Original Article

J Gynecol Oncol Vol. 25, No. 2:105-110
http://dx.doi.org/10.3802/jgo.2014.25.2.105
pISSN 2005-0380 · eISSN 2005-0399

Journal of Gynecologic Oncology
JGO

Survival analysis of endometrial cancer patients with cervical stromal involvement

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Objective: Stage II endometrial cancer is relatively uncommon. There is no consensus for appropriate adjuvant therapy in endometrial cancer patients with cervical stromal involvement (International Federation of Gynecology and Obstetrics [FIGO] stage II). This study investigates how adjuvant treatments and tumor characteristics influence overall survival (OS) and disease-free survival (DFS) in stage II patients in order to establish better treatment guidelines.

Methods: This multi-institution, Institutional Review Board approved, study is a retrospective review of 40 endometrial cancer patients with cervical stromal involvement treated from 1993 to 2009. Kaplan-Meier estimates were used to evaluate OS and DFS.

Results: OS was 85% at three years and 67% at five years. There were no significant differences in age, histology, depth of invasion, comorbid conditions, surgical staging or recurrence between patients who received radiation therapy (RT) and those who did not. However, patients with FIGO grade 1 cancers were less likely to receive RT (p=0.007). Patients treated with RT had a similar 5 year OS (n=33, 69%) to those treated with surgery only (n=7, 60%, p=0.746). There were no OS differences when evaluating by grade, histology, or depth of invasion between patients who did and did not receive RT. Four patients recurred: three were locoregional failures only, and one failed locally and distant.

Conclusion: Patients receiving RT had higher grade tumors. Despite this, OS was comparable between the RT and the no RT cohorts. Local failure was the predominant pattern of failure. Endometrial cancer patients with cervical stromal involvement likely receive better locoregional control with the addition of adjuvant RT and we continue to advocate for RT in most cases.

Keywords: Adjuvant radiation therapy, Cervical involvement, Endometrial cancer, Survival outcome

INTRODUCTION

Endometrial cancer is the most common gynecological malignancy in the United States and the fourth most common malignancy in women [1]. The majority of patients are diagnosed while the tumor is confined to the uterine corpus, and these patients generally have a good prognosis. A minority of patients develop tumor in the cervical stroma (International Federation of Gynecology and Obstetrics [FIGO] stage II). Of note, in 2009 the FIGO staging criteria for this disease changed, such that endocervical glandular involvement alone with no stromal involvement is now considered stage I. In uterus-confined malignancies, it has been shown in prospective studies that lymphovascular space invasion, high grade histology, and deep myometrial invasion are all risk factors for adverse outcomes [2-4]. In uterus-confined malignancies, cervical stromal involvement has also been demonstrated to be an adverse risk factor [5]. There is a lack of consensus

Received Sep 13, 2013, **Revised** Jan 6, 2014, **Accepted** Jan 19, 2014

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for appropriate adjuvant therapy for this patient population given a generalized paucity of data from randomized controlled trials for this stage. This study is a multi-institutional, retrospective review of surgically staged endometrial cancer patients. The purpose of this study is to investigate how tumor characteristics and adjuvant treatments influence overall survival.

MATERIALS AND METHODS

The cancer registries within the Intermountain Healthcare system and the University of Utah with the affiliated Huntsman Cancer Hospital were used to identify patients with endometrial cancer treated from 1993 to 2009. The Institutional Review Boards of each organization approved the study. A total of 49 FIGO stage II patients were identified as having been treated surgically and adjuvantly at the aforementioned institutions. FIGO stage II was defined as per the FIGO 2009 staging system. Six patients were excluded with sarcomatous histologies. Two patients were excluded with previous malignancies. And, one patient was excluded having died on postoperative day number four. Thus, 40 patients were included in our analysis.

Hospital medical records were used to collect treatment and patient characteristics. This information was then combined with and confirmed by data from each institution's cancer registry. Follow-up information was abstracted through reviewing medical records at the time of the study in combination with annually recorded cancer registry data. The collection of data was standardized to ensure data definitions were consistent across facilities. The median follow up was 62 months. The primary endpoints for the study were overall survival (OS) and disease-free survival (DFS). Life Tables survival estimates and Kaplan Meier curves were used to evaluate OS and DFS. Significance was evaluated using log rank tests.

1. Surgery

Operations included: total abdominal hysterectomy (TAH, n=24), radical hysterectomy (n=1), modified radical hysterectomy (n=9), laparoscopic-assisted vaginal hysterectomy (n=2), total laparoscopic hysterectomy (n=2), and total vaginal hysterectomy (n=2). Bilateral salpingo-oophorectomy (BSO) was done in 36 patients. Lymphadenectomy was performed on 26 patients (65%) with a median of 19 lymph nodes dissected (range, 1 to 52) with 9 patients (22.5%) having paraaortic lymph node sampled. Of the operations performed, 31 were performed by a gynecological oncologist, eight by general gynecologists, and one was unknown.

2. Radiation

Thirty-three patients received radiation therapy (RT) with six patients receiving external beam radiation therapy (EBRT) alone, two patients receiving vaginal brachytherapy (VB) alone, and 25 patients undergoing both. EBRT was administered to the whole pelvis using a four-field technique. The EBRT was between 45 to 50.4 Gy. Intracavitary brachytherapy with high dose rate (HDR) brachytherapy was given to 20 patients, and seven patients received low dose rate (LDR) brachytherapy. No patients received chemotherapy adjuvantly.

RESULTS

Patient and tumor characteristics are found in **Table 1**. The median age for all patients was 61 (range, 36 to 83). The OS for all patients was 85% at 3 years and 67% at 5 years (**Fig. 1**). There were no significant differences in age, histology, depth of invasion, comorbid conditions, surgical staging and recurrences

Table 1. Clinical and pathologic characteristics of stage II endometrial cancer patients according to treatment group

Variable	Surgery alone (n=7)	Surgery+ radiation (n=33)	p-value
Age at diagnosis (yr), median (range)	64 (59–71)	60 (36–83)	0.271
Comorbid conditions			
Hypertension	3 (43)	14 (42)	0.983
Diabetes mellitus	3 (43)	6 (18)	0.176
Smoking	0	4 (12)	0.361
FIGO grade			
1	6 (86)	9 (28)	0.007
2	1 (14)	14 (44)	0.182
3	0	9 (28)	0.135
Histology			
Endometrioid	6 (86)	28 (85)	0.977
Non-endometrioid*	1 (14)	5 (15)	0.977
Deep myometrial invasion ≥1/2	2 (29)	16 (48)	0.684
Complete surgical staging	3 (43)	23 (70)	0.197
Pelvic LN dissected, median (range)	14 (5–26)	19 (1–52)	0.550
Recurrences	1 (14)	3 (9)	
Locoregional	1 (100)	3 (100)	0.655
Distant	0	0	

Values are presented as number (%).
FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node.
*Non-endometrioid histologies include: clear cell, adenosquamous, and mucinous.

http://dx.doi.org/10.3802/jgo.2014.25.2.105

between patients who received RT and those who did not. However, the group that did not receive RT was comprised of more FIGO grade 1 cancers (p=0.007). Treatment characteristics of RT and surgery are shown in **Table 2**.

Four patients recurred: three were locoregional failures only, and one failed locally and distant. One local failure only was salvaged and the others died of cancer after recurrence. Patient, tumor and treatment characteristics are outlined in **Table 3**. The only vaginal cuff recurrence had a grade 1 tumor and had not received adjuvant RT, but was salvaged with EBRT and VB. The remaining three recurrences occurred in patients who received an adjuvant RT, and all died due to progression of disease. Only one of the three recurred within their RT field. All four patients underwent TAH and BSO. Three of the patients who failed had their surgeries performed by gynecologic oncologists at high volume centers. The remaining 1 patient had her surgery performed by a general gynecologist. Only one of four patients underwent a lymphadenectomy during surgery.

Patients treated with RT (n=33) had a similar 5 year OS (69% vs. 60%, p=0.746) and DFS (69% vs. 63%, p=0.687) compared to those treated with surgery only (n=7). There were no differences in OS when evaluating by grade, histology, or depth of invasion.

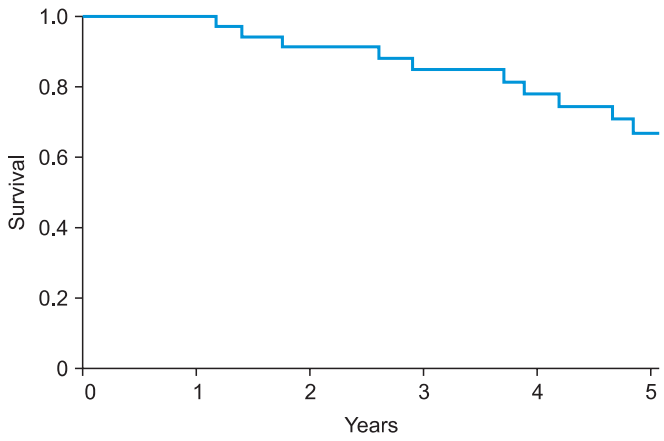

Fig. 1. Stage II endometrial cancer overall survival for all subjects.

DISCUSSION

It is important to note that this is the largest multi-institutional, retrospective study of stage II endometrial cancer using the 2009 FIGO staging system [6]. Previous retrospective stage II studies were predominantly performed using the 1988 FIGO staging system. The survival data for the 1988 FIGO stage IIB patients in these previous studies are similar to what we found in our study population [7-9]. **Table 4** outlines the survival data from these studies. Studies performed prior to 1993

Table 2. Treatment characteristics of radiation and surgery for stage II endometrial cancer patients

Variable	Surgery alone (n=7)	Surgery+WPRT+VB (n=24)	Surgery+WPRT (n=6)	Surgery+VB (n=3)
Type of hysterectomy				
Total abdominal hysterectomy	5	15	3	1
Total vaginal hysterectomy	1	0	1	0
Total laparoscopic hysterectomy	1	0	0	1
Radical abdominal hysterectomy	0	1	0	0
Modified radical hysterectomy	0	7	1	1
Laparscopic assisted vaginal hysterectomy	0	1	1	0
Bilateral salpingo-oophorectomy	5	23	5	3
Nodal dissection				
Lymph node dissection performed	3	17	3	3
Average number of nodes (range)	14 (5–26)	21 (3–52)	14 (8–19)	16 (1–28)
External beam				
Average dose in Gy (range)	NA	46 (35–50.4)	45.4 (45–47)	NA
Average days on treatment (range)	NA	41 (26–59)	35 (34–35)	NA
Vaginal brachytherapy				
Average HDR dose in Gy (range)	NA	12.3 (6–25)	NA	18.75 (18–19.5)
Average LDR dose in Gy (range)	NA	24.9 (15–45)	NA	NA

HDR, high dose rate; LDR, low dose rate; NA, not available; VB, vaginal brachytherapy; WPRT, whole pelvic radiation therapy.

Table 3. Clinicopathologic characteristics of the patients who had a recurrence (n=4)

Treatment received	Age (yr)	Type of surgery	LN dissectioin	Operator	Grade	Histology	RFS (day)	Site of recurrence	DOD	Recurrence within RT field
Surgery	61	TAH+BSO	Not done	GO	1	Endometrioid	420	Vaginal cuff	No	NA
Surgery+WPRT+VB	61	TAH+BSO	PLN, PALN	GO	3	Endometrioid	274	Periurethral vagina	Yes	No
Surgery+WPRT+VB	64	TAH+BSO	Not done	GO	1	Endometrioid	829	Lung, liver and retroperitoneum	Yes	No
Surgery+WPRT+VB	41	TAH+BSO	Not done	GG	NA	Clear cell	937	Pelvis	Yes	Yes

BSO, bilateral salpingo-oophorectomy; DOD, dead of disease; GG, general gynecologist; GO, gynecologic oncologist; LN, lymph node; NA, not available; PLN, pelvic lymph node; PALN, paraaortic lymph node; RFS, recurrence-free survival; RT, radiation therapy; TAH, total abdominal hysterectomy; VB, vaginal brachytherapy; WPRT, whole pelvic radiation therapy.

Table 4. A literature review of retrospective studies of stage II endometrial cancer

Study	No. of patients	Study population	Adjuvant radiation (%)	Recurrence rate (%)	Recurrence rate (%) by location	5-Year OS (%)
Current study	40	Pathologic stage II (FIGO 2009)	83	10	7.5 Locoregional, 2.5 Locoregional and distant	67
Lee et al. [6] (2013)	29	Pathologic stage II (FIGO 2009)	Neoadjuvant radiation	27.6	20 Out of RT field, 3 In RT field	79 (3-year OS)
Pitson et al. [8] (2002)	94	Pathologic IIA	84	25	10 Locoregional, 15 Distant	77
	76	Pathologic IIB				
Sartori et al. [7] (2001)	111	Pathologic IIA	59	10	5 Locoregional, 5 Distant	86
	92	Pathologic IIB	73	19	11 Locoregional, 8 Distant	74
Boente et al. [9] (1993)	24	Pathologic IIA and IIB	NA	NA	NA	76
Lanciano et al. [13] (1990)	184	Surgical or clinical IIA and IIB	92 7 Received definitive RT	28	4 Locoregional, 13 Distant, 11 Locoregional and distant	70
Larson et al. [12] (1987)	64	Clinical stage II	100 Neoadjuvant and adjuvant	NA	NA	68
Wallin et al. [11] (1984)	52	Clinical stage II	48	NA	NA	69
Onsrud et al. [10] (1982)	84	Pathologic II	100 65 Also received neoadjvant VB	19	10 Locoregional, 10 Distant	82

FIGO, International Federation of Gynecology and Obstetrics; NA, not available; OS, overall survival; RT, radiation therapy.

predominantly employed a clinical staging system, which inevitably included surgical stages III and IV in their analyses given the limitations of clinical staging [10-13].

It is also important to keep in mind the paucity of data for stage II patients in prospective, randomized trials. These patients have often been excluded from the large early stage trials [2-4,14]. The knowledge for treatment of stage II patients has largely been extrapolated from trials that included mainly stage I patients. In all of these trials, RT caused an improvement in local control without an improvement in survival [2-4,14]. Our study did not show a decreased risk of recurrence with RT in any subgroup: however, the practice patterns were to offer RT to patients with generally more adverse features. The tumors of the patients who were treated with surgery alone were largely grade 1, whereas the patients receiving RT consistently had tumors with grade 2 or more. As surgery is the crux of treatment for this patient population, surgical skill and experience is paramount. The surgical experience for the four patients who recurred is outlined in **Table 3**. All four patients who recurred either failed locally alone or were found to have concurrent local and distant failure. Only one of the four patients underwent lympadenectomy. Of the remaining three, the patient who did not receive RT recurred in the vaginal vault. The surgery for this patient was performed by

http://dx.doi.org/10.3802/jgo.2014.25.2.105

an experienced, gynecologic oncologist at a high volume center. It is unlikely that this patient would have benefited from a lymph node dissection. The remaining two patients who recurred had pelvic or paraaortic nodal components to their failure. Lymphadenectomy, both pelvic and paraaortic, in these two patients may have played a beneficial role in preventing recurrence.

Omitting lymph node dissection from early stage endometrial cancer is a common practice that is extrapolated from the Medical Research Council (MRC) A Study in the Treatment of Endometrial Cancer (ASTEC) trial, a phase III trial randomizing patients to standard surgery (hysterectomy and BSO, peritoneal washings, and palpation of paraaortic nodes) or standard surgery plus lymphadenectomy, which included removal of the iliac and obturator nodes, with paraaortic nodal sampling left to the discretion of the surgeon [15]. To be included in the study, the patients had to have disease thought preoperatively to be confined to the corpus, thus excluding FIGO stage II patients from their initial inclusion criteria. At a median follow up time of 37 months, with adjustment for baseline characteristics and pathology, lymphadenectomy provided no significant OS or DFS benefit. Surgical pathology revealed 8% of the patients in the study had disease involving the cervical stroma, without nodal involvement (FIGO stage II). A post hoc analysis on this sub-group has not been performed to examine the benefit of lymphadenectomy for this population. The role of lymph node dissection in this patient population needs further investigation.

The strengths of this study include the following: this is the largest study on stage II patients using the FIGO 2009 staging system and there was a excellent rate of OS. Patients were followed up closely and site of recurrence is included. The weaknesses of this study include: the small size of study population; the imbalance of patient number between surgery alone group and surgery+RT group; there were no patients who received chemotherapy; and the nonrandomized retrospective nature of the study.

In this retrospective series, patients receiving RT had higher grade tumors. Despite this, OS was comparable between RT and no RT cohorts. Local pelvic failure was the predominant site of failure in this series. Although this study did not demonstrate a definite benefit of locoregional control from the adjuvant RT, given the volume of evidence favoring RT in stage I patients, we continue to advocate for RT in most cases for this patient population [2-4]. This patient population historically has been excluded from the major prospective, randomized trials addressing the surgical and adjuvant approach for early stage endometrial cancers [2-4,15]. Thus, the role of adjuvant RT needs further investigation.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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