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The Role of Adjuvant Radiation in High Risk Early-Stage Endometrial Cancer

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Abstract

Endometrial cancer is the most commonly diagnosed malignancy of the female genital tract in the United States. The role of adjuvant radiation for the treatment of patients with early stage disease is still heavily debated, as no overall survival benefit has been demonstrated in large prospective trials. There is, however, evidence to suggest a decrease in recurrence risk with administration of adjuvant radiotherapy, especially in patients with high-risk features. In this review, we describe the relevant literature to date, define how we determine which patients are considered high or intermediate risk, and describe the findings related to the addition of chemotherapy to adjuvant brachytherapy.

Keywords: Endometrial cancer; Early stage; Adjuvant radiation

Introduction

In the United States, endometrial cancer is the most commonly diagnosed gynecologic malignancy. In 2013, approximately 49,000 patients were diagnosed with an endometrial cancer, with approximately 8,000 deaths attributed to this disease [1]. A vast majority of patients are diagnosed with early stage disease since the most common symptom is irregular vaginal bleeding, which typically prompts timely medical evaluation. In patients with Stage I or II disease, certain risk factors including patient age, depth of myometrial invasion, presence or absence of lymphovascular invasion (LVSI), and tumour grade are predictive of recurrence risk. These risk factors are utilized to divide patients into subgroups of low risk, intermediate risk and high-intermediate risk for recurrence [2,3]. Patients with low risk disease have a recurrence risk of <5%, and thus will not benefit from adjuvant therapy [4]. Adjuvant therapy in the form of radiation has been explored for intermediate and high intermediate risk groups with mixed results. Decreases in the number of pelvic recurrences have been appreciated, however, there has been no improvement in overall survival reported. Adjuvant radiation can include pelvic radiation, vaginal cuff brachytherapy, or some combination of both. More recent studies have focused on comparing pelvic radiation therapy (RT) to vaginal cuff brachytherapy (VCB), as the vaginal cuff is most common site of recurrence. The combination of chemotherapy to VCB was recently explored in a prospective trial conducted by the Gynecologic Oncology Group (GOG) – initial findings from this study will also be discussed. This review presents a summary of the major clinical trials involving the use of adjuvant RT in the treatment of early stage endometrial cancer.

Endometrial Cancer Staging

Until approximately 25 years ago, endometrial carcinomas were assigned stage based on clinical assessment alone. In 1988, however, the International Federation of Gynecology and Obstetrics (FIGO) adopted a surgically-based staging system. Currently, a comprehensive surgical staging procedure for endometrial carcinoma includes: total hysterectomy, bilateral salpingo-ophorectomy (BSO), and systematic pelvic and aortic lymphadenectomy. After further analysis of contemporary evidence related to prognosis and survival outcomes, the original 1988 surgical staging system (Table 1) was more recently revised to the current 2009 staging guidelines (Table 2). It is important to keep in mind the change in staging for endometrial carcinoma, as it not only affects how we treat our patients, but also how we analyze and interpret the existing literature. Major changes between the 1988 system and the 2009 system include: combining non-invasive lesions and lesions with <50% myometrial invasion into Stage IA, removing cervical glandular involvement as a criteria for upstaging to Stage II, sub-division of Stage IIIC into IIIC1 or IIIC2 based on anatomic location of nodal involvement, and removal of positive peritoneal cytology as a criteria for Stage IIIA disease.

Stage	**Anatomic Involvement**
Stage I	Tumor confined to the uterine corpus
IA	No Myometrial Invasion
IB	<50% Myometrial Invasion
IC	≥ 50% Myometrial Invasion
Stage II	Cervical Involvement
IIA	Endocervical Glandular Involvement
IIB	Cervical Stromal Invasion
Stage III	
IIIA	Positive peritoneal cytology, and/or Tumor invasion into uterine serosa, and/or Adnexal involvement
IIIB	Vaginal Involvement
IIIC	Metastases to pelvic and/or pelvic lymph nodes
Stage IV	

IVA	Bladder and/or Bowel Involvement
IVB	Distant metastases, including abdominal disease, and/or Inguinal lymph node involvement

Table 1: 1998 FIGO Staging System for Endometrial Cancer.

Stage	**Anatomic Involvement**
Stage I	Tumor confined to the Uterine Corpus
IA	No or <50% Myometrial Invasion
IB	≥ 50% Myometrial Invasion
Stage II	Cervical Stromal Involvement
Stage III	Local and/or Regional Tumor Spread
IIIA	Tumor invasion into uterine serosa, and/or Adnexal involvement
IIIB	Vaginal and/or Parametrial Involvement
IIIC	Metastases to Lymph Nodes
IIIC1	Positive Pelvic Lymph Nodes
IIIC2	Positive Para-Aortic Lymph Nodes
Stage IV	
IVA	Bladder and/or Bowel Involvement
IVB	Distant metastases, including abdominal disease, and/or Inguinal lymph node involvement

Table 2: 2009 FIGO Staging System for Endometrial Cancer.

Adjuvant Whole Pelvic Radiation

Based upon the results of 2 large, prospective, randomized trials, current data demonstrate that there is no overall survival benefit from adjuvant pelvic RT in women with early stage endometrial cancer. However, this data does demonstrate that adjuvant RT can lead to reductions in pelvic disease recurrence and that there also exists a sub-group of high-intermediate risk patients who may benefit from adjuvant pelvic RT.

The PORTEC-1 Trial (Post Operative Radiation Therapy in Endometrial Carcinoma 1) was a multi-center, prospective, randomized trial designed to address the question of whether adjuvant pelvic RT leads to improved local-regional control and overall survival in patients with stage 1 endometrial carcinoma [2]. This trial was conducted from 1990 to 1997 in Europe and Canada. Women with presumed stage 1 disease [grade 1 with deep (≥ 50%) myometrial invasion, grade 2 with any depth of invasion, and grade 3 with superficial (<50%) invasion] who did not undergo lymphadenectomy at the time of hysterectomy and BSO were enrolled. A total of 715 patients were randomized to receive either no further adjuvant treatment (control arm, 361 patients) or adjuvant pelvic RT (treatment arm, 46 Gy, 354 patients). At a median follow-up time of 52 months, the 5-year actuarial overall survival rates did not differ between the control group and treatment group (81% versus 85%, p=0.31). The 5 year actuarial local-regional recurrence rate, however, was found to be significantly higher in the control group than the treatment group (14% versus 4%, p<0.001). Treatment-related complications were reported to occur in 6% of patients in the control group and 25% of patients in the radiation group (p<0.0001).

A prospective, randomized study was also performed by the Gynecologic Oncology Group (GOG-99) to determine if adjuvant pelvic RT results in lower recurrence risk and increased overall survival in women with endometrial carcinoma [3]. This trial enrolled 488 patients with intermediate risk endometrial adenocarcinoma (Stages IB, IC, and occult stages IIA-B) from 1987 to 1995. All patients were required to have undergone lymph node dissection at the time of hysterectomy and BSO. After surgery, patients were randomized to receive either no further adjuvant treatment or whole pelvic RT (50.4 Gy). At a median follow-up time of 69 months, the estimated 4 year survival did not differ significantly between the group that received no further treatment and the group that received radiotherapy (92% versus 86%, p=0.0557). The cumulative incidence of recurrence at 2 years was, however, found to be higher in the observation group than the RT group (12% versus 3%, p=0.007).

Defining a High Risk Population of Early Stage Patients

Sub-group analyses from the PORTEC-1 Trial and GOG 99 indicated that there exists a population of patients with Stage I and II disease that have a higher recurrence risk and therefore, would potentially benefit from adjuvant RT. Results from PORTEC-1 suggested that patients under the age of 60 years had a lower risk of loco-regional relapse (4% versus 10%, p=0.02). Also, tumours with Grade 3 histology were associated with a similar risk of locoregional recurrence as tumours with Grade 1 or 2 histology and deep invasion (approximately 10%), however, distant recurrences were more common with Grade 3 tumours (11% versus 5%, p=0.05). Multi-variate analyses revealed that cancer-related deaths were higher for patients over the age of 60 (HR 3.1, p=0.02) and for patients with Grade 3 tumours (HR 4.9, p=0.0008), suggesting this sub-group might benefit from adjuvant RT.

Another sub-set analysis was reported for patients with Stage IC Grade 3 tumours who were registered for and followed in the PORTEC-1 study, but excluded from randomization [5]. Ninety-nine patients with Stage IC Grade 3 disease were treated with adjuvant radiation. Loco-regional failures were found to 14% in this group (compared to 1-3% in enrolled patients) and distant failures occurred in 33% of patients in this group (compared to 3-8% in enrolled patients), further providing evidence that pelvic RT provides additional pelvic control when compared to observation. Distant failures in this higher risk group were frequent and additional adjuvant treatments, in addition to pelvic RT, may be warranted.

Similarly, GOG-99 defined a high-intermediate risk group of patients who accounted for a majority of the observed treatment differences. Risk criteria, as defined from regression models from data published in GOG-33, included: increasing age, Grade 2-3 histology, positive LVSI, and outer 1/3 myometrial invasion [6]. Sub-group analysis defined this high-intermediate risk group of patients as: (1) any age with 3 of the above risk factors, (2) age ≥ 50 years with 2 of the above risk factors, and (3) age ≥ 70 years with at least one of the above risk factors. One-third of the patients enrolled in the trial met criteria for high-intermediate risk. This group of patients accounted for almost two-thirds of cancer-related deaths and cancer recurrences.

While sub-group analyses of these large randomized trials suggest a benefit to administration of adjuvant RT for high-risk populations, the

original randomization was planned and powered for inclusion of all patients with early stage disease. This may help explain why no overall survival advantage was observed. Newer prospective studies looking at the role of adjuvant radiation have thus focused on this high-intermediate risk group, as these patients seem to have more to be gained from adjuvant therapies.

Adjuvant Vaginal Brachytherapy

Both the PORTEC-1 study and GOG-99 demonstrated a reduction in local-regional recurrence without an associated overall survival benefit. Specific anatomic sites of failure from these trials are summarized in Table 3. The majority of loco-regional recurrences occurred in the vagina. This has led to further investigation into the use of VCB instead of pelvic radiation as adjuvant treatment for early stage disease. The PORTEC-2 trial (Post Operative Radiation Therapy in Endometrial Carcinoma 2) was an open-label, non-inferiority, Dutch trial which randomized Stage I or IIA patients with high-intermediate risk features to receive adjuvant pelvic RT (46 Gy) or VCB (21 Gy high-dose rate in 3 fractions or 30 Gy low-dose rate) [7]. High intermediate risk was defined as: (1) >60 years old with Stage IC Grade 1 or 2 disease, (2) >60 years old with Stage IB Grade 3 disease, or (3) any age with Stage IIA Grade 1 or 2 disease with ≤ 50% myometrial invasion. Between 2002 and 2006, 427 patients were enrolled and randomized. The primary endpoint was vaginal recurrence. Median follow-up was 45 months. 5-year vaginal recurrence rates did not differ between the VCB group and the pelvic RT group (1.8% versus 1.6%, p=0.74). Loco-regional relapse also did not differ between the 2 groups (5.1% versus 2.2%, p=0.17). Rates of distant metastases in the VCB group (8.3%) did not differ significantly from the external beam group (5.7%, p=0.46). Overall survival (82.7% versus 78.1%, p=0.74) and disease-free survival (84.8% versus 79.5%, p=0.57) did not differ significantly. Subjects in the pelvic radiation arm experienced a significantly higher rate of acute grade 1-2 gastrointestinal side effects. A quality-of-life assessment was also performed, which revealed that patients that received VCB reported improved functioning and lower GI symptom scores [8]. These data suggest that adjuvant vaginal brachytherapy should be incorporated into the treatment of intermediate-risk endometrial cancer patients instead of pelvic radiation for local-regional control, with the knowledge that overall survival will not be improved.

	Vagina	Pelvis	Extra-Pelvic
GOG-99: Observation Group (n=202)	13 (6.4%)	5 (2.5%)	13 (6.4%)
GOG-99: Radiotherapy Group (n=190)	2 (1.1%)	1 (0.5%)	10 (5.3%)
PORTEC-1: Observation Group (n=360)	30 (8.3%)	10 (3.6%)	20 (5.6%)
PORTEC-1: Radiotherapy Group (n=354)	7 (2.0%)	4 (1.1%)	24 (6.8%)

Table 3: Sites of Endometrial Cancer Recurrence.

Combination Chemotherapy and Brachytherapy

Since neither pelvic nor vaginal vault radiation has been shown to improve overall survival or affect distant recurrence, adjuvant chemotherapy has been researched as a way to control local and distant recurrences. Doxorubicin, Cisplatin, and Taxol have been shown in previous studies by the Gynecologic Oncology Group (Protocols 107, 163 and 177) to have activity in advanced and recurrent endometrial cancer [9-11]. To assess the effects of combination chemotherapy and vaginal cuff brachytherapy in high-risk early stage patients, the GOG designed protocol 249. Patients with high-intermediate risk Stage I disease (as defined previously in GOG-99), occult Stage II disease, and Stage I-II clear cell and papillary serous histology were randomized to receive VCB followed by 3 cycles of intravenous carboplatin and paclitaxel versus whole pelvic radiation. The primary endpoint of this study was recurrence-free survival. Results from this trial were recently presented at the Society of Gynecologic Oncology annual meeting [12]. A total of 601 patients were enrolled 301 patients were randomized to receive pelvic radiation and 300 were randomized to receive VCB and chemotherapy. Baseline characteristics did not differ between the assigned groups. Seventy-four percent of patients had stage I disease and 89% underwent lymphadenectomy at the time of hysterectomy. The most common histologic type was endometrioid (71%). Acute toxicity was more common in the chemotherapy/vaginal cuff brachytherapy group. At a median follow-up time of 24 months, recurrence-free survival was 82% for patients receiving pelvic RT and 84% for patients receiving chemotherapy/vaginal cuff brachytherapy (HR 0.97, 95% CI 0.635–1.43). Overall survival also was not significantly different between the 2 groups (93% vs. 92%; HR 1.28, 95% CI 0.69–2.36). High completion rates were seen in both arms. Based on these results, it cannot be concluded that the addition of chemotherapy to VCB resulted in a superior disease-free survival as compared to standard treatment with whole pelvic RT.

Biomarkers as Prognostic Indicators in Endometrial Cancer

In addition to the clinical risk factors used to stratify patients into risk categories, recent studies have focused on the identification of biomarkers present in endometrial cancer patients. Biomarkers that have been identified include growth factors, oncogenes, cancer supressor genes, as well as markers of genetic aneuploidy. Specific markers that have been studied include k-ras, HER2/neu, epithelial growth factor (EGFR), phosphatase and tensin homolog (PTEN), p53, hMLH1, hMSH2, and hMSH6 [13]. A few of these have been explored as possible prognostic indicators. Specifically, a poor prognosis is associated with overexpression of p53. The presence of HER-2 mutation has also been reported to be associated with a reduced survival rate in some studies. Studies of PTEN are ongoing with mixed results in regard to prognosis thus far. Steroid receptor expression is associated with a better prognosis, while aneuploidy of the tumour has a poor prognosis. The identification of these and other biomarkers allows for development and use of molecularly targeted agents which are currently being tested in endometrial cancer [13].

Conclusion

Clear indications for administration of adjuvant radiation for early stage endometrial cancer have not been firmly established for patients with high-risk features. The decision to prescribe RT (either whole pelvic or vaginal brachytherapy) must be tailored according to specific patient risk factors. Since the overall prognosis for patients with early stage disease is favourable, even large studies may not be able to demonstrate a survival benefit for this intervention, thereby justifying why recurrence-free survival is a suitable and appropriate endpoint for past and future studies. With research efforts now being put forth to study high-risk sub-populations of patients with early stage disease, indications for adjuvant radiotherapy may become more concrete.

Clinical risk features (grade, depth of invasion, stage, and LVSI) may not be sufficient to reliably stratify early stage patients into low, intermediate, or high-risk categories. Numerous studies have been undertaken to help identify tumour biomarkers for endometrial cancer. While a number of biomarkers have been identified, only a subset has been examined with respect to effects on cancer prognosis [13]. Given our expanding knowledge of these biomarkers and ability to perform comprehensive genomic analysis of endometrial cancer, molecularly-targeted therapies are now being investigated to exploit abnormalities in various pathways (hormonal pathways, PI3K, and mTOR) and to inhibit angiogenesis (anti-VEGF and anti-VEGFR agents) [13]. These trials will hopefully help optimize adjuvant treatment for endometrial cancer by allowing for incorporation of personalized molecular therapies.

References

1. Nahleh ZA (2006) Hormonal therapy for male breast cancer: A different approach for a different disease. Cancer Treat Rev 32: 101-105.
2. Creutzberg C, Van Putten W, Koper P, Lybeert ML, Jobsen JJ, et al. (2000) Surgery and post-operative radiotherapy versus surgery alone for patients with stage 1 endometrial carcinoma: Multicentre randomized trial. Lancet 355: 1404-1411.
3. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, et al. (2004) A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 92: 744-751.
4. Sorbe B, Nordström B, Mäenpää J, Kuhelj J, Kuhelj D, et al. (2009) Intravaginal brachytherapy in FIGO stage I low-risk endometrial cancer: a controlled randomized study. Int J Gynecol Cancer 19: 873-878.
5. Creutzberg CL, van Putten WL, Wárlám-Rodenhuis CC, van den Bergh AC, de Winter KA, et al. (2004) Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the Postoperative Radiation Therapy in Endometrial Carcinoma Trial. J Clin Oncol 22: 1234-1241.
6. Creutzberg CL, Van Putten W, Koper P, Lybeert ML, Jobsen JJ, et al. (2003) Survival after relapse in patients with endometrial cancer: Results from a randomized trial. Gynecol Oncol 89: 201-209.
7. Nout RA, Smit VT, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, et al. (2010) 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 375: 816-823.
8. Nout RA, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, et al. (2009) Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial. J Clin Oncol 27: 3547-3556.
9. Thigpen JT, Brady MF, Homesley HD, Malfetano J, DuBeshter B, et al. (2004) Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a gynecologic oncology group study. J Clin Oncol 22: 3902-3908.
10. Fleming GF, Filiaci VL, Bentley RC, Herzog T, Sorosky J, et al. (2004) Phase III randomized trial of doxorubicin + cisplatin versus doxorubicin + 24-h paclitaxel + filgrastim in endometrial carcinoma: A Gynecologic Oncology Group study. Annals Oncol 15: 1173-1178.
11. Fleming G, Brunetto V, Cella D, Look KY, Reid GC, et al. (2004) Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial cancer: A GOG study. J Clin Oncol 11: 2159-2166.
12. McMeekin DS, Filliaci VL, Aghajanian C (2014) A randomized phase III trial of pelvic radiation therapy versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy in patients with high risk, early stage endometrial cancer: A Gynecologic Oncology Group Study. Abstract presented at Society of Gynecologic Oncologists Annual Meeting, Tampa, Florida.
13. Banno K, Kisu I, Yanokura M, Tsuji K, Masuda K, et al. (2012) Biomarkers in endometrial cancer: Possible clinical applications (Review). Oncol Lett 3: 1175-1180.

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