oncology (GEC ESTRO), some centers in Europe prescribed the dose to a reference volume (i.e., tissue volume encompassed by a reference isodose surface, 60 Gy) to be able to compare intracavitary treatments performed in different institutions regardless of the applicator system, insertion technique, method of treatment, and prescription used. However, this practice has been applied only minimally in gynecologic intracavitary brachytherapy specifications, because no correlation has been shown with primary cervical tumor control [222, 223]. A retrospective single institution

study described this two-dimensional volume-based treatment planning was recently published. They used the tumor topography assembled on a two-dimensional film where they draw an envelope that encompasses the target volume and prescribes the brachytherapy dose to this envelope. The dose was reported to an isodose of 60 Gy that usually would encompass the envelope and report the volume encompassed by this isodose (Fig. 1.1). The study included 95 patients, the 3-year overall survival, progression-free survival, local control rate, and distant metastases rate were 83.8, 72.4, 84.8, and 15.4%, respectively. Gastrointestinal and genitourinary grades 3 and 4 acute adverse events were reported in 11.6 and 3.3% and chronic grade 3 and 4 adverse events were reported in 3.2 and 4.2% of all patients, respectively [259].

Recently, 3D treatment-planning systems have been increasingly used in most radiotherapy (RT) facilities. This technology allows radiation oncologists to shape the spatial dose distribution to conform to the target volume and reduce the dose to normal tissues. With this approach, it is possible to decrease the probability of normal tissue toxicity and to escalate the dose to the tumor to produce greater rates of local control [260].

Ultrasonography, CT, and MRI have been considered standard imaging modalities for cervical tumors. Transabdominal ultrasonography is capable of determining uterine size, shape, thickness, and diameter. Transabdominal intraoperative ultrasonography can be of assistance during difficult intracavitary insertions to guide proper tandem placement and avoid uterine perforation. It has also been used to establish the relative positions of the bladder and rectum during gynecologic brachytherapy applications. The rectal and bladder doses determined using ultrasound localization are often greater than those calculated using the conventionally defined dose-specification points [225–227]. Computerized treatment-planning software using CT rather than radiography to plan brachytherapy insertions is currently widely available. These CT-based methods have accurately localized intracavitary applicators and demonstrated the 3D anatomic relationship of the applicators and neighbouring structures, thereby

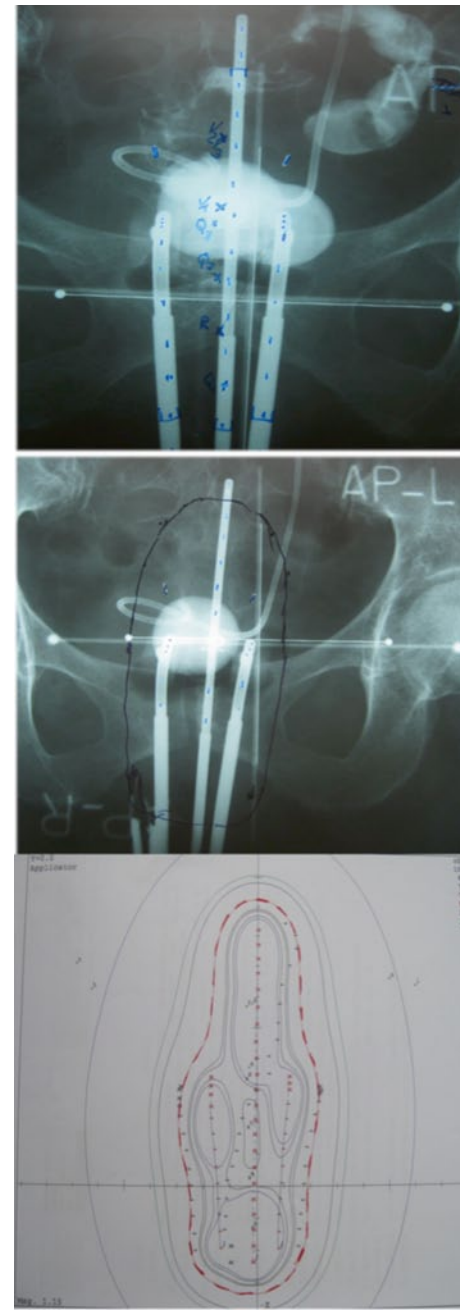

Fig. 1.1 A case of stage IIIB squamous cell carcinoma of the cervix, initial tumor volume was 70 cc. An envelope is drawn around the TV and an isodose—in *red*—encompassed this envelope (*127 cc*). The patient received a 50 cGy pulse/h for 40 h delivering total of 20 Gy to the entire envelope. The reported max and mean rectal doses were 19.87 and 18.41 Gy and the max and mean bladder doses were 19.75 and 17.67 Gy, respectively. The planning system and machine utilized is produced by Nucletron, an Elekta company (Elekta AB, Stockholm, Sweden)

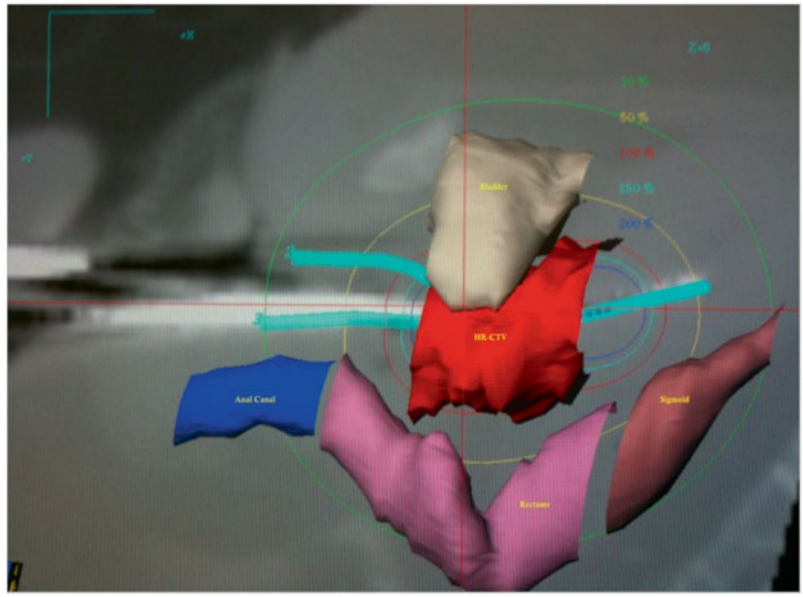

Fig. 1.2 Illustrative image of contouring HR-CTV, organs at risk and source reconstruction

obtaining the dose delivered to the tumor volume and neighbouring organs. Patients are typically scanned with contrast material in the bladder or with a bladder catheter, as well as rectal contrast [231–234]. CT is helpful in defining uterine wall thickness and the relationship of the bladder and rectosigmoid to the tandem [238]. CT has also been used to guide interstitial implantation and is helpful in defining the depth of needle insertion and evaluating the position of the inserted needles relative to the bladder and rectosigmoid [261]. CT images have significant limitations that include difficult identitfication of the tumor from the cervix and uterus which make the MRI much superior imaging modality when compared to the CT. The value of MRI in imaging gynecologic malignancies lies in its superior contrast resolution, which enables visualization of the cervical tumor size and volume, distinction of tumor from normal uterus and cervix, and definition of parametrial and vaginal infiltration of disease [260–263].

Both European (GEC ESTRO) [264, 265] and American (ABS) [266] recommendations for 3D and adaptive (4D) intracavitary brachytherapy have been published (Fig. 1.2). The European GEC ESTRO recommendations are supported by published clinical data with systematic use of MRI and partly CT-based planning of intracavitary brachytherapy [156–160]. It has been agreed upon by representatives of both societies in 2005 [161] to base further clinical and research work in regard to image-guided gynecologic brachytherapy on the GEC ESTRO recommendations I and II as published in 2005 and 2006 [264, 265].

The primary advantage of 3D and 4D adaptive brachytherapy is the possibility to adapt and conform the dose given by brachytherapy to the anatomy of each individual patient taking into account both tumor regression obtained by preceding EBRT and chemotherapy and also the position of nearby organs at risk. Based on the current experience, this technique has the potential for reducing both local failure rate and rate of moderate-to-severe morbidity [267] This goal can only be achieved provided that both gynecological examination and MRI (or CT) with brachytherapy applicator in situ are performed at the time of brachytherapy [154]. Visualization of the tumor is very difficult with CT, which makes MRI necessary [268]. Because changes of localization of the target and organs at risk in relation to the position of the applicator may occur, ideally each brachytherapy implant should be followed by a new

MRI study with the applicator in situ and a new dose plan. This seems to be relevant in particular for sigmoid, bowel, and bladder [269–271]. As these organs at risk can be also delineated on CT [272–274], it seems to be feasible to replace MRI by CT, if more than one fraction is applied for brachytherapy. For each fraction of brachytherapy contouring of the CTV, based on MRI [153] and organs at risk based on MRI or CT [275] are done in a 3D treatment-planning system. Subsequently, the applicator is carefully reconstructed and the conventional standard loading pattern matching the prescribed dose to point A is applied. From this starting point dose optimization is performed with the goal of adapting the dose to the target volume (GTV at the time of brachytherapy plus whole cervix plus suspected residual extra cervical disease) analogue to the dose level previously prescribed for point A or the reference volume without exceeding the dose volume constraints for the surrounding normal tissues [170]. Dose optimization should be conservative, i.e., the standard loading pattern should be retained as far as possible [265, 276]. Evaluation of the DVH parameters obtained by brachytherapy is most commonly done by use of the GEC ESTRO recommendations [154]. For each brachytherapy fraction the D90 and D100 for GTV, HR-CTV, and IR-CTV is recorded. For the organs at risk the D0.1 and D2 cc of rectum, sigmoid, and bladder are determined. Both the physical dose as well as the EQD2 is recorded. Assessment of dose from EBRT is done based on the assumptions given in the GEC ESTRO Recommendation (II) [265]: For the regions of interest (target volumes and organs at risk) it is assumed that they receive the full dose of EBRT as represented by the ICRU point. Thus, for dose reporting these doses are taken and calculated in EQD2 and then added to the dose for defined brachytherapy volumes like D90 for the CTV and D0.1 and D2 cc for organs at risk, which also have been expressed in EQD2.

Potter et al. reported the clinical outcome of MRI HDR IGBT combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer at 3 years: the LC was 95%; 100% for stage IB, 96% for stage IIB, and 86% for stage IIIB. The actuarial rates for grade 3 and 4 morbidity were 3–4% for the bladder and the rectum at 5 years, respectively [277]. Charra-Brunaud et al. [258] reported a large French prospective study, STIC PDR (Soutien aux Techniques Innovantes et Coûteuses), utilizing PDR or LDR image-based brachytherapy comparing two-dimensional (2D) vs. 3D brachytherapy planning and including three different treatment arms, patients in each arm were randomized to either 2D or 3D LDR or PDR brachytherapy. Almost all patients in the 3D arm had PDR brachytherapy (362/369), while only 36% of the patients in the 2D arm had PDR brachytherapy (122/336) with the majority receiving LDR brachytherapy. The study reported the results of 705 patients recruited in 20 French centers, the reported 2-year local relapse-free survival, local regional relapse-free survival were 73.9 and 78.5%, and 61.2 and 69.6% in 2D and 3D arms, respectively, in patients receiving CRT followed by brachytherapy and 84.7 and 93%, and 77.2 and 88.6% in 2D and 3D arms, respectively, in patients receiving CRT followed by brachytherapy and surgery. Most of the patients in the group receiving salvage surgery (80%) had stages IB2–IIB disease. Notably, the 2-year local relapse-free survival, local regional relapse-free survival reported in this study for patients receiving brachytherapy followed by surgery were 91.9 and 100%, and 87.9 and 96.1% in 2D and 3D arms, respectively; most of those patients had stage IB1 disease.

Vulvar Cancer

Vulvar cancer represents 5% of the gynecological malignancies and is the fourth most common gynecological cancer [1]. Early stage disease is treated with surgery that consists of excision of the primary lesion and the inguinal lymph nodes. Modified radical vulvectomy results in comparable tumor control but better cosmetic and is associated with less surgical morbidity [278–282].

Locally advanced disease should receive radiation therapy or concurrent chemoradiation as an integral part of the treatment plan (neoadjuvant, adjuvant, or definitive) [282–289]. A GOG

study enrolled 114 patients randomly allocated to postoperative pelvic and groin radiation (45–50 Gy, $n=59$) or to ipsilateral pelvic node resection ($n=55$) after radical vulvectomy and inguinal lymphadenectomy. An interim analysis led to early closure of the study due to the significantly superior advantage of radiation therapy over pelvic lymphadenectomy. The estimated 2-year survival rates were 68% for the radiation therapy group and 54% for pelvic node resection group. The most dramatic survival advantage for radiation therapy was in patients who had either clinically suspicious or fixed ulcerated groin nodes or two or more positive groin nodes. Six-year overall survival benefit for radiation in patients with clinically suspected or fixed ulcerated groin nodes ($P=0.004$) and two or more positive groin nodes ($P<0.001$) persisted. A ratio of more than 20% positive ipsilateral groin nodes (number positive/number resected) was significantly associated with contralateral lymph node metastasis, relapse, and cancer-related death. Late chronic lymphedema (16% compared with 22%) and cutaneous desquamation (19% compared with 15%) were balanced after radiation and pelvic node resection. The authors concluded that radiation therapy after radical vulvectomy and inguinal lymphadenectomy significantly reduces local relapses and decreases cancer-related deaths. Late toxicities remained similar after radiation or pelvic node resection [288, 290].

Vaginal Cancer

Vaginal cancer comprises approximately 3% of all gynecological malignancies, with around 3000 new annual cases diagnosed in the USA [1]. Most vaginal cancers are metastatic cancers from cervical or uterine cancers, while primary vaginal cancer is uncommon [291−293]. Radiation therapy with or without concurrent chemotherapy is the treatment modality of choice for the majority of vaginal cancers. Radiation is usually delivered through EBRT followed by intracavitary or interstitial brachytherapy [294−300].

Ovarian Cancer

Ovarian cancer is the most common cause of gynecologic cancer mortality and the second most common gynecologic malignancy [1]. Surgery is the mainstay of treatment of ovarian cancer. Chemotherapy has replaced radiation therapy as adjuvant treatment of ovarian cancer, but failure rates are still high with about 70% of patients demonstrating recurrence in the abdomen or pelvis after first-line chemotherapy. A recent comprehensive review of the literature aimed at redefining the role of radiation in ovarian cancer concluded that patients with nonserous variants (clear cell, endometrioid, and mucinous), intermediate-risk patients (stage I, II, and III disease with grades 1, 2, and 3, but no residual disease postsurgery), stage II and III disease, and recurrent disease (with residual disease less than 2 cm in diameter and confined to the pelvis), are potential candidates for radiation therapy. Radiation is definitely an option for palliation in metastatic ovarian cancer patients [301].

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The Role of Radiation in Urological Malignancies

2

Eric D. Donnelly and Bryan David Macrie

Introduction

Urologic malignancies represent a diverse group of neoplastic processes that include primary prostate, kidney and bladder cancers, which represent some of the most common cancers encountered in the United States of America (USA); seminomatous testicular germ cell tumors (GCT), which are less common tumors principally of younger men as well as primary ureter; and urethral and penile cancers, which are only rarely encountered in clinical practice. Collectively in 2014, more than 385,000 people in the USA are expected to be diagnosed with a urologic malignancy, accounting for an estimated 60,500 deaths [1]. Radiation therapy (RT) plays an important role in the definitive treatment of all of the aforementioned urologic cancers with the exception of kidney and ureter malignancies, where RT is primarily indicated for palliation of advanced or metastatic disease. Within urologic subsites, where RT is utilized with curative intent, there is considerable heterogeneity of RT type, technique, and use of concurrent systemic agents. Within subsites where surgery is utilized upfront, RT also plays an important role in an adjuvant or salvage capacity.

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Prostate Cancer

In 2014, an estimated 233,000 new cases of prostate cancer are expected in the USA, reconfirming prostate cancer's status as the most common genitourinary (GU) malignancy among US males [1]. Along with radical prostatectomy (RP) and active surveillance (AS), RT continues to be a mainstay of treatment in select patients.

Definitive RT for prostate cancer can be administered in the form of external beam RT (EBRT), interstitial brachytherapy (IB), or a combination of the two treatment modalities. In clinical practice, patients with prostate cancer are routinely classified as having low-, intermediate-, or high-risk disease based on their pretreatment prostate-specific antigen (PSA) level, clinical tumor stage, and biopsy specimen Gleason Grade [2]. Within this framework, definitive EBRT may be appropriate therapy for select patients in any of the three categories, while IB is typically appropriate as monotherapy for patients with low-risk disease or as a boost following EBRT for patients with intermediate-risk disease.

The choice of RT modality, the anatomic target, radiation dose, fractionation, and potential use of concurrent hormonal therapy are also based on a patient's risk factors, medical comorbidities, life expectancy and the potential impact of the proposed intervention on quality of life

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[3]. In addition, emerging evidence suggests that treatment choice and survival may also be influenced by demographic and socioeconomic factors outside of traditional, patient, tumor, and treatment characteristics [4].

The anatomic target for definitive EBRT is the intact prostate with inclusion of the seminal vesicles and/or pelvic lymph nodes based on the extent of disease and tumor characteristics. Additional margins are added to the target volume to account for microscopic tumor extension and daily setup uncertainty. Pelvic RT targeting the regional lymphatics has been employed in the past for patients felt to be at high risk for lymphatic spread of disease, though to date has provided no clear benefit in either control or survival based on level one data [5, 6].

Trends in the treatment of early-stage prostate cancer between 1973 and 2004 show relatively stable use of RT as first-line therapy for patients under 65. However, a steady increase in the use of RT for patients aged 65 and over has been identified [7]. Although AS has been increasingly gaining acceptance in the management of elderly patients, men aged 70 and over with favorable-risk prostate cancer continue to receive EBRT over 50% of the time [8].

With regards to optimal EBRT dose, several important prospective randomized control trials (RCTs) have shown that patients undergoing definitive EBRT derive a local control and survival benefit from escalation of dose to the prostate and seminal vesicles [5, 9–12]. As a result of increased dose to adjacent pelvic organs, patients in the dose-escalated arms on these trials were observed to have significantly increased toxicity including rates of late grade 2 or higher gastrointestinal (GI) toxicities ranging from 17.5 to 33% at between 5 and 10 years of follow-up [5, 9–12].

Advances in technology and evolution of treatment technique from traditional 2-dimensional to present day utilization of intensity modulated RT (IMRT) have enabled dose-escalation without commensurate increases in acute and late toxicity. Retrospective analyses have shown that patients treated to the intact prostate with IMRT have a statistically significant reduction in GI toxicities compared to patients treated to similar doses with 3-dimensional chemoradiation therapy (3D-CRT). Zelefsky et al. published the results of 1571 patients treated for intact prostate cancers with either 3D-CRT or IMRT at Memorial Sloan Cancer Center to doses ranging from 66 to 81 Gy. The use of IMRT was shown to significantly reduce the risk of GI toxicities compared to 3D-CRT (13% vs 5%, $p<0.001$) [13]. Likewise, subset analysis of the Dutch dose-escalation study of 68 Gy vs 78 Gy for intact prostate cancers demonstrated that the use of IMRT over 3D-CRT resulted in significant reductions in acute grade 2 or higher GI toxicity (20% vs 61%, $p=0.001$) [14]. Given improvement in the treatment toxicity profile, IMRT has increasingly been used in place of 3D conformal techniques. As demonstrated in a recent Surveillance, Epidemiology, and End Results (SEER) data analysis, use of IMRT increased from 0.15% in 2000 to 95.9% in 2008 [15]. Along with IMRT, daily imaging, real-time prostate tracking and methods to reduce rectal motion are now widely employed to safely deliver increased dose to the prostate while minimizing dose to normal structures of the pelvis and account for both inter-fractional and intra-fractional motion. Use of these techniques has enabled some groups to dose-escalate beyond 80 Gy with limited toxicity [16].

Prostate cancer cells are unique among human malignancies in that they have an alpha-to-beta ratio that is estimated to be lower than that of adjacent normal tissues [17]. Hypofractionated intensity modulated RT (HIMRT) to the prostate may hypothetically exploit this radiobiologic principle to provide increased tumor control without increasing overall toxicity. HIMRT also reduces overall treatment time and therefore expense, an important consideration given that dose-escalated conventional IMRT (CIMRT) with daily radiation fractions of 1.8–2 Gy can take up to 9 weeks to complete at considerable cost to the patient and health care system. A prospective trial from Fox Chase Cancer Center randomized patients with low-, intermediate- and high-risk prostate cancers to receive either CIMRT with 76 Gy in 2 Gy fractions vs HIMRT with 70.2 Gy in 2.7 Gy fractions. This study did not find any significant difference between treatment arms in

terms of 5-year biochemical and/or clinical failure rates (21.4% vs 23.3%, CIMRT vs HIMRT, $p = 0.745$). In addition, there was no difference in late toxicities and HIMRT treatment could be completed in 2.5 fewer weeks than CIMRT [18]. Additional multicenter prospective studies will be required to confirm the safety and efficacy of HIMRT for the treatment of intact prostate cancers.

Owing to the distinct dosimetric advantages of proton beam RT (PBRT) over conventional photon-based EBRT, including minimal entrance dose and no exit dose, proton beam therapy has become an increasingly attractive modality for treatment of intact prostate cancers. Presently, proton therapy for intact prostate cancer can be delivered in a highly conformal manner using two opposed lateral fields that reduce dose to the bladder and rectum as compared to CIMRT. To date, no prospective randomized study has been performed to directly compare outcome measures between PBRT and CIMRT. However, retrospective data have suggested that despite improved dosimetry, there may be little clinical advantage for PBRT over CIMRT but considerable extra expense. A retrospective comparison of Medicare beneficiaries treated for prostate cancer between 2008 and 2009 identified 27,647 men treated with PBRT and 27,094 patients treated with IMRT. The findings demonstrated that patients receiving PBRT were younger, healthier, and from more affluent areas than those patients receiving CIMRT and at 12 months posttreatment there was no difference in GI or GU toxicity between the two patient groups. Median Medicare reimbursement was US$32,428 for PBRT and US$18,575 for CIMRT [19]. Interestingly, in a SEER data analysis of patients treated for prostate cancer between 2002 and 2007, propensity score-match analyses between 684 men treated with PBRT and 6666 men treated using IMRT showed that IMRT patients actually had a lower risk of GI morbidity than those receiving PBRT [15].

Prostate IB conceptually represents an "inside-out" method of RT in which high doses of radiation are delivered to the target volume that rapidly fall off thereby limiting dose to adjacent organs at risk. Low-dose rate (LDR) IB may be performed via permanent implantation of LDR isotopes such as Palladium-103 or Iodine-125 and local control rates achieved with LDR IB in men with clinically localized, low-risk prostate cancer are comparable with those achieved with RP [20, 21]. Alternatively, high-dose rate (HDR) IB may be performed via temporary implantation of catheters in the prostate through which HDR isotopes are inserted and then removed after a prescribed duration of time. Despite its value as monotherapy for low-risk prostate cancer, SEER analysis shows that between 2004 and 2009 monotherapy IB use decreased from 30.4 to 25.6%, a finding the authors attribute to the rise in popularity of EBRT techniques including IMRT and PBRT, which are reimbursed at higher rates than IB. For patients with intermediate-risk prostate cancer, EBRT may be combined with an LDR or HDR IB boost. With respect to combined therapy utilization, SEER analysis shows a less drastic decline in utilization from 13.8% in 2004 to 12.3% in 2009 [22].

In addition to playing an integral role in the definitive treatment of intact prostate cancer, EBRT has also been employed postoperatively as either adjuvant therapy for patients with high-risk pathologic or surgical features or as salvage therapy for patients with a biochemical failure based on PSA or in those found to have a clinical local recurrence. In the setting of adjuvant or salvage treatment, the RT treatment target is the surgical resection bed with consideration for treatment of the pelvic lymph nodes and therapy is delivered with EBRT alone without any role for IB. Three large RCTs demonstrated that patients with at least one of the following: extra-capsular extension, positive surgical margins, or seminal vesicle involvement after RP derive a biochemical failure free survival benefit from adjuvant RT to the surgical prostate bed [23–25]. Two of the trials included patient subgroups with detectable PSA levels post-RP that received salvage RT. In these studies, salvage RT significantly reduced metastatic recurrence rates [24] and biochemical failure [23] among patients with detectable PSA post-RP, respectively.

Prior to the publication of these key postoperative RT RCTs, only 18.2% of patients received

adjuvant RT after RP with high-risk features [26]. Based on these trials, several clinical guidelines have been presented and updated to reflect these findings. As part of their published clinical guidelines, the American Society for Radiation Oncology (ASTRO) and the American Urologic Association (AUA) now jointly recommend adjuvant radiotherapy to patients with adverse pathologic findings at prostatectomy and salvage RT to patients with PSA or local recurrence after RP [27]. However, it appears as though biases may still influence practice patterns regarding adjuvant and salvage RT. A national web-based survey of post-RP RT beliefs was mailed to 926 radiation oncologists and 591 urologists showed that 68 % of respondents recommended adjuvant RT based on adverse pathologic features. However urologists were much less likely to recommend adjuvant RT than radiation oncologists (78 % vs 44 %, Radiation Oncologists vs Urologists, $p < 0.001$). Likewise, PSA thresholds for recommending salvage RT were significantly higher among Urologist responders than responding Radiation Oncologists [28].

The past two decades have witnessed an incredible evolution in RT for prostate cancer that has resulted in impressive gains in biochemical control and reduction in toxicity. The improvement in the therapeutic ratio has resulted largely from technological advances that have enabled dose-escalation with sparing of adjacent normal tissues. Additional gains may come from further refinement of image-guidance techniques and organ-motion compensation that enable reduction in the size of target margin expansions. In addition, novel treatment modalities and techniques that utilize hypofractionation to exploit the unique radiobiology of prostate cancers may also prove to further increase local tumor control without adding toxicity. Given the anticipated changes in health care economics and the massive expense of modern prostate cancer treatments, new treatment strategies will need to be rigorously tested and evaluated through multi–institutional trials to prove their safety, efficacy, and superiority to current standards of care.

Bladder Cancer

Bladder cancer is the second most common GU malignancy in the USA, with 74,690 total new cases expected in 2014 [1]. The large majority of patients with new bladder cancers present with superficial tumors that are commonly managed with local therapies, with radiation playing only a limited role in select patients. However, patients found to have muscle-invasive bladder cancers have significantly worse survival and require more aggressive management. RT is presently an integral component of trimodal bladder preservation therapy, which has emerged as an important alternative to radical surgery in this patient population.

Historically, the treatment options for muscle-invasive bladder cancer without distant disease included partial or radical cystectomy (RC), RT to the pelvis alone in those patients deemed to be poor surgical candidates or some combination of surgery and either preoperative or postoperative radiation. Despite similar disease-free survival (DFS) outcomes in nonrandomized studies, RC and pelvic lymphadenectomy has generally been favored over radical radiation for medically operable patients [29]. While considerable advances in surgical technique have occurred in recent decades, a reduction in quality of life remains an unavoidable consequence of urinary diversion following RC.

In light of the morbidity of RC and historical 5-year survival of only 40–60 % an international effort attempted to refine bladder preservation therapy via the addition of concurrent radiosensitizing chemotherapy [30, 31]. This work culminated in the current approach to bladder preservation consisting of maximal transurethral resection of bladder tumor (TURBT) followed by concurrent induction CRT. Patients achieving complete response on cystoscopy proceed to consolidation CRT therapy and close follow-up, while those without complete response were recommended to undergo RC. Prospective analyses of this technique have demonstrated overall survival (OS) rates of 50–60 % with 75 % bladder preservation [32].

Despite results demonstrating nearly equivalent survival when compared to historical trials and greater preservation of bladder and urinary function, strongly held views regarding treatment efficacy may be limiting widespread adoption of bladder-preservation therapy. A retrospective SEER analysis of patterns of care for nearly 27,000 patients with muscle-invasive bladder cancers treated between 1988 and 2006 found that 87% of patients received definitive surgery alone or with adjuvant RT. Importantly, the SEER database did not include details regarding chemotherapy use but 10.9% of patients received EBRT up-front with or without surgery and ostensibly many of the patients in this group would have received chemotherapy concurrent with their EBRT. Medical operability was also not available from the data but the patients who received EBRT up-front were more likely to be older, female, and have squamous cell carcinomas or poorly differentiated tumor. Interestingly, the year of diagnosis was not an independent variable for predicting the use of bladder preservation, suggesting that even as prospective data emerged suggesting a benefit to concurrent CRT there was little change in the firmly entrenched beliefs of the superiority of RC [33].

To date, no direct comparison of modern, CRT-based bladder preservation therapy and RC has been successfully conducted for muscle-invasive disease. A study designed by the Medical Research Council in the United Kingdom attempting to compare these two treatment modalities in a prospective manner closed after accruing only 45 patients in 30 months. Given potential biases in the USA regarding CRT for bladder cancer, it is likely a similar RCT here would meet the same fate. Despite this, ongoing research is refining and expanding the role of RT in bladder cancers in other ways. The Radiation Therapy Oncology Group (RTOG) is presently conducting a legacy phase II study investigating whether bladder preservation with definitive CRT is appropriate for patients who have undergone maximal TURBT revealing grade 2–3, stage T1 bladder cancers for whom RC is being considered. For patients who are older or medically inoperable there may also be an emerging role for bladder-sparing hypofractionated IMRT with concurrent chemotherapy. A preliminary study from Canada of 24 patients treated in this manner to a dose of 50 Gy in 2.5 Gy fractions with concurrent gemcitabine or cisplatin revealed a complete response rate of 83% with acceptable toxicity rates [34].

Seminomatous Testicular Cancer

Testicular cancers are the most commonly diagnosed malignancy of men between the ages of 20 and 45 with an estimated 8820 new cases expected in 2014 [1]. Cancers of the testis can be broadly subdivided into pure seminomatous germ-cell tumors (SGCT) and nonseminomatous germ-cell tumors (NSGCT). RT plays an important role in the treatment of testicular SGCT but does not typically have a role in the treatment of nonseminomatous testicular cancers where chemotherapy is presently the foundation of therapy.

Testicular SGCT are remarkably sensitive to both chemotherapy and radiation with high salvage rates following relapse. As such, following transinguinal orchiectomy patients with stage I disease may be candidates for adjuvant EBRT, chemotherapy, or surveillance.

In general, there has been a trend over the last decade to omit or limit adjuvant RT for early-stage testicular seminoma. SEER data from 1999 indicated that during the late 1990s 84% of patients with localized testicular SGCT received RT after orchiectomy [35]. However, this routine practice was called into question after data emerged indicating a 2.6-fold increase in the long-term development of secondary non-germ cell malignancy after subdiaphragmatic RT for long-term survivors of testicular seminoma [36]. In light of the increased risk of secondary malignancy, high rates of salvage after recurrence and emerging data on observation, the National Comprehensive Cancer Network (NCCN) guidelines were changed in 2009 to reflect a preference for observation. Follow-up analysis of SEER data demonstrated that the same year adjuvant RT use fell to 37.7% [37]. Even with these recommendations, select patients with stage I disease remain

candidates for adjuvant RT, including those with findings of a primary tumors >4 cm, rete testis involvement or for those patients at high risk for noncompliance with the recommended stringent follow-up measures required during observation.

The utilization of radiation, including targets and doses, has been influenced by several key randomized trials. The MRC-UK TE 10 study randomized early stage patients receiving adjuvant EBRT to treatment of the para-aortic (PA) nodal chain and ipsilateral iliac lymph nodes vs PA nodal chain alone. The trial found equivalent 5-year survival in each group [38]. Thus, for stage I patients without other risk factors or nodal disease, radiation is typically delivered to the PA nodal chain alone, omitting the pelvic nodes, with classic field borders extending from T10–11 down through L5–S1, and laterally 2 cm beyond the vertebral bodies with an additional 1 cm border on left renal hilum and sacroiliac joint if the primary tumor was left-sided. In an effort to determine the appropriate dose, MRC-UK TE 18 randomized patients with stage I disease treated to the above field to either 20 Gy in 2 Gy fractions vs 30 Gy in 2 Gy fractions and found no difference in 5-year relapse rates. Based on this, the current recommended doses are for 20–25 Gy in 1.25–1.5 Gy fractions [39].

For stage I patients, there are several treatment options including observation, radiation and chemotherapy. However, patients with stage IIA–IIB seminoma have a higher likelihood of pelvic nodal failure and so radiation remains the standard of care. Radiation fields typically utilize an extended "dog-leg" field to treat both the PA nodal chain and at-risk ipsilateral iliac lymph node regions. The field borders for patients with IIA–IIB disease, as employed in MRC-UK TE 10, include a superior edge of T10–T11, inferior border at mid-obturator foramen, ipsilateral border from renal hilum down to L5–S1 interspace then diagonally in parallel with the ipsilateral border then vertically downwards to mid-obturator level (Fig. 2.1). As in stage I patients, the "dog-leg" field used in IIA–IIB disease is treated to 25 Gy in 1.25 Gy fractions with consideration for an additional boost to involved lymph nodes (Fig. 2.2). In spite of the benefits of radiation in stage IIA–IIB, patients with stage IIC and higher seminoma commonly receive adjuvant chemotherapy first as opposed to RT due to a higher concern for distant over local failure.

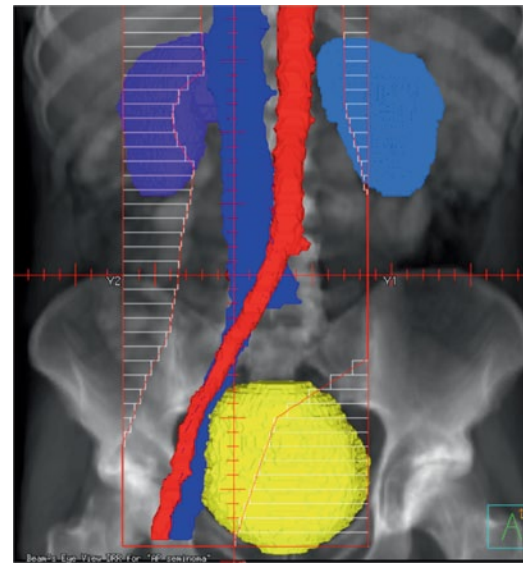

Fig. 2.1 RT fields for a stage I seminoma

Urethral Cancer

Primary urethral cancers are extremely rare malignancies. SEER analysis from 1973 to 2002 identified an annual age-adjusted incidence rate of 4.3 per million US men and 1.5 per million US women [40]. A multimodal approach to treatment is commonly employed with a goal of organ preservation whenever possible; however, given the relative rarity of the disease and historical lack of treatment uniformity, the role of RT is not well described through randomized clinic trials.

RT has historically played a limited role in the treatment of male urethral cancers. Rabbani et al. identified 2065 men from the SEER database from 1988 to 2006 with primary urethral cancer. Of these patients, 78% had urothelial carcinoma histology, 67% presented with less than or equal to T1 disease and 61% of patients were managed with simple surgical excision alone. Only 10% of patients received radical resection and RT was utilized to only 10% of

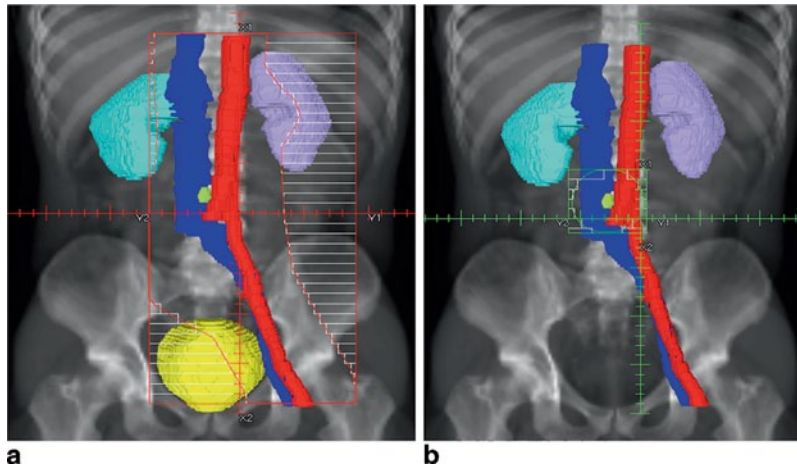

Fig. 2.2 **a** Initial RT fields for a stage IIA seminoma. Enlarged PA node in *yellow-green*. **b** Boost field for stage IIA seminoma

patients as well. The SEER database did not distinguish between proximal vs distal tumors and so it is unclear how tumor site may have influenced treatment choice [41]. Outcomes regarding male urethral cancers treated with radiation are limited. In one of the larger retrospective series on the topic, Dalbagni et al., retrospectively reviewed 46 men with primary urethral carcinoma treated at Memorial Sloan Kettering Cancer Center (MSKCC) between 1958 and 1996. Forty patients received surgery alone and 6 received RT followed by salvage surgery. In this study, none of the RT patients responded to RT though the authors posit that this was due in large part to selection bias and higher T stage among RT patients [42]. Radical CRT for more advanced male urethral carcinoma has showed promise in at least one small, single-institution analysis. Eighteen men in this study with T2–4, N0–2 disease were treated on a protocol of 45–55 Gy, to a field encompassing the inguinal, external iliac lymph nodes and genitalia from the perineum to the upper sacrum using AP/PA technique with a boost of 12–15 Gy to the primary lesion. Radiation was given concurrently with mitomycin and 5-fluorouracil (5-FU). Results demonstrated that 83 % of patients had a complete response to treatment with 5-year overall and disease-specific outcomes of 60 and 83 %, respectively. Three of the nonresponders and four of the complete responders who recurred required salvage surgeries [43].

Radiation has a more established role in the treatment of female urethral cancers though outcomes remain poor irrespective of the choice of treatment modality. Several long-term retrospective series have analyzed the role of RT in female urethral cancers. Grigsby et al. published the results of 44 patients with urethral carcinoma, of whom 12 received RT with surgery (either pre- or postoperatively, dose range: 30–73.68 Gy, median 50.4 Gy) and 25 received EBRT and brachytherapy (EBRT doses 12–70 Gy, median 42.72 Gy; brachy doses 15–145 Gy, median 80 Gy). EBRT fields included bilateral groins in all women. The 5-year OS rate was 42 % and the 5-year cause-specific survival was 40 % with the aggressive treatment regimens resulting in high complication rates [44]. Similarly, Garden et al. reviewed the outcomes of 97 women treated for primary urethral carcinoma at MD Anderson Cancer Center. Of those, 86 received radiation after excision or biopsy, including 35 treated with combined EBRT and IB (EBRT doses 20–70 Gy, median 46 Gy, Brachy doses 20–70 Gy, median 30 Gy), 21 treated with EBRT only (40–71 Gy, median 61 Gy), and 30 with IB only (45–75 Gy, median 60 Gy). There was significant heterogeneity among treatment techniques and fields employed. The overall

actuarial 5-, 10-, and 15-year survival rates for all 97 patients were 41, 31, and 22%, respectively, and the type of treatment did not predict outcome [45]. Princess Margaret Hospital published results of 34 women with urethral carcinomas treated with radiation that was directed to the primary lesion in 15 patients vs the primary tumor and regional lymph nodes in 19 patients. Of these patients, 20 received combined EBRT and brachytherapy. The median dose to the primary tumor, accounting for the contributions of both EBRT and brachytherapy doses for all 34 patients, was 57 Gy (range 30–83 Gy). The 7-year actuarial overall and cause-specific survivals were 41 and 45%, respectively, and brachytherapy reduced the risk of local recurrence by a factor of 4.2 [46].

Penile Cancer

Penile cancer is a rare GU malignancy in the USA with estimated 1600 new cases in 2014, accounting for less than 1% of male malignancies [1]. Although uncommon in Europe and the USA, it represents a more significant cause of male cancer in the Indian subcontinent, Africa, and Latin America. The conventional treatment for early stage penile squamous cell carcinoma has been total or partial penectomy, which results in rates of local control in excess of 90% [47]. In recent years, however, there has been a trend towards organ-sparing treatments including definitive EBRT and/or brachytherapy as a means to limit functional and psychosexual morbidity associated with penectomy. In the USA, however, use of RT for treatment of penile cancers remains limited. A recent SEER database analysis of 2427 men with penile cancer treated between 1988 and 2006 demonstrated 90.0% received surgery alone, 2.2% received EBRT alone, and 7.4% received EBRT after surgery. One subject received brachytherapy alone and eight subjects received brachytherapy after surgery either with or without EBRT. Patients who received EBRT alone or in conjunction with surgery were more likely to have advanced T and N stages. The study authors posit that underutilization of RT for penile cancer is a function of referral bias, with patients presenting first to a dermatologist or urologist being offered specialty-specific therapy instead of referral to a radiation oncologist [47].

Despite the lack of widespread utilization, retrospective data have shown promising results for definitive RT for penile cancers. Ozsahin et al. published the results of a multicenter retrospective review of 60 patients with penile carcinoma. In total, 27 patients underwent surgery with or without adjuvant radiation vs 29 who underwent definitive EBRT alone. After biopsy, four patients refused RT. Of the patients receiving definitive EBRT, local control was obtained in 39% and four patients who recurred underwent salvage surgery resulting in a penis preservation rate of 52%. The 5-year and 10-year probability of surviving with an intact penis was 43% and 26%, respectively, and there was no significant survival difference between the patients treated with definitive RT and primary surgery (56% vs 53%; $p = 0.16$) [48]. A review of 67 men with T1–T3 penile cancers treated at two Canadian centers with penile-conserving primary brachytherapy revealed 10-year actuarial OS and cause-specific survival rates of 59% and 83.6%, respectively. Salvage penectomy was required for eight local failures and two cases of necrosis, for an actuarial penile preservation rate at 5 years of 88% and 10 years of 67% [49].

Although the role of adjuvant RT for penile cancer is not well defined in the literature, it appears to be most important in patients with positive pelvic lymph nodes. Franks et al. retrospectively analyzed the results of 23 men with pathologic N1–N3 penile cancer treated with adjuvant RT after local surgery and unilateral or bilateral groin dissection. The RT dose was 45 Gy in 20 fractions to the pelvis and bilateral groins delivered AP/PA. A 12-Gy boost in five fractions could be given if indicated. 3-year OS and locoregional relapse-free survival was 66% and 56%, respectively [50].

Summary

RT has a well-established and continually evolving role in the treatment of many of the most common and some of the rarest GU malignancies in the USA. Outcomes in many of these disease sites have sufficiently improved such that patients will live long enough to manifest not only the acute but also late-effects of treatment. There is an important duty on the part of all medical practitioners involved in the care of patients with GU malignancies to learn to appropriately prevent, diagnose and manage these treatment-related toxicities.

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Role of Radiation in Rectal Cancers

3

Angelita Habr-Gama, Jose Marcio Neves Jorge and Leonardo A. Bustamante-Lopez

Introduction

The results of surgical treatment of rectal tumors have been limited by the development of local-regional recurrence following "curative operations." This is expected to occur in about one-fourth of patients [1−3]. Thus, adjuvant therapy has been used to decrease pelvic recurrence rates and improve overall survival [1, 4].

Advances in pelvic radiation techniques, new adjuvant systemic therapies and experimentation of different neoadjuvant (preoperative) regimens and adjuvant (postoperative) therapies have contributed to reduce the high rates of local recurrence in patients with rectal cancer [5]. This multimodality intervention associated with refinement of surgical techniques, particularly the standardization of sharp total mesorectal excision and improvements in perioperative care, has contributed to improve both management and overall survival of these patients during the last three decades [6].

Other factors that add to this change include the introduction of new imaging studies to improve accuracy in preoperative staging (particularly endorectal ultrasound (ERUS) and magnetic resonance imaging), and the standardization of enhanced histopathological evaluation [7–9]. As a result of this integrated effort, management of rectal cancer has evolved tremendously. It is widely accepted that decisions regarding therapeutic options need to be individualized and should preferably be based on a multidisciplinary discussion.

Adjuvant Radiotherapy

Radiotherapy for rectal cancer was introduced in the 1980s with an aim to decrease local recurrence (as high as 50% at that time), in patients with locally advanced rectal cancer. In 1985, the Gastrointestinal Tumor Study Group published one of the first randomized controlled trials to demonstrate significantly decreased local recurrence rates with the use of combined chemoradiotherapy [10]. This trial and other randomized controlled trials have shown the efficacy of adjuvant chemoradiotherapy in reducing local recurrence from 55% to 33%, with significantly prolonged disease-free survival in patients with locally advanced rectal cancers (T3–4/Nx or Tx/N1–2) [10–12]. Consequently, The National Cancer Institute in a consensus statement in 1990, recommended adjuvant therapy for stage II and III rectal cancer [13]. In addition, moderate quality evidence (1B) has been shown for the use of adjuvant chemoradiotherapy in patients with

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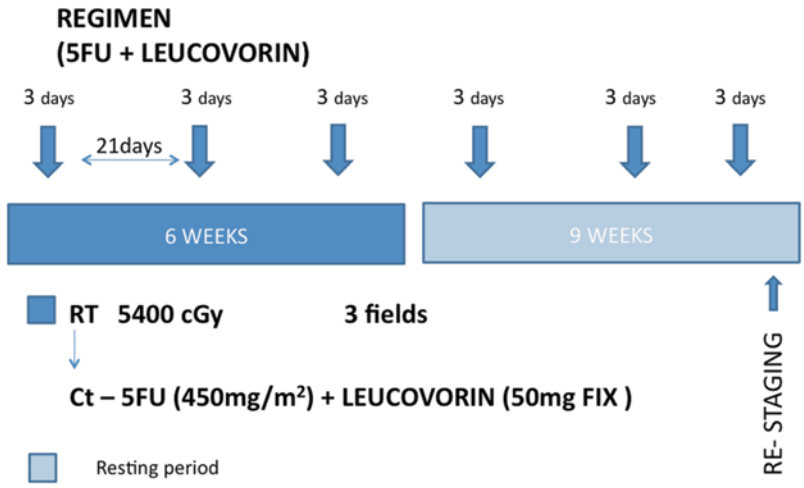

Fig. 3.1 Scheme demonstrates conventional neoadjuvant chemoradiotherapy regimen. Neoadjuvant chemoradiation regimen including cycles of bolus 5-fluorouracil (*5FU*) and leucovorin administered every 21 days including during the "resting" period after radiation completion. *RT* Radiotherapy

stage III or high-risk stage II rectal cancer who have not received neoadjuvant therapy [14].

Although initially administered postoperatively, there is evidence that neoadjuvant or preoperative chemoradiotherapy is preferable. The disadvantages of postoperative chemoradiation compared to neoadjuvant therapy include: increased toxicity of the small bowel in the radiation field, a potentially more radioresistant hypoxic postsurgical bed, and impaired healing of the perineal wound after abdominoperineal resection [15]. In addition, neoadjuvant chemotherapy has superior efficacy and long-term results [16].

Neoadjuvant Radiotherapy

In order to improve local control and long-term survival, many studies on adjuvant radiotherapy were conducted in the 1990s and from these efforts the concept of neoadjuvant radiotherapy was originated.

There are two different regimens of neoadjuvant radiotherapy currently in use, termed as "long-course" preoperative chemoradiotherapy and "short-course" radiotherapy. Long-course chemoradiotherapy is more commonly used in United States of America (USA) and South American countries. It consists of conventional doses of external beam radiation, 1.8–2.0 Gray (Gy) per fraction given over 5–6 weeks to a total dose of 45–50.4 Gy with concurrent administration of 5-fluorouracil (5-FU)-based chemotherapy. This is followed by surgery 8–12 weeks later. During the first protocols, a resting period of 8 weeks was recommended, but longer periods (10–12 weeks) are also used to achieve a more definitive effect from chemoradiotherapy [14]. The most commonly used conventional neoadjuvant chemoradiotherapic regimen is shown in Fig. 3.1.

In short-course radiotherapy, 5 Gy external beam radiation is administered daily over 5 days without chemotherapy, followed by surgery within 1 week. This regimen is mainly used in Northern Europe and Scandinavia countries. According to the Swedish Rectal Cancer Trial, compared with surgery alone, patients who received "short-course" radiotherapy had reduced local recurrence (11% vs 27%, $p<0.00$) and improved 5 year overall survival (58% vs 48%, $p=0.004$) [17]. The benefits of the short-course radiotherapy regimen continued at 13 years' follow-up (local recurrence: 9% vs 26%, $p<0.001$; overall survival: 38% vs 30%, $p=0.008$) [18]. Patients who received Short-Course Radiotherapy,

however, had a higher rate of hospitalization over the 6-month period after surgery and more gastrointestinal complications [19]. Accordingly, in the Dutch TME Trial, patients who received "short-course" neoadjuvant therapy combined with total mesorectal excision (TME) had significantly lower local recurrence compared to those who had TME alone (2.4% vs 8.2%, $p<0.001$); however, no long-term survival benefit was found in the "short-course" group [20, 21].

The efficacy of preoperative versus postoperative chemoradiotherapy has been investigated by the German Rectal Cancer Study Group [22]. This trial randomly assigned 823 patients with T3 or T4 and/or node-positive rectal cancers to receive either pre- or postoperative chemoradiation. Chemoradiotherapy consisted of 50.4 Gy of external beam radiation in 28 fractions with concurrent 5-FU (1000 mg/m^2 per day for 5 days in the first and fifth week of radiation). Total mesorectal excision was performed in all patients and all patients received additional 4 cycles of 5-FU-based chemotherapy. Local recurrence rates were significantly higher in the postoperative chemoradiotherapy group (15%) compared to the preoperative group (6%) ($p=0.006$). Rates of disease-free survival, overall survival, and sphincter preservation did not differ between the two groups. These authors recommended that preoperative long-term chemoradiotherapy as the standard treatment for patients with locally advanced disease that requires downstaging.

Recently, a meta-analysis was performed to assess the effectiveness and safety of neoadjuvant radiotherapy in the management of rectal cancer [23]. The authors identified 17 trials comparing neoadjuvant therapy versus surgery alone. A total of 8568 patients were enrolled. In the five trials comparing neoadjuvant chemoradiotherapy to neoadjuvant radiotherapy, 2393 patients were enrolled. The investigators found that neoadjuvant radiotherapy resulted in improved local disease control (hazard ratio 0.59; 95% confidence interval 0.48–0.72) compared to surgery alone even after total mesorectal excision, whereas its benefit in overall survival failed to reach statistical significance (0.93; 0.85–1.00). Short-course radiotherapy, however, was followed by significantly increased perioperative mortality (1.48; 1.08–2.03), particularly if a dose of 5 Gy per fraction was administered (1.85; 1.23–2.87). Chemoradiotherapy improved local control compared to radiotherapy alone (0.53; 0.39–0.72), with no impact on perioperative outcome and long-term survival. The authors concluded that neoadjuvant radiotherapy had a favorable impact on local control in patients with rectal cancer, particularly when combined chemotherapy is administered. The question of whether use of more active, modern chemotherapy protocols or targeted therapy in the neoadjuvant setting will improve overall survival after curative resection requires further investigation.

Most studies of the adverse impact of neoadjuvant therapy on perioperative morbidity and mortality occurred in patients treated before 1980. Some authors have associated the incidence of late bowel obstruction and increased postoperative mortality with the large irradiation volume, including paraortic lymph node regions [19, 24]. Radiotherapy techniques have evolved enormously since that time, including increased accuracy of target definition and more precise dose delivery, using intensity-modulated techniques. Use of these modern radiotherapy strategies need to be evaluated in future studies.

Benefits of Neoadjuvant Radiotherapy

At present, neoadjuvant chemoradiation is the preferred treatment for patients with locally advanced rectal cancer. In addition to the benefits in improving local disease control, the majority of patients receiving "long-course" neoadjuvant chemoradiation obtain significant tumor regression and downshift of their T and/or N status, leading to a downstage of the primary tumor [25]. Downsizing may alter surgical planning, particularly in low rectal tumors, by making a sphincter saving operation possible. In addition, up to 20–30% of patients will have a complete pathological response, with no viable tumor cell found in the resected rectum [26]. Although radical surgery including total mesorectal excision remains the primary treatment after neoadjuvant

chemotherapy, new local excision alternatives have been developed for selected patients.

Colonoscopic and radiological aspects of incomplete clinical response after neoadjuvant chemoradiation are shown in Figs. 3.2 and 3.3. Figure 3.4 shows magnetic resonance imaging (MRI) before and after neoadjuvant chemoradiotherapy in a case of complete clinical response.

While long-course neoadjuvant chemoradiotherapy and short-course radiotherapy are both efficacious, there are limited data specifically comparing these two regimens. In 2006, the Polish Colorectal Study Group published the long-term results of a trial comparing short- and long-course neoadjuvant therapy in 312 patients with T3/4 mid-to-low rectal cancer [27, 28]. All patients underwent total mesorectal excision. The rates of sphincter preservation were similar in both groups [58–61%, respectively, for the long- and short-course neoadjuvant therapy arms ($p=0.570$)]. However, the circumferential margin at the time of surgery was positive in 4% of patients receiving long-course neoadjuvant chemoradiotherapy, compared with 13% of patients in the short-course radiotherapy group. No differences were found in local recurrence, late toxicity, or overall survival. However, complete pathological response was higher in patients receiving long-course neoadjuvant chemoradiotherapy (16.1–0.7%, respectively). This can be explained by the fact that in the short-course protocol surgery is performed within a week after the end of radiotherapy, an approach that does not allow for preoperative downstaging.

Significant rectal tumor downstaging following neoadjuvant chemoradiation has raised the issue of offering patients with small residual cancers restricted to the bowel wall, an alternative to total mesorectal excision in order to avoid its associated morbidities, particularly urinary and sexual disturbances due to autonomic denervation. In patients who develop significant tumor regression, excision and node sterilization may be appropriate for less aggressive techniques such as transanal endoscopic microsurgery [29].

Although still considered controversial, nonoperative management of patients with a complete clinical response after completion of neoadjuvant chemoradiation is steadily increasing. In order to avoid postoperative morbidity and functional disorders, our group has considered withholding immediate surgery (the "Watch and Wait" approach) for patients with complete clinical response after neoadjuvant chemoradiotherapy for distal rectal cancer. Figure 3.5 demonstrates findings on colonoscopy, MRI, and anal ultrasound in a patient who received neoadjuvant chemoradiation.

In 1997, our group published the results of a study involving 118 patients with potentially resectable cases of histologically proven low rectal adenocarcinoma [25]. Treatment consisted of external beam radiotherapy 5040 cGy for 6 weeks and concurrent leucovorin (20/mg/m^2/day) with bolus doses of 5-FU administered intravenously at 425 mg/m^2/day for three consecutive days on the first and last 3 days of radiation therapy. After 2 months, all patients underwent repeat evaluation and biopsy of any suspected residual lesions or scar tissue [30]. Thirty-six (30.5%) patients were classified as being complete responders. In six of these patients, complete response was confirmed by the absence of tumor in the surgical specimens (three abdominal resections and three proctosigmoidectomies with coloanal anastomosis). In the remaining 30 patients, complete response was confirmed by the absence of symptoms, negative findings on physical examination, biopsy, ERUS, and pelvic computed tomography (CT) results, during a median follow-up of 36 months. Eighty-two patients (69.5%) were considered incomplete responders. Residual lesion was identified during the first examination in 74 patients, and after 3–14 months in the remaining 8 patients. Except for one patient who refused surgery, all patients in this group underwent surgical treatment, including coloanal anastomosis (36 patients), local excision (9 patients), and abdominal resection (4 patients). In this study, combined up-front chemoradiotherapy was associated with tolerable and acceptable side effects. Thus, our study showed that 30 patients (25%) were spared from surgical treatment. Sphincter-saving management occurred in 38% of patients who might otherwise have required an abdominoperineal resection. The preliminary

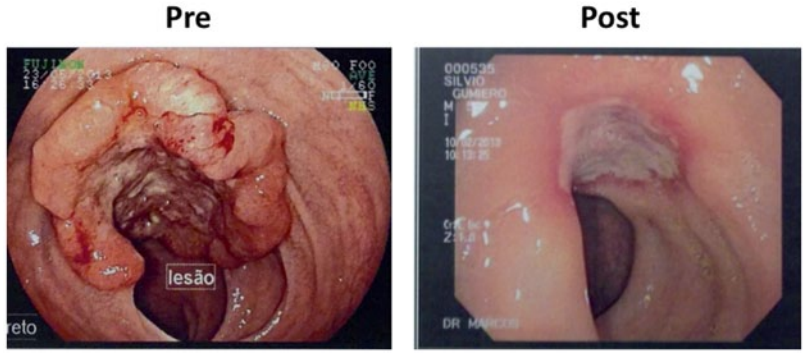

Fig. 3.2 Colonoscopic findings demonstrate incomplete response after neoadjuvant chemoradiotherapy

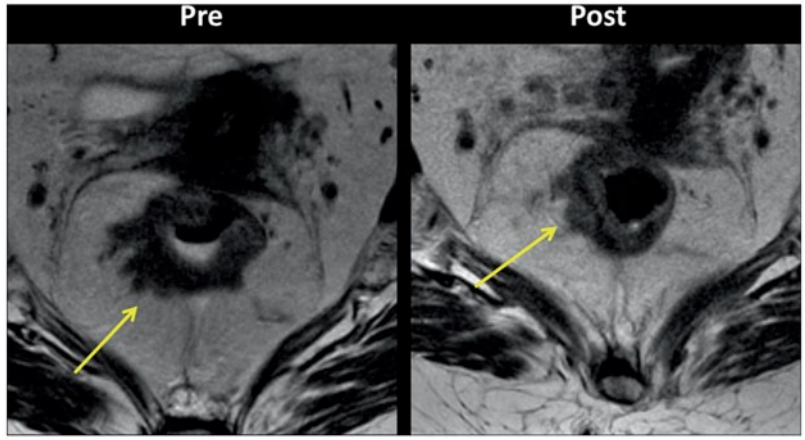

Fig. 3.3 Pelvic magnetic resonance imaging (*MRI*) findings demonstrate incomplete response after neoadjuvant chemoradiotherapy

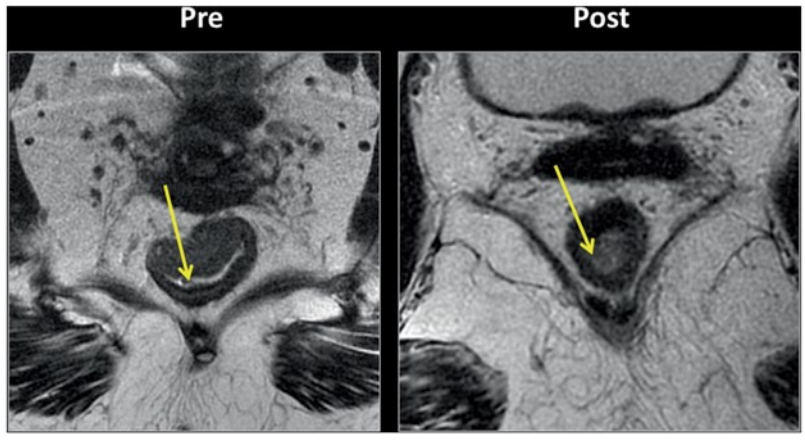

Fig. 3.4 Pelvic magnetic resonance imaging (*MRI*) findings demonstrate complete response after neoadjuvant chemoradiotherapy

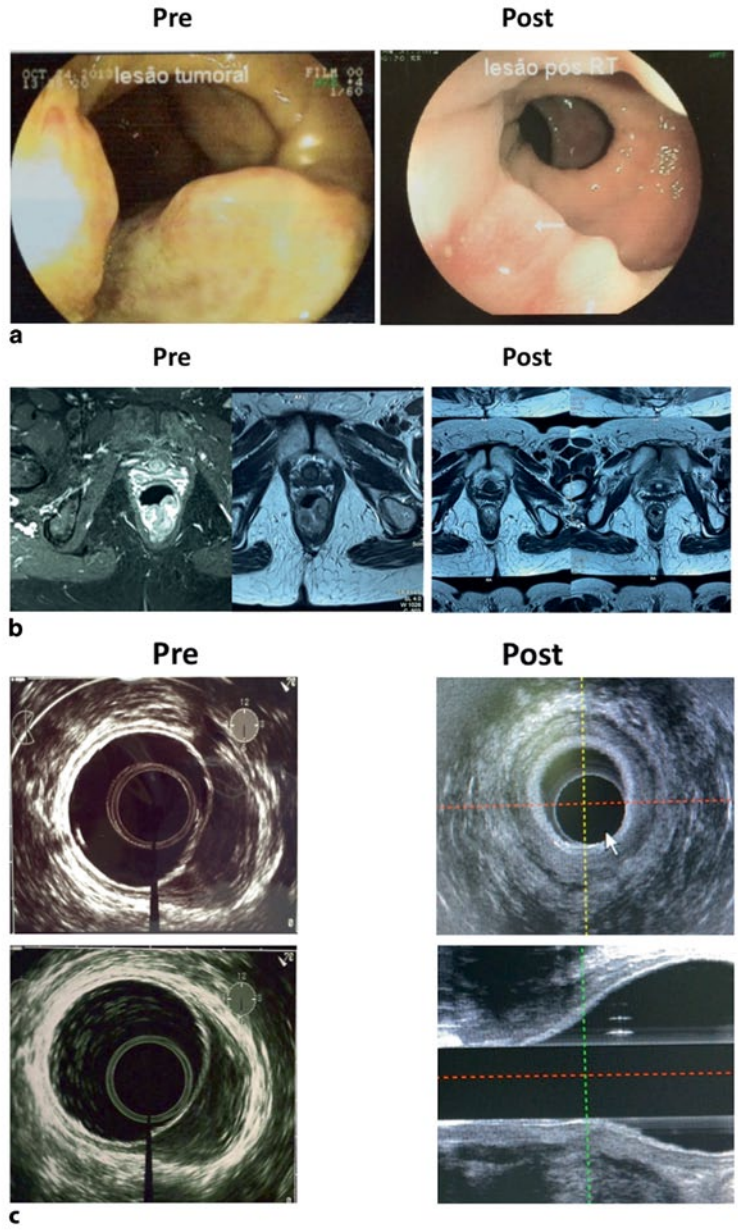

Fig. 3.5 Complete response after neoadjuvant chemoradiation: results in the same patient of colonoscopy (**a**), pelvic magnetic resonance imaging (*MRI*) (**b**), and endorectal ultrasound (**c**), before and after (10 weeks) the end of radiotherapy

results of this trial suggested a reduction in the number of local recurrences and reinforced the concept that in some selected cases, infiltrative low rectal cancer should be initially treated by chemoradiotherapy.

In a subsequent study, the impact of an extended neoadjuvant chemoradiation regimen on complete response rates was evaluated [31]. Radiotherapy consisted of 45 Gy, delivered by a three-field approach with daily doses of 1.8 Gy

on weekdays to the pelvis, followed by a 9 Gy boost to the primary tumor and perirectal tissue (a total of 54 Gy administered over a 6-week period). Concomitantly, patients received three cycles of bolus 5-FU (450 mg/m^2) and a fixed dose of 50 mg of leucovorin for three consecutive days every 3 weeks. After completion of radiation therapy, patients received three additional identical cycles of chemotherapy every 3 weeks until 9 weeks after completion of radiation therapy (Fig. 3.1). Patients with biopsy-proven resectable adenocarcinoma located no more than 7 cm from the anal verge and no evidence of systemic metastatic disease were eligible for inclusion in the study. All patients underwent complete physical examination, digital rectal examination, and rigid proctoscopy. Disease staging modalities included either pelvic MRI or ERUS with three-dimensional (3D) technology for T and N staging, in all patients. In addition, carcinoembryonic antigen (CEA) and abdominal and chest CT scans to exclude metastatic disease were performed at initial staging. Patients with radiological evidence of T3 or T4 tumors were included in this novel neoadjuvant chemoradiation strategy. Tumor response was assessed immediately after completion of chemotherapy, at 10 weeks from completion of radiation, using complete physical examination, digital rectal examination, and rigid proctoscopy. The same imaging studies that were performed at initial assessment were performed again at tumor response assessment. Patients with complete clinical response were strictly monitored and surgery was deferred to a later time. Patients with incomplete clinical response were immediately referred to surgery.

Twenty-nine patients completed 12 months of follow-up and were included in this preliminary analysis; 28 (97%) of them successfully completed treatment. Median follow-up was 23 months. Fourteen patients (48%) were considered as complete clinical responders sustained for at least 12 months (median, 24 months). Fifteen of 16 patients had skin-related grade III toxicities (93%). This preliminary series suggested that extended 5-FU-based neoadjuvant chemotherapy regimens during the "resting period" after radiation completion are well tolerated and may increase radiosensitivity of the primary tumor [31].

As these studies suggest, increased rates of complete clinical tumor response are expected for Stage I through Stage III distal rectal cancers with extended 5-FU-based neoadjuvant chemotherapy. This in turn suggests that the increment in chemotherapy doses could result in higher radiosensitivity of the primary tumor and improve rates of complete clinical response. Recently, Gerard et al. reported that modifications in both radiotherapy and chemotherapy regimens have been implemented, and the results seem to support the idea of improved tumor response secondary to radiotherapy dose escalation [32]. These authors suggest that there are slightly improved complete pathological response rates in the group with an increased radiotherapy dose, with oxaliplatin offering no advantage over capecitabine alone as a radiosensitizer. The increased number of overall cycles of chemotherapy could have potentially positive benefits on long-term survival and decreased risk of late systemic relapses.

In a recent prospective study, the long-term results of patients who had complete clinical response following the extended chemoradiation regimen previously described, and managed nonoperatively using the "Watch and Wait" approach, were analyzed. Seventy consecutive patients with T2–4, N0–2M0, distal rectal cancer were studied. Neoadjuvant chemoradiotherapy included 54 Gy external beam radiation and 5-FU/leucovorin delivered in 6 cycles every 21 days, as previously described (Fig. 3.1). Patients were assessed for tumor response after all 6 cycles of chemotherapy, at 10 weeks from radiation completion. The assessment of response included clinical (digital rectal examination), endoscopic (proctoscopy), and radiological studies (MRI, ERUS imaging, and/or positron emission tomography (PET)/CT). Patients were considered as having an initial complete clinical response in the absence of residual ulceration, mass or significant rectal wall irregularity at the 10-week postradiotherapy follow-up. Radiological evidence of complete response was also required for inclusion in the "Watch and Wait" approach. Radiological features of

complete response included the presence of residual low-signal-intensity areas (on MRI), absence of restriction to diffusion (on diffusion-weighted MRI) or absence of residual fluorodeoxyglucose (FDG) uptake within the rectal wall (on PET/CT). Patients with radiological evidence of residual tumor in the mesorectum and/or within the rectal wall were considered as incomplete responders, irrespective of clinical and endoscopic findings. Patients with incomplete clinical response were referred for immediate surgery.

Patients with a complete clinical response were not offered surgery, and were enrolled in a strict follow-up regimen, including monthly follow-up visits, with reassessment of tumor response without additional chemotherapy. Patients with any suspicious small residual abnormalities were managed by full-thickness transanal excision for diagnostic purposes [30, 33].

The study demonstrated that extended chemoradiation therapy with additional chemotherapy cycles and 54 Gy of radiation results in sustained (>12 months) complete clinical response rates, with over 50% of patients ultimately avoiding rectal resection. Local failures in up to 17% of cases occur more frequently during the initial 12 months of follow-up. Late recurrences are less common, but an additional 10% of patients developed late recurrence after sustaining a complete clinical response for at least 12 months. Strict follow-up allows early recognition of recurrence and may allow appropriate salvage therapy in the majority of these patients. Although the high complete clinical response rate seen after chemoradiotherapy seen in the treatment of anal cancer is not yet seen for low rectal cancers, the fact that more than half of these patients are spared radical resection is quite significant.

Techniques

Conventional technique in pelvic irradiation is based on the bony landmarks visualized on radiological exams, in order to identify the level of the tumor and important surrounding normal structures such as the small bowel and the femoral heads. When a low anterior resection is planned, the anal sphincter is always included within the field of radiation and when an abdominoperineal resection is planned, the field is extended inferiorly, in order to include the perineal incision area.

So-called "sphincter-preserving radiotherapy" is performed by placing a sphincter block to exclude the anal canal. This technique represents an interesting preventive strategy, particularly for tumors of the upper of the rectum, allowing the coloanal anastomosis to be performed with a nonirradiated transitional zone. This technique still requires studies using anorectal manometry parameters in addition to anal incontinence severity indexes and specific quality of life instruments to confirm its benefit.

Sexual and Anorectal Function Outcomes

Yarpe et al. [34] evaluated 74 patients with rectal cancer who underwent abdominoperineal resection or anterior resection. A validated RAND 36-item health survey of quality of life and self-administered questionnaires with reference to anorectal and urogenital function were answered preoperatively and 1 year after surgery in 65 patients who were alive and without signs of recurrence. Postoperative general quality of life was similar and mental functioning was better after surgery. Problems with physical functioning included anal dysfunction after anterior resection. Problems with social functioning were present and were associated with urinary dysfunction. At 1 year after surgery, urinary incontinence and male sexual function were worse, and the incidence of dysuria was higher after abdominoperineal resection than anterior resection. Anorectal dysfunction was more troublesome among patients who underwent anterior resections. Preoperative radiation therapy was associated with postoperative ejaculatory problems and anal incontinence.

Long-Term Functional Results

Over the last two decades, there has been a decline in colorectal cancer mortality rates in most European and North American countries [35]. Consequently, there is an increasing concern about the long-term effects of the current therapeutic regimens on anorectal function and quality of life in colorectal cancer survivors. Knowles et al. [35] recently studied the prevalence of pelvic dysfunction and its impact on quality of life after curative rectal cancer surgery with or without radiotherapy. Of 667 patients studied, 381 (57%) responded three validated questionnaires; the median time interval following treatment was of 4.4 years. The authors found the following defecatory complaints in the subset of patients with a history of rectal cancer ($n=138$): incontinence of gas: 32%, fecal leakage: 16%, wearing of a pad: 17%, and incomplete evacuation: 31%. Preoperative radiotherapy and the presence of an anastomosis <6.0 cm from the anal verge were associated with increased defecatory problems. In their conclusion, the authors discuss the need for individually targeted follow-up of symptoms, support, and consideration for a trial of new models of comprehensive evaluation and interventions in patients who are at risk of experiencing these late adverse effects.

New Perspectives

Several methods have been studied that attempt to optimize the effects of radiotherapy and/or minimize its side effects. These include: (1) new techniques such as 3D conformal radiotherapy and intensity-modulated radiation therapy, (2) the use of complementary therapies such as radiosensitizing agents, and (3) better patient selection according to their intrinsic radiosensitivity and tumoral response to irradiation [36–38]. In addition, methods such as brachytherapy and intraoperative radiotherapy have been reevaluated and new chemotherapic agents introduced [39, 40]. Despite higher postoperative morbidity, recent studies have shown that intraoperative brachytherapy is a viable option for locally advanced or recurrent colorectal cancer. Further prospective studies are required [41]. High-dose-rate interstitial brachytherapy might be a promising treatment in locally recurrent rectal cancer because of limited toxicity and the high concentration doses that can be delivered to the tumor, as compared to external-beam radiotherapy [42].

Advances in pelvic radiation techniques, and experimentation of different regimens of neoadjuvant (preoperative) and adjuvant (postoperative) therapies have contributed to reduce the high rates of local recurrence related to the treatment of rectal cancer. A number of randomized controlled trials have shown the efficacy of adjuvant chemoradiotherapy in reducing local recurrence and cancer-related mortality. Therefore, adjuvant chemoradiotherapy should be recommended in patients with stage III or high-risk stage II rectal cancer who have not received neoadjuvant therapy.

Both neoadjuvant regimens: long-course chemoradiotherapy and short-course radiotherapy are adequate for local control in patients with locally advanced tumors of the mid- and lower third of the rectum. Although better tolerated, with lower acute toxicity and better compliance, short-course radiotherapy may lead to more long-term complications due to higher dose per fraction in short-course radiotherapy. Short-course radiotherapy can be useful when the tumor margin is threatening the mesorectal fascia, in patients in whom tumor downsizing would not improve resection or sphincter preservation.

Current chemoradiation regimens are still based on general protocols, because it is still difficult to predict the potential radioresistence of a tumor or the radiation hypersensitivity of health tissue [38]. Advances in radiobiology and radiation oncology will allow identification of predictive biomarkers that can discriminate radiosensitive tumors or tissues from the more radioresistant ones, therefore allowing oncologists to tailor protocols and allow treatments to follow a more personalized approach.

Summary

The treatment of rectal cancers has dramatically improved during the last two decades. Factors for this change include the introduction of new imaging studies to improve accuracy in preoperative staging, particularly ERUS and magnetic resonance imaging, the refinement of surgical techniques, and the evolution of combined modality treatment.

Therapeutic decisions need to be individualized and should be based on a multidisciplinary approach, involving radiation oncologists, medical oncologists, radiologists, pathologists, and primary care physicians.

Long-course neoadjuvant therapy has advantages of preoperative tumor regression and downstaging, which may make sphincter saving operations possible in many cases. In addition, complete pathological response is possible in a significant percentage of patients. For these reasons, at present it is the most commonly used neoadjuvant regimen in Brazil, as well as the USA.

The combination of neoadjuvant radiotherapy and TME surgery may result in significant long-term adverse effects, including sexual and anorectal sphincter dysfunctions. This should be taken into account during selection of patients for radiotherapy. In addition, ongoing trials are addressing quality of life issues with modern radiation techniques and newer chemotherapeutic agents.

Editor's Note We wish to thank the authors for their contribution. The authors discuss the option of performing less than radical surgery following preoperative combined modality therapy for rectal cancer, an approach that they have been instrumental in developing. Additional research is advised to develop a complete understanding of the appropriate ways to apply this approach for individuals with rectal cancer. At the present time, definitive surgery (low anterior resection (LAR) vs abdominoperineal resection (APR) remains the standard of care.

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Prevention of Injury from Pelvic Irradiation

4

Michelle S. Gentile and William Small Jr.

Introduction

Pelvic radiotherapy is utilized for a number of malignancies in the definitive, neoadjuvant, and adjuvant settings. Pelvic radiotherapy can contribute to substantial bowel, bladder, and hematological toxicity along with changes in sexual quality of life (QOL). In addition to radiation therapy, factors that may influence rates of toxicity include prior surgery and addition of systemic therapy. While there can be effective management of late toxicities once established, preventive strategies including use of different treatment modalities, optimization of treatment technique and planning, and administration of various agents and radioprotectors should also be considered to minimize risk of toxicity when possible.

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Intensity-Modulated Radiation Therapy

Intensity-modulated radiation therapy (IMRT) is an advanced form of three-dimensional conformal radiation therapy (3D-CRT) that manipulates radiation beams of varying intensities to precisely radiate a tumor (Fig. 4.1). Numerous studies assessing differences in dose distribution have shown decreased toxicity with the use of IMRT over 3D-CRT in the treatment of pelvic malignancies especially regarding bone marrow, gastrointestinal (GI), and genitourinary (GU) toxicity. IMRT may be well suited for gynecological, lower GI and GU malignancies because adjacent normal structures such as small bowel, bladder, external genitalia, skin, femoral heads, and bone marrow can potentially be spared from the higher radiation doses needed to treat the primary disease. While IMRT may be helpful in reducing dose to adjacent normal tissue, there are concerns of using IMRT, including potential geographic miss and increased risk of secondary malignancies. When the use of IMRT is indicated, however, it may significantly reduce toxicity.

Gynecological Malignancies

Radiation Therapy Oncology Group (RTOG) 0418 is a multiinstitutional phase II study designed to assess the feasibility of pelvic IMRT with and without concurrent chemotherapy for the treatment of 48 cervical and endometrial

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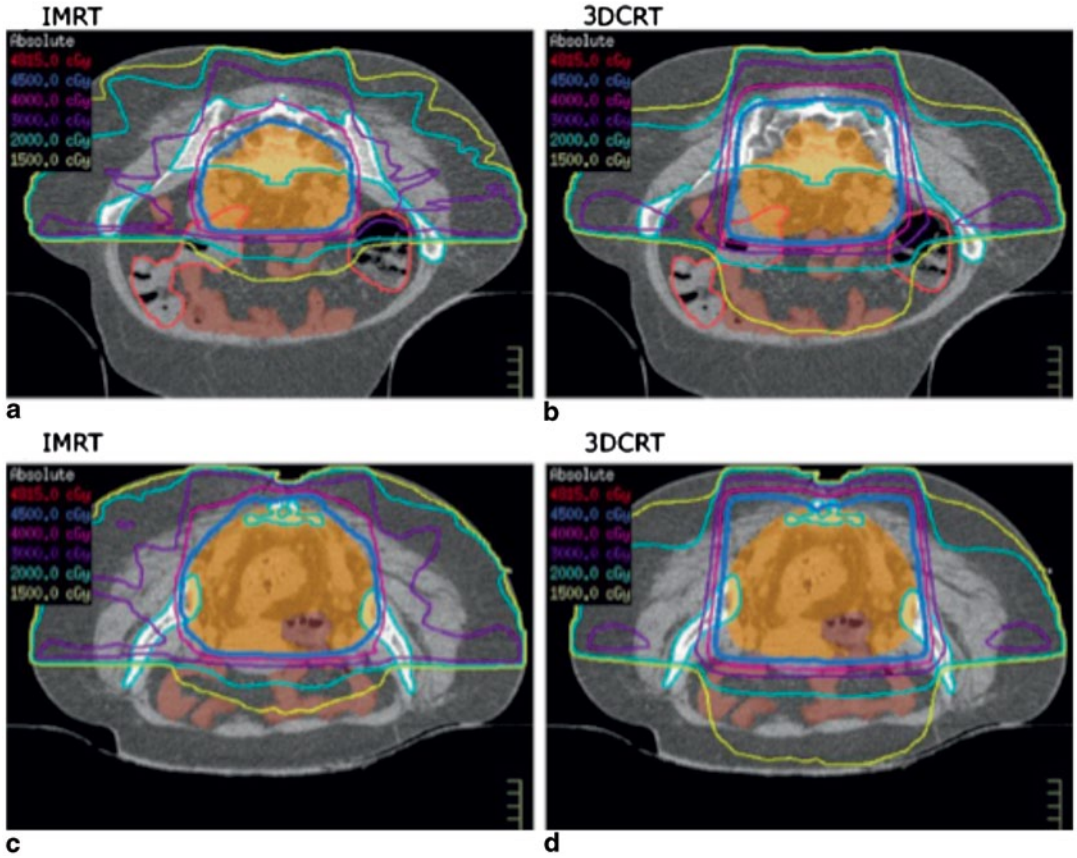

Fig. 4.1 Representative axial slices showing isodose distributions for two planes for an (**a**, **c**) IMRT and (**b**, **d**) 3D-CRT plan. The central (high dose) isodose line is more conformal with regards to the target and the peripheral (low dose) isodose lines spare more of the bowel in the IMRT versus 3D-CRT plans, respectively. *IMRT* intensity-modulated radiation therapy, *3D-CRT* three-dimensional conformal radiation therapy. Figure reproduced with permission from Mok H, Crane C, Palmer MB, Briere TM, Delclos ME, Krishnan S, Das P. Intensity modulated radiation therapy (IMRT): differences in target volumes and improvement in clinically relevant doses to small bowel in rectal carcinoma. Radiat Oncol. 2011 Jun 8; 6: 63. Note figure legend has been modified from original. (License: http://creativecommons.org/licenses/by/4.0/)

cancer patients in the postoperative setting. Following hysterectomy, treatment of the pelvis can expose greater amounts of small bowel that have fallen into the vacated space to radiation and lead to greater toxicity. The risk of severe injury from postoperative radiation therapy even to moderate doses is 5–15%. Preliminary results showed equivalent 2-year disease control compared to previous trials where standard pelvic radiation was used but with a reduction in ≥grade 2 acute GI toxicity for patients treated with IMRT [1]. Longer follow-up is needed before estimates of chronic GI toxicity may be reported. RTOG 1203 is a randomized phase III study of standard four-field radiation treatment versus IMRT pelvic radiation for postoperative treatment of endometrial and cervical cancer (TIME-C) and is currently accruing. RTOG 1203 is designed to measure patient reported acute GI toxicity through an instrument evaluating multiple components of radiation enteritis including cramping, looseness, pain, and frequency of bowel movements. Other endpoints include acute GU and hematological toxicity, QOL, and chronic GI and GU toxicity in addition to disease control. Another multicenter phase II trial reported <30% acute grade 2 GI toxicity in

patients undergoing adjuvant IMRT for endometrial cancer [2]. In addition, Mundt et al. reported toxicity from a small single-institution study of 40 patients with gynecological malignancies who underwent IMRT. Acute grade 2 toxicity was significantly less common in the IMRT as compared to historical controls treated with 3D-CRT with 60% versus 91%, respectively. In addition, only 75% of patients required little or no antidiarrheal medication as compared to 34% of patients undergoing 3D-CRT. There were no significant differences in GU toxicity between groups. Chronic GI toxicity was also reported to be lower in the IMRT group with 11.1% versus 50% in the 3D-CRT group [3, 4].

Gastrointestinal Malignancies

Similar results have been shown for decreased GI toxicity in rectal and anal cancer patients undergoing IMRT. RTOG 0822 was the first multi-institutional prospective and largest phase II study of use of IMRT for preoperative concurrent chemoradiotherapy for 68 patients with rectal adenocarcinoma. There was reduced, although not statistically significant, acute ≥grade 2 GI toxicity as compared to previous trials where standard pelvic radiation with 51% versus 58%, respectively. There was a high rate of contouring and planning compliance and pathological complete response rates suggesting tumor coverage was not compromised by use of IMRT [5]. In addition, Samuelian et al. conducted a retrospective single-institution review evaluating acute toxicity in 92 patients with rectal cancer who were treated with conventional 3D-CRT (66%) or IMRT (31%) to a median dose of 50.4 Gy using standard fractionation with concurrent chemotherapy in the neoadjuvant or adjuvant setting. Patients who received IMRT had significantly less GI toxicity, with 62% of patients who underwent 3D-CRT experiencing ≥grade 2 GI toxicity compared with 32% of patients who underwent IMRT, mainly attributed to an improvement in lower GI toxicity. Among patients undergoing 3D-CRT, 48 and 30% of patients experienced ≥grade 2 diarrhea and enteritis, respectively, compared with 23 and 10% of patients undergoing IMRT. There was no significant difference in hematologic or acute GU toxicity, pathological complete response rates or postoperative morbidity between groups [6].

RTOG 0529 was a phase II study of concurrent chemoradiotherapy with 5-Fluorouracil and Mitomycin-C with IMRT for the definitive treatment of 52 anal cancer patients. Two-year clinical outcomes were similar to previous trials with standard pelvic radiation. While the primary endpoint of reduced acute ≥grade 2 GI and GU toxicity was not met, there were significant reductions in acute ≥grade 2 hematologic (73% vs 85%), acute ≥grade 3 GI (21% vs 36%), and acute ≥3 dermatological toxicity (23% vs 49%) with IMRT as compared to historical controls, respectively [7]. Chuong et al. compared toxicity in a single-institution retrospective review of 89 patients with anal squamous cell carcinoma treated with definitive concurrent chemoradiotherapy with either 3D-CRT (42%) or IMRT (58%). With a median follow-up of 26.5 months, there was significantly decreased acute ≥grade 3 toxicity in the IMRT group with 21% versus 60% in the 3D-CRT group, and significantly decreased ≥acute grade 3 skin toxicity in the IMRT group with 12% versus 65% in the 3D-CRT group. In addition, there was significant improvement in late ≥grade 3 GI toxicity in the IMRT group with 6% versus 24% in the 3D-CRT group. There were no differences in clinical outcomes [8].

Genitourinary Malignancies

IMRT has long been established as a well-tolerated treatment modality that is associated with excellent long-term tumor control outcomes in patients with localized prostate cancer [9]. Forsythe et al. compared toxicity in a single institution retrospective review of 1571 patients with intermediate- or high-risk prostate cancer who underwent definitive combination therapy with 3D-CRT (64%) in the earlier years or IMRT (36%) in the later years with brachytherapy boost consisting of Pd-103 or I-125. With a median 10-year follow-up, patient-scored acute

moderate urinary toxicity was similar, but there was significantly less severe acute urinary toxicity in the IMRT group with 17% versus 44% in the 3D-CRT group, with no difference in toxicity at 1 year. There was also significant improved urinary QOL in the IMRT group with 35% versus 51% in the 3D-CRT group and significantly decreased ≥grade 2 rectal bleeding in the IMRT group with 11% versus 7% in the 3D-CRT group [10]. Another large single-institution study has reported on rates of improved long-term GI toxicity in patients undergoing prostate radiotherapy with IMRT versus 3D-CRT alone in the definitive setting [11].

IMRT has also been applied to the adjuvant and salvage setting for prostate cancer patients with improvements in toxicity. Alongi et al. compared acute toxicity in a single institution retrospective review of 172 patients with prostate cancer undergoing adjuvant or salvage treatment with whole pelvis radiotherapy. There was a statistically significant decrease in acute ≥grade 2 upper GI toxicity, with 7% versus 22% for patients undergoing IMRT (53%) and 3D-CRT (47%), respectively. There was a trend towards decreased acute ≥grade 2 GU toxicity, with 7% versus 12% and acute ≥grade 2 lower GI toxicity with 3 and 9% for patients undergoing IMRT and 3D-CRT, respectively [12]. In addition, another single institution retrospective study has reported on acute GI and GU toxicity with excellent long-term toxicity in prostate cancer patients who underwent pelvic radiotherapy with IMRT helical tomotherapy in the adjuvant or salvage setting [13].

Proton Therapy

Proton therapy is an additional modality to be considered for the treatment of prostate cancer given its precision that may allow for dose escalation with potentially less side effects as compared to conventional treatment modalities. Gray et al. compared toxicity patterns in 371 prostate cancer patients who underwent treatment with 3D-CRT ($n=123$), IMRT ($n=153$), or proton beam therapy ($n=95$) in a prospective study through review of patient-reported outcomes at 2–3, 12, and 24 month follow-up. At first post-treatment follow-up, patients who received 3D-CRT or IMRT reported clinically meaningful decreases in bowel QOL as compared to those patients who received proton therapy. In addition, patients who received IMRT reported a clinically meaningful decrease in urinary QOL in terms of urinary irritation, obstructive symptoms, and incontinence. At 12 months, only patients who received proton therapy reported a clinically meaningful decrease in urinary irritation and obstructive symptoms. At 24 months, there were no meaningful changes in urinary QOL for all groups. At 12 and 24 months, all patients reported a clinically meaningful decrease in bowel QOL. Thus, only the timing of urinary and bowel toxicity appeared to differ among groups [14]. In a population-based study using Surveillance, Epidemiology, and End Results-Medicare-linked data comparing treatment of patients with localized prostate cancer using IMRT, 3D-CRT, or proton therapy, use of IMRT as compared to 3D-CRT was associated with less GI toxicity and fewer hip fractures but more erectile dysfunction. When IMRT was compared with proton therapy, use of IMRT was associated with less GI toxicity [15]. A meta-analysis including 20 published reports and 11,835 patients undergoing radiotherapy for prostate cancer showed when doses >74 Gy were delivered, use of IMRT or proton beam radiotherapy was associated with a significant decrease in the rate of severe GI toxicity compared with 3D-CRT [16].

Treatment Techniques

Treatment Position and Immobilization Devices

For pelvic malignancies, in some cases, it may be advantageous to treat the patient in the prone position with studies showing a decrease in bowel dose and toxicity. This is especially relevant if IMRT is not being used such as in the case of definitive treatment of gynecological or GI malignancies.

Drzymala et al. compared the effect of the volume of bowel with dose received in the prone and supine positions in a prospective study of 19 patients with rectal cancer who underwent preoperative concurrent chemoradiotherapy using a three-field 3D-CRT technique to a total dose of 54 Gy in standard fractionation. For each patient, the planning target volume (PTV), bladder, and small bowel were outlined in both positions and the volume of bowel receiving doses in 5 Gy increments form 5–45 Gy was calculated using dose volume histogram (DVH). At 5 and 10 Gy dose levels, a significantly higher volume of bowel was irradiated in the supine position as compared to the prone position, at 15 Gy it was marginally significant and for 20–45 Gy there was no significant difference in the volume of bowel irradiated with each 5 Gy increment. Thus, radiotherapy delivered in the prone position for rectal cancer treatment may decrease small bowel dose for doses < 15 Gy, but may not provide an advantage for higher doses [17]. Koebl et al. showed similar results with a decrease in mean dose to the bladder and small bowel for patients undergoing postoperative radiotherapy for rectal cancer treated in the prone position as compared to the supine position [18].

Ghosh et al. compared volume of small bowel in the field in a prospective single-institution study in 21 cervical cancer patients who underwent adjuvant radiotherapy using a four-field 3D-CRT approach to a median dose of 47.8 Gy in the supine and prone positions with and without a belly board device. Patients were treated with a full bladder and abdominal radiographs with contrast were obtained to evaluate the volume of small bowel in the radiation fields. The belly board device was effective at minimizing the amount of small bowel in the lateral fields, whereas the prone position without the belly board device spared the smallest bowel in the anterior–posterior/posterior–anterior (AP/PA) fields. At median follow-up 37 months, there was no significant acute GI or GU toxicity and no patients experienced a small bowel obstruction [19].

Bladder Filling

Bladder filling has been shown to be an important factor to decrease GI and GU toxicity during elective pelvic nodal irradiation for prostate cancer. Jain et al. compared toxicity in a prospective single institution study of 230 patients undergoing whole pelvic radiotherapy using a four-field approach with a concomitant hypofractionated IMRT boost to the prostate as compared to IMRT applied to two different nodal volumes described as a 2 cm clinical tumor volume (CTV) margin around the pelvic vessels or by the RTOG prostate pelvic contouring atlas. Initially patients were treated with an empty bladder, with the remainder treated with a full bladder. The 4-field approach had significant higher rates of grade 3 urinary frequency (8 % vs 0 % vs 0 %) and significant grade 2 acute GI toxicity (31.9 % vs 20.8 % vs 7.2 %) as compared to the IMRT groups, respectively. Multivariate analysis suggested the factor that most influenced toxicity was bladder filling, followed by use of IMRT [20].

Treatment Planning

Organs at Risk Contouring

Radiation treatment planning is comprised of several steps; to begin, the radiation oncologist contours the tumor and target volumes and prescribes doses as well as contours critical structures that need to be avoided known as organs at risk (OAR). In the case of IMRT, the physicist then assigns dose constraints or restrictions on the dose to targets and OARs and importance factors for each. This information is then used by an optimization program to determine the treatment plan that best satisfies all the input criteria. By setting dose constraints for OARs, dose, and thus toxicity, can be decreased to adjacent normal tissue.

Bone marrow sparing to prevent hematological toxicity may be an important consideration in pelvic irradiation. Mahantshetty et al. conducted a phase II prospective study of 47 patients with cervical cancer treated with IMRT and concurrent

chemotherapy. The authors compared volumes and DVH parameters for CT-based bone marrow contoured by two methods including whole bone and freehand inner cavity of bone and correlated these with ≥grade 2 hematological toxicity. Various subvolumes were made for each set. Free-hand inner cavity volumes were 25–30% of whole bone contours and were shown to be a better surrogate of active bone marrow on CT. There were significant differences between the DVH parameters of the two sets of subvolumes except for the V20 ischium, V10 sacrum, and V10 lumbosacral spine. Leukopenia, neutropenia, anemia, and thrombocytopenia >grade 2 was seen in 53, 29.8, 65.9, and 10.6%, respectively. On both univariate and multivariate analysis, free hand inner cavity volumes V40≥40% significantly correlated with ≥grade 2 leukopenia and neutropenia with a statistically significant odds ratio (OR) of 4 [21].

Treatment Volume

The target volumes of importance consist of the gross tumor volume (GTV) comprising areas of gross tumor, CTV, or areas of microscopic disease and the PTV, which accounts for day-to-day motion and set-up inaccuracies. While the CTV is based on tumor type and risk of lymph node involvement along with other clinical or pathological risk features, larger treatment volumes, especially for pelvic malignancies, may lead to increases in toxicity.

De Jong et al. compared toxicity among 75 patients with endometrial carcinoma treated with adjuvant 3D-CRT using small (44%), standard (37%), or extended pelvic field (19%). A small pelvic field including the central pelvis and proximal vagina was used for patients who had negative lymph nodes after adequate lymphadenectomy (>10 lymph nodes), a standard field was used for patients with positive pelvic lymph nodes or inadequate lymphadenectomy and an extended pelvic field was used for patients with involved common iliac and/or para-aortic lymph nodes. Late GI toxicity was significantly different with 60.7% versus 33.3% in the standard and small field groups, respectively.

There were significant differences in acute side effects such nausea and anorexia with 32.1 and 3.0% of patients in the standard versus small groups, respectively. There was also a significant difference in ileus with 14.3 and 0% of patients in the standard versus small groups, respectively [22].

A secondary analysis of the RTOG 9413 randomized controlled trial of 324 prostate cancer patients who had a risk of lymph node involvement >15% who were randomized to whole pelvis or prostate-only or "mini" pelvis radiation therapy with neoadjuvant and concurrent hormonal therapy for a total of 6 months, correlated late toxicity with field size. Late grade 3 GI toxicity correlated with increasing field size in the "mini" pelvis versus prostate-only group while there was no correlation between field size and late grade 3 GU toxicity [23]. A single institution retrospective study correlated DVH parameters of the anal canal and rectum with rates of fecal incontinence for 44 prostate cancer patients who received 3D-CRT to 58–72 Gy versus 30 control patients. At a median of 1.5 years, there was worse incontinence in the radiation group with 27 and 14% of patients reporting slight and severe incontinence, respectively, with continence similar among a range of doses administered. Severe incontinence was correlated with a significantly higher minimum dose to the anal canal, accompanied by portals extending significantly further inferiorly with respect to the ischial tuberosities [24].

Dose Constraints

Prevention of Hematological Toxicity

Radiotherapy of the pelvis involves treatment to a significant portion of the active adult bone marrow. Dose constraints to the pelvic bone marrow may be effective for decreasing hematological toxicity in patients undergoing concurrent pelvic chemoradiotherapy. Klopp et al. investigated hematological toxicity in 83 patients undergoing postoperative IMRT to 50.4 Gy with standard fractionation to the pelvic lymphatics and vaginal

cuff with concurrent weekly cisplatin for cervical cancer patients in the prospective multi-institutional study RTOG 0418. The V10, V20, V30, and V40, as defined by a CT density-based autocontouring algorithm, and median dose was correlated with hematological toxicity. 75% of patients with a V40 > 37% had ≥ grade 2 hematological toxicity, compared with 40% of patients with a V40 ≤ 37%, which was statistically significant. 74% of patients with a median bone marrow dose > 34.2 Gy had ≥ grade 2 hematological toxicity compared with 43% of patients with a dose of ≤ 34.2 Gy, which was also statistically significant. Thus, IMRT may make it possible to decrease the V40 and median dose to the bone marrow in order to decrease hematological toxicity [25].

Mell et al. showed in a retrospective single-institution review of 48 consecutive anal cancer patients who underwent concurrent chemoradiotherapy using IMRT to a median dose of 45–50.4 Gy in standard fractionation, 56, 50, 8, and 27% of patients experienced grade 3–4 leukopenia, neutropenia, anemia, and thrombocytopenia, respectively. On multiple regression analysis, V5, V10, V15, and V20 were significantly associated with decreased white blood cell (WBC) and absolute neutrophil count nadirs, as well as female gender, decreased BMI, and increased lumbosacral bone marrow receiving 10, 15, and 20 Gy. Lymph node positivity was also significantly associated with a decreased WBC nadir on multiple regression analysis. Thus, increased low-dose radiation to pelvic bone marrow was associated with acute hematologic toxicity during chemoradiotherapy for anal cancer and techniques to limit bone marrow irradiation may reduce hematologic toxicity [26].

Prevention of Genitourinary Toxicity

Studies have shown, the bladder V78–80 is the most predictive of late GU toxicity in patients undergoing radiotherapy for prostate cancer. Dose volume modeling of bladder toxicity is sparse, and may indicate the difficulty in assessing bladder toxicity given wide variations in bladder dose due to variable filling [27].

Prevention of Gastrointestinal Toxicity

Pederson et al. in a retrospective single-institution study of 296 patients treated with IMRT for prostate adenocarcinoma to a median dose of 76 Gy to the prostate with or without proximal seminal vesicles, correlated bladder, and rectum V70, V65, and V40 with maximal ≥ grade 2 GU and GI toxicity. At a median follow-up of 41 months, there was 9% and 5% ≥ grade 2 GU and GI toxicity, respectively. Freedom from ≥ grade 2 GU and GI toxicity at 4 years was 100% for patients with rectal V70 ≤ 10%, V65 ≤ 20%, and V40 ≤ 40%; 92% for patients with rectal V70 ≤ 20%, V65 ≤ 40%, and V40 ≤ 80%; and 85% for patients exceeding these criteria. Age ≥ 70 years had a higher associated with GI toxicity. There were no bladder dose–volume relationships observed for risk of GU toxicity [28].

Smeenk et al. investigated in a single-institution retrospective review, the dose-effect relationships for fecal-incontinence-related complaints following radiotherapy in 48 patients with localized prostate cancer. DVH parameters of the pelvic floor muscles including the internal anal sphincter (IAS), the external anal sphincter (EAS), the puborectalis muscles (PRM), the levator ani muscles (LAM), and the anal wall (AW) and rectal walls (RW) were compared for patients with and without fecal urgency, incontinence, and frequency. AW and RW dose parameters and doses to all pelvic floor muscles were associated with urgency, with mean doses ≤ 30 Gy, to the IAS, ≤ 10 Gy to the EAS, ≤ 50 Gy to the PRM, and ≤ 40 Gy to the LAM described as constraint values to observe. Incontinence was associated with mainly doses to the EAS and PRM and there were no dose–effect relationships observed for bowel frequency [29].

Chopra et al. in a single institution retrospective review investigated the relationship between dose–volume parameters and severe bowel toxicity after postoperative radiation treatment for 71 cervical cancer patients. 64% of patients underwent IMRT and 36% of patients underwent 3D-CRT. 89% of patients received concurrent chemotherapy. The V15, V30, and V40 was calculated for the small and large bowels and correlated

with bowel toxicity. At a median follow-up of 18 months, 30.9% had ≥grade 2 toxicity and 12.6% had ≥grade 3 toxicity. On multivariate analysis, small and large bowel V15 were predictors of late ≥grade 3 toxicity. It was concluded that limiting the small bowel V15<275 cc and large bowel V15<250 cc could reduce ≥grade 3 toxicity to <5% [30].

Image-Guided Radiotherapy

In recent years, image-guided radiotherapy (IGRT) has become increasingly used for the treatment of pelvic malignancies. IGRT is the process of using 2D or 3D imaging at the time of delivery of radiotherapy to localize the patient to the coordinates used for the actual treatment plan, making treatment delivery more precise. IGRT makes it possible to decrease PTV margins that are added to account for day-to-day motion and set-up inaccuracies and decreases treatment of adjacent normal tissue. Use of IGRT may make it possible to treat smaller target volumes to higher doses and possibly increase tumor control with similar or improved rates of toxicity when compared with standard IMRT.

Gynecological Malignancies

There is a strong rationale for the use of IGRT in gynecological patients given difficulty with daily patient set-up, considerable organ motion, and rapid shrinkage of tumors. Image-guided external beam treatment delivery includes ultrasound, kilovoltage (KV) or megavoltage (MV) portal imaging, and cone beam CT technologies with or without the prior placement of fiducial markers.

There are few published studies assessing the improvement in toxicity of delivering radiotherapy using IGRT in gynecological malignancies. Monroe et al. assessed toxicity in 26 high-risk endometrial cancer patients requiring adjuvant radiation to the vaginal cuff and regional lymph nodes treated with vaginal cuff fiducial-based IGRT to a mean dose of 47.5 Gy. 42% of patients also received sequential vaginal cuff brachytherapy and 65% received sequential chemotherapy. All fractions were successfully imaged and treated daily. 1, 1.5, or 2 cm and greater shifts relative to clinical set-up with skin tattoos were performed in 43, 14, and 4% of patients, respectively. 30% of patients experienced acute grade 2 GI toxicity and only 1 patient experienced grade 3 toxicity. Two year overall survival was >95% with no local or regional failures [31].

Genitourinary Malignancies

IGRT for treatment delivery for prostate cancer typically involves fiducial marker placement with cone beam CT imaging or beacon transponder placement with ultrasound imaging to localize markers with submillimeter accuracy.

Kok et al. compared late toxicity in a single institution retrospective review of 554 patients with prostate cancer undergoing definitive radiation therapy using implanted fiducial marker guided radiotherapy to 78 Gy in the later years and those treated with standard IMRT to 74 Gy in the earlier years. At a median follow-up of 22 months, there was a statistically significant hazard ratio (HR) of 3.66 for ≥grade 2 GI toxicity in the standard IMRT group compared to the IGRT group. There was no difference in ≥grade 2 GU toxicity between the two groups, however, there was a quicker recovery from GU toxicity in the IGRT group with a statistically significant HR of 0.24. There was no difference in biochemical failure-free survival between groups [32].

In addition, IGRT may make dose escalation possible with an acceptable toxicity profile. Zelefsky et al. compared toxicity profiles in a retrospective single institution review of 376 patients with clinically localized prostate cancer treated with high-dose IGRT to a dose of 86.4 Gy with daily correction of the target position based on KV imaging of implanted prostatic fiducial markers and standard IMRT. With a median follow-up of 2.8 years, 10.4 and 20% of patients in the IGRT and standard IMRT groups, respectively, experienced statistically significant ≥grade 2 urinary toxicity. Predictors of late ≥grade 2 urinary toxicity using multivariate analysis included

standard IMRT treatment, among other factors. There was no significant difference in ≥grade 2 rectal toxicity between groups [33].

Use of Vaginal Dilator for Prevention of GU Toxicity

Regular vaginal dilator use is often recommended for female patients following pelvic radiotherapy to prevent vaginal stenosis and shortening leading to painful intercourse and uncomfortable pelvic examinations. A single-institution retrospective study of curative treatment of 480 cervical cancer patients using radiation alone or concurrent chemoradiotherapy consisting of 3D-CRT and brachytherapy components resulted in 3-year ≥grade 3 vaginal toxicity of 20.2 and 35.1%, respectively. Rates of vaginal toxicity were correlated with frequency of dilator use with high and low compliance defined as > than twice weekly for the first 2 years posttreatment and at least monthly thereafter and less then monthly, respectively. Moderate dilator compliance defined the remaining situations. It was also shown that moderate and poor dilator compliance as compared to high dilator compliance correlated with greater vaginal severe late toxicity. Age >50 was associated with greater vaginal severe late toxicity [34]. In a Cochrane-style systematic review of literature addressing vaginal dilation and stenosis attributable to radiation therapy, seven relevant studies contributed to the final analysis. The authors concluded that there was no evidence for the use of vaginal dilators during or immediately after radiotherapy in preventing stenosis or acute toxicity, but may be effective if initiated after the inflammatory phase [35].

Statins and ACE-Inhibitors for Prevention of GI Toxicity

It has been shown in preclinical studies that the angiotensin-converting enzyme (ACE), Captopril may protect endothelial cells from radiation-induced cell damage. RTOG 0123 was a phase II clinical study that randomized 81 lung cancer patients undergoing radiotherapy with and without chemotherapy and at high risk of pulmonary toxicity to maintenance captopril to determine the incidence of 1-year pulmonary toxicity. The incidence of ≥grade 2 pulmonary toxicity attributable to radiation therapy was 23% versus 14% in the observation and Captopril groups, respectively [36]. Other preclinical studies have shown that ACE-inhibitors may reduce acute GI toxicity. Wedlake et al. evaluated the efficacy of statins and ACE-inhibitors on GI toxicity in 237 patients undergoing pelvic radiation in a prospective single-institution study. It was shown that statin use (16%) and combined statin and ACE-inhibitor use (7.6%) was associated with reduced cumulative acute toxicity during treatment with decreased toxicity in users maintained at 1 year [37].

Modified Diet and Supplementation for Prevention of GI Toxicity

Chitapanarux et al. performed a prospective randomized controlled study of 63 locally advanced cervical cancer patients undergoing pelvic radiation therapy with concurrent weekly cisplatin randomized to probiotic containing live lactobacillus acidophilus plus bifidobacterium bifidum (51%) or placebo (49%) to determine the efficacy of probiotic on radiation-induced diarrhea. Grade 2–3 diarrhea was observed in 45% of the placebo group and 9% of the study group with antidiarrheal medication used significantly less in the study group [38]. Other studies, however, have not shown a benefit to the use of probiotic for radiation-induced diarrhea [39].

A number of studies have assessed the efficacy of a low or modified diet on GI toxicity in patients undergoing pelvic radiotherapy. Wedlake et al. conducted a prospective study of 117 patients undergoing radiotherapy for pelvic malignancies who were randomized to a low, modified, or normal fat diet based on the percentage of total energy consumed from long and medium chain triglycerides. There were no difference in GI symptoms scores between groups from the start to the end of radiotherapy, however, compliance

with diet was felt to be inadequate [40]. A meta-analysis consisting of 22 randomized control trials, controlled trials, and case series for patients who received radiation therapy for pelvic malignancies using nutritional interventions to reduce GI toxicity were included. Study quality was felt to be highly variable with few studies assessing the compliance with the intervention. Evidence for elemental, low- or modified-fat, fiber, and low-lactose interventions was felt to be low while evidence for probiotics was felt to be more promising, but dose, strains, and methodologies were variable [41].

Sulfasalazines for Prevention of GI Toxicity

Sulfasalazine has been shown to help reduce the incidence and severity of radiation-induced enteropathy in patients receiving pelvic radiotherapy. Kilic et al. showed in a randomized, placebo-controlled study evaluating the effectiveness of sulfasalazine to prevent GI toxicity in 87 patients undergoing pelvic radiotherapy randomized to twice daily sulfasalazine (2 g/day) or placebo that sulfasalazine was effective in decreasing the symptoms of acute radiation enteritis. Diarrhea occurred in 55 and 86% of the sulfasalazine and placebo groups, respectively. GI toxicity was seen in 80 and 93% of the sulfasalazine and placebo groups, respectively [42]. Review of four double-blind and placebo-controlled studies using 5-aminosalycilates in the prevention of acute radiation enteritis showed a positive effect was proven for only when doses of sulfasalazine of 2 g/day were administered [43].

Amifostine and Other Radioprotectors for Prevention of Toxicity

Amifostine is a free-radical scavenger and has been used as radioprotectant for many sites undergoing radiotherapy. Kouloulias et al. conducted a phase II randomized study of intrarectal administration of amifostine (1500 mg) for prevention of acute radiation rectal toxicity in 67 patients receiving 3D-CRT through a four-field approach. Patients receiving intrarectal amifostine (51%) showed a significantly lower incidence of grade 1–2 proctitis with 15% versus 44% in the control groups, respectively. There were no differences in urinary toxicity between groups [44]. RTOG 0116 randomized 45 cervical cancer patients receiving extended field radiation therapy, brachytherapy, and concurrent cisplatin to amifostine (5000 mg) or not. At a median follow-up of 22.9 months, there were no differences in acute or late grade 3–4 toxicities between groups. Thus, in this setting amifostine did not reduce toxicity [45].

Esco et al. conducted a randomized single institution study of 100 rectal cancer patients who underwent adjuvant radiotherapy randomized to receive orgotein/superoxide dismutase (50%) for 7 weeks or no treatment. At 2 years, the orgotein/superoxide dismutase group has significantly less late grade 1–2 toxicity than the control group. Patients not treated with orgotein/superoxide dismutase had a 37% greater chance of developing late grade 2 toxicity, and 26% greater chance of developing late grade 2 GI toxicity, specifically of the lower GI tract [46].

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Part II

Consequences of pelvic radiation and their treatment

Pathology of Radiation Effects on Healthy Tissues in the Pelvis

5

Curtis Ray Hall

Introduction

While appropriate steps may be taken to minimize radiation exposure to healthy tissues in those patients who require radiation therapy, some degree of radiation injury to healthy tissues is unavoidable. This is a particular problem in the pelvis, where several organs are relatively fixed in position and closely spaced. Familiarity with the diagnosis and treatment of radiation-induced pathology in nontarget tissues is an important component of clinical management in this group of patients.

Radiation produces its effects, in both target and nontarget tissues, via DNA damage (specifically by breaks in double-stranded DNA) within the various types of cells that compose any organ. To a large extent, the sensitivity of any particular type of cell to radiation injury is determined by its proliferation rate [1]. Epithelial cells, the cells that line the lumen of the gut and form glands and ducts in other organs, are much more mitotically active than the fibroblasts, smooth muscle cells, Schwann cells, neurons, and endothelial cells that form (along with extracellular matrix materials) the supporting framework of the various organs. Therefore, the most dramatic short-term effects of irradiation of any particular organ will be seen in the epithelial compartment [1, 2]. Here, the loss of cells is rapidly followed by proliferative changes and the regenerative capacity of the epithelium allows it to recover to nearly normal morphology in most cases (a mathematical model of this process has been developed [3]). Of consequence for the long-term survivor of a malignancy treated with radiation therapy are persistent radiation-induced effects on previously healthy tissue. These include vascular insufficiency and fibrosis, which may be troublesome despite their subtlety and nonspecificity upon gross and microscopical examination. In addition, new malignancies may develop in irradiated tissues [4, 5]. The following discussion will review short- and long-term effects of radiation exposure to normal tissue on an organ-specific basis. Knowledge in this area has developed from findings in animal models and human tissues.

Rectum

The effects of irradiation of the rectum and large intestine have been well studied. The findings from endoscopic biopsies of human rectal mucosa during radiation therapy have been corroborated and supplemented by well-controlled, rigorous gross and microscopic examination of the rat rectum performed at intervals after an index dose of radiation (Fig. 5.1). The changes seen in the irradiated rectum, in rats and in humans, are commonly called radiation proctitis, but a more appropriate term is radiation proctopathy, since

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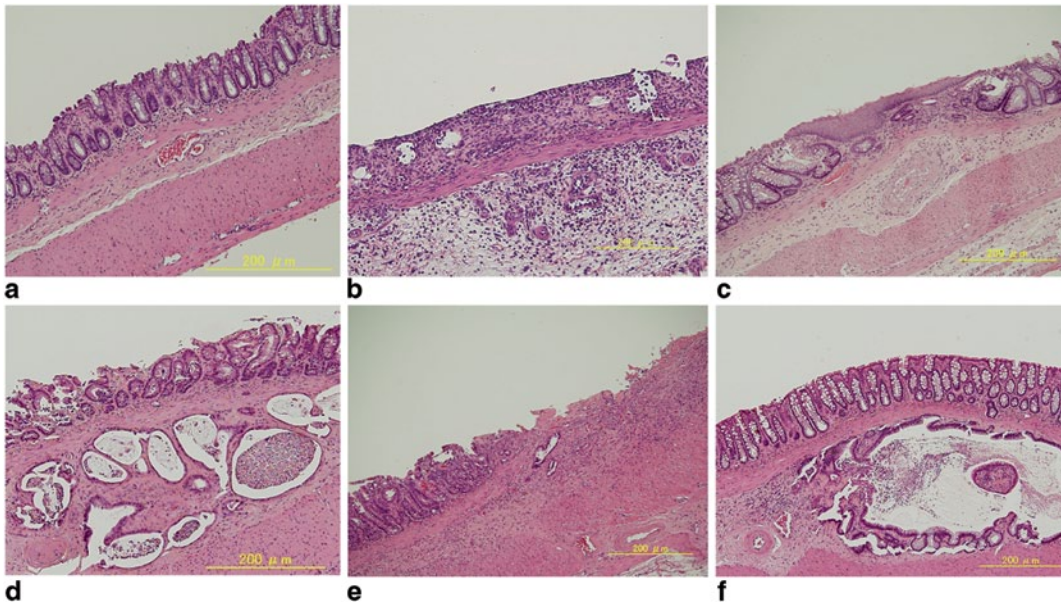

Fig. 5.1 **a** Rectal mucosa of non-irradiated rat. **b**–**f** Rectal mucosa of rat 10 days, 4 weeks, 12 weeks, 24 weeks, and 37 weeks following index irradiation, respectively. (With permission [2] © Oxford University Press)

Table 5.1 Histologic findings in acute radiation proctopathy

Nuclear atypia
Reduced mitotic activity
Crypt abscesses with eosinophils
Mucosal ulceration

little primary inflammation occurs. In the rat model [6], the beginnings of epithelial damage, manifested by crypt dilatation and mild inflammation, are first seen 4 days after the index radiation dose. Over the next several days, epithelial atrophy occurs and erosions appear and progress such that by day 10, frank ulcerations are present. Parallel to the development of ulceration, there are findings of cellular regeneration, characterized by crypt distortion and increased mitotic activity amongst crypt epithelial cells. By day 14, there is extensive regenerative change and the ulcers are healed. While previous investigators have suggested that these processes result from injury and death of epithelial stem cells, it has been proposed that the keystone cell in this sequence is the radiation-damaged and apoptotic endothelial cell in adjacent microvasculature [7], and that the recovery response of the intestinal epithelium is regulated by these cells [8]. This hypothesis has been disputed by some [9]. By 4–6 weeks after the index dose of radiation, there is complete regeneration of the rectal mucosa, albeit with some permanent architectural changes as discussed below [2, 6]. In humans, biopsies of the rectum taken during radiation therapy show reduced numbers of mitoses amongst epithelial cells accompanied by the presence of nuclear atypia that is characterized by enlargement and loss of polarity [10]. Other findings in humans during the course of radiation include the development of crypt abscesses with eosinophils, superficial mucosal ulceration, submucosal edema, and mildly increased numbers of inflammatory cells; increased fibrin was also seen (Table 5.1).

After the cessation of radiation, in rats and humans, the mucosal epithelium reverts to normal in some individuals, while others can show atrophy, loss of goblet cells, and mild nuclear atypia. There may be persistent ulcers sometimes requiring surgical intervention [11]. The base of these ulcers will often have atypical fibroblasts and endothelial cells. The manner in which the epithelium relates to the rest of the organ may have changed as well; this “architectural” change, a

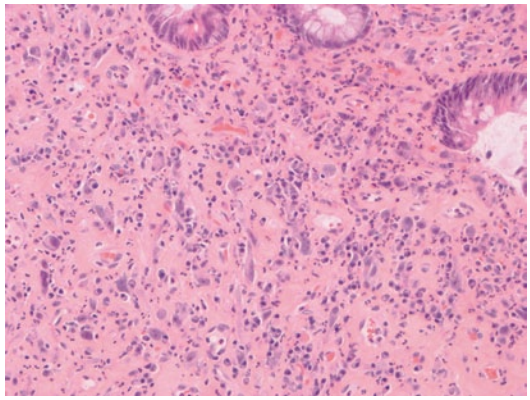

Fig. 5.2 This high-power image is taken from a pseudopolyp in an irradiated rectum. Note the presence of atypical fibroblasts, mixed inflammation, and expansion of the lamina propria

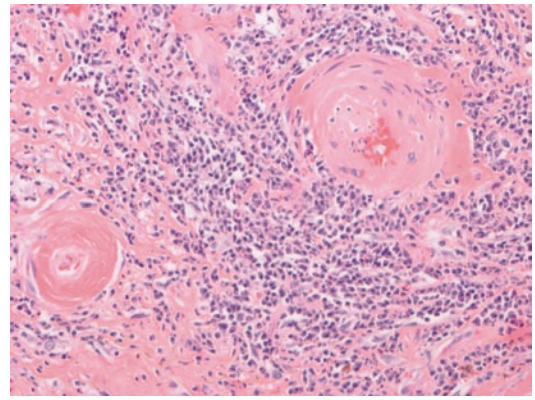

Fig. 5.3 These blood vessels in an irradiated uterine cervix show the typical changes induced in such structures by radiation. Note the replacement of smooth muscle in the walls of these vessels by hyaline fibrosis and the luminal narrowing

consequence of healing of the ulcers seen in the acute phase, may take the form of dilated crypts displaced into the submucosa, and even at times between layers of the muscularis propria. This phenomenon in rats, coupled with the accompanying fibrosis, was termed "radiation-induced proctitis fibrosa cystica profunda" by Hubmann [12]. The equivalent lesion has been well described in humans [10]. Another, dramatic, architectural change that has been described is the presence of epithelium directly in contact with the muscularis propria with loss of intervening submucosa. Given that these architectural changes result from healing of the ulcers seen in the acute phase, it is reasonable to presume that the degree of these architectural changes depends on the severity of the acute-phase ulceration. There are also more generalized connective tissue changes in the long term: what had begun as edema and accumulation of mucin-like material in the submucosa transforms over time into hyaline fibrosis populated by occasional atypical fibroblasts (Fig. 5.2). As is true in all irradiated tissues, chronic changes in arteries, arterioles and veins, characterized by intimal fibrosis, accumulation of foam cells, loss of smooth muscle from muscular arteries, and luminal narrowing will supervene, accompanied by occasional atypical endothelial cells. These changes lead to vascular insufficiency and, in some cases, chronic ulcerations (Fig. 5.3). It has been argued that many of the changes ascribed directly to irradiation are more accurately considered a consequence of vascular insufficiency. Another vascular change is the development of vascular telangiectasias in the mucosa and submucosa; these dilated, tortuous vessels with stiff walls (see above) are delicate and prone to injury, leading to the sometimes persistent rectal bleeding in radiation proctopathy [13, 14]; a similar process is seen in the urinary bladder (see below). Fibrosis of the bowel wall, leading to stenosis and shortening, can be progressive and develop over a period of months to years. Because of this, patients may present with bowel obstruction after a long symptom-free period. Finally, though there has been some uncertainty as to the degree of risk for development of new malignancies in the irradiated rectum [15], one study showed a relative risk of 1.26 for rectal carcinoma in men who had been treated with external beam radiation for adenocarcinoma of the prostate as compared to those who had been treated with surgery alone [16]. Adenocarcinomas of the rectum induced by radiation, similar to adenocarcinomas that develop in a background of idiopathic inflammatory bowel disease, get their start as flat areas of dysplasia which may be difficult to detect endoscopically (Table 5.2) [17].

Table 5.2 Histologic changes of chronic radiation proctopathy

Dilated and displaced crypts
Epithelium in direct contact with the muscularis propria
Hyaline fibrosis of connective tissue
Atypical fibroblasts
Radiation angiopathy

Urinary Bladder and Ureters

The interior lumena of the urinary bladder is lined by the urothelium, which is water and ion impermeable and has a low mitotic rate. These properties of the urothelium decrease its immediate sensitivity to radiation relative to the epithelium of the GI tract [15]. Because of this, the incidence of radiation cystitis is less than 10% for patients given pelvic radiation for nonurinary malignancies. In those subjects that do develop radiation cystopathy, the earliest finding on endoscopic examination is transient erythema (during the first 24 h) [1]. Three to six weeks later, this is followed by edema, necrosis of basal urothelial cells, urothelial desquamation and hyperemia, as well as occasional shallow ulceration [1, 18]. Urothelial atrophy (thinning, with fewer layers of cells than normal) will often supervene, and the topmost layer of cells, the umbrella cells, may be lost. In consequence, the urothelium may lose its property of impermeability, which can lead to increased frequency of urination. Paradoxically, focal urothelial hyperplasia (an increased number of cell layers) and squamous metaplasia can develop alongside of urothelial atrophy. At this time, atypia will appear amongst urothelial cells, complicating interpretation of urine cytology in those patients being followed for urothelial malignancies. Over the long term, the radiated bladder may develop ulcers that may penetrate into the muscular wall. Replacement of the normal bladder wall muscle by collagen leads to rigidity and fibrosis of the bladder wall which leads to reduced capacity (and increased urinary frequency). Development of telangiectatic vessels contributes to persistent hematuria. All these effects of radiation may also manifest themselves in the distal ureters. However, the most important manifestation of ureteral exposure to radiation is fibrosis, which may lead to ureteral stenosis.

Urothelial hyperplasia noted above may lead to cellular atypia in the late period, and there is a risk for the development of urothelial tumors. In a rat model, at 20 months post index bladder irradiation, 10 of 17 rats had such tumors [18]. Also, the bladder is no exception to the general rule that irradiated tissues develop atypical fibroblasts; these may form lesions ("pseudosarcomas") which must be differentiated from true neoplasms. Reactive epithelial proliferations may develop, incorporating benign radiation-induced atypia, that may be difficult to distinguish from true invasive carcinomas (Table 5.3) [19, 20].

Prostate Gland and Proximal Penis

The effects of radiation on the prostate gland include glandular atrophy, squamous metaplasia, and cytological atypia amongst the epithelial elements while the stroma will show fibrosis and rare atypical fibroblasts [21]. Over time, arterial structures within the irradiated prostate will show myointimal proliferation and luminal narrowing, as seen in other organs under these conditions. While these radiation-induced changes in the prostate gland are of uncertain, if any, clinical significance, radiation-induced changes in adjacent tissues have more concrete implications. Radiation-induced changes in the arteries of the proximal penis (apoptosis of smooth muscle cells, replacement of smooth muscle by collagen) were seen to occur in the rat model developed for the study of prostate radiation-induced erectile dysfunction [22]. In another rat study, a decrease in the numbers of nitric oxide synthase-containing nerve fibers in the rat penis was documented [23].

Ovaries and Fallopian Tubes

Animal models have contributed little to our understanding of the effects of radiation of the ovaries in humans [15]. Rather, this endeavor has

Table 5.3 Acute and chronic histologic changes of the bladder following radiation exposure

Acute	Chronic
Erythema	Chronic ulcer
Urothelial necrosis	Telangiectasias
Urothelial atrophy and hyperplasia	Urothelial atypia
	Fibroblastic atypia
	Fibrosis of bladder wall

largely been advanced by the careful examination of ovaries in juvenile and adult females either intentionally or unintentionally exposed to radiation, coupled with an understanding of ovarian physiology and microanatomy. These studies have included an examination of the ovaries in a 13-year-old victim of the atomic explosion over Hiroshima, who succumbed 2 weeks after the event. Unlike other organs, the most radiosensitive cells in the ovary are not epithelial cells since there are none to speak of in the normal, postfetal ovary. Instead, the most radiosensitive cells in the ovary are the oocyte-supporting, mitotically active granulosa cells which surround the oocyte in the maturing ovarian follicle [15, 24, 25]. The oocytes themselves are relatively radioresistant after birth, because they are in a resting phase (meiosis). In fact, in childhood and throughout the age of reproduction, most follicles in the ovary are present as relatively inert primary follicles. During the age of reproduction (and, in a less organized manner, during childhood), during each menstrual period a cohort of primary follicles undergo maturation; this process includes the proliferation of the previously mitotically inactive granulosa cells [23]. It is during this time of mitotic activity that the granulosa cells are most radiosensitive, and will succumb within hours of a radiation exposure. The continued viability of the oocyte requires a healthy granulosa cell layer. Once the loss of granulosa cells reaches a certain threshold, there will be loss of the oocyte and atrophy of the follicle. Primary follicles, for the reasons given above, are more radioresistant than maturing follicles, but they will succumb to sufficiently strong doses of radiation. Ovaries studied months after radiation exposure demonstrate fibrosis of the cortex, absence of follicles and oocytes, and generalized atrophy (Fig. 5.4). The vascular changes and atypical fibroblasts typical of radiation injury may be seen in the ovary as well. The clinical manifestations of these radiation-induced changes may include sterility (either permanent or temporary), early onset of menopause, and loss of libido. In children, there may be failure to develop secondary sexual features. In regards to the risk for radiation-induced neoplasia, though there are anecdotal reports of malignancies arising in the previously healthy irradiated ovary [5, 26], there are at most slightly more than the expected number of ovarian tumors in patients status postradiation therapy [15].

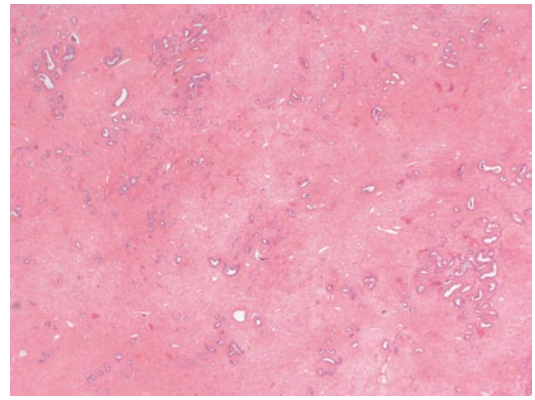

Fig. 5.4 This is a low power image taken from an irradiated ovary. Note that the ovarian stroma, normally characterized by the presence of cellular fields of spindle cells and follicles in various stages of maturation, is instead a sea of *pink* fibrosis

Cellular atypia and fibrosis may develop in the irradiated fallopian tubes, as one might expect, but isolated radiation injury of the fallopian tubes is not a significant cause of sterility (Table 5.4) [15].

Table 5.4 Ovarian effects of radiation exposure

Atrophy
Fibrosis

Uterus

The uterus and cervix may be subjected to either externally or internally sourced radiation. The degree of radiation injury varies with the strength of the dose of radiation delivered by these modalities [15]. At the lower dosages of radiation generally delivered by external beam radiation, the endometrium may remain essentially normal or may show various degrees of atrophy, cellular atypia, papillary hyperplasia, or microcystic degeneration that develop in the days and weeks after an index exposure. At higher dosages (often achieved through the placement of radiation sources in the endometrial cavity in order to treat endometrial malignancies), there will be necrosis of almost the entire endometrium, with preservation of only the deepest parts of the nonneoplastic endometrial glands (in addition to the desired effects upon the malignancy itself). These residual viable endometrial glands may show cytological atypia and cytoplasmic vacuolization (Fig. 5.5). In the weeks to months after an index dose of radiation, as in other organs, there will be replacement of normal cells and tissues by fibrosis, development of vascular lesions (telangiectasias and fibrotic lumenal narrowing), and persistent cellular atypia within fibroblasts and epithelial cells [27]. This latter phenomenon leads to the problem of distinguishing new or recurrent malignancy from benign radiation-induced atypia in cervical cytology specimens from patients with a history of radiation. Cells with benign radiation-induced nuclear atypia (characterized by hyperchromasia, irregularity in outline, and enlargement of nuclei) will also have a low nuclear to cytoplasmic ratio relative to truly dysplastic or malignant cells. This is due in part to an accompanying increase in cytoplasmic volume in benign, irradiated cells. Unfortunately, distinguishing these damaged cells from malignant cells still can be a very difficult task, leading the pathologist to express uncertainty in individual cases (Fig. 5.6) [28].

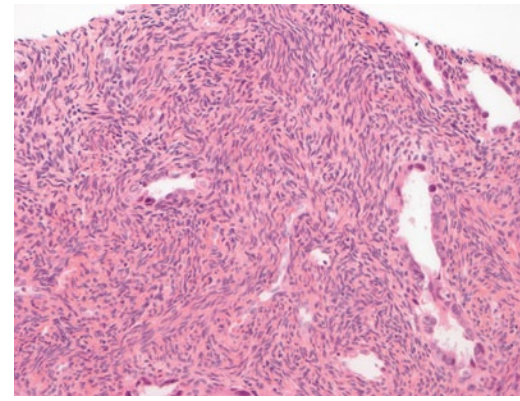

Fig. 5.5 This medium power image shows endometrium status postirradiation. It is atrophic, with widely spaced glands in which there are atypical epithelial cells

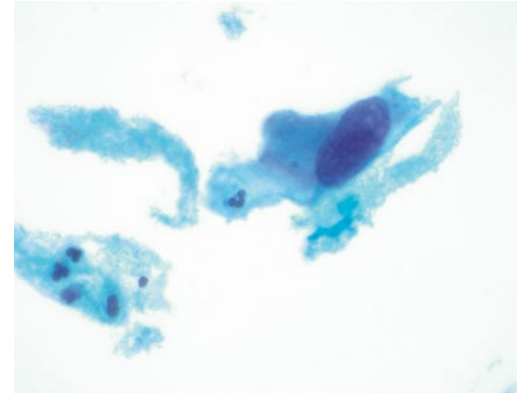

Fig. 5.6 This is a high power image of a cervical cytology tissue in a woman who has been irradiated for cervical carcinoma. Note the markedly enlarged, hyperchromatic nucleus (compare with adjacent neutrophils) but also the expansion of the cytoplasm, keeping the N/C ratio relatively low

There are reports of radiation-induced sarcomas and carcinomas of the uterus [29–31]. The incidence of this phenomenon is not firmly understood, but appears to be very low. For example, the incidence of radiation-induced endometrial carcinoma is reported to be between 0.5 and 0.8%. Radiation-induced endometrial carcinomas, which arise after an average latent period of approximately 14 years, tend to be of more aggressive phenotype (e.g., serous carcinoma) than those that arise sporadically (Table 5.5) [30, 32].

Table 5.5 pathologic effects of radiation on the uterus and cervix

Endometrial necrosis
Atrophy
Radiation-induced atypia of endometrial and stromal cells
Fibrosis

Vagina and Vulva

Since the vagina and vulva are both covered by squamous epithelium having a high turnover, these organs are sensitive to the effects of radiation exposure. Furthermore, relatively high dosages of radiation are used to treat the squamous cell carcinomas that may arise in this region. Therefore, the vagina and vulva are prone to the clinical effects of radiation injury [15, 24, 33]. After any acute phase ulcers are healed (healing may take place over 3–6 months), longer term effects include replacement of subepithelial tissues (including muscle and elastin) by collagenous fibrosis, vascular changes typical of radiation injury, and atrophy or loss of subepithelial accessory glands. Fibrosis, coupled with the loss of the accessory glands, can lead to vaginal dryness, diminished pliability, and a harsher texture of these organs. Fibrosis may be severe enough to cause stenosis or even complete obliteration of the vagina. All told, these changes can have a significant impact on the patient's sexual function and psychosexual health [15, 24].

Summary

The changes caused by radiation in the previously healthy tissues of the pelvis vary according to the organ at issue. In general, they are associated with: (1) acute phase retrenchment of the more proliferative cellular elements, followed by, depending on the degree of lethality of the radiation dose, regeneration of these elements that may or may not restore these compartments to normal function; (2) chronic replacement of normal cellular and extracellular elements by collagenous fibrosis coupled with luminal narrowing and fibrosis of the blood vessels, causing altered organ function which may take months or years to manifest itself; and (3) altered DNA in stem cells producing risk of subsequent neoplasia.

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Contribution of Chemotherapy to the Toxicity of Pelvic Irradiation

6

Amikar Sehdev and R. de W. Marsh

Abbreviations

CRT	Chemoradiation
CT	Chemotherapy
OS	Overall Survival
DFS	Disease-Free Survival
RTOG	Radiation Therapy Oncology Group
EORTC	European Organization for Research and Treatment of Cancer

Introduction

Cancer remains a major health problem of the twentieth century accounting for significant morbidity and mortality worldwide [1]. Moreover, the incidence of cancer is on the rise, especially in the developing countries. The ongoing efforts to combat this scourge have resulted in an increased understanding of the pathogenesis of cancer and in the development of newer therapies, which have lead to a modest improvement in cancer outcomes. The modern management of oncology patients frequently combines surgery, radiotherapy (RT) and chemotherapy (CT) in a multidisciplinary approach. With few exceptions, surgery is integral to a cure but unfortunately many patients have advanced stage at diagnosis making surgery impossible. Over the past two decades, combined chemoradiation (CRT) has emerged as an essential component of the standard of care in the treatment of many of these patients, converting initially unresectable to resectable disease, and improving the outcomes for those fortunate enough to present with operable disease. Therefore, it has become increasingly important to understand both the benefits and the toxicities incurred when CRT is used, in order to best select the patients who will benefit from such an approach. In this chapter we will discuss, (1) the rationale for combining CT and RT, (2) mechanism of interaction of CT and RT, (3) commonly used chemotherapeutic agents, (4) risk factors and an overview of common toxicities, (5) specific toxicities reported in CT versus CRT trials for specific pelvic malignancies, and (6) conclusions and future directions.

The Rationale for Combining Chemotherapy and Radiotherapy

As alluded to above, most cancer is diagnosed in an advanced stage (local spread of cancer), which makes many patients ineligible for curative resection. In addition, in those fortunate to be diagnosed at an early stage, poor health status due to comorbidities or personal choices might limit their

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ability to undergo curative resection. Preoperative (neoadjuvant) chemoradiotherapy may convert unresectable to resectable disease and offers the added bonuses of addressing systemic micrometastatic disease earlier, providing in vivo evidence of response, improving R0 resection rates and increasing pathological complete response (pCR) rates. Randomized phase III trials have shown improved survival at an acceptable toxicity with radiation therapy combined with either CT or hormonal therapy, in many pelvic malignancies such as cervical, bladder, rectal, anal, and prostate cancer [2–4]. Additionally, these approaches, as opposed to either CT, radiation, or surgery alone, can help in organ preservation, convert unresectable tumor into a resectable tumor, and in some cases may serve as definitive therapy thereby eliminating the morbidity of surgery altogether [5]. The original premise in combining radiation and CT was that these modalities would function independently to improve overall therapeutic efficacy. However, we now know that there are radiosensitizing effects of CT [6]. The exact mechanism(s) by which CT and RT work together synergistically remains an area of ongoing active research and is discussed in the next section.

Mechanisms of Interaction of Chemotherapy and Radiotherapy

The success of CRT is mainly based on heuristic attempts to improve the treatment of various cancers and dates back to the 1960s [7]. The landmark paper by Steel and Peckham in 1979 provided the first theoretical framework for the interaction between CT drugs and radiation [8]. They described four potential mechanisms of interaction: (1) spatial cooperation, (2) protection of normal tissue, (3) toxicity independence, and (4) tumor response enhancement.

The concept of spatial cooperation means systemic therapy with a drug and locoregional therapy with radiation are mutually exclusive and desired outcome can be achieved by combining full doses of each modality. This concept has been hard to translate to practical use with concurrent CRT; however, sequential therapy as used in nonsmall cell lung cancer provides a good example.

The second concept, protection of normal tissue, refers to a drug acting on normal tissue to prevent it from the toxic effects of radiation therapy. However, what was originally thought to be a protective effect after cytotoxic drugs is now better understood to be a result of induced cellular repopulation after the first cytotoxic insult. Thus far, we have been unable to exploit this concept.

Toxicity independence means toxicity of drug and radiation will not be additive and therefore dose amplification will be feasible without additive toxicities. This is self-explanatory and seems to have only limited applicability to current oncology practice.

The final concept, tumor response enhancement, simply means that a drug will interact with radiation in such a way that the eventual response to CRT will be more than expected [6]. This will be explored further in subsequent sections of this chapter.

Newer mechanistic frameworks are becoming necessary both owing to the development of molecularly targeted therapies, and as a result of the practical failure to exploit two of the four concepts in Steve and Peckham's mechanisms framework. One such framework was proposed by Bentzen et al. in 2007 and consists of five mechanisms: spatial cooperation, protection of normal tissue, cytotoxic enhancement, biological cooperation, and temporal modulation [9]. This framework will hopefully provide more rigorous concepts for the understanding and explanation of the scientific basis of the drug–radiation interaction of novel therapies (see Table 6.1).

Chemotherapeutic Agents Used as Radiosensitizers in Pelvic Malignancies

Fluoropyrimidines (5-Fluorouracil and Capecitabine)

5-Flurouracil (5-FU) is certainly one of the most commonly used radiosensitizing drugs. It is a

Table 6.1 Mechanistic framework of drug and radiation interaction to provide a useful preclinical and clinical framework for understanding drug radiation interaction

Mechanism	Explanation	Clinical example	Comments
Spatial cooperation	Working on different anatomical regions of the body to improve outcome without additive toxicity	RT in SCLC	Chemotherapy does not cross blood brain barrier which is a sanctuary site for SCLC cells
Protection of normal tissue	Drug interacts with radiation in a way to prevent harmful effects on adjacent normal tissue	Amifostine is used in head and neck cancer to prevent radiation induced xerostomia	Clinical benefit is not proven in clinical trials
Biological cooperation	The drug targets cells that escape RT within the tumor tissue itself	Tirapazamine in head and neck cancer	Newer concept that needs clinical evidence
Temporal modulation	Drug targets cancer cells in between RT fractions by inhibiting repair, repopulation, redistribution, and reoxygenation	Cetuximab in head and neck cancer	Needs clinical evidence with concurrent chemoradiation

RT radiotherapy, *SCLC* small cell lung cancer

pyrimidine analog of uracil and through its inhibition of folate metabolism works as an antimetabolite. While it interacts with both DNA and RNA, its radiosensitizing effects are primarily due to inhibition of thymidylate synthase and eventually DNA biosynthesis [10]. 5-FU has been used both as a bolus and by continuous infusion in the initial CRT trials, but currently continuous infusion is the preferred method owing to better side effect profile, the short half life of 5-FU, and phase III trials in rectal cancer establishing continuous infusion to be better in terms of treatment outcomes [11]. Combined CRT with cisplatin or 5-FU is the current standard of care in the treatment of head and neck cancer and many gastrointestinal cancers, including rectal and anal cancers.

Capecitabine is an oral 5-FU prodrug, which goes through a three-step enzymatic process to be transformed into its active form. Thymidine phosphorylase (TP) is a key rate-limiting enzyme in this conversion process. Since the TP activity is higher in tumor tissue and liver, it results in a preferential effect at these sites. Randomized controlled trials (RCTs) comparing infusional 5-FU with capecitabine in neoadjuvant CRT treatment of rectal cancer have established therapeutic equivalency and perhaps superiority of capecitabine over 5-FU [12, 13]. The ease of administration of capecitabine is unbeatable when combined with CRT. It is to be noted that capecitabine and 5-FU have slightly different toxicity profiles. The most important acute toxicities related to 5-FU are nausea, vomiting, fatigue, myelosuppression, hand-foot syndrome (HFS), mucositis of the gastrointestinal tract, cardiotoxicity (arrhythmias and coronary ischemia), and cerebellar neurotoxicity (ataxia and nystagmus). While capecitabine has a similar toxicity profile to 5-FU, some trials have shown that it causes less hematological toxicity and more dermatological toxicity (HFS) as well as fatigue [13]. The toxicity of 5-FU and its analogues is dose dependent except in dihydropyrimidine dehydrogenase deficient patients who are highly sensitive to even small doses owing to their impaired ability to metabolize these drugs.

Finally, capecitabine, but not 5-FU, is affected both by compliance and also pharmacokinetic issues such as absorption, drug interaction, and renal clearance (especially in elderly patients).

Platinum Agents

Cisplatin (Cis-diamminedichloroplatinum; CDDP) is an alkylating agent. CDDP is a classic drug used in the treatment of many cancers and it also works as an excellent radiosensitizer. The drug

forms covalent bonds with nucleotide bases in the DNA strand, resulting in inter- or intrastrand crosslinks (adducts). This results in single strand breaks, which are detected and removed by DNA mismatch repair processes. The potentially repairable single-strand break becomes an irreparable double-strand break when combined with radiation. An inherent resistance to radiosensitization by cisplatin and carboplatin (but not oxaliplatin) is manifest by mismatch repair defective cells [14]. A large body of randomized phase III trials supports the beneficial effect of concurrent CRT with CDDP in improving overall survival (OS) for patients with cervical and bladder cancer compared to either modality alone.

Carboplatin is a second-generation platinum analogue that was introduced for clinical use in 1992. Comparative trials in many different malignancies (ovary, germ cell, bladder, NSCLC, and head and neck) have established a better toxicity profile for carboplatin over cisplatin. However, cisplatin has mostly superior therapeutic efficacy compared to carboplatin, especially in the setting of combined modality therapy.

Oxaliplatin is a third generation platinum analogue, which is currently under study as a radiosensitizer [15]. The DNA nucleoside crosslinks formed by oxaliplatin are not repaired by the DNA mismatch repair system. Oxaliplatin is therefore unique as it can be effective against DNA mismatch repair deficient cells which are resistant to CRT with cisplatin and carboplatin [14]. Despite this interesting observation, the role of oxaliplatin as a radiosensitizer remains controversial and undetermined in last 13 years [16]. The results of several neoadjuvant CRT rectal cancer trials [12, 17–19] have shown that the addition of oxaliplatin to the preoperative CRT regimen with either 5-FU or capecitabine is associated with higher toxicity without improving OS, disease-free survival, or pathological CR. Therefore, at this time it should not routinely be used in combination with radiation therapy. The most common acute toxicities of cisplatin include nausea, vomiting, alopecia, myelosuppression, nephrotoxicity (azotemia, acute renal failure, hyperuricemia), allergic reaction, and neurotoxicity (peripheral neuropathy, ototoxicity) [20]. Carboplatin shares the same toxicity profile; however nausea, vomiting, neurotoxicity, and nephrotoxicity are relatively less. Cisplatin, and the platins in general, can also cause significant late toxicity. Cisplatin has been widely used for the treatment of young, germ cell tumor (GCT) patients, providing long-term data on delayed toxicity at least for male patients. Nephrotoxicity and neurotoxicity continue to be a major problem. About 20–30% of GCT patients treated with curative intent can have irreversible renal damage resulting in persistent reduction of glomerular filtration rate. Similarly, persistent peripheral neuropathy and ototoxicity has been reported in 20–40% and ototoxicity alone in 20% of GCT patients [21]. Cardiovascular toxicity, predominantly ischemic heart disease and resultant complications, has been well described in GCT patients [22].

Mitomycin C

Mitomycin C is an antibiotic derived from *Streptomyces caespitosus*. It is inactive as such, but reduction by DT-diaphorase (DTD) and other reductases results in activation of the drug [23]. It is an alkylating agent and the mechanism of action is similar to platinum drugs. Additionally, mitomycin C is an effective cytotoxic agent even under hypoxic conditions [6]. Mitomycin C is not cell cycle specific as opposed to platinum drugs. Although controversial, some reports suggest that bioactivity of mitomycin C in tissue is correlated with its DTD concentration. Mitomycin C is a potent radiosensitizer and active against many tumor types but is primarily used for the combined modality treatment of locally advanced anal cancer in combination with 5-FU. Common acute toxicities include nausea, vomiting, myelosuppression, acute renal failure, and alopecia. The complication of hemolytic uremic syndrome (HUS)/thrombotic thrombocytopenia purpura (TTP) is also seen with this drug and is potentially life threatening. Due to its significantly higher toxicity rate when combined with radiation, e.g., 36% of the study population suffered grade ≥ 3 toxicity in a cervical cancer trial, it is often replaced by platinum drugs [24]. Furthermore, some acute toxicities continue

for long periods of follow-up and bowel complications (bleeding, stricture, obstruction, perforation, or fistula formation) are especially high, accounting for about 15% morbidity in cervical cancer patients [25].

Androgen Deprivation Therapy

Huggins and Hodges first described the role of androgen in metastatic prostate cancer [26]. The androgen receptor is central to the growth and progression of prostate cancer and therefore androgen deprivation therapy (ADT) has been the backbone of prostate cancer treatment. There is no doubt that ADT inhibits the growth of the primary tumor as well as controlling micrometastatic disease [27]. Prostate cancer patients with high-risk locally advanced disease are traditionally treated with external beam radiation therapy and ADT. This approach is based upon the results of many phase III, RCTs showing improvement in OS as well as disease-specific survival in patients treated with combined modality therapy as compared to RT or ADT alone [28–30]. Some studies in tumor xenograft and animal models suggest that ADT positively interacts with radiation therapy to achieve maximal cytotoxic effect. However, it is as yet unclear whether ADT sensitizes prostate cancer cells to RT [31]. The side effects of ADT include hot flashes, skeletal complications (osteopenia, osteoporosis, and fractures), sexual dysfunction (erectile dysfunction, decreased libido), metabolic derangement (increased body mass index, hyperlipidemia), cognitive and mood changes, and poor quality of life (QOL) [27].

Hydroxyurea

Hydroxyurea was first recognized and used as a radiosensitizer in the 1960s [23]. It inhibits ribonucleotide reductase resulting in inhibition of DNA synthesis. It is a cell cycle-specific agent that adds to its potency when combined with radiation. In addition, hydroxyurea is also effective under hypoxic conditions and can impair the repair of near fatal DNA damage after radiation resulting in cell death. The most common acute toxicities of hydroxyurea are myelosuppression, abnormal liver enzymes, and renal impairment. Hydroxyurea can be leukemogenic with long-term use. A recent systematic review analyzing eight RCTs using hydroxyurea as the radiosensitizer in cervical cancer concluded poor OS benefit. The authors summarized that there is inadequate evidence to support the use of hydroxyurea in treatment of cancer of cervix [32] and therefore, hydroxyurea is almost never used in the treatment of pelvic malignancies in the United States of America (USA).

Risk Factors and an Overview of Toxicities

Risk factors: Patient Related and Treatment Related

The risk factors for toxicity with use of combined modality therapy can be separated into patient-related and treatment-related factors. However, these are not completely independent of each other and should rather be considered as codependent. The patient-related risk factors include age, performance status, and end organ function, including renal, liver, and bone marrow reserve. Most combined chemoradiotherapy trials include only patients under the age of 70 years with a few trials having an age cut off of ≤75 years [33, 34]. Additionally, the trial inclusion criteria often require that patients have a **performance status of ≤2** and normal renal, liver, and bone marrow function indirectly indicating the importance of intact end organ function for CT clearance [2, 33, 34].

The treatment-related side effects of radiation are mainly dependent upon the treatment volume and radiation dose [20]. For example, Albuquerque et al. studied factors including age, body mass index, transfusions, and bone marrow volumes irradiated to assess the radiation-related predictors of hematological toxicity due to radiation therapy [35]. In a multivariate logistic regression analysis, they found that if the volume of bone receiving 20 Gy in the pelvis exceeds 80%, there is significantly higher risk of hematological toxicity of

grade≥2 (odds ratio 4.5, 95%, confidence interval, 1.08–18.69, $p<0.05$) [35]. The toxicities of the commonly used CT agents for pelvic malignancies have been reviewed above and these are clearly related to the dose, number of cycles, and pharmacokinetics of the drugs. Some of these factors will be further elaborated in the discussion about specific clinical trials below.

Specific Toxicities

Toxicity due to combined chemoradiotherapy is usually grouped into acute and late/chronic categories. Although previously published studies have used different definitions for acute and late toxicities, for the purposes of this review we will define acute toxicity as any adverse effect occurring after CRT and within 90 days of treatment completion in concordance with other authors [20, 36]. Late/chronic toxicity will be defined as any adverse effect occurring after 90 days. Generally, acute toxicity is considered to be reversible; conversely late toxicity is often permanent and has dramatic effects on QOL.

The most significant acute toxicities are hematologic (leukopenia, granulocytopenia, thrombocytopenia, and anemia) and gastrointestinal (nausea, vomiting, diarrhea, mucositis, and abdominal pain). Other less common acute toxicities include genitourinary (increased frequency, incontinence, dysuria, urinary obstruction, and renal failure), cutaneous (dermatitis, skin ulcerations), and neurologic toxicities. The details of each of these toxicities with combined therapy as compared to radiation therapy alone will be discussed below (see Tables 6.2, 6.3, and 6.4).

The late toxicities include gastrointestinal (enteropathy, colopathy, proctopathy, and effects on the anus), genitourinary (cystitis and obstructive uropathy), effects on the male and female reproductive system, neurological (lumbosacral plexopathy and miscellaneous effects), and vascular insufficiency fractures are each discussed in subsequent chapters (see Tables 6.2, 6.3, 6.4, and 6.5). It should be noted, however, that the late/chronic toxicities are notoriously underreported and certainly not reported in all studies.

Specific Toxicities Reported in Studies of Radiation therapy Alone Versus Concurrent Chemoradiation (CRT) in Pelvic Malignancies

The standard of treatment for several pelvic malignancies is currently based on a concurrent CRT approach. Below we will discuss a selection of randomized clinical trials of all the pelvic malignancies where concurrent CRT with or without surgery is currently the standard of care. There are a few notable issues pertaining to toxicity reporting in the combined CRT trials [36], such as:

I. Variable toxicity reporting scales used across different studies. Although the two main toxicity scoring systems in the USA are Radiation Therapy Oncology Group/Acute Radiation Morbidity Scoring Criteria (1987) (RTOG/ARMSC) and the National Cancer Institute/Common Toxicity Criteria (1988) (NCI CTC). The RTOG/ARMSC was used for reporting acute radiation toxicity and NCI CTC was used for reporting CT toxicity. The NCI CTC scale was based on WHO scale which is also used in some studies for CT toxicity [37]. Up until 1998, there was no combined modality toxicity scoring system [38] however it should be noted that the National Cancer Institute Common Toxicity Criteria (NCI CTC) scale was later changed and is currently the only scale used for measurement of all toxicities including those from surgery, CT, and radiation.
II. Different studies used different definitions of acute toxicity limiting it to 42[38], 60[39], or 90 days[40].
III. There is no consistency in reporting toxicities; some studies reported all grades of toxicities while other only reported severe toxicities (grade≥3). Additionally, the physiologic system-based reporting was not consistent between trials (see Tables 6.2, 6.3 and 6.4).
IV. The late toxicities were only described in a limited number of trials.
V. There was no reporting of QOL.

Table 6.2 The grade 3 and 4 acute toxicities as reported in chemoradiation trials by cancer site. Where the percentage of adverse effect not provided, it was calculated by dividing number of patient with the adverse effect by the total number of patients in that arm. If the toxicity is not listed in the first column but provided in the clinical trial it was grouped under category "other"

Acute toxicity	Trials																																			
	Cervical cancer													Bladder cancer		Prostate cancer										Rectal cancer						Anal cancer					
	Whitney et al. [2]		Rose et al. [41]			Keys et al. [42]		Peters et al. [34]		Morris et al. [39]		Pearcey [33]		James et al. 2010		Roach et al. [56]		Bolla et al. [28]		Pilepich et al. [29]		Denham et al. [53]		Bosset et al. [4]	Bujko et al. [60]		Gerard et al. 2006 [59]		James et al. [5] and 2010 (Not Necessarily G3/4) [66]		Bartelink et al. [64] (Unclear N in count or %)		Ajani et al. [65]	
	CRT (CF) %	CRT (HU) %	CRT (C)	CRT (CFH)	CRT (H)	CRT	RT	CRT	RT	CRT	RT	CRT (CDDP)	RT	CRT	RT	ADT + RT	RT	ADT + RT	RT	CRT	RT	CRT	RT	CRT	RT	CRT	RT	CRT	RT	CRT	RT	CRT	RT	CRT (CDDP)	CRT (MMC)
Overall	–	–	–	–	–	–	–	–	–	–	–	–	–	36	27.5	2	4	–	–	–	–	–	–	54.3	37.7	–	–	15	2.9	48	38.5	–	–	83	87
Hematological (other)	3.0	5.9	15	33	18	21.3	1.6	–	–	73	2	6	0	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	42.1	61.4
Thrombocytopenia	0	0.5	2	4	1	–	–	0.8	0	–	–	–	–	–	–	–	–	0	1	–	–	–	–	1.8	0.5	–	–	–	–	4.7	0	–	–	–	–
Leucopenia	3.6	24.7	23	46	21	–	–	35	0.9	–	–	–	–	–	–	–	–	0	1	–	–	–	–	7	0.8	–	–	–	–	6.5	0	–	–	–	–
Anemia	–	–	–	–	–	–	–	3.2	0	–	–	–	–	–	–	–	–	1	0	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Granulocytopenia	–	–	–	–	–	–	–	28.6	2.6	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Genitourinary	1.2	1.6	5	2	3	1.6	3.2	–	–	2	0	3	1	–	–	–	–	7	9	–	–	–	–	5.3	5.8	–	–	–	–	1	0.3	–	–	3.3	3.4
Renal failure	–	–	–	–	–	–	–	0	0					–	–	–	–			–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Cutaneous	2.4	1.6	2	5	4	0	2.1	3.2	0	5	1	3	0	–	–	–	–	<1	2	–	–	–	–	26	20	–	–	–	–	17.1	13.6	29	26	41.25	47.8
Neurological	0	0	1	1	2	1	0	–	–	–	–	2	0	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5.6	5
Gastrointestinal	7.7	4.3	12	18	14	14	5	–	–	–	–	16	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4.7	1.7	–	–	45.6	35.4
Diarrhea	–	–	–	–	–	–	–	9.8	0	–	–	–	–	–	–	–	–	5	11	–	–	–	–	34	17	–	–	–	–	–	–	10	4	–	–

Table 6.2 (continued)

Acute toxicity	Trials																																							
	Cervical cancer													Bladder cancer		Prostate cancer											Rectal cancer						Anal cancer							
	Whitney et al. [2]		Rose et al. [41]			Keys et al. [42]		Peters et al. [34]		Morris et al. [39]		Pearcey [33]		James et al. 2010		Roach et al. [56]		Bolla et al. [28]		Pilepich et al. [29]		Denham et al. [53]		Bosset et al. [4]	Bujko et al. [60]		Gerard et al. 2006 [59]		James et al. [5] and 2010 (Not Necessarily G3/4) [66]		Bartelink et al. [64] (Unclear N in count or %)		Ajani et al. [65]							
	CRT (CF) %	CRT (HU) %	CRT (C)	CRT (CFH)	CRT (H)	CRT	RT	CRT	RT	CRT	RT	CRT (CDDP)	RT	CRT	RT	ADT + RT	RT	ADT + RT	RT	CRT	RT	CRT	RT	CRT	RT	CRT	RT	CRT	RT	CRT	RT	CRT	RT	CRT (CDDP)	CRT (MMC)						
Bowel and rectal abnormalities	–	–	–	–	–	–	–	1.6	0.9	17	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–						
Pulmonary	0.6	0.5	0	0	0	–	–	0.8	0.9	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3	1.5						
Cardiovascular	0.6	0	0	2	0	–	–	0.8	0	–	–	3	0	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8.1	4.3						
Fever/ Infection	1.2	1.1	0	0	1	–	–	0.8	0.9	–	–	2	0	–	–	–	–	–	–	–	–	–	–	2.8	0.5	–	–	–	–	–	–	17.5	10						
Other	0	0.5	7	5	1	6.5	2.6	2.5	0	11	0	3	0	–	–	–	–	–	–	–	–	–	–	4.8	0.3	–	–	–	–	–	–	30.8	40.6						
Fatigue	–	–	0	1	1	–	–	1.6	0.9	–	–	–	–	–	–	–	–	1	2	–	–	–	–	–	–	–	–	–	–	–	–	1	0						

ADT androgen deprivation therapy, *CDDP* cis-diamminedichloroplatinum, *CRT* chemoradiotherapy, *MMC* mitomycin, *RT* radiotherapy, *CF* cisplatin plus infused 5-F, *HU* hydroxyurea, *CFH* cetuximab

Table 6.3 The grade 3 and 4 chronic toxicities as reported in chemoradiation trials by cancer site. Where the percentage of adverse effect not provided, it was calculated by dividing number of patient with the adverse effect by the total number of patients in that arm

Chronic toxicity	Trials																																			
	Cervical cancer														Bladder cancer		Prostate cancer								Rectal cancer						Anal cancer					
	Whitney et al. [2]		Rose et al. [41]			Keys et al. [42]		Peters et al. [34]		Morris et al. [39]		Pearcey [33]			James et al. 2010		Roach et al. [56]		Bolla et al. [28]		Pilepich et al. [29]		Denham et al. [53]		Bosset et al. [4]		Bujko et al. [60]		Gerard et al. 2006		James et al. [5] and 2010 (Not Necessarily G3/4)		Bartelink et al. [64]		Ajani et al. [65]	
	CRT (CF)	CRT (HU)	CRT (C)	CRT (CFH)	CRT (H)	CRT	RT	CRT	RT	CRT	RT	CRT	RT	CRT	RT	CRT	RT	ADT + RT	RT	ADT + RT	RT	CRT	RT	CRT	RT	CRT	RT	CRT	RT	CRT	RT	CRT	RT	CRT (CDDP)	CRT (MMC)
Overall	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9	12	–	–	–	–	–	–	–	–	7.1	10.1	–	–	–	–	–	–	–	–
Hematological	–	–	–	–	–	–	–	–	–	–	–	0	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Thrombocytopenia	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Leucopenia	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Anemia	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Granulocytopenia	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Genitourinary	–	–	–	–	–	–	–	–	–	5	3	17	10	–	–	–	–	–	–	–	–	–	–	–	–	1.4	2.1	–	–	6.1	6.6	–	–	<1	<1
Renal failure	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Cutaneous	–	–	–	–	–	–	–	–	–	1	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2.8	0	–	–	20.2	16.4	12	4	4.7	3.5
Neurological	–	–	–	–	–	–	–	–	–	–	–	3	2	–	–	–	–	–	–	–	–	–	–	–	–	2.8	2.9	–	–	–	–	–	–	–	–
Gastrointestinal	–	–	–	–	–	–	–	–	–	–	–	6	13	–	–	–	–	–	–	–	–	–	–	–	–	1.4	5.1	–	–	28.7	27	5	4	–	–
Diarrhea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Table 6.3 (continued)

Chronic toxicity	Trials																																			
	Cervical cancer														Bladder cancer	Prostate cancer							Rectal cancer								Anal cancer					
	Whitney et al. [2]		Rose et al. [41]			Keys et al. [42]		Peters et al. [34]		Morris et al. [39]		Pearcey [33]		James et al. 2010		Roach et al. [56]		Bolla et al. [28]		Pilepich et al. [29]		Denham et al. [53]		Bosset et al. [4]		Bujko et al. [60]		Gerard et al. 2006		James et al. [5] and 2010 (Not Necessarily G3/4)		Bartelink et al. [64]		Ajani et al. [65]	
	CRT (CF)	CRT (HU)	CRT (C)	CRT (CFH)	CRT (H)	CRT	RT	CRT	RT	CRT	RT	CRT	RT	CRT	RT	ADT + RT	RT	ADT + RT	RT	CRT	RT	CRT	RT	CRT	RT	CRT	RT	CRT	RT	CRT	RT	CRT	RT	CRT (CDDP)	CRT (MMC)
Bowel and rectal abnormalities	–	–	–	–	–	–	–	–	–	22	26	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6	6	3.1	1.6
Pulmonary	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Cardiovascular	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Fever	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Other	–	–	–	–	–	–	–	–	–	6	6	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.7	1.4	–	–	7.8	4.9	–	–	4.4	5.1

CRT chemoradiotherapy, *RT* radiotherapy

Table 6.4 Selected chemoradiation trials in cervical cancer

Study	FIGO stage	*N*	Intervention	Results					Toxicity ($G \geq 3$)	
				OS (%) 3 years	DFS (%) 3 years	LR (%) 3 years	Type of RT	pCR (%)	Acute (%)	Late (%)
Whitney et al.[2] GOG 85	IIB–IVA	177	CRT (Cisplatin 50 mg/m^2+5-FU 4 g/m^2/96 h)	65 (5-year)	57	25	EBRT+Intra-cavitory	–	Reported by System, consider separate table	–
		191	CRT (HU, 3 g/m^2 twice/week)	43 $P=0.018$	47 $P=0.03$	30		–		–
Rose et al. [41] GOG 120	IIB–IVA	177	CRT (Cisplatin 40 mg/m^2/week)	65	67	–	EBRT+Intra-cavitory	–	Reported by system, consider separate table	–
		173	CRT (Cisplatin 50 mg/m^2/week+5-FU 4 g/m^2/96 h+HU 2 g/m^2/twice weekly)	65	64	–		–		–
		176	CRT (HU 3 g/m^2/twice weekly)	47 P 0.005	47	–		–		–
Keys et al. [42] GOG 123	IB bulky disease	183	CRT (Cisplatin 40 mg/m^2/week)—S (Extrafascial H)	83	79	9	EBRT+Intra-cavitory brachytherapy	52	21 Heme 14 GI	–
		186	RT—S (Extrafascial H)	74 $p=0.008$	63 P 0.001	21		41	2 Heme 5 GI	–
Peters et al. [34] Intergroup 01–07/SWOG 87–97	I–IIA after hysterectomy with high-risk features	127	CRT (Cisplatin 70 mg/m^2+5-FU 4 g/m^2/96 h, every 3 week×4)	81 (4 Yr.)	80	16	EBRT	–	–	–
		116	RT	71	63	6		–	–	–
Morris et al. [39] Eifel [46] RTOG 90–01	IB–IIA IIB–IVA	195	CRT (Cisplatin 75 mg/m^2+5-FU 4 g/m^2/96 h Q 3 weekly×3)	73 (5-Year)	68		EBRT+Intra-cavitory	–	–	–
		193	RT	52	43			–	–	–
Pearcey [33] NCIC	IB–IVA	127	CRT (Cisplatin 40 mg/m^2/week)	69	No Difference (numbers not reported) $P=0.39$	–	EBRT+Brachy-therapy	–	40 overall 6 Heme 16 GI	30 GU 13 GI
		126	RT	66 $p=0.42$	–			–	4 Overall 0 Heme 1 GI	18 GU 24 GI

RT radiotherapy, *CRT* chemoradiotherapy, ADT androgen deprivation therapy, *EBRT* external beam radiotherapy, *OS* overall survival, *LR* local recurrence, *DFS* disease-free survival, *GI* gastrointestinal, *GOG* gynecologic oncology group, *SWOG* Southwest Oncology Group, *RTOG* radiation therapy oncology group, *5-FU* 5-Flurouracil, *pCR* pathological complete response, *HU* hydroxyurea

Table 6.5 Selected chemoradiation trials in prostate cancer

Study (prostate cancer)	Stage	*N*	Intervention	Results					Toxicity ($G \geq 3$)	
				OS (%) 10 years	DFS (%) 10 years	Biochemical failure rate, 10 year	Disease-specific mortality/survival, 10 year	Distant metastases, 10 year	Acute (%)	Late (%)
Bolla et al. [48, 49 and 28] EORTC 2286	T1–4, N0 * No sig. diff. in cardiovascular mortality	415	RT+ADT (goserelin × 3 years)+ cyproterone (150 mg per day × 1 month)	58	48	6 (locoregional failure)	10	51 (DM free survival)	–	–
			RT	40 $p = 0.0004$	23 p 0.0001	23.5 p 0.0001	30 p 0.0001	30 p 0.0001	–	–
Pilepich et al. [50 and 29] and Lawton 2005 RTOG 85–31	T3 with or without regional nodal involvement	977	RT+ ADT (long-term adjuvant goserelin)	49			49 (Ds. Sp. survival)	24	–	–
			RT	39 ADT preferentially benefited men with higher gleason scores			39	39	–	–
Denham et al. [53 and 30] TROG 96–01	T2b–4 N0 M0	272	RT+ADT (Goserelin plus flutamide 6 months before, plus concomitant suppression)	29 (all cause mortality)	36	52.8	11	10 13.3 (local failure)	Detailed separate articles	–
		270	RT+ ADT (Goserelin plus flutamide 3 months before, plus concomitant suppression)	37	29	60.4	19	14.5 15.7 (local failure)		
		276	RT (66 Gy 3D-CRT)	42.5	13	73.8	22	13.5 28.2 (local failure)		
Roach et al. [56] RTOG 86–10	T2–T4 * No sig. diff. in local progression rates and fatal cardiac events.	224	RT+ADT (goserelin plus flutamide starting 2 months before and with RT)	43	11	65	23	35	3	8
		232	RT	34 $p = 0.12$	3	80	36	47	7	8

ADT androgen deprivation therapy, *RT* radiotherapy, *TROG* Trans Tasman Radiation Oncology Group, *CRT* chemoradiotherapy, *RTOG* radiation therapy oncology group, *3D* three-dimensional, *OS* overall survival, *DFS* disease-free survival, *DM* distant metastasis

* $p > 0.05$

Cervical Cancer

Many phase III RCT have shown that cisplatin-based radiation therapy improves OS and locoregional control in locally advanced cervical cancer (LACC) when compared to radiation therapy alone or other CRT combinations (see Table 6.4). [2, 36, 39, 41, 42] This led to release of a clinical alert by National Cancer Center on February 23, 1999 outlining the findings of these trials and recommending strong consideration for combined chemoradiotherapy with cisplatin for women who need radiation for their cervical cancer [43]. This benefit was subsequently also validated in the Cochrane Meta-analysis of 2010 [44]. However, combined CRT is also associated with more toxicity, especially gastrointestinal and hematological toxicity [36, 44].

There are six landmark RCTs of combined CRT versus radiation therapy alone in LACC. Three of the six trials were conducted by the Gynecological Oncology Group (GOG). GOG 85 randomized 368 patients with stage IIB–IVA disease to two different CT regimens concurrently with RT, arm A getting CT with cisplatin (50 mg/m^2 on day 1 and day 29) and 5-FU (4 g/m^2/96 h on days 2–5 and days 30–33), and arm B getting CT with HU (hydroxyurea) (3 g/m^2 twice/week) [2]. Arm A had significantly better 5-year OS (65% vs 42%, $p=0.018$) compared to arm B [2, 6, 45]. There were significantly more severe (grade≥3) hematological toxicity (leukopenia, 24% vs 4%) in arm B compared to arm A, respectively. There was slightly higher gastrointestinal toxicity (8% vs 4%) in arm A as compared to arm B but not statistically significant. There was no difference in other acute toxicities (see Table 6.4) or the rate of late complications (16.2% vs 16.5%) in arm A and B, respectively. Of note, specific details on late complication were not reported in this trial. Finally, QOL was not assessed on this trial [2].

GOG 120 was a three-arm study with three different CT regimens (arm A, cisplatin 40 mg/m^2/week; arm B, cisplatin 50 mg/m^2/week+5-FU 4 g/m^2/96 h+HU 2 g/m^2/twice weekly; arm C, HU 3 g/m^2/twice weekly) given concurrently with RT [41]. The trial recruited a total of 526 patients with stage IIB–IVA disease and found a significant improvement in 3-year OS (65% vs 47%, $p<0.005$) with cisplatin-containing regimens (arm A and B) compared to HU-containing arm (arm C), respectively. In terms of toxicity, rate of grade≥3 leukopenia and granulocytopenia, were double in arms B and C compared to A. There was no reporting of late toxicity or QOL in this trial. This trial established the efficacy and favorable toxicity of single agent cisplatin as opposed to cisplatin plus other drugs.

GOG 123 tested concurrent CRT with cisplatin (40 mg/m^2/week) versus RT alone in 389 patients with bulky stage IB disease [42]. The study showed 3-year OS benefit with concurrent CRT as opposed to RT alone (83% vs 74% respectively, $p=0.008$). In terms of toxicity, concurrent CRT was associated with higher overall grade≥3 acute toxicity (35% vs 13%), most notable for hematological toxicity (21% vs 2%) and gastrointestinal toxicity (14% vs 5%), respectively (see Table 6.4). There was no reporting of late toxicity or QOL assessment in this trial.

In all the above GOG trials, there was no treatment-related mortality directly attributable to concurrent CRT itself. When there was a death, it was related to a series of complications; for example a patient with stage IVA disease died in GOG 85 due to radiation therapy causing vesicovaginal fistula requiring urinary diversion that was complicated by pulmonary embolus causing death [2].

A combined Intergroup and Southwest Oncology Group (SWOG) study compared concurrent CRT with cisplatin (70 mg/m^2 every 3 weeks) and 5-FU (4 g/m^2/96 h every 3 weeks) with RT alone in 268 patients with stage IA–IIA disease who were treated with hysterectomy and pelvic lymphadenectomy and who had high-risk features such as positive margins, lymph node involvement, or microscopic spread to parametrium [34]. Of note, a total of four cycles of CT were given every 3 weeks and only the first and second cycle was given concurrently with radiation therapy. The study showed a 4-year OS benefit of 10% with concurrent CRT as compared to RT alone (81% vs 71%, $p=0.007$). Again, there was a higher grade≥3 hematological (anemia, leukopenia, granulocytopenia, and thrombocytopenia)

and gastrointestinal (nausea, vomiting, abdominal pain, diarrhea, and stomatitis) acute toxicity (see Table 6.4) in the CRT group. Late toxicity and QOL was not reported. There was one death that may be treatment related in the patient allocated to concurrent CRT, however this patient did not get CT. The patient developed ureteral fibrosis, bilateral ureteral obstruction, renal failure, and sudden death 39 months after completion of RT.

The RTOG 90–01 trial randomized 388 patients with stage IIB–IVA disease and IB–IIA disease, if the tumor size was more than 5 cm or pelvic lymph nodes were positive, to either concurrent CRT with cisplatin (75 mg/m^2) and 5-FU (4 g/m^2/96 h) or RT alone [39]. The CT was administered on day 1–5 of RT with two additional cycles given at 3 weekly intervals. There was significant improvement in OS with concurrent CRT compared to RT alone (73% vs 52%, $p < 0.0001$). The trial reported detailed acute and late toxicity. Acute toxicity, especially hematological and gastrointestinal, was higher in the concurrent CRT arm compared to RT alone (see Table 6.4). The authors concluded that these toxicities were generally grade 3 and self-limiting. In terms of late toxicity, there was no difference between the two arms (~14%) [39, 46]. There were three treatment-related deaths in each arm [46]. Again, QOL was not reported in this trial.

Lastly, Pearcey et al. reported a trial sponsored by National Cancer Institute of Canada in 2002 comparing cisplatin-based (40 mg/m^2/wk) concurrent CRT versus RT alone for patients with LACC [33]. A total of 253 patients with stage IB–IVA tumor were randomized. Surprisingly, there was no significant difference in the OS at 3 years (69% vs 66%) or 5 years (62% vs 58%) between the CRT and RT arms, respectively. Despite being a multicenter, RCT with patients receiving standard doses of cisplatin and RT, the results were opposite to five previous RCTs. The trial has been criticized for its wide confidence interval (−0.3, 0.40), which possibly explains why it did not show the expected benefit of CRT over RT alone [47]. The trial showed higher grade≥3 acute toxicity (40% vs 4%) in the concurrent CRT arm compared to RT alone arm, respectively (see Table 6.4). However, there was no significant difference in the rates of grade≥3 late toxicity. There was no delay in treatment due to acute toxicities.

A Cochrane Meta-analysis of all the RCTs comparing concurrent CRT with RT alone, including 19 studies and about 4921 patients, concluded that concurrent CRT improves OS and progression-free survival with absolute benefits of 10% and 13%, respectively [44]. As expected, there was significantly greater acute hematological and gastrointestinal toxicity with concurrent CRT. Due to paucity of reporting on late toxicity, the impact of concurrent CRT on these effects was not adequately determined. Finally, treatment-related deaths were rare [44].

Kirwan et al. analyzed the acute and late toxicities seen in 19 RCTs comparing concurrent CRT with CT for locally advance uterine cervical cancer [36]. They found a significantly higher severe hematological toxicity (grade≥3) in the CRT arm with grouped hematological toxicity approximately nine times higher in CRT arm compared to CT arm (OR 8.7, 95% CI, 5.18–14.62, $P < 0.001$). In terms of specific hematologic toxicities, they found two-fold higher white cell toxicity and three-fold higher platelet toxicity in the CRT arm but no significant hemoglobin toxicity except with cisplatin based concurrent radiation. In terms of other acute toxicities, although gastrointestinal toxicity was twice as common in the CRT arm, there were no significant differences in genitourinary, neurological, or skin toxicities. Mortality was higher in the CRT arm as compared to CT (12 vs 2, respectively). Overall, only eight trials reported long-term toxicities, with seven showing no significant difference. A trial by Tseng et al. showed about 10% higher rate of overall long-term toxicity [38]. However, most experts believe that there is no difference in late toxicity with concurrent CRT as opposed to CT alone [20, 36].

Prostate Cancer

It has been shown that ADT used with radiation therapy for locally advanced (high-risk) prostate

cancer (extracapsular or node positive disease) improves biological and spatial cooperation [6] resulting in improved OS when compared to radiation therapy alone. This has been shown in many phase III RCTs, and here we will discuss a few selected trials of prostate cancer eliciting the beneficial effect of ADT combined with RT and the toxicities encountered with the same (see Table 6.5). The toxicity with adding ADT is primarily urinary and bowel related.

The European Organization for Research and Treatment of Cancer (EORTC) conducted a phase 3 trial, randomizing 415 patients with locally advanced prostate cancer (LAPC) to receive either ADT and RT versus RT alone [28, 48, 49]. In the combination arm, gonadotropin-releasing hormone agonist (GnRH-A) goserelin was administered starting on day 1 of RT and continuing for 3 years. There was significant improvement in the 10 years OS with combination therapy compared to RT alone (58.1% vs 39.8%, respectively, $p=0.0004$) [28]. In terms of toxicity, diarrhea was the only significant grade≥3 acute toxicity which was seen more commonly in the RT arm compared to combined therapy (11% vs 5%, respectively). The late toxicities were balanced between the two arms except for grade 1–3 incontinence seen more commonly in combined therapy arm (29% vs 16%, $P=0.002$). Of note, 19% patients developed adverse reactions (grade≤2) to ADT, most commonly hot flashes (9% patients) [48]. There was no QOL assessment on this study.

In the RTOG Trial 85–31, a total of 945 patients with LAPC were randomized to either GnRH-A after RT or RT alone. The GnRH-A was started after definitive irradiation (in the last week of radiation therapy) but continued indefinitely [29, 50, 51]. Updated analysis of this trial showed improved 10 years OS in the adjuvant arm as compared to control arm (49% vs 39%, respectively, $p=0.002$). There was no significant increase in cardiovascular mortality with adjuvant ADT [52]. The same results were seen in EORTC 22863 [28] There was no QOL reporting.

In the RTOG 96–01 trial, 818 men were randomized to either RT alone (arm A), RT plus 3 months of neoadjuvant ADT (arm B) or RT plus 6 months of neoadjuvant ADT (arm C). The ADT consisted of goserelin monthly injection (3.6 mg s/c) and flutamide (250 mg orally three times daily) in arm B and C, starting 2 months and 5 months before the administration of RT, respectively [30, 53]. The study showed decreased distant progression (0·49, 0·31–0·76; $p=0·001$), prostate cancer-specific mortality (0·49, 0·32–0·74; $p=0·0008$), and all-cause mortality (0·63, 0·48–0·83; $p=0·0008$) with 6-months of neoadjuvant ADT compared with RT alone. However, no benefit was noted with 3-months of neoadjuvant ADT. In patients treated with ADT there was worsening of bowel function, especially bowel frequency, by two grades that was seen more commonly with 6 months of ADT compared to 3 months (7.6% vs 4.4%, respectively). Treatment-related morbidity was not increased with ADT within the first 5 years after randomization (54). Increased urinary frequency was also seen more commonly with 6 months of ADT compared to 3 months (72.9% vs 62.8%, $P<0.02$) [54]. Flutamide was specifically associated with worsening of liver function and bowel-related side effects resulting in early discontinuation in 27% of patients in the 6-month ADT arm and 20% patients in the 3-month ADT arm [54]. Moreover, varying grades of delayed rectal (bowel frequency, bowel looseness, bowel pain, urgency, rectal blood, and inconvenience) and urinary symptoms (daytime frequency, nighttime frequency, urinary pain, urinary stream, and inconvenience) were seen in almost 80% of the patients. The urinary symptoms improved over the course of the first 4 years and had no clear correlation with the treatment allocation. However, ADT was associated with a reduction in prevalence and time to occurrence of bowel related symptoms, which was statistically significant only for 3-month arm [55].

Another study that evaluated the efficacy of neoadjuvant ADT plus RT as compared to RT alone was RTOG 86–10. The trial design and treatment dose and schedules were same as RTOG 96–01 arm A and B [56]. This trial showed a non-significant improvement in 10-year OS in arm B compared to arm A (43% vs 34%, respectively; $P=0.12$). There was no significant difference in

grade 3 and 4 acute or late toxicities between the two arms. The grade ≥3 acute toxicity rate was less than 5% in both arms however grade ≥3 late toxicities were reported to be higher in both arms (about 8% patients) [56].

Rectal Cancer

Although there is still room for further study and clearly some controversies remain, we have seen tremendous improvement in the treatment of locally advanced rectal cancer (LARC; cT3 or cT4 and cN0 or cN+disease) in the last two decades. This is mainly because of the widespread adoption of combined modality therapy and the improved understanding of the optimal timing of this intervention relative to surgery. Two landmark trials, EORTC 22921 and FFCD 9203, and a Polish study, compared preoperative chemoradiotherapy with preoperative RT only and are discussed below (see Table 6.6).

The EORTC 22921 was a 2×2 factorial trial, designed to address the benefit of preoperative CRT over RT alone and the role of adjuvant CT [4, 57, 58]. In this trial, 1011 LARC patients were randomized to preoperative RT (45 Gy in 25 fractions during 5 weeks), preoperative concurrent CRT with infusional 5-FU and leucovorin (5-FU/L) administered during the first and fifth week of RT, preoperative RT with postoperative CT (5-FU/L×4 cycles), or preoperative CRT with postoperative CT (5-FU/L×4 cycles). Surgery was performed within 3–10 weeks after completion of RT. There was no significant difference in 5-year OS or DFS between the concurrent CRT arm and RT alone arm; however, a significantly lower local recurrence rate (8.7% vs 17.1%, respectively) and higher pCR rate (13.7% vs 5.3%) was observed favoring preoperative concurrent CRT. The benefits came at the cost of a higher rate of grade≥3 acute toxicity in the preoperative CRT arm compared to RT arm (13.4% vs 7.4%, respectively; see Table 6.6). There was no difference in the rates of late toxicity (actual numbers not reported).

The Fe´de´ration de Francophone de Cance´rologie Digestive FFCD 9203 Trial randomized 733 LARC patients to either receive preoperative RT or concurrent CRT followed by surgery (within 3–10 weeks) and then adjuvant CT with 5-FU/L regimen [17, 59]. Of note, the dose and schedule of preoperative and postoperative CT and RT was same as in the EORTC 22921 trial. There was no significant difference in the OS or DFS, but as before the local recurrence rate was significantly lower in the CRT arm compared to RT alone (8.1% vs 16.5%, $p=0.004$). However, once again there was a significantly higher rate of grade≥3 acute (11.4% vs 3.6%, $p<0.001$) and late toxicity (14.6% vs 2.7%, $p<0.05$) in the preoperative CRT arm (see Table 6.4).

Lastly, the Polish study randomized 312 patients with LARC to either preoperative concurrent CRT with 5-FU/L or RT alone followed by surgery and then adjuvant CT with 5-FU/L [60]. Again, the dose and schedule of preoperative and postoperative CT was same as in EORTC 22921 trial, but the radiation dose and schedule was different in the concurrent CRT arm (50.4 Gy×28) compared to RT alone arm (25 Gy×5). As expected, there was no improvement in OS or DFS, but pCR rates were improved with preoperative concurrent CRT. The acute grade ≥3 toxicity was higher with combined modality therapy then RT alone (18.2% vs 3.2%, respectively, $p<0.001$). There was no significant difference between the rates of late toxicity.

A subsequent meta-analysis of EORTC 22921, FFCD 9203, and the Polish Trial showed an improvement in pCR (11.8% vs 3.5%) and local control (16.5% vs 9.4%) with preoperative concurrent CRT as compared to radiation therapy alone [61]. The disadvantages of combined modality therapy were higher rate of grade≥3 toxicity (15% vs 5%) without any increase in postoperative morbidity or mortality. Finally, there was no significant impact on OS or disease-free survival, and it thus remains controversial whether improvement in pCR eventually translates into any survival advantage.

Table 6.6 Selected chemoradiation trials in rectal cancer

Study (rectal cancer)	Stage	*N*	Intervention	Results					Toxicity ($G \geq 3$)	
				OS (%) 5 years	DFS (%) 5 years	LR (%) 5 years	SSS (%)	pCR (%)	Acute (%)	Late (%)
Bosset et al. [4] EORTC 22921	II and III	1011	RT (45 Gy × 25)—S	64.8* in preop RT groups vs 65.8 in preop CRT groups $p=0.84$	54.4 in preop RT groups vs 56.1 in preop CRT groups $p=0.52$	17.1	50.5 in preop RT group	5.3 in preop RT group	7.4 in preop RT group	No significant difference (numbers not reported)
			CRT (45 Gy × 25+ 5-FU/L)—S			8.7				
			RT (45 Gy × 25)—S—C (5-FU/L)	67.2* in adj. chemo groups vs 63.2 in no adj. chemo groups $p=0.12$	58.2 in adj. chemo groups vs. 52.2 in no adj. chemo groups $p=0.13$	9.6	52.8 in preop CRT group $p=0.47$	13.7 in preop CRT group	13.9 in preop CRT group	
			CRT (45 Gy × 25+ 5-FU/L)—S—C (5-FU/L)			7.6 $p=0.002$				
Bujko et al. [60] Polish Trial	II and III (T3 or T4)	312	CRT (50.4 Gy × 28+ 5-FU/L)—S—C (5-FU/L)	66.2* (4-year)	55.6	14.2	58	16.1	18.2	10.1
			RT (25 Gy × 5)—S—C (5-FU/L)	67.2* $p=0.96$	58.4 $p=0.82$	9 $p=0.17$	61.2 $p=0.57$	0.7	3.2 p 0.001	7.1 $p=0.36$
Gerard et al. 2006 FFCD 9203	II and III	733	CRT (45 Gy × 25+ 5-FU/L)—S—C (5-FU/L)	67.4*	59.4	8.1	No difference (as in Polish trial)	11.4	14.6	-
			RT (45 Gy × 25)—S—C (5-FU/L)	67.9* $P=0.68$	55.5	16.5 $p=0.004$		3.6 ($p<0.001$)	2.7 P 0.05	-

CRT chemoradiotherapy, *RT* radiotherapy, *Gy* Gray (unit), *FU* fluoruracil, *EORC* European Organization for Research and Treatment, *FFCD* Fédération Francophone de Cancérologie Digestive, *OS* overall survival, *DFS* disease-free survival, *pCR* pathological complete response, *LR* local recurrence, *SSS* sphincter saving surgery
* $p>0.05$

Anal Cancer

Anal cancer is another perfect example of the positive interaction of CT and radiation resulting in a good cure rate and the elimination of surgery from the multimodality approach [6]. Nigro and collegues revolutionized the treatment of anal cancer when they first published a preliminary report of three patients treated with concurrent CRT with 5-FU and mitomycin C and noticed complete disappearance of tumor [62]. Subsequently, there have been many phase III RCTs to confirm and refine the CRT regimen as discussed below (see Table 6.7).

The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) conducted the first of these trials known as Anal Cancer Trial-1 (ACT-1) [5, 63]. A total of 585 patients were randomized to either CRT with 5-FU and mitomycin C or RT alone. The 5-FU was given as 750 mg/m^2 per day over 5 days during the first and last weeks of radiation and mitomycin (12 mg/m^2 on day 1 only). The primary endpoint was local failure and was found to be significantly lower in the CRT arm as opposed to RT (36% vs 59%, respectively; $p<0.0001$). However, this did not translate into an OS benefit (65% vs 58%, respectively; $p=0.25$) [5]. Addition of CT did not result in treatment delays or lower treatment completion rates. Compared to RT alone, the CRT arm had significantly higher acute morbidity (48% vs 38%) and mortality (6 vs none). The latter resulted in a protocol amendment for dose reduction of mitomycin C in patients over 80 years to 8 mg/m^2 along with close hematological monitoring and antibiotic prophylaxis. The acute toxicity was dominated by hematological adverse effects besides dermatological, gastrointestinal, and genitourinary complications (see Table 6.7). The rates of late toxicity were the same between the two arms. There was no QOL assessment in this trial.

EORTC conducted the second large phase III trial randomizing 110 patients to either combined CRT or RT alone [64]. The CT dose and schedule was the same as in ACT-1 except the mitomycin dose was 15 mg/m^2. Compared to RT alone, CRT resulted in improvement of the CR rate (80% vs 54%) as well as locoregional control by 18% ($p=0.02$). Again there was no difference in OS. The authors reported no significant difference in the acute or late toxicity between the two arms. However, it should be noted that there were two deaths in the concurrent CRT arm secondary to infectious complications of grade IV hematological toxicity. The hematological toxicity was believed to be due to overdosage of CT in one patient and was complicated by severe mucositis in the other patient.

Due to significant hematological toxicities of mitomycin, attempts have been made to improve the CT by replacing mitomycin with cisplatin. A recent study by the US Gastrointestinal Intergroup and RTOG randomized 682 patients to receive concurrent CRT with either 5-FU plus mitomycin (arm A) or 5-FU plus cisplatin [65]. The primary end point was DFS and was not statistically different between arm A and B (60% vs 54% respectively; $P=0.17$). There was no difference in the rate of acute grade$\geq$3 nonhematologic toxicity (74% in both arms). However, there was significantly more grade$\geq$3 hematological toxicity in arm A compared to arm B (61% vs 42%; $P<0.001$). Finally there was no difference in the rates of severe long-term toxicity (about 11% in both arms) [65].

Bladder Cancer

Radical cystectomy remains the gold standard for muscle invasive bladder cancer (MIBC) with very few exceptions. Attempts were undertaken in 1990 to establish an organ-preserving strategy for the urinary bladder on the lines of anal, breast, esophageal, and laryngeal cancer [6]. Many prospective trials were conducted by the RTOG in patients with MIBC who were not candidates of radical cystectomy. The treatment approach was usually TURBT followed by concurrent CRT, and depending upon the response rate, either radical cystectomy or consolidative CRT. All together, only 415 patients entered in these trials and the 5-year OS was approximately 50% with organ preserving multimodality regimen, which is the same as seen in surgical series [3, 6].

Table 6.7 Selected chemoradiation trials in anal cancer

Study (anal cancer)	Stage	*N*	Intervention	Results					Toxicity (*G*≥3)	
James et al. [5] and Northover et al. [63] ACT-1 UKCCCR [5 and 63]	T1–T4	292	CRT (45 Gy × 25 + 5-FU)	65 (3 year)		36	-	39	48	No difference
		285	RT (45 Gy × 25) + boost (15 Gy EB or 25 Gy B)	58		59	-	30	38.5	
Bartelink et al. [64] EORTC	T3–4 or N1–3	51	CRT (45 G × 25 + 5-FU + Mitomycin)	56	Improved in CRT arm		-	80	GI-10 Skin-29	Similar
		52	RT (45 Gy × 25) + Boost (15–30 Gy)	56	$P = 0.03$		-	54	GI-4 Skin-26	
Ajani et al. [65] RTOG 98–11		341	CRT (45 Gy × 25 + 5-FU + Cisplatin)	70	54	33	-	-	Heme-61 Non-Heme-74	Similar
		341	CRT (45 Gy × 25 + 5-FU + Mitomycin)	75 $p = 0.1$	60 $p = 0.17$	25	-	-	Heme-42 None Heme-75	

CRT chemoradiotherapy, *RT* radiotherapy, *Gy* Gray (unit), *FU* fluoruracil, *ACT*-1 UKCCCR Anal Cancer Trial, *UKCCCR* United Kingdom Co-ordinating Committee on Cancer Research, *EORC* European Organization for Research and Treatment, *EB* external beam, *GI* gastrointestinal

Table 6.8 Selected chemoradiation trials in bladder cancer

Study (bladder cancer)	Stage	*N*	Intervention	Results					Toxicity ($G \geq 3$)	
				OS (%) 5 years	DFS (%) 5 years	LR (%) 5 years	Radiation type	pCR (%)	Acute (%)	Late (%)
James et al. [66] BC2001	T2–4a (2×2 factorial design with second randomization to dose of RT)	182	CRT with MMC (12 mg/m^2 i.v. bolus) day 1 of RT and 5-FU continuous infusion at 500 mg/m^2/24 h for 10 days	63 (2-year)	71 (2-year LRDFS)	-	64 Gy×32 fractions (f) or 55 Gy×20 fractions (as per centre policy)	-	8.5	2.2
		178	RT	58 $p=0.1$	58 $p=0.01$	-		-	5.2 $p=0.2$	2.3 $p=0.95$

CRT chemoradiotherapy, *RT* radiotherapy, *LRDFS* locoregional disease-free survival, *MMC* mitomycin, *Gy* Gray (unit), *DFS* disease-free survival, *LR* local recurrence, *OS* overall survival, *FU* fluoruracil, *pCR* pathological complete response

Overall, these data support the use of trimodality therapy as an alternative to radical cystectomy for patients who cannot, or for personal reasons do not, want to undergo radical cystectomy and urinary diversion [3]. It must be noted that trimodality therapy is not meant to replace radical cystectomy but can be offered as an alternative.

A recent phase III RCT was reported with 360 MIBC patients randomized to either concurrent CRT with 5-FU (500 mg/m^2/day on days 1–5 and 16–20) and mitomycin (12 mg/m^2 on day 1) or RT alone [66]. The primary end point was survival-free of locoregional disease (see Table 6.8). At 2 years, rates of locoregional DFS were higher with combined modality therapy than RT alone (67 % vs 54 %, respectively; $P=0.03$). The 5-year OS was also improved with CRT (48 % vs 35 %, respectively; $P=0.16$). In terms of acute toxicity, concurrent CRT was associated with more grade ≥ 3 adverse events that were mainly gastrointestinal (36.0 % vs 27.5 %, respectively; $P=0.07$). The overall late toxicity was also more in the CRT arm compared to RT alone (15.7 % vs 8.3 %, respectively, $P=0.07$). The authors concluded that concurrent CRT with 5-FU and mitomycin C improves locoregional control of bladder cancer as compared to RT alone without any significant toxicity [66].

Conclusions and Future Directions

Clearly, the use of concurrent CRT improves the OS in many pelvic malignancies with an increase in acute toxicities. There are limited data on long-term toxicity and QOL in most combined CRT trials. As of now, there is no clear evidence that giving CT with radiation results in either under dosing of radiation or treatment prolongation. Importantly, there is a cost involved in the management of complications arising from concurrent therapy as well as cost from psychosocial impact on the patient from such complications. Future trials should focus on collecting thorough and long-term toxicity data along with QOL surveys to improve our understanding of toxicities inflicted by combined CRT. Further, the use of biologically driven and individualized treatment plans appears to be a likely evolution of the current expansion of genetic and molecular data in all cancers. This may well impact the next generation of studies, and it is hoped will lead to improved efficacy with diminished toxicity. Finally, we need to move away from the description of post combined modality toxicities as radiation related. Term such as radiation enteritis need to be limited to patients that only receive radiation—all other toxicities are treatment related.

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Radiation Cystitis: Acute and Chronic

7

Surendra B. Kolla and Atreya Dash

Introduction

Radiotherapy (RT) is a standard treatment option and an essential component of multimodal organ sparing treatment for various malignancies in the pelvis including cancers of the prostate, uterine cervix, rectum, and urinary bladder. Malignancies originating in these organs constitute up to 18% of all cancers [1]. Due to its anatomic location, the urinary bladder is frequently exposed to radiation during treatment for pelvic cancers giving rise to a variety of urinary adverse effects (AEs). With about 360,000 Americans diagnosed with cancers of pelvic organs each year and about half of them receiving RT [2], the burden of these AEs is significant and will increase in importance as the long-term survival of these patients improves.

Pathogenesis of Radiation Injury of Bladder

Radiobiological studies in mice demonstrate a triphasic response of the murine urinary bladder to radiation. The early or acute phase occurs up to 4–6 weeks after treatment. This is followed by a latent period, the duration of which is inversely related to the amount of radiation dose received and can be 10 years or longer [3–5]. This is followed by a progressive and irreversible late phase characterized by bladder wall fibrosis leading to a decrease in bladder storage capacity. It is believed that the human bladder also responds to radiation in a similar triphasic manner (Fig. 7.1).

Normal bladder urothelium consists of several layers of polyhedral (transitional) cells divided into three main layers from surface to base: umbrella, intermediate, and basal cells. Basal cells divide to form intermediate cells and intermediate cells fuse to form umbrella cells. Under normal conditions, the rate of turnover of urothelial cells is very slow ranging anywhere from 6 weeks to 1 year in the mouse bladder [5, 6]. The urothelium acts as a protective barrier that allows urine to be stored for a longer time while maintaining initial concentration.

The acute effects of radiation on urothelium are characterized by mucosal edema, hyperemia, and inflammation. Using measurements of urinary frequency and cystometry, Stewart et al. noticed that the acute phase of radiation-induced damage manifests as a dose-dependant increase in urinary frequency. Data on cellular and molecular mechanisms underlying radiation effects in the murine urinary bladder suggest that the acute effects are associated with changes in urothelial protein expression such as Uroplakin III, CD 18, CD 44, or syndecan [7]. It is hypothesized

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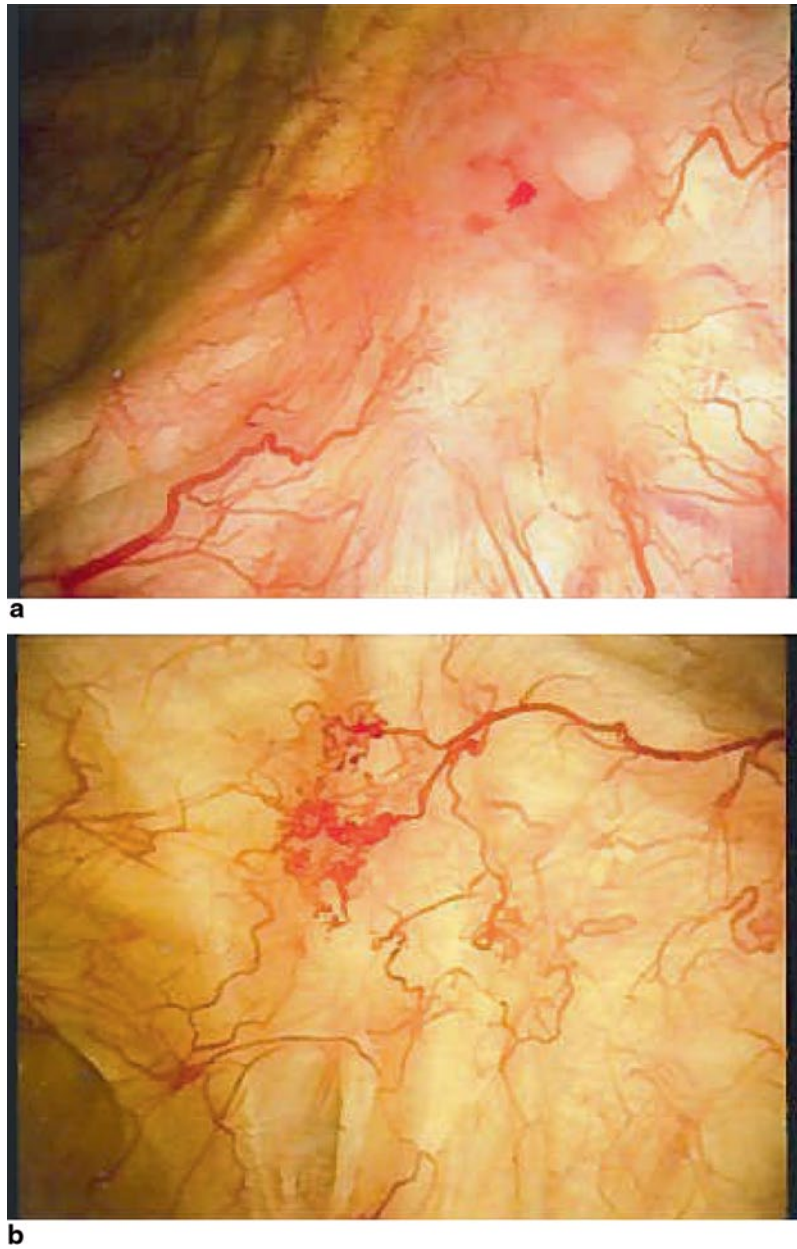

Fig. 7.1 **a** and **b** Cystoscopic view of radiation cystitis

that these proteins maintain the integrity of the normal urothelial barrier to urine. Altered expression of these proteins leads to disruption of the urothelial barrier with increased exposure of underlying tissue to urine and its toxic solutes contributing to irritative voiding symptoms. Experimental studies also indicate that altered prostaglandin metabolism, with increased cyclo-oxygenase-II expression which regulates the tone of the bladder wall, results in increased baseline

tone of the detrusor muscle corresponding to a reduction in bladder capacity. [8]. Unlike other epithelia, urinary epithelial cell depletion is not noted in the acute phase of radiation damage due to the very long turnover time of the urothelium. However, the presence of infection may complicate this early response, which may then progress to desquamation and ulceration.

Late damage is irreversible and is characterized by epithelial denudation, and ulceration with focal hyperplasia and fibrosis [9]. Kraft et al. showed that transforming growth factor-β (TGF-β) is overexpressed in the mouse urinary bladder between days 90 and 360 after radiation [10]. The increased expression was associated with increased collagen deposition in the bladder wall; however, these changes did not correlate with the functional radiation response, and hence are considered a secondary effect to organ damage rather than a primary radiation effect. In contrast, a clear correlation was noted between changes in bladder function and urothelial changes. The latter presents as focal urothelial denudation and a hyperproliferative response [10]. Jaal et al. noted that these late effects appear to be correlated with increased urothelial expression of intercellular adhesin molecule 1 (ICAM-1) [11].

Radiation-induced damage is also observed in the bladder vasculature. Edema of the vascular endothelium is noted by approximately 3 months following radiation. By 6 months to 2 years, endothelial cell proliferation, perivascular fibrosis, and vascular occlusion occur. Focal bladder wall ischemia leading to bladder wall fibrosis can be seen in severe cases [12]. The loss of balance between endothelial cell proliferation and small vessel maturation is believed to cause development of telangiectasia [13]. These thin-walled tortuous abnormally dilated vessels are prone to rupture and bleeding, resulting in microscopic or gross hematuria. Radiation effect is also noted in the smooth muscle layer of the bladder in the form of loss of smooth muscle, infiltration of fibroblasts, and increase in collagen deposition contributing to loss of bladder compliance and capacity [14].

Clinical Manifestation of Radiation Bladder Injury

The clinical manifestations of radiation injury to the bladder can be classified into acute and late reactions. Acute reactions occur within 3 months after radiation exposure and subside within several weeks after radiation therapy. Late reactions are those that occur at least 3 months after radiation exposure.

Acute Toxicity

Acute lower urinary tract symptoms due to radiation can be irritative or obstructive. Irritative symptoms include urinary frequency, urgency, dysuria, and nocturia. Obstructive symptoms include weak urinary stream, hesitancy, and incomplete bladder emptying or complete bladder outlet obstruction with overflow incontinence. The reported incidence of acute radiation toxicity varies from 20 to 80% [15–17]. Such wide range in incidence rates reflects the differences in treatment techniques, radiation dose, and treatment fields for various pelvic malignancies. Due to the frequency of such symptoms and the fact that most subside with conservative measures, they are not usually reported as complications but regarded as acceptable outcome to RT. The Radiation Therapy Oncology Group (RTOG) has defined scoring criteria for qualitative assessment of the degree of acute radiation morbidity (Table 7.2). [18] Acute toxicity is scored from day 1 to 90.

Late Toxicity

Late effects from pelvic RT are the result of bladder fibrosis and microvascular alterations resulting in decreased bladder capacity and fragile bladder mucosa. In contrast to acute toxicity, late manifestations tend to be chronic and irreversible. Depending on the dose and treatment plan of the pelvic radiation, late toxicity can involve

Table 7.1 RTOG radiation morbidity scoring criteria [18]

Grade	RTOG-acute	RTOG-chronic
0	No change	None
1	Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication	Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)
2	Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Phenazopyridine hydrochloride)	Moderate frequency and dysuria; generalized telangiectasia; intermittent macroscopic hematuria
3	Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain, or bladder spasm requiring regular, frequent narcotic/gross hematuria with/without clot passage	Severe frequency and dysuria; severe telangiectasia; frequent hematuria; reduction in bladder capacity (< 150 cc)
4	Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration, or necrosis	Necrosis/contracted bladder (< 100 cc)
5	Death	

RTOG Radiation Therapy Oncology Group

Table 7.2 CTCAE (Cancer Therapy Evaluation Program) version 4.0: A systematic grading system for adverse events of cancer therapy [19]

Grade	CTCAE
0	No change
1	Asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated
2	Moderate, local, or noninvasive intervention indicated; limiting instrumental activities of daily living (ADL)
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death

the entire bladder or a portion of bladder. In general, the time to onset of late toxicity typically is 2–3 years after treatment. Patients with a severely contracted bladder present with debilitating urinary frequency and incontinence. Another chronic manifestation of pelvic RT is late recurrent hematuria or hemorrhagic cystitis, defined as acute or insidious diffuse vesical bleeding that can sometimes be life threatening. It is important to distinguish the side effects of radiation from the effects of underlying disease as well as from the effects of previous pelvic surgery and chemotherapy. It is also important to rule out secondary malignancies such as urothelial carcinoma or recurrence of the primary tumor. The RTOG has published criteria to grade late effects of radiation to the bladder; noting that late effects tend to accrue with time and that long-term follow-up is necessary to accurately assess the late effects of radiation (Table 7.1) [18].

Scoring Systems

Several validated grading systems have been proposed to rate the bladder toxicity secondary to radiation. The main use of these scoring systems is to achieve standardization among different studies on this subject. In 1995, working groups of the RTOG and European Organization for Research and Treatment of Cancer (EORTC) developed the Late Effects in Normal Tissue subjective, objective, management and analytic (LENT-SOMA) scales in an attempt to provide a comprehensive system for assessment and recording of RT-related morbidity [18] (Table 7.1). In 2003, the National Cancer Institute (NCI) published the Common Terminology Criteria for Adverse Events (CTCAE) [19], which incorporated the LENT-SOMA items with early and late effects contained in one system (Table 7.2). An RTOG grading system specifically addressing the severity

Table 7.3 RTOG/EORTC grading of hematuria events [20]

Grade	Acute hemorrhagic radiation cystitis (RTOG scale)	Late hemorrhagic radiation cystitis (RTOG/EORTC scale)
1	NA	Minor telangiectasia (microscopic hematuria)
2	NA	Generalized telangiectasia (macroscopic hematuria)
3	Gross hematuria with or without clot passage	Severe generalized telangiectasia (macroscopic hematuria)
4	Hematuria requiring transfusion	Severe hemorrhagic cystitis
5	Death from uncontrolled hematuria	Death from uncontrolled hematuria

EORTC European Organization for Research and Treatment of Cancer, *RTOG* Radiation Therapy Oncology Group

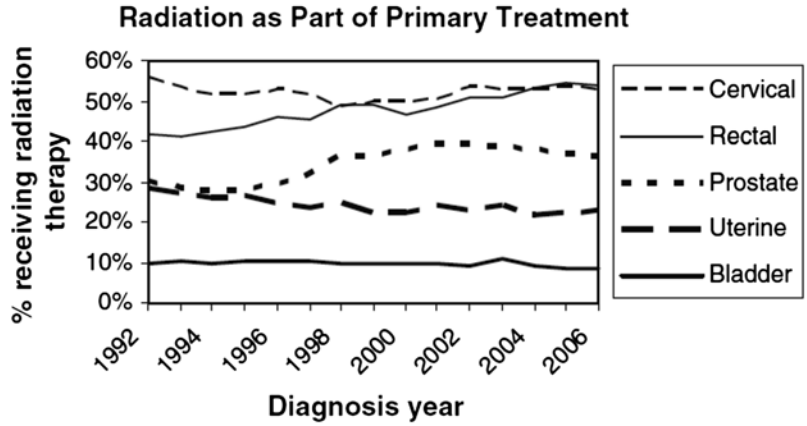

Fig. 7.2 Rates of radiotherapy (EBRT or BT) within 6 months of diagnosis of pelvic malignancy. Note the significant rise in RT rates among prostate and rectal cancer patients. (*Raw data compiled from SEER* (*Surveillance Epidemiology and End Results*) *public use file*. EBRT = External Beam Radiation Treatment; BT = Brachytherapy; RT = radiotherapy [2]

of hematuria has also been proposed (Table 7.3) [20]. This is now seen as the preferred platform for documenting toxicity in clinical trials. In addition, the American Urological Association's symptom score can be used to grade the severity of urinary symptoms in these patients. Scores of 0–7, 8–19, and 20–35 signify mild, moderate, and severe symptoms, respectively [21].

Extent of the Problem

Radiation Therapy and Prostate Cancer

Prostate cancer is the most common pelvic malignancy in men. According to a review of the Surveillance, Epidemiology, and End Results (SEER) database, 37% of prostate cancer patients were treated with RT within 6 months of diagnosis, with 26% receiving External Beam Radiation Treatment (EBRT), and 15% Brachytherapy (BT) (Fig. 7.2) [2]. The treatments were delivered alone or in combination. Urinary AEs following EBRT for prostate cancer are varied. In general, the incidence of persistent grade 1 symptoms (90 days after RT) is reported to be 20–43% with a follow-up of up to 10 years [22, 23]. The incidence of late grade 2 AEs is reported to be 7–19% [22, 23]. However, these symptoms continue to accrue with time: the actuarial risk of genitourinary AEs of grade 2 or greater was 15% following three-dimensional conformal radiation therapy (3D-CRT) at 3 years and 19% by 5 years [24]. Of those who develop mild-to-moderate AEs, many appear to resolve, either spontaneously or with treatment.

Grade 3 urinary AEs occur in 5–13% after EBRT [25, 26]. Hemorrhagic cystitis is the most common grade 3 complication of prostate RT. A study of prostate cancer patients treated with

high dose of radiation suggested that as many as 50% will have had one episode of hematuria by 15 years [27]. With advancements in technology for radiation delivery resulting in decreased radiation to adjacent organs, radiation oncologists were able to increase delivered dose to the target organ resulting in better tumoricidal activity but also increased damage to the target organ. With short follow-up, grade 4 urinary AEs (life-threatening hematuria or necrotic/contracted bladder) appear to be rare (1%) after BT or EBRT; however, with extended follow-up, the rate increases to 2% after EBRT or 3.3% after BT [28]. A SEER-Medicare examination showed that within 2 years of BT, 10% had a procedure performed for a urinary AE [29].

Radiotherapy and Bladder Cancer

Late grade 2 AEs with EBRT for bladder cancer have been reported to occur in 18–27% [30]. In a study by Fokdal et al., 261 patients received 60 Gy of EBRT. With a median follow-up time of 29 months (range 18–103), 45% registered changes in their bladder habits and 14% reported moderate-to-severe impact of the treatment on their bladder function [31]. The cumulative incidence of grade 3 or higher urinary AEs after bladder RT is 6–17% with follow-up ranging from 29 to 76 months [31]. Urinary blood clots can occur in 18%, incontinence in 20%, and urinary frequency more than once an hour in 50% at 3 years [32]. Two series report the incidence of grade 3–4 AEs collectively as 14.5 and 25%; when separately recorded, grade 4 AEs occur in 0–3% [30, 33]. It is important to realize that any hematuria that occurs following RT for cancer of the bladder must initially be assumed to be due to disease recurrence.

Radiotherapy and Colorectal cancer

While surgical resection is the most common treatment for colorectal malignancy, preoperative external beam RT has been shown to have survival benefit in rectal cancer, particularly in patients with T3 disease or local lymphadenopathy. Urinary AEs have not been properly evaluated in the setting of RT for rectal cancer. The only trial that describes urinary AEs mentions "bladder problems" in 2–4% [34].

Radiotherapy and Cervical Cancer

Radical hysterectomy and primary radical RT are equivalent in Stage IB to IIA disease, and RT is integral to the treatment of more advanced disease (CIIB). Radical RT is delivered as 40–50 Gy EBRT plus 20–40 Gy high dose rate BT (HDR-BT) for total doses to the cervix of up to 90 Gy. The risk of developing grade 1 and 2 AEs following RT for cervical cancer has been reported to be 28% and increases to 45% at 5 years [35]. Patients who survived 3 years after treatment had a 7.7% probability of a major (grade 3) complication from RT. At 5 years, the risk of a major complication was 9.3% and there was a subsequent continuous risk of 0.34% per year, resulting in an actuarial risk of major complications of 11.1% at 10 years, 13% at 15 years, and 14.4% at 20 years [35–37]. Ureteral stricture and radiation cystitis were the most common urinary complications.

In summary, the majority of urinary complications from pelvic radiation are low grade (grade 1–2), with grade 3 or higher complications being less common. Urinary adverse events tend to accrue with time. Severe late urinary complications are more common with prostate, bladder, and cervical RT. This could be due to higher radiation doses used for treatment (sometimes with combination of BT + EBRT) as well as the anatomic proximity of these tumors to the lower urinary tract. Late urinary adverse events tend to be detected more often after prostate or bladder RT as these patients continue to be followed by urologists. The type of long-term complications varies with primary tumor type for which radiation was administered—urethral stricture after prostate BT, bladder hemorrhage and necrosis after bladder RT, and ureteral strictures most common after cervical RT.

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Acute and Chronic Radiation Enteropathy

8

Amir Patel and Eli D. Ehrenpreis

Introduction

The small intestine is a common site of injury in patients undergoing abdomino/pelvic radiation therapy (RT). Injury to the small intestine can follow RT for thoracic, abdominal, and pelvic malignancies. Injury can occur early or late, can be progressive, and may lead to a variety of clinical consequences depending upon the timing and extent of injury. Early or acute reactions, occurring during or right after radiation treatment (within 2–6 weeks), can give rise to diarrhea, nausea, gastrointestinal (GI) hemorrhage, and abdominal pain. Chronic reactions (>90 days to years after treatment) can result in bleeding, ulceration, stricture formation, and bowel obstruction. Toxicity to the GI tract frequently limits the dose of radiation that can be delivered for many tumor types. Understanding how to recognize, prevent, and treat radiation enteropathy is important for clinicians in a variety of specialties. This chapter discusses the pathophysiology of early and late responses of the small intestine to radiation exposure. The diagnosis and management of these conditions are also reviewed.

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Pathogenesis

Acute Radiation Injury

The epithelial lining of the small intestine has a high proliferative rate, making it extremely susceptible to damage from radiation. The intestinal lining is normally replaced every 3–5 days. Radiation affects intestinal stem cells within the crypts of Lieberkuhn. Stem cell damage, as a result of direct radiation injury or occurring indirectly from microvascular damage, causes inflammation with subsequent edema. Villous atrophy and malabsorption may follow. Histologic changes can be seen within hours or days. A few weeks after radiation exposure, infiltration of leukocytes with microabscess formation may be present. Acute injury can lead to GI hemorrhage as a consequence of ulcer formation and penetration into local vasculature. Malabsorption of nutrients results from villous atrophy within all parts of the small intestine and reduced bile salt absorption in affected ileum. Furthermore, impaired digestion of lactose from loss of lactase enzyme from microvillous destruction can aggravate symptoms of malabsorption. Altered gut motility following RT may complicate the

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clinical symptoms [1]. Small intestinal bacterial overgrowth may compound these problems.

As a result of these processes, patients with acute radiation enteropathy can develop diarrhea, abdominal pain, nausea, vomiting, distension, weight loss, and GI bleeding. Radiation-induced diarrhea often appears during the third week of a course of fractionated RT, with reported rates of 20–70% [2]. In general, symptoms subside and pathologic changes spontaneously resolve 2–6 weeks after completion of RT [3]. However, there is evidence suggesting that patients who develop acute small intestine toxicity are at higher risk for chronic radiation toxicity [4].

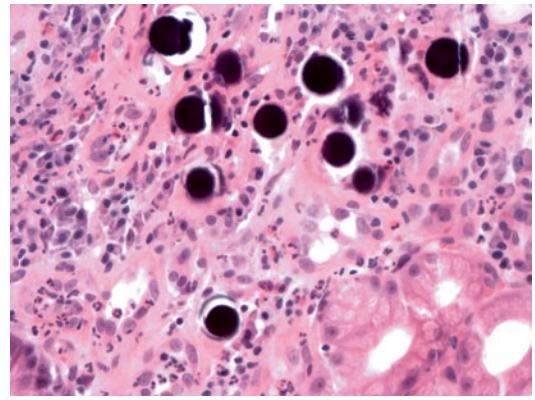

Fig. 8.1 Histopathology revealing gastritis with foveolar hyperplasia, vascular ectasia, granulation tissue, and scattered yttrium 90 selective internal radiation microspheres

Chronic Radiation Injury

Chronic radiation enteropathy generally occurs as a response to vascular changes caused by radiation injury, including progressive occlusive vasculopathy, collagen deposition, and fibrosis. Telangiectasia formation, an important complicating factor in the condition, is believed to occur as a secondary response to decreased tissue oxygenation and perfusion. Ongoing ischemic injury causes obliteration of vessel walls of small arterioles, enhancing ischemia [5]. Lymphatic damage and constriction of the lymphatic channels, further contribute to mucosal edema and inflammation [6]. Histologically, mucosa atrophy, atypical hyperplastic glands, and intestinal wall fibrosis is found [7]. As a consequence, tissue hypoxemia, mucosal ulceration, and fibrosis may follow. Intestinal stricturing, fistulization, and abscess formation are serious complications of these processes. Intestinal perforation may occur from tissue necrosis and deeply penetrating ulcers. Further descriptions of these processes are found in Chap. 5.

Symptoms and signs of chronic radiation enteropathy include diarrhea, abdominal pain and distension, anemia, and nutrient deficiencies. Late radiation injury to the small intestine occurs at a median of 6–12 months following RT, though it can appear years later [8]. A review of 20 randomized trials (with the largest including 632 patients receiving adjuvant RT for rectal cancer) was performed by Ooi et al. They reported a varied prevalence for severe long-term complications (including radiation enteropathy, small bowel obstruction, and rectal strictures) ranging from 1.2% to as high as 15% [9]. Severe chronic radiation enteropathy has a negative effect on long-term prognosis with a mortality rate of approximately 10% over an average of 10 years [10–16].

There have been case reports of microsphere selective internal radiation (SIR) causing acute and chronic radiation enteropathy as well [17]. SIR therapy with yttrium 90 microspheres is increasingly used as an alternative therapeutic modality for patients with inoperable liver tumors. During administration of microspheres via the hepatic artery branches, some may on occasion be misdirected and be caught in the capillary bed of the duodenum and/or stomach. In the aforementioned study, three patients who received SIR developed SIR-microsphere-induced gastroduodenitis. Cases occurred 10 days to 5 months after treatment. On pathology, mucosal ulceration, epithelial changes, glandular cystic dilatation, and epithelial flattening are seen (Fig. 8.1). As a result of the increased use of SIR microspheres, awareness of this potential complication is imperative (see Chap. 5. Pathology of Radiation Effects on Healthy Tissues in the Pelvis).

Risk Factors

Some patients have increased susceptibility to radiation enteropathy. However, late bowel injury is generally multifactorial. It is uncommon to have a small bowel injury in preoperative rectal or cervical cancer patients, but very common in postoperative patients. Given that there are a number of risk factors (medical comorbidities and anatomical/surgical comorbidities), any injury after multimodality cancer therapy should be considered "treatment related," and not solely based on radiation toxicity itself [18]. An example of this is seen in patients with small bowel toxicity after receiving 5-fluorouracil (5-FU) and pelvic radiotherapy. Although 5-FU is known to cause GI comorbidity [19], it is common to describe chemoradiation-induced small bowel toxicity as radiation enteropathy. One can argue, however, that the correct term should be "treatment-related enteropathy."

Besides medication, medical comorbidities may also increase the risk for radiation enteropathy and these include diabetes, hypertension, and cardiovascular disease. The risk is higher in these patients due to preexisting vascular damage or occlusion [20]. Radiation damage accelerates underlying vascular disease by increasing the severity of endarteritis and ultimately, tissue fibrosis. Patients with collagen vascular disease and inflammatory bowel disease also have a higher risk of acute as well as chronic radiation-induced injury. These conditions and their associated small intestinal pathology result in poorer GI tolerance to RT [21–23].

Anatomical variation also increases a patient's risk for treatment-related enteropathy. Women, older patients, and thin patients may have augmented volumes of the small intestine in the pelvic cul-de-sac, increasing the probability of radiation injury following treatment for pelvic malignancies [24]. Furthermore, patients with a history of pelvic inflammatory disease or endometriosis also appear to be at a higher risk of small intestinal injury [25, 26]. In addition, patients with a history of previous intra-abdominal surgery or peritonitis are especially susceptible, as immobility and restriction may cause areas of the small intestine affected by adhesions to be consistently exposed to higher radiation fractions [27, 28].

Effects of Radiation Dosage

The volume of radiation given and other risk factors, most importantly surgery, total dose, treatment time, and technique of pelvic irradiation all influence the likelihood of occurrence of small intestinal damage. Patients can generally receive 45–50 Gy in 1.8–2 Gy daily fractions to a pelvic field without significant bowel toxicity [29]. For postoperative patients, radiation of 45–50 Gy over 5 weeks is associated with an approximate 5% incidence of small bowel obstruction requiring surgery, while at doses greater than 50 Gy, the incidence of toxicity rises to as high as 50% [24]. When lesser volumes of small intestine are exposed to radiation, the degree of toxicity is diminished [30]. This concept was confirmed in a study of rectal cancer patients treated preoperatively with chemoradiotherapy showing a strong correlation between the occurrences of severe diarrhea and irradiated small bowel volume. In this study, 40 patients receiving concurrent 5-FU-based chemotherapy and pelvic irradiation for the treatment of rectal carcinoma had treatment—planning computerized tomography (CT) scans with small bowel contrast. A median isocentric dose of 50.4 Gy was delivered using a posterior–anterior and opposed lateral field arrangement. Bowel exclusion techniques were used including prone position on a vacuum bag cradle to allow anterior displacement of the abdominal contents and bladder distension to limit radiation exposure. The volume of small bowel receiving each dose between 5 and 40 Gy was recorded at 5-Gy intervals. Ten patients (25%) experienced high-grade acute small bowel toxicity. A statistically significant association between the development of acute small bowel toxicity and the volume of small bowel irradiated was found at each dose level. The volume of small bowel receiving at least 15 Gy was strongly associated with the degree of toxicity. The authors advised that limiting the volume of small bowel receiving greater than 15 Gy may significantly improve treatment tolerance [31].

Furthermore, as noted previously, the combination of radiation and chemotherapy increases the risk of small intestinal toxicity as chemother-

apy can cause significant small bowel toxicity without radiation. In a randomized trial delivering 40–48 Gy to 202 patients with rectal cancer, the incidence of severe small bowel complications were significantly higher in patients who received postoperative 5-FU and RT than in those who received radiation alone (35 % vs 15 %) [32, 33]. The infusion modality of chemotherapy with radiation has also been studied, revealing higher risk in those who receive bolus doses of chemotherapy instead of continuous infusion. In one study, 660 patients with TNM stage II rectal cancer received intermittent bolus injections or protracted venous infusions of 5-FU during postoperative radiation to the pelvis. With a median follow-up over 46 months, patients who received a protracted infusion of fluorouracil had significantly increased time to relapse and improved survival in comparison to bolus doses. Furthermore, although continuous 5-FU with radiation to 50.4 Gy in 1.8-Gy fractions was associated with an increase in acute diarrhea, there was no increased risk of chronic or severe small bowel toxicity when compared to bolus 5-FU therapy [34]. Although the addition of concurrent chemotherapy increases the acute toxicity of external radiotherapy, its contribution to late bowel toxicity is still poorly understood [8].

Diagnosis

The diagnosis of radiation enteropathy is a clinical diagnosis made by a history of prior radiation exposure, suggestive clinical features, and supportive radiologic findings. Details of the patients' previous radiation history (including last dose, fractioned and total doses, and distribution of the radiation field) should be obtained during the initial evaluation.

Diagnosing radiation enteropathy may be difficult as it is not simply a function of the radiation dose from previous treatment and involves a number of presumed physiologic and functional changes in the small bowel based on the patient's medical risk factors. One study showed that radiation enteropathy is not a single disease. In this study, a total of 265 patients were referred with urologic, gynecologic, and GI cancers and after therapy it was found that one-third of the patients' symptoms were not related to RT itself [35]. More than half of the patients had at least two diagnoses, while the remaining were determined to be considered to be due to radiation damage solely. As a result, prior to beginning a work up to determine if radiation enteropathy is the direct result of intestinal damage or a codependent factor, other disease states need to be ruled out or as potential contributors. Due to limited treatment options that directly improve radiation enteropathy, emphasis on finding additional factors that may be accentuating symptoms is advised. These include Infectious, inflammatory, or medication-related injury, which can be treated with additional medication or the discontinuation of offending agents.

Upper GI radiography with barium and CT have been the mainstay tests for diagnosing treatment/radiation-related enteropathy. Upper GI series with small bowel follow-through can be used as an initial test to evaluate the extent of disease, but is not as sensitive as enteroclysis [36]. Enteroclysis, involving infusion of contrast material via nasoenteric tube into the small bowel using a pump, provides more complete visualization of the small bowel mucosa in comparison to standard upper GI series [37]. However, its sensitivity and specificity have not been well defined in the setting of suspected radiation enteropathy.

Abdominal CT is commonly used for the evaluation of small intestinal radiation injury, particularly in evaluating areas of suspected stricture. CT enteroclysis produces superior imaging compared to conventional CT, with a sensitivity and specificity of 88 and 82 %, respectively, when evaluating low-grade and intermittent obstruction [38, 39].

Radiographic abnormalities detected on small bowel series and CT typically include thickening of the small bowel folds and the intestinal wall with or without intramural hemorrhage, edema, and mucosal ulceration (Figs. 8.2, 8.3, 8.4**).** In chronic radiation injury, stenosis, adhesions, or fistulas can be seen. In some cases, features classically labeled as "ribbon" or "toothpaste" bowel

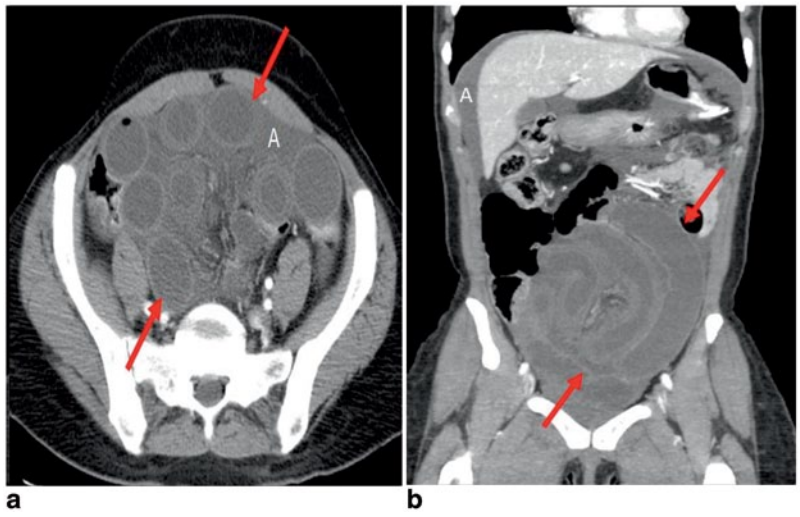

Fig. 8.2 Diffuse acute radiation enteritis. Axial (**a**) and coronal (**b**) multiplanar reformatted CT images show diffuse mural thickening of the small bowel with submucosal edema and increased intraluminal secretions with ascites. (*Courtesy of Richard Gore, MD*)

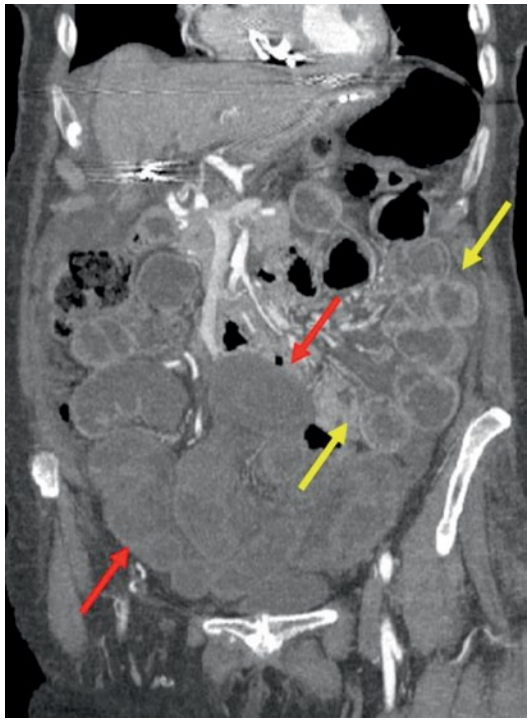

Fig. 8.3 Chronic radiation enteritis—poor perfusion and mural thickening on this coronal reformatted CT image (*red arrows*). Notice the bowel not within the mantle enhances normally (*yellow arrows*). (*Courtesy of Richard Gore, MD*)

Fig. 8.4 Chronic radiation enteritis—small bowel follow through shows mucosal irregularity, thickening of the valvulae conniventes, and minimal separation of distal ileal segments (*red arrows*). (*Courtesy of Richard Gore, MD*)

are displayed, reflecting the small intestinal mucosal destruction.

Magnetic resonance (MR) enterography for the evaluation of Crohn's disease is well described in literature, and has an evolving role in the evaluation of other small-bowel diseases including radiation enteritis. MR enterography may be particularly useful for the evaluation of intermittent and low-grade small-bowel obstructions in patients with radiation enteropathy. Advantages of MR over CT as an imaging modality include superb contrast resolution, lack of exposure to ionizing radiation, and the use of several intravenous contrast media with improved safety profiles. Limitations of MR include higher cost, less availability, variability of image quality, and lower spatial resolutions (the measure of how closely lines can be resolved in an image). Comparisons between MR enterography and MR enteroclysis are in process [40], although some studies suggest that MR enteroclysis results are comparable and possibly more sensitive than CT enteroclysis [37].

Capsule endoscopy can be used to diagnose radiation enteropathy, but is generally avoided given the risk of the capsule becoming trapped in a strictured segment requiring surgical removal. Colonoscopy with intubation of the ileum can be helpful if ileal involvement is suspected. Endoscopic features consistent with radiation injury include mucosal atrophy and edema, friability, pallor, and the presence of telangiectasias [41], Unfortunately, even if the ileal mucosa appears to be normal, patients can still be at risk for complications of radiation enteropathy including spontaneous perforation [42]. Mucosal biopsies are usually not diagnostic, but can eliminate other causes of small bowel injury including inflammatory bowel disease, infections, and nonsteroidal anti-inflammatory drug (NSAID)-induced damage.

Prevention

If RT is anticipated after surgery, attempts have to be made at the time of surgery to displace the bowel outside the radiation field [43]. One technique is the surgical placement of polyglycolic, biodegradable mesh that moves the intestines out of the pelvis [44, 45]. In two published studies, one with 8 children and another including 60 adults receiving RT, placement of a mesh reduced the occurrence of delayed symptoms of radiation enteritis. In both of these studies, radiological evaluation was used to confirm that the small bowel was out of the pelvis and the area of irradiation posttreatment. A reduction of 50% of the volume of the small bowel exposed to the radiation has been demonstrated with placement of a mesh during surgery, allowing a higher dose of radiation to be given postoperatively where indicated [46]. Other techniques such as pelvic reconstruction, omentoplasty, and transposition of the colon may also significantly decrease the volume of bowel exposed to RT [46–49]. In many patients, treatment in the prone position with a special "belly board" (a customized polyurethane and styrofoam bowel immobilization mold), allows the displacement of the small intestines out of the radiation field (Fig. 8.5) [50, 51].

Fig. 8.5 Koilia Mikros Belly Board allows displacement of the small intestines from the radiation field during treatment. (*With permission from CDR Systems*)

Advances in computer technology have also led to the development of three-dimensional (3D) RT planning systems and computer-controlled RT delivery [52–54], which theoretically will improve the efficiency. With these techniques, external beam RT can be planned and delivered with a reduction in complications and cost.

Table 8.1 Therapy for radiation enteropathy

Therapy	Dose	Indication
Loperamide	4 mg twice a day (titrate as needed)	Diarrhea
Sucralfate	1 g four times a day (titrate as needed)	Diarrhea
Cholestyramine	2–4 g twice to four times a day (titrate as needed)	Diarrhea (especially with bile salt diarrhea)
Rifaximin	1200 mg a day for 7–10 days	Small intestinal bacterial overgrowth
Amoxicillin/clavulanate	30 mg/kg a day for 7–10 days	Small intestinal bacterial overgrowth
Metronidazole with Cephalexin or Trimethoprim-sulfamethoxazide or Gentamycin	Metronidazole (20 mg/kg/day) Cephalexin (30 mg/kg/day Trimethoprim-sulfamethoxazide (10–12 mg/kg/day) Gentamycin (10 mg/kg/day) *For 7 to 10 days	Small intestinal bacterial overgrowth
Norfloxacin	800 mg a day for 7–10 days	Small intestinal bacterial overgrowth
TPN ± Methylprednisolone	Methylprednisolone 80 mg a day	Malnutrition
Hyperbaric oxygen		Severe malnutrition

Intensity-modulated RT (IMRT) requires the same careful 3D radiation treatment planning, but takes it a step further by utilizing variable, computer-controlled intensities within each RT beam. As a result it can achieve a higher degree of accuracy in conformation of the radiation to the planned target, and spare normal tissue. One phase II trial, studying 83 patients with endometrial and cervical cancer receiving IMRT, showed lower hematologic toxicity by reducing the volume of bone marrow irradiated [55]. Another retrospective review of patients with rectal cancer comparing 61 patients treated with conventional RT versus 31 patients with IMRT showed a significant reduction in acute lower GI toxicity [56]. Yet another study of patients with prostate cancer receiving pelvic radiotherapy found that patients receiving IMRT had a 40% relative reduction in the volume of bowel receiving 45 Gy in comparison to conventional two-dimensional (2D) planning. This newer technology has promise in reducing the rates of acute and late GI morbidity when using RT.

Preventive therapeutic strategies currently being studied include investigation of antioxidants, free-radical scavengers, cytokine modification, enterotrophic strategies, novel anti-inflammatory agents, modulators of intraluminal contents, modulators of endothelial dysfunction, as well neuroimmunomodulators [57].

For further details, please see Chap. 4-Prevention of Injury from Pelvic Irradiation.

Treatment

Treatment for acute and chronic radiation enteropathy has been directed to relieve symptoms and for management of disease complications. Unfortunately, specific medical treatment has been driven by small clinical trials, retrospective studies, and case series. At present, no pharmacotherapy has been shown to alter the natural history of the condition.

A variety of symptomatic treatments for radiation enteropathy have been suggested (see Table 8.1). Loperamide has been used to control the symptoms of acute and chronic disease. In one study of patients, loperamide 3 mg twice a day for 14 days was associated with a significant reduction in the frequency of bowel movements, slower intestinal transit, and improvement in the absorption of bile acids [58]. A study of oral sucralfate in patients receiving pelvic irradiation showed a decrease in frequency and improvement in consistency of bowl movements. The study was a double-blind, placebo-controlled trial including 70 patients with prostate or bladder cancer without distant metastasis. Radiotherapy was conventionally delivered. Dose

granules of sucralfate or placebo were dispensed to each patient 2 weeks after radiation and continued for 6 weeks. The frequency of defecation and stool consistency was significantly improved by sucralfate, where 14 patients in the placebo group versus 3 patients in the sucralfate group ultimately required loperamide. Furthermore, in this study, not only did loperamide reduce acute symptoms occurring during radiotherapy, but was also effective for chronic symptoms 1 year after completion of RT [59].

Cholestyramine to treat diarrhea from bile acid malabsorption has also shown some benefit. Of concern with the use of cholestyramine is the risk of resin aggregation within small intestinal strictures, resulting in mechanical bowel obstruction. Great caution is also generally advised regarding the use of anti-diarrheal agents in patients with suspected small or large bowel obstruction.

In the setting of malnutrition related to chronic radiation injury, total parenteral nutrition (TPN) can improve clinical outcome, and methylprednisolone may add to the effects of TPN. In a published study, 24 patients with severe radiation injury to the small bowel seen over a 4-year period were randomized to four different treatment groups: (1) methylprednisolone 80 mg intravenously plus Vivonex-HN 2 L/day, (2) methylprednisolone 80 mg intravenously plus TPN 2.5 L/day, (3) TPN 2.5 L/day, and (4) Vivonex-HN 2 L/day [26]. Patients were treated over an 8-week period. Improvement was gauged by overall nutritional assessment measurements, nitrogen balance data, and by radiologic and clinical parameters. There was a marked improvement noted in groups that received TPN and bowel rest (groups 2 and 3), and significant improvement in the group that received methylprednisolone (group 2).

A recent approach to treatment of chronic radiation enteropathy is the administration of hyperbaric oxygen [60, 61]. In a retrospective study of 44 patients with severe radiation enteropathy, marked mainly by severe malabsorption, vitamin deficiency, and fistula formation that were refractory to medical management, improvement of clinical symptoms was reported in two-thirds of patients treated with hyperbaric oxygen [62]. It has been hypothesized that there may be potential benefit of prophylactic hyperbaric oxygen use to prevent frank small intestinal damage in high-risk patients. On the other hand, there is concern of enhancing of growth or precipitation of malignancy recurrence with hyperbaric oxygen. Further investigation of this modality is warranted.

A conservative approach to surgery for radiation enteropathy is advised because of the many potential operative problems encountered in these patients. Problems encountered during surgery include intestinal fibrosis, and dense adhesions in the abdominal and pelvic cavities. This results in a high risk of leakage when creating anastomosis between irradiated tissues. In addition, extensive intestinal resection may be required. Combined with the risk for inadvertent iatrogenic enterotomies, the overall result of surgery may be the development of short bowel syndrome, requiring lifelong nutritional support [60, 63, 64]. Unfortunately, despite attempts at conservative management, up to one-third of patients will progress to the requirement for surgical management [15]. The most common reasons for surgery in these patients include persistent ileus, fistula formation, and massive adhesions [64, 65]. A study of 109 patients showed that five patients (5 %) died postoperatively post resection while 33 patients (30 %) had postoperative complications. Furthermore, repeat surgery was required in 40 % of patients [15]. Another retrospective study of 18 patients showed more optimistic findings with good survival in patients with diffuse chronic radiation enteritis that underwent extensive intestinal resections. Three patients were treated conservatively while 15 underwent surgical procedures. Operative deaths occurred in four patients in this series, however, there was no difference in mortality between the operated and nonoperated cases [66].

Endoscopic stricturoplasty may offer a less invasive approach to the management of strictures, but at present, experience in this patient group is very limited [67].

Additional material on this topic can be found in Chap. 16, Surgical Management of Radiation Effects on the Intestines.

Conclusion

Acute and chronic radiation enteropathy is associated with significant morbidity including diarrhea, weight loss, malabsorption, hemorrhage, obstruction, and perforation. It is important to determine if radiation enteropathy is the direct result of intestinal damage or a codependent factor by ruling out or considering other coexisting disease processes. Prevention and treatment of radiation enteropathy requires a multidisciplinary approach with multiple specialties involved (surgery, gastroenterology, oncology, radiation oncology, and radiology). Despite conservative measures, surgery for persistent ileus, fistula formation, and dense adhesive small bowel disease is relatively common. Prognosis is variable since chronic radiation enteropathy is often progressive. Treatments to alter the natural history of the disease are lacking and are highly recommended. Due to limited treatment options that directly improve radiation enteropathy, emphasis on finding additional factors that may be contributing to or accentuating symptoms is advised.

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Radiation Proctopathy

9

Andrew Mazulis and Eli D. Ehrenpreis

Introduction

Malignancies commonly treated with pelvic radiation therapy (RT) include prostate, cervical, uterine, rectal, testicular, and bladder cancer, as well as several lymphomas [1, 2]. The rectosigmoid colon and the rectum are common sites of injury in patients undergoing pelvic RT for these cancers. Radiation proctopathy is defined as damage to the rectosigmoid colon or rectum that results from RT to adjacent pelvic organs for the treatment of pelvic malignancies [3]. Anorectal dysfunction occurring in these patients may or may not involve concomitant damage to the anal sphincters. RT delivery for treatment of cancer of the pelvic organs may also unfortunately include a portion of the rectum within the therapeutic field. Delivered radiation can initially damage normal rectal mucosa and subsequently lead to late gastrointestinal (GI) complications, including rectal bleeding, pain, and evacuation difficulties. Severe consequences of intestinal radiation injury can include ulcerations, fistula formation, and secondary cancers [4]. Despite advances in treatment delivery techniques, radiation toxicity to local healthy tissue remains an important barrier to subsequent quality of life in patients receiving treatment for pelvic malignancies.

Acute Radiation Proctopathy (ARP)

It is estimated that >200,000 patients in the United States of America receive abdominal or pelvic radiation per year and 60–80 % of these patients experience symptoms of acute bowel toxicity. Acute radiation proctopathy (ARP) can be defined as rectal symptoms that occur during or immediately following RT. By inference, ARP improves and eventually resolves following completion of RT. Common symptoms of ARP include diarrhea, irregular bowel habits, hematochezia, cramping, and tenesmus. These symptoms correlate with loss of rectal mucosal cells, acute inflammation in the rectal lamina propria, and endothelial swelling [5–6] (see Chap. 5). ARP occurs within 3 months of RT and significantly affects quality of life. It has been estimated that more than 75 % of patients that receive pelvic radiation develop acute anorectal symptoms [7]. These symptoms have a known negative effect on quality of life in patients with pelvic malignancies [8].

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Chronic Radiation Proctopathy (CRP): The Basics

Chronic radiation proctopathy (CRP) is defined as radiation-induced anorectal symptoms occurring at least 3 months or more after completion of RT. The median onset for symptoms of CRP is 8–12 months, but delayed symptoms may start as late as 30 years following radiation treatment [9]. Depending on definition and the method for collecting epidemiologic data, the prevalence of CRP has been estimated to occur in 5–80 % of patients after pelvic radiotherapy [8, 10]**.** Common symptoms of CRP include hematochezia, pain, difficulty with evacuation, urgency, frequent elimination, and fecal incontinence [3].

Risk Factors for the Development of Proctopathy

Some patients have increased susceptibility to developing CRP, and because of this, the incidence and severity of radiation proctopathy is dependent on several factors. Therapy-related causes include the dose of radiation, the length of bowel exposed, time-dose fractionation parameters, and use of concomitant biotherapy or chemotherapy. Patient-associated factors also contribute to the development of CRP. For example, previous abdominal surgery increases the risk of intestinal injury. Other comorbidities including inflammatory bowel disease [11], diabetes mellitus [12], and collagen vascular diseases [13–14] also increase the risk of ARP and CRP. Radiation damage accelerates underlying vascular disease by increasing the severity of endarteritis and tissue fibrosis. Tobacco smoking is also a predictor of complications after RT. Of interest, obese tissue appears to be more resistant to radiation injury and an elevated Body Mass Index (BMI) has a protective affect against radiation-induced bowel disease [15].

Pathogenesis

Symptoms of ARP correlate with the pathologic changes of loss of mucosal cells in the rectum, acute inflammation in the lamina propria, and endothelial arteriole swelling [5–6]. Early intestinal injury may manifest within days of beginning radiation and is primarily due to cell death in rapidly proliferating crypt epithelium. Crypt cell death produces insufficient replacement of villi as well as breakdown of the mucosal barrier [16]. Pathogenesis of delayed proctopathy is complex and involves changes in many intestinal wall compartments. Chronic radiation injury is associated with damage to microvasculature. This in turn leads to ischemia, neovascular mucosal lesions, and fibrosis [6]. Endoscopic findings of CRP include telangiectasia formation, spontaneous hemorrhage, edema, friability, and mucosal pallor [10, 17]. Infrequently, ulcers, strictures, fistulas, and secondary malignancies may occur. Hematochezia occurs from rupture of radiation-induced telangiectasias, friable ischemic mucosa, and mucosal ulceration. Functional symptoms of radiation proctopathy such as urgency, incontinence, and fecal difficulties occur from loss of compliance in the rectal wall [18]. Rectal bleeding may be severe, causing patients to require blood transfusions and hemodynamic support and monitoring. Patients with isolated colonic injury or proctopathy have significantly fewer problems with fluid and electrolyte balance and nutrition, and long-term prognosis is better than it is in patients with small intestinal involvement.

Diagnosis and Histopathology

The diagnosis of radiation proctopathy is made by a history of prior radiation exposure, clinical features of the disease, and suggestive endoscopic findings. Details of the patients' previous radiation history (including last dose, distribution of the radiation field, and fractionated and total doses) should be obtained during initial evaluation. The diagnosis of bleeding secondary to radiation proctopathy must, of necessity, include exclusion of other causes. The severity of radiation proctopathy can be monitored by colonoscopy or flexible sigmoidoscopy.

Radiation proctopathy can be monitored and graded by its severity (Table 9.1) or using the Rectal Telangiectasia Density Grading (RTDG) Scale. Grade 0 is entirely normal mucosa. Grade

Table 9.1 Endoscopic classification of radiation proctopathy (Grade A (mild, 2 points), grade B (moderate, 3 points), grade C (severe, 4–5 points))

Distribution of telangiectasias	Surface area covered by telangiectasias	Presence of fresh blood
Distal rectum (within 10 cm from anal verge): 1 point	Less than 50%: 1 point	No fresh blood: 0 points
Entire rectum ± sigmoid (more than 10 cm from anal verge: 2 points	More than 50%: 2 points	Fresh blood: 1 point

Adapted from Zincola et al [36].

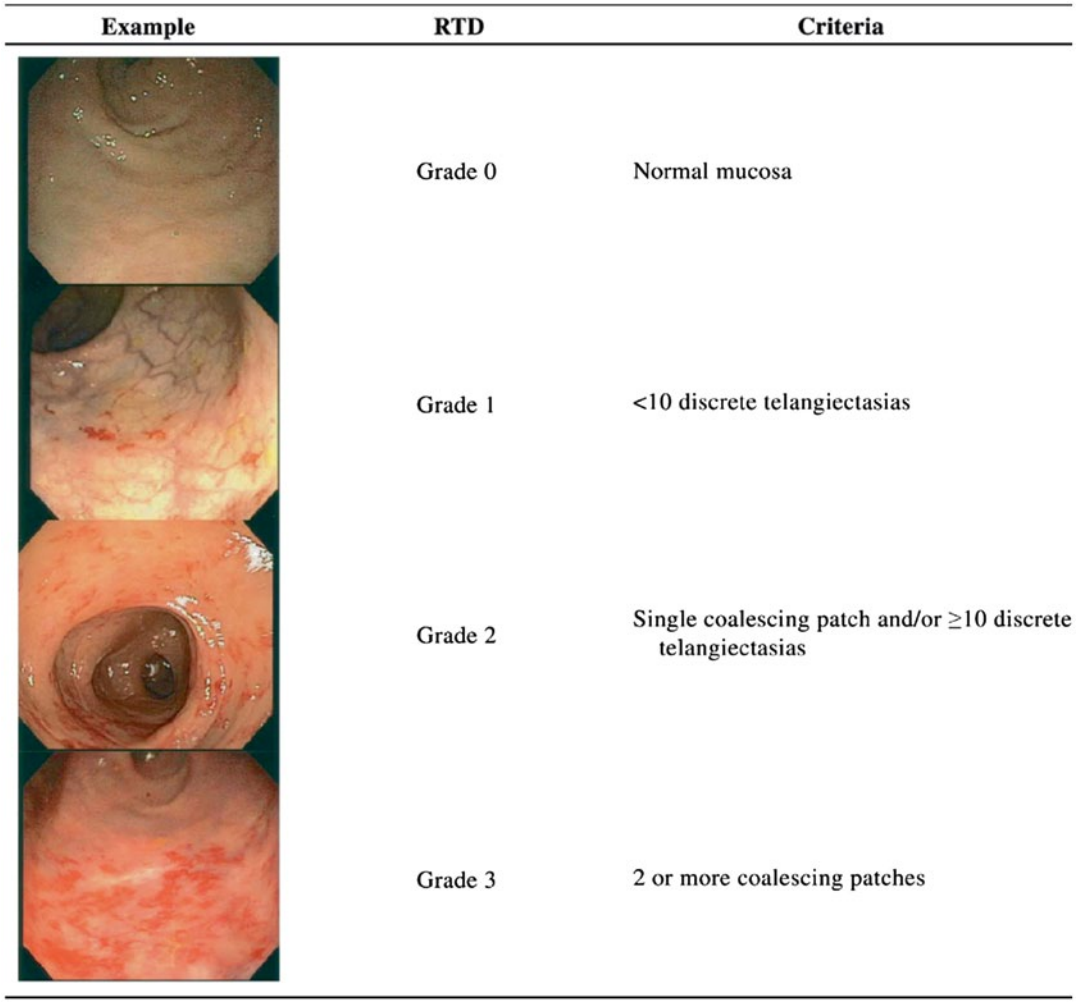

Fig. 9.1 Rectal Telangiectasia Density (RTD) grading scale. (The highest grade visualized during endoscopic evaluation with colonic lumen in view represents the RTD grade of the patient). Adapted from Chi KD, et al. [19]

1 is fewer than 10 discrete telangiectasias in a luminal view. Grade 2 is defined by a single coalescing patch of telangiectasia patches. Grade 3 is the presence of two or more coalescing telangiectasia patches. This grading scale is scored endoscopically through either a colonoscopy or flexible sigmoidoscopy [19]. Figure 9.1 describes each grade of proctopathy based on the RTDG Scale.

Pathology from endoscopy biopsies of ARP reveals formation of eosinophilic crypt abscesses, loss of mucosal cells, extensive inflammation, and endothelial arteriole swelling [20–21]. On the other hand, CRP endoscopic findings usually start around the dentate line and include pallor, mucosal friability, strictures, fistulas, telangiectasias, and ulcerations. Connective tissue fibrosis and arteriolar endarteritis are seen on histologic analysis of biopsy specimens [20].

Further information regarding histological changes in ARP and CRP can be found in Chap. 5, Pathology of Radiation Effects on Healthy Tissue in the Pelvis.

Therapeutic Modalities There are two main goals of treatment for CRP—obliteration of mucosal telangiectasias and the control of functional symptoms to date—a wide variety of endoscopic cautery techniques, pharmacological options, and surgical procedures have been proposed for the treatment of radiation proctopathy. However, there has been a significant lack of randomized placebo-controlled studies for most interventions. In fact, there has been only one randomized placebo-controlled trial for functional symptoms of CRP, namely the use of oral retinol palmitate [22].

Medical Management

Management of ARP is largely aimed at symptomatic therapy. Initial treatments include fiber supplements, antidiarrheal, and anal topical analgesics [23]. Some authors have recommended the administration of a somatostatin analogue to patients who experience severe diarrhea that does not respond to first-line treatments [24]. Amifostine protects against the DNA damaging effects of ionizing radiation and chemotherapy drugs and is the only current FDA-approved drug for reduction of radiation toxicity. Amifostine affects redox sensitive transcription factors, chromatin stability, enzyme activity, and gene expression and has both anticarcinogenic and antimutagenic properties [25]. Although amifostine has shown promising effects in some animal studies, a controlled clinical trial of amifostine for prevention of radiation proctopathy has not been performed. Side effects of amifostine include nausea, vomiting, and hypotension [26].

Sucralfate enemas have been used to treat bleeding from CRP [27–28]. Kochhar et al. [27] studied 37 patients with radiation-induced proctosigmoiditis randomized to receive a 4-week course of oral sulfasalazine plus 20 mg BID rectal prednisolone enemas or 2.0 g BID rectal sucralfate enemas plus oral placebo. At 4 weeks, both groups showed significant improvement in symptoms and endoscopic healing**.** Symptoms were scored as follows: diarrhea (1–3 stools daily: 1 point, 4–6 stools daily: 2 points, >6 stools daily: 3 points), tenesmus (absent: 0 points, mild tenesmus not requiring drug: 1 point, tenesmus requiring medication: 2 points), bleeding per rectum (no bleeding: 0 points, mild bleeding 1 point, bleeding requiring blood transfusion: 2 points). Based on the cumulative score of three symptoms, patients were classified into three grades: I (< or =2 points), II (3–4 points), or III (> or =5 points). Endoscopic injury was graded according to criteria of Gilinsky et al. [28]: mild/grade I (erythema ± telangiectasia, edema, thickening, and pallor), moderate/grade II (above plus friability), and severe/grade III (ulceration ± necrosis). Clinical response was measured as improvement, no change, or worsening. Endoscopic response was analyzed similarly with improvement, no change, or worsening. When compared head to head, sucralfate enemas showed a significantly better clinical response than placebo ($p<0.05$), although there was no endoscopic difference detected**.**

5-Aminosalicylic acid (5-ASA) is the active compound found in sulfasalazine. 5-ASA compounds are established and well tolerated for the treatment of inflammatory bowel disease. Its anti-inflammatory mechanisms include inhibition of biosynthesis of prostaglandins, inhibition of the transformation of leukotriene A_4 to leukotriene B_4, and promotion of endogenous cytoprotective prostaglandins [29]. Rectal suppositories of 5-ASA were administered by Freund et al. [30] to eight patients at the time of RT. 75% of patients receiving 5-ASA developed severe symptoms of radiation proctopathy, suggesting that

these suppositories actually stimulated development of radiation proctopathy. Baum et al. [31] treated four patients with nightly 5-ASA enemas for 2–6 months and symptoms were followed monthly along with periodic sigmoidoscopy examinations. No significant changes were seen in the degree of mucosal inflammation at follow-up sigmoidoscopy. Only one of the four patients noted initial improvement in symptoms; however, even in this patient symptom improvement was not sustained. These studies have essentially concluded that rectal 5-ASA has no role in the prevention or treatment of radiation proctopathy.

Sodium pentosan polysulfate, a heparin-like macromolecular carbohydrate, has a role in the treatment of radiation cystitis, presumably by reinforcement of the damaged mucosal lining of the bladder. A phase I/II trial of 3 month's duration with sodium pentosan polysulfate was performed in 12 patients with CRP [32]. Nine patients (82%) in the study obtained a complete response and only one patient (8%) showed no improvement. However, five patients relapsed at 11 month follow-up.

Ehrenpreis et al. [22] performed a study to investigate the use of retinol (retinyl) palmitate for the treatment of CRP, with improvement in functional symptoms. Retinyl palmitate has been demonstrated to accelerate wound healing after burn injuries and surgeries in laboratory animals [33]. The mechanism has not been fully clarified, however, increased cross-linking of myofibrils and collagen [34] has been demonstrated to occur after use of retinol palmitate. Prior to randomization, a questionnaire of the six most common symptoms of CRP, using a Likert system for grading of frequency and severity, was completed. These symptoms include diarrhea, rectal bleeding, rectal pain, rectal urgency, tenesmus, and fecal incontinence. Severity scores ranged from one to five. Ehrenpreis et al. developed a scale called the Radiation Proctopathy Symptom Assessment Scale (RPSAS). The components of the RPSAS are shown in Fig. 9.2. Initial RPSAS scores on enrollment were considered a patient's baseline score. Patients were contacted by phone every 30 days by the same investigator for a total of 90 days. Response to treatment was defined as a reduction of at least two symptoms by at least two points on the RPSAS. Secondary end points of the study included a comparison of total RPSAS score before and after treatment in the retinol palmitate and placebo groups. Neither patients nor the investigators were aware who was receiving retinyl palmitate or placebo. The dose of retinol palmitate was 20,000 IU per day. Patients who received placebo and had not responded were offered treatment with retinyl palmitate on an open-label basis.

Nineteen patients participated in the study, ten of whom were randomized to retinyl palmitate and nine to placebo. Based on criteria for therapeutic response, seven patients treated with retinyl palmitate responded to therapy and two patients did not. Two patients treated with placebo responded to therapy and six patients were non-responders. This difference demonstrated a trend towards statistical significance ($p = 0.057$). Of six patients who did not respond to placebo, five were enrolled in the open-label retinyl palmitate treatment arm. All five of these patients met criteria for response to therapy. This study demonstrated that retinyl palmitate is a safe and readily obtainable form of vitamin A that potentially significantly reduces symptoms of CRP. Additional trials of retinyl palmitate are underway.

Endoscopic Therapy

Endoscopic therapy appears to be the most effective treatment for the bleeding of CRP, with better success rates than medical management. Minimizing blood loss and controlling rectal bleeding allows for improved quality of life through decreased need for transfusions, iron replacement, and less frequent hospitalization [35].

Several endoscopic classifications for the severity of mucosal changes in CRP have been proposed. Chi et al. [19] performed a retrospective study using the RTDG scale and found the system to be reproducible among GI fellows and expert endoscopists. The study reviewed 131 endoscopic images of the rectum in 74 consecutive patients undergoing colonoscopy who had received pelvic radiation. The images were rotated

Severity

- No problem
- Mild problem-can be ignored when you don't think about it
- Moderate problem-cannot be ignored; no effect on daily activities
- Severe problem-influences your concentration on daily activities
- Very severe problem- markedly influences your daily activities and/or requires rest

Frequency

- Monthly
- Weekly
- Several times per week
- Daily
- Throughout the day

	Severity	Frequency
Diarrhea		
Urgency		
Rectal pain		
Tenesmus		
Rectal bleeding		
Fecal incontinence		

Fig. 9.2 The radiation proctopathy symptom assessment scale (RPSAS). Adapted from Ehrenpreis ED, et al [22]

and duplicated for a total of 262 images. Images were shown in random order using a computer program and each image was to be scored from grade 0 to grade 3 based on the RTDG scale. The RTDG scale is shown in Fig. 1. A study by Zinicola et al. [36] used a scoring system composed of three factors: presence of blood, distribution of telangiectasias, and the surface area involved. Zinicola's scoring system divides radiation injury into three classes: mild, moderate, or severe (see Table 1). Studies utilizing these systems to demonstrate improvement are limited. Another grading scale focuses on the functional symptoms of CRP. Ehrenpreis et al. [22] developed a scale called the RPSAS. This scale looks at the severity of symptoms on a scale of one to five, with one being no problem to five being very severe and markedly influencing daily activities and/or requiring rest. Frequency is described as either monthly, weekly, several times per week, daily, or throughout the day. The score on the RPSAS for a completely asymptomatic patient is 6 (see Fig. 2). Monopolar heater probe and bipolar electrocautery, Neodymium/yttrium aluminum garnet (Nd:YAG), titanyl phosphate (KTP), and argon lasers have been studied as a means of

reducing bleeding by obliteration of telangiectasias. Nd:YAG was one of the first endoscopic procedures used to treat CRP [37]. The Nd:YAG laser penetrates to a depth of 5 mm and has a low affinity for hemoglobin and H_2O but is well absorbed by protein in tissues. This makes it ideal for deep vessel coagulation [20]. Complications secondary to Nd:YAG include transmural necrosis, stricture formation, fibrosis, and rectovaginal fistula. The use of Nd:YAG for CRP has declined due technical difficulties, high costs, and possibility of severe endoscope damage if the laser strikes the endoscope in the retroflexed view [35].

Bipolar electrocautery utilizes a system with a probe containing two or more electrodes in the tip through which current is passed [38]. The heater probe is Teflon coated with a monopolar heating element at the tip. Both devices have been studied for active bleeding due to telangiectasias formation in CRP [39].

Formalin is a solution of formaldehyde gas used for glues, embalming, and fire proofing. Application of formalin covalently bonds proteins, causing cell necrosis. In animal studies, administration of formalin enemas result in formic acid levels detectable in the serum. Formic acid toxicity includes acidosis, coma, and renal failure. Formalin has been applied topically as an enema or "dab" from a cotton swab in several clinical studies in patients with bleeding from CRP. Enema treatment is often administered in the operating room with general or spinal anesthesia. Although formalin enemas have been demonstrated to reduce the severity of rectal bleeding in patients with CRP, significant and serious complications of formalin instillation including anal pain, fissure formation, rectal strictures, and rectal fistulas have been described. In addition, chemical proctosigmoiditis as a direct toxicity of topical formalin has been described (see Fig. 9.3). Surgical complications of formalin instillation are not rare. In the largest series reported so far, Luna-Perez described 20 female patients with bleeding from radiation proctopathy. 50 Ml aliquots of 4% formalin were instilled with a dwell time 30–180 s with a total 500 mL instilled. Five of these patients (25%) developed pelvic pain. Three (15%) required surgery for complications of formalin treatment, one requiring a resection and Hartmann's pouch for rectosigmoid necrosis. Two of these patients ultimately required colostomies for rectovaginal fistulas, and one had a subsequent APR for pelvic sepsis [40]. Our group only recommends topical formalin applied for patients with areas of telangiectasias that are too large to treat with argon plasma coagulation (APC) or perhaps in patients with bleeding rectal ulcers.

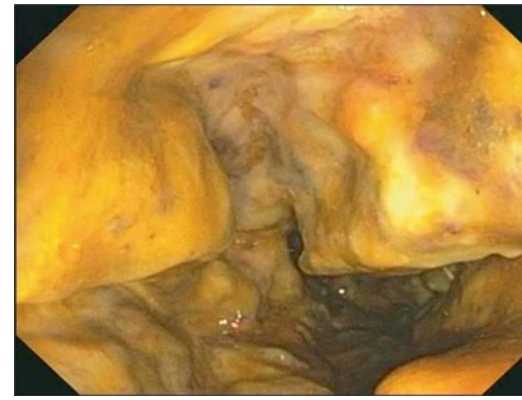

Fig. 9.3 Endoscopic demonstration of severe chemical proctitis induced by formalin enema treatment for bleeding from chronic radiation proctopathy. The patient ultimately required a diverting colostomy for refractory pain and anorectal dysfunction

APC consists of high frequency monopolar electrosurgical generator, an argon gas source, a foot switch for energy and gas delivery, flexible delivery catheters, a gas flow meter, and a grounding pad [41]. Monopolar current travels from an electrode in the probe tip through the argon plasma to the tissue. The technique usually requires several sessions for adequate obliteration of rectal telangiectasias. Preparation for colonic APC treatment always requires a full colonoscopy preparation [42]. Side effects include luminal distension with argon gas, rectal pain, and tenesmus. Serious complications are rare (< 1%) and include APC-induced ulcerations, rectal strictures, and rectal fistula formation, often requiring surgery such as a diverting colostomy. Several cases of explosions in the colon due to the ignition of methane gas from inadequate colon preparation have been reported [43, 44].

There have been several case studies evaluating APC use for the treatment of radiation proctopathy. Villavicencio et al. [45] reported successful use of APC in their study of 21 patients with proctopathy and anemia. Twelve patients had failed prior pharmacotherapy, four had received blood transfusions in the past, and five had not responded to prior endoscopic therapy. The mean number of sessions needed to control bleeding was 1.7, and 10 of the 21 patients responded after only one session. Sato et al. [46] performed a study to determine the optimal parameters for APC by using swine rectum and to assess safety and effectiveness of APC in hemorrhagic radiation proctopathy (HRP) patients**.** APC in swine rectal wall ex vivo was found to be optimal with a 40-W current, 2 s application, and 1.2-L/min gas flow rate that adequately treated the telangiectasia without adversely affecting the muscle layer. Sixty-five patients with HRP occurring at a mean of 20 months after radiation were studied. Seven patients had grade A (mild) proctopathy, 41 had grade B (moderate), and 17 had grade C (severe). Treatment success rate was 98.5 % after a median of 2 (range 1–5) APC sessions. The median clinical score for rectal bleeding was significantly decreased after APC ($p < 0.0001$) as assessed by the Chutkan scoring system [47]. This study is one of the largest studies confirming the efficacy of APC for the treatment of HRP and demonstrates long-lasting effects of APC that persists as long as 10 years. Figure 9.4 illustrates endoscopy images of a patient with CRP before and after treatment with APC.

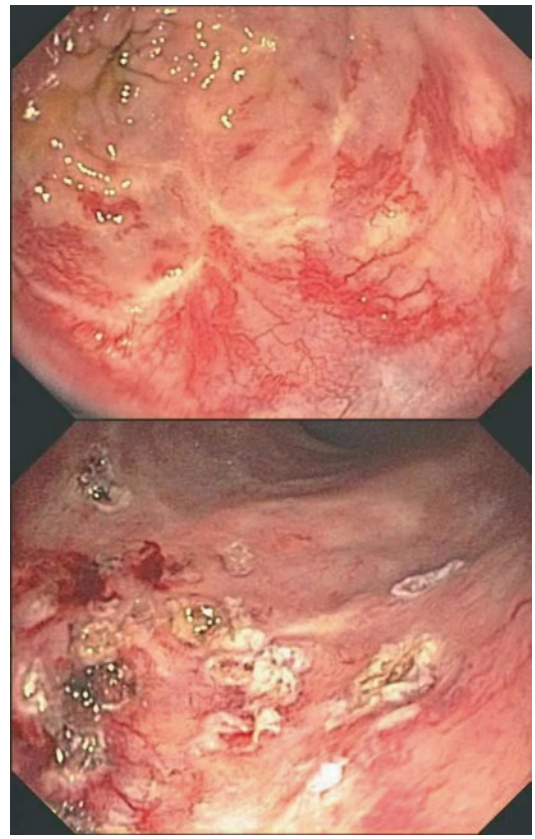

Fig. 9.4 Endoscopic views of the rectum before and after treatment with the argon plasma coagulator (APC)

Hyperbaric oxygen therapy has been suggested as a safe and effective treatment modality for CRP. Potential mechanisms of action include increased tissue oxygenation, reduction of capillary angiogenesis, and edema [48]. Potential side effects include middle ear and sinus barotrauma as well as pulmonary and central nervous system (CNS) oxygen toxicity. A major drawback to the use of hyperbaric oxygen is the large number of treatments needed. In study by Dall'era, patients received 100 % oxygen in a multiplace hyperbaric chamber at pressure of 2.4 atmospheres absolute for 90 min 5–7 days weekly for an average of 36 sessions [49]. Hyperbaric oxygen therapy is also very expensive. Woo et al. [50] published a retrospective review of 18 patients who underwent hyperbaric oxygen therapy and he demonstrated complete or partial resolution of symptoms in ten (56 %) of the patients. The average number of hyperbaric oxygen sessions was 24. Hyperbaric oxygen therapy is very expensive with a cost estimated at US$1200 for 90 min of high-pressure therapy using 100 % oxygen at a major medical center, and a typical course of treatment running near 40 or more sessions [51].

Patients failing these treatments may require surgical management including intestinal diversion or proctectomy (see Chap. 16).

Table 9.2 is a summary of therapies for CRP.

Table 9.2 Treatments for chronic radiation proctopathy

Pharmacotherapies
5-Aminosalicylic acid
Suppositories
Enemas
Corticosteroid enemas
Sucralfate
Oral
Enemas
Formalin
Short chain fatty acid enemas
Retinol Palmitate
Other therapies
Estrogen/progesterone
Hyperbaric oxygen
Antioxidants
Sodium pentosan polysulfate
Misoprostol
Cautery
Laser
Argon plasma coagulator
Bipolar electric cautery
Surgery
Diverting colostomy
Proctectomy

Prevention

Advances in computer technology have led to development of three-dimensional (3D) RT planning systems and computer-controlled RT delivery [52, 53], which will potentially improve the efficiency with which external beam RT can be planned and delivered with a reduction in complications and cost. Intensity-modulated RT (IMRT) requires the same 3D radiation treatment planning, but takes it further by utilizing variable, computer-controlled intensities within each RT beam. This allows for a higher degree of accuracy in conformation of the radiation to the planned target, while sparing normal tissue. A phase II trial studying 83 patients with endometrial and cervical cancer receiving IMRT showed lower hematologic toxicity by reducing the volume of bone marrow irradiated [54] as compared to conventional radiotherapy (CRT). Another retrospective review of patients with rectal cancer comparing 61 patients treated with conventional RT versus 31 patients with IMRT showed a significant reduction in acute lower GI toxicity including enteritis, diarrhea, and proctitis [55]. A different study of patients with prostate cancer receiving pelvic radiotherapy found that those receiving IMRT had a 40% relative reduction in the volume of bowel receiving 45 Gy in comparison to conventional two-dimensional (2D) planning. This newer technology has promise in reducing rates of acute and chronic GI morbidity when using RT.

Preventive therapeutic strategies currently being studied include the use of antioxidants, cytokine modification, free-radical scavengers, novel anti-inflammatory agents, enterotrophic strategies, modulators of intraluminal contents, modulators of endothelial dysfunction, as well neuroimmunomodulators [56]. For further details, please see Chap. 4, Prevention of Injury from Pelvic Irradiation.

Conclusion

ARP and CRP are common complications of pelvic RT. CRP is associated with significant morbidity due to rectal bleeding from telangiectasia formation and both profound blood loss and fistulization are severe consequences of severe CRP. Functional symptoms that occur from loss of rectal compliance including urgency, tenesmus, increased stool frequency, and fecal incontinence have received less attention in the medical literature. APC is currently recommended as optimal treatment for bleeding from telangiectasias. Retinol palmitate is under active study and symptomatic treatments can be used for functional symptoms.

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Effects of Radiation Therapy for Rectal Cancer on Anorectal Function

10

Jose Marcio Neves Jorge, Angelita Habr-Gama and Leonardo A. Bustamante-Lopez

Introduction

Pelvic irradiation is an essential part of the curative treatment of advanced pelvic malignancies, including rectal, prostate, uterine, and cervical carcinoma. In spite of advances in the implementation of radiation therapy, the adjacent healthy tissues remain at risk for damage. The rectum, due to its fixed position in the pelvis and location near other frequently irradiated organs, is the most common site of injury after pelvic irradiation; more specifically, the rectum is negatively affected in more than 70 % of patients with radiation gastrointestinal injury [1].

The effects of irradiation on anorectal function are dose-dependent. The total radiotherapy dose, dose per fraction, and volume of rectum irradiated are risk factors for development of injury. Patient-related risk factors include conditions such as diabetes, connective tissue diseases, malnutrition, and general medical condition. In addition, patients who develop acute radiation proctopathy are probably more likely to develop late radiation proctopathy [2].

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Although patients with rectal cancer receive a lesser total radiation dose than patients with cervical, prostatic, or anal cancer, impairment of anal sphincter function has been demonstrated in this patient group [3]. Regardless of the regimen (adjuvant or neoadjuvant), pelvic radiotherapy adversely affects anorectal function; although survival remains the primary goal in treatment of rectal cancer, an adequate anorectal sphincter function is crucial for preservation of quality of life.

Several mechanisms altering anal continence occur with radiation therapy, including the development of abnormal stool consistency and increased frequency, diminished rectal capacity and compliance, decreased anorectal sensation, and direct damage to the anal sphincters and their innervations (Fig. 10.1) [4]. These adverse effects can occur early or late in the course of treatment.

Radiation Proctopathy

Acute radiation proctopathy develops during or shortly after a course of radiation therapy. It presents as diarrhea, rectal pain, and tenesmus and is usually of short duration.

Chronic radiation proctopathy occurs at least 6 months after radiotherapy; about 85 % of cases present within the first 2 years after radiotherapy. Although the true incidence of chronic radiation proctopathy is unknown, data from retrospective studies suggest that between 2 and 20 % of

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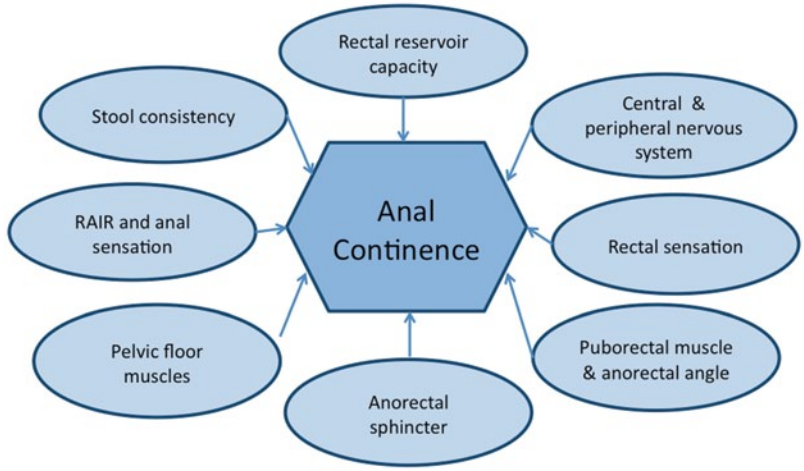

Fig. 10.1 Mechanisms involved in the complex physiopathology of anal incontinence secondary to pelvic irradiation

patients who receive radical pelvic irradiation are at risk of developing chronic radiation proctitis [5]. This condition is characterized by painless passage of blood per rectum, mucous rectal discharge, frequent bowel movements, urgency, and fecal incontinence rectal pain. Less commonly, severe rectal bleeding, ulceration, fistulas, bowel perforation, and bowel obstruction can occur.

Late radiation damage is often characterized histologically by a loss of parenchymal cells and an overproduction of collagen. The classic theory of late radiation injury states that depletion of parenchymal cells leads to late injury, and that the latent period preceding the development of late effects is caused by the long cell cycle of many of these target cells. Haboubi et al. [6] reported patients who underwent rectal biopsies during or shortly after completing radiotherapy (6 patients) or 4 months after radiotherapy (4 patients). Biopsies from the former group showed epithelioid meganucleosis, lack of mitotic activity, and patchy fibroblastic activity in the lamina propria, whereas the blood vessels appeared normal. Biopsies from the latter group showed subintimal fibrosis resulting in arteriole narrowing, telangiectasia of capillaries and postcapillary venules, endothelial degeneration, platelet thrombi formation, fibrosis of the lamina propria, and crypt distortion. These authors suggested that cellular epithelial change and fibroblastic proliferation occur initially followed by vascular changes.

Recent evidence has highlighted the importance of microvascular endothelial damage as a major contributor to normal tissue injury after radiation [7, 8]. The endothelium has been shown to be an important target for radiation in the lung, brain, and gut; apoptosis of the microvascular endothelial cell seems to be the earliest lesion in the gastrointestinal tract after radiation followed by stem cell dysfunction [7].

Effects of Pelvic Radiation on Anorectal Function

The most commonly irradiated pelvic organs are the prostate and cervix, followed by the anus [2]. The adverse effects of pelvic radiation in the anorectal sphincter (both muscular and neurogenic) and rectal reservoir capacity and compliance have long since been documented [1, 2]. Rectal cancer is a relatively common malignancy and more recently the role for neoadjuvant chemoradiation has been defined. Currently, patients undergoing treatment for rectal cancer require a multimodality approach. The adverse effects on anorectal function are very complex due to the combined effects of chemoradiation as well as the rectal resection.

Effects of Surgery

In the last decade, sphincter-preserving techniques have replaced abdominoperineal resection and a permanent stoma in patients with midrectal and low rectal cancer, as long as the mesorectum is totally excised and an adequate distal margin of 2.0 cm can be obtained. Therefore, the low and ultra-low coloanal anastomosis can be accomplished, and procedures such as intersphincteric resection of the rectum have been developed. However, when the level of the anastomosis becomes less than 3–4 cm to the dentate line, the patient's quality of life may be significantly compromised. In these patients, in addition to the loss of the rectal reservoir, the resting pressure barrier can be greatly compromised by damage to or removal of the internal anal sphincter. Therefore, the occurrence of incontinence in these patients is influenced by diminished rectal capacity and compliance, decreased internal anal sphincter tone, and impairment of rectoanal inhibitory reflex and anal sensitivity.

Neural injury after rectal resection, is manifested by a variety of symptoms, including urinary dysfunction (as high as 12 % of patients) and sexual dysfunction, in 10–35 % of patients after total mesorectal excision. New techniques have been designed to minimize these complications [9–11], particularly the introduction of the nerve sparing total mesorectal excision technique. The goal of these techniques is to provide negative circumferential margins while minimizing the incidence of complications due to neural injury, such as genitourinary dysfunction. Although only limited data are available regarding robotic-assisted total mesorectal excision, this recent innovative technique may improve functional outcome due to better preservation of autonomic nerves [12]. However, due to its cost, further studies are warranted to justify its role in routine application.

Restorative protectomy can adversely affect the mechanisms of anal continence in 30–90 % of patients after anterior resection. This condition is known as the anterior resection syndrome [13]. Symptoms include increased bowel frequency, urgency, fragmentation of stool and fecal incontinence, and have a negative effect on patient's quality of life. Multiple factors may produce the anterior resection syndrome. Although the loss of rectal reservoir and its mechanisms of capacity and compliance have been largely implicated, sphincter damage and autonomic nerve injury from surgery are other possible causes [14, 15]. Whenever the rectum is removed and a low colorectal or coloanal anastomosis is necessary, the option of adding a colonic pouch or a coloplasty should be considered. Although the functional results of this "neorectal reservoir" are controversial, a recent meta-analysis demonstrates equally beneficial effects on anorectal functional symptoms [16].

Radiotherapy adversely affects rectal function due to reduction in rectal capacity and compliance as a consequence of proctitis and fibrosis of the rectal wall [3, 17]. Preoperative or neoadjuvant chemoradiotherapy can minimize this problem because the irradiated rectum is excised and healthy colon is anastomosed to the lower rectum or anus. Intraoperative radiotherapy has also been employed to diminish impairment of anorectal function. Postoperative incontinence appears to be most pronounced when postoperative external beam radiotherapy was administered [18, 19].

Varma et al. [20, 21] studied anorectal manometeric findings in patients with prostate cancer receiving external beam radiation. They also reviewed histopathological aspects of formalin-treated tissue from the lower rectum obtained from eight other patients who had undergone excisional surgery for complications of radiation rectal injury. In these patients, damage to the myenteric (Auerbach's) plexus was demonstrated, and included marked hypertrophy of the nerve fiber with vacuolation of the nerve sheaths and changes in number (decreased) and morphology of ganglion cells. Although the function of the external anal sphincter remains relatively unaffected, dysfunction of the internal anal sphincters seems to be the main factor in the pathophysiology of anorectal dysfunction. Damage to the radiosensitive myenteric plexus is an important factor, although a degree of direct damage to the smooth muscle also occurs.

Deterioration of anorectal function after radiotherapy has also been attributed to direct

radiation damage to the anal sphincters. Decrease in resting and/or squeeze anal pressures has been demonstrated as an indirect evidence of this injury in many studies [22, 23]. Accordingly, DaSilva et al. [24] studied the internal anal sphincter from abdominoperineal resection specimens of 18 patients, 12 of who had preoperative chemoradiation for rectal cancer. These authors found increased fibrosis and nerve fiber density of the internal anal sphincter in specimens obtained from patients with prior chemoradiation.

In addition to the direct injury of the sphincters, it has been demonstrated that radiotherapy can cause lumbar plexopathy in up to 6% of patients after short course radiotheraphy for rectal cancer [20] (see Chap. 14 for additional information about lumbosacral plexopathy).

Radiotherapy for distal rectal cancer can also damage the pudendal nerve as it courses within the field of irradiation [25]. In a study of 66 patients with resectable rectal cancers who received 45 Gy doses over 5 weeks plus 5-fluorouracil (5-FU) (350 mg/m^2/day) and leucovorin (20 mg/m^2/day) concurrently on days 1–5 and 29–33 [23], a significant deterioration in incontinence score and anal squeeze pressures occurred while resting pressures remained unchanged. In this study, 26 patients who had rectal cancer with a distal margin within 6 cm of the anal verge had the anus included in the field of radiotherapy, whereas patients with more proximal tumors (6–12 cm from the anal verge; $N=40$) had shielding of the anus during radiotherapy. Both groups had similar functional results. In total, 18 patients (27%) developed unilateral or bilateral pudendal neuropathy after chemoradiation. Another four patients with unilateral prolonged pudendal latencies at baseline, developed prolonged terminal motor latencies of the contralateral pudendal nerve as well. These patients had worsened incontinence scores and squeeze pressures. These occurred independent of tumor response to chemoradiation. Pudendal neuropathy therefore, may explain the decrease in squeeze pressures following chemoradiation found in many studies and thus, contribute to poor functional results after restorative proctectomy for rectal cancer.

Not all studies of neoadjuvant chemoradiation show a high degree of fecal continence in rectal cancer patients. Pietsch et al. [26] compared clinical and manometric parameters before and after surgery (evaluations at 3–6 months and 6–12 months) in 27 patients who were treated by surgery alone and 12 patients who received neoadjuvant chemoradiation (5-FU, CPT-11, and 45+5.4 Gy boost). Preoperatively, none of the patients had symptoms of fecal incontinence and manometric parameters were normal. Postoperatively, fecal continence was impaired in both groups, but no significant difference was found between patients with or without chemoradiation. Similarly, anorectal manometry parameters revealed an impairment of anorectal function after low anterior resection regardless of treatment regime. The authors concluded that impairment of anal continence after low anterior resection is determined by the surgical procedure only and not aggravated by neoadjuvant chemoradiation. These results are in accordance with other reports in the literature [27–29]. In addition to the limited number of patients studied, the timing of postoperative measurements is a limiting factor in these studies and may explain discrepancy among authors [30–35]. With recent ongoing advances in neoadjuvant therapy regimes, a tendency to more favorable postoperative functional results can be expected, however results are still conflicting as seen in Table 10.1 [36–40].

In a recent systematic review and meta-analysis, Loos et al. [40] analyzed the long-term functional results of patients with rectal cancer undergoing preoperative chemoradiation. The methodological quality of the 25 studies identified was poor. The majority of studies reported higher rates of anorectal dysfunction (14/18 studies) and male sexual dysfunction (9/10 studies). A limited number of studies examined female sexual dysfunction (4 studies). Meta-analysis revealed that the symptom of fecal incontinence occurred significantly more often in irradiated patients and manometric parameters of resting and maximum squeeze pressures were significantly decreased after preoperative radiochemotherapy. The authors concluded that although the

Table 10.1 Effects of neoadjuvant radiotherapy on anorectal function: results of literature

Author	Year	Preoperative Regimen	*n*	Impairment of anorectal function	Follow- up	Manometric evaluation
Dahlberg et al. [30]	1998	Short term	171	Yes	5 years	No
van Duijvendijk et al. [32]	2002	Short term	34	Yes	1 year	Yes
Welsh et al. [33]	2003	Short term	124	Yes	3 years	No
Peeters et al. [34]	2005	Short term	597	Yes	5 years	No
Pollack et al. [35]	2006	Short term	21	Yes	14 years	Yes
Birnbaum et al. [27]	1994	Conventional	10	No	3 years	Yes
Gervaz et al. [31]	2001	Conventional	45	Yes	2 years	No
Denhi et al. [36]	2002	Conventional	28	Yes (Partially)	1 year	No
Nathanson et al. [28]	2003	Conventional	109	No	5 years	No
Ammann et al. [25]	2003	Conventional	28	Yes	1 year	Yes
Saito et al. [29]	2004	Conventional	20	No	1 year	Yes
Pietsch et al. [26]	2007	Conventional	12	No	6 months	Yes
Coco et al. [37]	2007	Conventional	100	Yes	1 year	No
Canda et al. [38]	2010	Conventional	31	Yes	1 year	Yes
Denost et al. [39]	2011	Conventional	51	Yes	5 years	No

data on long-term functional outcome are limited, current evidence demonstrates that preoperative radiochemotherapy negatively affects anorectal function after rectal resection (using total mesorectal excision technique) and patients need be informed about this potential harm of treatment. A multitude of additional factors, including the inherent effect of age or comorbidities such as diabetes mellitus in the sphincter mechanism and the effects of many conditions that alter stool consistency, can participate in the complex etiology of fecal incontinence.

Since survival from rectal cancer has improved substantially over the last two decades, therefore there is also increasing concern about the long-term consequences of the current therapeutic regimens on quality of life. Knowles et al. [41] recently studied the prevalence of pelvic dysfunction and the impact on quality of life after curative colorectal cancer surgery with or without radiotherapy. Patients responded three validated questionnaires; the median time interval following treatment was of 4.4 years. In the 138 patients studied that had undergone treatment for rectal cancer, the following defecatory complaints were found: incontinence of gas: 32%, fecal leakage: 16%, wear of pad: 17%, and incomplete evacuation: 31%. Preoperative radiotherapy and low level of anastomosis (< 6.0 cm) were associated with increased defecatory problems. New models of comprehensive evaluation and interventions in patients who are at risk of experiencing these late adverse effects should be designed.

Management of Radiation-Related Functional Problems

A wide variety of strategies have been employed to treat radiation proctopathy, including anti-inflammatory agents in combination with retinyl palmitate, rectal steroids, rectal sucralfate, short-chain fatty acid enemas, and different types of thermal therapy [42–44]. General concepts to keep in mind regarding the management of these patients: (1) treatment of rectal bleeding is generally most successful if it involves topical application of cautery or a sclerosing agent to obliterate telangiectasias; (2) other symptoms may benefit from therapy directed at pathophysiological changes; (3) anti-inflammatory agents have a small role in the management of this condition; and (4) intractable pain, large rectal ulcers and intractable bleeding may require surgical management [44] (see Chap. 15).

Treatment of Fecal Incontinence

Fecal incontinence is a major problem for many patients surviving treatment for rectal cancer, the treatment of this condition varies tremendously among authors and the evidence on the most commonly used treatments is sparse [45]. This lack of standardization is largely due to the multitude of mechanisms that can be involved in fecal incontinence.

After a low colorectal or coloanal anastomosis, about 30–60% of patients will develop anal dysfunction due to the loss of the rectum and internal sphincter [46]. These patients develop clinical symptoms and signs of the so-called anterior resection syndrome, which includes stool frequency, urgency, fragmentation, and soiling. However, because functional outcomes tend to improve overtime, even in the absence of biofeedback, the symptoms of anterior resection syndrome usually improve gradually or even disappear during the first 1–2 years after resection. Therefore, waiting for improvement of symptoms during this period of adaptation is one of the most commonly used strategies for postradiation fecal incontinence [47].

First line therapy for functional disturbances after treatment for rectal cancer should be conservative and aimed at symptomatic relief. Dietary regimens, fibers, constipating agents, anal plugs, enemas, and domiciliary (Kegel's) anal sphincter exercises are the most commonly used measures within initial conservative therapy. However, the evidence for this initial approach has never really been established.

If the symptoms of fecal incontinence persist, therapeutic decision should be reached after accurate assessment of the underlying cause of anorectal dysfunction [4]. This assessment includes a thorough history, physical and endoscopic examination, and anorectal physiology studies. The most helpful studies are of anorectal manometry, and if there is an indication for assessment of neuromuscular integrity, external anal sphincter electromyography and motor pudendal nerve latencies are also indicated. Other studies such as anal canal sensitivity tests, although important for understanding the mechanisms involved, are of limited use in clinical practice [48].

Biofeedback has been widely used to treat fecal incontinence, and may be an effective treatment for patients with anterior resection syndrome after surgery for rectal cancer. In a nonrandomized retrospective study of 3012 patients treated for primary rectal cancer Kim et al. [48] reported good results with biofeedback in 70 patients with fecal incontinence. Patients who started biofeedback therapy 18 months or more after surgery had significantly greater improvement in fecal incontinence score compared to those who started biofeedback less than 18 months after surgery. Thus, delaying the start of biofeedback therapy may enhance its effectiveness; this finding is probably related to the above-mentioned adaptation period required after low anterior resection. Interestingly, satisfaction scores were significantly higher after biofeedback therapy in patients treated with surgery plus radiotherapy than in patients treated by surgery alone. Both of these groups had significant improvements in fecal incontinence score and number of bowel movements, but only the radiotherapy group had statistically significant improvement in anorectal manometry parameters [47].

Injections of bulking agents can be offered to patients with passive incontinence particularly when injury is limited to the internal anal sphincter. Even though this treatment does not result in significant increase in anal pressures, improvement in sphincter asymmetry index, associated to symptomatic improvement has been reported [49]. Based on a recent systematic review, the long-term outcome of injectable bulking agents has been questioned [50]. Sacral neuromodulation has been advocated as a safe and effective therapy for severe fecal incontinence and shown to be associated with minimal morbidity [51, 52]. In the literature, the experience with sacral neuromodulation in patients with fecal incontinence related to the anterior resection syndrome is still limited [53–57]. However, this minimally invasive therapeutic option been considered as the first choice in surgical treatment when conservative therapies fail [54–56].

Recently, Schwandner [56] reported his experience with nine patients (three females; mean age 61 years) who underwent sacral neuromodulation for fecal incontinence and "low anterior resection syndrome" following neoadjuvant therapy for rectal cancer. The implantation rate was 100 % and no septic morbidity was observed. After a mean follow-up of 12 months, the mean Cleveland Clinic Incontinence score was reduced from 18.2 to 6.0 ($p < 0.01$). Incontinence episodes were significantly reduced from 7 to 0.5 per day and 20 to 8 per week. Fecal urgency, fragmented defecation, and anal soiling were improved or resolved in two-thirds of the patients. Although anorectal manometry did not correlate with clinical success, quality of life was significantly improved. The author reported that preliminary results of sacral neuromodulation in patients with fecal incontinence and symptoms of low anterior resection syndrome are promising and enrich the therapeutic modalities if conservative management has failed.

Complex procedures such as gracilis muscle transposition and artificial sphincter implantation should be considered only in highly selected cases [51]. Finally, formation of an abdominal stoma must always be considered as a valid option for patients with severe fecal incontinence not responding to standard continence regimens [51].

Summary and Future Outlook

Because survival from rectal cancer has improved over the last decades, there is an increasing concern about the long-term consequences of the current therapeutic regimens on anorectal function and quality of life.

Regardless the regimen, adjuvant or neoadjuvant, it is widely accepted that pelvic radiotherapy adversely affects anorectal function, and although survival remains the primary goal in treatment of rectal cancer, an adequate anal continence is necessary for a good quality of life.

Radiation damages primarily the internal anal sphincter, and although direct muscular lesion occurs, the myenteric cells are more frequently damaged. Other mechanisms of continence potentially affected by radiotherapy include: decreased stool consistency, impaired rectal capacity, and decreased anorectal sensation. These side effects, associated with a progressively increasing indication of sphincter-preserving operations, have demanded newer pelvic radiation techniques. Recent developments in computer-based treatment planning and medical imaging have facilitated this advance and more favorable postoperative functional results are expected in the future.

Symptoms of urgency and fecal incontinence are common after anterior resection, with or without neoadjuvant chemoradiotherapy, but usually improve during the first 2 years after surgery. In patients with persistent symptoms of fecal incontinence, conservative therapy, including biofeedback should be offered.

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11 Effects and Management of Pelvic Radiation on Female Reproductive System: Sexual Dysfunction, Fertility Effects, and Premature Menopause

Claudine Domoney and Dimitrios Nikolaou

Introduction

As a result of advanced treatment techniques, great strides have been made in the enhancement of survival in patients with pelvic malignancies. However, control and even cure of these malignancies come with a price; and all health professionals involved in the care of these patients must be aware of the issues of post-treatment sexual dysfunction as well as treatment-related hormonal effects on fertility and menopausal status. Instead of focusing solely on cancer recurrence and direct physical effects of treatment, sexual function and dysfunction, signs and symptoms of premature menopause and when relevant, fertility issues should be reviewed on a regular basis during follow-up evaluations. Unfortunately, although interest is increasing, these aspects of post-treatment care in women with pelvic malignancies have not been well-studied, and therefore the data discussed in this chapter are, in part, extrapolated from the range of published work and personal experiences related to these conditions.

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Pelvic Radiation and Sexual Function

Prevalence of Sexual Dysfunction

The high prevalence of female sexual dysfunction or difficulties in the general population makes it challenging to extract information regarding the changes in female sexuality in women who have been treated for pelvic cancers. Estimates of their prevalence in the general population are highly dependent on definitions. Nonetheless, a study of the general USA female population suggests a prevalence of female sexual difficulties of up to 43 % [1]. A survey from the UK reported 15.6 % of women had a persistent sexual difficulty lasting over 6 months [2]. Sexual dysfunction in women treated for gynaecological cancers is considerably higher and is estimated to range from 50 to 80 % [3]. Although, there is controversy regarding the impact of age and hormonal status on female sexuality in general, both may alter the effects of surgery, radiotherapy and chemotherapy on the female reproductive organs and female sexual function. The physical, physiological, behavioural and psychological impact varies over the time from diagnosis of pelvic cancer, the treatment phase and during follow-ups.

Attitudes of Patients and Clinicians About Sexual Concerns

A better understanding of the attitudes and behaviours of patients and clinicians has been achieved

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about sexual issues going a long way in helping to enhance the legitimacy of these issues and to improvise the clinical approach of treatment. Healthcare professionals may have limited impact because of time constraints, lack of training and lack of expertise in approaching these problems. Women's attitudes about sexual function may be suppressed as they focus on treatment of their cancer and enhancement of their survival. Loss of female sexual function may be viewed as an appropriate cost to be paid in this process. This attitude is further reinforced by a lack of emphasis amongst clinicians having a 'biomedical gaze' [4] on scientific goals such as clinical effects of treatment and risk of recurrent disease. A low priority for addressing sexual difficulties may be compounded by the lack of input from the oncology services. The treatment and survival components of cancer care may also strongly impact sexual partners who may feel that their needs and wishes are of minor importance.

Medicalization of women with pelvic cancers persists indefinitely. Although, quality of life issues are sometimes addressed, for example, in oncology consultations it is clear that sexual issues are an infrequent focus. However, female patients appreciate initiation of these conversations, even if they are not a current priority [4]. There is evidence that overall women are willing to accept that a change in sexuality is a consequence of cancer treatment survival. A 'response shift' and modification of expectations amongst patients have been shown to occur following the diagnosis of pelvic cancer [5, 6]. Nonetheless, in our view, health care professionals should not accept this as a reason not to address the possibility of sexual concerns. Women report an interest in obtaining information about the impact of treatment of pelvic cancer on sexuality [7]. In this study, 74% of patients wanted their health care professional to discuss sexual concerns; however, a discussion only took place in 38%. Lindau et al. [7] also reported that conversations with a physician about sexual matters decreased the likelihood of complex issues in long-term vaginal and cervical cancer survivors. Interestingly, discussions about sexual side effects of treatment for prostate cancer are common, perhaps due to the accessibility of the phosphodiesterase inhibitors that have allowed a readily available solution for erectile dysfunction, a common consequence of pelvic irradiation. Only one out of a number of studies reports that sexual concerns were discussed in 50% of male prostate cancer clinic consultations [8].

The assessment of female sexual function based on medical literature, particularly in this group of women, has many challenges. Questionnaires have varying recall periods (1 week to 6–12 months), and are invalidated or have validation in different patient groups and ages. There has been little attention toward the assessment of 'distress', despite this being a key component of a significant sexual problem. What is the 'true' prevalence of female sexual dysfunctions? Does the way we assess these conditions have an impact? [9]

In addition, evaluation of those not sexually active or lacking a partner (with measurement of sexual feelings, confidence and body image issues), has not been performed. An improved understanding of the sexual effects occurring during the time of treatment and recovery, as well as clarification of the duration and persistence of these effects are critically important to quantify.

Gynaecological Cancers and Their Association with Sexual Functioning

Patients with gynaecological cancers frequently associate a relationship between the occurrence of their cancer and sexual activity. A common presentation of cervical cancer is postcoital bleeding, and cancer recurrence may also cause vaginal bleeding during intercourse. Even if the bleeding is from a benign cause, such as vaginal atrophy, cancer survivors still have a negative association of symptoms being present due to sexual activity. The impact of gynaecological and breast cancers appears to have more impact on sexuality rather than other cancer diagnoses [10].

Having a diagnosis of human papilloma virus (HPV) infection alone is known to negatively impact sexual function, in part, because of the knowledge that HPV is a sexually transmitted infection and implications related to its association with

cervical cancer [11]. Patients with known cervical infection with HPV have feelings of self-blame, guilt and decreased interest in sexual activity.

Patient perception of mutilation of their genital organs from treatment of gynaecological cancers, particularly surgery and radiotherapy, has profound psychosexual effects. Focusing on the function of the vagina as a receptive organ affected by the impact of pelvic irradiation, often, is not the appropriate model for addressing psychosexual concerns. This is particularly the case in non-sexually active patients (with or without a sexual partner). Women report feelings that their vagina is no longer a place of pleasure but an area of treatment, investigation and examination [12]. Fantasies around this are powerful and affect sexual desire, arousal and orgasmic potential.

Physical Effects of Pelvic Radiotherapy

Irradiation of pelvic tissue causes acute and latent effects. The severity of many effects, including degree of fibrosis, oedema, inflammation and tissue necrosis, may have delayed presentation. Physical changes in genital organs, bladder and bowel have an impact on body image and female sexuality after pelvic radiation, with or without surgery. Sexual confidence and feelings of femininity, in turn, exacerbate psychosexual issues. The physical effects of vaginal pain, dryness, bleeding and reduced vaginal elasticity can interfere with arousal and orgasmic potential. Overall lack of libido or reduced sexual desire is a common consequence [13]. Acute effects of radiotherapy on the vulva and vagina include epithelial shedding leading to thinning of vaginal wall. Generally, acute effects resolve after 2–3 months but the longer-term effects emerge 6–12 months later (please see Chap. 6: Pathophysiology of Radiation Effects on Healthy Tissue).

Late effects that often worsen over time include adhesions, atrophy and fibrosis with resultant narrowing and shortening of the vagina. Reduced vaginal intercourse perpetuates these problems, and may result in irreversible total vaginal stenosis.

Interventions are aimed at the physical changes to limit reduction in vaginal capacity. Vaginal dilators have been proven to be valuable in reducing permanent scarring due to radiotherapy. A complete patient education on the technicalities of dilator use and psychosocial support is critical for patient treatment adherence [14]. Without focus on the psychosexual difficulties that women have after pelvic irradiation, their use or engagement with these interventions may be limited. There is currently lack of correlation of dilator use with sexual activity and function in the medical literature.

Vaginal bleeding is associated with the signs of gynaecological cancer, and therefore, causes fear and apprehension, both, for the women and their sexual partners. A study of treated patients with cervical cancer observed that 25% of patients had bleeding during or after sexual intercourse and 28% observed a significant reduction in lubrication persisting for 2 years after radiotherapy [15]. Vaginal effects of radiation therapy that includes mucosal atrophy and desquamation, shortening and stenosis are inadequately assessed in studies and clinical practice. There are a few grading scales that are reliable measurement instruments, but is making reproducible prospective assessments problematic. Stenosis prevalence is reported to be 24–88% [16]. Interestingly, this prospective study suggests that vaginal stenosis is highly associated with radiation administration to women over 50 years of age but is not dependent on the hormonal status. The authors suggest that reduced sexual activity and lack of vaginal oestrogen were factors critical for the development of vaginal stenosis, despite lack of data to prove their hypothesis.

Grading of the severity of vaginal toxicity has been used for assessment of treatment effects. Brand et al found Grade 1 (partial stenosis or shortening) in 27%, grade 2 (complete vaginal occlusion) in 11%, grade 3 (ulcer formation) 1.7% and grade 4 (fistula formation) in 2.3% of the patients. Overall, 58% of the patients had insignificant or no change. Presence of bowel or bladder symptoms was independent of the impact on the vagina but important for sexual function-

ing. Overall, the impact of systemic oestrogen deficiency has been poorly addressed in this group.

Bladder-related side effects of pelvic radiation therapy include stenosis and fibrosis causing overactive bladder symptoms with or without urge incontinence and bladder pain syndrome. These abnormalities are also independently associated with sexual dysfunction [17, 18]. The occurrence of radiation enteropathy, colopathy or proctopathy as well as other anorectal symptoms developed from radiation therapy has received little attention in the medical literature, especially with respect to sexual function in women [19]. However, incontinence of faeces and/or flatus is associated with significant sexual difficulties [20, 21]. Women receiving a stoma after treatment for anorectal cancers have an even higher risk of sexual dysfunction related to poor body image and anxiety [22].

Radiation therapy applied to the ovaries affects the granulosa cells that support ovarian follicles and the maturation process of oocytes. These are the most rapidly dividing cells and iff the majority of these cells are destroyed, lack of hormonal functionality and irreversible infertility is likely to occur, particularly, in older women. Even females receiving radiotherapy and chemotherapy for childhood cancer have reduced ovarian reserve [23]. The impact of premature oestrogen deficiency is discussed later in this chapter. Other more general effects of radiotherapy treatment including fatigue, skin changes and hair loss may be important factors in general sexual function, and result in a diminished body image.

Sexual Dysfunction in Gynaecological Cancers

Cervical Cancer

The management of cervical cancer in early-stage diseases is radical hysterectomy and pelvic lymphadenectomy. Patients with advanced disease and with lymph node metastases are treated with radiotherapy and administered, both, external beam radiation and brachytherapy. Several longitudinal and cross-sectional studies have examined sexual activity and function in women treated with radiotherapy for cervical cancer [24–28]. These studies demonstrate that radiation therapy can result in progressive sexual dysfunction. Manifestations include physical, behavioural and psychological effects. In addition to the direct effects from the treatment for cervical cancer, sexual dysfunction can also occur as a reaction to the diagnosis itself.

With respect to the physical effects of radiation treatment on cervical cancer, Jensen et al [26] reported significant sexual dysfunctions compared to controls for over 2 years. Almost half of the treated patients reported that the vagina was too small and 43 % were either unable or only occasionally able to complete intercourse. One-third of them reported significant lubrication problems resulting in distress in half of these women. In a small study, Flay and Matthews reported dyspareunia, concern regarding bleeding, low back pain, vaginal dryness, shortening and narrowing in one- to two-thirds of the observed women at 14 weeks post treatment [24]. This study also suggested that there was an increase in the belief that sex would cause a recurrence of disease. Comparing this belief before and after treatment, 37 % thought sexual activity would cause a recurrence pre-treatment, 47 and 43 % of patients believed this at 6 and 14 weeks after treatment, respectively. One-third of patients also believed that sexual activity would aggravate their cancer. These studies support the important role of education before and after therapeutic interventions for cervical cancer. Continuous education about the disease should be offered at follow-up visits. Other educational means, such as patient support groups and written information, is strongly advised to prevent these erroneous and harmful beliefs.

A review of sexual difficulties and quality of life after cervical and endometrial cancer treatment was performed by White et al [1]. Their study developed the hypothesis that the contribution of bladder and bowel abnormalities as well as fatigue in combination with the psychosocial factors contribute to the overall reduction in quality of life and as a consequence, sexual well-being.

The impact of surgery for gynaecological carcinoma on sexual function requires additional study. Radical hysterectomy disrupts the vascularity, innervation and autonomic regulation of the pelvic organs. It has been challenging to separate the effects of the surgery from radiotherapy when assessing changes in sexual well-being in women being treated for cervical cancer [6]. Clearly, the immediate impact of surgery on hormonal status has further effects. This is again infrequently investigated in the medical literature. One of the papers reported a significant influence of radical hysterectomy and pelvic lymphadenectomy on dyspareunia, when this group was compared to an age-matched general population control group [26]. They reported that dyspareunia occurred secondary to reduction in vaginal capacity and vaginal mucosal dryness.

Sexual activity, interest in sex and pain tolerance decreases in women prior to treatment, i.e. after diagnosis of cancer or related to the symptoms [29]. However, there is also an increase in orgasmic difficulty in the first 6 months post surgery [30]. Reassuringly, 91 % of women who were sexually active before surgery had resumed sexual activity within 12 months, although there was a significant reduction in frequency being reported. Women receiving radiotherapy for cervical cancer were less sexually active than those with surgery alone; although other aspects of sexual function were no different, 24 months after treatment.

Endometrial Cancer

A few studies have addressed issues of quality of life and sexual functioning of women after treatment of endometrial cancer with surgery alone or surgery and radiotherapy. As the majority of patients with endometrial cancer present early in their disease, curative treatments including surgery and radiation therapy may have a significant impact on long-term quality of life. There is a suggestion that post-operative brachytherapy may have fewer side effects and less diminution of quality of life than external beam radiotherapy. No differences in the recurrence rate of endometrial cancer are seen with these two treatments [31, 32]. Unfortunately, published studies addressing effects of these treatments having equal function have used nonvalidated questionnaires [33–35].

The vaginal mucosa commonly exhibits changes following radiation as its cells have a high turnover rate. Subsequent effects including telangectasia formation, adhesions and stenosis have been found in 50–63 % of the exposed patients after treatment for endometrial cancer [34]. In this study, no difference in mucosal atrophy was found when external beam radiation was given in addition to brachytherapy, yet only a small number of patients (20 out of 75) were sexually active before treatment. Thirteen of these 20 patients (65 %) reported decreased sexual activity and interest after radiation, and 12 (60 %) of them reported pain. Dyspareunia may be progressive and is worsened by stenotic effects of radiation damage.

Assessment of long-term morbidity of treatment for endometrial cancer can help improve the decision-making process for management, but at present more evidence and data are required than are currently available. Although the limitations and difficulties of this work are recognized, it is imperative that these studies are undertaken with appropriate measurement instruments in sufficiently large study groups to allow for accurate interpretation of study results.

Vulval Cancer

The impact of vulval cancer on sexual functioning is well-recognized [36, 37]. Surgery for vulvar cancer can be significantly mutilating, as can adjuvant radiotherapy used for positive lymph nodes and radical radiotherapy for more advanced lesions. These treatments also readily compromise other structures in the lower urogenital and anorectal regions. Most studies of sexual function have examined the effect of the surgical procedure rather than the radiotherapy itself. One of the studies reported a high risk of reduction in sensation and orgasm with increase in the narrowing of the introitus after surgery. Little

recovery from these effects occurred over time [38]. Other work confirms the high risk of severe dysfunction after surgery [39, 40]. There is a perception particularly amongst younger women with vulval disease that they have an "old ladies' disease" that then severely impacts body image and female sexuality.

Bladder Cancer

There is a paucity of sexual function follow-up in women treated for bladder cancer. More studies have been performed on complications of therapy for bladder cancer in men. In the available published literature, women who were sexually active pretreatment reported a loss of sexual desire [41, 42]. Due to the small number of women studied, it is not possible from these numbers to determine the differential effects of surgery and radiotherapy.

Colorectal Cancer

There is more information with respect to sexual consequences of radiation treatment of the rectum compared to other pelvic cancers. In women, there is a clear detrimental effect of adjuvant radiotherapy that occurs in addition to surgical consequences. A longitudinal study documented progressive reduction in sexual activity attributed to the preoperative radiotherapy. This decline is seen in around 50 % of the women who were sexually active pre-treatment, one-third of patients at 3 months and less than 20 % at 2 years [43]. Development of secondary urinary symptoms (seen in up to one-third of the patients) adds to the morbidity. Other studies show that sexual dysfunction occurs in at least half of the men and women treated for rectal cancer, with a significant proportion of that morbidity caused by preoperative radiotherapy [44]. Newer nerve sparing surgical techniques has not yet demonstrated a great deal of benefits. Anal cancers are sparsely studied, but significant sexual dysfunction has also been reported [45].

Ovarian Irradiation

The ovaries may be irradiated as 'innocent bystanders' during the course of treatment for other malignancies, causing an abrupt transition to menopause in premenopausal women and loss of androgens in those who are post menopausal. Techniques exist in which the ovaries can be transposed to an area not exposed to the radiation field, but this can still disrupt the blood and nerve supply, causing ovarian insufficiency. Gonadotrophin-releasing hormone analogues (GnRH analogues) may induce a menopausal state, and theoretically offer protection of the ovaries from the effects of chemotherapy and possibly radiation, although the role of these methods has yet to be proven.

Treatment of Sexual Dysfunction After Radiotherapy

Management of sexual difficulties after pelvic cancers and their treatment should always start with anticipating and acknowledging their occurrence. Addressing an individual woman's fears and concerns regarding their cancer and its treatment has positive therapeutic effects in itself. Giving written information is helpful in legitimizing sexual concerns that a woman may have, as many may feel that their sexuality is a low priority, relative to issues such as cancer survival. Timing these discussions such that they occur within initial consultations, at diagnosis, after surgical and radiotherapy treatment, additionally during follow-up surveillance is important. Although training in the specifics of sexual difficulties in these patients would be ideal for all healthcare professionals managing oncology patients, a focus on their prevalence and having referral pathways in place with access to trained professionals would be an ideal initial approach. Enhanced survival and increased focus on quality of life issues make this approach important. Appropriately administered consent will help to normalize this approach, i.e. some women and their sexual partners will need authorization to return to normal sexual activities. Resumption of

these activities can help patients feel less need to focus on their cancer survivorship. Acknowledging sexual difficulties, even within a time-pressured clinic is advised. Developing goals for future appointments, perhaps with other healthcare professionals within the multidisciplinary team is likely to be therapeutic.

There have been specific interventions used for treatment of physical sexual difficulties in women post pelvic radiation. However, these have not well studied within these populations. Significant overlap in the causes of sexual dysfunction can make assessment and treatment difficult; therefore, input from a sex therapist may be required. Sensitivity is required prior to offering physical interventions and recognition of psychosocial issues is advised. This may obviate the need for onward referral.

A Cochrane review of interventions for sexual dysfunction following treatments for gynaecologic cancer reported effectiveness of vaginal oestrogen cream after radiotherapy [46]. However, this was a synthetic form oestrogen cream that has limited availability now, and the study reviewed was published in 1971 [47]. A subsequent Cochrane review published in 2012 reported benefit from topical estrogens and benzydamine douches on acute radiation changes, although statistically the evidence is not robust. The use of vagina dilators and intercourse to prevent the development of vaginal stenosis was supported by weak evidence although all studies are of limited quality [48]. This Cochrane review specifically warns against the rare but serious risks, such as local trauma and fistula formation, with dilatation during the acute phases of irradiation. The time to initiate, frequency and duration of dilator use has not been clarified, and different organizations have recommended a variety of different regimes. Professional support has great value in the use of vaginal dilators. In the UK, a clinical nurse specialist or a specialist women's health physiotherapist is employed to assist with dilator use. Using vaginal dilators can be associated with bleeding and pain. For selected women, vibrators rather than dilators may be more appropriate. A report of educational interventions for women after hysterectomy was suggested to have a positive effect on all areas of sexual function. On the other hand, educational interventions have not been confirmed in a radiotherapy group [49, 50]. A small study of a clitoral vacuum device for women with sexual arousal and/or orgasmic difficulties after radiotherapy reported improvements in all areas of sexual functioning including reduced pain [51], and deserves further investigation, although vibrators may be of greater value and cheaper.

There are anecdotal reports of improvement for those women who have dyspareunia secondary to stenosis using individualized surgical reconstruction and hyperbaric oxygen, although formal studies are lacking. No impact of 5PDE inhibitors has been seen for women overall despite reports suggesting a minimal improvement in arousal [52].

The impact of hormonal replacement therapy, systemic or topical estrogens is of significant importance, but is very poorly assessed. The staging and type of cancer will clearly be important in the appropriateness of using hormone therapy, but it should be acknowledged that oestrogen and testosterone deficiency will have an impact on female sexual functioning, particularly those, who have become menopausal as a consequence of their treatment. For most women with pelvic cancers, the use of topical oestrogen to improve vaginal tissues and lubrication will be suitable. For those who cannot or do not wish to use topical oestrogen (although this is generally undetectable in the systemic circulation with current preparations), there are other vaginal-based remoisturizers available (such as Replens MD, Hyalofemme etc). Suitable lubricant may be used with and without intercourse, either branded or simple vegetable or but oils such as sweet almond oil or organic olive oil.

All the studies in the area have been small with variable methodological quality.

Premature Menopause

Premature ovarian insufficiency is a common consequence of treatment for pelvic cancer whether due to surgery, effects of radiation or

Table 11.1 Symptoms of oestrogen deficiency

Hot flashes	Vaginal dryness
Night sweats	Overactive bladder
Mood swings	Skin changes
Headache	Hair loss
Insomnia	Irritability
Lack of concentration	Weight gain
Poor memory	Lack of libido
Joint pains	Depression

from chemotherapy. Ovarian insufficiency can have a profound impact on general well-being, quality of life, sexual functioning and vaginal health, irrespective of prior menopausal status. Postmenopausal ovaries produce androgens that have an impact on energy and libido. Therefore, even postmenopausal women may have some change in quality of life with this reduction in circulating sex steroid hormones. Although, the use of hormonal treatment may be limited in patients with hormone sensitive tumours including some endometrial and breast cancers, many patients are suitable candidates for systemic and/or topical hormone replacement therapy (HRT). Ideally, hormone replacement should be discussed and evaluated prior to treatment, particularly in younger women who are likely to have an induced menopause. Women should be informed of the menopausal symptoms that may be attributable to oestrogen deficiency (see Table 11.1), rather than the general effects of their cancer and its treatment.

Apart from the climacteric symptoms, increased cardiovascular disease, cerebrovascular and musculoskeletal deterioration are taken into consideration. Women with an early menopause have a higher incidence of ischemic heart disease and overall mortality risk is reduced with HRT in observational studies [53–55]. Unfortunately, there is little information that allows the clinician to determine the least disadvantageous HRT combination. There is an ongoing research to establish the impact of body identical hormones (particularly the progesterone component) compared to synthetic hormones, suggesting a reduced metabolic impact of estradiol, and natural progesterone compared to synthetic progestogen, in addition to possible reduced breast cancer risk [56]. It seems logical to replace women's hormones with identical compositions, if possible. Younger women with cervical cancer may wish to have replacement in the form of the combined oral contraceptive pill, although this may have a more disadvantageous metabolic impact. Those who have been hysterectomised do not require progestogen or progesterone to protect the endometrium from oestrogen stimulation, thus conferring no additional breast cancer risk. There is also no additional risk with combined HRT used before the average age of menopause, (approximately age 51). There are practitioners withdrawing progesterone opposition in systemic HRT regimens for women who have had pelvic radiotherapy with an intact uterus; but there is no published evidence to support the safety of this regimen, even though the endometrium is likely to have been ablated in most.

Table 11.2 details HRT that can be administered to those without hormone-sensitive cancers, or who are judged to have minimal risk of recurrence and a significant beneficial impact of oestrogen deficiency on their quality of life. Different routes of administration will have varying metabolic pathways with different risks and benefits. Transdermal oestrogen products in the form of patch or gel have less impact on coagulation, and therefore lower the risk of thrombosis (although the overall risk is low in younger women being treated for iatrogenic menopause compared to older naturally menopausal women). However, pelvic cancer itself confers an increased risk of venous thrombosis. Progestogen can be administered orally or transdermally in a combined patch or using an intrauterine device. Progesterone is available on oral, vaginal or rectal preparations. Androgenic properties of some progestogens may counteract the beneficial effect of estradiol on lipoproteins and increase insulin resistance [57, 58].

Although not specifically studied in a treatment group with gynaecological cancer, continuous combined or non-bleeding HRT is safer for the endometrium long-term (i.e. daily dosing of progesterone or progestogen). There may be difficulties in assessing postmenopausal bleeding in this group of women after radiation therapy due

Table 11.2 Hormone replacement therapy

Systemic hormone replacement therapy	Topical genital treatments
Oral combined HRT-—sequential or continuous combined	Oestrogen (oestradiol/oestriol) cream
Patch combined HRT—sequential or continuous combined	Oestrogen pessary/ovule
Oestrogen only tablet	Oestrogen ring
Oestrogen only patch	Replens
Oestrogen only gel	Hyalofemme
Oestrogen and testosterone implants	possible benefit from topical DHEA/testosterone
Testosterone patch/gel	Lubricants
Tibolone	–
Progestogen tablet/IUS	–
Progesterone tablet, vaginal gel/rectal suppository	–

to other causes including vaginal and/or cervical stenosis, and changes in the appearance of the endometrium on imaging. Sampling the endometrium may also be difficult in this group.

Topical estrogens are an alternative for promoting vaginal health, with a significant reduction in recurrent cystitis or urinary tract infection that can be provoked by intercourse or dilator use in addition to improvement in vaginal symptoms of itching, burning and irritation, secondary to vaginal atrophy. These agents are safe even in those with hormone sensitive cancers in the vast majority of patients. Vaginal tablets, pessaries, creams and a ring are available for use. These could potentially be used indefinitely for those who are symptomatic and not using systemic HRT. They may also reduce bleeding with dilator use and intercourse. Topical estrogens are minimally absorbed during the first 2 weeks of daily use only. After this, levels are generally consistently below the normal postmenopausal levels.

Consideration of androgen deficiency should also be undertaken, particularly in younger surgically menopausal women. There is data to suggest benefits for women's sexual satisfaction, well-being, energy levels and musculoskeletal strength, although this is a controversial area in hormone replacement [59, 60]. Tibolone is a gonadomimetic alternative to combined hormone replacement with estrogenic, progestogenic and androgenic effects, and proven benefits for tissues, vasomotor symptoms and sexual functioning [61, 62].

The current recommendations regarding hormone replacement in women with induced menopause after cancer, is to administer HRT until at least the average age of natural menopause, i.e. 51 years. This approach should be assessed on a regular basis in line with current evidence. Alternatives can be considered but oestrogen with or without progestgen/progesterone is the only treatment for all consequences of oestrogen deficiency. Many herbal therapies, such as phytoestrogens, work via pathways that are not clarified, and may have hormone-like effects and therefore exhibit similar risks. Venlafaxine and gabapentin may reduce vasomotor symptoms but cause significant side effects for some [63]. Bisphosphonates can be used for prevention and treatment of osteoporosis, but long-term use is associated with fragility fractures. All these women should be counselled with respect to maintaining their cardiovascular and bone health by weight-bearing exercise, sufficient calcium and vitamin D and good diet with screening for bone density and cardiovascular risk factors as required.

Fertility

In the last 20 years, an increasing number of women have been long-term survivors after radiotherapy for cancer [64]. In addition, radiotherapy is used successfully for other conditions such as autoimmune or hematological and CNS conditions. This, in combination with the fact that women tend to postpone childbearing for social reasons, means that many want to start a family well after receiving radiotherapy. Many want to be informed about the effects of radiotherapy on their options for fertility and age of menopause, as well as future pregnancies and neonatal outcome.

Ovarian Reserve

The term ovarian reserve describes the quality and quantity of ova in a woman's ovaries at a specific age. Women are born with a finite number of oocytes, usually around 1–2 million, and by the age of menarche they are left with 500,000. The follicles are lost exponentially, mostly with atresia, and reach a number of around 25,000 at an average age of 37–38, and less than 1000 at menopause, normally around the age of 51. However, there is huge variability in these numbers at any age. The rate of follicle loss depends mainly on the number of remaining follicles, and accelerates towards the end of reproductive life. There is no direct way to assess the ovarian reserve. Most so-called tests of ovarian reserve tests basically predict ovarian response to stimulation with gonadotrophins and, at best, they provide quantitative estimates. Antral follicle counts and animullerian hormone measurements are the most accurate. By extrapolation, they can provide a rough prediction of the age of menopause, but they cannot assess a woman's current level of fertility as this is dependent mainly on the quality, not the number of eggs.

Early Ovarian Ageing

Early ovarian aging is a term introduced in 2003 [65] to describe women who are destined to develop menopause before the age of 46, having started an accelerated decline of their ovarian reserve from their early 30s. Most of these women were actually born with significantly fewer oocytes in their ovaries than the average woman, and the reasons for this are usually genetic. However, there are a number of acquired causes of early ovarian aging, which act through reductions of the ovarian reserve. These include radiotherapy, chemotherapy and surgery. Detection of asymptomatic women with early ovarian aging in their late 20s or early 30s may be possible by screening of high-risk groups.

Effects of Radiotherapy on Ovarian Function

Radiation causes direct damage to the ovarian reserve by destroying follicles. The most vulnerable of these are the growing follicles, whereas primordial follicles seem to be relatively protected. The extent of damage to the ovarian reserve depends on the patient's age, the dose of radiation and the field of radiation. Mathematical models have been developed to assist physicians to predict the likely effect of radiation to the ovaries on the ovarian reserve, in order to counsel the patients and their families [66]. It has been estimated that the radiation dose that will destroy half of the existing immature oocytes is 2Gy (LD50). Injury is worse with higher doses of radiation. In addition, older patients or patients with poor ovarian reserve are more sensitive to these radiation effects. The extent of the radiation field has an effect on the degree of ovarian damage. With total-body irradiation, 90% of patients have been observed develop premature ovarian failure. This increases to 97% in patients receiving abdominal radiation.

Effects of Radiation on the Hypothalamic-Pituitary-Ovarian Axis

Many studies have been performed to determine the effect of cranial or whole-body irradiation on the pituitary-hypothalamic-ovarian axis [67, 68]. Damage seems to occur at the level of the hypothalamus and pituitary gland. Subsequent hormonal alterations include hypogonadism and oligomenorrhoea, but also low lutenizing hormone and prolactin levels. There seems to be a long-latent period for these abnormalities; therefore, women who have received radiotherapy should be monitored for these potential abnormalities for several years after radiation exposure.

Effects on the Uterus

Pelvic irradiation puts women at increased risk of pregnancy-related complications, such as miscarriage, intrauterine growth retardation, preterm la-

bour; and placental abnormalities such as placenta accreta [69]. The uterus of women post irradiation decreases to 40% of the normal size, and also the endometrium becomes relatively thin. Radiation causes damage to the uterine muscle with fibrosis and, this affects uterine expansion during pregnancy. It also produces potentially chronic damage of the uterine blood vessels. The extent of uterine damage depends on the dose of radiation, the radiation field and the age of the patient. The pre-pubertal uterus is much more sensitive to radiation effects. It is estimated that the dose required to cause uterine dysfunction is around 14Gy.

Strategies to Minimize Radiation Damage

Ovarian transposition or oophoropexy is an operation to move the ovaries away from the uterus and pelvis in order to spare them from radiation exposure. It was introduced in the 1950s for cervical cancer patients, but is now considered in many other cases, including Hodgkin's lymphoma, pediatric sarcomas and rectal cancer. Traditionally, it was performed during laparotomy for radical hysterectomy or staging for Hodgkin's lymphoma, but is now also performed laparoscopically. The ovary and fallopian tube are dissected from the uterus and attached to the peritoneum laterally and as high as possible. Studies have shown this technique to be effective [69]. Ovarian shielding is also used, depending on the required field of radiation. Newer radiotherapy protocols are generally more effective and cause smaller collateral damage. Another approach is pre-treatment with GnRH analogues, which seem to offer some protection for the ovarian reserve and endometrium.

Fertility Preservation

There are various possibilities for fertility preservation for pre-menopausal women who have a risk of ovarian injury [70]. The most effective of these is embryo freezing, but this requires in vitro fertilization (IVF) with partner sperm or donor sperm. IVF is not always feasible and may be contraindicated. Egg-freezing does not require sperm rather is a much newer technique, and the possibility of a live birth is far less certain. Ovarian tissue cryopreservation is another possibility, which can also be used for pre-pubertal women. This is becoming more successful, although the number of known live births is still very small. Women can try to conceive using donated eggs or a surrogate mother's uterus, but obviously this involves ethical and legal issues that need to be discussed [70, 71].

Best Practice

As the survival of female cancer patients continues to improve, it is critical to consider the long-term reproductive health and fertility of patients when planning radiotherapy and other treatments for their cancers. This is achieved through a multidisciplinary approach, involving medical and radiological oncologists, gynaecologists and paediatricians. It is important to individualize treatments including methods to minimize damage to the ovarian reserve and uterus. The issue of future fertility should be discussed with the patient prior to radiotherapy. Possible options for the minimization of damage to the female organs and fertility preservation should be reviewed. Women and their families should be offered counselling and other services to assist with preservation of sexual, health and overall well being.

Conclusion

There are significant acute and chronic effects of radiation treatment for pelvic cancer. It is imperative that healthcare professionals inform their patients of these effects, including lifestyle-related and sexual side effects that may occur. Recognition of patient fears and concerns, and the consequent adaptive behaviours are needed by practitioners. Information, given in both verbal and written forms will provide support for these women. An understanding of hormonal changes

and minimization of their consequences are required to preserve quality of life. Research with validated instruments needs to be undertaken to enhance the understanding of sexual dysfunction and fertility issues in these patients. Better information will improve patient decision-making. Quality of life issues must be addressed in patients undergoing treatment for gynaecological malignancies as increased survivorship necessitates more research to facilitate overall improved health care for these women.

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Miscellaneous Pelvic Effects: Pelvic/Sacral Insufficiency Fractures

12

Nickolas B. Reimer, Lukas M. Nystrom and Cooper W. Dean

Introduction

Insufficiency fractures can result from normal physiologic loading through bone with decreased mineralization and elastic resistance. Pelvic insufficiency fractures are a potentially serious complication after pelvic irradiation. Radiographic evidence of pelvic insufficiency fractures after radiation therapy is common and occur in up to 45 % of treated cohorts [1]. Fortunately, clinically significant or symptomatic fractures only occur in 4–20 % of these patients [2–5]. Although clinically significant fractures occur in the minority of patients, their presence can have great impact on the patient's functional status. The vast majority of symptomatic patients with a pelvic insufficiency fracture can be treated medically as an outpatient although admission to an inpatient setting is sometimes required during initial work up of an acute fracture [4]. Surgical intervention for pelvic insufficiency fractures is fraught with complications and therefore reserved primarily for pelvic or spinopelvic instability and periarticular fractures around the hip joint.

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The incidence of pelvic insufficiency fractures varies by cancer site treated. Treatment for anal cancer is associated with the highest risk of fracture, followed by rectal cancer, cervical cancer, and prostate cancer [5]. Fractures occur more commonly in cases with intent to cure compared to palliative therapy [2]. There is not an increased risk of fracture associated with concurrent chemotherapy [2, 6–8]. Radiation technique and dose are implicated with fractures occurring more commonly with the anterior–posterior/ posterior–anterior (AP/PA) parallel opposing technique compared to the four-field box technique [2]. Intensity modulated radiation therapy allows for greater conformity of the radiation to the target and has a theoretical advantage over conventional radiation therapy when it comes to sparing pelvic anatomy; however, the differences in techniques as related to the incidence of pelvic insufficiency fractures have not been thoroughly investigated. There is also an anatomic predilection of fracture location toward the posterior pelvis, especially the sacral ala, while the anterior pelvic ring and periacetabular region are relatively protected [1, 4].

Epidemiology

A dose threshold for development of osteonecrosis after pelvic irradiation has not been established. However, pelvic insufficiency fractures have been observed in patients receiving as little as 25 Gy [9]. Since conventional therapeutic

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doses generally range from 45 to 55 Gy, it is reasonable to assume that all patients treated for malignancies with pelvic irradiation are at risk of fracture. Multiple studies have demonstrated a dose-dependent relationship with fractures occurring more commonly with treatment doses greater than 45 Gy [2, 7]. While the prevalence of pelvic insufficiency fractures increases with time in a treated cohort, the typical time frame from completion of pelvic irradiation to symptomatic pelvic insufficiency fracture ranges from 14 to 20 months with nearly 85% presenting within 2 years of therapy [2]. Fractures after 3 years posttherapy are rare. Female gender, age of more than 60 years, body weight less than 55 kg, and preexisting osteoporosis have been found to be independent risk factors for development of pelvic insufficiency fractures. Multiple fractures sites are common and the vast majority of patients have sacral involvement with many having bilateral, symmetric lesions of the sacral ala. The distribution of fractures decreases as one moves away from the sacrum where nearly 85% of pelvic insufficiency fractures occur. The next most common site is the dome of the acetabulum, followed by superior (pubic) rami, inferior (ischial) rami, and femoral heads.

Diagnostics

The evaluation of new onset or progressive pelvic pain in a patient with a history of pelvic malignancy treated with prior radiation therapy (and possibly surgery) can be challenging given the broad differential diagnosis for such symptoms—the most ominous of which would be the recurrence of the primary malignancy or development of a secondary radiation-associated malignancy.

Given that many patients receive care at multiple institutions, when ordering an imaging study to evaluate such symptoms, it is imperative to obtain prior studies to evaluate assess for interval changes as well as document preexisting findings such as degenerative joint disease, prior trauma, prior surgery, osteoradionecrosis, etc.

Radiography

Radiographic examination of the pelvis, typically obtained in the AP view, can sometimes demonstrate interval development of insufficiency fractures, particularly of the sacral ala as well as the superior and inferior pubic rami. However, radiographs alone remain insensitive for detecting nondisplaced fractures as the findings can often be subtle [10–12], particularly in the context of underlying bony changes related to osteoradionecrosis.

Progression versus healing of insufficiency fractures can also be followed radiographically. These may demonstrate reactive bone formation along fracture planes as well as bony callus formation. Radiographs can also demonstrate changes in the alignment of the fracture fragments. The AP view of the pelvis in the setting of vertical sacral ala fractures can be useful for assessing stability and the lateral view of the sacrum can be helpful to demonstrate changes in sagittal alignment of the sacrum in the setting of an insufficiency fracture with a transverse component crossing the sacral body. Insufficiency fractures of the pubic rami may be followed with AP as well as inlet and outlet views of the pelvis to evaluate for fracture healing versus progression of displacement. Standard two-view radiographic studies of the hip obtained in the AP and lateral position can be helpful to detect progression of osteoradionecrosis along the femoral head and acetabular roof, can also be used to assess for interval development of articular surface collapse. Acetabular fractures can be initially evaluated and followed using AP and Judet views of the pelvis obtained in 45° obliquity bilaterally. However, cross-sectional imaging with computed tomography is often necessary to completely characterize such fractures.

Computed Tomography

Even in situations where the patient's symptoms are adequately explained by radiographic findings, cross-sectional imaging is often necessary

to more rigorously evaluate the structures of the bony pelvis. Computed tomography (CT) is widely available, offers inherent high-contrast resolution and has been demonstrated to be far superior to conventional radiography for visualizing insufficiency fractures, particularly those that are not displaced [11]. CT data reconstructed in both bone and soft tissue windows can demonstrate subtle fracture lines, endosteal callus formation without a discrete fracture line and/or cortical disruption. In addition, evaluation for the presence of an underlying soft tissue mass along the fracture sites to help exclude a pathologic fracture can be performed [4]. CT data reformatted into coronal and sagittal planes can also better demonstrate the morphology of the insufficiency fractures and demonstrate potential involvement of adjacent structures such as joints, neural foramina, etc.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has evolved into an important tool for the evaluation of pelvic insufficiency fractures. Multiple studies have characterized the imaging findings of bland and radiation-induced insufficiency fractures of the pelvis and proximal femur [10–14]. Furthermore, comparison of sensitivities between radiographs, CT, and MRI has demonstrated the superiority of MRI for detecting insufficiency fractures of the pelvis and proximal femur [11], which may present as geographic marrow edema prior to the development of a discrete fracture line. As with CT, the multiplanar sequences of MRI can help to better demonstrate the alignment as well as evaluate for involvement of adjacent anatomic structures. MRI also offers the ability to evaluate the fracture site for an underlying pathologic lesion.

Nuclear Medicine Imaging

Bone scans using technetium-labeled methylene diphosphonate (^{99m}Tc-MDP) have also been used for evaluating radiation-induced insufficiency fractures. Increased radiotracer uptake vertically along the sacral ala deep to the sacroiliac joint (usually bilaterally) with or without a transverse component crossing the upper sacral body is strongly suggestive of sacral insufficiency fractures [15]. The H-shaped morphology of this pattern of radiotracer uptake has been referred to as the "Honda sign" given the similarity in appearance to the carmaker's corporate logo. Positive findings on nuclear medicine are often further evaluated with cross-sectional imaging using CT or MRI to exclude the possibility of a pathologic fracture. Figure 12.1 demonstrates CT, MRI, and bone scan characteristics of a sacral insufficiency fracture in an 86-year-old female who received chemoradiation including 45 Gy of external bean radiation therapy.

Positron emission tomography/CT (PET/CT) using 2-[F-18] fluoro-2deoxy-D-glucose (FDG) has also been used in the evaluation of pelvic fractures in patients with a history of pelvic malignancy who have received prior radiation therapy with the aim of differentiating radiation-induced insufficiency fractures from fractures occuring through recurrent or metastatic bone neoplasms. Maximum standardized uptake values (SUVmax) measured at fracture sites as well as the distribution of uptake at the fracture site (cortical vs. intramedullary) have been used to differentiate insufficiency from pathologic fractures [16]. However, in the setting of radiation-induced pelvic insufficiency fractures, the SUVmax alone has not been shown to reliably differentiate between pathologic and insufficiency fractures [8,16]. It should be noted, however, that the distribution of increased FDG uptake in radiation-induced pelvic insufficiency fractures of the sacrum may appear as an incomplete variant of the H-shaped pattern described on ^{99m}Tc-MDP bone scans [8, 17]. Often, the CT component of the PET/CT scan can offer crucial information regarding the presence of a fracture line, reactive bone formation about a nondisplaced fracture or the presence of an underlying pathologic lesion.

Treatment Overview

The vast majority of patients with pelvic insufficiency fractures can be treated medically; although, early consultation with an orthopedic

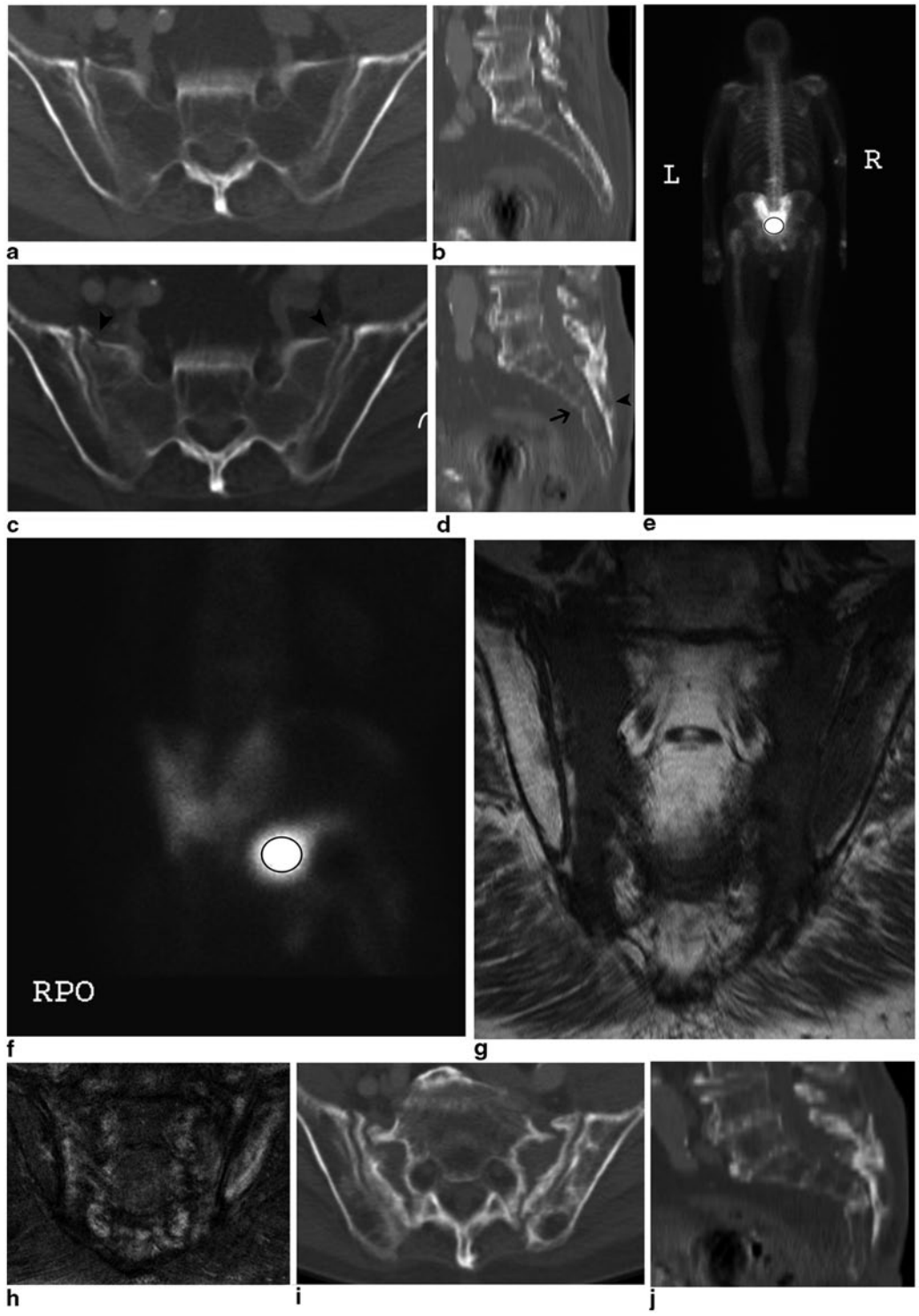

Fig. 12.1 Sacral insufficiency fracture. 86-year-old male with a history of T3 N0 M0 adenocarcinoma of the rectosigmoid colon who received neoadjuvant chemoradiation therapy including 45 Gy administered at 1.8 Gy per fraction. CT images of the pelvis were obtained 1 month after completion of the radiation therapy. There was a

surgeon is recommended. The orthopedic surgeon will be able to assess the stability of the fracture pattern, help determine weight bearing and activity restrictions, as well as follow the patient's course and determine if surgical intervention is indicated. Although some patients with acute fractures may require a short hospital stay for initial evaluation, pain control, and to facilitate a safe rehabilitation plan, this is not the norm. Most patients can be evaluated and managed on an outpatient basis.

Patients often require a brief period of narcotic analgesics for comfort, but the treatment goal should be that of early transition to nonnarcotic analgesics as to avoid side effects and dependence. An orthopedic surgery consultation should be sought to evaluate the stability of the fracture pattern and to offer weight-bearing recommendations. Stability is generally defined as the ability of the structure involved to maintain alignment under physiologic loading. These assessments are best made by orthopedic surgeons comfortable with fracture management. After weight-bearing recommendations are made by the orthopedic surgeon, a physical therapy consultation should be sought. The physical therapist can perform a functional assessment and determine the patient's ability to safely mobilize given their restrictions. The therapist will then be able to provide gait training with an assistive device that fits the patient's needs. In patients with unstable pelvic or periarticular fractures around the acetabulum or femoral head, toe-touch weight-bearing (enough for balance only) is recommended for several weeks to months. Elderly patients and those with coordination or muscle deficits may not be able to comply with these restrictions and may fully weight bear if permitted to mobilize with restrictions. If there is sufficient concern for fracture displacement, this type of patient may require a wheelchair. Alternatively, if a patient has a stable fracture pattern, they may be allowed to fully weight bear. Although they are cleared to walk without fear of displacement, pain may preclude walking without some type of assistive device such as a walker, crutches, or a cane.

Next, an investigation into the patient's risk factors such as vitamin D deficiency and

baseline of mildly decreased bony mineralization diffusely which was thought to be related to the patient's age. **a** Axial CT image of the pelvis at the level of S1 demonstrates no sacral ala fractures. **b** A *sagittal* reformation of the pelvis shows that the sacral alignment is preserved. Similarly acquired CT images of the pelvis respectively were obtained 8 months after the initial postradiation therapy CT study. **c** Axial CT image of the sacrum at the level of S1 demonstrates focal discontinuity of the anterior cortices of the bilateral sacral ala with small fractures tracking posteriorly (*ARROWHEADS*). **d** *Sagittal* reformation of the sacrum demonstrates a small minimally displaced fracture through the anterior cortex of S3 (*ARROW*), propagation of the fracture through the neural arch (*Arrowhead*) and subtle kyphotic angulation at the fracture site. **e** A nuclear medicine bone scan was performed 13 months after the initial postradiation therapy CT study using Tc-99m MDP. *This study* shows delayed posterior planar image of the entire body demonstrates focal radiotracer uptake longitudinally along the bilateral sacral ala with band of transverse uptake at the level of S3—the so-called "Honda sign" named for the similarity of the radiotracer uptake pattern to the H-shaped corporate logo. The transverse band of radiotracer uptake at S3 is partially obscured by the prominent amount of radiotracer present within the overlying urinary bladder (*CIRCLE*). **f** shows a *right* posterior oblique image which better demonstrates the H-shaped distribution of the radiotracer uptake along the sacrum when the radiotracer in the urinary bladder (*CIRCLE*) is rotated away from the sacrum by altering patient position. An MRI of the pelvis was performed 15 months after the initial postradiation therapy CT. **g** A coronal T1-weighted image of the sacrum demonstrates the H-shaped pattern of low signal which delineates the morphology of the sacral insufficiency fractures through the bilateral sacral ala and transversely crossing the superior margin of the S3 vertebral body. **h** A coronal STIR sequence of the sacrum shows abnormal increased signal suggestive of edema about the fracture planes. CT images of the pelvis were obtained 28 months after the completion of radiation therapy. **i** Axial CT image of the superior sacrum at the level of S1 show progression of fracture planes along the sacral ala bilaterally without extension into the sacroiliac joints or adjacent S1 neural foramina. There is no discrete osseous bridging along the fracture planes however there is reactive bone formation along the fracture margins. **j** *Sagittal* reformation of the sacrum demonstrates similar reactive bone formation along the margins of the transverse S3 fracture site without osseous bridging across the fracture planes. There has been progression of the compression deformity at the S3 fracture site with worsening of the associated kyphotic angulation. *STIR* Short T1 Inversion Recovery

underlying osteoporosis should be performed and acted upon. Many would argue that this investigation should be done prior to or during radiation therapy; although, the concept of prescreening and treating hypovitaminosis D patients in hopes of reducing pelvic insufficiency fractures has not yet been investigated. Treatment of patients with pelvic insufficiency fractures should include, at the very minimum, adequate analgesia and calcium/vitamin D supplementation. Additionally, bisphosphonate and teraparatide therapy could be indicated in certain scenarios.

Although bisphosphonate therapy is heavily studied in fragility fractures including pelvic fractures, the same level of investigational interest has not occurred in patients who have fractured through irradiated bone. However, animal research has shown that prophylactic treatment of irradiated mice with a bisphosphonate prevented a rise in osteoclast number, bone loss, and impaired microarchitecture when compared to controls [18]. Despite laboratory data, we cannot directly apply this animal model to human subjects nor can we determine if the difference observed would be clinically significant. It remains unknown if prophylactic treatment with bisphosphonates prior to pelvic irradiation would reduce pelvic insufficiency fractures. Clinical investigation is clearly needed in this area.

Although clinical study of direct treatment with bisphosphonates after fracture through irradiated bone has not been conducted, the sentinel event of a pelvic insufficiency fracture often prompts an investigation leading to a diagnosis of osteoporosis. Many of these patients will eventually be treated with bisphosphonates in order to prevent additional fragility fractures. Bisphosphonate therapy is certainly reasonable in such cases; however, bisphosphonate treatment for patients with radiation-induced pelvic insufficiency fractures in the absence of osteoporosis is not indicated.

Parathyroid hormone (PTH) is the newest treatment modality in the armamentarium for pelvic insufficiency fractures. PTH is a systemic regulator of calcium homeostasis [19]. It is released from the parathyroid gland in response to hypocalcemia and increases serum calcium concentration by promoting osteoclast-mediated bone resorption, calcium reabsorption in the kidneys and intestinal absorption of calcium through the production of the active vitamin D metabolite 1,25-dihydroxy vitamin D. Continuous exposure to PTH is catabolic and results in hypercalcemia and a decrease in bone volume [20]. Intermittent exogenously administered PTH leads to an anabolic effect on bone. Two preparations for intermittent therapy are available in Europe: PTH 1-84 and PTH 1-34. Naturally occurring PTH is a polypeptide containing 84 amino acids, while recombinant PTH (PTH 1-34), also called teraparatide, consists of the first 34 amino acids of the human PTH. Only teraparatide is currently available in the United States of America. Extensive scientific analysis in various skeletal repair models in animals including fracture repair have demonstrated the importance of PTH in mesenchymal cell proliferation and differentiation, enchondral bone formation, membranous bone formation, and callus remodeling [20].

Human studies have been performed as well. Treatment of distal radius fractures in postmenopausal women and elderly osteoporotic women with pubic bone fractures have been reported. There are several reports of level IV data as well, including the successful treatment of patients with tibial and humeral delayed unions, which are very promising [20–23]. Most pertinent for this discussion, is the effect of PTH on the clinical and radiographic outcome in elderly osteoporotic women with pubic fractures. Treatment resulted in a mean time to fracture union in the treatment group of 7.8 weeks compared to 12.6 weeks in the control group [20]. Visual analog scale pain scores and functional testing also significantly favored PTH treatment group. These findings suggest that use in the radiation-induced pelvic insufficiency fracture cohort may be indicated.

In very rare circumstances, surgical intervention may be considered. Given the low energy mechanism associated with pelvic insufficiency fractures, it is extraordinarily rare to have an unstable pelvic ring fracture that meets operative criteria. If operative intervention is to be considered, a more likely scenario would be that

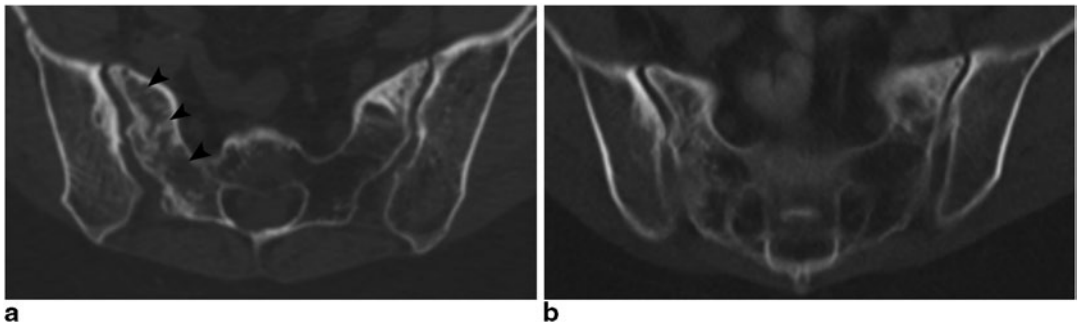

Fig. 12.2 Sacral insufficiency fracture. 44-year-old female with a history of stage Ib squamous cell carcinoma of the cervix status postradical hysterectomy with pelvic lymph node dissection and postoperative chemoradiation therapy which included cisplatin as well as external beam radiation therapy involving a total dose of 45 Gy administered over 5 weeks with additional 5 Gy brachytherapy to the vaginal cuff. **a** CT axial images of the pelvis at the level of the S2 vertebral body obtained 3 years after completion of radiation therapy demonstrate an irregular longitudinal fracture (*ARROWHEADS*) obliquely traversing the *right* sacral ala medial to the *right* sacroiliac joint and lateral to the S1 and S2 neural foramina. Heterogeneous bony mineralization about the sacroiliac joints and along the bilateral sacral ala was thought to reflect a background of underlying osteoradionecrosis. **b** The *right* sacral ala insufficiency fracture was managed conservatively. CT axial image of the pelvis at a similar level to (a) obtained 6 years after completion of radiation therapy shows interval healing of the previously demonstrated *right*-sided sacral alar insufficiency fracture with osseous bridging and bony remodeling along the fracture site

of a periarticular fracture of the acetabulum that results in joint incongruity, posttraumatic degenerative joint disease, femoral head osteonecrosis with associated subchondral fracture, or a femoral neck fracture. Shared decision making between the orthopedic surgeon and patient may result in pursuance of a total hip arthroplasty with or without a stabilization procedure for the acetabulum. It is important to set appropriate expectations in these patients because the outcomes in this scenario are not the same as for patients with primary arthritis. Joint replacement in irradiated bone is fraught with complications such as increased incidence of wound healing issues, infection, and component loosening. The result is a prosthetic joint replacement with longevity that is inferior to total hip arthroplasty in the nonirradiated patient.

Sacral Insufficiency Fractures

Nearly 80% of patient's sustaining pelvic insufficiency fractures associated with pelvic irradiation have sacral involvement, making this the most common site of fracture. They occur in about 15% of patients treated with radiation therapy, with a wide range of 3–45% reported in the literature [1, 2, 24]. The most common site within the sacrum is the sacral ala, which is lateral to the sacral foramina and medial to the sacroiliac joints. An example of this fracture pattern is illustrated in this 44-year-old female with cervical cancer treated with 45 Gy external beam radiation therapy and an additional 5 Gy brachytherapy at the vaginal cuff (Fig 12.2). There is no laterality predilection and half will have bilateral sacral ala involvement. Over 60% will have multiple fractures, such as a sacral fracture with an associated pubic ramus fracture [1, 2].

In studies that have concentrated on radiographic screening with clinical correlation, about half of all sacral insufficiency fractures identified on either MRI, CT, or bone scan are symptomatic [1]. Clinical presentation is usually that of low back pain without radicular symptoms but can include reports of hip or groin pain if there is an associated anterior lesion. The traditional thinking is that like any ringed structure, the pelvic ring rarely breaks in just one place, so one should have a high suspicion for the presence of anterior and posterior lesions in patients presenting with low back and hip or groin pain, even if there is only one radiographically visible fracture. Neu-

rologic deficits are exceedingly rare and the presence of a neurologic deficit does not preclude nonoperative treatment.

Although symptoms are usually mild to moderate, narcotic analgesics may be required during the acute period after sustaining a sacral insufficiency fracture. Orthopedic consultation should be sought early so recommendations on weight bearing and activity as well as a discussion on treatment options can commence immediately. There remains debate on whether to treat patients with a short period of bed rest or with early mobilization. There is no evidence implicating early mobilization with extended duration of symptoms or even increased narcotic use. There are however several reports illustrating the deleterious effects of bed rest, especially in the elderly, with respect to the development of deep vein thrombosis and decubiti, decreased muscle strength, as well as cardiopulmonary, gastrointestinal, and genitourinary complications. Despite no clear guidance in the literature in treating this particular cohort, the authors' treatment preference is early mobilization as to reduce potential complications associated with bed rest. A physical therapy consultation should be arranged as to facilitate a functional assessment of the patient's ability to protectively weight bear and subsequent pairing of the safest ambulatory assist device for the patient.

There is no role for rigid bracing in this injury pattern and early surgical intervention is rarely indicated. The average duration of symptoms in this group is 20 months but pain can be permanent in some cases. In a study by Ikushima et al., 72 % of patients required analgesics for an average duration of 4 months, while 44 % required inpatient hospitalization for symptom control [4]. The typical medical treatment algorithm is that of acute treatment with narcotic analgesics with early transition to nonnarcotic analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs) and a rehabilitation program. For patients with persistent disabling pain, percutaneous CT-guided sacroplasty could be offered; however, this treatment modality has not been studied extensively.

Surgical management of high energy traumatic pelvic ring injuries is constantly evolving and more surgical indications have been realized in recent years. Large open surgical exposures for treatment of these injuries are rapidly being replaced by percutaneous placed pelvic external fixators and minimally invasive screw placement and plating techniques. Although these techniques have become popular in orthopedic traumatology, they are typically performed in multiple injured patients to facilitate early mobilization and in patients with large fracture displacement or unstable injuries and do not apply to the pelvic insufficiency fractures cohort. These techniques however could be reserved for the rarest of circumstances in which a patient with pelvic insufficiency fractures goes on to displacement or persistent symptomatic nonunion.

The Anterior Pelvic Ring

Anterior pelvic ring insufficiency fractures involve the superior and inferior pubic rami and pubic symphysis. They are second most common site of pelvic insufficiency fractures associated with pelvic radiation therapy. This site of injury accounts for 15–20 % of patient with pelvic insufficiency fractures but are often associated with a sacral fracture [3, 4, 25]. The patient in Fig. 12.3 developed anterior pelvic ring, ilium, and femoral head complications after radiation therapy. The superior pubic ramus is the most common site within the anterior pelvic ring to be affected, followed by the inferior pubic ramus. The pubic symphysis is a rare site of injury.

Patients typically present with complaints of hip or groin pain and difficulty ambulating. The anterior lesion is usually unilateral although bilateral injuries can occur. Those with associated posterior lesions, will report back for buttock pain as well. Fractures though the rami are stable, even when displaced or when associated with a small posterior lesion. Therefore, patients are allowed to weight bear as tolerated with an assistive device. An injury to the pubic symphysis is extremely rare and should raise the suspicion of an alternate etiology or higher energy mechanism of injury. Nonetheless, symphyseal widening may indicate the presence of substantial pel-

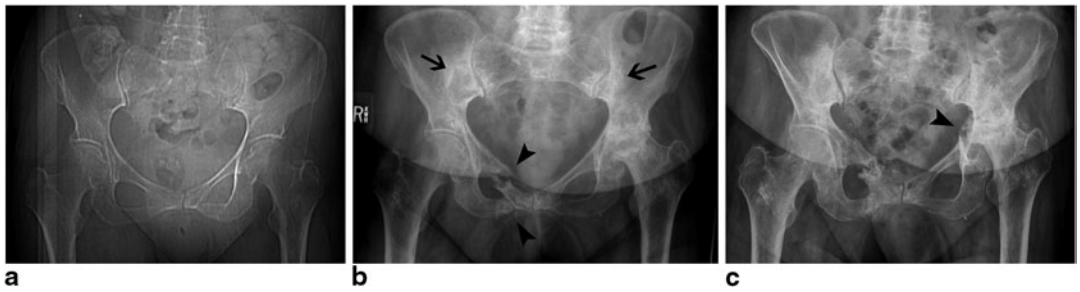

Fig. 12.3 Pubic ramus insufficiency fracture. 70-year-old female with a history of stage IIb endometrial cancer status postradical hysterectomy and bilateral salpingo oophorectomy treated with pre- and postoperative radiation therapy including external beam radiation to the pelvis as well as tandem/ovoid placement with a total dose of 75 Gy. **a** Scout radiograph of the pelvis in the anteroposterior projection from a CT scan obtained 4 months after completion of radiation therapy demonstrates preserved bony mineralization, preservation of the hip joint alignments, smooth curvatures of the femoral heads and no evidence of fractures. **b** Anteroposterior radiograph of the pelvis obtained 8 years after completion of radiation therapy shows interval development of heterogeneous bony mineralization along the bilateral sacroiliac joints predominantly along the iliac sides (*ARROWS*), chronic appearing mildly displaced *right* superior and inferior pubic rami fractures (*ARROWHEADS*) as well as progression of osteoradionecrosis of the *left* femoral with articular surface collapse superiorly, severe *left* hip joint space loss and associated excavation of the *left* acetabulum. **c** Anteroposterior radiograph of the pelvis obtained 11 years after completion of radiation therapy shows progression of the osteoradionecrosis along the bilateral sacroiliac joints, reactive bone formation along the margins of the displaced *right* superior pubic ramus fracture site, healing of the *right* inferior pubic ramus fracture as well as progressive excavation of the *left* femoral head and acetabulum with associated acetabula protrusion deformity (*ARROWHEAD*). Despite the severity of the imaging findings, the patient was managed conservatively as she remained ambulatory with the assistance of a four-point walker and did not report symptoms that significantly limited her activity

vic instability and urgent orthopedic consultation should be sought.

Acetabular Fractures

Acetabular fractures occur in 2–6% of patient who sustain a pelvic insufficiency fracture after pelvic irradiation [3, 4, 25]. Most are minimally displaced and can be treated with toe-touch or protected weight bearing with a walker. Some patients will present with fracture displacement or develop displacement during a period of conservative management. Surgery may be indicated in these patients. In young patients, a formal open reduction and internal fixation of the fracture may be indicated in order to spare their native hip from prosthetic replacement; however, this must be carefully considered as attempts at osteosynthesis in irradiated bone have exceedingly high rates of nonunion. In older patients, or those with posttraumatic degenerative changes, reconstructive options are limited. These include surgery to stabilize or reconstruct the fracture along with total hip arthroplasty. The patient in Fig. 12.4 presented 13 years after external beam radiation therapy of 45 Gy for anal cancer with advanced femoral head complications.

Open reduction and internal fixation of irradiated bone has not been studied and no evidence-based guidance is available. In treating acetabular fractures in the elderly and osteoporotic, orthopedic surgeons have had to find novel, unconventional techniques because of the unacceptably high failure rates of patients treated by conventional methods. One would assume that an equally high failure rate would exist in patients with an irradiated pelvis as well, compounded by the fact that radiation necrosis may be a pathophysiologic factor. Anecdotally, open reduction and internal fixation in this cohort often results in delayed union or nonunion, resulting in the requirement for conversion to another reconstructive option such as total hip arthroplasty.

Treatment of arthritis of the hip in patients with a history of pelvic irradiation is well described in

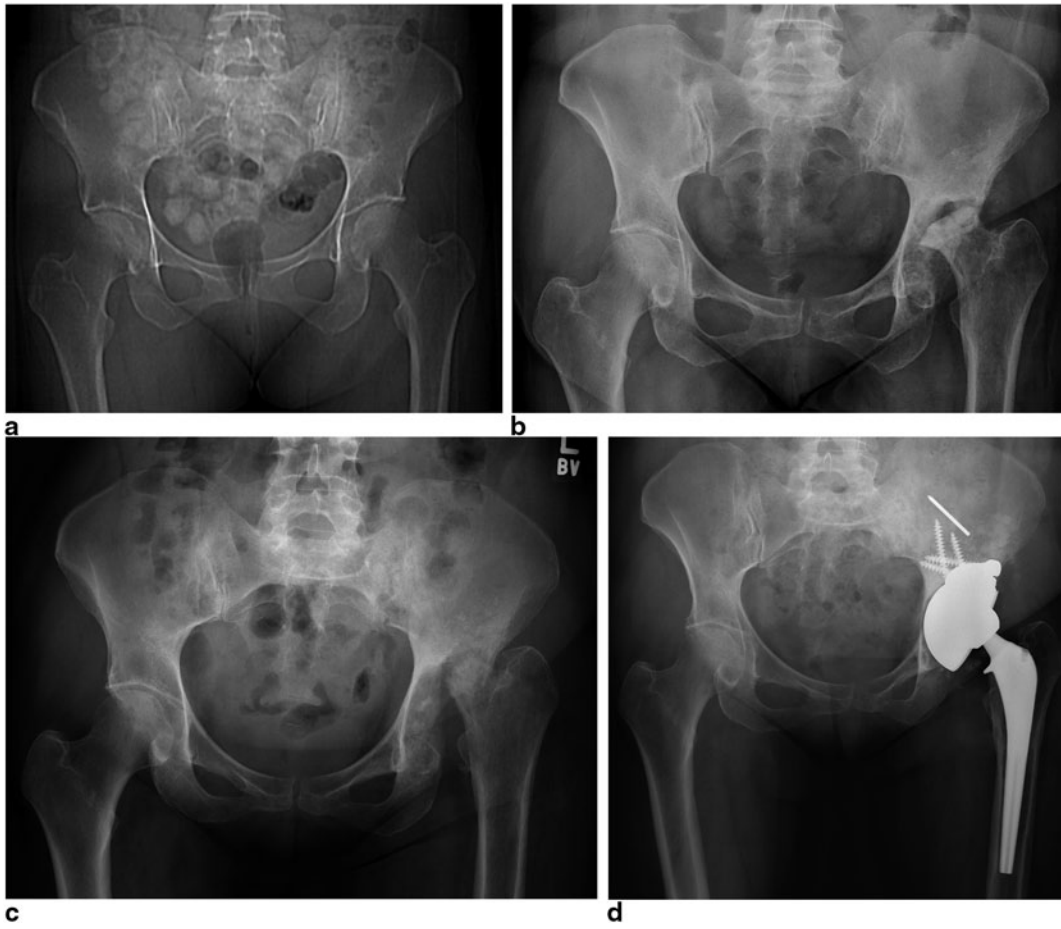

Fig. 12.4 Femoral head osteoradionecrosis with progressive excavation of the hip joint treated with THA. 51-year-old female with history of T2n0m0 squamous cell carcinoma of the anal canal status postexternal beam radiation therapy with implant boost received a total dose of 45 Gy. **a** Scout radiograph of the pelvis in the anteroposterior projection from a CT scan obtained 8 months after completion of radiation therapy demonstrates preservation of the bony mineralization and no fractures or dislocations. **b** Anteroposterior radiograph of the pelvis obtained 13 years after the completion of radiation therapy demonstrates interval near total destruction of the femoral head with excavation of the acetabular roof and superior migration of the *left* femur within the excavated joint space. Bony debris is present within the *left* hip joint. **c** Anteroposterior radiograph of the pelvis obtained 14 years after the completion of radiation therapy demonstrates total destruction of the *left* femoral head, worsening excavation of the *left* acetabular roof and worsened superior migration of the *left* femur. Additionally, the progression of osteoradionecrosis along both sides of the *left* sacroiliac joint is more apparent. **d** Anteroposterior radiograph of the pelvis demonstrates interval placement of a *left* total hip arthroplasty with augmented acetabular component. *THA* total hip arthroplasty

the literature and good results have been attained; however, studied patients did not have acetabular fractures [26]. Meanwhile, total hip arthroplasty for acetabular fractures has been gaining popularity in orthopedic traumatology. It is effective for both acute fractures and in a delayed manor for posttraumatic arthritis. To date, no reports exist on the use of total hip arthroplasty in the irradiated pelvis with an acetabular fracture. One should expect that total hip arthroplasty, performed as a salvage operation for failed open reduction internal fixation or primary treatment of either an acute fracture or posttraumatic degenerative changes after fracture, all have higher complica-

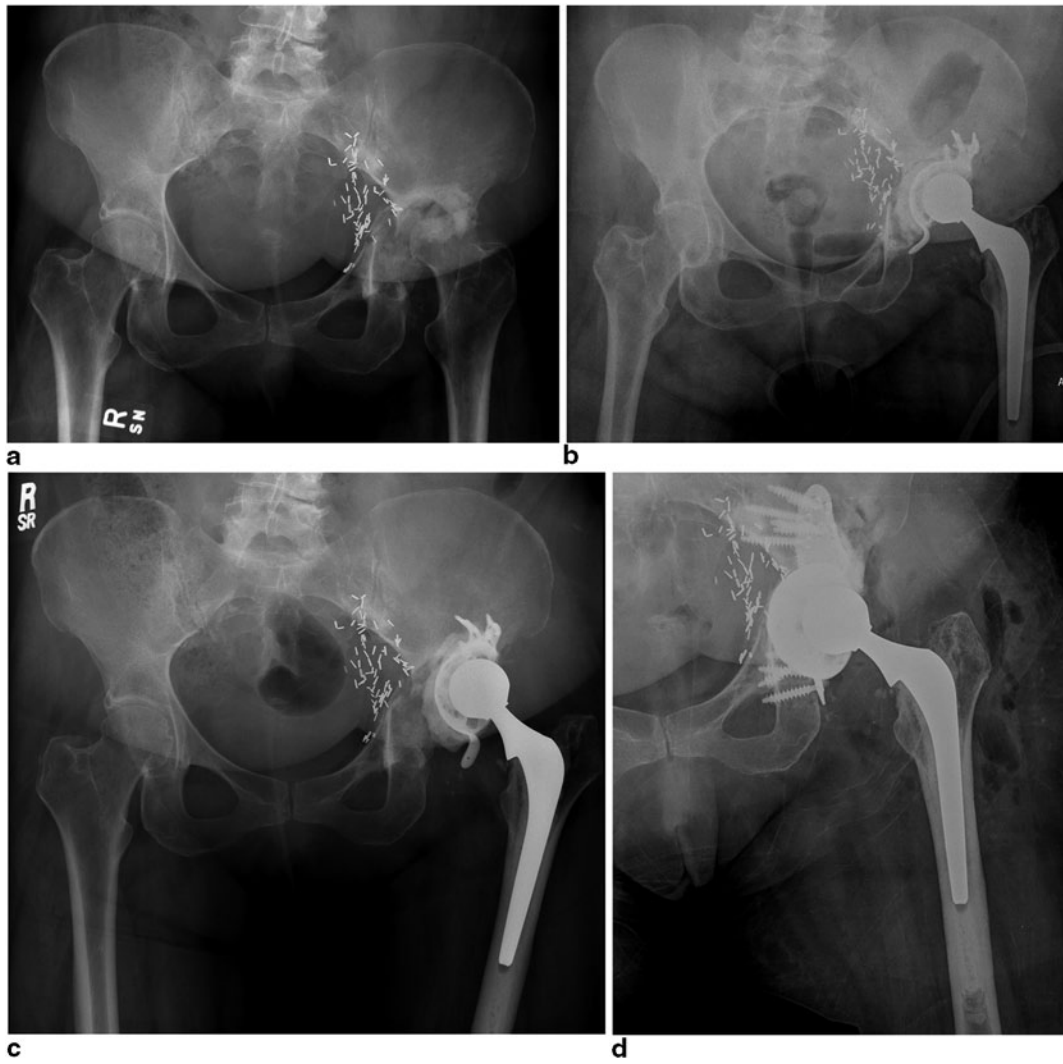

Fig. 12.5 Acetabular fracture with osteoradionecrosis of the femoral head. 56-year-old female with a history of *left* pelvis liposarcoma treated with surgery and pelvic radiation. **a** Anteroposterior radiograph of the pelvis obtained 9 years after completion of radiation therapy demonstrates a transverse fracture through the *left* acetabulum with distraction of the fracture fragments as well as deformity of the *left* femoral head likely reflecting osteoradionecrosis. Surgical clips along the *left* hemipelvis were from the prior surgical resections. **b** Anteroposterior radiograph of the pelvis demonstrates interval placement of a *left* total hip arthroplasty with cemented acetabular and femoral components with improved alignment of the *left* hip joint. **c** Anteroposterior radiograph of the pelvis obtained 5 months later shows interval abduction and lateral migration of the acetabular component with failure at the bone—cement interface. **d** Anteroposterior radiograph of the *left* hip shows improved alignment after revision of the previous total hip arthroplasty

tion rates and lower longevity compared to total hip arthroplasty in patients without fractures and/or a history of pelvic irradiation. The patient in Fig. 12.5 developed an acetabular fracture which was treated with a cage reconstruction and total hip arthroplasty. In cases where all reconstructive options have been exhausted, a Girdlestone resection of the proximal femur can be performed. This, of course leaves the patient with a flail hip which primarily only functions for assisted ambulation.

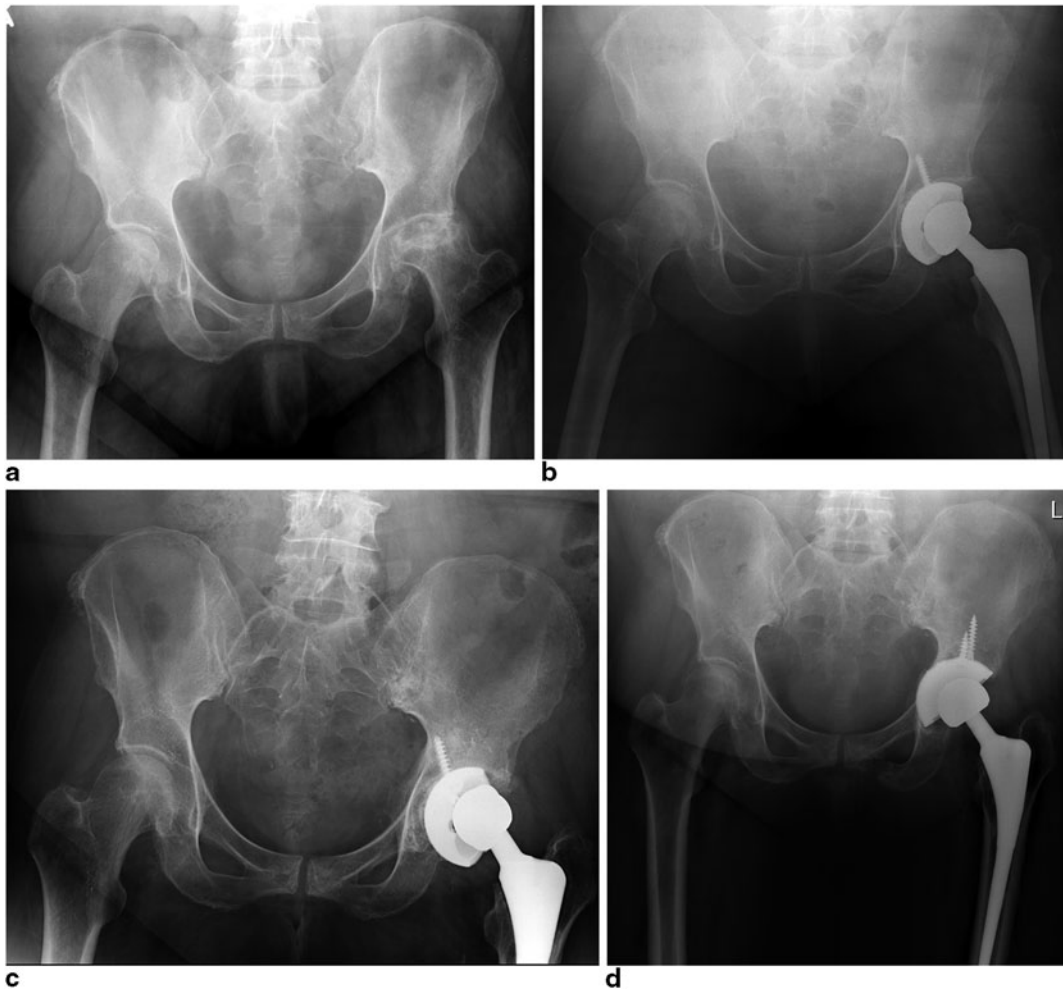

Fig. 12.6 Femoral head osteoradionecrosis. 58-year-old female with history of cervical cancer treated with radiation therapy to the pelvis. **a** Anteroposterior radiograph of the pelvis obtained 1 year after the completion of radiation therapy demonstrates deformity and collapse of the superior articular surface of the *left* femoral head with associated severe superior joint space narrowing. There is only mild excavation of the *left* acetabular roof laterally. There are bony changes of osteoradionecrosis along the *left* sacroiliac joint as well. **b** Anteroposterior radiograph of the pelvis obtained 7 months later shows interval placement of a *left* total hip arthroplasty. **c** Anteroposterior radiograph of the pelvis obtained 4 years after placement of the total hip arthroplasty demonstrates interval abduction and anteversion of the acetabular component with uncovering of the head of the femoral prosthesis. **d** Anteroposterior radiograph of the pelvis obtained 14 months later shows revision of the *left* total hip arthroplasty with improved alignment

Proximal Femoral Osteoradionecrosis and Hip Fractures

Femoral neck fractures and osteoradionecrosis of the femoral head occur in approximately 1% of those treated with pelvic irradiation. The patient in Fig. 12.6 presented several years after external beam radiation therapy of 45 Gy for anal cancer with advanced femoral head complications. There are several confounding factors that make it difficult to determine if these complications are directly associated with radiation therapy or if they are due to use of steroids or alcohol. Nonetheless, they are a rare event in the treated

cohort. Femoral neck fractures are a surgical problem while osteonecrosis of the femoral head can be treated with protected weight bearing and observation or one of several described surgical procedures.

Femoral neck fractures represent an intracapsular hip fracture and have an unacceptably high revision surgery rate if displaced or if surgical repair is delayed [27]. In the young patient with a femoral neck fracture, open reduction and internal fixation should ideally be performed within 8 hours of the fracture to reduce the chance of avascular necrosis and subsequent nonunion and need for revision surgery [27]. In the elderly with displaced fracture patterns or when surgery cannot be performed in a timely manner, treatment with prosthetic replacement is favored. In the low demand elderly patient and certainly those with cognitive dysfunction, hemiarthroplasty is indicated. Elderely patients with higher functional demands and no cognitive dysfunction can undergo total hip arthroplasty with reproducibly superior results compared to open reduction and internal fixation or hemiarthroplasty [28, 29].

Patients with femoral head osteoradionecrosis can be treated in several different ways. Patients with small lesions and those in relatively protected areas of the femoral head, without evidence of subchondral fracture or collapse can be treated with a period of protected weight bearing and observation. Patient with larger lesions but absence of subchondral fracture or collapse can be treated surgically with core decompression or vascularized bone grafting. Hip resurfacing and total hip arthroplasty are reserved for patients with subchondral collapse who have developed degenerative changes and subsequent pain. The patient in Fig. 12.6 was treated with total hip arthroplasty for osteoradionecrosis of the femoral head and like many in this cohort, went on to require revision surgery for early failure.

Summary

Pelvic insufficiency fractures after radiation therapy are a rare but potentially serious treatment consequence. Patients may be asymptomatic or have protracted pain for several months that can require narcotics, hospitalization, and at times, surgical intervention. Although additional studies are needed to determine optimal medical therapy in these patients, intermittent PTH therapy followed by bisphosphonates seems to provide a logical treatment algorithm for reconstituting and then maintaining bone density [30]. Surgery in this cohort is technically difficult and requires specialized techniques and implants. Surgical complications are encountered with increased frequency compared to nonirradiated patients with similar fractures. Unfortunately, some patients have little choice but to pursue surgical intervention when supportive therapy and medications fail to control their disease process. Because of the complex nature of the problem and treatment, a multidisciplinary approach to patients is mandatory. Management of patients with pelvic insufficiency fractures requires involvement of experts in radiation oncology, medical oncology, orthopedic surgery, and physical therapy to ensure optimization of outcomes in these patients.

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Radiation-Induced Lumbosacral Plexopathy

13

Ryan T. Merrell

Anatomy of the Lumbosacral Plexus

Radiation complications involving the lumbosacral plexus are different than those involving the brachial plexus, which has much to do with the anatomy of the two regions. In the neck, the cervical spinal cord, the cervical nerve roots, and the brachial plexus may all be in the same radiation field. In the lumbar region, the spinal cord and the exiting nerves are separated vertically and are unlikely to be within the same radiation field. The motor neurons that travel through the lumbosacral plexus originate in the lumbosacral enlargement of the spinal cord, which is located at the corresponding vertebral levels of about T8–T9 to L1–L2. Thus, the motor neurons, from which the motor nerves originate, are largely superior to the pelvis, and are not usually encompassed in radiation fields that involve the pelvis. Consequently, radiation to the pelvis avoids the spinal cord and mainly causes damage to nerve roots or more peripheral elements. The motor nerve roots extend from vertebral level L1–L2 through the spinal canal, and may be exposed to radiation fields encompassing the pelvis while they are still within the spinal canal. Radiation injury to the descending lumbar nerve roots may be indistinguishable from injury to the more peripheral elements, e.g., the true lumbosacral plexus. The motor nerve roots exit the spinal canal below the lumbar vertebra which gives them their name, e.g., the L5 nerve root exits between the L5 and S1 vertebrae. Once the lumbosacral nerve roots leave the spinal canal, they divide into anterior and posterior divisions and then divide again to organize into nerve trunks. This dividing and reorganizing collection of nerve roots, divisions, and trunks comprises the lumbosacral plexus, which can be complex from an anatomic perspective. The femoral nerve, for example, includes motor nerves from L2, L3, and L4, while the sciatic nerve trunk includes contributions from L4 through S3. The femoral nerve, once it exits, lies in the pelvis next to the psoas muscle and overlies the iliacus muscle. The sciatic nerve passes through the sciatic notch (from which it derives its name) in the bony pelvis, passes in between several small muscles (piriformis anteriorly, and obturator internus, the gemelli, and quadratus femoris posteriorly) and then lies medial to the femur. Consequently, lumbar motor nerves can be affected from their outflow in the lumbar spinal canal, through the pelvis, and as nerve trunks or peripheral nerves in the upper leg. Sensory nerve involvement is similar. The sensory neurons lie in the dorsal root ganglia or within the spinal cord. Consequently, the sensory nerves may be exposed to radiation while traversing the true lumbosacral plexus, or exposed as the lumbar nerve roots travelling in the lumbar spinal canal and damage at one level may be indistinguishable from damage to the

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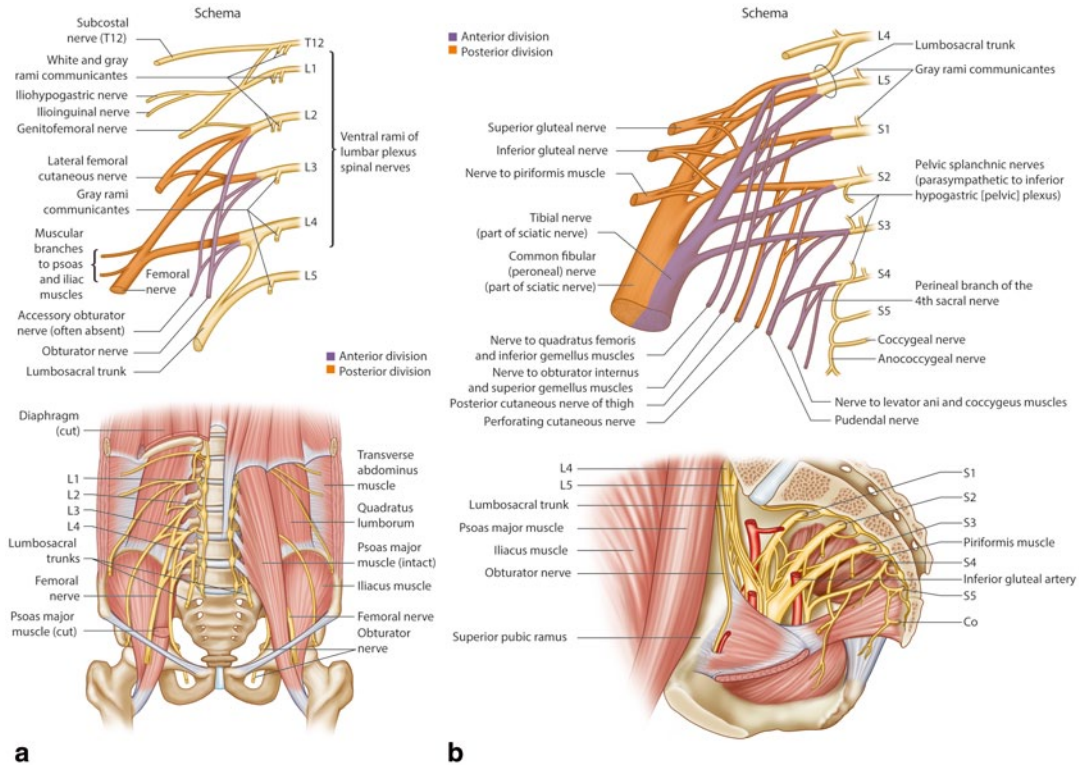

Fig. 13.1 Anatomy of the lumbosacral plexus

other. Figure 1 shows the anatomy of the lumbosacral plexus (Fig. 13.1).

Epidemiology

RILSP is a very rare complication of radiotherapy (RT), due to improvements in designing radiation fields (ports) and the improvement of radiation administration schedules. In fact, plexopathy is statistically much more likely to occur on the basis of tumor infiltration than as a result of RT. The incidence and prevalence of RILSP is largely defined by the malignancies in which it has been reported. The vast majority of cases have been described in cervical and uterine carcinoma. There also have been reports of RILSP in colorectal, testicular, bladder cancers, lymphoma, and sarcoma. The incidence of RILSP in gynecological malignancies has been estimated to be 1–2 per 1000 patients based on two large case series [1, 2]. The estimated dose in these cases was between 70 and 80 Gy. The general principles of radiation oncology incorporate dose constraints to avoid damaging the lumbosacral plexus [1, 3]. In gastrointestinal malignancies, the estimated dose for development of RILSP is between 50 and 60 Gy [4]. This dose relationship was demonstrated in a small case series of patients treated for rectal carcinoma where one patient treated with a dose of 58.6 Gy developed RILSP [5]. One case series reported a 3.2% incidence of neurologic impairment in patients with testicular seminoma treated with RT. A subset of these patients had RILSP [6]. This series reported a dose effect relationship where no patients treated with doses less than 36 Gy developed motor impairment [6].

General risk factors for developing RILSP include many conditions that either cause neuropathy or increase its risk. These include including past or concurrent neurotoxic chemotherapy, diabetes, hypertension, hyperlipidemia, and collagen vascular disease. The addition of brachytherapy to standard RT has also been suggested to be a risk

factor for RILS [1]. In fact, if combined modality therapy is delivered (chemotherapy and radiation therapy) RILSP should be termed "treatment related" not RILSP as it can minimize the importance of cytotoxic chemotherapy plays in toxicity.

Pathophysiology

The general principles of radiation-induced effects on tissue are described in earlier chapters. Radiation can damage myelin, axons, or the microvascular blood supply of the nerves. Radiation damage to myelin and axons often produces a very slowly progressive symmetrical polyneuropathy, while radiation injury to microvascular supply often produces an asymmetric pattern referred to as mononeuritis multiplex. In the latter case, the specific effects on the nervous system are thought to be mediated by microvascular injury which ultimately leads to varying degrees of perineural fibrosis, from inflammation to sclerosis. Radiation-induced fibrosis is thought to be mediated by excessive production of oxidative free radicals which ultimately leads to fibrogenesis [7].

Clinical Manifestations

Symptoms of RILSP are typically insidious and chronic in onset and develop several months to years after RT with a median of 5 years and a range of 1–31 years [8], particularly when the mechanism is a demyelinating or axonal neuropathy. The most important clinical distinction is whether a patient has plexopathy as a result of previous RT or from direct tumor infiltration of the plexus [9]. Symptoms of direct invasion are often more acute in their presentation. The distinction between direct tumor involvement and RILSP is guided by the clinical features, imaging findings, and electromyography (EMG). In fact, RILSP should be considered a diagnosis of exclusion after exhaustive testing has ruled out the possibility of tumor plexopathy. It is possible that tumor plexopathy and RILSP may be present in the same patient.

Pain is often a symptom that can be helpful in distinguishing RILSP from tumor plexopathy.

Table 13.1 Factors that distinguish RILSP from direct tumor infiltration of plexus

RILSP	Tumor plexopathy
Pain is delayed	Pain at onset
Edema present	Edema absent
Bilateral weakness	Unilateral weakness
MRI unremarkable	MRI shows nerve enhancement
EMG shows myokymia	EMG rarely shows myokymia

RILSP Radiation-Induced Lumbosacral Plexopathy, *MRI* magnetic resonance imaging, *EMG* electromyography

Pain often develops later in the course of RILSP than in tumor plexopathy and after other sensory symptoms have occurred. In one series, pain was the presenting complaint in 10% of patients with RILSP and 93% of patients with tumor plexopathy [8]. Although pain is not often an initial symptom in RILSP, it often manifests at some point in its course. If present, the pain in RILSP is not as debilitating and is more manageable than in tumor plexopathy.

The most common presenting symptom and sign in RILSP is bilateral distal leg weakness followed by lower extremity paresthesias. The weakness may affect any muscles but has predilection for muscles innervated by L5–S1. Limb edema is common in RILSP. Bowel and bladder dysfunction are rarely reported. As is typical for a peripheral neuropathic process of any cause, deep tendon reflexes are decreased or absent. Later in the course of RILSP, there may be muscle atrophy and fasciculations. Paresthesias usually occur in the same distribution as the muscle weakness.

In contrast, the weakness in tumor plexopathy is usually unilateral. Similarly, the sensory loss in tumor plexopathy is almost exclusively unilateral, whereas in RILSP it is almost always bilateral. Objective sensory findings in RILSP can affect all sensory modalities and are not specific to small fiber or large fiber deficits. Sensory loss usually occurs months to years after the motor impairment [2]. Survival is another factor that differentiates RILSP from tumor plexopathy, in that patients with RILSP tend to have longer survival than patients with tumor plexopathy. The clinical and diagnostic features that distinguish RILSP from tumor plexopathy are outlined in Table 13.1.

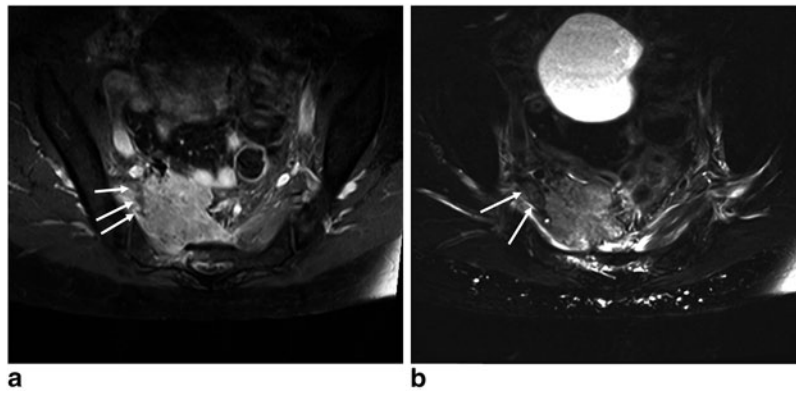

Fig. 13.2 Magnetic Resonance Imaging of lumbosacral plexus. **a** T2-weighted images demonstrating hyperintensity along the sacral roots (S1–2). **b** T1 post contrast images demonstrating pathologic enhancement of the upper sacral roots (S1–S2)

Neuroimaging is an important diagnostic tool for ruling out tumor plexopathy. Magnetic resonance imaging (MRI) has largely replaced computed tomography (CT) in imaging the lumbosacral plexus. Enhancement of nerve roots and T2 hyperintensity along the plexus on MRI indicates tumor infiltration and are findings not seen in RILSP. MRI is sensitive and specific for demonstrating either direct tumor involvement of the plexus or tumor involvement of surrounding structures which may compress the plexus. One series showed direct involvement of the plexus by MRI in 29 of 31 patients with known tumor plexopathy [10]. Therefore, MRI can be an effective tool to rule out direct tumor involvement of the plexus in order to support the diagnosis of RILSP (Fig. 13.2). In contrast, MRI is not a good tool for diagnosing RILSP as there are no specific radiographic findings. In a series of seven patients with radiation plexopathy of the brachial plexus, the investigators demonstrated that radiographic signs of fibrosis in surrounding tissue were present in the majority of the patients. However, these signs were not reliable enough to be used as diagnostic criteria of radiation-induced brachial plexopathy [11] In summary, MRI studies of plexopathy due to direct tumor involvement will often show a focal process, while in RILSP MRI may be negative or nonspecifically abnormal.

EMG is helpful in the localization and classification of disease processes affecting the lumbosacral plexus. As with MRI, symmetrical involvement often points to RILSP, while focal involvement, e.g., unilateral involvement, should raise suspicion of tumor involvement. EMG in RILSP reveals a reduction in motor and sensory action potential amplitudes and mild slowing of motor conduction velocities. Myokymia is a specific finding that points to RILSP and is seen in about 60 % of patients [8]. Myokymic discharges on EMG are bursts of motor unit potentials that occur in groups semi rhythmically, occurring several times per second (Fig. 13.3) [9].

RILSP usually leaves patients with chronic motor and sensory deficits that may slowly improve with time. A few case series have reported acute onset and/or reversible neurologic symptoms. A case report in cervical cancer revealed a patient who experienced bilateral lower extremity weakness 10 weeks after external beam and intracavitary RT that was found to be consistent with RILSP. The patient did not experience any neurologic improvement at the time of follow-up [12]. A series of 11 men treated with RT for testicular seminoma revealed five of the patients who experienced motor impairment that completely reversed after a range of 3 months to 14 years [6]. In a series of 59 patients treated with neoadjuvant RT for colon carcinoma in the year 1993, three patients experienced continuous neurologic

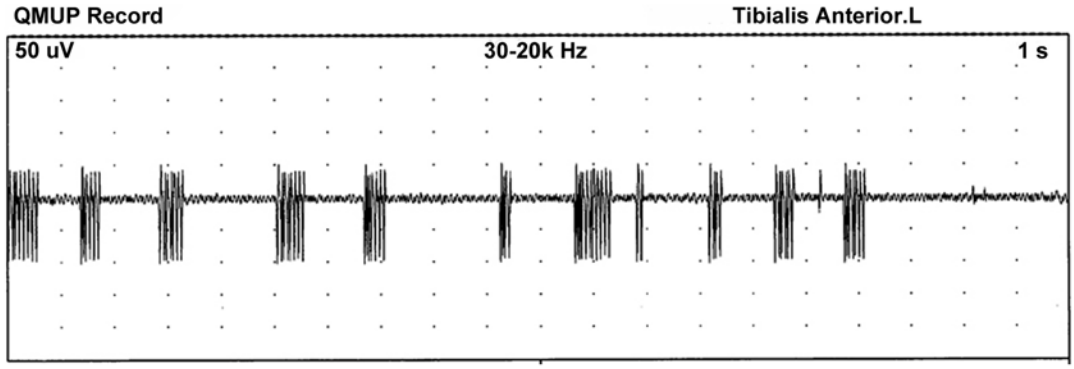

Fig. 13.3 Electromyogram demonstrating myokymia. *With permission from Jaeckle KA. Neurologic manifestations of neoplastic and radiation-induced plexopathies. Semin Neurol 2010 Jul;30(3):254–62 © Thieme 2010* [9]

symptoms suggestive of RILSP. In two patients, the symptoms were acute in onset, while subacute in the third. Despite a thorough analysis, the authors did not determine why there was a high incidence in their patients treated during 1993 [6].

Besides direct tumor plexopathy, other etiologies that may mimic RILSP need to be excluded. Malignancy can also affect the plexus through bony and soft tissue compression and through bulky lymphadenopathy. Carcinomatous meningitis (CM) and paraneoplastic neuronopathy are other direct and indirect effects of malignancy that can produce lumbosacral plexopathy. Non-neoplastic etiologies in the differential diagnosis include pelvic fracture, diabetic lumbosacral plexopathy, epidural cord compression, lumbosacral radiculopathy, postinfectious plexopathy, and plexopathy as a result of chemotherapy. The history and examination alone are helpful in making many of these distinctions. For example, pelvic fracture and diabetic lumbosacral plexopathy can be excluded by history, radiographic findings, and serum glucose. Epidural cord compression and lumbosacral radiculopathy are almost always accompanied by pain and unilateral deficits, respectively. Neuroimaging with CT or MRI will often reveal a clear structural deficit in these etiologies. Postinfectious plexopathy is heralded by a known infection such as herpes simplex or zoster and can also be tested for in serum. Chemotherapy-induced plexopathy results from treatment with intrathecal chemotherapy. CM may present with bilateral leg weakness that mimics RILSP. However, the cerebrospinal fluid in CM often shows elevated protein, low glucose, and malignant cells. Paraneoplastic neuronopathy is a rare etiology and perhaps the most difficult diagnosis to make. The diagnosis is based on subacute to chronic development of motor and sensory deficits in the setting of known or suspected malignancy. The diagnosis is supported by inflammatory CSF and/or the presence of paraneoplastic antibodies in the serum or CSF.

It is important to emphasize that in suspected cases of RILSP, careful review of the radiation ports should be conducted by a radiation oncologist to ensure that the lumbosacral plexus could have been radiated enough to produce the complication. It may be falsely assumed that this region was radiated, when in fact it was not.

Treatment

The first step in treatment is to distinguish radiation injury (RILSP) from active involvement of nerves by tumor. Treatment of RILSP is largely supportive and aimed at preserving neurologic function. Physical and occupational therapy and use of gait aides are important components of maintaining maximal use of the lower extremities. Medications such as tricyclic antidepressants, gabapentin, pregabalin, and selective serotonin re-uptake inhibitors (SSRIs) can be used to manage neuropathic pain. Nonmedication approaches include acupuncture and massage.

Directed treatments for RILSP have achieved mixed success. Hyperbaric oxygen was studied in small case series of patients with brachial plexopathy without clear benefit [13]. Its efficacy in RILSP is unknown. Warfarin has been used in an attempt to reverse endothelial injury, but case series have not had enough power to demonstrate a clear benefit [14]. Corticosteroids may be effective for treating inflammatory effects.

A more recent treatment paradigm has used the combination of pentoxifylline (PTX) and alpha-tocopherol (vitamin E). The mechanism of PTX in treating RILSP is to induce vasodilatation and decrease inflammatory mediators such as tumor necrosis factor. Vitamin E acts as a scavenger for oxygen free radicals [15]. A study revealed neurologic improvement after 3 years with clodronate, a bisphosphonate in combination with PTX and vitamin E in two patients with RILSP [16]. This led to plans for a larger, randomized clinical trial in France. This combination also showed improvement in a larger series of patients with mandibular radiation necrosis [17].

Conclusion

RILSP is a rare complication of pelvic RT that has been described in association with RT in several malignancies. Although risk factors for its development are unclear, there appears to be a dose relationship that has been demonstrated in the treatment of gynecological and GI tumors. The most important task of the clinician is to distinguish RILSP from direct tumor infiltration of plexus. Clinical, radiographic, and electromyographic findings allow for making this determination. This distribution is important as it influences prognosis and treatment. New treatments for radiation-induced brachial plexopathy, a much more common neurologic complication of cancer, may ultimately lead to similar treatments for RILSP.

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Part III

Treatment and Prevention of pelvic radiation injury

The Management of Radiation Cystitis

14

Joshua A. Cohn, Kyle A. Richards
and Gary D. Steinberg

Introduction

Pelvic radiation therapy comprises an important component in the management of a number of gynecologic [1, 2], urologic [3–6], and gastrointestinal malignancies [7, 8]. The goal of radiotherapy is delivery of high doses of radiation to the diseased organ while minimizing damage to surrounding tissues [9]. Advances in the delivery of radiation, such as conformal radiation therapy (CRT), intensity-modulated radiation therapy (IMRT), and brachytherapy, have considerably reduced toxicity [9, 10]. Nonetheless toxicity does occur. It is estimated that up to 9% of the patients who have received full dose radiation will develop radiation-induced hematuria [11], and 5% of patients will develop severe hemorrhagic cystitis [12]. With radiation therapy indicated for a significant portion of the 12,000 cases of cervical cancer, 47,000 cases of endometrial cancer, 247,000 cases of prostate cancer, and 40,000 cases of rectal cancer that occur in the United States of America annually, radiation cystitis remains a common condition in urologic practice [13].

The aim of this chapter is to describe the pathophysiology, clinical presentation, and management of radiation cystitis. Discussion of management will focus on options and indications for intravesical therapies, systemic agents, endoscopic and percutaneous management, hyperbaric oxygen therapy (HBOT), and aggressive surgical management with cystectomy and urinary diversion.

Pathophysiology

The mechanism by which radiation causes cell death is thought to be related to irreparable damage caused to cellular DNA [9]. Direct damage to DNA is hypothesized to be a relatively rare event [14]. Rather, indirect damage, caused by free radicals created by ionization of intracellular water is the primary mechanism by which DNA is injured [15]. The bladder mucosa is relatively sensitive to radiation toxicity because its cells divide rapidly [16, 17]. Acute injury to the mucosa may lead to loss of tight junctions with resultant exposure of underlying tissues to the hypertonic urine, which subsequently leads to an increase in immature and atypical cells. These histologic findings are associated with the onset of what are usually self-limited lower urinary tract symptoms. However, physiologic changes from radiation can progress. Three months following therapy, intermediate and basal urothelial

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cells display nuclear irregularity, cellular edema, and increased cytoplasmic elements. At 6–12 months, urothelial proliferative activity and perivascular fibrosis are increased, which may lead to ischemic insult that can impact the urothelium as well as the smooth muscle of the bladder wall. Ultimately, ischemia may lead to replacement of the smooth muscle by fibrosis with subsequent loss of bladder compliance [16].

Late toxicity results when vascular endothelial cells and connective tissues that had sustained injury at the time of treatment begin to replicate but fail to adequately regenerate. This can occur anywhere from 3 months to 3 years or more following treatment. The resultant submucosal fibrosis and inflammation can lead to further ischemia with necrosis and ulceration. Neovascularization in response to this process is hypothesized to give rise to the superficial, fragile vessels responsible for bleeding in hemorrhagic cystitis [17, 18].

Clinical Presentation and Risk Factors

Radiation cystitis can be acute, occurring either during or shortly following treatment, or late-onset. Acute radiation cystitis rarely lasts beyond 3 months from the end of radiation therapy. Treatment typically consists of anticholinergic drugs for management of urinary frequency and irritative voiding symptoms with consideration of phenazopyridine for dysuria [19]. Symptoms are generally self-limited, and drugs can be discontinued as symptoms improve. The Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) standardized acute and late radiation morbidity scoring criteria for the bladder describe the spectrum of symptomatology and are provided in Table 14.1 [20, 21].

Late-onset radiation cystitis has a mean onset 35 months following completion of radiation therapy. However, it may occur after a latent period of >20 years [22]. Therefore, radiation cystitis should be suspected in any patient with new onset hematuria who has a history of pelvic radiation regardless of time since therapy. Nonetheless, it is essential to evaluate for infection (with dipstick urinalysis and culture) or de novo bladder or upper urinary tract malignancy (with cystoscopy +/− biopsy and upper urinary tract imaging), as the risk of bladder cancer is increased following pelvic radiotherapy [23–25]. Radiation-induced hematuria can be mild or life-threatening, and it may be necessary to initially defer further diagnostic work up as the patient is stabilized.

Increased risk of late-onset radiation cystitis is related to the dose and type of radiation (e.g., combination external beam and brachytherapy) delivered. Diseases that may predispose a patient to poor healing and/or local tissue ischemia such as diabetes and vascular disease may also confer increased risk [16]. Chemotherapy, particularly cyclophosphamide, may also increase the risk of late and potentially debilitating bladder toxicity [26, 27].

Initial Management

As described, the severity of hematuria can range from mild to life-threatening. Therefore, initial management must be tailored to each individual patient depending on presentation. If necessary, aggressive fluid resuscitation and blood transfusion should be administered. A transurethral catheter designed for clot irrigation should be inserted into the bladder. If tolerated, the bladder should be manually irrigated at the bedside to remove all clots, with initiation of continuous bladder irrigation with normal saline, if necessary [19, 28]. If patient discomfort and/or organized clot prevent adequate bedside irrigation, rigid cystoscopy and clot evacuation in the operating room may be required [28]. Most patients will respond to initial conservative management (manual irrigation and continuous bladder irrigation), but refractory cases may require one or more additional interventions. It is critically important that the presence or absence of urinary tract malignancy is determined during evaluation and management.

Table 14.1 Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria. (Adapted from Cox et al. [20])

	Grade	0	1	2	3	4
Early	Symptom complex	No change	Frequency of urination or nocturia twice pretreatment habit/ dysuria, urgency not requiring medication	Frequency of urination or nocturia that is less frequent than every hour. Dysuria urgency, bladder spasm requiring local anesthetic (e.g., pyridium)	Frequency with urgency and nocturia hourly or more frequently/ dysuria, pelvis pain, or bladder spasm requiring regular, frequent narcotic/gross hematuria with/ without clot passage	Hematuria requiring transfusion/ acute bladder obstruction not secondary to clot passage, ulceration, or necrosis
Late	Symptom complex	None	Slight epithelial atrophy; minor telangeictasia (microscopic hematuria)	Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria	Severe frequency and dysuria; severe generalized telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (< 150 cc)	Necrosis/contracted bladder (capacity < 100 cc); severe hemorrhagic cystitis

Intravesical Agents

Aluminum Salts

Alum (aluminum ammonium sulfate or aluminum potassium sulfate) induces protein precipitation on cell surfaces and superficial interstitial spaces [28, 29]. Two case series reported cessation of bleeding in all patients treated with intravesical alum [30, 31], and another reported complete response in 10/15 (67%) patients [32]. The authors from the latter series observed that alum tended to fail in more severe cases as the precipitant clotted, interfering with continuous irrigation [32].

Protocols for the use of alum have used 1% alum solution (50 g of alum dissolved in 5 L sterile water or 400 g of potash of alum in 4 L hot sterile water to create a stock solution where 300 mL of stock is added to 3 L of normal saline) with irrigation at a rate of 250–300 mL/h if in sterile water or up to 30 L in 24 h if run with normal saline [28]. No anesthesia is required, and side effects associated with treatment are generally mild, consisting mainly of bladder spasms and pain. Nonetheless, severe aluminum toxicity, characterized by lethargy, confusion, seizures, metabolic acidosis, or elevated serum aluminum [33], has been reported [34], and the use of alum is cautioned in patients with renal impairment. Therapy should be stopped if symptoms of aluminum toxicity are encountered.

Formalin

Formalin is a tissue fixative that precipitates cellular proteins within the bladder mucosa [35]. Intravesical instillation results in edema, inflammation, and necrosis of all layers of the bladder [36, 37]. The concentration of formalin instilled varies in the literature, and it has been suggested that lower concentrations (1–4% vs 10%) can be efficacious while reducing the risks of complications [28]. When all causes of intractable hematuria are considered, success rates have been reported at 80% or greater, even in cases of massive bleeding [35, 38–42].

Formalin must be instilled under spinal or general anesthesia. Choong et al. suggest starting with a concentration of 1–2 %, increasing concentration only if needed [28]. Cystography should be performed prior to instillation to exclude reflux, with Fogarty balloon occlusion of the ureteral orifices if reflux exists. Blood clots should be evacuated and bleeding vessels coagulated to limit systemic absorption. The skin is protected with Vaseline and the vagina packed to prevent leakage. The bladder is irrigated with the formalin solution under gravity at <15 cm H_2O, and contact time should be limited to 15 min or less.

Major toxicities associated with formalin treatment occur in about one-third of patients [43] and can include skin irritation, urinary incontinence, reflux, ureteral stricture, uretero-vesical junction obstruction, fistula, bladder rupture, permanent bladder and/or upper tract damage, sepsis, or even death [28]. Therefore, its use should be limited only to those cases in which more conservative measures have been exhausted or in patients unfit for more aggressive management. If formalin must be used, consideration should be given to modified techniques in which formalin-soaked pledgets are endoscopically placed on sites of bleeding, which has been reported to limit toxicity [44, 45].

Placental Extract

Topical placental extract has been successful in improving epithelialization of venous ulcers [46]. Based on its success in this setting, it was hypothesized that the high concentrations of growth and angiogenic factors in placental extract would promote healing of the bladder mucosa in radiation cystitis [17]. Mićić and Genbacev prospectively studied 35 women with radiation cystitis [47]. In the treatment arm, placental extract in saline was instilled in the bladder for 2 h, 3 days per week for 1 month and then weekly for 2 months. All 21 treated patients had relief of symptoms at 15 months with objective improvement in appearance of the bladder mucosa in 18/21 (86 %), which was a significant improvement in both outcomes compared to the 14 controls. Treatment-related morbidity was not reported, and there were no treatment-related deaths.

Aminocaproic Acid

Epsilon aminocaproic acid (EACA), used as an intravesical instillation, is thought to act by stabilizing the clotting process through its inhibition of fibrinolysis [48]. EACA instillation at a dose of 200 mg/L had a reported success of 93 % (13/14) in controlling bleeding in patients with intractable bleeding from radiation cystitis [49]. However, problems with Foley catheter obstruction and excessive clot formation may become problematic and require repeat trips to the operating room for clot evacuation. In general, we have not found EACA to be useful.

Hyaluronic Acid

Hyaluronic acid (HA) is a mucopolysaccharide found in connective and epithelial tissues that has been shown to inhibit immune complexes and neutrophil function while regulating fibroblast and endothelial cell proliferation [50]. Shao et al. randomized 36 patients with radiation-induced hemorrhagic cystitis to intravesical HA (40 mg for 20 min weekly for 1 month then monthly for 2 months) or HBOT (60 min, 7 days per week for at least 1 month) [51]. There were no significant differences found between the two groups in the proportion of patients with complete or partial response at 6, 12, and 18 months and no reported side effects with intravesical HA, suggesting a role for its consideration in refractory radiation-induced hematuria.

Silver Nitrate

Silver nitrate is an oxidizing agent that precipitates in water resulting in the release of free radicals [52]. The resulting tissue oxidation can serve to control bleeding. Intravesical silver nitrate irrigation has been associated with complications such as anuria [53] and reflux with extravasation

and retroperitoneal inflammation [54]. Its use in the treatment radiation-induced hematuria is limited.

Prostaglandins

Prostaglandins are thought to increase cyclic adenosine monophosphate (cAMP) and sodium transport with resultant reduction in edema and inflammation [17]. Several case studies have reported success with intravesical prostaglandins either alone or in combination with hyperbaric oxygen for the treatment of radiation-induced hemorrhagic cystitis [55–57]. The durability of response is unknown, and though well tolerated, its use in cyclophosphamide-induced hematuria has been associated with a response in only 50% of patients [58].

Liposomal Tacrolimus-Based Therapy

Tacrolimus is an immunosuppressive agent that inhibits interleukin-2-dependent T-cell activation via its inhibition of calcineurin phosphatase [59]. Systemic administration is associated with side effects such as nephrotoxicity and hypertension [60] that are not seen in topical administration [61]. Liposomes permit suspension of tacrolimus for intravesical delivery, and its use has been shown to effectively inhibit inflammatory cystitis in rats [62]. Assessment of its potential utility in humans will require further investigation.

Systemic Agents

Pentosan Polysulfate

Pentosan polysulfate is a sulfated polysaccharide that functions as a synthetic glycosaminoglycan, which is thought to reinforce the damaged mucosal lining of the bladder [63]. Success rates have been reported at 60–100% with no reported toxicity [63–65]. Initial therapy consists of 100 mg of oral sodium pentosan polysulfate three times daily, and in many cases the dose can be reduced to once daily or stopped completely as hematuria improves [65].

Estrogens

Systemic estrogen has improved bleeding in advanced renal failure and may function to limit bleeding in radiation cystitis by decreasing capillary wall fragility [17, 19]. Liu et al. treated four patients with late hemorrhagic radiation cystitis with oral estrogen 5 mg daily (2/4 had received 1 mg/kg intravenously twice daily for 2 days prior to initiation of oral therapy) [66]. Three out of four patients had resolution of hematuria at 15 months, and no adverse effects were reported.

WF10

WF10 is a 1:10 dilution of tetrachlorodecaoxide that is delivered intravenously. It is thought to improve tissue repair through modification of macrophage activity via stimulation of phagocytosis and cellular defense systems. Down regulation of antigen presentation ultimately leads to reduced chronic inflammation and improved healing [67]. Veerasarn and colleagues conducted two studies evaluating the efficacy of intravenous WF10 in refractory radiation-induced hematuria. In the first study, 100 women were randomized to standard therapy (consisting of antibiotics, irrigations, and antispasmodics) or standard therapy plus WF10 at a dose of 0.5 mL/kg for 5 days every 2 weeks for a total of two cycles [67]. There was no significant difference in complete resolution between the treatment group and control group at 7 weeks (74% vs 64%, $P=0.28$), however, the WF10 group had significantly lower use of antibiotics and antispasmodics. Furthermore, Kaplan–Meier analysis found that recurrence of objective hematuria occurred significantly later in the treatment arm. A second study prospectively evaluated 16 patients with grade 2–3 radiation-induced hematuria [68]. Fourteen of 16 (88%) improved to grade 0–1 toxicity upon completion of therapy, with 4 (28%) having recurrent grade 2 hematuria at a mean follow-up of 51 months.

No serious treatment effects were attributable to the drug in either study.

Pentoxifylline

Pentoxifylline is an orally administered drug used to treat vascular occlusive disorders. Pentoxifylline increases prostacyclin release, which results in increased red cell deformity and improved flow through capillaries. Dion et al. reported complete healing of 13/15 (87%) radiation-induced necrotic ulcers at the time of analysis in patients treated with pentoxifylline, with an average time course of healing of 9 months [69]. In one case of chronically nonhealing suburethral ulcer, pain resolved after 8 weeks of pentoxifylline 400 mg three times daily, and the ulcer healed completely at 10 weeks, suggesting a potential role for this agent in the treatment of chronic radiation-induced ulceration of the genitourinary tract. Pentoxifylline is generally well-tolerated, with the most common side effect being gastrointestinal-upset [70].

Endoscopic or Percutaneous Management

Cystoscopy and Fulguration

When intravesical and/or systemic agents fail to control bleeding from radiation cystitis, various endoscopic and/or percutaneous management strategies can be performed. Cystoscopy, clot evacuation, and fulguration of bleeding sites using electrocautery or various other energy sources is a reasonable first step when conservative measures fail. Kaushik et al. reported a novel treatment strategy for refractory radiation-induced hemorrhagic cystitis using a 980 nm diode laser [71]. The 980 nm wavelength is ideal as it is highly absorbed by both hemoglobin and water resulting in improved hemostasis [72]. The authors reported their experience using the 980 nm diode laser in four patients with refractory radiation-induced hemorrhagic cystitis who failed conservative therapy and standard cystoscopy and electrocautery fulguration. All four patients remained hematuria-free postprocedure with mean follow-up 11 months (range 3–17). Additionally, the neodymium-doped yttrium aluminum garnet (Nd:YAG) laser has been shown to be safe and effective for control of bleeding from radiation cystitis, but due to the increased depth of penetration, care must be taken to avoid bladder perforation [73]. Zhu et al. utilized the Greenlight ^{TM} potassium-titanyl-phosphate (KTP) laser in 10 patients with refractory hematuria from radiation cystitis [74]. At a mean follow-up of 17 months (range 6–36 months), 1 patient had recurrence of significant hematuria 7 months after initial laser fulguration.

Botulinum Toxin A

Botulinum toxin A is FDA approved for the treatment of neurogenic and non-neurogenic overactive bladder in adults who have failed treatment with anticholinergic medications. Chuang and colleagues injected 200 units of botulinum toxin A into the bladder of six patients with refractory radiation cystitis [75]. Patients were followed with clinic visits and 3-day voiding diaries. One patient had no subjective improvement, three had moderate improvement, and two had significant improvement at 1-week follow-up with durability of results at a 6-month follow-up visit. At 2-month follow-up, 3-day voiding diaries revealed a mean increase in bladder capacity from 105 to 250 mL and a mean decrease in urinary frequency from 14 to 11 episodes per day. No complications were reported and no patients developed urinary retention. Botulinum toxin A bladder injections appear to be a reasonable option for patients with refractory urinary storage symptoms related to radiation cystitis, although its use in this context is off-label.

Orgotein

Orgotein is a copper–zinc superoxide dismutase (SOD) that is found in the cytoplasm of all eukaryotic cells and functions to convert superoxide radicals into oxygen and hydrogen peroxide.

Superoxide radicals are formed during the acute phase inflammatory process during radiation therapy and can induce tissue damage. It is hypothesized that orgotein could function at the extracellular level and inhibit the acute phase inflammatory processes mediated by free radicals thereby reducing the risk of late side effects from radiation therapy [76]. Marberger et al. initially reported a retrospective series of 30 patients with late radiation cystitis treated with orgotein injections into the bladder wall and noted clinical and cystoscopic improvement in 25 patients [77]. Other randomized prospective studies have reported a benefit of intramuscular orgotein injections administered at the time of radiation therapy to prevent early and late radiation cystitis [78, 76]. While the evidence is fairly strong for the use of orgotein to prevent early and late radiation cystitis, further studies are needed to determine the role of orgotein bladder injections in treating patients with late radiation cystitis.

Percutaneous Nephrostomy Tubes

Insertion of bilateral percutaneous nephrostomy tubes is a viable minimally invasive option in patients with refractory radiation-induced hemorrhagic cystitis who have failed other bladder-directed therapies. It is thought that diverting urine away from the bladder prevents its overdistention and limits the action of endogenous urokinase [79]. Sneiders and Pryor reported success with this strategy in two patients in whom bleeding gradually ceased during a 1-week period [79]. Both patients were alive and voiding spontaneously at 6 months follow-up. Additionally, Zagoria et al. treated six patients with refractory hemorrhagic cystitis with bilateral percutaneous nephrostomy tubes noting favorable results in five of the six patients [80]. There are no data on long-term follow-up of these patients, and while percutaneous nephrostomy tube insertion may ameliorate bleeding, questions remain regarding its long-term efficacy.

Embolization of Bladder Vessels

Embolization of the arteries to the bladder has been reported as a useful adjunct for the management of radiation-induced hemorrhagic cystitis. Potential drawbacks of embolization include the need for skilled interventional radiologists, the extensive network of collateral circulation of the bladder, and the potential for postembolization gluteal pain, claudication, and tissue necrosis. However, De Berardinis et al. reported success using super-selective embolization of the bladder arteries in a patient with refractory hemorrhagic cystitis following radiation therapy for invasive bladder cancer [81]. The super-selective embolization technique avoids embolization of the gluteal circulation and permits the utilization of adaptable embospheres, which offer better occlusion of the vessels. Despite these purported advantages, long-term durability remains questionable. Liguori et al. reported long-term results of selective embolization of the internal iliac arteries in 44 patients with intractable gross hematuria secondary to advanced pelvic malignancies [82]. Despite an initial success rate of 82 %, at a mean follow-up of 10.5 months after embolization rebleeding had occurred in all but 43 % of patients. Nonetheless, embolization of the arteries to the bladder remains a viable treatment option in patients unfit for more aggressive surgical management.

Hyperbaric Oxygen Therapy

HBOT for the management of radiation-induced hemorrhagic cystitis was first reported by Weiss and researchers in 1985 [83]. Proposed mechanisms of action of HBOT include angiogenesis and capillary regrowth stimulated by large plasma to tissue oxygen gradients, mediation of fibroblastic stromal process, and mobilization of stem cells. Patients typically undergo 30–40 treatment sessions with each session consisting of 2 h of pressurization at 1.5–2.5 absolute atmospheric pressure. During each 2-h session, 90 min are spent breathing 100 % oxygen at maximum pressure. Advantages of HBOT include its

Table 14.2 Studies assessing hyperbaric oxygen therapy for radiation cystitis

Study	Number of patients	Number of treatments' mean ± SD (range)	Length of treatment session (min)	Response rate (%)	Follow-up duration
Hampson et al. [84]	44	42 ± 9 (34–60)	120	89	No follow-up after HBOT
Nakada et al. [85]	38	62 ± 12 (39–92)	90	74[a]	11.6 ± 3.7 years
Oliai et al. [86]	19	29.8 (10–40)	90–120	81	39 months (7–70)
Shao et al. [51]	20	30	60	75	18 months
Yoshida et al. [87]	8	19 (10–42)	90	75	15.5 months (2–31)
Vilar et al. [88]	38	31.2 (10–48)	90	89	56 months (4–72)
Mohamad Al-Ali et al. [89]	10	30	60	20	18 months (12–72)
Chong et al. [90]	60	33 (9–63)	90	80	12 months
Corman et al. [91]	57	33 (9–68)	90	86	10–120 months
Del Pizzo et al. [92]	11	40	90	27	5.1 years median
Bevers et al. [93]	40	20	90	93	23.1 months (1–74)

[a] Response rate at final follow-up, i.e., 74% of patients did not have recurrent radiation cystitis

noninvasiveness and its favorable safety profile, whereas its cost and lack of widespread availability are certain drawbacks. Multiple single-centers have reported success with HBOT for the management of refractory radiation-induced hemorrhagic cystitis (Table 14.2) [51, 84–93]. Furthermore, HBOT appears safe and effective in children with hemorrhagic cystitis [94].

Hampson and colleagues prospectively evaluated HBOT in 525 patients (411 had complete data) treated for six categories of radiation tissue injury of whom 44 patients were treated for soft tissue radionecrosis of the bladder [84]. At the completion of an average of 42 (range 34–60) HBOT treatments, 89% of the patients had either complete resolution or 50–90% improvement in their radiation cystitis. While the short-term results appear promising, there are few reports on the long-term efficacy of HBOT for the treatment of radiation cystitis. Nakada and associates evaluated the long-term outcomes in 38 patients with refractory radiation cystitis treated with HBOT at their institution from 1988–2011 [85]. With a mean follow-up of 11.6 years (range 7.4–19.2), gross hematuria was improved in 95% 2 years after HBOT versus 81% 10 years after HBOT, suggesting the potential durability of the aforementioned treatment. The 74% of patients considered cured by HBOT in the study by Nakada et al. received less radiation, a greater number of HBOT treatments, and initiated HBOT at an earlier onset of hematuria compared to the patients who had recurrent radiation-induced hemorrhagic cystitis post-HBOT. Despite these encouraging long-term results, Del Pizzo et al. reported that 8 of 11 patients initially treated with HBOT ultimately required urinary diversion due to recurrent symptoms at a median follow-up of 5.1 years, underscoring the varied presentation and disease course in radiation cystitis [92]. The Baromedical Research Foundation designed a multicenter randomized, double-blinded, phase 3 clinical trial comparing HBOT to sham treatment in patients with late radiation tissue injury (www.clinicaltrials.gov NCT00134628). Unfortunately, the study was closed due to poor enrollment. Despite the lack of definitive level I evidence in favor of HBOT, the cost of treatment, and the limited access to treatment centers, HBOT remains a promising management option due to its safety profile, short-term efficacy, and noninvasiveness.

Cystectomy and Urinary Diversion

Cystectomy and urinary diversion for the management of radiation cystitis is considered a treatment of last resort. While cystectomy and urinary diversion provides a definitive cure for refractory radiation-induced hemorrhagic cys-

titis, the morbidity and potential mortality from the procedure in a complex patient population are certain drawbacks. Radiation therapy to the pelvis can lead to fibrosis and obliteration of tissue planes resulting in a more difficult surgery. Kim and colleagues compared 23 patients with invasive bladder cancer and a prior history of pelvic radiation who underwent radical cystectomy and urinary diversion to a control group of 23 patients without prior radiation who also underwent radical cystectomy and urinary diversion by a single surgeon [95]. There was a trend towards more overall complications in the radiated group (48%) versus the nonradiated group (30%, $P=0.183$), and surgical complications were higher in the radiated group (39% versus 9%, $P=0.045$). Abratt et al. studied 46 patients who underwent salvage radical cystectomy and urinary diversion following failed radiation for bladder cancer and noted a mortality rate of 7% and an overall 5-year complication rate of 35% [96]. Similarly, Smith and Whitmore reviewed 189 patients at their center who underwent salvage cystectomy following failed radiation for bladder cancer and noted a 5% postoperative mortality rate, infectious complications in 33%, and urine leak in 8% [97].

As surgeons become more comfortable with complex laparoscopy and robotic surgery, minimally invasive cystectomy and urinary diversion may be a reasonable treatment option in centers with experienced teams. Alkan et al. reported the first case of laparoscopic cystectomy and extracorporeal ileal conduit urinary diversion in a 77-year-old man with refractory radiation-induced hemorrhagic cystitis [98]. The patient was discharged on postoperative day 12 without any complications. Fergany and co-workers reported their experience with laparoscopic cystectomy and extracorporeal urinary diversion in three patients with refractory radiation-induced hemorrhagic cystitis [99]. The treatment was successful in all three patients with mean total operative time of 4.75 h, estimated blood loss of 50–200 mL, and an uneventful postoperative course other than ileus in one patient. While open, laparoscopic, and robotic cystectomy following radiation therapy to the pelvis are feasible, the appropriate choice for urinary diversion remains critical.

Initial reports suggested that a transverse colon conduit was the ideal urinary diversion in patients with high-dose radiation to the pelvis with the advantage of utilizing nonradiated bowel and ureters for diversion [73]. However, Chang et al. reviewed their experience with ileal conduits in patients with prior pelvic radiation and noted a low complication rate and high rate of upper tract preservation [100]. In their series, 35 of the 36 patients who had undergone prior radiation therapy to the pelvis underwent cystectomy with ileal conduit, whereas it was decided to use colon for diversion in one patient based on the gross appearance of the small bowel at the time of the operation. Furthermore, in select patients with prior radiation to the pelvis, continent cutaneous urinary diversion and orthotopic neobladder can also be considered [101, 102].

Other forms of urinary diversion without cystectomy have been suggested for the management of refractory radiation-induced hemorrhagic cystitis. Andriole and associates described the treatment of two patients with cyclophosphamide-induced hemorrhagic cystitis with open cystotomy, temporary urinary diversion via externalized ureteral stents, and continuous postoperative bladder packing with hemostatic agents [103]. Both patients noted a dramatic improvement in hematuria immediately postoperatively, and the one patient with prolonged follow-up was free of the recurrence of hematuria. However, this technique has not been reported elsewhere. Furthermore, in patients treated with supravesical urinary diversion alone, concerns remain in regards to the defunctionalized bladder. Fazili et al. reviewed the fate of 24 patients who underwent supravesical urinary diversion for a variety of benign conditions including radiation and/or hemorrhagic cystitis in two patients [104]. After a median follow-up of 48 months, 54% experienced problems related to the retained bladder, including 33% with frank pyocystis, and 25% ultimately required cystectomy.

While associated with significant morbidity, it would appear that cystectomy is a viable treatment option in patients with radiation cystitis,

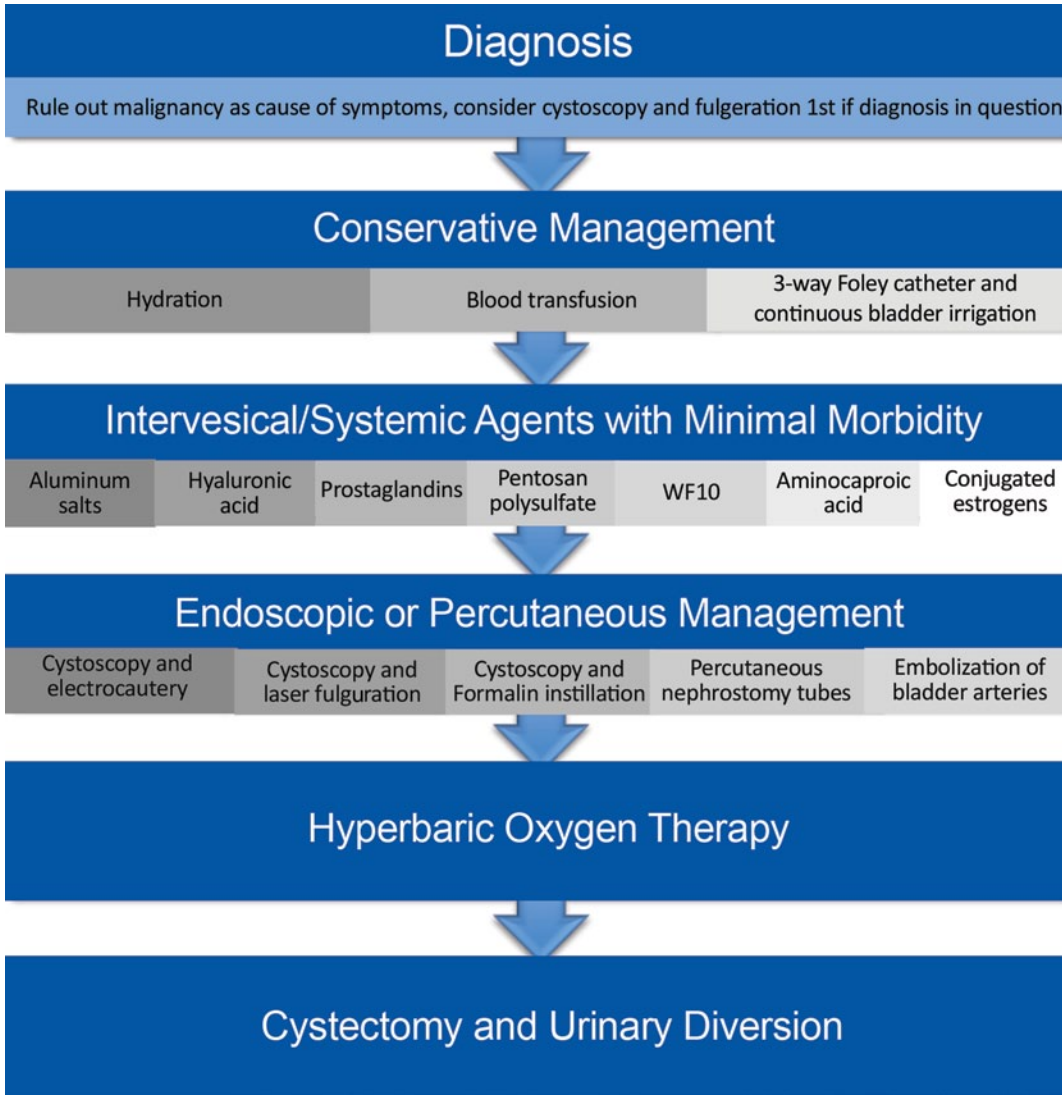

Fig. 14.1 Management algorithm for late radiation-induced hemorrhagic cystitis

fit for surgery, who have exhausted conservative measures. The choice of urinary diversion is critical and should be based on intraoperative findings as well as the patient's physiologic age, preferences, and comorbid status.

Future Directions and Conclusions

The management of radiation cystitis should be individualized as patient age, comorbidities, and symptoms can be highly variable. Fortunately, early radiation cystitis is usually self-limited and managed effectively with anticholinergic medications and other conservative measures. Late radiation-induced cystitis and radiation-induced hemorrhagic cystitis can be more challenging to manage. While there are certainly many choices for management of these complications (Fig. 14.1), most of the data in their support are limited to small underpowered trials, case series, and retrospective reviews. The management of radiation-induced hemorrhagic cystitis should start with conservative measures before escala-

tion to more invasive surgeries and procedures. If the diagnosis is in question, cystoscopy, clot evacuation, and possible biopsy/fulguration of bleeders should be performed prior to administration of any intravesical or systemic agents. While HBOT remains an attractive treatment option, cystectomy and urinary diversion provides a definitive cure for patients willing to accept the potential morbidity of major pelvic surgery.

A potential area in need of further research is the use of either vascular endothelial growth factor (VEGF) and/or undifferentiated endothelial cells (EC) for the management of radiation cystitis. Soler et al. showed positive effects of VEGF and EC bladder wall injections in a rat model for radiation cystitis [105]. Angiogenesis-directed therapy could potentially induce neovascularization, and like other therapies undergoing further study, such as liposomal tacrolimus and pentoxiphylline, could potentially correct the underlying pathology of late radiation-induced cystitis rather than merely temporarily controlling the bleeding.

Novel treatment strategies for radiation cystitis are needed to provide improved outcomes with minimal morbidity for this complex patient population; however, better studies of existing therapies are also required. Ultimately, high-quality, head-to-head studies are needed to further evaluate efficacy and side effects associated with the agents currently available and developing therapies proposed for the management of radiation-induced hematuria. This will require a multi-institutional collaboration of multidisciplinary teams of urologists, radiation oncologists, medical oncologists, and basic scientists.

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Medical Management of Radiation Effects on the Intestines

15

Deepak Parakkal and Eli D. Ehrenpreis

Introduction

Despite advances in the delivery of pelvic radiotherapy, radiation exposure to the small and large intestines, as "innocent bystanders," remains a significant dose-limiting factor. The gastrointestinal (GI) tract is the most prominent organ developing chronic toxicity associated with radiation treatment. Conservative estimates of the number of patients with postradiation intestinal dysfunction living in the United States of America exceed 1 million and likely approaches 2 million persons [1]. In this chapter, we discuss evolving therapeutic options for treatment of acute and chronic radiation injury to the GI tract divided anatomically between the intestines (small and large) and the rectum (and anus) followed by a discussion of preventive strategies.

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Intestinal Involvement: Enteropathy and Colopathy

Acute Radiation Enteropathy

The most common symptoms of acute radiation enteropathy include diarrhea, abdominal cramping or pain, nausea and vomiting, anorexia, and malaise. Most cases are self-limited, requiring only supportive treatment with antidiarrheal medications (loperamide, diphenoxylate with atropine, other anticholinergic agents, and opioids), sometimes in combination with antiemetic agents (Table 15.1). Dietary modifications such as low-fat, lactose-free diets have been recommended to improve symptoms. A double-blind placebo-controlled trial evaluated oral sucralfate (1 g six times a day) in 70 patients with carcinoma of the prostate or urinary bladder receiving pelvic irradiation. Each patient received sucralfate 2 weeks after radiation was started. Treatment was continued for a total of 6 weeks. The study showed a decrease in frequency and improvement in consistency of bowel movements, as well as improved chronic symptoms 1 year after completion of radiation treatment [2]. Animal models have shown some benefit of pretreatment with bile salts binders such as cholestyramine. Rats received 4 g of cholestyramine per day for 10 days followed by 1000 rads of mid-abdominal radiation. A significant decrease in diarrhea was seen in the treated group (45%) compared to the control group (67%, $p<0.05$) [3]. A double-blind, randomized

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Table 15.1 Medical management of radiation enteropathy

Acute radiation enteropathy
Antidiarrheal medications
Low-fat, lactose-free diets
Oral sucralfate
Oral cholestyramine
Acetylsalicylate
Parental fluids
Chronic radiation enteropathy
Low-residue lactose-free diet
Total parenteral nutrition
Antidiarrheal medications
Antibiotics
5–Aminosalicylates
Hyperbaric oxygen therapy

trial was performed to evaluate anti-inflammatory agents (acetylsalicylate) in 28 women receiving pelvic radiation for uterine cancer. A significant reduction in the number of bowel movements was seen in the treated group (78.6% decreased vs 21.4% decreased, $p<0.004$). There was complete reduction in colicky abdominal pain ($p<0.001$), and flatulence ($p<0.03$) was seen in the treatment group compared while no reduction of these symptoms occurred in the controls [4].

Administration of parenteral fluids and electrolytes may be helpful to prevent and treat dehydration.

Chronic Radiation Enteropathy

Minimizing small intestinal exposure to radiation is paramount in avoiding chronic radiation enteropathy. However, once established, recommend treatment for patients with chronic radiation enteropathy that is not complicated by intestinal obstruction, perforation, or fistula formation is usually conservative and focused on relief of symptoms. Some therapeutic options are discussed below and are shown in Table 15.1.

Nutritional management—Vitamin and micronutrient deficiencies need to be corrected. A low-residue diet is often advised as even normal portions of foods with moderate-high fiber content may worsen diarrhea and urgency [5]. Lactose intolerance, secondary to small intestinal injury as well as bacterial overgrowth, may improve following antibiotic treatment (described below) and avoidance of lactose [1].

Total parenteral nutrition (TPN) is a mainstay of the medical therapy for patients with severe chronic radiation enteropathy and patients requiring intestinal resection. The application of TPN has approximately the same degree of success seen in other intestinal disorders [6]. In the largest study of this modality to date, 54 patients (39 women and 15 men) with radiation enteropathy who received home TPN were evaluated. TPN was initiated at a median of 20 months (range 2–432) after beginning radiation therapy [7]. The causes of intestinal failure resulting from radiation therapy in these patients were intestinal obstruction (27 patients), short bowel syndrome [17], malabsorption [5], enteric fistulas [3], and dysmotility [2]. The mean duration of TPN was 20.4 months (range 2–108 months) with an overall estimated probability of 5-year survival of 64%. Another study compared the long-term outcome of 30 patients with radiation-induced intestinal obstruction treated either surgically (17 patients) or with intestinal rest and home parenteral nutrition (13 patients) [8]. Nutritional autonomy and 5-year survival were 100% and 90%, respectively, in the home TPN group versus 59% and 68%, respectively, in the surgically treated group.

Intestinal Dysmotility

Use of antidiarrheal agents (such as loperamide) can help improve diarrhea if stricturing and obstruction of the bowel have been ruled out. The efficacy of loperamide was evaluated in a trial involving 18 patients with diarrhea secondary to chronic radiation enteropathy. The participants were randomly assigned to loperamide or placebo for 14 days separated by a 14-day washout period, followed by a crossover [9]. Loperamide was associated with a significant reduction in the frequency of bowel movements, slower intestinal transit as measured using radiopaque markers, and improved absorption of bile acids [9].

Small Intestinal Bacterial Overgrowth (SIBO)

Patients with chronic radiation enteropathy are at risk for SIBO. Some have suggested testing for bacterial overgrowth and using antibiotics to reduce symptoms in those patients that test positive [1]

Other Therapeutic Options

5-Acetylsalicylic acid (ASA) drugs—A case study of four patients with chronic radiation enteropathy suggested a possible benefit from sulfasalazine with or without oral prednisone. Positive effects were evidenced by both radiographic as well as clinical improvement in stool frequency [10].

Hyperbaric oxygen—Hyperbaric oxygen (HBO) therapy has been used to treat chronic radiation enteropathy. Its beneficial effects have been attributed to inhibition of small intestinal bacterial growth [11], and decreased bacterial toxin production [12]. Other possible mechanisms include the production of an oxygen gradient within a hypoxic tissue bed that stimulates neovascularization, improving the blood supply, and reversing ischemia and necrosis responsible for severe complications [13]. The beneficial effect of HBO in chronic radiation enteropathy was first published as a case report of a patient who received 20 treatments over 1-month period with objective improvements in symptoms and absorption of D-xylose [14]. HBO was also noted to be useful in treating a patient with severe hypomagnesemia secondary to radiation enteropathy [15]. A retrospective study of 36 patients with severe radiation enteropathy refractory to medical management was performed. Patients received an average of 67 sessions of HBO at 2.5 atmospheres. Improvement of clinical signs and symptoms (wound healing, rectal bleeding, profuse diarrhea, and/or recurrent anal abscess) was reported in two-thirds of the patients [16].

HBO may also be helpful in management of bleeding due to chronic radiation enteropathy not controlled with other measures such as laser therapy and formalin [17]. In a large clinical series of 65 consecutive patients with chronic radiation enteropathy (primarily manifested as chronic bleeding), an initial treatment with 30 consecutive daily treatments of HBO was given at 2.36 atmospheres. The response rate (defined as a greater than 50% reduction of bleeding), was 70%. Response for other symptoms (pain, diarrhea, weight loss, fistula, and obstruction) was 58% [18]. There are a number of studies demonstrating the beneficial effects of HBO for radiation proctopathy as described later in this chapter.

Several issues are associated with the use of HBO in this setting. Equipment needed for HBO is expensive and requires the local availability of specialized centers. Side effects of HBO therapies are usually mild and reversible but can be severe and life threatening [19]. In general, if pressures do not exceed 300 kPa and the length of treatment is less than 120 min, HBO therapy is considered to be safe. Reversible myopia, due to oxygen toxicity to the lens, the commonest side effect, occurs in up to 20% of patients [19]. Symptomatic otic barotrauma (that is reversible) occurs in 15–20% of patients and pulmonary symptoms are present in 15–20%. Severe central nervous system symptoms such as seizures are seen in 1–2% of treated patients. These do not typically result in permanent structural brain damage [19].

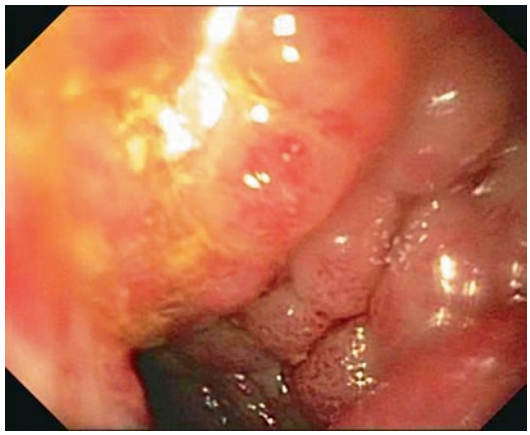

Fig. 15.1 Endoscopic appearance of a patient with chronic radiation colopathy and lower gastrointestinal bleeding

Large Intestine

Specific treatments for large intestinal injury or colopathy (not including the rectum) have not been determined in clinical trials. Symptomatic management for acute colopathy with antidiarrheal agents is recommended. Management of chronic colopathy at this point is similar from a clinical standpoint to the management of chronic radiation proctopathy and is covered in the next section. These treatments are often directed at reducing bleeding from colonic telangiectasias (see Fig. 15.1)

Rectum

Acute Radiation Proctopathy

Treatment of acute radiation proctopathy generally is directed at symptomatic relief. Topical lignocaine preparations may have a soothing effect for anorectal irritation, and loperamide will reduce stool, frequency, and tenesmus [1]. When inflammatory symptoms such as anorectal urgency and tenesmus are severe, use of corticosteroid-containing suppositories has been suggested [1]. Butyrate enemas may work to accelerate healing in acute radiation proctopathy. In a randomized, double-blind, crossover protocol, 20 patients (11 male and 9 female) presenting with acute radiation proctopathy within 3 weeks of radiation therapy for malignant pelvic disease were treated for 3 weeks each with topical sodium butyrate or saline enemas [20]. Patients were assessed clinically, endoscopically, and histologically before entry to the study, at week 3, and at the end of the study. Topical butyrate, led to remission of symptoms. This effect was not seen in the saline group. Clinical scores decreased from 8.2 (SE 1.6) to 1.5 (0.7) in the butyrate-treated group but no change was seen in the saline-treated group (clinical score 7.9 (SE 1.8) to 8.1 (3.4)). Furthermore, crossover resulted in eight out of nine of the patients treated previously with placebo going into remission. Three patients previously treated with butyrate relapsed when switched to saline enemas.

Another study prospectively evaluated 31 patients with radiation-induced acute grade II proctopathy (increased stool frequency, bleeding, mucus discharge, rectal discomfort requiring medication, or anal fissure) per Common Toxicity Criteria (CTC) [21]. Twenty-three of 31 patients (74%) experienced a decrease of CTC grade within 8 days of treatment with sodium butyrate enemas. A statistically significant decrease in the incidence and severity (CTC grade) of proctopathy after 14 days of butyrate enema treatment and at the end of the treatment course with radiation (compared to before the start of treatment) was seen. There was no preventive effect on the incidence and severity of chronic radiation proctopathy.

Chronic Radiation Proctopathy

Two forms of symptoms of chronic radiation proctopathy occur, based on the pathophysiology of the disease. Rectal bleeding occurs from mucosal telangiectasias and ulcerations while chronic functional symptoms including urgency, tenesmus, and pain are due to loss of rectal compliance. At present, most of the literature on treatment of radiation proctopathy has focused on reduction of bleeding, leaving few therapeutic options for patients with functional symptoms. In addition, failure to recognize the importance

Table 15.2 Medical management of chronic radiation proctopathy

Nonendoscopic management
Sucralfate (rectal administration, oral has less evidence)
Oral metronidazole (in combination with oral 5-aminosalicylates and corticosteroid enema)
Oral vitamin E and C in combination (weak evidence)
Oral retinyl palmitate (vitamin A)
Hyperbaric oxygen therapy
Formalin (dab technique or instillation in rectum)
Short chain fatty acid enemas (weak evidence for long-term management)
Oral 5-aminosalicylate (in combination with corticosteroid enemas)
Endoscopic management
Argon laser
Nd:YAG laser
Bipolar electrocoagulation
Heater probe electrocoagulation
Argon plasma coagulation
Cryoablation

Nd:YAG neodymium-doped yttrium aluminum garnet

of these functional symptoms in patients has resulted in an underestimation of the prevalence of symptomatic chronic radiation proctopathy. Natural history studies suggest that in patients with low-grade rectal bleeding, 35% stopped bleeding spontaneously by 6 months [22]. In contrast, patients whose symptoms are more severe requiring frequent blood transfusions or are predominantly pain and bowel dysfunction, do not have such a favorable prognosis and require treatment.

A systematic review of nonsurgical interventions for chronic radiation proctopathy (updated in 2009) analyzing nine randomized controlled trials and one phase II study found insufficient data to make firm conclusions regarding any therapy for either bleeding or functional symptoms [23]. Some treatments (e.g., rectal sucralfate, metronidazole combined with topical anti-inflammatory treatment, and heater probe application) were reported to appear promising. Short chain fatty acid enemas were reported to be no more effective than placebo ($n=2$ studies). Heater probe compared to the use of bipolar electrocautery ($n=1$ study), showed no discernible differences in severe bleeding after 1 year, but was associated with a greater increase in the hematocrit and reduced transfusion requirements. Other modalities identified included the use of HBO and retinyl palmitate. All of these therapeutic options are discussed below in detail including nonendoscopic medical options and endoscopic approaches (see Table 15.2).

Nonendoscopic Medical Management

Sucralfate—Sucralfate may play a role in ulcer healing by promoting angiogenesis mediated via its interaction with basic fibroblast growth factor (bFGF) and increasing mucosal glutathione [24]. A prospective, double-blind trial evaluated 37 patients with chronic radiation-induced proctosigmoiditis, compared a 4-week course of either 3.0 g oral sulfasalazine plus 20 mg twice daily rectal prednisolone enemas versus 2.0 g twice daily rectal sucralfate enemas plus oral placebo [25]. The groups were evaluated clinically using a composite score for diarrhea, bleeding, and tenesmus classified into three grades: I (≤ 2 points), II (3–4 points), or III (≥ 5 points) and used endoscopic criteria of developed by Gilinsky et al.: mild/grade I (erythema ± telangiectasia, edema, thickening, pallor), moderate/grade II (above plus friability), or severe/grade III (ulceration ± necrosis). Although clinical and endoscopic improvement was noted in both groups, the clinical response was better for sucralfate enemas. These were also better tolerated. Another study conducted by the same authors evaluated

longer duration of therapy with sucralfate enemas in 26 patients with moderate-to-severe radiation proctosigmoiditis [26]. Patients were treated with sucralfate enemas (20 mL of a 10% suspension twice daily) until bleeding stopped or failure of therapy was acknowledged. Severity of rectal bleeding was graded as severe (≥15 bleeding episodes per week), moderate (8±14 episodes per week), mild (2±7 episodes per week), negligible (0±1 episode per week), or normal (no bleeding). Response to therapy was considered to be an improvement in the severity of bleeding by two grades. Rectally administered sucralfate achieved good response in 20 (76.9%) patients at 4 weeks, 22 (84.6%) patients at 8 weeks, and 24 (92.3%) patients at 16 weeks ($P<0.01$).

Successful treatment with oral sucralfate was initially reported in a case series involving three cases of hemorrhagic chronic postradiation proctopathy. All patients demonstrated decreased bleeding in the long-term follow-up period [27].

Metronidazole—The effectiveness of metronidazole in combination with corticosteroids enema and mesalazine was evaluated in a randomized study involving 60 patients with chronic radiation proctopathy (bleeding and diarrhea) [28]. Patients were divided into two equal groups and treated with mesalazine (3 g orally per day) and betamethasone enema (once a day) with or without metronidazole (1200 mg orally per day). The groups were compared for both clinical symptoms (diarrhea and rectal bleeding, with scores between 0 and 3) and rectosigmoidoscopic findings (rectal erythema, ulcers, and/or telangiectasias). The incidence of diarrhea and rectal bleeding was significantly lower in the metronidazole group at 4 weeks, 3 months, and 12 months, respectively. Similarly, endoscopic findings of erythema and mucosal ulcers were also lower in the metronidazole group at 4 weeks after treatment.

Vitamins—The antioxidant vitamins E and C have been postulated to prevent tissue damage in radiation injury and ischemia/reperfusion injury. Twenty consecutive symptomatic outpatients with endoscopically documented findings of chronic radiation proctopathy following pelvic radiotherapy were given a combination of vitamin E (400 IU tid) and vitamin C (500 mg tid) for a minimum of 4 weeks [29]. A significant ($p<0.05$) improvement was reported in a symptom index (before vs after treatment with vitamins E and C) for bleeding (median score: 4 vs 0), diarrhea (median score: 5 vs 0), and urgency (median score: 6 vs 3), but not rectal pain. Since the study had a poor follow-up, a control group was absent, and the fact that these vitamin doses may predispose to toxic side effects, these findings need confirmation with a controlled trial.

Vitamin A (retinyl palmitate) has been demonstrated to accelerate wound healing after burn injury and surgeries in laboratory animals, possibly secondary to increased cross-linking of collagen and myofibrils. In the only controlled trial performed to evaluate patients with functional symptoms of radiation proctopathy, our group investigated retinyl palmitate 10,000 IU by mouth for 90 days in randomized, double blind placebo-controlled trial in 19 patients (ten with retinyl palmitate and nine with placebo). Symptoms were scored using a novel scale termed the Radiation Proctopathy System Assessments Scale (RPSAS) [30]. Symptoms measured for severity and frequencies using the RPSAS were diarrhea, rectal urgency, rectal pain, difficulty initiating evacuation, rectal bleeding, and fecal incontinence. The severity of symptoms was scored from 1 to 5 while frequency was scored from 0 to 5. Seven of ten retinyl palmitate patients responded, whereas two of nine responded to placebo ($P=0.057$). The mean pre- and post-treatment change in RPSAS was 11±5 in the retinyl palmitate group and 2.5±3.6 in the placebo group ($P=0.013$). Additionally, all five placebo nonresponders who were crossed over to treatment with retinyl palmitate responded to treatment.

Hyperbaric oxygen—A potential role for HBO has been described in an observational study involving 27 patients with chronic radiation proctopathy secondary to pelvic radiotherapy for prostate cancer [31]. Patients received HBO at a pressure of 2.4 atmospheres absolute for 90 min 5–7 days weekly for an average of 36 sessions (range 29–60). Overall 67% of patients had

a partial to good response; while 33% showed no response or disease progression. A randomized, sham controlled, double-blind crossover trial evaluated 120 patients with chronic radiation proctopathy, randomized to receive to HBO at 2.0 atmospheres absolute (Group 1) or air at 1.1 atmospheres absolute (Group 2) [32]. The primary outcome measures were the late effects normal tissue subjective, objective, management, analytic (SOMA-LENT) score and standardized clinical assessment. For Group 1, the mean SOMA-LENT score was lower ($p=0.0150$) and the amount of improvement nearly twice as great (5.00 vs 2.61, $p=0.0019$) as Group 2. Similarly, Group 1 also had a greater portion of responders per clinical assessment than did Group 2 (88.9% vs 62.5%, respectively; $p=0.0009$). After completion of the crossover, no differences were detected ($p=0.6594$). The authors concluded that HBO therapy significantly improved the healing responses in patients with refractory radiation proctopathy, generating an absolute risk reduction of 32% (number needed to treat of 3) between the groups after the initial allocation. Adverse events associated with HBO therapy described in this study included ear pain in 19 patients (16%), transient myopia in four (3%), and confinement anxiety in two (1.7%) patients.

Formalin—Formalin is a mixture containing formaldehyde and methanol. The rationale for its use in chronic radiation proctopathy presenting with bleeding is that formalin-induced denaturation of proteins cause local chemical cauterization of telangiectatic mucosal vessels [33]. Application of formalin has been described in various studies either by "dabbing" it on to bleeding and telangiectatic spots on the rectal mucosa with a pledget of formalin-soaked gauze or cotton-tip applicator, or by "instilling" the solution in single or multiple aliquots into the rectum. The volume of formalin aliquots per installation and total volume (between 250 and 2000 mL) reported has been variable. While most studies of dab and instillation methods have used 4% formalin, one of the studies utilized a 10% formalin dab [34]. Aside from endoscopic flushing and removal of residual formaldehyde with saline, protection of the anoderm is advised. Intrarectal formalin therapy, particularly using the instillation technique is associated with significant morbidity including rectal strictures, intractable anal fissures, and the development of formalin colopathy (Fig. 15.2).

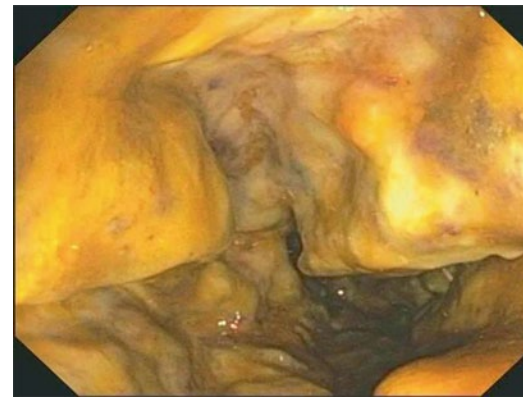

Fig. 15.2 Sigmoidoscopic view of severe formalin colopathy

In a prospective study, 33 patients with chronic radiation proctopathy received treatment with 4% formalin using the "dabbing" technique [33]. One application was performed in 23 patients while ten patients required a second application because of the persistent bleeding. The treatment was effective in 23 cases (70%): 13 patients with complete cessation of bleeding and ten patients with residual minor bleeding. The study reported morbidity secondary to the application with six anal or rectal strictures, four of whom had been treated for anal cancer. These were all successfully managed with dilation. Additionally, fecal incontinence worsened in 5 of the 11 patients who had received radiation therapy for anal cancer (45%) and occurred in 4 of the 22 other patients (18%). The authors emphasized concerns about local morbidity with this technique. Another study ($n=100$) investigated the direct application of a 10% buffered formalin solution using a 16-inch cotton tip applicator [34]. Overall, 93% of patients had cessation of bleeding after an average of 3.5 formalin applications at 2-week to 4-week intervals. Of note, this study only had a 4% complication rate (three patients with anal pain and one patient with postprocedure dizziness).

Formalin instillation technique involves administration of small aliquots of about 40–60 mL each, up to a total to 500 mL, with a dwell time in the rectum usually of 30 s. This method is usually performed in the operating room, using a perianal block and sedation, with perianal skin and sigmoid colon protection. The largest study of formalin instillation evaluated 20 female patients with hemorrhagic chronic radiation proctopathy who had failed treatment with topical steroids and/or mesalazine [35]. The study utilized 500 mL of 4% formalin instilled into the rectum in 50-mL aliquots. While the study had an overall success of 90%, five patients (25%) had moderate pelvic pain after instillation and one developed rectosigmoid colon necrosis that required resection plus a Hartmann procedure. Two patients developed rectovaginal fistulas that required a colostomy. One of these further required an abdominoperineal resection en bloc with the posterior wall of the vagina due to pelvis sepsis. Larger volumes and longer dwell times have also been associated with toxic levels of formic acid in the blood [36]. These adverse consequences of the formalin instillation technique suggest that this method should be abandoned except perhaps in cases of extensive rectosigmoid involvement not amenable to Argon Plasma Coagulation (APC) or formalin dab technique.

Short-chain fatty acid enemas—Short-chain fatty acid (SCFA) enemas may be effective in the short-term management of chronic hemorrhagic radiation proctopathy by inhibiting the inflammatory response including the NF-κB pathway. A prospective, randomized, double-blind, placebo-controlled trial evaluated treatment with SCFA enema (60 mM sodium acetate, 30 mM sodium propionate, and 40 mM sodium butyrate) in 19 patients with ongoing hemorrhage secondary to chronic radiation proctopathy [37]. Study endpoints included changes in the number of days in the week with rectal bleeding, hemoglobin measurements, endoscopic score (hyperemia and neovascularization), friability, edema and erosions. After a 5-week treatment period, the SCFA enema group showed a significant decrease in the number of days with rectal bleeding from the previous week (4.4+/−1.8 to 1.4+/−2.2; $P=0.001$) and an improvement of their endoscopic scores (4.8+/−1.4 to 2.2+/−1.2; $P=0.001$). However, after a 6- month follow-up, differences between the two groups were no longer observed.

Pentosan polysulfate—Pentosan polysulfate (PPS) a glycosaminoglycan, is a semisynthetic sulfated polyanion with heparin-like properties shown to be effective in treating radiation-induced sequelae of the bladder. A multicenter phase III study was performed. Fifty-seven patients received 100 mg PPS three times per day, 53 patients who received 200 mg PPS three times per day and 59 patients that received placebo [38]. Response to the treatment was measured as either complete or partial. Quality of life endpoints were measured using both a symptom assessment questionnaire, the Functional Alterations Due to Changes in Elimination, as well as general quality of questionnaires—the Medical Outcomes Survey and the Spitzer Quality of Life Index. The study failed to show any differences in response rates or quality of life measures compared to placebo.

Sulfasalazine and aminosalicylates—An initial pilot study of oral aminosalicylate in four patients with chronic radiation enteropathy and/or colopathy showed striking clinical progress accompanied by improvement in radiological appearance [10]. However, another pilot trial evaluating 5-aminosalicylic acid enemas in four patients with chronic radiation proctopathy failed to show any sustained benefit in symptoms (bleeding, pain, or tenesmus) or degree of mucosal inflammation on follow-up sigmoidoscopies [39]. A prospective, double-blind trial comparing sucralfate enema plus placebo to 3.0 g sulfasalazine and 20 mg twice daily rectal prednisolone enemas, showed significant clinical and endoscopic improvement in the 15 patients receiving sulfasalazine and prednisolone at 4 weeks [25].

Hormonal therapy—A single case report described the use of estrogen-progesterone combination therapy (ethinyl estradiol 0.07 mg/day, norethisterone 1 mg/day) in a patient with hemorrhagic chronic radiation proctopathy, with reduction in the requirement for blood transfusions and hospitalizations [40]. However, the therapy has been associated with serious side effects including thromboembolism.

Endoscopic Management of Bleeding

Because rectal bleeding in chronic radiation proctopathy is primarily due to the presence of mucosal telangiectasias that are fragile and prone to hemorrhage, a variety of endoscopic methods have been used to obliterate these vessels.

Lasers—Argon and neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers have been used to coagulate bleeding angiodysplasias in chronic radiation proctopathy. The potential benefit of Nd:YAG lasers were shown in a study from Mayo Clinic of 47 patients with hemorrhagic chronic radiation proctopathy despite previous medical treatment (98%) or bypass colostomy (6%) [41]. The median number of laser sessions was two (one to nine). Within a 3–6-month period after laser treatment, the number of patients with daily hematochezia decreased significantly (85–11%; $p < 0.001$), and the median hemoglobin level increased from 9.7 g/dL to 11.7 g/dL ($p < 0.001$). Six patients (12.8%) were not improved by laser treatment and two (4%) ultimately required surgical treatment for bleeding control. No deaths were reported. However, three patients (6%) developed complications including a patient with a rectovaginal fistula requiring rectosigmoid resection with end sigmoid colostomy.

Experience with argon laser has been published in a smaller study of 14 patients with bleeding from chronic radiation proctopathy [42]. A total of 51 procedures were described with a median of three procedures performed per patient, with two sessions required for initial control of bleeding. Ten patients (71%) required maintenance therapy with mean interval between maintenance sessions of 7 months. No immediate or late complications were reported in the study.

Bipolar and heater probe electrocoagulation—Bipolar and heater probe electrocoagulation (BiCap) are other endoscopic modalities that have been used in the treatment of hematochezia secondary to chronic radiation proctopathy that are widely available and inexpensive compared to lasers. The efficacy and safety of bipolar or heater probe endoscopic coagulation was evaluated in a prospective, randomized trial involving 21 patients with chronic recurrent hematochezia and anemia (after 12 months of medical therapy with corticosteroid or salicylate enemas) due to radiation-induced injury [43]. Patients were treated with either BiCap or heater probe therapy as needed. Rectal bleeding stopped within four treatment sessions. Compared to the 12 months of medical therapy, severe bleeding episodes diminished significantly for bipolar probe (75% vs 33%) and heater probe therapy (67% vs 11%). Mean hematocrit also rose significantly with both bipolar (38.2 vs 31.9) and heater probe (37.6 vs 28.4) treatments. Additionally, no serious complications were reported in the study.

Argon plasma coagulation—APC is a non-contact thermal coagulation procedure, in which electrical energy is transferred to the target tissue using ionized argon gas (argon plasma). Inert argon gas is pumped at a specified flow rate through a probe passed through the endoscope channel. The gas gets ionized by a high voltage current (earthed) producing thermal energy that heats the surface in a uniform manner to a depth of around 0.5–3 mm [44]. Thus, this technique coagulates superficial blood vessels without damaging deeper tissues or causing perforation.

APC causes regression of bleeding in 80−90% of the cases and improves diarrhea and tenesmus in 60 –75% of cases [44]. APC treatment, when available, represents the safest and most effective thermal contact method for chronic radiation proctopathy. However, it generally requires more than one treatment session to decrease or prevent bleeding. Table 15.3 shows all published studies on APC for chronic radiation proctopathy. In a study by Swan et al. [56], 50 patients with chronic radiation proctitis, 17 (34%) patients with grade A endoscopic severity, 23 (46%) grade B, and 10 (20%) grade C, received APC treatment. APC was applied at an average power of 50 W with flow rates between 1.4 and 2.0 L/min. The mean number of treatments required was 1.4 (range 1–3) with a 98% success rate. This included improvement in bleeding scores in all patients ($P < .001$). Complications were mainly short term and resolved spontaneously in 17 (34%) patients (proctalgia in 13 patients, rectal mucous discharge in 4, incontinence in 1, fever

Table 15.3 Overview on argon plasma coagulation (APC) use in chronic

Authors (year) (Ref.)	*N*	Requiring transfusion (%)	Settings (L/min)	Mean no. of APC sessions	Success rate (%)
Silva et al. (1999) [45]	28	53	50 W 1.5	2.9	93
Fantin et al. (1999) [46]	7	–	60 W 3.0	2.4	100
Tam et al. (2000) [47]	15	20	60 W 2.0	2.0	100
Kaassis et al. (2000) [48]	16	19	40 W 0.6	3.7	100
Tjandra & Sengupta (2001) [49]	12	33	40 W 1.5	2.0	83
Taieb et al. (2001) [50]	11	64	50 W 0.8–2	3.2	100
Villavicencio et al. (2002) [51]	21	19	45–50 W 1.2–2	1.7	95
Zinicola et al. (2003) [52]	14	21	65 W 2.0	1.7	86
Canard et al. (2003) [53]	30	17	30 ± 80 W 0.8 ± 2.0	2.3	87
Ben−Soussan et al. (2004) [54]	27	30	40 ± 50 W 0.8 ± 1.0	2.66	92
Karamanolis et al. (2009) [55]	56	16	40 W 2	2	89
Swan et al.(2010) [56]	50	–	50 W 1.4–2	1.4	98
López-Arce et al. (2010) [57]	19	26.3	40 ± 50 W 1–1.5	1.5	100
Sato et al. (2011) [58]	65	18.8	40 W 1.2	2.1	98.5

L liter, *W* watts

in one, and bleeding in 1 patient). One patient had an asymptomatic rectal stricture on subsequent screening colonoscopy that did not require dilation.

Sato et al. [58], studied 65 patients with chronic radiation proctopathy over a 10-year period. Seven patients (10.8%) had grade A (mild), 41 (63.1%) had grade B (moderate), and 17 (26.2%) had grade C (severe) proctopathy. The study utilized APC at 40 W current, 1.2-L/min gas flow rate, and 2-s applications. The treatment success rate was 98.5% after an average of 2.1 APC sessions. The median clinical score for rectal bleeding was significantly decreased after APC ($P<0.0001$), and the hemoglobin level was significantly increased ($P<0.0001$). Importantly, APC was well tolerated, with no serious side effects or complications. In the follow-up period, only 4 patients (6.3%) had minor recurrent rectal bleeding and 60 (93.8%) remained in remission.

The most common procedure-related symptom is of anal or rectal pain which is mild and self-limiting [44]. It is most likely to occur following APC treatment near the dentate line. Major complications from APC are rare. The frequency of perforation was 0.27% in a study of 1062 patients [59]. Colonic explosion is another rare but preventable complication of APC, with seven published case reports involving eight patients in nine separate incidents of colonic explosion reported. Four of these occurred during treatment of chronic radiation proctopathy [60]. Bowel preparation with an oral polyethylene glycol-based preparation is essential before performing an APC to prevent these explosions and should also be used for any follow-up APC procedures in the same patient [60]. Treatment-related ulcers are seen in 52% of the patients. One investigator has suggested avoiding these ulcer sites during repeat APC sessions [61]. Our practice is to discontinue APC in the setting of deep rectal ulcerations. These patients may be candidates for carefully applied formalin dab therapy if ongoing bleeding from remaining telangiectasias occurs or HBO treatments if ulcers are symptomatic and do not heal. Clinically, retinyl palmitate probably also has a role in these patients. APC treatment around radiation-induced rectal strictures may worsen the severity of the stricture as the treated mucosa heals and hence may be inappropriate in this setting. Rectovaginal fistulas have also been reported as a rare and late complication of APC in this patient group [44].

Cryoablation—Cryoablation is a technique involving noncontact application of liquid nitrogen or carbon dioxide gas to tissue for superficial ablation that has been used in the treatment of esophageal high-grade dysplasia and early cancer. A recent prospective case-series pilot study assessed response and tolerability to cryo-ablation

Table 15.4 Pharmacological methods for prevention of radiation enteropathy and proctopathy

Regimen	Mechanism	Clinical trial
Amifostine	Active metabolite WR-1065 scavenges radiation-induced free radicals	Yes
5-Aminosalicylates	Anti-inflammatory	Yes
Octreotide	Reduced secretion of pancreatic enzymes	No
Selenium	Antioxidant role via increased biosynthesis of the different glutathione peroxidase and thioredoxin reductase isozymes	Yes
Prostaglandin E2 analogs	Trophic effect on enterocytes	No
Sucralfate	Angiogenesis mediated via bFGF and increased mucosal glutathione	No
Glutamine	Trophic to enterocytes	No
TGF-beta type II receptor fusion protein	Modulation of fibrogenic cytokine TGF-beta type I involved in radiation-induced fibrosis	No

therapy in ten patients with chronic radiation proctopathy [62]. Endoscopic severity (measured by rectal telangiectasia density) improved from 2.7 to 1.7 ($P=0.004$). Overall subjective clinical scores on RPSAS (scale described previously) improved from 27.7 to 13.6 ($P=0.003$). One complication of cecal perforation due to gaseous over-distention decompression tube failure was seen. Additional controlled trials to establish the safety and efficacy of cryoablation are advised.

In patients with mild symptoms of obstructive defecation from chronic radiation proctopathy, stool softeners have been recommended. If these are not helpful, balloon or Savary-Gilliard dilation may be effective in patients with obstructive symptoms from distal colonic strictures that are short and are present in nonangulated areas of the colon or rectum [63]

Prevention

Apart from improvements in the radiation technique and dosing, a number of other preventive strategies to decrease the incidence and severity of chronic radiation proctopathy have been investigated (Table 15.4). One of the major concerns in this field is the development of agents that are radioprotective to normal tissue without directly enhancing tumor activity or diminishing the effects of radiation therapy.

bFGF basic fibroblast growth factor, *TGF* transforming growth factorAmifostine—Amifostine is a prodrug that undergoes intracellular dephosphorylation by alkaline phosphatase to the active metabolite WR-1065. It appears to be selective in its entry in nonmalignant cells and attenuates cell injury from radiation by scavenging of radiation-induced free radicals [64]. It is one of the most thoroughly studied radioprotective agents. Evidence for efficacy in the reduction of acute radiation-induced GI toxicity with monitoring for of tumor protective effects was investigated in a prospective, randomized trial of 205 patients with pelvic malignancies [64]. The participants were randomized to receive radiotherapy with or without amifostine (administered at 340 mg/m2 i.v., 15 min before radiotherapy). A significant reduction in Radiation Therapy Oncology Group/European Organization Research and Treatment of Cancer (RTOG/EORTC) grade 2–3 acute lower GI tract toxicities occurred in the amifostine group ($p<0.05$, weeks 3–7). More importantly, no statistically significant difference between the two groups was observed in terms of response at 6 weeks after radiotherapy completion (complete response plus partial response was 98.3% in the amifostine arm vs 96.8% in the control group). Amifostine infusions were well tolerated, with only moderate hypotension occurring in two patients and moderate nausea in one patient. No long-term toxicities related to amifostine infusion were reported during the follow-up period.

In another prospective, randomized trial of 100 patients with inoperable, unresectable, or recurrent adenocarcinoma of the rectum, patients were randomized to receive radiotherapy with

or without amifostine (340 mg/m^2 i.v., 15 min before RT) [65]. No moderate or severe normal pelvic tissue late effects were seen in the 34 evaluable patients in the amifostine group whereas 5 of 37 evaluable patients in the control group exhibited late effects of moderate or severe degree ($P=0.03$). More convenient and less expensive routes of administration of amifostine have also been tested. In a study by Kouloulias et al. [66], patients were randomized to receive amifostine, either as a 1500 mg dose in 40 mL enema ($n=27$) or a 500 mg subcutaneous dose ($n=26$) before irradiation. Intrarectal amifostine demonstrated significantly lower incidence of RTOG/EORTC grades I–II rectal radiation morbidity (11 % vs 42 %, $p=0.04$) 1–2 days after radiotherapy completion but had inferior results for urinary toxicity (48 % vs 15 %, $p=0.03$). Rectal amifostine was well tolerated without any toxicity while World Health Organization (WHO) Grade 1 nausea was noted in three (11 %) of the patients who received amifostine via subcutaneous route, lasting nearly 6 h after amifostine injection. Four patients (15 %) in this group also complained of severe asthenia (WHO Grades 2–3) that was cumulative, occurring from the 4th to the 20th day of amifostine injection. This symptom resulted in discontinuation for 24 h until the symptoms of asthenia had regressed. As a result of these and other trials, the updated clinical practice guidelines developed by the Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology suggest that amifostine in a dose $\geq$340 mg/m^2 may prevent acute and chronic radiation proctopathy in patients undergoing standard-dose radiotherapy for rectal cancer [67].

Sulfasalazine and balsalazide —5-Amino salicylic acid may have a role in preventing or reducing acute radiation proctopathy. Twenty-seven prostate cancer patients receiving external beam radiotherapy were administered 2.25 g of balsalazide or an identical-appearing placebo twice daily beginning 5 days before radiotherapy and continuing for 2 weeks after completion [68]. A symptom index was calculated for individual toxicity consisting of the toxicity's numeric grade multiplied by the number of days it was experienced, and summed throughout the course of radiotherapy. All toxicities were lower with balsalazide, with the exception of nausea and vomiting seen in three patients on balsalazide and two on placebo. Scoring of acute symptoms showed statistical improvement, with a mean proctitis index of 35.3 in balsalazide patients and 74.1 in placebo patients ($p=0.04$).

Results from controlled clinical trials evaluating mesalazine or sulfasalazine in the prevention of acute radiation enteropathy have been discordant. In a randomized double-blind placebo-controlled trial involving 87 patients receiving pelvic radiotherapy, diarrhea occurred in 55 % and 86 % of the sulfasalazine and placebo groups, respectively ($P=0.001$) [69]. However, another randomized double-blind placebo-controlled trial evaluating mesalazine in 153 patients receiving pelvic radiotherapy failed to show an improvement in diarrheal symptoms seen in 69 % of the mesalazine and 66 % of the placebo group, $P=0.22$ [70]. Nonetheless, the European Society for Medical Oncology guidelines for management of oral and GI mucositis published in 2009 recommends the use of 500 mg sulfasalazine orally twice daily to reduce the incidence and severity of radiation-induced enteropathy in patients receiving external beam radiotherapy to the pelvis [71].

A number of other agents have been investigated in animal models or preliminary clinical studies. Pancreatic enzymes have been shown to exacerbate acute intestinal radiation toxicity in animal models [72]. Reducing pancreatic secretion with a synthetic somatostatin receptor analog such as octreotide was thought to be a strategy that may confer a dose-dependent protection against delayed small bowel radiation toxicity and ameliorate radiation fibrosis predominantly by reducing acute mucosal injury [73]. This was evaluated in a randomized, double-blinded, placebo-controlled trial of 125 patients receiving pelvic radiotherapy. Patients were randomized to receive octreotide (100 mcg, administered subcutaneously on day 1, followed by depot octreotide, 20 mg, administered intramuscularly on days 2 and 29; $n=62$) or to receive a placebo injection ($n=63$) [74]. Grade 0, 1, 2, and 3 diarrhea

were observed in similar percentages of patients in both groups ($P=0.64$). Some other symptoms such as nocturnal bowel movements (70% vs 45%; $P=0.004$) and bleeding with bowel movements (57% vs 35%; $P=0.01$) were worse in the octreotide arm. Hence, octreotide injection is not recommended for prevention of diarrhea during pelvic radiation therapy.

Selenium supplementation was studied in a small multicenter phase III trial involving 81 patients receiving pelvic radiotherapy for uterine and cervical cancer and with initial selenium concentrations of less than 84 mcg/L [75]. The participants were randomized before radiotherapy to receive 500 mcg of selenium (sodium selenite) by mouth on the days of radiotherapy ($n=39$) and 300 mcg of selenium on the days without radiotherapy or to receive no supplement ($n=42$) during the radiotherapy. A significantly lower incidence of CTC (version 2) Grade 2 or higher diarrhea was seen in the selenium supplementation group compared with the control group (20.5% vs 44.5%; $P=0.04$). A larger controlled trial to confirm these findings was advised before definite recommendations can be made for prophylactic selenium supplementation to reduce acute radiation enteropathy.

Prostaglandin E2 and prostaglandin analogs displayed initial promise in radiation protection in animal studies [76]. However, in a phase III randomized, placebo-controlled, double-blind study of 100 patients who underwent radiotherapy for prostate cancer, no differences were found in proctitis symptom onset or duration. In addition, significantly more patients receiving the prostaglandin analogue misoprostol experienced rectal bleeding compared to placebo ($p=0.03$) [77]. Sucralfate has also been evaluated for prophylaxis against acute radiation enteropathy and proctopathy. A meta-analysis failed to show a beneficial role for sucralfate either orally or as enema as a prophylaxis for acute radiation proctopathy [78]. Additionally, a double-blind, placebo-controlled, randomized trial evaluated 338 patients receiving definitive radiotherapy for prostate cancer randomized to receive either 3 g of oral sucralfate suspension or placebo twice daily, failed to demonstrate a statistically significant reduction in the incidence of late rectal toxicity in patients randomized to receive sucralfate [79].

Enterotrophic strategies to increase the resistance of the bowel to radiation injury and/or enhance its capacity for recovery for protection against radiation injury have focused on glutamine. However, a phase III, randomized, double-blind study, involving 129 patients failed, to show any beneficial effect for glutamine given as 4 g orally, twice a day, beginning with the first or second day of RT and continuing for 2 weeks after RT. No difference was seen in diarrhea levels (maximum CTC grade of diarrhea, incidence of diarrhea, and average diarrhea score) [80]. Finally, preliminary animal models have identified a putative role for modulation of the fibrogenic cytokine transforming growth factor (TGF) beta 1 in ameliorating radiation enteropathy. Recombinant TGF-beta type II receptor fusion protein has been shown to function as a "scavenger" of active TGF-beta 1, thus suggesting a possible future therapeutic tool. This remains an ongoing area of investigation [81].

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Surgical Management of Radiation-Induced Intestinal Injury

16

Barak Benjamin and Shmuel Avital

Introduction

Radiation therapy is a major tool for the treatment of some common pelvic malignancies, among them cervical, rectal, and prostate cacncers. As a results, the parts of the bowel that may, as side efeect, be injured by radiation therapy are those parts located in the pelvis and lower abdomen: the small intestines, the colon, and the rectum. Severe manifestations of radiation injury to the intestine tend to occur late, often months and years after treatment with radiation [1].

Surgery has the potential to cure the manifestations of chronic radiation injury of the intestine, if the affected segment is resected and continuity of the bowel is re-established. Fortunately, only a minority of patients would experience complications or severe refractory symptoms that necessitate surgical intervention [1–3]. On the other hand, operations in these patients often pose formidable challenges to the surgeon. Difficulties encountered during surgery include friability of tissues, extensive pelvic fibrosis with loss of anatomical planes, increased risk of iatrogenic damage to adjacent structures, and impaired healing of sutured areas with an increased rate of anastomotic failure and wound dehiscence [1, 4]. These challenges are further augmented when acute complications of radiation injury are superimposed on a state of chronic malnutrition caused by the same disease. This results in the not uncommon scenario of the necessity of an operation in a poor candidate for extensive surgery.

In this regard, Marks commented almost four decades ago that "the spirit of gloom and fear characterizing the treatment of the radiation-injured rectum to date has condemned those afflicted to life with a stoma and an abandoned rectum, but the exchange of a cancer for a stoma and cure is a reasonable one to which most patients and physicians subscribe" [5]. Our accumulated knowledge and improved understanding of these conditions has led to better care, avoidance of complications, and the use of novel operative techniques. In addition, advanced perioperative care and nutritional support improved morbidity and mortality in these patients, such that current practice generally allows a favorable outcome when surgery is required [6–10].

The vast majority of published literature on the surgical treatment of the radiation-induced bowel injury consists of retrospective cohort studies, usually representing the experience of a single institution. Within this limitation, this chapter will present currently practiced surgical solutions to various problems encountered in patients with radiation-induced injury of the bowel, and outline the principles of surgery in these patients.

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Table 16.1 Modalities for the assessment of radiation damage to the bowel

Imaging	Endoscopy
Plain abdominal films	Flexible proctosigmoidoscopy
Computed tomography (CT)	Colonoscopy
Positron emission computerized tomography (PET-CT)	Endoscopic transrectal ultrasound (TRUS)
Magnetic resonance imaging (MRI)	–

Preoperative Evaluation

It is important to perform careful pre-operative investigations to define the extent and severity of bowel injury to appropriately plan for the intervention ahead. Of great importance is the ruling out of recurrence of the originally treated tumor. The main tools for this purpose are imaging and endoscopy (see Table 16.1). It is noteworthy that it can at times be extraordinarily difficult to differentiate between benign findings related to radiation injury and the presence of malignant lesions. In some cases, especially those that seem to be refractory to treatment, a high index of suspicion for recurrent tumor should be maintained and in certain cases repeated imaging of the bowel may be required to diagnose or rule out recurrent cancer.

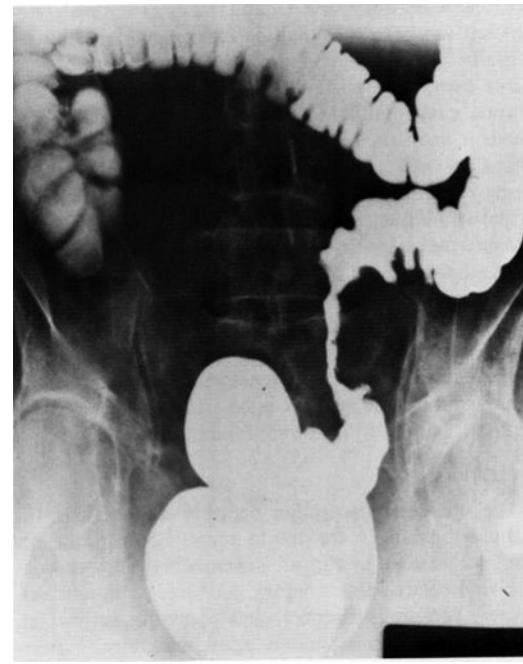

Fig. 16.1 Rectosigmoid stricture secondary to internal radiation therapy for carcinoma of the uterus. (Source: With permission from Anseline PF, Lavery IC, Fazio VW, et al.: Radiation injury to the rectum: evaluation of surgical treatment. Ann Surg 1981;194(6);716–24 Lippincott Williams and Wilkins 1981 (24))

Imaging

Plain abdominal films can be used as an initial tool to screen for gross intestinal abnormalities, but are of otherwise limited value due to low sensitivity and specificity. A double-or triple-contrast computerized tomography (CT) scan is usually very valuable to get an immediate assessment of the extent of bowel involvement, and to rule out recurrent tumor or metastatic disease. Points of obstruction, fistulization, perforation, and abscesses can be readily identified (Fig. 16.1). The relationship of the involved bowel segment to and involvement of adjacent structures can also be assessed with CT [8, 11]. Injured bowel has a thickened and distorted appearance on CT, with associated smooth strictures and distended proximal bowel loops [12]. However, it should be kept in mind that injured bowel may be found intraoperatively in radiographically normal appearing bowel. Enteroclysis and CT enterography are sometimes very helpful to assess the extent of small bowel involvement. Positron emission tomography CT (PET-CT) may be used to identify tumor uptake of FDG in cases when new mass lesions are found on standard CT scanning. When assessing the abdomen and/or pelvis for fistulas, magnetic resonance imaging (MRI) and MR enterography may also be used when available, but generally do not appear to provide much additional information for the assessment of the small intestine or colon, compared to CT [13].

Endoscopy

Proctosigmoidoscopy or full colonoscopy is used for diagnostic investigation of the rectum and colon, and may also have a therapeutic role in management of radiation-induced colon and rectal disease. Visualization of the small intestine can be achieved with colonoscopic intubation of the terminal ileum, or with enteroscopy [14]. Video capsule endoscopy is also described as an investigative tool for this purpose, but due to the risk of the capsule becoming lodged in a stricture or twisted bowel it is advised to first test its passage by using a sham capsule [8, 15]. Transrectal endoscopic ultrasound may be used for the assessment of rectal fistulas [41].

General Preoperative Considerations

In additional to diagnostic evaluations, assessment of the physiological and nutritional well-being of the patient, through the measurement of the body mass index (BMI), complete blood counts, blood chemistries including serum albumin, other biochemical tests of nutrient status, and coagulation tests. Tumor markers are helpful in identification of patients suspected to harbor a recurrence of their primary tumor.

The extent of the pre-operative work-up should be tailored by the patient's history, symptoms and physical signs, and should be as extensive as time permits and logic advises, depending on the urgency of the operation. If symptoms can at least partially be controlled with medical therapy, valuable time can be used to improve the patient's overall status through re-nourishment with parenteral nutrition and addressing any other medical problems when present [11].

Table 16.2 lists the common surgical approaches to complications related to small intestinal injury, while Table 16.3 shows the surgical management for radiation injury of the colon and rectum.

Table 16.2 Surgical treatments for complications of radiation enteropathy

Obstruction
Resection and anastomosis (preferred)
Diverting stoma alone
Stricturoplasty
Fistulization (to skin, bowel, other organs)
Resection ± anastomosis
Diverting stoma
Perforation
Resection ± anastomosis
Intractable hemorrhage
Resection ± anastomosis

Table 16.3 Procedure-based and surgical treatments for complications of radiation colopathy and proctopathy

Hemorrhagic proctopathy
Endoscopic APC
Endoscopic Nd:YAG laser therapy
Heater probe
Formalin application
Operative (resection, diversion)
Perforations
Resection with reconstruction (colo-rectal anastomosis, coloanal anastomosis, pull-through procedures)
Resection with permanent stoma
Strictures and fistulas
Resection with reconstruction (colo-rectal anastomosis, coloanal anastomosis, pull-through procedures)
Diversion alone
Flaps and pedicled grafts to treat fistulas

APC argon plasma coagulation, *Nd:YAG* neodymium-doped yttrium aluminum garnet

Surgical Management of Radiation Enteritis

Obstruction is the most common indication for surgery in patients with radiation enteropathy [3, 6, 10]. Other indications include fistulization to the skin, adjacent bowel or other organs, intractable bleeding, and perforation (with local or generalized peritonitis). When operating for obstruction or other complications of radiation enteropathy, it is important to be cognizant of the fact that radiated small bowel may have stenosis or fistulizations at several concomitant location points [17–18]. In addition, removal or decom-

pression through a stoma of a long segment of involved small intestine can leave the patient with short bowel syndrome, even if the remaining length of small intestine is measured to be 150 cm or more [19]. Radiation-injured intestine heals poorly after surgery and does not provide healthy support for anastomoses or stricturoplasties; suture-line leakage in radiated bowel is estimated at 30–50% [3, 10]. Another point of consideration is that radiation may cause considerable damage to the skin and the abdominal wall. In turn, this damage may lead to wound dehiscence, intestinal eventration, and stoma failure. Due to these considerations, incision lines and stoma sites should be kept outside of the radiation field.

Various strategies have been attempted to manage small intestinal obstruction in these patients. At present, it appears that the best treatment option is the complete removal of all injured bowel and creation of an anastomosis with healthy intestine at both ends. This strategy minimizes symptom recurrence and possibly results in fewer repeat operations. In addition, this approach would be expected to have the lowest anastomotic leak rate [1, 3, 6, 10]. On the other hand, these operations necessitate considerably more extensive and time-consuming small intestinal dissections in a hostile environment, namely diffuse pelvic fibrosis, (also known as the "frozen pelvis"). Dissection of "cocconed" bowel that is densely adhered to surrounding structures results in a significant risk for damage to the intestine and adjacent organs (estimated to be about 23 %) (Fig. 16.2) [19]. However, the presence of dense adhesions should not pose a contra-indication for complete resection, as the anticipated damage to pelvic organs, namely the uterus, vagina, and urinary bladder, can be repaired primarily. During these operations intact preservation of the ureters is critical, and use of ureter catheters is advised to help to safely guide the dissection.

If complete resection of all injured bowel is contemplated, wide margins should be planned. Although some authors have advocated the preservation of the ileocecal valve with creation of an anastomosis between the jejunum and terminal ileum, when possible, it should be noted that it is difficult to make an intraoperative distinction between diseased and healthy bowel based on serosal appearance alone (Fig. 16.3). Therefore, an attempt should be made to avoid all bowel located below the pelvic inlet. Inclusion of the right

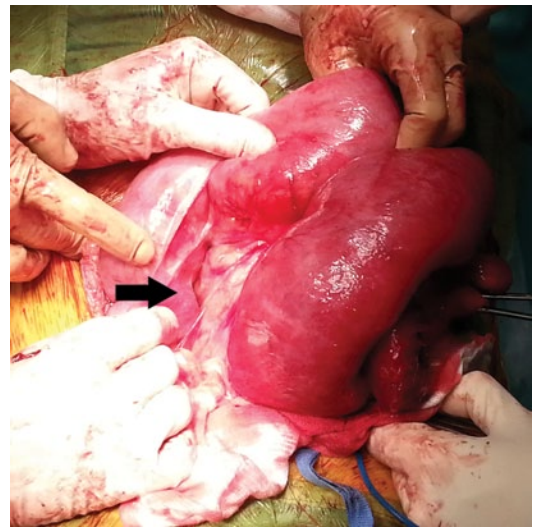

Fig. 16.2 Laparotomy for a patient with small bowel obstruction secondary to radiation enteritis. After extensive adhesiolysis to separate a conglomerate of short bowel, a thickened, fibrosed, and strictured distal segment (*arrow*) that caused the obstruction had to be freed from dense adhesions to the abdominal wall before resection. Distended proximal bowel shows mottling and serosal changes that indicate chronic obstruction but also radiation-induced injury. Note the thickening and shortening of the mesentery.

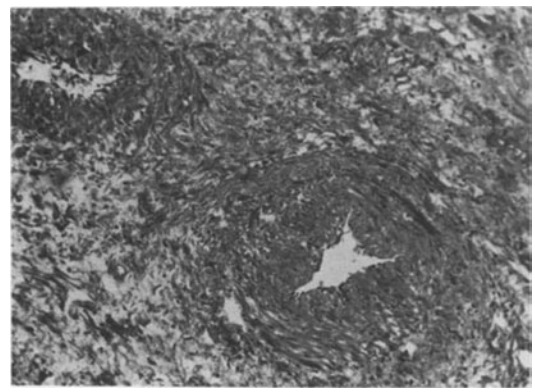

Fig. 16.3 Endothelial proliferation and subendothelial deposition of hyaline material causes narrowing of intestinal blood vessel lumen. These changes do not always directly correlate with gross serosal appearance of the bowel. (Source: With permission from Lippincott Williams and Wilkins 1981 (24)

colon in the resected specimen is also advised, since it is also frequently affected to some extent by radiation [19]. Creation of an anastomosis between the proximal end of the small bowel to the transverse colon has proven useful in minimizing the rate of anastomotic leaks, with one report describing a dramatic reduction in anastomotic leakages from 50 to 7% with this kind of anastomosis [1]. This finding is of considerable interest, since anastomotic failure is especially lethal in surgical patients with radiation-induced enteropathy due to their overall poor preoperative and post-operative state.

If complete resection and anastomosis are deemed impractical or too dangerous, whether because of intraoperative findings or due to the general poor health of a patient, a decompressive procedure or other less extensive options should be utilized. A decompressing proximal enterostomy is the safest of these, since it entails minimal if any dissection, avoids intestinal resection, and leaves no suture lines on diseased bowel. The disadvantage of this approach is the continued presence of the injured bowel. This poses a risk of later complications, including recurrent fistulization, bleeding, and perforation thus potentially necessitating further operations. Furthermore, the diseased segment represents a potential site of new or recurrent cancer [10]. A bypass operation of an obstruction or fistula, produced by creating an anastomosis between bowel that is proximal and distal to the diseased segment (usually healthy jejunum to transverse colon) has been popular in the past. This surgery avoids dissection of the inflammatory mass. However, bypassing of intestine damaged by radiation has now generally been abandoned as an operative option because of poor long-term outcomes from blind loop syndrome, maldigestion, progression of diseased bowel as well as the aforementioned complications. Their use is reserved when other surgical options are not possible [3, 19]. A staged operative strategy is often the best solution for complex cases of radiation enteropathy. In this setting, an initial operation addresses the acute obstruction or perforation with a diverting stoma, and after the patient's condition has improved a second, definitive procedure is undertaken.

Lysis of adhesions alone without resection is unsatisfactory as treatment for obstructed, radiated bowel, as this approach is associated with a high rate of recurrent obstruction [19–20]. Deserosations and frank enterotomies should be anticipated consequences during dissection in patients with a frozen pelvis, and the outcomes of primary repair in injured bowel in this setting are poor.

Stricturoplasty has been advocated as an alternative approach in select cases of discrete, long, and/or multiple strictures. Stricturoplasty has the advantage of avoiding the resection of large segments of small intestine and the associated risk of the short bowel syndrome. Some authors have reported good outcomes using this operative strategy [21, 22]. However, it is important to note that stricturoplasty still carries a similar risk of leakage as anastomoses of diseased bowel, and do not prevent recurrent obstructions or other complications of radiation enteropathy [22].

Patients with short bowel syndrome and intestinal failure have poor prognosis, and should be referred to intestinal failure units or intestinal transplantation [22–23].

Surgical Treatment of Radiation Colitis and Proctitis

There are several medical endoscopic and non-operative options for patients with symptomatic radiation colopathy and proctopathy. These are described in Chap. 15, *Medical management of radiation effects on the intestines*. A relatively small subset of patients will fail these, resulting in the necessity for operative management. The other indications for surgery are perforations, fistulas, and strictures.

Radiation proctopathy is characterized by fibrosis of the rectal wall and the formation of mucosal telangiectasias. Damaged small blood vessels severely impair wound healing and accentuate the pathophysiology of the condition (see Chap. 5). Rectal bleeding is caused by disrupted telangiectasias or ulcerations, while tenesmus, frequency, incontinence, and urgency occur from loss of the reservoir capacity of the fibrosed rectum. These symptoms are further aggravated by

diarrhea, which is caused by co-existing radiation enterocolitis or other reasons.

Surgeons may attempt to control bleeding by sclerosis of telangiectasias with formalin application [29–30]. The procedure can be performed under light sedation with rigid proctoscopy. Since formalin is a toxic substance, complications of the distal colon (strictures, formalin colopathy) or perianal skin (intractable fissuring) have been reported [31–32].

Endosopic methods to obliterate telangiectasias include argon plasma coagulation (APC), Nd:YAG laser, and heater probes. APC is the most common approach due to ease of use and effectiveness in treatment [33–34]. An average of two to three sessions is usually needed to control bleeding [34–35]. Most complications of APC are mild, such as tenesmus, cramps, and mucus discharge. Serious complications, including ulceration, fistulization, and perforations have been reported. APC and other thermal methods are not recommended in the setting of ulcerated mucosa, as this finding represents an ischemic bed that may be worsened with cautery. For additional information, see Chap. 15.

Surgical intervention is indicated for patients with perforations, fistulas, obstructing strictures, and uncontrollable bleeding. Perforations with peritonitis are treated with a Hartmann procedure, or sometimes anterior resection with anastomosis and production of a defunctioning stoma [4, 24–25]. Pelvic perforations are treated with adequate drainage and diversion. Intractable bleeding, fistulas, and strictures can be addressed by primary diversion alone [24–25]. Diverting the fecal stream from the rectum, usually by means of a loop colostomy, is a well-tolerated intervention suitable that has demonstrated to stop rectal bleeding in more than 80% of patients [36]. Diversion alone can also aid to control sepsis, alleviate obstruction, and diminish symptoms such as rectal pain but may not entirely prevent the later occurrence of complications such as fistula formation. Use of a loop of the proximal transverse colon for diversion is preferred over the sigmoid colon. This is suggested for two reasons: (a) the transverse colon is expected to be positioned outside of the radiation field and therefore is not diseased, and (b) the descending colon is left intact for later use if a staged intervention is anticipated.

If the patient is in an adequate general state and can undergo an extensive procedure, resection of the injured rectum and restoration of bowel continuity should be the intervention of choice. This can be performed using a transabdominal approach, a combined abdominal-transsacral approach (known as the Marks pull-through anastomosis), or a combined abdomino-transanal approach (termed the Soave pull-through anastomosis). In order to avoid damage to adjacent structures such as pelvic viscera and nerves, the ureters, and the iliac vessels, dissection is carried on the rectal wall, leaving the fibrosed mesorectum in place [37]. Alternatively, rectal dissection can be carried within the rectal wall in the form of a mucosectomy. In this setting, the proximal colon is passed through a sleeve consisting of the serosal and the muscular layers of the rectum (called the modified Parks or the modified Soave procedures) [38]. As previously mentioned, the use of ureteral catheters is advised for safe dissection. An anastomosis is prepared between healthy bowel ends of the proximal colon and distal rectum or anal canal, sometimes in the form of a colonic J-pouch [4, 39]. Healthy tissue from outside the radiation field, usually the omentum, should be used as a buttress for the anastomosis and to serve as a divide between the anastomosis and the bladder.

Separation of the neorectum from adjacent organs with interposition of healthy tissue is crucial for the management of radiation-induced fistulas. It is generally accepted that poor healing of radiated tissues will cause a primary repair to fail, although the pull-through technique alone was previously shown to be successful for fistulizing disease [40]. The interposed tissue must have its own blood supply from outside the radiation field [41]. For this purpose, there is accumulating experience with use of the gracilis muscle and other thigh muscles as rotation grafts [42–43]. Other treatment options include an omental flap, a rectus muscle pedicle, or use of the proximal colon as a pedicled graft to close a vaginal or urethral defect (termed the modified Parks colo-anal anastomosis).

It should be stressed that an endeavor to remove the rectum from the fibrosed pelvis without injury to adjacent structures (including other pelvic organs and potentially the small intestine), may pose extreme technical difficulties. Because of this, even current improvements in the state of the art of performing these surgeries leave a substantial number of patients remaining as poor candidates for extensive surgical intervention. In these individuals, the diseased rectum remains in situ and a permanent stoma is required. In general, surgery in these patients has generally been shown to have high complication rate (50–80 %) and poor overall outcome. However, these grim numbers reflect the fact that many of these patients in whom surgery is performed, go to the operating room because they have developed the most severe consequences of radiation-induced intestinal disease.

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Index

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