

Adjuvant vaginal cuff brachytherapy for high-risk, early stage endometrial cancer

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Abstract

Purpose: To report outcomes following adjuvant high-dose-rate vaginal brachytherapy (VBT) with or without chemotherapy for high-intermediate risk (HIR) and high-risk, early stage endometrial cancer as defined in Gynecologic Oncology Group trial 0249.

Material and methods: From May 2000 to January 2014, 68 women with HIR and high-risk endometrial cancer underwent surgical staging followed by VBT. Median VBT dose was 21 Gy delivered in three fractions prescribed to 0.5 cm depth. Paclitaxel 175 mg/m² and carboplatin area under the curve 6 was administered every 21 days in sequence with VBT. Actuarial survival estimates were calculated using the Kaplan-Meier method.

Results: Patient demographics included a median age of 66 years (range: 36-91) and stages IA (49%), IB (38%), and II (13%), respectively. Thirty-one (46%) patients had HIR disease with endometrioid histology, and 33 (48%) patients had serous or clear cell histology. Thirty-seven (54%) patients received a median 3 cycles (range: 3-6) of chemotherapy in addition to VBT, and 65 patients (96%) completed all prescribed therapy. During a median follow up of 33.1 months (range: 4.0-161.7), four patients have recurred, including one vaginal recurrence. The 3-year estimates of vaginal, pelvic, and distant recurrences were 1.9%, 2.4%, and 9.1%, respectively. The 3-year rates of disease-free and overall survival were 87.7% and 93.9%, respectively.

Conclusions: Early outcomes with adjuvant VBT with or without chemotherapy demonstrate high rates of vaginal and pelvic control for women with HIR disease. Early vaginal and pelvic relapses in high-risk patients suggest that pelvic external beam radiotherapy is warranted in this subgroup, but additional data from large phase III trials is warranted.

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Purpose

There is significant controversy surrounding adjuvant radiation therapy for early-stage endometrial cancer. Four large randomized trials have demonstrated a reduction in pelvic recurrences with the addition of pelvic external beam radiotherapy (EBRT) following standard surgical therapy [1-4]. However, this improvement in local control owed to EBRT is not without commensurate toxicity and does not improve survival [1-7].

In three of the randomized control trials, patient subgroups were identified in whom an important benefit in local control was derived from adjuvant radiotherapy [1,2,4]. For example, in Gynecologic Oncology Group

(GOG) 99, the high-intermediate risk (HIR) subgroup was formulated based on previously identified high-risk features (i.e. high grade tumors, advanced age, lymphovascular invasion (LVI), and deep myometrial invasion). This HIR subgroup was found to not only compose two-thirds of those patients who recurred, but also derived the largest benefit in local control from the addition of pelvic EBRT. At four years, the risk of recurrence or death in the HIR subgroup decreased from 36% to 17% with the addition of pelvic EBRT – a 53% reduction in relative risk. In women with low-risk disease, the benefits of pelvic EBRT were less clinically significant [1]. There is significant prognostic heterogeneity among women with early stage endometrial cancer and, accordingly, there is strong

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evidence for the routine use of adjuvant radiation therapy in well-defined HIR and high-risk patient subgroups.

A widely recognized benefit of radiotherapy is its ability to reduce recurrences at the vaginal cuff, the most common site of local failure [1-4,8]. With this notion, the second Post-operative Radiation Therapy in Endometrial Cancer (PORTEC) trial further refined the role of adjuvant radiotherapy. The results of this trial showed that vaginal brachytherapy (VBT) was non-inferior in providing vaginal local control compared to pelvic EBRT in women with features similar to the HIR group defined in GOG 99 [1,9]. Despite the adequate local control and reduced toxicity observed with VBT, relapses were common and disease-free survival (DFS) approached only 82% at five years, suggesting a need for new strategies to improve outcomes [9].

Despite the plethora of data from randomized trials, unanswered questions still remain. Of particular interest is defining the role of chemotherapy in early stage disease, with early data already emerging [10-12]. Furthermore, appropriate adjuvant therapies for early-stage carcinomas with high-risk, papillary serous or clear cell histology are not well established as this subgroup has not been consistently included in randomized trials for endometrial cancer [1,9]. Collective experience suggests stage I and II serous, and clear cell carcinomas carry similar recurrence rates as HIR disease [13-27]. Thus, contemporary clinical trials in endometrial cancer are challenged to define the optimal adjuvant therapy for patients with HIR and high-risk, early stage disease [14,28,29]. GOG 0249 is a trial in which HIR and high-risk patients were randomized following surgical staging to adjuvant pelvic EBRT alone (control arm) or VBT with three cycles of chemotherapy (experimental arm) [14,30]. The objective of this trial is to determine if the combination of chemotherapy and VBT can increase DFS when compared to pelvic EBRT and final results have not been reported.

Clinical practice in North America has migrated towards the use of VBT without EBRT for early-stage disease [31]. Our institutional preference is to deliver VBT with or without chemotherapy as an adjuvant strategy in patients with early stage, HIR and high-risk disease. Given this evolution in practice, the purpose of this study is to review the outcome of patients with HIR and high-risk disease, as defined in the contemporary trial GOG 0249 [14], to determine if acceptable rates of local control and DFS have been achieved at our institution without the use of pelvic EBRT.

Material and methods

Following approval by the Institutional Review Board, an institutional database was queried to identify patients with endometrial cancer who were treated with VBT between May 1, 2000 and January 5, 2014 and met criteria for International Federation of Gynecology and Obstetrics (FIGO) 2009 stage I and II disease. Sixty-eight women who met GOG 0249 criteria for HIR and high-risk disease were included [14,30]. The patient cohort includes: (1) FIGO stage I endometrioid adenocarcinomas with HIR disease as defined in GOG 99 with or without positive peritoneal cytology, and two subgroups of pa-

tients with high-risk, early stage disease. High-risk, early stage disease includes: (a) stage II endometrial carcinoma with cervical stromal invasion, and (b) FIGO stage I-II patients with type II, high-risk histology (clear cell or serous) and negative peritoneal cytology. Patients with non-epithelial uterine malignancies were excluded.

All women underwent surgical staging, which consisted of a hysterectomy, bilateral salpingo-oophorectomy, and peritoneal washings. Pelvic lymphadenectomies with or without para-aortic lymph node dissection were performed according to physician discretion. In women who had serous or clear cell histology, an omental biopsy and para-aortic lymph node sampling was performed. Patient demographics and tumor characteristics were obtained using electronic medical records and pathology reports. Pathologic stage in the present series has been designated according to FIGO 2009.

Patient cases were routinely reviewed in a multi-disciplinary conference in order to establish treatment recommendations for adjuvant therapy. Chemotherapy was recommended for patients with: (1) serous or clear cell carcinoma, or (2) grade 3 tumors with deep (greater than 50%) myometrial invasion or LVI. Adjuvant chemotherapy was carboplatin and paclitaxel administered every three weeks with initial dosing of area under the curve 6 and 175 mg/m², respectively. Beginning in 2011, our institution adopted a policy of administering chemotherapy prior to VBT so; chemotherapy typically began 3-6 weeks following surgery. In scenarios where VBT was administered first, chemotherapy began within three weeks of completion of VBT. Toxicity due to adjuvant therapy was assessed and scored every three weeks according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0.

VBT was administered with high-dose-rate (HDR) brachytherapy using Iridium-192 and a remote afterloader system. All patients underwent a pelvic exam prior to applicator insertion to ensure adequate healing of the vaginal apex after surgery [32]. While in the dorsal lithotomy position, a single-channel vaginal cylinder with the maximum tolerated diameter was inserted into the vagina. Pretreatment planning and dosimetry was performed prior to the first treatment, including routine use of three-dimensional treatment planning which began in 2008. Image-guidance with orthogonal images or cone beam computed tomography was performed prior to each fraction delivery as a quality assurance measure in order to confirm applicator position and size. The treatment length included one-half to two-thirds of the vaginal length from the apex extending distally toward the meatus, with a minimum treatment length of 4 cm. There are several acceptable fractionation regimens for VBT and, as a result, prescription dose varied and was most commonly: (1) 7 Gy × 3 fractions prescribed at a depth of 0.5 cm from the cylinder surface, or (2) 6 Gy × 5 fractions prescribed to the vaginal surface. The later fractionation was favored in young or sexually active patients. Patients were treated on non-consecutive weekdays over a two-week treatment course and chemotherapy was not administered on days that brachytherapy was delivered.

Routine surveillance after completion of adjuvant therapy included history and physical exam every 3-6 months for two years and then every 6 months thereafter. Vaginal cytology and imaging were performed annually or as clinically indicated.

The Kaplan-Meier method was used to determine rates of actuarial survival. DFS and overall survival (OS) were calculated based on time from surgery until progression or death. Patients alive without progression were

censored at the date of last clinical follow-up for endometrial cancer. Vaginal relapses occurred in the vagina; pelvic relapses included intra-pelvic recurrences outside of the vagina, and distant relapses occurred outside of the pelvis or retroperitoneum. DFS was defined as time to first relapse in any location with events including recurrence or death. Log-rank test was used for univariate analysis. Due to small number of disease recurrences and deaths, a multivariate analysis was not possible.

Table 1. Patient and tumor characteristics

Characteristic	All patients n = 68 (%)	VBT + chemotherapy n = 37 (%)	VBT alone n = 31 (%)
Median age (range)	66 (36-91)	65 (36-83)	70 (51-91)
Race			
White	52 (76)	28 (76)	24 (77)
Black	16 (24)	9 (24)	7 (23)
Stage			
IA	33 (49)	22 (59)	11 (35)
IB	26 (38)	11 (30)	15 (48)
II (occult)	9 (13)	4 (11)	5 (16)
High-intermediate risk [1]	31 (46)	6 (16)	25 (81)
High risk	37 (54)	31 (84)	6 (19)
Histology			
Endometrioid	30 (44)	4 (11)	26 (84)
Adenocarcinoma, NOS	3 (4)	2 (5)	1 (3)
Papillary serous	24 (35)	23 (62)	1 (3)
Clear cell	6 (9)	5 (14)	1 (3)
Mixed serous and clear	3 (4)	2 (5)	1 (3)
Adenosquamous	2 (3)	1 (3)	1 (3)
Grade 1	6 (9)	1 (3)	5 (16)
Grade 2	17 (25)	1 (3)	16 (52)
Grade 3	45 (66)	35 (94)	10 (32)
< 50% myometrial invasion	33 (49)	25 (68)	8 (26)
≥ 50% myometrial invasion	35 (51)	12 (32)	23 (74)
Tumor size (cm)			
Median	3.5	3.1	4
Range	0.6-10	0.6-6	1.2-10
LVI present	21 (31)	9 (24)	12 (39)
LVI absent	47 (69)	28 (76)	19 (61)
Peritoneal cytology positive	3 (4)	2 (5)	1 (3)
Peritoneal cytology negative	65 (96)	35 (95)	30 (97)
Lymph node			
Sampling	13 (19)	5 (14)	8 (26)
Dissection	47 (69)	29 (78)	18 (58)
None	8 (12)	3 (8)	5 (16)
Number of nodes dissected			
Median (range)	20 (4-49)	18 (4-38)	20 (6-49)

VBT – vaginal brachytherapy, NOS – not otherwise specified, LVI – lymph-vascular invasion

Results

Patient and tumor characteristics

Sixty-eight women with HIR and high-risk endometrial cancer received adjuvant VBT without pelvic EBRT and were included in this study. Baseline patient and tumor characteristics are illustrated in Table 1. The median age was 66 years and all but one patient were post-menopausal. The FIGO 2009 stage was IA in 33 (49%), IB in 26 (38%), and occult II in 9 (13%) patients. Approximately half of patients (n = 31) met criteria for HIR endometrial adenocarcinoma, as defined in GOG trial 99 [1]. Additionally, approximately half of patients (n = 33) had aggressive histologic subtypes including serous, clear cell carcinoma, and carcinoma with mixed serous and clear cell features. Approximately one-third (n = 21) of patients had LVI, but positive peritoneal cytology was not common (4%). Fifty-nine (87%) patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, while nine patients (13%) underwent laparoscopic-assisted vaginal hysterectomy and bilateral salpingo-oophorectomy. Sixty patients (88%) had staging of the pelvic lymph nodes with a median of 20 nodes examined, while para-aortic lymph node staging was performed in 45 (66%).

Thirty-seven (54%) of patients received both adjuvant chemotherapy and VBT. Thirty-one (46%) patients received adjuvant VBT alone including: four patients who refused chemotherapy, eight patients with medical contraindications to chemotherapy, and 19 patients for whom chemotherapy was not recommended. The characteristics of these patient subgroups are also described in Table 1. In short, the majority of patients who received both chemotherapy and VBT had papillary serous or clear cell histology. In contrast, the women who received VBT alone, commonly had HIR endometrioid adenocarcinomas.

Treatment compliance and toxicity

Sixty-five of the 68 patients (96%) completed the planned course of adjuvant therapy. Thirty-seven (54%) patients received a median of 3 cycles (range: 3-6) of chemotherapy in sequential fashion with VBT. Twenty patients received chemotherapy prior to VBT and 14 patients received VBT prior to chemotherapy. Three patients with papillary serous carcinoma and deep myometrial inva-

sion received therapy in a “sandwich” fashion – six cycles of chemotherapy with VBT given between the third and fourth cycle.

Chemotherapy was carboplatin and paclitaxel in all but two patients: one patient received paclitaxel alone and a second patient received carboplatin and docetaxel due to pre-existing peripheral neuropathy. Two patients required a dose reduction of the taxane due to grade 2 peripheral neuropathy that limited instrumental activities of daily living. One patient required dose reduction of carboplatin due to grade 3 neutropenia and immune system toxicity. Thirty four patients (92%) were able to complete all cycles of prescribed chemotherapy. Acute chemotherapy-related toxicities are illustrated in Table 2 and are largely characterized by mild, grade 1-2 peripheral neuropathy, hematologic and gastrointestinal toxicities. There were no grade 4 or 5 toxicities observed. There were two grade 3 toxicities including community acquired pneumonia in an immune-compromised patient and one episode of symptomatic anemia requiring transfusion.

All 68 patients were able to complete VBT. The most common fractionation schemes used during VBT were: 21 Gy in three fractions prescribed to 0.5 cm depth (n = 42), 30 Gy in five fractions prescribed to cylinder surface (n = 14), or other fractionation (n = 12). The median cylinder diameter and treatment length were 3.0 cm (range: 2.5-4.0) and 4.8 cm (range: 4-9 cm), respectively. The reported acute toxicities occurring during VBT were all mild and are illustrated in Table 2. Furthermore, after a median follow-up of 33.1 months (range: 4.0-161.7), late toxicities continue to be mild and include only grade 1 vaginal stenosis (n = 13) and grade 2 vaginal stenosis (n = 1). Twenty-six patients were compliant with use of a vaginal dilator. Nine patients reported that they were able to remain sexually active following VBT.

Patient outcomes

After a median follow up of 33.1 months, four patients developed relapsed disease, two of which occurred in patients who had not received adjuvant chemotherapy. The overall 3-year estimates of vaginal, pelvic, and distant recurrences are 1.9%, 2.4%, and 9.1%, respectively. One high-risk patient with stage II, grade 2, endometrioid carci-

Table 2. Reported acute toxicities during adjuvant therapy

Adverse effect	During chemotherapy (n = 37)					Adverse effect	During vaginal brachytherapy (n = 68)				
	1	2	3	4	5		1	2	3	4	5
Grade	1	2	3	4	5	Grade	1	2	3	4	5
Fatigue	7	–	–	–	–	Fatigue	8	–	–	–	–
Peripheral neuropathy	3	15	–	–	–	Vaginal	13	1	–	–	–
Gastrointestinal	8	10	–	–	–	Gastrointestinal	5	1	–	–	–
Neutropenia	4	3	1	–	–	Genitourinary	4	1	–	–	–
Non-neutropenia hematologic	3	1	1	–	–						
Myalgias	3	1	–	–	–						
Pruritis	1	2	–	–	–						

noma and deep myometrial invasion developed an isolated vaginal apex recurrence 15 months after VBT. This recurrence was successfully salvaged with pelvic EBRT and repeat VBT, but the patient later developed pulmonary metastases. A second high-risk patient with stage IA papillary serous carcinoma developed a recurrent mass in the true pelvis with associated abdomino-peritoneal carcinomatosis two years after adjuvant chemotherapy and VBT and has died due to disease. A third patient had a grade 3, endometrioid carcinoma with LVI and > 50% myometrial invasion was treated with VBT alone and developed metastatic disease in thoracic spine and orbit four months after surgery and has died due to disease. Finally, a fourth patient with grade 3, endometrioid carcinoma, and > 50% myometrial invasion (HIR disease) was treated with VBT and chemotherapy, and developed an isolated intra-thoracic recurrence and is alive with disease.

At the time of analysis, four deaths have occurred including two that were due to endometrial cancer. Three-year site-specific recurrence rates and survival rates are presented in Tables 3 and 4. Distant recurrences occurred more frequently than loco-regional recurrences. The 3-year rates of DFS and OS are 87.7% and 93.9%, respectively. Outcomes were assessed for the HIR and high-risk subgroups. In patients with HIR disease, there were no recurrences in the vagina or pelvis. In patients with high-risk disease (cervical stromal invasion or type II histology), 3-year estimates of vaginal and pelvic relapse were 3.2% and 3.8%,

respectively (Table 4). Univariate analysis (Table 5) demonstrated age younger than 65 years to be associated with improved DFS at three years ($p = 0.02$).

Discussion

The findings of this study indicate that adjuvant VBT without pelvic EBRT is well tolerated and could be a sufficient radiation strategy in women with HIR and high-risk endometrial cancer. At three years, the rates of vaginal recurrence, pelvic recurrence, DFS, and OS were 1.9%, 2.4%, 87.7%, and 93.9%, respectively. These outcomes occurred in the setting of excellent treatment compliance, mostly mild, grade 1-2 acute toxicity and minimal vulvo-vaginal late toxicity, to date. To the authors knowledge, this is the only series to examine outcomes following VBT in HIR and high-risk patients defined in the contemporary trial GOG 0249 [14].

Traditionally, standard adjuvant therapy for women with high-risk endometrial cancer has included pelvic EBRT [1-7]. In the past decade, there has been a perceptible change in clinical practice favoring the use of VBT alone without EBRT. In fact, a recent analysis of the Surveillance Epidemiology and End Results registry detected an increase in use of VBT from 52.9% to 59.3% in women with HIR disease as defined by GOG 99 following publication of the trial in 2004. Growth in VBT usage occurred with a simultaneous decrease in use of EBRT [31]. This shift in clinical practice likely stems from the

Table 3. Estimated 3-year rate of relapse and survival following vaginal brachytherapy with or without chemotherapy

Endpoint	Number events	Estimated 3-year rate			p value
		All patients (n = 68) Percent (95% CI)	VBT + chemotherapy (n = 37) Percent (95% CI)	VBT alone (n = 31) Percent (95% CI)	
Vaginal failure	1	1.9 (0.2-12.9)	0	4.5 (0.6-28.1)	0.24
Pelvic failure	1	2.4 (0.4-15.8%)	4.0 (0.6-25.2)	0	0.39
Distant metastasis	4	9.1 (3.6-23.2)	7.9 (2.1-28.0)	10.1 (2.4-37.6)	0.79
Disease free survival	6	87.7 (74.4-94.3)	88.5 (68.4-96.2)	86.9 (63.8-95.7)	0.64
Overall survival	4	93.9 (82.1-98)	96.2 (75.7-99.5)	90.8 (67.4-97.7)	0.81

Table 4. Estimated 3-year rate of relapse and survival among patients with high-risk and high-intermediate risk endometrial cancer

Endpoint	Number events	Estimated 3-year rate			p value
		All patients (n = 68) Percent (95% CI)	High risk [†] (n = 37) Percent (95% CI)	High-intermediate risk [1] (n = 31) Percent (95% CI)	
Vaginal failure	1	1.9 (0.2-12.9)	3.2 (0.4-20.8)	0	0.41
Pelvic failure	1	2.4 (0.4-15.8%)	3.8 (0.5-24.3)	0	0.43
Distant metastases	4	9.1 (3.6-23.2)	8.9 (2.3-31.6)	8.9 (2.2-32.7)	0.67
Disease free survival	6	87.7 (74.4-94.3)	89.5 (70.7-96.5)	85.4 (60.1-95.2)	0.63
Overall survival	4	93.9 (82.1-98)	96.4 (77.2-99.5)	90.4 (66-97.6)	0.68

[†]Includes stage II with cervical stromal invasion or stage I-II with clear cell or serous carcinoma.

findings that VBT offers DFS in HIR patients that is comparable to pelvic EBRT, with no compromise in OS, and diminished treatment-related toxicities [9,33]. PORTEC-2 played an integral role in establishing a role for adjuvant VBT alone and, currently, VBT may be considered as an adjuvant monotherapy in the majority of women with surgically-staged stage I endometrial cancer [34].

A substantial portion of the literature reporting outcomes following VBT without EBRT include women with low-intermediate or intermediate-risk endometrial cancer. As such, there is more controversy surrounding the use of VBT without pelvic EBRT in women with high-risk endometrial cancer. For example, National Comprehensive Cancer Network (NCCN) Clinical Practice

Table 5. Univariate analysis for disease-free and overall survival

Characteristic	3-year DFS (%)	<i>p</i> value	3-year OS (%)	<i>p</i> value
Age < 65	100	0.02	100	0.08
Age ≥ 65	78		89	
FIGO stage I	90	0.27	95	0.80
FIGO stage II	78		89	
High-intermediate risk	85	0.63	90	0.68
High risk	90		96	
Type I histology	79	0.07	83	0.15
Type II histology	96		100	
Grade 1 or 2	86	0.82	92	0.76
Grade 3	88		95	
< 50% myometrial invasion	91	0.32	96	0.93
≥ 50% myometrial invasion	83		92	
LVI present	83	0.49	82	0.11
LVI absent	89		97	
Chemotherapy	89	0.64	96	0.81
No chemotherapy	87		91	

DFS – disease free survival, OS – overall survival, FIGO – International Federation of Gynecology and Obstetrics, LVI – lymph-vascular invasion
 Type I – endometrioid, adenocarcinoma not otherwise specified, adenosquamous, Type II – papillary serous or clear cell carcinoma

Table 6. Reported outcomes of select series investigating vaginal brachytherapy without pelvic external beam radiotherapy for high-intermediate and high-risk, early stage endometrial cancer

Author	<i>n</i>	Population	Surgically staged	Percent receiving chemo [‡]	Time point (years)	Vaginal failure (%)	Pelvic failure (%)	DM (%)	DFS (%)	OS (%)
Nout RA [9]	213	HIR [†]	No	0	5	1.8	3.8	8.3	82.7	84.8
Atahan IL [35]	128	Intermediate- to high-risk stage I [†]	Yes	0	5	1.6	–	3.1	93.0	96.0
McCloskey SA [36]	77	HIR	No	0	4	1.2	3.4	4.6	–	–
Eldredge-Hindy [Present series]	68	HIR, stage II, stage I-II UPSC and CC	Yes	54	3	1.9	2.4	9.1	87.7	93.9
Barney BM [20]	103	Stage I UPSC and CC	Yes	34	5	3.0	7.0	10.0	88.0	84.0
Townamchai K [25]	37	Stage I-II UPSC and CC	Yes	75	2	3.2	6.5	–	89.3	100
Desai N [37]	77	Stage I-II UPSC and CC	Yes	79	5	2.7	5.8	6.6	88.0	91.0
Kiess AP [24]	41	Stage I-II UPSC and CC	Yes	100	5	0	9.0	10.0	85.0	90.0

N – number, chemo – chemotherapy, DM – distant metastases, DFS – disease free survival, OS – overall survival, HIR – high-intermediate risk, UPSC – uterine papillary serous carcinoma, CC – clear cell

[‡]Carboplatin and paclitaxel, [†]Some variation exists in the definition of high-risk groups in the referenced studies and within the present series

Guidelines state that treatment options for women with high-grade, stage I tumors with deep myometrial invasion, and adverse risk factors include observation alone, radiation therapy alone, or radiation therapy with chemotherapy. Radiation therapy offers an additional range of choices: pelvic EBRT alone, VBT alone, or pelvic EBRT with VBT [34]. Treatment guidelines for early-stage papillary serous and clear cell carcinoma are similarly varied.

Data are now emerging for early outcomes following VBT with or without chemotherapy in well defined, HIR and high-risk subgroups of women with stage I and II endometrial cancer. Specifically, the rates of vaginal and pelvic failure in these studies ranged 1.2-3.2% and 3-9%, respectively, after 2-5 years of follow up (Table 6) [9,20,24,25,35-37]. The most notable study of VBT in women with HIR disease comes from the experimental arm of the second PORTEC trial (PORTEC-2) [9]. The definition of HIR disease in PORTEC-2 and GOG 99 differ, however, there is considerable overlap in these patient populations. At five years, VBT provided excellent vaginal control (98.2%), with pelvic recurrence (3.8%) and distant metastases (8.3%) being the predominant patterns of failure [9]. Additionally, a second study from Mayo Clinic reported outcomes from 103 high-risk women with stage I papillary serous and clear cell carcinoma treated with adjuvant VBT with or without chemotherapy. The 5-year estimates of vaginal recurrence (3%) and loco-regional recurrence (7%) were similarly low [20]. Data from PORTEC-2 has provided high-level evidence for the use of VBT without pelvic EBRT in patients with HIR disease; however, similar data for patients with high-risk, early stage disease (cervical stromal invasion and type II histology) is limited to retrospective, single-institution studies like the present series [20,24,25,37]. Therefore, results should be interpreted with caution as pelvic EBRT may provide an important benefit in loco-regional control for early stage patients at high-risk for recurrence.

We report rates of vaginal (1.9%), pelvic (2.4%), and distant (9.1%) recurrences that are consistent with many contemporary series using VBT in subgroups of HIR and high-risk, early stage endometrial cancer (Table 6). At only three years, however, the relapse rates in our study cohort already approach the five-year outcomes from PORTEC-2 in which vaginal, pelvic, and distant relapse rates were 1.8%, 3.8%, and 8.3%, respectively, in HIR patients treated with adjuvant VBT without chemotherapy. This can be attributed to the inclusion of high-risk patients in our study cohort and, in fact, all loco-regional recurrences described in this study occurred in high-risk patients. The inclusion of HIR patients dilutes the overall recurrence rates. In the present series, three-year rates of vaginal relapse were 3.2% and 0% among high-risk and HIR patients, respectively. Similarly, three-year rates of pelvic relapse were 3.8% and 0% among high-risk and HIR patients, respectively. While the difference between these recurrence rates and those of HIR patients was not statistically significant, the data were not powered to detect such a difference. The higher rates of loco-regional recurrences in high-risk patients argue that pelvic EBRT is warranted for this subgroup. The anticipated treatment benefit afforded

by EBRT may justify the risk of added toxicity. Currently, the standard of care for high-risk patients remains pelvic EBRT with consideration of chemotherapy until future larger studies can provide definite conclusions regarding the role of VBT with chemotherapy [38].

This study does not address the potential importance of chemotherapy in this patient population and the results neither argue for or against the routine use of combined chemotherapy and radiotherapy. In the present series, the subgroup of patients who received chemotherapy cannot be effectively compared with the subgroup that did not receive chemotherapy due to inherent biases that were present while recommending adjuvant therapies for patients treated at our institution. There are, however, data that support a role for chemotherapy in this patient population, including from the Japanese Gynecologic Oncology Group [10,12,39]. In a randomized trial of pelvic EBRT versus cisplatin-based chemotherapy in patients with stage IC-IIIC disease with deeper than 50% myometrial invasion, chemotherapy improved progression free survival and OS compared to pelvic EBRT in a high- to intermediate-risk subgroup [10]. Included in this subgroup were patients with stage II disease, and patients over 70 years old with grade 3 tumors or stage IC disease – a population similar to the present series. Whether chemotherapy should be included as a standard portion of adjuvant therapy in this patient population remains a topic of active investigation in GOG 0249 and other trials [14,28].

Important limitations of this study include the lack of a second cohort for comparison and inherent biases associated with retrospective study. Additionally, the findings in this study might be heavily influenced by the small number of observed relapse events and could change substantially with longer follow up. The number of patients in this study is too low for any firm conclusions, and standard treatment for high-risk patients should continue to involve pelvic EBRT with chemotherapy as we await additional prospective data. The results of contemporary clinical trials will be forthcoming as to whether pelvic EBRT may be omitted in women with high-risk, early stage endometrial cancer [14].

Conclusions

The contemporary clinical trial GOG 0249 has defined practical criteria that identify a population of patients with high-risk, early stage endometrial cancer. Adjuvant pelvic EBRT remains a standard of care in this patient population and data regarding VBT and chemotherapy are limited. This regimen is well tolerated by patients with mostly mild, grade 1-2 acute toxicities. Distant metastases remain prevalent in patients receiving VBT alone, suggesting a role for chemotherapy. Early outcomes following adjuvant VBT with or without chemotherapy demonstrate high rates of vaginal control, pelvic control, and survival among the HIR subgroup, while early loco-regional relapses in the high-risk subgroup argue that pelvic EBRT with chemotherapy should remain a standard of care. Additional data with long-term follow up are needed to determine whether pelvic EBRT can be omitted in women with high-risk, early stage disease.

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Disclosure

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References

- Keys HM, Roberts JA, Brunetto VL et al. 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* 2004; 92: 744-751.
- Creutzberg CL, Nout RA, Lybeert ML et al. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial cancer. *Int J Radiat Oncol Biol Phys* 2011; 81: e631-e638.
- ASTEC/EN.5 Study Group, 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 randomized trials): pooled trial results, systematic review, and meta-analysis. *Lancet* 2009; 373: 137-146.
- 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.
- Nout RA, van de Poll-Franse LV, Lybeert ML et al. Long-term outcome and quality of life in patients with endometrial carcinoma treated with or without pelvic radiotherapy in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial. *J Clin Oncol* 2011; 29: 1692-1700.
- Creutzberg CL, van Putten WL, Koper PC et al. The morbidity of treatment for patients with stage I endometrial cancer: results from a randomized trial. *Int J Radiat Oncol Biol Phys* 2001; 51: 1246-1255.
- Kellas-Ślęczka S, Wojcieszek P, Białas B. Adjuvant vaginal brachytherapy as part of a management in early endometrial cancer. *J Contemp Brachyther* 2012; 4: 247-252.
- 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.
- 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, randomized trial. *Lancet* 2010; 375: 816-823.
- 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.
- Greven K, Winter K, Underhill K et al. Final analysis of RTOG 9708: Adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer. *Gynecol Oncol* 2006; 103: 155-159.
- Jutzi L, Hoskins P, Lim P et al. The importance of adjuvant chemotherapy and pelvic radiotherapy in high-risk early stage endometrial carcinoma. *Gynecol Oncol* 2013; 131: 581-585.
- Ayeni TA, Bakkum-Gamez JN, Mariani A et al. Comparative outcomes assessment of uterine grade 3 endometrioid, serous, and clear cell carcinomas. *Gynecol Oncol* 2013; 129: 478-485.
- Gynecologic Oncology Group (GOG). Pelvic radiation therapy or vaginal implant radiation therapy, paclitaxel, and carboplatin in treating patients with high-risk stage I or II endometrial cancer. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 [cited 2013 Nov 8]. Available from: <http://clinicaltrials.gov/show/NCT00807768>. NLM Identifier: NCT00807768.
- Alektiar KM, Makker V, Abu-Rustum NR et al. Concurrent carboplatin/paclitaxel and intravaginal radiation in surgical stage I-II serous endometrial cancer. *Gynecol Oncol* 2009; 112: 142-145.
- Tchabo NE, McCloskey S, Mashtare TL et al. Treatment of early-stage uterine papillary serous carcinoma at Roswell Park Cancer Institute, 1992-2006. *Gynecol Oncol* 2009; 115: 249-256.
- Viswanathan AN, Macklin EA, Berkowitz R et al. The importance of chemotherapy and radiation in uterine papillary serous carcinoma. *Gynecol Oncol* 2011; 112: 542-547.
- Growdon WB, Rauh-Hain JJ, Cordon A et al. Prognostic determinants in patients with stage I uterine papillary serous carcinoma: a 15-year multi-institutional review. *Int J Gynecol Cancer* 2012; 22: 417-424.
- Kim A, Schreiber D, Rineer J et al. Impact of adjuvant external-beam radiation therapy in early-stage uterine papillary serous and clear cell carcinoma. *Int J Radiat Oncol Biol Phys* 2011; 81: e639-e644.
- Barney BB, Petersen IA, Mariani A et al. The role of vaginal brachytherapy in the treatment of surgical stage I papillary serous or clear cell endometrial cancer. *Int J Radiat Oncol Biol Phys* 2013; 85: 109-115.
- Yechieli R, Rasool N, Robbins JR et al. Adjuvant radiation therapy for patients with type II endometrial carcinoma: Impact on tumor recurrence and survival. *Int J Gynecol Cancer* 2013; 23: 763-768.
- Huh WK, Powell M, Leath CA et al. Uterine papillary serous carcinoma: Comparisons of outcomes in surgical stage I patients with and without adjuvant therapy. *Gynecol Oncol* 2003; 91: 470-475.
- Sutton G, Axelrod JH, Bundy BN et al. Adjuvant whole abdominal irradiation in clinical stage 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.
- Kiess AP, Damast S, Makker V et al. Five-year outcomes of adjuvant carboplatin/paclitaxel chemotherapy and intravaginal radiation for stage I-II papillary serous endometrial cancer. *Gynecol Oncol* 2012; 127: 321-325.
- Townamchai K, Berkowitz R, Bhagwat M et al. Vaginal brachytherapy for early stage uterine papillary serous and clear cell endometrial cancer. *Gynecol Oncol* 2013; 129: 18-21.
- Creasman WT, Kohler MF, Odicino F et al. Prognosis of papillary serous, clear cell, and grade 3 stage I carcinoma of the endometrium. *Gynecol Oncol* 2004; 95: 593-596.
- Crisano FD, Robboy SJ, Dodge RK et al. The outcome of stage I-II clinically and surgically staged papillary serous and clear cell endometrial cancers when compared with endometrioid carcinoma. *Gynecol Oncol* 2000; 77: 55-65.
- Leiden University Medical Center. Randomized trial of radiation therapy with or without chemotherapy for endometrial cancer (PORTEC-3). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 [cited 2013 Nov 8]. Available from: <http://clinicaltrials.gov/show/NCT00411138>. NLM Identifier: NCT00411138.

29. Van der Steen-Banasik E. Primary brachytherapy as a radical treatment for endometrial carcinoma. *J Contemp Brachytherapy* 2014; 6: 106-112.
30. McMeekin DS, Filiaci VL, Aghajanian C et al. A randomized phase III trial of pelvic radiation therapy (PXRT) versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy (VCB/C) in patients with high risk (HR), early stage endometrial cancer (EC): a Gynecologic Oncology Group trial. Proceedings of the 45th Annual Meeting on Women's Cancer, Society of Gynecologic Oncology, Tampa, FL (2014, March 22).
31. 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.
32. Albuquerque K, Shah K, Potkul R. Vaginal dehiscence after intracavitary brachytherapy for endometrial cancer. *J Contemp Brachytherapy* 2012; 4: 111-112.
33. Donnelly ED, Rakhra S, Helenowski I et al. Dosimetry and toxicity outcomes in postoperative high-dose-rate intracavitary brachytherapy for endometrial cancer. *J Contemp Brachytherapy* 2012; 4: 135-140.
34. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Uterine neoplasms, version 3.2012. National Comprehensive Cancer Network; 2012.
35. Atahan IL, Ozyar E, Yildiz F et al. Vaginal high dose rate brachytherapy alone in patients with intermediate- to high-risk stage I endometrial carcinoma after radical surgery. *Int J Gynecol Cancer* 2008; 18: 1294-1299.
36. McCloskey SA, Tchabo NE, Malhotra et al. Adjuvant vaginal brachytherapy alone for high risk localized endometrial cancer as defined by the three major randomized trials of adjuvant pelvic radiation. *Gynecol Oncol* 2010; 116: 404-407.
37. Desai NB, Kiess AP, Kollmeier MA et al. Patterns of relapse in stage I-II uterine papillary serous carcinoma treated with adjuvant intravaginal radiation with or without chemotherapy. *Gynecol Oncol* 2013 (In Press). <http://dx.doi.org/10.1016/j.ygyno.2013.09.019>.
38. Klopp A, Smith BD, Alektiar K et al. The role of postoperative radiation therapy for endometrial cancer: Executive Summary of the American Society for Radiation Oncology evidence-based guideline. *Pract Radiat Oncol* 2014; 4: 137-144.
39. Randall M, Filiaci V, Muss H et al. Randomized phase III trial of WART versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: A GOG study. *J Clin Oncol* 2006; 24: 36-44.