

Radiation Therapy in Early Endometrial Cancers: Con

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Jamie N. Bakkum-Gamez, MD
 Andrea Mariani, MD
 Karl C. Podratz, MD, PhD

Introduction

Endometrial cancer (EC) represents a heterogeneous spectrum of disease. Over 75% of EC diagnoses will be FIGO stage I and most women will require only surgical extirpation to achieve a cure. However, certain factors have been identified that prognosticate a relative high risk of recurrence in otherwise apparent early-stage disease. These factors include histologic subtype, grade 3 histology, myometrial invasion $\geq 50\%$, lymphovascular space invasion (LVSI), primary tumor diameter of >2 cm, cervical stromal invasion (CSI), and lymph node status (1, 2). It is generally accepted that low-risk, stage I ECs do not benefit from pelvic external beam radiotherapy (EBRT) given their low loco-regional recurrence rate. The current consensus on adjuvant EBRT for high-risk, early-stage EC is one of debate.

The objective in the management of any disease process is to optimize treatment outcomes. One goal of adjuvant cancer therapy is to reduce the risk of disease recurrence. Ideally, this should minimize both overtreatment and undertreatment and maximize the rates of cure. In EC, the modalities of surgery, radiation, and chemotherapy are currently utilized in management of the disease. Several randomized trials of chemotherapy in EC have been performed and this modality is generally reserved for advanced disease.

To date, four prospective randomized trials have been published on the utilization of pelvic EBRT in presumed early stage EC (1-4). The efficacy of adjuvant pelvic EBRT alone in presumed early stage endometrial cancer has been the focus of two of these prospective randomized trials (Table 1) (1, 2); the other two prospective trials included patients who also had vaginal brachytherapy (Table 2) (3, 4). In addition, the results of the first prospective randomized trial comparing pelvic EBRT to vaginal brachytherapy have been presented in abstract form (5). A worldwide consensus on the ideal surgical and adjuvant management of EC as a spectrum of disease has yet to be reached.

Importance of Lymphadenectomy in High-Risk Apparent Early Stage EC

Comprehensive management of EC begins with individualized recurrence risk stratification. Retrospective data has helped identify risk factors for lymphatic spread and recurrence in early-stage EC. Those at lowest risk for lymphatic spread and treatment failure include patients with endometrioid histology, grade 1 or 2, myometrial invasion of $< 50\%$, and primary tumor diameter of < 2 cm. In a cohort of surgically staged patients (all had pelvic lymphadenectomy) fulfilling

Table 1. Comparison of the only 2 published prospective randomized trials of adjuvant pelvic EBRT alone vs. observation in early-stage endometrial cancer.

	No. of patients	Stages and Grades Included in Study	Vaginal Recurrences n (%)		Pelvic Recurrences n (%)		Distant Recurrences n (%)		Overall survival ^a %	
			EBRT	Observation	EBRT	Observation	EBRT	Observation	EBRT	Observation
Creutzberg, et al (PORTEC-1) (2000) (1)	714	Presumed stage I ^b ; Grade 1, $\geq 50\%$ invasion; Grade 2, any invasion; Grade 3, $< 50\%$ invasion	N= 354 7 (2.3)	N= 360 30 (10.2)	N= 354 4 (2.0)	N= 360 10 (3.4)	N= 354 24 (7.9)	N= 360 20 (7.0)	N= 354 81%	N= 360 85%
Keys, et al (GOG 99) (2004) (2)	392	Presumed stage I ^c ; all grades, stages IB, IC and IIA	N= 190 2 (1.1)	N= 202 13 (6.4)	N= 190 1 (0.5)	N= 202 5 (2.5)	N= 190 10 (5.3)	N= 202 13 (6.4)	N= 190 92%	N= 202 86%

^aFor PORTEC-1, 5-year overall survival; for GOG 99, 4-year overall survival

^bLymph node assessment based on palpation of lymph node bearing areas and selective lymph node biopsy if enlarged.

^cLymph node assessment based on selective lymph node biopsy and removal of enlarged or suspicious lymph nodes.

all of these requirements, Mariani et al, found that no patients had positive pelvic lymph nodes and no patients died of disease. Utilizing primary tumor diameter only in this low-risk cohort with negative pelvic lymph nodes, only 2% of patients with tumors < 2 cm failed. All were vaginal failures which were successfully cured with radiotherapy at the time of recurrence. There were no distant failures in this low-risk sample (6). Similar low-risk cohorts have been described by the two published prospective, randomized trials evaluating the impact of pelvic EBRT alone in presumed early-stage EC (1, 2). However, tumor diameter was not assessed as a risk factor in these two prospective trials. Mariani et al, did observe that increasing tumor diameter was also a risk factor for recurrence; among patients with a primary tumor diameter of > 2 cm, despite grade 1 or 2, endometrioid tumors with < 50% myometrial invasion, 8% had a recurrence and 75% of those who recurred died of disease. Also, those who had a recurrence were more likely to have LVSI and LVSI portended a higher risk of distant recurrence (6).

Pelvic and para-aortic lymphadenectomy have helped to clarify the true extent of disease and more adequately stage presumed early-stage EC. Retrospective data has also helped to define those presumed early-stage cancers that are at high risk for nodal failure. Both cervical stromal invasion (CSI) and lymph node involvement are significant predictors of nodal failure. Among a sample of 292 ECs, those with CSI and/or lymph node involvement had a 5-year pelvic sidewall failure rate of 26%. In patients with neither CSI nor lymph node involvement, there were no nodal failures (7). Thus, both CSI and lymph node positivity are important predictors of lymphatic metastasis. Given that 1 in 4 patients with these high-risk features will recur along the pelvic lymph node bearing areas, complete pelvic lymphadenectomy appears imperative to determine true surgical stage

for prognosis counseling and adjuvant treatment recommendations. In addition to a higher rate of pelvic nodal failure, pelvic lymph node involvement alone portended an increase in the rate of failure in the para-aortic nodal region (7), underscoring the additional importance of para-aortic lymph node assessment.

Pelvic EBRT—The Early Years

The first prospective, randomized trial of EBRT in presumed early stage EC was published in 1980. Aalders and colleagues randomized 540 women with EC who had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy followed by 6000 rads of intravaginal radium irradiation to either observation or 4000 rads of EBRT to the pelvic lymph nodes. Loco-regional recurrences were reported as combined vaginal and pelvic recurrences and the addition of pelvic EBRT reduced the risk of loco-regional recurrence to 1.9% from 6.9% in the observation cohort. However, distant recurrences were higher in the EBRT group (9.9%) compared to the observation cohort (5.4%) and 5-year overall survival (OS) was the same between cohorts (Table 2) (3). Thus, conclusions from the first prospective trial of pelvic EBRT in presumed early-stage EC nearly 30 years ago included the finding that there is no overall survival advantage associated with the addition of this adjuvant modality.

PORTEC-1

The role of postoperative pelvic EBRT in presumed stage I EC was the focus of the Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC-1) trial. PORTEC-1 was the first randomized trial to evaluate the impact of pelvic EBRT alone on loco-regional recurrence, overall survival

Table 2. Randomized prospective trials evaluating pelvic external beam radiotherapy (EBRT) in early-stage endometrial cancer. Both studies included patients who received adjuvant vaginal brachytherapy.

	No. of patients	Stages and Grades Included in Study	Vaginal Recurrences n (%)		Pelvic Recurrences n (%)		Distant Recurrences n (%)		Overall survival 5-year	
			EBRT	Observation	EBRT	Observation	EBRT	Observation	EBRT	Observation
Aalders, et al (1980) ^a (3)	540	All presumed stage I ^b , grades 1-3	NA		N=263 5 (1.9)	N=277 19 (6.9) ^c	N=263 26 (9.9)	N=277 15 (5.4)	N=263 89%	N=277 91%
ASTEC/EN.5 (2009) ^d (4)	905	Presumed early-stage ^e Endometrioid: stage IA and IB, grade 3; IC all grades; IIA/IIB all grades Papillary serous or clear cell; any stage I or II	N=452 7 (1.5)	N=453 17 (3.8)	N=452 6 (1.3)	N=453 12 (2.6)	N=452 34 (7.5)	N=453 31 (6.8)	N=452 84%	N=453 84%

^aAll patients received 6000 rads of intravaginal radium irradiation prior to randomization to EBRT or observation.

^bNo lymph node assessment performed

^cRecurrences were reported as combined vaginal and pelvic recurrences.

^d51% of those observed received vaginal brachytherapy; 52% of those receiving pelvic EBRT also received vaginal brachytherapy. Only 47% of observation group were observed without adjuvant treatment.

^eLymphadenectomy not required; palpation of lymph node bearing areas not required.

val, and treatment-related morbidity in high-risk presumed early-stage endometrial cancer. Patients accrued to the PORTEC-1 trial underwent surgical assessment of their endometrial cancer which included a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and palpation of lymph node bearing areas. Suspicious lymph nodes were sampled or biopsied but lymphadenectomy was not required for enrollment in the study. Patients presumed to be FIGO stage I, grade 1 with deep myometrial invasion ($\geq 50\%$), grade 2 with any invasion, or grade 3 with superficial invasion ($\leq 50\%$) were eligible. Patients were randomized to receive pelvic EBRT of 46 Gy in 23 fractions with the superior treatment margin at the L5/S1 disc versus no further treatment.

The primary endpoints of PORTEC-1 were loco-regional control and overall survival (OS). The secondary endpoints were treatment-related morbidity and survival after relapse. Loco-regional failure was defined as pelvic, vaginal or both. Distant failures included para-aortic lymph node metastases, abdominal relapses, liver, lung, bone, and diffuse metastases.

In this cohort of presumed stage I endometrial cancers, pelvic EBRT did reduce the 5-year loco-regional failure rate from 14% in the observation arm to 4% ($p < 0.001$), however pelvic EBRT offered no survival benefit (5-year OS 85% in control arm, 81% in pelvic EBRT arm; $p = 0.31$). In addition, $> 80\%$ of the loco-regional recurrences were at or near the vaginal vault and the absolute number of non-vaginal pelvic recurrences amounted to 10 women in the control group (3.4% in 5 years) and 4 women in the EBRT group (2% in 5 years) (Table 1). Among those with a loco-regional relapse, 75% could be salvaged with curative intent using EBRT, intracavitary brachytherapy, surgery or a combination of modalities and 85% of them achieved a complete remission. The salvage rate for previously unirradiated patients was high and the overall survival after first recurrence was higher for the control group than for the EBRT group ($p = 0.02$). Two-year survival after vaginal recurrence was 79% (compared to 21% after pelvic or distant recurrence) and 3-year survival was 69% (compared to 13% after pelvic or distant recurrence). In addition, with substratification of the patients included in PORTEC-1, a cohort with a less than 5% 5-year loco-regional relapse rate was elucidated: grade 2 tumors with less than 50% myometrial invasion (1). With an already low rate of recurrence, these patients did not see any reduction in loco-regional recurrence and thus received no benefit from adjuvant EBRT.

Perhaps most notable in PORTEC-1 was the high rate of radiation-related complications. During treatment, 63% of the EBRT group required medical or dietary treatment for acute radiation toxicity. In addition, 2% (7 patients) discontinued EBRT secondary to severe toxicity. Overall, late complications associated with the primary treatment occurred in 25% of EBRT group and 6% of the control group

($p < 0.001$), suggesting that radiation enhances postoperative sequelae. Late radiation-associated toxicity occurred in 26% of patients treated with parallel opposed fields and in 22% of patients treated with 3-field or 4-field techniques. Two percent (7 patients) of the EBRT group had grade 3-4 complications and 20% developed long-term (mostly grade 1) toxicity (1). Given the excellent salvage rates of vaginal recurrences and the similar non-vaginal pelvic recurrence rate between the EBRT and control group in addition to the high rate of radiation-related complications, it would seem that EBRT is overtreatment for this population of patients.

While EBRT reduced the rate of loco-regional recurrence, it had no effect on overall survival or on EC-related deaths (9% in EBRT group, 6% in control group at 5 years). The higher rate of loco-regional relapse in the control group did not by itself affect overall survival or EC-related deaths. In the highest-risk subgroup in PORTEC-1 (grade 3 or deeply invasive grade 1 or 2), higher rates of EC related deaths were observed, but these rates remained similar between treatment groups (11% in EBRT group, 8% in control group). In addition, another important finding was that even in the highest-risk patients in this study, EBRT did not have an effect on the rate of distant metastasis (6% in EBRT and 5% in the control group). But, once distant failure occurred, EC-related survival plummeted with 63% (19 of 30 distant failures) of distant failures dying of disease (1). One must remember that lymphadenectomy was not required for patients to be enrolled in PORTEC-1. Lymph node assessment included palpation of lymph node bearing areas and only removal of suspicious nodes. Thus, a portion of the included patients were likely stage IIIC, but were included in the study given inadequate staging. The similar rate of distant failures suggests that metastases had already occurred at the time of surgery and that pelvic EBRT was undertreatment for this cohort of distant failures (1).

GOG 99

The second prospective randomized trial of pelvic EBRT alone in early-stage EC was conducted by the Gynecologic Oncology Group (GOG) and published in 2004. GOG 99 included 392 patients with stage IB, IC, or IIA, all grades. Patients were required to undergo total abdominal hysterectomy, bilateral salpingo-oophorectomy, and selective lymph node sampling (lymph node counts were not required). Following surgery, if no pelvic lymph nodes were positive for metastasis, patients were randomized to either observation or to receive either EBRT of 50.4 Gy given in more than 28 fractions with L4/L5 disc as the superior border of the radiation field. Neither group received vaginal brachytherapy (2).

The primary outcome of GOG 99 was recurrence-free survival and the secondary outcome was all-cause survival. The 2-year cumulative incidence of recurrence was 12% in

the control group and 3% in the EBRT group. However, when broken down into sites of first recurrence, the major difference between the EBRT arm and the observation arm was in vaginal recurrences (2 (1%) in EBRT arm; 13 (6.4%) in observation arm). The rate of distant recurrences was not significantly different (10 (5.3%) in EBRT arm; 13 (6.4%) in observation arm) (Table 1) (2). The rates in distant failures in GOG 99 were nearly identical to the distant failure rates in PORTEC-1 and the Aalders trial (1-3), in which patients did not undergo staging lymphadenectomy. Once again, this suggests that the patients included in GOG 99 either had inadequate staging and had unrecognized advanced stage disease or that there are subgroups of early-stage patients that are at high risk for distant recurrences that should be treated with systemic therapy rather than localized adjuvant therapy.

Further analyses identified a high-intermediate risk cohort of patients in GOG 99. These were patients with moderate-poorly differentiated tumors with LVSI and invasion into the outer third of the myometrium OR were over 50 years of age with any two of the above risk factors OR over 70 years of age with any one risk factor above. This high-intermediate risk group accounted for 1/3 of the entire cohort, but was responsible for 2/3 of the recurrences and cancer-related deaths. Among this high-intermediate risk group, the 2-year cumulative incidence of recurrence was 26% for observation arm and 6% for EBRT arm. However, 4-year overall survival was similar in both arms: 86% for observation arm and 92% for EBRT arm ($p=0.56$). The overall comparative survival was also similar within the remaining 2/3 of the study cohorts considered low-intermediate risk (2). Thus, despite a higher cumulative incidence of recurrence in the observation arm, EBRT had no effect on OS.

In addition to no improvement in OS, severe complications occurred in 8% in EBRT group. There were significant differences ($p<0.001$) in frequency and severity of hematologic, gastrointestinal, genitourinary, and cutaneous toxicities between the two groups. Six women in the EBRT group experienced grade 3-4 bowel obstruction with only one in the observation group. Two women (1%) in the EBRT group died from complications from radiation-related intestinal injury (2).

The conclusions of GOG 99 are similar to those of the PORTEC-1 and Aalders trials: EBRT improves loco-regional recurrence but yields no difference in overall survival. Nearly identical rates of distant failure were seen in all three studies; suggesting inadequately-staged, advanced-stage patients or women with occult disseminated disease were included in both studies (Tables 1 and 2) (1-3). In addition, there were significantly high rates of radiation-related complications, including life-threatening complications, associated with EBRT in both GOG 99 and PORTEC-1. Both studies substratified the total cohort and identified low-risk pa-

tients that already had rates of recurrence $<5\%$ and would not benefit from EBRT (1, 2). In GOG 99, these low-risk ECs comprised 66% of the entire cohort (2). Such low-risk women are at risk for radiation-related complications without a survival benefit.

ASTEC/EN.5

The most recent published prospective trial assessing pelvic EBRT in presumed early-stage EC combined data from the EN.5 trial of the National Cancer Institute of Canada (NCIC) Clinical Trials Group and the UK Medical Research Council (MRC) ASTEC trial. Both trials were initially individual trials designed to assess the impact of pelvic EBRT in patients with presumed intermediate or high-risk early stage EC. EN.5 began in 1996, but recruitment to the study was not sufficient to complete it. The ASTEC trial began in 1998 and ASTEC/EN.5 represents combined prospective data on 905 women from two trials with separate randomizations spanning the years 1996 to 2005. Ultimately, the cohort consisted of apparent FIGO stages IA and IB, grade 3; stage IC, all grades; papillary serous; or clear cell histology, all early stages and grades. The cohort had primarily endometrioid histology (83% in both the observation and pelvic EBRT cohorts), but also included were 59 (7% of total) combined clear cell and papillary serous ECs. Pelvic lymphadenectomy was not required and over 60% of the entire cohort had no lymph nodes removed for pathologic assessment. Patients received 40-45 Gy in 20-25 daily fractions to the pelvis. In addition, receipt of vaginal brachytherapy was allowed in both the observation and pelvic EBRT cohorts. Fifty-one percent of the observation arm received vaginal brachytherapy; 52% of the pelvic EBRT arm received both modalities (4).

Overall, there was no difference in 5-year overall survival, disease-specific survival, or disease-specific recurrence-free survival between the pelvic EBRT and observation cohorts. The pelvic EBRT cohort had a small reduction in both isolated vaginal recurrences (1.5% v. 3.8% in the observation cohort) and isolated pelvic recurrences (1.3% v. 2.6% in the observation cohort), but had higher rates of all degrees of toxicity (Table 2). In fact, a majority of patients in the EBRT cohort reported toxicity, with 57% reporting acute toxicities and 61% reporting long-term toxicities. In addition, the distant recurrence rate was not impacted by pelvic EBRT and the rate of isolated local recurrence in patients who did not receive EBRT but did receive vaginal brachytherapy was low at 6.1% (4). Thus, the conclusion from ASTEC/EN.5 is that the minimal improvement in local control achieved with pelvic EBRT does not justify the toxicity. In addition, this most recent prospective trial once again demonstrated that pelvic EBRT offers no improvement in survival.

Vaginal Brachytherapy

Certainly, a loco-regional relapse rate of 10-15% for high-risk stage I EC (1, 2) is not an acceptable risk and some form of adjuvant treatment is warranted to reduce this risk. However, when approximately 60% of patients experience some degree of radiation toxicity (1, 4), the ideal treatment would be one that decreases the risk of loco-regional recurrence with minimal lasting toxicity.

Vaginal brachytherapy is an attractive alternative to EBRT. High-dose rate (HDR) brachytherapy has been shown to be well tolerated with low rates of severe or chronic complications. Vaginal control rates for the more efficient, better tolerated HDR brachytherapy are comparable to control rates with the lengthier low-dose rate (LDR) brachytherapy. Pearcey and Peterit established the HDR dosing of 21 Gy to 5mm depth in 3 fractions as the standard brachytherapy dose as this provides local control rates greater than 98% (8). And additional retrospective data supports 98 to 100% vaginal control rates with HDR in high risk early-stage EC (9, 10). As shown by the PORTEC-1 and GOG 99 trials, EBRT predominantly reduces the risk of vaginal failures. Retrospective data suggests vaginal relapse rates after brachytherapy averages 5-6% (Table 3) (9, 11-15) and this is similar to the 5-year vaginal failure rate of 3.5% reported among the highest-risk patients who received EBRT in PORTEC-1 (1). Unfortunately, the rate of vaginal failure after pelvic EBRT in the high-intermediate risk group in GOG 99 was not reported, however the overall 2-year vaginal failure rate among those receiving pelvic EBRT reported in GOG 99, including the 66% of patients of low-intermediate risk, was 1% (2). In addition, retrospective data comparing vaginal brachytherapy directly to EBRT suggests vaginal brachytherapy alone may be an equally effective, more

tolerable alternative to EBRT for reducing vaginal failures (16).

PORTEC-2

The question for a prospective, randomized trial to answer is: Can the same effect of pelvic EBRT be achieved with vaginal brachytherapy alone in patients at high risk for loco-regional recurrence? The results of PORTEC-2, the first prospective, randomized trial comparing pelvic EBRT to vaginal brachytherapy, has been completed and published in abstract form. In PORTEC-2, patients with apparent uterine-confined EC at high risk for recurrence (>60 years of age with grade 1 or 2, stage IC and grade 3, stage IB; or any age, any grade IIA with <50% myometrial invasion) were randomized to either pelvic EBRT (46 Gy, in 23 fractions) or vaginal brachytherapy (21 Gy in 3 HDR fractions or 30Gy LDR, to a depth of 0.5 cm). At 3 years, there was no difference in vaginal failure rate (0.9% for vaginal brachytherapy, 2% for pelvic EBRT; $p=0.97$). There was a higher rate of non-vaginal pelvic relapse in the brachytherapy group (3.6 %) compared to the EBRT group (0.7%) ($p=0.03$), however the absolute difference was small and there was no difference in overall survival (5). In addition, the difference between non-vaginal pelvic recurrences may be a reflection of EBRT treatment of unrecognized lymph node metastases at the time of initial staging. One concern regarding PORTEC-2 is that there was not a surgery-only control in the study. However the highest risk EC subgroup in PORTEC-1 (patients >60 years of age with grade 3 or deeply invasive grade 1 or 2, all stage I) was similar to the cohort included in PORTEC-2 and the loco-regional recurrence rate in patients who did not receive adjuvant EBRT in PORTEC-1 was 18% (1).

Table 3. Recurrence in high-risk, comprehensively staged, early-stage endometrial cancer after adjuvant vaginal brachytherapy alone (no pelvic EBRT).

	No. of patients	Lymphadenectomy performed	Postoperative vaginal brachytherapy	No. of recurrences N (%)
Orr (1997) ¹⁵	115	+	+	6 (5.2%)
Mohan (1998) ¹³	28	+	+	2 (7%)
Chadha (1998) ¹¹	38	+	+	3 (7.9%)
Fanning (2001) ¹²	66	+	+	2 (3%)
Horowitz (2002) ⁹	102	+	+	10 (9.8%)
Straughn (2003) ¹⁴	56	+	+	0 (0%)
TOTAL	405			23 (5.7%)^a

^aIncludes 18 distant (78% of all recurrences), 3 vaginal (13%), 1 isolated pelvic sidewall (4.3%), 1 unknown site (4.3%).

Conclusions

The principal criticism of pelvic EBRT is not the documented efficacy in loco-regional control of tumor, but rather in the morbidity associated with its use. Both PORTEC-1 and GOG 99 found that the rate of non-vaginal pelvic failures occurring in patients who underwent pelvic EBRT was only 2%. Interestingly, the rate of non-vaginal pelvic failure in patients who underwent no additional treatment in PORTEC-1 was 4% and only 1% in GOG 99 (1, 2). This suggests that pelvic EBRT adds minimal, if any, benefit to non-vaginal pelvic control. And since most loco-regional failures are actually at or near the vagina, vaginal brachytherapy appears to provide loco-regional control equal to that of EBRT with a fraction of the treatment-related morbidity. In addition, salvage rates for previously unirradiated patients recurring in the most common site—the vagina—is high (1, 14). Table 4 outlines the findings of the current literature on pelvic EBRT in high-risk presumed early-stage EC.

Progress has been made in better understanding patterns of failure in EC. Contemporary literature strongly suggests that in early-stage EC, when patients undergo appropriate risk stratification (including comprehensive surgical staging) and adjuvant therapy is indicated, it should be focused on the vagina and distant sites. Thus, non-selective use of adjuvant pelvic EBRT in inadequately-staged, presumed early-stage EC is not warranted.

In summary, the overall goal in treating women with endometrial cancer should be one of achieving the highest rate of cure paired with the lowest rate of morbidity. This encompasses the concept of limiting both undertreatment and overtreatment. In high-risk, uterine-confined endometrial cancers, there is no level I evidence that any adjuvant therapy appreciably impacts overall survival. While pelvic EBRT improves loco-regional control of disease in patients at high risk for local recurrence, radiation is not innocuous. Ap-

Table 4. Summary of current data on pelvic EBRT in high-risk apparent early-stage EC.

- Pelvic EBRT in unstaged or incompletely staged presumed early-stage EC decreases loco-regional recurrence.
- Vaginal brachytherapy appears to be equivalent to pelvic EBRT in preventing vaginal recurrences.
- In none of the published prospective trials comparing pelvic EBRT to observation was there a difference in overall survival.
- The rate of distant failure is the same between pelvic EBRT and observation.
- Lymphadenectomy identifies those patients who have lymphatic dissemination and might potentially benefit from EBRT to the involved nodal areas.
- Up to 60% of patients who receive pelvic EBRT will have long-term toxicity.
- Isolated vaginal recurrence in previously non-irradiated patients has a high salvage rate.
- Pelvic EBRT should be abandoned in adequately-staged node-negative EC.

proximately 60% of patients will have some degree of radiation toxicity and nearly 1 in 10 patients will have a severe complication from radiation. In addition, adjuvant loco-regional treatment does not prevent distant recurrences and does not affect overall survival. Since vaginal brachytherapy appears to purvey a similar reduction in loco-regional recurrence with a fraction of the complications associated with pelvic EBRT, then pelvic EBRT, as adjuvant therapy for early-stage endometrial cancer, should be abandoned.

Abbreviations: endometrial cancer (EC), International Federation of Gynecology and Obstetrics (FIGO), lymphovascular space invasion (LVSI), cervical stromal invasion (CSI), external beam radiotherapy (EBRT), Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC), overall survival (OS), Gynecologic Oncology Group (GOG), National Cancer Institute of Canada (NCIC), UK Medical Research Council (MRC), high dose rate (HDR) brachytherapy, low dose rate (LDR) brachytherapy

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