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