

Original Article



Clinical outcomes of stage I endometrial carcinoma patients treated with surgery alone: Siriraj Hospital experiences

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OPEN ACCESS

Received: Jan 12, 2016

Revised: Apr 20, 2016

Accepted: May 8, 2016

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ABSTRACT

Objective: To evaluate the recurrence rates and patterns of failure in patients with stage I endometrial carcinoma after surgical staging without adjuvant therapy.

Methods: Medical records of 229 patients with stage I endometrial carcinoma, treated with surgery alone between 2002 and 2010 at Siriraj Hospital were retrospectively reviewed. The primary objective of this study was recurrence rates. The secondary objectives were patterns of failure, disease-free survival, overall survival, and prognostic factors related to outcomes.

Results: During median follow-up time of 53.3 months, 11 recurrences (4.8%) occurred with a median time to recurrence of 21.2 months (range, 7.7 to 77.8 months). Vaginal recurrence was the most common pattern of failure (8/11 patients, 72.7%). Other recurrences were pelvic, abdominal and multiple metastases. Factors that appeared to be prognostic factors on univariate analyses were age and having high intermediate risk (HIR) (Gynecologic Oncology Group [GOG] 99 criteria), none of which showed significance in multivariate analysis. The recurrence rates were higher in the patients with HIR criteria (22.2% vs. 4.1%, $p=0.013$) or patients with stage IB, grade 2 endometrioid carcinoma (9.4% vs. 4.3%, $p=0.199$). Five-year disease-free survival and 5-year overall survival were 93.9% (95% CI, 89.9 to 5.86) and 99.5% (95% CI, 97.0 to 99.9), respectively.

Conclusion: The patients with low risk stage I endometrial carcinoma had excellent outcomes with surgery alone. Our study showed that no single factor was demonstrated to be an independent predictor for recurrence.

Keywords: Endometrial Neoplasms; Stage I; Surgery

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in the developed countries including the United States [1]. It is estimated that 47,100 new endometrial cancer cases occur in 2012, with 8,000 deaths resulting from the disease [2]. The incidence is lower in the developing countries, however it becomes increasingly important [3]. In 2007 to 2009, its incidence was 2 to 4 per 100,000 of Thai females [4].

Funding

This study was supported by the Siriraj Research development Fund.

Conflict of Interest

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

Surgery is the mainstay of treatment, consists of total hysterectomy with bilateral salpingo-oophorectomy (TH-BSO) [5]. The role of pelvic and para-aortic lymph node sampling or lymphadenectomy is still debatable [6-8]. After surgery, patients are divided into three risk groups of recurrences (low, intermediate, and high), based on multiple factors, including patients' age, histologic subtype, tumor grade, staging of disease and presence of lymphovascular space invasion [9-13].

Low risk endometrial cancer (International Federation of Gynecology and Obstetrics [FIGO] 1988, stage IA–IB grade 1, and stage IA grade 2) has a minimal risk for pelvic lymph node metastasis ($\leq 5\%$) [14] or vaginal recurrence (0.4% to 3.1%), with high disease-free survival (DFS) rate (95%) [15]. It is generally accepted that low-risk, stage I patients do not benefit from adjuvant treatment [15,16].

The purpose of this study was to evaluate the treatment outcomes and patterns of recurrence in stage I patients who were surgically treated without adjuvant treatment. Clinical and pathological factors were evaluated for prognostic significance. The results will potentially facilitate the selection of patients who may benefit from adjuvant treatment, and adjust the standard of care.

MATERIALS AND METHODS

After receiving an approval by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital, a retrospective review of medical records was performed in 229 patients with stage I endometrial cancer, who were treated with surgery alone between 2002 and 2010. The primary outcome of this study was to identify the recurrence rate in surgically managed stage I endometrial cancer patients. The secondary outcomes were to explore the failure patterns, DFS, overall survival (OS), and prognostic factors relating to the survival.

The inclusion criteria were stage I endometrial cancer (FIGO 1988) [5], who underwent standard surgical treatment with at least removal of the uterus and adnexal structures (TH-BSO) with no adjuvant postoperative radiation therapy (PORT) or chemotherapy. As our study was retrospectively review, FIGO 1988 staging system was used during that period of time for treatment selection. Therefore we used the FIGO 1988 system for data analyses. Also, the recent rationale for treatment recommendation was generally based on the details of the FIGO 1988 system. We excluded the patients who had insufficient follow-up data or patients who were diagnosed with other malignancies within 5 years prior to endometrial cancer diagnosis.

All pathologies were centrally reviewed. Histologic subtypes were determined according to World Health Organization (WHO) classification [17]. All of patients' information were reviewed. The follow-up visits were scheduled every 3 to 4 months during the first 2 years, every 6 months to 5 years, then annually. During the follow-up evaluation, data regarding medical history and pelvic examination were obtained. Vaginal recurrence was confirmed by tissue biopsy and pathology. Regional and distant recurrences were diagnosed by physical examinations and imaging studies. Computed tomography (CT)/magnetic resonance imaging (MRI) scan of abdomen was not performed routinely, unless patients developed clinically suspicious recurrent diseases.

For sample size calculation, we used 5% of any recurrences after treating with surgery alone [18]. Calculation of the sample size with acceptable tolerance at 3% and confidence level at 0.95, required a sample size of 203 cases (using a nQuery program, Statistical Solutions Ltd., Ireland) with 10% sparing due to incomplete data in retrospective study. The total of at least 223 patients were recruited in this study. Descriptive data were described with median, mean and standard deviation. Chi-square tests were performed to compare categorical variables. Cox regression method was used in univariate and multivariate analyses. Survival analyses were performed with Kaplan-Meier curve.

RESULTS

From 2002 to 2010, 229 patients with stage I endometrial cancer treated with surgery alone were included. We excluded two patients who had insufficient data, leaving 227 patients for analysis. Of these 227 patients, 180 patients (79.3%) underwent TH-BSO and pelvic lymph nodes removal; the remaining 47 patients (20.7%) underwent hysterectomy without surgical evaluation of lymph nodes by different reasons (morbid obesity, severe medical comorbidities, discretion of the operators). Para-aortic lymph node evaluation was performed in 37% (84/227 patients) of patients. Most of cases underwent para-aortic lymph node sampling up to the level of inferior mesenteric artery. Only four cases were dissected to the level of renal vessels. The most common pathology was endometrioid carcinoma (97.8%). Patients' characteristics, clinicopathological features were demonstrated in **Table 1**.

During median follow-up of 53.3 months (range, 0.2 to 120.7 months), 11 recurrences (4.8%) occurred with a median time to recurrence of 21.2 months (range, 7.7 to 77.8 months). Most common pattern of recurrence was vaginal recurrence (72.7%, 8/11 patients). Other recurrences were pelvic failure (one patient), abdominal failure (one patient), and multiple metastases (one patient). **Table 2** demonstrates the distribution of patients with recurrence according to each stage and grade. The recurrence rate was 4.3% (8/186 patients) in low risk group (FIGO 1988 stage IA, grade 1–2 and stage IB, grade 1). Remarkably, the recurrence rate was higher in the patients with patients with high intermediate risk (HIR) based on Gynecologic Oncology Group (GOG) 99 criteria (22.2% vs. 4.1%, $p=0.013$) [12]. Also, patients with stage IB, grade 2 showed a trend to have higher recurrence than those with lower stage or grade (9.4% vs. 4.3%, $p=0.199$). Median number of pelvic lymph nodes harvested was 12. Number of pelvic lymph nodes harvested did not significantly affect recurrence (1.1% vs. 7.6% for ≥ 12 nodes vs. < 12 nodes, $p=0.080$). FIGO 1988 stage IA was not different from stage IB to predict recurrence (stage IA 5.3% vs. stage IB 4.7%, $p=0.786$).

Most of the patients (8 out of 11 patients) received salvage radiation therapy, with median OS of 53.3 months (range, 14.9 to 105.3 months) after recurrence. In overall, 5-year DFS and 5-year OS for the whole group were 93.9% (95% CI, 89.9 to 5.86) and 99.5% (95% CI, 97.0 to 99.9), respectively (**Figs. 1, 2**).

In univariate analysis, older age (>70 years old) and having HIR according to the GOG 99 criteria [12] appeared to be prognostic factors to predict recurrence. There was no independent predicting factor for recurrence on multivariate analysis (**Table 3**).

Table 1. Patients' characteristics, staging, pathology, and treatment

Characteristic	Value
Total no. of patients	227
Age (yr)	55 (28-82)
≤70	209 (92.1)
>70	18 (7.9)
Body mass index (kg/m ²)	25.8 (15.2-49.8)
<30	178 (78.4)
≥30	49 (21.6)
Pelvic lymph node harvested (node)	12 (0-72)
<12	92 (51.1)
≥12	88 (48.9)
Histology	
Endometrioid	222 (97.8)
Non-endometrioid	5 (2.2)
Histologic grade	
1	174 (76.7)
2	47 (20.7)
3	6 (2.6)
Tumor size (cm)	
≤2	108 (47.6)
>2	119 (52.4)
Myometrial Invasion (%)	
No	95 (41.9)
≤50	129 (56.8)
>50	3 (1.3)
Lower uterine segment involvement	
Absent	187 (82.4)
Present	40 (17.6)
Lymphovascular space invasion (LVSI)	
Absent	219 (96.5)
Present	8 (3.5)
FIGO 1988 stage	
IA	95 (41.9)
IB	129 (56.8)
IC	3 (1.3)

Values are presented as median (range) or number (%).

FIGO, International Federation of Gynecology and Obstetrics.

Table 2. Recurrence rates by stage and grade

FIGO 1988 stage	Grade 1 (n=174)	Grade 2 (n=47)	Grade 3 (n=6)
IA (n=95)			
Total	77	14	4
Recurrence	4 (5.2)	1 (7.1)	0
IB (n=129)			
Total	95	32	2
Recurrence	3 (3.2)	3 (9.4)	0
IC (n=3)			
Total	2	1	0
Recurrence	0	0	0

Values are presented as number (%).

FIGO, International Federation of Gynecology and Obstetrics.

DISCUSSION

To our knowledge, this is the largest report of stage I endometrial cancer treated with surgery in Thailand. Most of patients in our study underwent TH-BSO with pelvic lymph nodes removal, although 20.4% of the patients underwent only TH-BSO. The primary treatment of endometrial cancer is surgery, consists of at least TH-BSO. The role of systematic lymphadenectomy is controversial. The former studies reported no benefit of

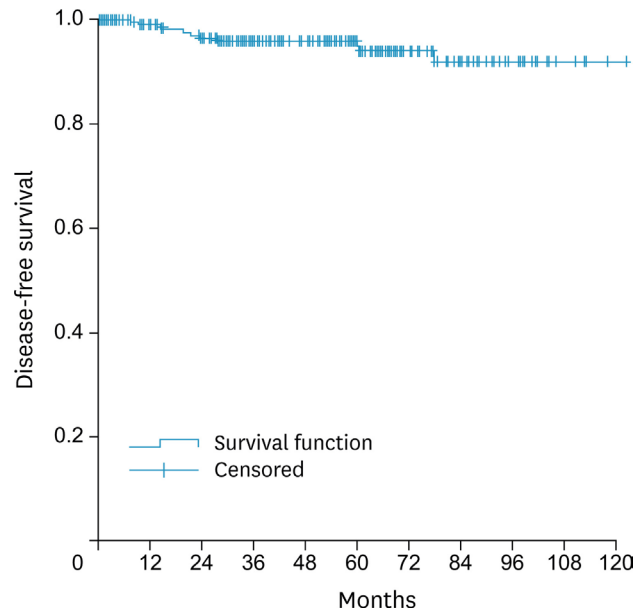


Fig. 1. Five-year disease-free survival.

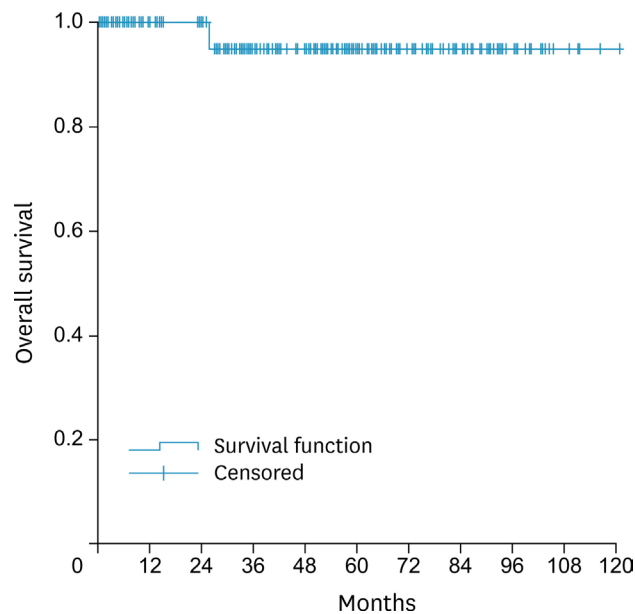


Fig. 2. Five-year overall survival.

lymphadenectomy in terms of either OS or recurrence-free survival in patients with early stage endometrial cancer [6,7,13,19]. However, the results have been criticized due to the potential bias from adjuvant radiotherapy (RT) [8]. Our study confirmed no significant correlation between number of pelvic lymph nodes harvested and recurrence in patients with early stage disease who underwent surgery alone. This was in accordance with our institute's prior study, which showed no benefit of extensive lymphadenectomy for endometrial cancer patients who received adjuvant RT [20]. In the present study, pelvic/para-aortic lymph nodes evaluation and the level of para-aortic lymph node evaluation were dependent on the operator and the feasibility of the procedures. Four cases that underwent para-aortic lymph

Table 3. Univariate and multivariate analyses of prognostic factors for recurrence

Prognostic factor	Total (n=227)	No. of recurrence	Univariate for recurrence		Multivariate for recurrence	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yr)				0.045		0.435
≤70	209	8	1.0		1.0	
>70	18	3	10.14 (1.05-97.64)		2.95 (0.19-44.86)	
Body mass index (kg/m ²)				0.074		0.256
<30	178	6	1.0		1.0	
≥30	49	5	2.96 (0.90-9.37)		2.34 (0.54-10.13)	
FIGO 1988 stage	224			0.786		
IA	95	5	1.0		1.0	
IB	129	6	0.85 (0.26-2.79)		-	-
PLN harvested (node) [†]	180			0.082		0.118
≥12	88	1	1.0		1.0	
<12	92	7	6.42 (0.79-52.15)		5.47 (0.65-46.23)	
Histologic grade				0.253		
1	174	7	1.0		1.0	
2-3	53	4	2.05 (0.60-7.00)		-	-
Tumor size (cm)				0.875		
≤2	108	5	1.0		1.0	
>2	119	6	1.10 (0.34-3.61)		-	-
Lower uterine segment involvement				0.995		
Absent	187	9	1.0		1.0	
Present	40	2	1.00 (0.22-4.61)		-	-
LVSI				0.241		
Absent	219	10	1.0		1.0	
Present	8	1	3.43 (0.44-26.80)		-	-
HIR criteria [†]				0.013		0.180
No	218	9	1.0		1.0	
Yes	9	2	6.96 (1.50-32.32)		4.90 (0.48-49.99)	

FIGO, International Federation of Gynecology and Obstetrics; HIR, high intermediate risk; HR, hazard ratio; LVSI, lymphovascular space invasion; PLN, pelvic lymph node.

[†]According to MRC ASTEC trial [6]. [†]HIR criteria from a Gynecologic Oncology Group (GOG) trial-99 [12]. Women in the HIR group were (1) patients with moderate or poorly differentiated tumors with LVSI and invasion into the outer third of the myometrium, or (2) were over 50 years of age with any two of the above risk factors, or (3) over 70 years of age with any one risk factor above.

nodes evaluation up to the level of renal vessels had body mass index (BMI) less than 25 kg/m². None of five patients with BMI more than 40 kg/m² underwent either pelvic or para-aortic lymph node evaluation.

Patients with grade 1 and 2 endometrioid carcinoma confined to the endometrium are considered as low risk with 2% to 4% recurrence rate [21-23]. Our study reported 4.3% recurrence rate in low risk patients (FIGO 1988 stage IA, grade 1-2 and stage IB, grade 1) within the same range of other studies. This group of patients demonstrated an excellent prognosis after comprehensive surgical staging. No study of adjuvant treatment has shown survival benefit in low risk group patients [11,12]. Thus, postoperative therapy is usually withheld [15,23,24]. Our study showed that patients with age of >70 years or having high-intermediate risk criteria (according to GOG 99 [12]) are potentially at increased risk of recurrence.

PORT is typically recommended in patients with intermediate risk, aiming to reduce locoregional recurrence from 6.9% to 14% down to 1.6% to 5% at 2 to 10 years [10,12,25]. Our study demonstrated 9.4% recurrence rate among patients with stage IB, grade 2 diseases. This result confirmed that this group of patients should be recommended to receive PORT. The prior study from our institute showed no recurrence in low intermediate risk patients (FIGO 1988 stage IA grade 3, IB grade 2) who received adjuvant radiation therapy [20].

In this study, we classified nine patients into HIR group (according to the GOG 99 study [12]) for subgroup analyses. These patients experienced significantly high recurrence rate compared to those without HIR criteria (22.2% vs. 4.1%, HR, 6.9; 95% CI, 1.5 to 32.3; $p=0.013$). The most common pattern of recurrence in this study was vaginal recurrence, which is in concordance with other studies, although there are some pelvic and extra-pelvic recurrences [10-13,18]. Recent data from Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC-2) study showed equivalent benefits in vaginal control, DFS, and OS in the HIR patients between adjuvant vaginal brachytherapy and pelvic external beam radiation therapy (EBRT). Importantly, grade 1-2 gastrointestinal toxicities were lower with vaginal brachytherapy compared to pelvic EBRT (12.6% vs. 53.8%) [26]. Therefore, we suggest that PORT, meaning vaginal brachytherapy, should be given to patients with either stage IB grade 2 or HIR (GOG 99 criteria [12]) after surgery in order to achieve good locoregional control [27]. Due to small number of patients with FIGO 1988 stage IC, the statistical significance of this group of patients could not be tested.

FIGO staging has been revised since 2009 [28]. The FIGO 2009 staging system was validated by various studies for its clinical relevance for risk stratification [29-32]. Most studies showed that FIGO 2009 has improved prediction of prognosis. Likewise, our study confirmed that there was no difference in recurrence rate between FIGO 1988 stage IA and IB.

Recently, there were several studies which developed nomograms to predict the locoregional and distant controls in early stage endometrial cancer. Age, stage of disease, depth of myometrial invasion, histologic subtype, grade, lymph node status, and vascular invasion were factors used to create those nomograms [33,34]. In the future, molecular biological genetic markers such as L1 cell adhesion molecule (L1CAM), TP-53 mutation, DNA polymerase ϵ (POLE) mutation, and microsatellite instability will play significant role to determine patients' prognoses in addition to current prognostic factors [35].

Nonetheless, our study demonstrated good outcome with salvage radiation therapy with a median OS of 53.3 months. There are evidences from the literature that salvage treatment, combining pelvic EBRT and vaginal brachytherapy, can successfully treat isolated vaginal recurrence with 5-year survival rate ranging from 50% to 60% [36-38].

There are several weaknesses in our study, including a retrospective manner, lack of some follow-up data, and routine surveillance without CT/MRI imaging unless clinically indicated and relatively small sample size. However, this is the first report of stage I endometrial cancer treated with surgery alone in our institute and Thailand. These results represent our practice and treatment outcomes showing some subgroup of patients do require adjuvant treatment rather than surgery alone.

In conclusion, low risk endometrial cancer patients had excellent outcomes with surgery alone. Our study showed that no single factor was demonstrated to be an independent predictor for recurrence. Specific group of patients whose pathology revealed moderately differentiated endometrioid carcinoma with myometrial invasion should receive adjuvant treatment rather than surgery alone.

ACKNOWLEDGMENTS

We would like to thank Ms. Wipa Paholpak for patients' information providing, and Mr. Suthipol Udompunthurak (Siriraj Medical Research Center) for statistical analyses.

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