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Surgical staging of low-risk Stage IA endometrioid endometrial cancers

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Summary

Purpose: Surgical staging in early endometrial cancer is not universally done and lymphadenectomy in early-stage disease is controversial. Aim of the present study was to evaluate surgical staging in patients with endometrioid histology, FIGO Stage IA endometrial cancer. *Materials and Methods:* Eighty-seven patients with FIGO Stage IA, low-risk patients were included in the study. Staging surgery group included patients who had comprehensive surgical staging (hysterectomy, oophorectomy, and pelvic lymph node dissection with or without para-aortic lymph node dissection). Non-staging surgery group included patients who had hysterectomy, and bilateral oophorectomy with or without lymph node sampling. Two groups were compared for lymph node status, occult cervical involvement, other prognostic factors, and outcome were analyzed. *Results:* In total 17.2% of patients were upstaged in final pathological examination; 12.9% in non-staging surgery group and 24.2% in staging surgery group. Upstaging was due to lymph node involvement (6%), cervical stromal invasion (13.7%), and myometrial invasion greater than 50% (1.1%). Median pelvic lymph node number was 23 and pelvic lymph node metastases was found in 3% of the patients. Median para-aortic lymph node number was 11.5 and there was one isolated para-aortic lymph node metastases (5.8%). *Conclusion:* Of the patients, 17.2% had stage migration. Until the issue is solved by future studies, surgical staging might be considered standard surgery for endometrial cancer.

Key words: Endometrial cancer; Staging; Lymph node dissection; Upstaging.

Introduction

Endometrial cancer is the most common gynecological cancer with an age adjusted rate of 16-34 per 100,000. Incidence is highest in Northern America and Europe, while incidence is lowest in Africa and Asia [1]. Lifetime risk of endometrial cancer is 2.8%. Estimated new cases and deaths in 2015 are 54,870 and 10,170, respectively [2]. Incidence and death rates did not change since 2000. Natural course of disease is slow and 67.5% of cases are confined to the uterus [2, 3]. Five-year survival rate in Stage I is 50-95% depending on the presence of histopathological risk factors. Staging of endometrial cancer was clinical before 1988, now it is only utilized in patients in which surgery is contraindicated. Particularly, findings of GOG 33 and other studies led to surgical staging after 1988 [4]. Surgical staging of endometrial cancer consists in exploration of abdomen, collection of cytology, total hysterectomy and salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy. In 2009, FIGO staging was revised; patients with no myometrial invasion and with invasion less than 50% of myometrium were collapsed into same stage as FIGO Stage IA. Stage IIIC was divided into Stages IIIC1 and IIIC2, reflecting different prognosis in pelvic and para-aortic lymph node involvement, respectively [5]. However, surgical staging in early endometrial cancer is not universally done and lymphadenectomy in early stage disease is controversial. Although there has been studies evaluating role of staging in intermediate and high-risk patients, the data is limited in low-risk patients. Aim of the present study was to evaluate surgical staging in patients with endometrioid histology, FIGO Stage IA endometrial cancer.

Materials and Methods

Institutional Review Board approved the study and the records of all endometrial cancer patients between 2007 and 2015 were reviewed. Stage IA patients with endometrioid histology, less than 50% of invasion and grades 1 and 2 in preoperative biopsy and frozen section were included in the study. Staging surgery group included patients with pelvic lymph node number > 8, regardless of para-aortic lymph node dissection. Non-staging surgery was regarded as hysterectomy and bilateral salpingo-oophorectomy without pelvic lymph node sampling. Patients that had lymph node sampling (pelvic lymph node number < 8) were included to non-staging group as the lymph node status is not determined by a comprehensive lymph node dissection. Patients who had surgical staging were compared to patients whom did not have it. Age, tumor histology, grade, depth of myometrial invasion, cervical stromal involvement, lymphovascular space invasion, number and location of lymph nodes, nodal metastasis, upstaging in final pathology, and the reason for upstaging were abstracted. Follow-up time, recurrence, and death rate were recorded. Patients in both

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Table 1. — *The mean age and clinicopathological prognostic factors in both surgical groups.*

	Non-staging surgery (n=54)	Staging surgery (n=33)	*p* value
Age (years)	55.9 ± 10	56.1 ± 7.5	> 0.05
Grade 1	88.9% (n=48)	60.6% (n=20)	< 0.001
Grade 2	11.1% (n=6)	39.4% (n=13)	
No myometrial invasion	27.7% (n=15)	9%(n=3)	> 0.05
Myometrial invasion < 50%	34.4% (n=39)	28.9% (n=30)	
LVSI +	11.1% (n=6)	3% (n=1)	> 0.05
Tumor size	4.0 ± 3.0	4.9 ± 3.2	> 0.05
Age > 60 years	31.5% (n=17)	27.7% (n=9)	> 0.05

groups were analyzed also for poor prognostic factors, such as age greater than 60 years old, lymphovascular space invasion, myometrial invasion, grade, and tumor size.

Results

A total of 87 patients with endometrioid histology, FIGO Stage IA, grades1 and 2 endometrial cancer in frozen section were included in the study. All patients were in low-risk group. Four patients with grade 3 endometroid cancer were excluded. Mean age of patients was 56 ± 9.1 years and 74.7% of women were postmenopausal. Fifty-four patients were in non-staging group. Thirty-three patients had comprehensive staging surgery ($p > 0.05$), 20.7% (n=18) had no myometrial invasion, and 79.3% (n=69) had invasion less than 50% of myometrium. Grades 1 and 2 were observed in 78.2% and 21.8%, respectively. Lymphovascular space invasion was negative in 92% (n=80) and it was positive in 8% (n=7) patients. 70.1% of women were less than 60 years of age whereas 29.9% were older than 60 years. Mean age and clinicopathological prognostic factors in both surgical groups are shown in Table 1.

In total 17.2% (n=15) of patients were upstaged; seven patients (12.9%) in non-standard surgery group and eight patients (24.2%) in staging surgery group were upstaged in final pathological examination. Upstaging was due to lymph node involvement (6%, 2/37), cervical stromal invasion (13.7%, 12/87), and myometrial invasion greater than 50% (1.1%, 1/87) in final pathology (Table 2).

Six patients in each group were upstaged because of cervical involvement in final pathology ($p > 0.05$). All of these patients migrated to Stage II were grade 1, had no lymphovascular space invasion or lymph node metastasis, and all had superficial myometrial invasion except one. All were less than 60 years of age, except one (62-years-old). Five of six patients with cervical involvement in standard surgery group received brachytherapy. One of six patients with cervical involvement in non-standard surgery group received brachytherapy. There was no recurrence or death in both groups.

Table 2. — *The comparison of up-staging, occult cervical involvement, lymph node metastasis, myometrial invasion, median pelvic lymph node, and median para-aortic lymph node statement between groups*

	Non-staging surgery (n=54)	Staging procedure (n=33)	*p* value
Up-staged	12.9% (n=7)	24.2% (n=8)	> 0.05
Occult cervical involvement	11.1% (n=6)	18.2% (n=6)	> 0.05
Lymph node metastasis	0/2 in pelvic node sampling; unknown in 52	3% (n=1)	–
Myometrial invasion >50%	1.8% (n=1)	–	
Pelvic lymph node median (range)	4.5 (r:3-6) (n=2)	23 (r:8-51) (n=37)	< 0.05
Para-aortic lymph node median (range)	–	11 (r:1-23) (n=17)	

Figure 1. — Intraoperative situs after comprehensive para-aortic lymph node dissection. Abdominal aorta and vena cava inferior are elevated with loop. Retro-aortic and retrocaval lymph nodes have been dissected.

Comprehensive pelvic lymphadenectomy was performed in 33 patients. Median pelvic lymph node number in staging surgery group was 23 (range: 8-51) and in one patient, pelvic lymph node metastases was found (3%,1/33). Median pelvic lymph node number in two pa-

Table 3. — *The comparison of median follow-up time, recurrence, and death in two groups.*

	Non-staging surgery (n=54)	Staging procedure (n=33)	*p* value
Median Follow-up (month)	33	19	< 0.05
Recurrence	n = 2 (3.7%)	n = 1 (3%)	> 0.05
Death	n = 3 (5.5%)	n = 1 (3%)	> 0.05

tients with sampling was 4.5 (range: 3-6) and no metastases were detected. Para-aortic lymphadenectomy was performed in 17 patients (Figure 1). Median para-aortic lymph node number was 11.5 (range 1-35) and there was one isolated para-aortic lymph node metastasis (5.8%,1/17). Patients with lymphatic metastasis had no cervical involvement and all had myometrial invasion less than 50% (Stage IA). Tumor grade was grade 2 in women with pelvic lymph node metastasis, and grade 1 in para-aortic lymph node metastasis. All patients with lymph node metastasis received external radiotherapy and vaginal brachytherapy. All of these patients are alive and none have recurrence. There were three recurrences (Table 3) in lung, abdominal wall, and vaginal cuff. There were three deaths in unstaged patients in the follow-up period.

Discussion

Surgical staging is of importance in high-risk early-stage and advanced-stage endometrial cancer. There is no consensus on extent of surgery in low-risk, early-stage endometrial cancer patients (Figure 1). Surgical staging provides prognostic variables, allows accurate planning of adjuvant treatment, and may improve survival [6-12]. There is still controversy on need of lymphadenectomy based on ASTEC trial and Italian study, and the extent of lymphadenectomy [13-15]. In ASTEC trial the surgical procedure was not standard, the median number of lymph nodes were low, the size of study was small to detect overall survival, and patients with low- and high-risk were combined [8, 16]. However, both studies did not include para-aortic lymphadenectomy [8]. While some retrospective studies suggest lymphadenectomy regardless of grade and myometrial invasion [9-11], some advocate identifying patients that are at high-risk for lymph node metastasis [15, 17]. Mayo Clinic criteria indicated that there was no lymph node metastasis in patients with type I endometrial cancer, grades 1 and 2; myometrial invasion ≤ 50%, and primary tumor diameter ≤ two cm [17]. Therefore, all other patients except the mentioned criteria were candidates for systematic lymphadenectomy. By using Mayo Clinic criteria, 33% of endometrioid tumors did not require lymphadenectomy [15].

Risk of pelvic and para-aortic lymph node metastasis is reported to be zero (grade 1) to 4% (grade 2) in patients with no myometrial invasion. However, patients with 50% myometrial invasion and no intraperitoneal disease had a 3% to 10% (grades 1 and 2) incidence of pelvic lymph node metastasis, and a 2% incidence of para-aortic lymph node involvement [4, 18,19]. The present authors have found 3% pelvic lymph node metastasis and 5.8% para-aortic lymph node metastasis in this group of patients.

In the present study, 17.2% of patients had stage migration. This percentage might be important to consider low-risk patients for routine staging because it is reported that accurate staging in Stage I endometrial cancer provides a five-year survival greater than 90% [20]. At least ten pelvic lymph nodes should be removed to affect survival [8, 12]. However, size and follow up time of the present study was limited to make a conclusion on recurrence and survival. Another limiting factor in the present study was the extent of para-aortic lymphadenectomy. Dissection limits were up to inferior mesenteric artery or above IMA on surgeons preference. The present authors have found a 5.8% of para-aortic metastases in 17 low-risk patients. It is reported that 77% of patients with para-aortic node involvement had metastases above the IMA [15]. Todo *et al.* showed that para-aortic lymphadenectomy has survival benefits in intermediate- and high-risk early-stage endometrial cancer and pelvic lymphadenectomy alone may be an insufficient surgery in high-risk patients [8]. More studies are needed assessing the role of para-aortic lymphadenectomy in low-risk early endometrial cancer.

Morbidity and mortality of lymph node dissection is low in high-volume centers and is related to the experience of the surgeon [21, 22]. Blood loss, hospital stay, and complication rates in comprehensive staging is similar to hysterectomy [22, 23]. Staging provides information on extent of disease, prognostic factors, classifies patients into same groups, allows comparison of same groups, and modulates postoperative treatment. The present data is interesting in that it may indicate that patients with cervical involvement and superficial myometrial invasion without any other risk factor can be managed without adjuvant treatment.

Cervical stromal involvement has been regarded as adverse prognostic factor and comprises Stage II. Occult cervical involvement rate in this study was 13.8%. A preoperative cervical biopsy or MRI is recommended in suspected or grossly involved cervix [24]. Currently endocervical curettage is not routinely performed [19]. Evident Stage II patients were not included in the present study group in order to have homogenous group of low-risk endometrial cancer patients. Although survival in Stage II patients is reported to be lower, Morrow *et al.* reported that "it is unclear that cervix invasion per se diminishes survival, because it is more often associated with poor tumor differentiation and deep myometrial invasion

than cases without cervical invasion" [25, 26]. It has been reported that radical hysterectomy is not prognostic and other clinicopathologic factors, such as histological grade, lymph node metastasis, lymphovascular space invasion, and myometrial invasion affects the prognosis more strongly [26-28].

Staging facilitates clinical research and helps dissemination of knowledge by providing a common international language for information sharing. Pathologist and the surgeon can affect the staging and the outcome. An overall discrepancy rate of 42.7% is reported between an original pathology report and review by a gynecologic pathologist [29]. The number of lymph nodes and detection of involvement can be influenced by pathologist. Surgeon may provide a complete staging by resection of the uterine corpus along with involved lymph nodes. Comprehensive staging of endometrial cancer may also ensure to separate effect of pathologist and surgeon. The major task of gynecologic oncologist is to document extent of disease and prognostic factors [30].

The present results and findings in the literature indicate that there is considerable risk of stage migration in patients with superficial myometrial invasion. It is also possible that a more comprehensive staging may underscore the present findings. Endometrial cancer is the most common gynecologic malignancy which can be cured or have a good five-year overall survival. While surgical staging can be practiced in the setting of a clinical trial, it also holds true for a surgery consisting of only hysterectomy and oophorectomy. Endometrial cancer may require a standard comprehensive surgical staging regardless of grade and myometrial invasion by a gynecologic oncology team until the controversy is solved by prospective randomized studies with good designs [23]. More studies are need to address upstaging and pelvic and para-aortic lymph node metastases in low-risk early -stage endometrial cancer.

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