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Stage IB Endometrioid Type Endometrial Cancer: The Role of Lymphadenectomy and Adjuvant Radiation Therapy

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ABSTRACT

OBJECTIVE: Both performances of lymphadenectomy and benefit of adding adjuvant radiotherapy are controversial for patients with International Federation of Gynecology and Obstetrics stage IB endometrioid type endometrial cancer. We aimed to identify the role of lymphadenectomy and adjuvant radiation therapy as well as clinicopathological prognostic factors for this group of patients.

STUDY DESIGN: Records of all patients (n=132) with stage IB endometrioid endometrial cancer who were referred to or treated in our institution between Jan 1992 and Dec 2013 were retrospectively reviewed. Cox Proportional Hazard Regression Analysis was used to determine the effects of lymphadenectomy and adjuvant radiation as well as other clinicopathological factors on disease free survival and overall survival.

RESULTS: Mean age was 59.9 years (range, 45-82). Lymphadenectomy didn't perform in 36 (27.3%) patients and 23 (17.4%) patients did not have any kind of adjuvant treatment. Mean lymph node count was 18.8 (range, 3-67). Federation of Gynecology and Obstetrics grade, lymphovascular space invasion, lymphadenectomy, receiving adjuvant treatment and type of received adjuvant therapy were not associated with disease free survival and overall survival for the entire cohort. In a subgroup of patients with grade1&2 tumor, 5-year disease free survival rates were 80% and 50% (*p*=0.4), respectively and overall survival rates were 94.8% and 93.8% (*p*=0.2), respectively for patients who had or didn't have adjuvant radiotherapy. While performance of lymphadenectomy was not significantly associated with disease free survival in this subgroup (*p*=0.56), this association was statistically significant for overall survival (97.9% vs. 86.4%, (*p*=0.04).

CONCLUSION: Benefit of adjuvant radiotherapy in regard to prevention of recurrence needs to be confirmed by further studies. Lymphadenectomy had a survival benefit for patients with myometrial invasion greater than a half of myometrial thickness.

Keywords: Endometrial cancer, Early stage, Lymphadenectomy, Adjuvant therapy

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Introduction

Although endometrial cancer (EC) is the most common gynecologic malignancy in the developed countries and the majority of cases are diagnosed at an early stage, both proper surgical approach and the need for adjuvant treatment are still being debated. Standard surgery consists of total hysterectomy and bilateral salpingo-oophorectomy. The performance of extensive staging surgery which includes pelvic and para-aortic lymphadenectomy and omentectomy shows wide variations between the centers worldwide (1-3). Tumor type, grade, tumor size, and depth of myometrial invasion (MI) are key prognostic factors for lymph node metastasis and recurrence and are used to assess the need for lymphadenectomy as well as adjuvant radiation treatment (4,5). The recommendation of the International Federation of Gynecology and Obstetrics (FIGO) which was revised in 2009 has been adequate surgical staging in EC since 1988 (6). However, the survival benefit of systematic lymphadenectomy in early stage EC is not clear (5, 7-9) and lymphadenectomy procedures are associated with

morbidity including; blood loss, vascular injury, longer operating times and prolonged postoperative hospital stays (10-12). On the other hand, surgical staging may allow the identification of patients with documented lymphatic tumor status and potentially reduce the morbidity related to unnecessary radiation therapy by selecting the group of patients in whom adjuvant therapy can be omitted (11).

2009 FIGO classification system identifies 2 subgroups of stage I according to the depth of myometrial invasion (IA: MI <50%, IB: MI ≥50%) (6). Specifically for endometrioid tumor type, the 5-year survival rate is 90% in stage I patients (13) and no further treatment is recommended for patients with stage IA and grade 1 & 2 diseases (14). Both observations and adjuvant radiotherapy and/or chemotherapy can be chosen for the management of stage IB disease according to the presence or absence of poor prognostic factors (14-18).

In this paper, it's aimed to identify the role of lymphadenectomy and adjuvant radiation therapy as well as clinicopathological prognostic factors for stage IB endometrioid type endometrial cancer.

Material and method

All patients (n=132) with stage IB endometrioid endometrial cancer who were operated and followed at our institution or whose hysterectomy (not staging surgery) was made somewhere else and referred to us based on the diagnosis of EC, between Jan 1992 and Dec 2013, were identified. The data were abstracted from the electronic database of the institution and pathology reports. The staging was undertaken according to FIGO 2009 staging system. Lymphovascular space invasion (LVSI) was assessed on H&E-stained slides, as carcinoma cells present within a definite endothelial-lined space, at a distance from the tumor. Pathologic examination of hysterectomy specimen was done on at least 4 sections. Pathology slides of those that were operated elsewhere were reviewed at the time of application to our institution.

In our institution lymphadenectomy decision for apparently uterine confined EC is made routinely based on the frozen/section results if pathologic examination of pre-operative probe curettage indicates grade 1 tumor. Total hysterectomy and bilateral salpingo-oophorectomy were performed and lymphadenectomy was omitted in those patients with all of the following: 1) MI less than <50% 2) tumor size smaller than 2 cm and 3) grade 1 tumor. Otherwise, patients undergo complete staging surgery that includes total hysterectomy and bilateral salpingo-oophorectomy as well as pelvic/para-aortic lymphadenectomy and omental biopsy. However, lymphadenectomy was omitted in some patients because; 1) operation was made somewhere else as incomplete staging surgery and the patient refused a repeat operation 2) frozen/section revealed a stage IA disease but final pathology indicated stage IB and the patient refused a repeat operation and 3) of discretion of the senior surgeon. Lymphadenectomy was performed in most of the patients by skeletonizing pelvic and para-aortic regions. Nevertheless, there were patients treated by the sampling of the suspicious lymph nodes at the discretion of the surgeon.

Adjuvant radiotherapy was given as vaginal brachytherapy or external beam radiotherapy or both. External beam pelvic radiotherapy was given to a total dose of 5000-5400 cGy in 200 cGy fractions and vaginal brachytherapy was given to a dose of 1500-2750 cGy in 550-750 cGy fractions.

The period from surgery to recurrence or last visit was defined as disease-free survival (DFS) and period from surgery to death or last visit was defined as overall survival (OS). Patients were followed-up every 3 months for 2 years after adjuvant therapy, every 6 months until the fifth year following treatment and yearly thereafter. In every visit, pelvic examination, abdominal ultrasonography, complete blood count and blood chemistry were performed. Chest X-ray was utilized yearly unless there is a clinical suspicion. Thoracic and/or abdominal computerized tomography was used when needed. Recurrences that occurred in true pelvis or vaginal cuff were defined as locoregional recurrence.

Data analyses were performed by using SPSS for Windows 11.5 package program. Categorical variables were analyzed with Kaplan-Meier Survival Analysis using Log-Rank Test to determine whether they had statistically significant effects on DFS and OS. Whether the continuous and discrete numeric variables had statistically significant effects on DFS and OS were calculated using univariate Cox Proportional Hazard Regression Analysis. $P<0.05$ was considered statistically significant for the results. The institutional review board approved the research.

Results

The data of 132 patients with stage IB and endometrioid type histology were analyzed. The median age was 59.9 years (range, 45-82). The mean tumor size was 3.4 cm (range, 1.6-6 cm). The mean lymph node count was 18.8 (range, 3-67). Out of 132 patients, 36 (27.3%) had the only hysterectomy with bilateral salpingo-oophorectomy without lymphadenectomy and 23 (17.4%) did not have any kind of adjuvant treatment. Distribution of patients by surgicopathological characteristics and treatment modalities are summarized in table 1. The median follow-up period was 59.5 months (range, 3-178). That patient with a follow-up period shorter than 3 months (n=11) was excluded from the survival analyses. Overall, 22 (18.2%) patients had a recurrence and 7 patients died. Two of these 7 patients died in 2 months postoperatively so they were excluded from the survival analysis. Recurrences were locoregional in 9 patients whereas recurrence pattern was distant metastasis in 13 patients. The median recurrence time was 22.5 months. Five-year DFS and OS rates for the entire group were 76.6% and 94%, respectively.

Table 1: *Surgicopathological characteristics and treatment modalities, n= 132*

Parameters	n (%)
FIGO Grade	
Grade 1	38 (28.8)
Grade 2	73 (55.3)
Grade 3	21 (15.9)
Lymphovascular space invasion	
Negative	80 (60.6)
Positive	52 (36.4)
Lymphadenectomy	
No	36 (27.3)
Yes	96 (72.7)
Adjuvant treatment	
No adjuvant treatment	23 (17.4)
Chemotherapy	1 (0.8)
Brachytherapy alone	30 (22.7)
External beam pelvic radiation alone	61 (46.2)
Brachytherapy + External beam pelvic radiation	6 (4.5)
Radiotherapy field N/A	11 (8.3)

There was no clinicopathological factor or treatment modality associated with DFS and OS (Table 2). However, we observed that 5-year DFS rate was lower for patients who did not receive any kind of adjuvant treatment compared to those who had, although this difference was not statistically significant (50% vs. 78.1%, p=0.51).

Analysis of patients with grade 1, 2, 3 was made in respect to the association between the treatment modalities and survival. In all patients, adjuvant radiotherapy and type of adjuvant radiation were not associated with DFS and OS (p=0.283 and p=0.315 respectively, for DFS and p=0.423 and p=0.398, respectively, for OS) (Table 3).

Table 2: *Survival rate by clinicopathological factors and treatment modalities*

Parameters	5-year DFS (%)	*p* value	5-year OS (%)	*p* value
Age	80.1		95.1	
≤60	72.3	0.68	92.4	0.49
>60				
Tumor grade				
Grade 1	84.1		94.7	
Grade 2	75.1	0.4	93.9	0.82
Grade 3	66.2		92.9	
Lymphovascular space invasion				
Negative	74.8		94.1	
Positive	79.2	0.95	94	0.92
Lymphadenectomy				
No	74.5		87.7	
Yes	77.1	0.95	96.8	0.1
Adjuvant treatment				
No	50		94.1	
Yes	78.1	0.51	94.5	0.32
Radiotherapy received				
BRT alone	86		100	
EBRT alone	77.6	0.16	92.9	0.28
EBRT+BRT	50		83.3	

DFS: Disease - free survival, OS: Overall survival, BRT: Brachytherapy, EBRT: External beam pelvic radiation
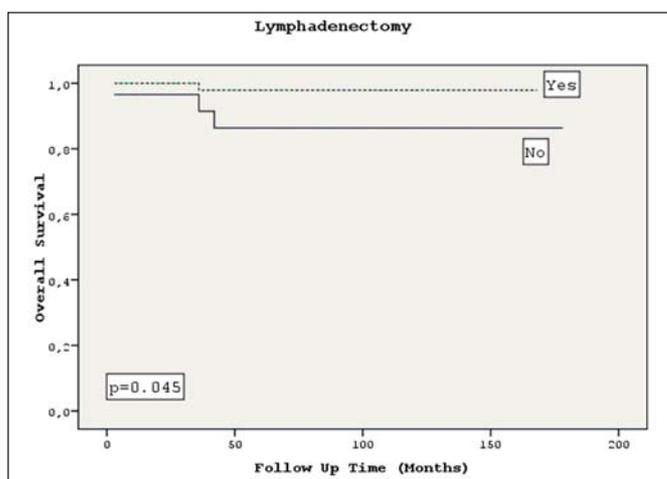
Table 3: *The survival effects of lymphadenectomy and adjuvant treatment on patients with grade 1, 2,3 tumor*

Parameters	5-year DFS (%)	*p* value	5-year OS (%)	*p* value
Lymphadenectomy				
No	74.8		85.3	
Yes	77.1	0.95	95.8	0.08
Adjuvant Radiotherapy				
No	47.7		97.8	
Yes	78.8	0.283	89.7	0.423
Field of adjuvant radiation				
BRT alone	75.4		100	
EBRT alone	75.8	0.315	91.4	0.398
BRT+EBRT	57.1		83,3	

DFS: Disease - free survival, OS: Overall survival, BRT: Brachytherapy, EBRT: External beam pelvic radiation

Similar to the entire group, patients who received adjuvant radiation had a lower recurrence compared to those who did not have adjuvant radiation (47.7% vs. 78.8%), although this was not statistically significant. The performance of lymphadenectomy was not significantly associated with DFS and OS in all cohort (p=0.95, p=0.08). However, in the subgroup analysis in patients with grade 1&2 tumor, lymphadenectomy was associated with better OS outcomes (97.9% vs. 86.4%, p=0.04) (Figure 1). Furthermore, adjuvant treatment modalities were similar between the group of patients who had or did not have lymphadenectomy in this subgroup (Table 4).

There was no clinicopathological factor that had a p value of <0.25 except the presence or absence of lymphadenectomy, therefore multivariate analysis was not applied.

Figure 1: Survival effect of lymphadenectomy

Table 4: *Distribution by adjuvant treatment for patients with grade 1 & 2 tumor*

Lymphadenectomy	Adjuvant treatment, n (%)		*p* value
	No	Yes	
No	5 (17.2)	24 (82.8)	0.78
Yes	11 (15.1)	62 (84.9)	

Discussion

2009 FIGO classification system identifies 2 subgroups of stage I according to the depth of myometrial invasion (IA: MI <50% and IB: MI ≥50%) (6). As low-risk patients that defined as stage IA and grade 1 & 2 have a negligible risk of lymphatic spread and recurrence, they can be treated with only hysterectomy (4,19). However, management of the patients with MI greater than half of myometrial thickness (stage IB) is controversial (15,16). Most of the studies about this issue are retrospective and include all histopathological subtypes together. Furthermore, the performance of lymphadenectomy varies between these studies.

Histological subtype and grade, tumor size, LVSI, MI and stage were shown as prognostic factors in various studies (19-23). However, we only included the patients with stage IB (72% of which were surgically staged) and endometrioid type histology and did not found any association between LVSI and DFS or OS. Maybe, LVSI could predict higher stages or lymphatic spread in patients with apparently uterine confined disease but may not be a predictor of survival in patients with established negative nodes. Furthermore, although, DFS and OS tended to be lower in patients with higher grades, this was not statistically significant (Table 2). This may be explained by the fact that almost all patients with grade 3 tumor received adjuvant treatment and underwent lymphadenectomy compared to those with grade 1 & 2 tumor in whom adjuvant treatment or lymphadenectomy was omitted to a certain extent.

Adjuvant therapy for patients with early stage disease is tailored according to FIGO stage and compiled prognostic factors (5, 15, 24-26). In low-risk patients, external beam radiation carries more risk than benefit and women treated with radiotherapy had more risk for developing secondary malignancies and had experienced a lower quality of life due to radiation toxicity (27).

A prospective randomized study (PORTEC-1) of patients with stage I endometrial carcinoma (patients with both grade

1 tumor and MI <50% were excluded) revealed that postoperative external beam radiotherapy reduces locoregional recurrence but has no impact on overall survival when lymphadenectomy is not carried out. Control group had almost four-fold increased risk of recurrence compared to radiotherapy group, however, there is no significant difference in respect to OS (15). GOG 99 trial evaluated the effect of adjuvant pelvic radiation in patients with intermediate risk endometrial cancer which was defined as any degree of myometrial invasion and any degree of histological grade. Non-endometrioid subtypes were excluded and all patients had lymphadenectomy. Patients were subdivided into a group with high intermediate risk which was defined as those with one or more risk factors (moderate to poorly differentiated tumor, presence of lymphovascular invasion, and outer third myometrial invasion) according to their age in this study. This group accounted for nearly two-thirds of the recurrences and cancer-related deaths. Adjuvant radiotherapy decreased the risk of recurrence in this subgroup of patients (26% vs. 6%) and those on the RT arm demonstrated a somewhat lower overall death rate which was not significant (25). Our study differs from PORTEC-1 and GOG 99 in some aspects; we included only patients with MI ≥50% whereas in PORTEC-1, patients with MI <50% were included if they had grade 2 & 3 tumors, no patient had lymphadenectomy and patients with non-endometrioid histopathology were included and distinct from GOG 99; our cohort consisted of patients all with MI ≥50%, almost all patients with poorly differentiated tumor received adjuvant treatment and 72.9% of patients had lymphadenectomy. We observed that half of the patients in our cohort who didn't have adjuvant radiotherapy had recurrence compared to 12% of those who had, even though it didn't reach a statistical significance and there was no difference in respect to OS. The absence of significance in respect to DFS may be due to the low number of patients who did not receive radiotherapy in our entire cohort (n; 23 vs. 109).

The role of comprehensive surgical staging in endometrial cancer remains controversial. Among different institutions, the extent of lymphadenectomy varies from lymph-node sampling alone in the patients who have a high risk for nodal metastases to complete lymphadenectomy in all patients with endometrial uterine cancer, irrespective of grade and depth of myometrial invasion (1). Knowledge of the presence or absence of nodal metastases might guide the treatment interventions in some patients through the survival effect of this guidance remains to be established (7,28). In addition to the guidance, survival benefit of removing apparently benign lymph nodes in early stage endometrial carcinoma has been shown in several studies (29-31). Recently, SEPAL trial revealed a survival benefit of combined pelvic and para-aortic lymphadenectomy compared to pelvic lymphadenectomy alone in the treatment of endometrial cancer patients (32). On the contrary, MRC ASTEC trial could not show any therapeutic effect of systematic pelvic lymphadenectomy (5) and a more a recent study by Koskas et al., which included 66.210 patients, concluded that poor outcome associated with higher risk of lymph node metastasis, that was calculated according to a nomogram, is not counterbalanced by lymphadenectomy (9). In our study performance of lymphadenectomy was associated with a better OS for the subgroup of patients with grade 1 & 2 tumors (p=0.04), although it was not valid for the entire cohort. In this subgroup (n=102) 73 patients had lymphadenectomy and importantly, there was no difference in respect to adjuvant treatment between the patients with or without lymphadenectomy (Table 4). We couldn't evaluate the effect of lymphadenectomy for the patients with grade 3 tumor because only 4 patients did not undergo lymphadenectomy and only 1 patient did not have adjuvant treatment.

In conclusion, adjuvant radiation seemed beneficial for prevention of recurrence as half of the patients who did not have any adjuvant radiotherapy recurred compared to 12% of patients those with adjuvant treatment. This needs to be confirmed by further studies which will include more patients who don't have adjuvant radiation. Lymphadenectomy had survival benefit for the patients with myometrial invasion greater than a half of myometrial thickness.

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