EJGO European Journal of Gynaecological Oncology

Which is the appropriate surgical procedure for Stage I endometrial carcinoma?

L. Sun, X.G. Sheng, L. Wei, F. Gao, X. Li, N.F. Liu, D.P. Li, X. Zhang, T.T. Zhang, P. Wei

Department of Gynecologic Oncology, ShanDong Cancer Hospital & Cancer Institute, Shandong University, Jinan (China)

Summary

Objective: To study the appropriate surgical procedure for Stage I endometrial carcinoma (EC), the clinical and pathological features and prognosis factors, as well as types were analyzed retrospectively. *Materials and Methods:* This is a retrospective study of 277 patients with early-stage EC in clinical Stages I that received surgery between January 2000 and March 2008. The appropriate surgical procedures were divided into three types (procedure I-III: hysterectomy with or without ovary preservation, subradical hysterectomy plus pelvic lymph node biopsy, and radical hysterectomy pelvic plus lymphadenectomy) according to the clinical stage. *Results:* Tumor invasion of the cervix and deep muscularis as well as the parametrium, EC Stage Ib, grade 3 and ascites had carcinoma cells, were high-risk factors of EC metastasis to the retroperitoneum ($p < 0.05$). The ovarian preservation of EC Stage Ia had no effect on overall survival. The three types of procedure for the EC Stage Ia were not correlated significantly to the three-year and five-year survival rates. The three-year and five-year survival rates of three surgical procedures for the EC Stage Ib were significantly correlated. The survival rates of surgical procedures II and III were significantly higher than that of procedure I ($P < 0.05$). *Conclusion:* Subradical hysterectomy plus pelvic lymph node biopsy was recommended for EC Stage Ib with high-risk factors. There was no evidence of benefit in terms of overall or recurrence-free survival for radical hysterectomy plus pelvic lymphadenectomy in women with Stage I EC.

Key words: Endometrial carcinoma; Stage I; Surgical procedure.

Introduction

Endometrial carcinoma (EC) is one of the commonest gynecological cancers worldwide. Surgical evaluation and staging have been the cornerstone of management since 1988, when the International Federation of Gynecology and Obstetrics (FIGO) system was changed from clinical to surgical staging, and FIGO modified its staging system in 2009 [1]. Generally, the surgical procedure should include an adequate vertical abdominal incision, peritoneal fluid sampling for cytological evaluation, and meticulous exploration of the whole abdominal cavity. Then proceeding to extrafascial hysterectomy with bilateral salpingo-oophorectomy (BSO), peritoneal biopsy, and pelvic and para-aortic lymphadenectomy. The newly introduced staging incorporated pathological risk factors in order to better define the extent of disease, estimate prognosis, and guide adjuvant treatment recommendations. Despite implementation of this more accurate staging system, the optimal surgical procedure for the management of EC remains controversial, particularly in clinical early-stage patients. Within Stage I disease, 3-5% of women with well differentiated tumours and superficial myometrial invasion will have lymph-node involvement. This proportion rises to roughly 20% of women with poorly differentiated tumours and deep myometrial invasion. The decision to treat depends on whether the patient has risk factors such as histologic grade, myometrial invasion, extrauterine and lymph node involvement, and the age of the patient. Several retrospective series have suggested that these factors are important in determining the recurrence and death rate [2]. Management varies widely, particularly in Stage I EC patients with different risk factors. The initial treatment of Stage I EC is usually surgery involving a total abdominal hysterectomy (TAH) and BSO [3]. However, evidence is scarce of the therapeutic benefit for lymphadenectomy in terms of survival. The present study is focused on identifying the appropriate surgical procedure for Stage I EC, by considering the impact of ovarian preservation, high-risk factors, clinical and pathological features, and prognosis.

Materials and Methods

A retrospective analysis was performed on 277 patients with Stage I EC who received surgery in X hospital from January 1, 2000 to March 31, 2008.

These patients were treated primarily by surgery and certified with pathology and without pre-operative chemotherapy, radiotherapy or hormonal therapy. Staging was based retrospectively on the surgical and pathology reports and according to the FIGO EC staging [4]. On the basis of their etiologic and pathologic features, EC is classified into type I and type II [3,4]. In the study, 225 patients were EC type I (125 grade 1, 75 grade 2 and 55 grade 3) and 52 were EC type II. Table 1 outlines the distribution of clinical pathologic features for the EC groups.

Revised manuscript accepted for publication June 23, 2014

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XXXVI, n. 6, 2015
doi: 10.12892/ejgo2716.2015

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Table 1. — *Four surgical groups based on the surgical pathologic stage.*

	N	Procedure I	Procedure II	Procedure III
Stage Ia	112	55(31*)	36	21
Stage Ib	165	32	59	74
Total	277	87	95	95

*Number of patients with ovarian preserved.

Table 2. — *Clinicopathologic characteristics in 277 EC patients.*

Clinicopathologic Characteristics	N	Operative pathologic stage Stage Ia	Stage Ib
Lesion region			
Uterine basal part	137	59	78
Uterine cavity or inferior segment	140	53	87
Tumor diameter			
≤ 4cm	142	67	75
> 4cm	135	49	86
Depth of invasion			
Endometrium only	70	70	0
Inner half of myometrium	127	127	0
Deep myometrial invasion	80	0	80
Serous membrane invasion			
No	233	84	149
Yes	44	0	44
Cervical invasion			
No	254	112	142
Yes	23	0	23
Differentiation or grade adenocarcinomas			
Uncertain	5	2	3
G1	110	49	61
G2	65	24	41
G3	45	16	29
Undifferentiation	10	4	6
Non-adenocarcinomas	42	18	24
Ascites positive cytology			
Negative	245	97	148
Positive	32	12	20

Of the 277 patients included in this retrospective analysis, the surgical procedures were divided into three types according to the different therapeutics. Procedure I was TAH and BSO or unilateral ovary preserved for young patient who wanted to ovarian preservation. Procedure II was subradical hysterectomy with pelvic lymph node biopsy or sampling. Procedure III was radical hysterectomy with pelvic lymphadenectomy. Patients were divided into 4 groups according to the different pathologic stages (as shown in Table 1) in order to choose the most appropriate surgical procedure. Patients were stratified on the basis of whether bilateral salpingo-oophorectomy (BSO) was performed (BSO group) or whether the ovaries were retained (Ovary preserved group).

Patients with clinical stage I EC were surgically staged and were stratified into three risk categories. In the high-risk patients (stage Ib, high tumor grade, deep myometrial invasion, cervical involvement, pelvic and para-aortic lymph node involvement and serous or clear cell histology), pelvic external beam radiotherapy and/or vaginal brachytherapy and chemotherapy as well as hormone treatment can be given as an adjuvant treatment to reduce the risk of recurrence. The different operative pathologic stages between falling ill, high-risk factors, pathologic type, grade and ovaries or extrauterine as well as lymph node invasion and prognosis were analyzed.

Data are expressed as the median and range. All statistical tests were two-tailed. Survival was analyzed by the log-rank test and Cox multivariable regression analysis. Cox proportional hazards models were fit with potential factors associated with falling ill, high-risk factors, pathologic type, grade, ovarian or parametrium invasive, as well as lymph node metastasis and prognosis. Kaplan-Meier curves were generated to examine overall survival based on whether a BSO was performed. A $p < 0.05$ was set as the level of statistically significant difference. All statistical analysis was done with SPSS 11.3 (Statistical Package for Social Science).

Results

From 1 January 1, 2000 to March 31, 2008, 277 patients were diagnosed with endometrioid uterine cancer and underwent a surgical staging procedure including lymph node assessment and stage assignment based on the 1988 FIGO staging system [1]. Because FIGO modified its staging system in 2009, the authors retrospectively analyzed and staged their patients under the new version. The clinical pathologic characteristics of the study population are given in Table 2. With informed consent, confirmation of the absence of known risk factors, and intraoperative evidence suggesting the absence of advanced disease, BSO with or without lymph node dissection, and preserved ovaries were performed. Factors of ovaries, extrauterine involvement, lymphovascular space invasion, and lymph node metastases involvement analysis are given in Tables 3 and 4.

The survival of the patients whose ovarian preserved versus those who underwent BSO were compared. Of the 277 patients, 246 (88.9%) underwent BSO, and the remaining 31 (11.2%) had their ovaries preserved. A Kaplan-Meier analysis revealed no difference in overall survival between the two groups ($p > 0.05$) (Figure 1). Ovarian preservation had no significant influence on disease-free survival and metastatic tumor in patients with grade I EC ($p > 0.05$).

Data on chemotherapy, tumor invasion of the cervix and deep muscularis, as well as extrauterine involvement, EC Stage Ib grade 3, and ascites had carcinoma cells, and a raised Ca 125 blood test ($p < 0.05$) were high-risk factors of EC metastasis to the parametrium and ovary. Cervical involvement and deep myometrial invasion as well as periuterus, EC Stage Ib grade 3, and ascites had carcinoma cells, and were high-risk factors of EC metastasis to the retroperitoneum ($p < 0.05$). Estrogen and progesterone (ER/PR) positivity was not significantly correlated to the retroperitoneum and lymph node metastasis ($p > 0.05$). There was no statistically significant difference in overall survival in Stage Ia patients with BSO or unilateral salpingo-oophorectomy ($p < 0.05$).

The three-year and five-year survival rates of EC Stage Ia were 98.21% and 93.46%, respectively. The operation procedure I (TAH and BSO or unilateral salpingo-

Table 3. — *Factors of ovaries, parametrium and lymphovascular space invasion analysis*

Predictor			Ovarian metastases (n=8)				Parametrium metastases or lymphovascular space invasion (n=11)		
			N	N (%)	χ^2	p value	N (%)	χ^2	p value
Age	≤ 45years old		80	2 (2.50)			2 (2.50)		
	> 45years old		197	6 (3.05)	0.72	0.39	9 (4.57)	0.29	0.59
Lesion region	Uterine basal part		137	3 (2.19)			6 (4.38)		
	Uterine cavity or inferior segment		140	5 (3.57)	2.75	0.09	5 (3.57)	0.18	0.67
Tumor diameter	≤ 4cm		142	3 (2.11)			3 (2.12)		
	> 4cm		135	5 (3.70)	3.33	0.07	8 (5.93)	1.60	0.21
Depth of myometrial invasion	No		70	0 (0)			0 (0)		
	≤ 1/2		127	1 (0.78)	17.78	0	1 (0.78)	12.32	0.02
	> 1/2		80	7 (8.75)			10 (12.50)		
Serous membrane invasion	No		233	2 (0.86)			2 (2.45)		
	Yes		44	6 (13.64)	8.41	0.01	9 (20.45)	12.22	0
Cervical invasion	No		205	1 (0.49)			5 (2.44)		
	Yes		72	7 (9.72)	3.31	0.08	6 (8.33)	2.71	0.10
Histopathological types									
Endometrioid adenocarcinomas			225	6 (2.67)			8 (3.56)		
Non-endometrioid histology			42	2 (4.76)	9.54	0.01	3 (7.14)	6.64	0.01
Differentiation grade	Uncertain		8	0 (0)			0 (0)		
	G1		122	0 (0)			0 (0)		
	G2		80	3 (3.75)	9.21	0.01	1 (12.5)	11.09	0.01
	G3		55	3 (5.45)			7 (12.7)		
	Undifferentiation		12	1 (8.33)					
Ascites positive cytology	Negative		245	3 (12.2)			4 (16.3)		
	Positive		32	5 (15.6)	13.63	0	7 (21.8)	13.38	0.01
Serum CA125 level	Normal		92	4 (4.34)			3 (3.26)		
	Abnormal		185	4 (2.16)	6.49	0.01	8 (4.32)	3.42	0.06

oophorectomy), II (subradical hysterectomy with pelvic lymph node biopsy) and III (radical hysterectomy with pelvic lymphadenectomy) were not significantly correlated to the three- or five-year survival rate. The three- and five-year survival rates of EC Stage Ib were 97.74% and 93.26%, respectively. The survival rates of surgical procedures II and III were significantly higher than that of procedure I ($p < 0.05$). The survival rates of the surgical procedures II and III were not significantly correlated. The three- and five-year survival rates of the surgical procedures I, II, and III were significantly correlated ($p < 0.05$). The three-and five-year survival rates of procedure II and III were significantly higher than that of procedures I. The three-year survival rate was not significantly correlated to postoperative chemotherapy, radiotherapy or hormone treatment, but the five-year survival rate was significantly higher than that without postoperative chemotherapy and radiotherapy or without hormone treatment ($p < 0.05$).

Discussion

EC is the commonest gynecologic malignancy worldwide and more than 40,000 new cases are diagnosed each year [5]. Because vaginal bleeding is commonly associated with the presence of disease, more than 75% of patients with EC are diagnosed at an early stage, resulting in overall favorable prognosis, with a five-year overall survival rate of 80-85% and a cancer-specific survival rate of 90-95% [6]. Traditional management of women with Stage I EC has been surgery, typically combined with adjuvant radiotherapy for women whose pathological features suggest an increased risk of nodal metastases. The cornerstone of curative therapy for patients with EC is surgical treatment, including complete hysterectomy, removal of remaining adnexal structures, and appropriate surgical staging in patients considered at risk for extrauterine disease [7]. Treatment of EC has a generally favorable outcome when patients present in the early-stage of the disease. The need for a radical and complete surgical staging procedure is clinically important but has been poorly studied. On the basis of retrospective findings, the present study was focused on patients with Stage I EC as defined by the high-risk factors, clinical and pathologic features, and prognosis factors in the surgical specimen combined with respective adjuvant assessment. The present objective was to identify appropriate surgical procedure and adjuvant treatment for Stage I EC. Since FIGO introduced surgical staging of EC in 1988, various questions have remained unanswered [8]. One of the potential challenges for defining the most effective treatment of EC arises from inconsistency in the surgical staging. The staging system includes tumor grade, depth of myometrial invasion, occult extension to the cervix, ad-

Table 4. — *Factors of lymph node metastasis analysis.*

Predictor		N	N	Positive rate (%)	χ^2 value	*p* value
Age	≤ 45 years	80	3	3.75		
	> 45 years	197	12	6.09	3.57	0.06
Lesion region						
Uterine basal part		137	12	8.76		
Uterine cavity or inferior segment		140	9	6.43	0.39	0.54
Depth of myometrial invasion						
No		70	0	0		
≤ 1/2		127	8	7.87	0.47	0.02
> 1/2		80	13	16.25		
Cervical invasion	No	205	7	3.41		
	Yes	72	13	18.05	1.29	0.00
Histopathological types						
Endometrioid adenocarcinomas		115	8	6.95		
Non-endometrioid histology		42	11	26.19	1.13	0.00
Differentiation grade						
Uncertain		8	0			
G1		122	0	0		
G2		80	3	3.75	1.31	0.01
G3		55	10	18.18		
Undifferentiation		12	1	8.33		
Lymphovascular space involvement						
No		258	15	5.82		
Yes		19	11	57.89	24.25	0.00
Acites positive cytology						
Negative		245	13	5.31		
Positive		32	12	37.50	7.573	0.01
ER	Positive	105	8	7.62		
	Negative	172	9	5.23	0.56	0.45
PR	Positive	97	4	4.12		
	Negative	180	13	7.22	3.05	0.08

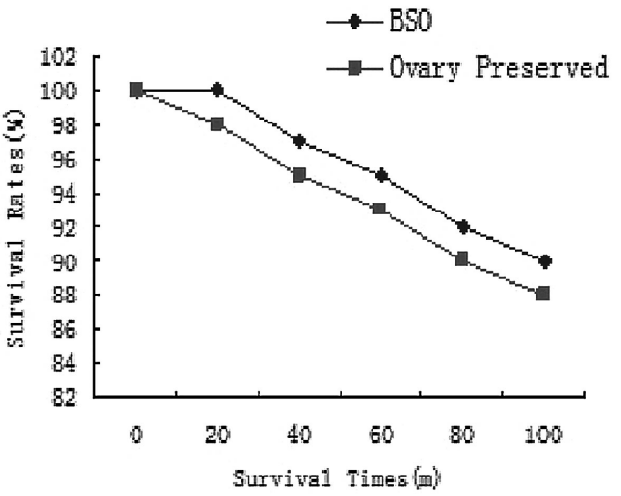

Figure 1. — Kaplan-Meier analysis of overall survival of patients with early-stage endometrial cancer stratified by BSO or preservation of the ovaries.

nexal involvement, peritoneal cytology, pelvic and periaortic lymph node involvement, and vaginal, inguinal or distant metastases. In particular, controversy has been focused on FIGO Stage I endometroid adenocarcinoma with different grades. Currently, the standard of care for patients with no contraindication to surgical intervention is TAH and BSO, pelvic and periaortic lymph node sampling or lymphadenectomy [9]. Patients and physicians are confronted with the dilemma of whether to follow the standard surgical guidelines or to accommodate the desire of the patients to avoid surgical menopause. Careful patient selection and surgical competence are instrumental in ensuring successful treatment. The concomitant use of surgical staging, hysterectomy, and resection of adnexal structures is currently recommended for most patients with endometrial malignancies [4, 5]. However, the extent of dissection necessary for adequate staging has not been standardized. On the basis of retrospective study of 277 patients, it is suggested that the surgical extent was determined by the preoperative evaluation of lesion region, depth of myometrial invasion, and presence of cervical invasion. When imaging is necessary for medically inoperable patients, magnetic resonance imaging (MRI) of the pelvis is superior to computed tomography (CT) for visualizing the uterus and surrounding tissues [10, 11]. Baseline cancer antigen levels can be useful for predicting extrauterine spread but are not sufficiently sensitive to replace surgical staging. In this study, the authors found that hysterectomy was appropriate for Stage Ia patients. To avoid the short- and long-term consequences of surgical menopause, there is a strong rationale for ovarian preservation in young women. The major risk factor of preserving the ovaries in young women with early-stage endometrial cancer is the risk of coexisting adnexal malignancy. In women with early-stage cervical cancers, the incidence of ovarian metastasis has been reported to be < 1% by several large-scale studies [12]. In the present study, ovarian preservation has not been shown to increase the risk of recurrence. There was no significant difference of overall survival whether the ovary was preserved or not.

For Stage Ib cases, however, univariate analysis demonstrated that radical hysterectomy or subradical hysterectomy was necessary according to the high-risk factors. Subradical hysterectomy with pelvic and para-aortic sampling should be used for EC Stage Ib patients. On the basis of this study, the risk factors that were predictive for distant recurrence were cervical involvement, deep myometrial invasion, tumor diameter > two cm, serous membrane invasion, ascites positivity, and high blood CA125 level.

Lee *et al.* reviewed 272 patients with a mean age of 51.8 years. They identified a non-endometrioid histologic subtype, intraoperative extrauterine disease, lymph node metastases, and age as independent risk factors for adnexal metastases in women with early-stage and grade of endometrial carcinoma [13]. They also concluded that after

extensive preoperative and intraoperative evaluation, and in the absence of risk factors, ovarian preservation might be an option in early-stage EC. Bilateral oophorectomy in pre-menopausal women causes significant adverse long-term effects in bone, heart, and neurologic health as well as in quality of life [14]. In the present study, the ovaries were not removed from any young EC Stage I patient who wanted to ovarian preservation and metastatic tumor was not discovered in ovaries at follow-up.

Several authors concluded in their study that lymphadenectomy can be omitted in patient without risk factors such as grade 3 cancer, deep myometrial invasion, age > 60 years, and clear cell or papillary serous histology [15, 16]. In the setting of significant morbidity related to premature menopause secondary to the BSO, and the effects of lymphadenectomy, hysterectomy with ovary preservation seems to lead to better disease-free survival in young endometrial cancer patients, especially with Stage Ia EC as in the present study. Subradical hysterectomy with or without pelvic and para-aortic biopsy was used for endometrial carcinoma Stage Ib EC.

Numerous studies have demonstrated that cell type, histologic grade, depth of myometrial invasion, cervical involvement, and lymphovascular involvement can predict recurrence and survival in patients with EC [17]. A number of recent retrospective studies have suggested that Stage I EC patients with negative lymph nodes after systematic surgical staging could have been treated with vaginal brachytherapy alone; historically, these women received adjuvant pelvic radiotherapy [18, 19]. Adjuvant therapy is necessary for a patient with high-risk factors that include high tumor grade, deep myometrial invasion, cervical extension, and serous or clear cell histology consists of vaginal brachytherapy, teletherapy, systemic chemotherapy or some combination thereof [20,21].

Survival is heavily dependent on surgical stage, which is determined at present using the classification system adopted by FIGO in 2009 [22]. Patients commonly present with postmenopausal bleeding and those with early-stage EC generally have an excellent prognosis. The five-year relative survival rate for Stage I disease is 97.4%. Without adjuvant chemotherapy or vaginal brachytherapy, the recurrence rate is 23% in patients with stage I disease [23]. The three- and five-year survival rates of operation procedures II and III were significantly higher than those of procedure I ($p < 0.05$). The three- and five-year survival rates of procedure III were significantly higher than those of procedures I and II. The extent of dissection might improve the chance of survival by removing micrometastatic disease and decreasing recurrence and metastases. Positron emission tomography (PET)/CT, MRI, and dilation and curettage preoperative studies are not accurate methods for the evaluation of lymph nodes. Likewise, intraoperative assessments such as lymph node palpation and examination of frozen sections have been shown to be inadequate. It appears that comprehensive surgical staging allows the surgeon to identify high-risk EC patients who would benefit from adjuvant therapy.

Treatment options for EC differ according to the disease status and vary from a primary surgical treatment to a combination of surgery and adjuvant radiotherapy or chemotherapy [24]. External pelvic radiotherapy and/or vaginal brachytherapy should be used postoperatively for patients with tumor characteristics that predict a high risk of local recurrence and a poor prognosis [25].

In conclusion, ovarian preservation in young Stage I EC patients may be safe and not associated with an increased risk of mortality. Continuous follow-up would be necessary for patients with preserved ovaries after hysterectomy. Subradical hysterectomy should be approached to Stage Ib EC patients, and subradical hysterectomy with pelvic biopsy should be performed to those patients with high-risk factors. There is no evidence of benefit in terms of overall or recurrence-free survival for radical hysterectomy plus pelvic lymphadenectomy in women with Stage I EC.

Acknowledgements

The project was supported by grants from the Medical Science and Technology Project of Shandong (2011HZ097), the Natural Science Foundation of Shandong (ZR2012HM010), and partly by Shandong Cancer Hospital, Shandong Academy of Medical Sciences, ShandongUniversity, Jinan, China.

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Address reprint requests to:
X.G. SHENG, PhD, M.D.
Department of Gynecologic Oncology
ShanDong Cancer Hospital & Cancer Institute
Shandong University
440# Ji Yan Road, Jinan 250117 (China)
e-mail: guishengxiu@163.com