Adjuvant Therapy in Early-Stage Endometrial Cancer: A Systematic Review of the Evidence, Guidelines, and Clinical Practice in the U.S.

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ABSTRACT

Endometrial cancer is the most common gynecologic malignancy in the U.S., with an increasing incidence likely secondary to the obesity epidemic. Surgery is usually the primary treatment for early stage endometrial cancer, followed by adjuvant therapy in selected cases. This includes radiation therapy [RT] with or without chemotherapy, based on stratification of patients into categories dependent on their future recurrence risk. Several prospective trials (PORTEC-1, GOG#99, and PORTEC-2) have shown that the use of adjuvant RT in the intermediate risk (IR) and the high-intermediate risk (HIR) groups decreases locoregional recurrence (LRR) but has no effect on overall survival. The ad hoc analyses from these studies have shown that an even

larger LRR risk reduction was seen within the HIR group compared with the IR group. Vaginal brachytherapy is as good as external beam radiotherapy in controlling vaginal relapse where the majority of recurrence occur, and with less toxicity. In the high-risk group, multimodality therapy (chemotherapy and RT) may play a significant role. Although adjuvant RT has been evaluated in many cost-effectiveness studies, high-quality data in this area are still lacking. The uptake of the above prospective trial results in the U.S. has not been promising. Factors that are driving current practices and defining quality-of-care measures for patients with early-stage disease are what future studies need to address. *The Oncologist* 2014;19:645–653

Implications for Practice: Several phase III randomized controlled trials have shown that adjuvant radiation for high-intermediate risk early-stage endometrial cancer confers a benefit by reducing local regional recurrence with minimal added toxicity, but at increased cost and without significant overall survival benefit. This article reviews key trials regarding adjuvant radiation in early stage endometrial cancer and summarizes current clinical practice patterns and available guidelines. These facets must be considered and reviewed with each patient individually to determine the relative benefit to each patient.

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in the U.S. The treatment of endometrial cancer with radiation therapy (RT) was first reported in 1909. The management of early-stage disease and the use of adjuvant RT has been rigorously evaluated and continued in numerous iterations. However, optimal modality and indication for its use remain unclear and controversial to this day.

In this review, we will focus on the use of adjuvant RT in early-stage disease and how the landmark trials (mainly PORTEC-1, GOG#99, ASTEC/EN.5, and PORTEC-2) influenced clinical practice in the U.S. However, management controversy because of the lack of a demonstrable survival benefit with adjuvant RT still exists. Given the current inconclusive data, several studies have examined the cost-effectiveness of adjuvant RT, providing another angle to weigh the risks and benefits of adjuvant RT.

METHODS

A literature search was conducted to identify studies assessing the adjuvant treatment of early-stage disease, practice patterns, and cost-effectiveness of adjuvant radiation. We performed PubMed, MEDLINE, and EMBASE database searches for studies using the following keywords: endometrial cancer, early stage, adjuvant treatment, radiation therapy, radiotherapy, current practice patterns, utilization rate, cost benefit, and cost effectiveness. Titles and abstracts were reviewed for relevance. Cross-referencing was used to identify any missing studies in the database search.

RESULTS

Clinical Trial Evidence

The standard treatment of early-stage endometrial cancer consists of hysterectomy, bilateral salpingo-oophorectomy (BSO),

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with or without lymph node dissection (LND). RT and chemotherapy, which is less likely, are considered adjuvant treatment, with the aim of reducing recurrence and improving overall survival. The balance between improving survival and minimizing morbidity is particularly pertinent because of the low likelihood of recurrence [1].

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In 2000, the Post-Operative Radiation Therapy in Endometrial Cancer (PORTEC-1) multicenter, randomized trial was published (Table 1) [2]. The objective was to determine whether adjuvant RT improved overall survival (OS) or affected local regional recurrence (LRR) in patients with stage I disease. Seven hundred fifteen patients underwent hysterectomy and BSO without requiring LND, and roughly half were randomized to adjuvant external beam radiation therapy (EBRT) (46 Gy) versus observation. In the intermediate risk (IR) group, RT reduced the rate of LRR at 5 years compared with controls (4% vs. 14%, respectively, $p < .001$). In their ad hoc analysis, a greater reduction (5% vs. 18%) was found in the high intermediate risk (HIR) group. However, this did not impact OS (5-year OS was 81% in the RT group compared with 85% in the control group) in the unadjusted or adjusted analysis. A 15-year follow up study on the same cohort confirmed the relevance of HIR criteria for treatment selection to decrease LRR [3].

In 2004, The Gynecologic Oncology Group (GOG) published the results of a similar prospective study on early-stage patients with intermediate-risk disease (GOG#99) (Table 1) [4]. Four hundred forty-eight patients with stage IB, IC, or II (occult) disease were randomized to EBRT (50.4 Gy) versus no additional therapy (NAT), following hysterectomy, BSO, and LND. The primary outcome was a recurrence-free interval; OS was a secondary endpoint. EBRT reduced the 24-month cumulative incidence of recurrence (CIR) (3% RT vs. 12% NAT, hazard ratio 0.42, $p = 0.007$). CIR decreased to 2% from 6% (hazard ratio 0.46, 90% confidence interval [CI]: 0.19–1.11) over 4 years. Within the HIR group, a greater reduction was seen (CIR of 13% vs. 27%, hazard ratio 0.42, 90% CI: 0.21–0.83). As in PORTEC-1, the difference in OS was not statistically significant.

In both PORTEC-1 and GOG#99, the majority (75%) of the LRRs were located in the vagina (mainly vaginal vault). The success of salvage therapy was higher after vaginal relapse compared with pelvic and distant recurrence. In PORTEC-1, the 3-year survival after salvaging vaginal recurrence was 73% compared with pelvic (8%) and distant relapse (14%). The 5-year survival after vaginal relapse was 65% in the control group compared with 43% in the RT group [5].

Following PORTEC-1 and GOG#99, the prospectively combined ASTEC and EN.5 trials were published in 2009 [6]. Nine hundred five patients with IR or high-risk (HR) (Table 1) were randomized after hysterectomy and BSO with or without LND to EBRT or observation. Vaginal brachytherapy (VB) was

allowed for all stage I or IIA patients, irrespective of randomization, which resulted in VB treatment of 52% in the observation group and 54% in the EBRT group. The primary outcome of OS was similar in both arms (84%). The 5-year LRR decreased in the EBRT group (3.2% vs. 6.1%, 95% CI: <0.1%–5.9%). Considering that the LRR rate in the ASTEC/EN.5 trials was lower than in earlier trials and VB was allowed in both study arms, it would seem natural to next investigate whether VB is sufficient to reduce vaginal recurrence, given its less morbid side effects.

In 2010, the results of PORTEC-2, a multicenter randomized noninferiority trial, were published [7]. VB was compared with EBRT in 427 patients with stage I to IIA disease with HIR features (Table 1) after undergoing hysterectomy and BSO, with removal of suspicious lymph nodes. Serous, clear cell histology or staging lymphadenectomy were excluded. The primary endpoint was vaginal recurrence, and secondary endpoints included LRR (vaginal plus pelvic), distant metastases, morbidity, and OS. The 5-year vaginal recurrence was not statistically different (1.6% after EBRT vs. 1.8% after VB). Although a higher rate of pelvic recurrence after VB was observed (3.8% vs. 0.5%, $p = .02$), the first-failure analysis showed that most patients with pelvic recurrence had simultaneous distant metastases, and the 5-year rates of distant metastases did not differ significantly between the two groups. OS was not statistically different between the two groups. Although there was significant reduction in the risk of acute grade 1–2 gastrointestinal toxicity in the VB group compared with the EBRT group (12.6% vs. 53.8%), these differences were no longer statistically significant after 24 months.

The 2012 updated Cochrane review [8] on the role of adjuvant RT in early-stage disease (examined eight trials: ASTEC/EN.5 [6], GOG#99 [4], PORTEC-1 [2], PORTEC-2 [7], and trials by Aalders et al. in 1980 [9], Soderini et al. in 2003 [10], and Sorbe et al. in both 2009 [11] and 2011 [12]) concluded that EBRT reduces LRR, but with significant acute and late toxicities (Table 2) and reduced quality of life. Six of the eight RCTs were high quality, and no significant heterogeneity in the data was observed.

High-Risk Disease

The HR group includes patients with early-stage disease that have higher potential risks of recurrence compared with the HIR group. HR also includes all early-stage disease with uterine serous carcinoma (USC) or clear cell histology, historically classified as type II endometrial cancers, which can be aggressive and lethal even at early stages [13]. There is some increasing evidence that grade 3 endometrioid adenocarcinomas may be better categorized as type II [14]. GOG#94 evaluated the role of whole-abdominal irradiation (WAI) in patients with Stage I-II UPSC and clear cell carcinoma [15]. Thirty-three patients received WAI with pelvic boost after hysterectomy and BSO with full staging. The 5-year OS was less than 40% for serous histology compared to just above 60% in clear cell histology. Given these poor outcomes, subsequent research started considering chemotherapy regimens.

A phase II nonrandomized prospective trial conducted by Obermair et al. [16] evaluated stage I–IV USC patients (48% were stage I–II) who underwent complete surgical staging followed by four cycles of taxane and platinum-based

Table 1. Randomized trials on adjuvant radiotherapy: inclusion criteria

Study	Histology	Study population: risk groups	Comments
PORTEC-1	Endometrial adenocarcinoma (squamous features, not otherwise specified, adenosquamous); serous and clear cell carcinoma	Intermediate risk <ul style="list-style-type: none"> • Endometrial adenocarcinoma of any histologic type • Stage I based on uterine factors • Grade 1 histology and myometrial invasion of $\geq 50\%$ • Grade 2 histology with any myometrial invasion • Grade 3 histology with myometrial invasion of $< 50\%$ High-intermediate risk <ul style="list-style-type: none"> • Age of > 60 years with grade 1 or 2 histology and myometrial invasion of $> 50\%$ • Age of > 60 with grade 3 histology and myometrial invasion of $< 50\%$ 	Routine LND not required
GOG#99	Endometrial adenocarcinoma	Intermediate risk <ul style="list-style-type: none"> • Positive myometrial invasion of any degree, based on FIGO staging prior to 2008: stages IB, IC, IIA (occult), and IIB (occult) • All histologic grades High-intermediate risk <ul style="list-style-type: none"> • Age of < 50 years old and <ul style="list-style-type: none"> ◦ Grade 2 or 3 histology ◦ Positive lymphovascular invasion ◦ Myometrial invasion to the outer third • Age of 50–69 years, with 2 of the 3 factors listed above • Age of 70 years or more, with 1 of the 3 factors listed above 	Excluded serous or clear-cell histology Full surgical staging including bilateral retroperitoneal pelvic lymph node dissection required
ASTEC/EN.5	All types	Intermediate risk <ul style="list-style-type: none"> • Any histology other than papillary serous and clear cell • Stage IA and IB (grade 3) • Stage IC and IIA (grades 1 and 2) High risk <ul style="list-style-type: none"> • All papillary serous and clear cell histology • Stages IC (grade 3), IIA (grade 3), and IIB 	Routine LND not required
PORTEC-2	Endometrial adenocarcinoma	High-intermediate risk <ul style="list-style-type: none"> • Age of > 60 years, stage 1C, grade 1 or 2; or stage 1B, grade 3 • Stage 2A disease, any age (apart from grade 3 with greater than 50% myometrial invasion) 	Excluded serous, clear-cell, or staging LND

Enrollment criteria of phase III randomized control trials of adjuvant radiation for early-stage endometrial cancer differed by histology, staging requirements, and definitions of intermediate risk, high-intermediate risk, and high risk.
Abbreviation: LND, lymph node dissection.

chemotherapy and EBRT with or without VB. Thirty percent of stage I patients recurred compared with 40% in stage II. Two-year survival was 85.6% for stage I–II versus 68.8% for stage III. Another phase II trial studied the efficacy of a “sandwich” regimen in 72 patients with stage I–IV USC (82% were stage I–II) who received postoperative treatment with 3 cycles of taxane

and platinum-based chemotherapy, followed by EBRT to 45 Gy with or without VB, followed by an additional 3 cycles of chemotherapy [17]. Progression free survival (PFS) and OS for stage I–II were 65.5 ± 3.6 and 76.5 ± 4.3 months, respectively. Other retrospective studies in USC have shown improved PFS but no difference in OS [18].

Table 2. Randomized trials on adjuvant radiotherapy: toxicities and complications**PORTEC-1**

- Late complications were reported in 25% in the RT group and 6% in the control group ($p < .001$).
- Most complications were gastrointestinal tract.
- Grade 3 complications occurred in 7 patients.
- Four patients with small-bowel complication needed surgical intervention.
- Three patients had sigmoid stenosis; sigmoid resection was done.
- Six of the 7 grade 3 complications occurred in the RT group.
- One patient died of an exacerbation of Crohn's disease soon after RT.

GOG#99

- The frequency and severity of hematologic, gastrointestinal, genitourinary, and cutaneous toxicities were significantly higher in the RT group.
- Two patients in the RT group died of complications involving intestinal injury.
- Although the frequency of bowel obstruction in the 2 arms was not statistically different, 6 patients in the RT group experienced grade 3 or 4 obstruction compared with only 1 patient in the NAT group.

ASTEC/EN.5

- The frequency of acute toxicity was higher in the EBRT group compared with the control group.
- Severe or life-threatening toxicity was seen in 3 patients ($<1\%$) in the control group compared with 14 patients (3%) after EBRT.
- Late toxicity (mainly gastrointestinal and genitourinary) was more common after EBRT.
- Severe toxicity was reported in 15 patients (3%) in the control group compared with 30 patients (7%) in the EBRT group.
- Four patients (1%) (all from the EBRT group) reported life-threatening toxicity.

PORTEC-2

- Late grade 3 GI toxicity were reported in 4 patients (2%) who received EBRT and in 1 patient ($<1\%$) who received VB.
- No treatment-related deaths occurred.
- Grade 1–2 mucosal atrophy increased significantly after VB compared with EBRT.
- Grade 3 atrophy was reported in 1 patient ($<1\%$) who received EBRT and 4 patients (2%) who received VB.

The table shows a summary of toxicity profiles of the phase III randomized controlled trials using adjuvant radiation for early stage endometrial cancer. Abbreviations: EBRT, external beam radiation therapy; GI, gastrointestinal; NAT, no additional therapy; RT, radiation therapy.

Combined Adjuvant Chemotherapy and Radiation

Four randomized trials evaluated the use of chemotherapy in early-stage disease (Table 3). An Italian study randomized 345 patients to chemotherapy or RT. No PFS or OS difference was seen between the two arms [19]. After randomizing 475 patients to chemotherapy or RT, the Japanese GOG concluded that chemotherapy had no PFS or OS benefit over RT [20]. In their ad hoc analysis, they found that chemotherapy significantly improved PFS and overall survival in a “high-to-intermediate-risk group” (stage IC in patients over 70 years or with grade 3 or stage II or IIIA with positive cytology) (PFS was 84% vs. 66%, $p = .024$; and OS was 90% vs. 74%, $p = .006$). A Finnish trial randomized 156 patients to RT with or without chemotherapy [21]. Although the sequential chemoradiotherapy tended to increase PFS by 7 months ($p = .134$) and to postpone death by 14 months ($p = .148$), no OS benefit was observed.

Two trials (NSGO-EC-9501/EORTC-55991 and MaNGO ILIAD-III) randomized 540 patients to RT with or without chemotherapy [22]. Their pooled results showed that RT with chemotherapy significantly improved 5-year PFS compared with RT alone (82% vs. 75%, hazard ratio 0.62; 95% CI: 0.40–0.97). OS approached statistical significance (hazard ratio 0.69, 95% CI: 0.46–1.03; $p = .07$). However, it should be noted that LND was optional (only 26% had LND and 46% with unknown status), and the concept of HR disease was not pre-defined in the inclusion criteria but was left to the discretion of the participating departments. The utility of combining chemotherapy with radiation for adjuvant treatment of early-stage

endometrial cancer, specifically those meeting HIR criteria, will hopefully be determined by results from GOG#249 (VB plus chemotherapy compared with EBRT) (Table 3).

Current Guidelines and Practice Patterns**Current Guidelines**

National Comprehensive Cancer Network (NCCN) guidelines for the treatment of uterine-confined endometrial cancer support the concept of selecting more aggressive adjuvant therapy (VB and EBRT) as tumor stage and/or grade worsen, taking into consideration other adverse risk factors (i.e., age, positive lymphovascular invasion, tumor size). For the highest-risk early-stage disease, the use of adjuvant chemotherapy is a category 2B recommendation. For USC and clear cell histology, NCCN recommends comprehensive surgical debulking and adjuvant treatment with taxane and platinum-based chemotherapy with or without tumor-directed RT depending on stage [23]. American Congress of Obstetricians and Gynecologists and Society of Gynecologic Oncology (SGO) practice guidelines state that patients with stage I disease may be offered adjuvant RT to decrease LRR, with appropriate counseling that there is no evidence to suggest it will improve survival, and benefits should outweigh potential side effects and cost concerns (level B evidence) [24].

Practice Patterns

In 1996, Partridge et al. [25] published one of the earliest reports that evaluated national practice in treating endometrial cancer. After evaluating 36,341 endometrial cancer patients

Table 3. Randomized trials on adjuvant chemotherapy

Study	Study population	Intervention	Comments
Maggi et al. (Italy) [19]	<ul style="list-style-type: none"> FIGO stage IC grade 3 or stage IIA–IIB grade 3 with 50% or more myometrial invasion FIGO stage III disease 	<p>Adjuvant chemotherapy: cyclophosphamide (600 mg/m²), doxorubicin (45 mg/m²), and cisplatin (50 mg/m²) given every 4 weeks for 5 cycles</p> <p>Adjuvant pelvic RT: 45–50 Gy in 5–7 weeks</p>	Patients who had lymph node involvement received additional para-aortic lymph node irradiation.
Susumu et al. (Japanese Gynecologic Oncology Group) [20]	<ul style="list-style-type: none"> FIGO stage IC–IIIC endometrial carcinoma with >50% myometrial invasion 	<p>Adjuvant chemotherapy: cyclophosphamide (333 mg/m²), doxorubicin (40 mg/m²), and cisplatin (50 mg/m²) every 4 weeks for 3 or more courses</p> <p>Adjuvant pelvic RT: anteroposterior fields, 45–50 Gy within 4–6 weeks</p>	Para-aortic irradiation was added in 6% with para-aortic metastases, and 3% received brachytherapy.
Kuoppala et al. (Finland) [21]	<ul style="list-style-type: none"> Patients with locoregional high-risk endometrial carcinoma FIGO stage IA–IB grade 3 Stage IC–IIIA grade 1–3 	<p>Adjuvant chemotherapy: cisplatin (50 mg/m²), epirubicin (60 mg/m²), and cyclophosphamide (500 mg/m²). The first cycle was given after 1–2 weeks after the operation, the second was given during the pause in RT, and the last was given within 2 weeks after the completion of the second RT course</p> <p>Adjuvant pelvic RT: in 2 courses of 28 Gy each, 3 weeks apart</p>	
Hogberg et al. (NSGO-EC-9501/EORTC-55991) [22]	<ul style="list-style-type: none"> Surgical stage I, II, IIIA (positive peritoneal fluid cytology only), or IIIC (positive pelvic lymph nodes only) High risk for micrometastatic disease to qualify for adjuvant therapy (according to departmental guidelines) Serous, clear-cell, or anaplastic carcinomas (regardless of risk factors) 	<p>Adjuvant chemotherapy: before 2004, 4 courses of cisplatin (50 mg/m²) and doxorubicin (50 mg/m²) or epirubicin (75 mg/m²); thereafter, paclitaxel (175 mg/m²), epirubicin (60 mg/m²), and carboplatin; AUC (5-6)</p> <p>Adjuvant pelvic RT: with or without VB</p>	<p>LND was optional.</p> <p>Examples of high-risk factors</p> <ul style="list-style-type: none"> Grade 3 >50% myometrial invasion DNA nondiploidy
GOG#249	<ul style="list-style-type: none"> Stage I, HIR (grade 2 or 3 tumor, presence of LVSI or outer-half myometrial invasion), meeting one of the following criteria <ul style="list-style-type: none"> Age of ≥70 years with 1 risk factor Age of ≥50 years with 2 risk factors Age of ≥18 years with 3 risk factors Stage II Serous or clear-cell histology with or without other risk factors (the disease is uterine-confined and with negative peritoneal cytology) 	<p>Adjuvant chemotherapy: VB and within 3 weeks, paclitaxel IV and carboplatin IV, repeated every 21 days for up to 3 courses</p> <p>Adjuvant pelvic RT: 5–6 weeks (total of 25–28 fractions)</p> <p>Clear-cell or serous histology may also undergo VB</p>	LND was not mandatory but required negative CT/MRI.

The table shows a summary of enrollment criteria and treatments provided in randomized trials incorporating chemotherapy into adjuvant treatment of early stage endometrial cancer.

Abbreviations: AUC, target area under concentration; HIR, high-intermediate risk; LND, lymph node dissection; LVSI, lymphovascular invasion; RT, radiation therapy; VB, vaginal brachytherapy.

from 1986 to 1992, minimal differences in multimodality therapy by the region of the country were observed. However, race influenced RT, whereby blacks were more likely to receive multimodality therapy or no therapy; this trend might be related

to higher stage at presentation. Also, a decrease in RT over time (41.9% in 1986–1987 to 34.8% in 1992) was observed.

In 2007, Lee et al. [26] published a retrospective analysis using the Surveillance, Epidemiology, and End Results (SEER)

data from 1988 to 2002. After evaluating 26,923 women with stage I and II endometrial adenocarcinoma, they found that geographic location influenced both the type and the utilization rate of RT, with significant heterogeneity across the country. The relative frequency of RT increased with worsening stage and grade. In stage I disease, the authors noticed that increasing substage and grade increased the odds of EBRT compared with VB alone. Although RT use was not affected by the age at diagnosis or race until the age of 70, it decreased substantially afterward. The use of EBRT for patients who had LND had been dropping especially for blacks (odds ratio of 2002 vs. 1988: 0.3 for blacks vs. 0.6 for whites). Although this study was the largest report of RT use in the U.S., the authors acknowledged the limited information in the individual registries in the SEER database (different registry start dates and the characteristics of patient subgroups with respect to disease status and race).

Similar trends were noticed by Patel et al. [27] after they reviewed 9,815 patients with stage I and II endometrial adenocarcinoma using the SEER database from 1985 to 2005 and found significant increase in the annual use of VB (12.9% in 1995 vs. 32.8% in 2005). On the contrary, the use of EBRT (56.1% in 1995 vs. 45.8% in 2005) and VB with EBRT (31.0% vs. 21.4%) significantly dropped between 1995 and 2005. Those without LND were more likely to receive EBRT or VB with EBRT and less likely to receive VB than those who underwent LND.

In 2013, Ko et al. [28] compared the use of RT before and after publication of PORTEC-1 (1996–1999 vs. 2000–2003) and GOG#99 (2000–2003 vs. 2004–2007) in the SEER database. RT use did not increase for the IR and HIR groups following PORTEC-1 publication or following GOG#99 publication, with approximately 50% of eligible patients receiving radiation. In their secondary analysis post-GOG#99, significantly fewer eligible women received EBRT (HIR: 77% pre vs. 65% post; IR: 72% pre vs. 58% post), more received VB (HIR: 53% pre vs. 59% post; IR 55% pre vs. 62% post), and fewer received combination EBRT with VB (HIR: 32% pre vs. 25% post; IR: 28% pre vs. 21% post). However, great heterogeneity in the use of radiation existed across the country without a discernible pattern by census region, even after adjusting for variance in distributions of risk factors. Nor were there patterns to explain areas that increased radiation versus areas that decreased radiation use. Similar trends were noticed after PORTEC-1 publication but were not statistically significant.

Naumann et al. [29, 30] surveyed the use of adjuvant RT by members of the SGO in 1999 and 2005. In 2005, the majority did not recommend any further treatment when no myometrial invasion or less than 50% uterine wall invasion was observed, except in poorly differentiated tumors. This survey, which was conducted after publication of PORTEC-1 and GOG#99, revealed that only 50% of respondents recommended pelvic RT in cases with moderately to poorly differentiated tumors and outer-half invasion. Observation after surgical staging increased as compared with 1999. Increasing use of VB and declining use of EBRT was a noticeable trend, especially in stage IB, grade 3 and all stage IC. Respondents from the 2005 survey were more likely to perform complete LND and less likely to recommend RT. Most also recommended no RT in the IR group. VB was favored over EBRT in most situations, except

in high-grade tumors with outer myometrial invasion. In contrast with previous studies, there was no significant difference in RT use based on the region of the country, the type of practice (academic vs. private), and the age of respondents.

Small et al. [31] evaluated the use of adjuvant RT in endometrial adenocarcinoma in a survey targeting members of the American Society for Therapeutic Radiology and Oncology (RTOG) in 2003. They found that 54% of the respondents believed that there was increasing referral for VB compared with EBRT only in negative nodal sampling/dissections. Forty percent of the respondents would treat the upper third of the vagina, and 54% would treat the upper half and would target the entire vagina in special situations (grade 3 tumor [19.8%], papillary serous or clear cell histology [26.6%]). The dose fractionation in high dose rate (HDR)-VB varied. Of the 4 most commonly reported schemas, the 7 Gy in 3 fractions delivered to 0.5 cm was the only HDR-alone fractionation scheme that was recommended by the American Brachytherapy Society.

The findings of the above survey were replicated in an international survey sent to the Gynecologic Cancer Intergroup (GCIG) members (Austria, Germany, Australia, New Zealand, Europe, the U.S. [GOG and RTOG], Japan, Italy, Great Britain, Canada, Scandinavia, Scotland, and Spain) in 2009 [32]. The most common indication for EBRT was stage IC or higher (48.5%) followed by stage IB, grade 2 or higher (30.3%) and positive LND (9.1%). EBRT dosing was relatively uniform across GCIG members. The upper border of the pelvic field was L4/L5 in 42.4% and L5/S1 in 39.4% of the respondents.

Evaluating the Cost-Effectiveness of Treatment Strategies

Several studies have examined the cost-effectiveness of adjuvant RT given the current inconclusive data from clinical trials. In 1997, Konski et al. [33] analyzed the cost from the payer's perspective for six different RT strategies: observation, low dose rate (LDR)-VB, LDR-VB and EBRT, EBRT only, HDR-VB, and EBRT/HD-VB for stage I disease, using retrospective data. Using cost-minimization analysis, observation was the most cost effective (\$120.60), with LDR having the next lowest cost (\$3,466.62), with HDR being the third most expensive (\$5,381.19), followed by EBRT/LDR (\$7,238.55), with EBRT/HDR-VB having the highest cost (\$9,153.14).

Barnes et al. [34] used the hospital-based costs per patient in evaluating three different treatment strategies. The strategies included the treatment approach at the authors' institution of total abdominal hysterectomy, bilateral salpingo-oophorectomy (TAH/BSO) with LND, followed by RT if greater than stage I; TAH/BSO with LND reserved for cases of myometrial invasion according to the NCCN clinical algorithm at that time, with RT if greater than stage IA, grade 1; and SGO clinical practice guidelines in 1998 for TAH/BSO with intraoperative frozen section and surgical consultation with a "surgical oncologist" for comprehensive staging, with radiation if greater than stage IA, grade 1. The costs were \$12,778.52 for algorithm 1, \$15,997.02 for algorithm 2, and \$17,343.33 for algorithm 3. The authors concluded that their institutional strategy of comprehensive surgical staging and limited use of RT appeared to be more cost-efficient. However, they did not

take into account the short- and long-term complications of comprehensive surgical staging.

Several early studies also suggested cost savings when adjuvant RT was not used in early-stage disease. Orr et al. [35] found a cost of \$3.8 million for VB in 444 patients with stage I disease after comprehensive surgical staging. These early cost-minimization studies were limited by the fact that the majority of the data used in the analyses was often being driven by retrospective evaluation of GOG#33 data that used the old FIGO clinical stage I–II, making their conclusions hard to apply to the current histopathological staging system [36].

In 1999, Ashih et al. [37] modeled life expectancy of women with early (stage I) disease treated with surgery alone compared with surgery and RT and with no treatment in a cost-effectiveness analysis. The authors excluded nonmedical costs and costs for treatment of recurrent/terminal cancer, and quality of life data were not available. Using retrospective data, they demonstrated that the life years gained are mainly attributed to hysterectomy (range, 18.9–34.5 years) compared with adjuvant RT (range, 1.9–4.5 years), and the cost per life year gained from hysterectomy (with an assumed cost of \$9,000) is affected by age at diagnosis, grade, and comorbidity but is very low (average of \$1,000) under all circumstances. The incremental cost per life years gained from adjuvant RT is also low but higher than hysterectomy alone. The calculated 5% overall increment in survival was attributed to adjuvant RT in high-risk cases, but with a much smaller effect on life years gained and at a significantly higher cost (\$4,240–\$33,448).

Barakat et al. [38] reported their institutional experience over a 12-year period. Cost data were available from 1999–2004 and demonstrated a significant decrease in the median cost of EBRT when comparing 1995–1998 with 1999–2004 (\$19,085 vs. \$17,314). This difference was attributed to a significant decrease in the use of EBRT from 16% to 9%. However, the cost of VB increased significantly from a median of \$904 to \$3,325.

In 2004, Fanning et al. [39] evaluated IR patients by comparing the survival, morbidity, and cost of treatment of VB (both LDR and HDR) to no radiation, from a payer perspective. This resulted in an overall cost per life saved in LDR (\$191,565 for all patients and \$63,855 for intermediate-risk patients) compared with HDR (\$116,292 for all patients and \$38,764 for intermediate-risk patients).

The low uptake might be also related to the shifting interest of the practitioner toward patient-focused management strategies that value quality of life. Upfront adjuvant radiation therapy to reduce future recurrences must be weighed against the physical and emotional burden of salvage therapy. This might explain the trend of using VB to minimize toxicity even before the publication of PORTEC-2.

Lachance et al. [40] designed a decision analysis model in 2007 to compare four treatment options for stage I disease: observation, HDR-VB, EBRT, or HDR with EBRT. Not

surprisingly, observation was the most cost-effective (\$437 million per 100,000 women) and HDR with EBRT had the highest cost (\$2.93 billion per 100,000 women). However, HDR-VB resulted in the highest 5-year quality adjusted survival at 86%, yielding an additional 8,200 quality-adjusted survivors compared with observation at a cost of \$65,900 per survivor.

Knops et al. [41] developed a tool to assess the benefit and harm in RT decision making. Using a decision model that incorporated the outcomes from 3 trials (PORTEC-1, GOG#99, and ASTEC) and a cohort of 1,000 intermediate-risk patients, the model predicted that recurrence (at a baseline rate of 10%) would be prevented by RT in 60 patients, and 908 patients would neither benefit nor be harmed from treatment, but 28 patients would suffer severe complications, and 4 patients would be expected to die.

Rankins et al. [42] evaluated intermediate-risk patients by comparing the estimated health and economic outcomes of EBRT compared with no treatment, using GOG#99 and PORTEC-1 data. The cost-effectiveness model was highly sensitive to the probability of recurrence and the efficacy of EBRT in the sensitivity analysis, with mean cost of observation at \$5,016 versus \$21,159 for EBRT. The incremental cost-effectiveness per recurrence prevented was \$225,215; however, in the HIR subgroup, this was reduced to a more acceptable \$50,000.

Havrilesky et al. [43] published a Markov model to evaluate the cost-effectiveness in grade 3 tumors. Using the SEER database and two randomized trials, they found that LND had an incremental cost-effectiveness ratio of \$40,183 per quality-adjusted life year compared with no LND. For grades 2 and 3 combined, the analysis revealed a much lower likelihood of finding LND cost-effective and concluded that a clinical trial assessing the survival effect of LND might be warranted.

DISCUSSION

The management of early-stage endometrial cancer has been studied extensively. However, the controversy around the use of RT still exists, partly because no survival benefit was observed in prospective trials; it was argued that surgical staging was not mandatory in the European studies, and this might affect their outcome. However, this argument did not hold after the publication of GOG#99, in which appropriate surgical staging was mandatory.

The ambivalence toward RT use in the U.S. after the publication of the above trials is well demonstrated in many studies. It has been shown that a delay of up to 9 years may be required to observe high adoption rates, and so it just may be too early to observe changes in clinical practice shortly after a published clinical trial [44]. The low uptake also might be related to the shifting interest of the practitioner toward patient-focused management strategies that value quality of life. Upfront adjuvant radiation therapy to reduce future recurrences must be weighed against the physical and emotional burden of salvage therapy. This might explain the trend of using VB to minimize toxicity even before the publication of PORTEC-2. These controversies led to an abundance of cost-effectiveness studies, but they were lacking pertinent aspects such as quality-of-life data. Future studies could address these important aspects.

Sending a new survey to SGO members may provide an update of current practice patterns, the potential factors that influence these patterns, the efficacy of disseminating trial results and new guidelines, and the practical aspects of affecting clinical practice. The noticeable discrepancy in the total and per-fractionation doses observed in the RTOG survey and how they affect clinical outcomes may also present potential areas for future research.

CONCLUSION

In the U.S., the adoption of the results of PORTEC-1 and GOG#99 has been inconsistent, even for the highest-risk patients. Although the use of adjuvant RT remains controversial, it may be particularly beneficial for the highest-risk group. Future studies should address defining quality-of-care

measures, including prioritizing outcomes and evaluating factors that are driving current practices of adjuvant radiation for patients with early-stage endometrial cancer.

AUTHOR CONTRIBUTIONS

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DISCLOSURES

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REFERENCES

1. Straughn JM Jr., Huh WK, Kelly FJ et al. Conservative management of stage I endometrial carcinoma after surgical staging. *Gynecol Oncol* 2002;84:194–200.
2. Creutzberg CL, van Putten WL, Koper PC et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: Multicentre randomised trial. PORTEC Study Group. *Post Operative Radiation Therapy in Endometrial Carcinoma*. *Lancet* 2000;355:1404–1411.
3. Creutzberg CL, Nout RA, Lybeert ML et al. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. *Int J Radiat Oncol Biol Phys* 2011;81:e631–e638.
4. Keys HM, Roberts JA, Brunetto VL et al. A phase III trial of surgery with or without adjuvant external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: A Gynecologic Oncology Group study. *Gynecol Oncol* 2004;92:744–751.
5. Creutzberg CL, van Putten WL, Koper PC et al. Survival after relapse in patients with endometrial cancer: Results from a randomized trial. *Gynecol Oncol* 2003;89:201–209.
6. Blake P, Swart AM, Orton J et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): Pooled trial results, systematic review, and meta-analysis. *Lancet* 2009;373:137–146.
7. Nout RA, Smit VT, Putter H et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): An open-label, non-inferiority, randomised trial. *Lancet* 2010;375:816–823.
8. Kong A, Johnson N, Kitchener HC et al. Adjuvant radiotherapy for stage I endometrial cancer. *Cochrane Database Syst Rev* 2012;4:CD003916.
9. Aalders J, Abeler V, Kolstad P et al. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: Clinical and histopathologic study of 540 patients. *Obstet Gynecol* 1980;56:419–427.
10. Soderini A, Anchezar J, Sardi J. Role of adjuvant radiotherapy (RT) in intermediate risk (1b G2-3-1C) endometrioid carcinoma (EC) after extended staging surgery (ESS). Preliminary reports of a randomized trial. *Int J Gynecol Cancer* 2003;13(suppl 1):Abstract P0147:78.
11. Sorbe B, Nordström B, Mäenpää J et al. Intravaginal brachytherapy in FIGO stage I low-risk endometrial cancer: A controlled randomized study. *Int J Gynecol Cancer* 2009;19:873–878.
12. Sorbe B, Horvath G, Andersson H et al. External pelvic and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma—a prospective randomized study. *Int J Radiat Oncol Biol Phys* 2012;82:1249–1255.
13. Brinton LA, Felix AS, McMeekin DS et al. Etiologic heterogeneity in endometrial cancer: Evidence from a Gynecologic Oncology Group trial. *Gynecol Oncol* 2013;129:277–284.
14. Viswanathan AN, Macklin EA, Berkowitz R et al. The importance of chemotherapy and radiation in uterine papillary serous carcinoma. *Gynecol Oncol* 2011;123:542–547.
15. Sutton G, Axelrod JH, Bundy BN et al. Adjuvant whole abdominal irradiation in clinical stages I and II papillary serous or clear cell carcinoma of the endometrium: A phase II study of the Gynecologic Oncology Group. *Gynecol Oncol* 2006;100:349–354.
16. Obermair A, Mileskin L, Bolz K et al. Prospective, non-randomized phase 2 clinical trial of carboplatin plus paclitaxel with sequential radical pelvic radiotherapy for uterine papillary serous carcinoma. *Gynecol Oncol* 2011;120:179–184.
17. Einstein MH, Frimer M, Kuo DY et al. Phase II trial of adjuvant pelvic radiation “sandwiched” between combination paclitaxel and carboplatin in women with uterine papillary serous carcinoma. *Gynecol Oncol* 2012;124:21–25.
18. Fader AN, Nagel C, Axtell AE et al. Stage II uterine papillary serous carcinoma: Carboplatin/paclitaxel chemotherapy improves recurrence and survival outcomes. *Gynecol Oncol* 2009;112:558–562.
19. Maggi R, Lissoni A, Spina F et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: Results of a randomized trial. *Br J Cancer* 2006;95:266–271.
20. Susumu N, Sagae S, Udagawa Y et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: A Japanese Gynecologic Oncology Group study. *Gynecol Oncol* 2008;108:226–233.
21. Kuoppala T, Mäenpää J, Tomas E et al. Surgically staged high-risk endometrial cancer: Randomized study of adjuvant radiotherapy alone vs. sequential chemo-radiotherapy. *Gynecol Oncol* 2008;110:190–195.
22. Hogberg T, Rosenberg P, Kristensen G et al. A randomized phase-III study on adjuvant treatment with radiation (RT) +/- chemotherapy (CT) in early stage high-risk endometrial cancer (NSGO-EC-9501/EORTC 55991). *J Clin Oncol* 2007;25:abstract 5503.
23. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Uterine Neoplasms, Version 1.2014. http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed April 30, 2014.
24. ACOG Bulletin: Management of Endometrial Cancer. http://www.acog.org/Resources_And_Publications/Practice_Bulletins/Committee_on_Practice_Bulletins_-_Gynecology/Management_of_Endometrial_Cancer. Accessed April 30, 2014.
25. Partridge EE, Shingleton HM, Menck HR. The National Cancer Data Base report on endometrial cancer. *J Surg Oncol* 1996;61:111–123.
26. Lee CM, Szabo A, Shrieve DC et al. Descriptive nomograms of adjuvant radiotherapy use and patterns of care analysis for stage I and II endometrial adenocarcinoma: A surveillance, epidemiology, and end results population study. *Cancer* 2007;110:2092–2100.
27. Patel MK, Cote ML, Ali-Fehmi R et al. Trends in the utilization of adjuvant vaginal cuff brachytherapy and/or external beam radiation treatment in stage I and II endometrial cancer: A surveillance, epidemiology, and end-results study. *Int J Radiat Oncol Biol Phys* 2012;83:178–184.
28. Ko EM, Funk MJ, Clark LH et al. Did GOG99 and PORTEC1 change clinical practice in the United States? *Gynecol Oncol* 2013;129:12–17.
29. Naumann RW, Higgins RV, Hall JB. The use of adjuvant radiation therapy by members of the Society of Gynecologic Oncologists. *Gynecol Oncol* 1999;75:4–9.
30. Naumann RW, Coleman RL. The use of adjuvant radiation therapy in early endometrial cancer by members of the Society of Gynecologic Oncologists in 2005. *Gynecol Oncol* 2007;105:7–12.
31. Small W Jr., Erickson B, Kwakwa F. American Brachytherapy Society survey regarding practice

patterns of postoperative irradiation for endometrial cancer: Current status of vaginal brachytherapy. *Int J Radiat Oncol Biol Phys* 2005;63:1502–1507.

32. Small W Jr., Du Bois A, Bhatnagar S et al. Practice patterns of radiotherapy in endometrial cancer among member groups of the gynecologic cancer intergroup. *Int J Gynecol Cancer* 2009;19:395–399.

33. Konski AA, Bracy PM, Jurs SG et al. Cost minimization analysis of various treatment options for surgical stage I endometrial carcinoma. *Int J Radiat Oncol Biol Phys* 1997;37:367–373.

34. Barnes MN, Roland PY, Straughn M et al. A comparison of treatment strategies for endometrial adenocarcinoma: Analysis of financial impact. *Gynecol Oncol* 1999;74:443–447.

35. Orr JW Jr., Holimon JL, Orr PF. Stage I corpus cancer: Is teletherapy necessary? *Am J Obstet Gynecol* 1997;176:777–788; discussion 788–789.

36. Morrow CP, Bundy BN, Kurman RJ et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: A Gynecologic Oncology Group study. *Gynecol Oncol* 1991;40:55–65.

37. Ashih H, Gustilo-Ashby T, Myers ER et al. Cost-effectiveness of treatment of early stage endometrial cancer. *Gynecol Oncol* 1999;74:208–216.

38. Barakat RR, Lev G, Hummer AJ et al. Twelve-year experience in the management of endometrial cancer: A change in surgical and postoperative radiation approaches. *Gynecol Oncol* 2007;105:150–156.

39. Fanning J, Hoffman ML, Andrews SJ et al. Cost-effectiveness analysis of the treatment for intermediate risk endometrial cancer: Postoperative brachytherapy vs. observation. *Gynecol Oncol* 2004;93:632–636.

40. Lachance JA, Stukenborg GJ, Schneider BF et al. A cost-effective analysis of adjuvant therapies for the treatment of stage I endometrial adenocarcinoma. *Gynecol Oncol* 2008;108:77–83.

41. Knops AM, Goossens A, Burger MPM et al. A tool to balance benefit and harm when deciding about adjuvant therapy. *Br J Cancer* 2009;100:913–917.

42. Rankins NC, Secord AA, Jewell E et al. Cost-effectiveness of adjuvant radiotherapy in intermediate risk endometrial cancer. *Gynecol Oncol* 2007;106:388–393.

43. Havrilesky LJ, Chino JP, Myers ER. How much is another randomized trial of lymph node dissection in endometrial cancer worth? A value of information analysis. *Gynecol Oncol* 2013;131:140–146.

44. Yuan CT, Nembhard IM, Stern AF et al. Blueprint for the dissemination of evidence-based practices in health care. *Issue Brief (Commonw Fund)* 2010;86:1–16.

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