

RESEARCH ARTICLE

Good Outcomes of Patients with Stage IB Endometrial Cancer with Surgery Alone

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Abstract

Background: Most patients with endometrial cancer have stage I disease. Adjuvant therapy in stage IB (formerly IC) endometrial cancer is controversial, treatment options including observation or brachytherapy/radiotherapy in grade 1-3 patients with or without chemotherapy. The purpose of this study was to assess the outcomes of our patients with stage IB endometrioid endometrial cancer. **Materials and Methods:** Sixty two patients with stage IB endometrial cancer and endometrioid histology were retrospectively evaluated. All patients were initially treated surgically by the same surgeon with comprehensive staging, i.e. total abdominal hysterectomy, bilateral salpingoopherectomy, bilateral pelvic and paraaortic lymph node dissection and omentectomy. Adjuvant radiotherapy was discussed with patients and utilized by those who accepted. Adjuvant chemotherapy was not given to any of the patients. **Results:** Median age was 62 (range, 42-95). Ninety percent of the patients had grade 1-2 disease. Thirteen patients (21%) received intra vaginal brachytherapy (IVBT) and one received whole pelvic radiotherapy (WPRT). Median follow-up time was 46 months (range, 9-77 months). Three patients experienced recurrence (4.8%), two of them died on follow-up and one was still alive at last visit. Two patients with recurrence had FIGO grade 2 tumors and one had a grade 3 tumor. Two patients (3.2%) died without evidence of recurrent disease. Relapse free survival at 5 years was 94.4% and overall survival was 93.1%. **Conclusions:** Patients with stage IB disease in our study demonstrated relatively low recurrence rates although the majority of them received no adjuvant treatment. Surgery alone may be sufficient for most patients with this stage of endometrial cancer.

Keywords: Endometrial cancer - stage IB - surgery - chemotherapy - radiotherapy

Asian Pac J Cancer Prev, 15 (9), 3891-3893

Introduction

Endometrial cancer is the sixth most common cancer worldwide and third most common cancer in developed countries. In United States it is the most common cancer of genital tract. It is estimated that 47,100 new endometrial cancer occurred in 2012 with 8100 women dying from the disease (Jemal et al., 2011). Approximately 75% of cases are confined to uterus and most patients with endometrial cancer have stage I disease. Socio economic factors are also important. African American race and low income neighborhoods decreased the cancer specific survival by 20% and 3% respectively at 5 years (Cheung, 2013).

Surgery is the primary treatment modality and adjuvant therapy in stage I endometrial cancer is controversial. Patients with grade 1-2 tumors have low risk of recurrence but those with grade 3 disease have higher risk (Wright et al., 2012). Overall survival in stage IB (formerly IC) is 87% and 84% for patients with grade 1 and 2 tumors and drops to 66% in those with grade 3 disease (Fleming

(2007). Radiotherapy reduces the risk of local recurrence but it has no survival benefit, (Scholten et al., 2005). This is to some extent because of the high salvage rate after vaginal relapse in a non-irradiated patient. Nearly one third of the patients with stage IB grade 3 cancer have distant metastases on follow-up, which justifies the use of an effective adjuvant chemotherapy. However data on adjuvant chemotherapy in this patient population is limited, although it was shown to improve progression free survival in a subgroup analysis of the Nordic Society of Gynecological Oncology/European Organisation for the Research and Treatment of Cancer(NSOG/EORTC) trial (Hogberg et al., 2010). Ongoing trials including GOG 249 and PORTEC 3 are investigating the role of chemotherapy in adjuvant setting. 1988 FIGO staging of endometrial cancer was revised in 2009. Formerly stage IC disease (>50% myometrial invasion, negative pelvic cytology, no cervical mucosal involvement) is now staged as IB. We herein aimed to analyze the treatment outcomes of our patients with stage IB uterine endometrioid cancer.

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Materials and Methods

Stage IB endometrial cancer patients with endometrioid histology treated in our institution from June 2006 until May 2012 were retrospectively evaluated. All patients were initially treated surgically by the same surgeon with comprehensive staging, i.e. total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), bilateral pelvic and paraaortic lymph node dissection (BPPLND) and omentectomy. Demographic features, tumor characteristics, treatment regimens and patient outcomes in terms of disease free survival (DFS) and overall survival (OS) were analyzed.

Statistical analysis

Descriptive analysis was performed for demographic and clinical characteristics of the patients. Kaplan–Meier analysis was performed to examine OS or DFS. Disease free survival was defined as the time from primary surgery until recurrence of tumor or death from any cause. Overall survival was defined as the interval from primary surgery to the date of death or last follow-up. Statistical analysis was performed with SPSS software version 17.0 (SPSS Inc., Chicago, IL) and statistical significance was set at p less than 0.05.

Results

Sixty two women with stage IB endometrioid type endometrial cancer were identified. Patient and tumor characteristics and treatment protocols are shown in Table 1. Median age was 62 (range, 42-95). Forty patients (65%) had at least one comorbid disease including diabetes mellitus, hypertension, goiter or ischemic heart disease.

None of the patients received adjuvant chemotherapy. Adjuvant brachytherapy is routinely offered to and discussed with patients with stage IB disease in our institution and performed in those who accept. Thirteen

patients (21%) received intra vaginal brachytherapy (IVBT) and one received whole pelvic radiotherapy (WPRT). Age, body mass index, tumor size, histological grade, lymphovascular invasion rate, myometrial invasion depth and number of lymph nodes dissected were similar between the patients who received brachytherapy and those who did not.

Median follow-up time was 46 months (range, 9-77 months). Relapse free survival at 5 years was 94.4% and overall survival was 93.1%. Three patients experienced recurrence (4.8%), two of them died on follow-up and one was still alive at last visit. Two patients with recurrence had FIGO grade 2 tumors and one had grade 3 tumor. Two patients (3.2%) died without evidence of recurrent disease. Characteristics of the patients who had recurrence and/or died are shown in Table 2.

Discussion

The treatment of early stage endometrial cancer is not well established. 5-year OS is 92.4% for stage IA, 87.3% for IB and 75.7% for IC disease (Abu-Rustum et al., 2011). Surgery is the mainstay of staging and treatment but chemotherapy and radiotherapy are also used in selected patients. Total laparoscopic hysterectomy or total abdominal hysterectomy may be preferred options (Wang et al., 2013). Observation, whole pelvic radiotherapy, brachytherapy and chemotherapy are all treatment options recommended for stage IB disease in NCCN guidelines but which treatment for which particular patient is not clear. Adjuvant radiotherapy was previously shown to reduce local recurrence but no effect was found on overall survival in a number of randomized studies as well as a recent Cochrane meta-analysis (Kong et al., 2012; Setakornukul et al., 2014). However these studies had limitations including no or low rate of pelvic/paraaortic lymph node dissection (Creutzberg et al., 2000), combination of patients at different disease stages and non-uniform high risk criteria. In contrast, the surgical procedure was more extensive in our study. All our patients had TAH+BSO, omentectomy and both pelvic and paraaortic lymph node dissection with median 8 paraaortic and 30 pelvic lymph nodes removed. PPLND was optional or selective in most of the previous studies. PPLND has a real diagnostic value and assumed therapeutic value in the management of endometrial cancer. As high as 30% of the patients with apparently stage I disease was found to have lymph node metastases depending on the depth of myometrial invasion and tumor grade (Creasman et al., 1987). Therefore when PPLND is not performed, the groups of patients in clinical studies with apparently stage I disease might also harbor patients with occult lymph

Table 1. Patient Characteristics

Patient characteristics	No. (%)
Age	62 (42-95)
BMI	31 (20-50)
Grade	1 23 (37.1)
	2 33 (53.2)
	3 5 (8)
Tumor size (cm)	3 (1-7)
Lymphovascular invasion	+ 21 (35.5)
	- 40 (64.5)
#of lymph nodes dissected (median)	37 (6-98)
Pelvic	30 (6-66)
Paraaortic	8 (0-32)
Whole pelvis radiotherapy	1 (1.6)
Intravaginal brachytherapy	13 (21)

Table 2. Characteristics of the Patients Who Died or Relapsed on Follow-up

Patient	Age	Grade	LVI	Adjuvant treatment	RFS	Site of recurrence	Outcome
1	85	2	+	-	-	-	Died without recurrence after 15 mos
2	72	2	+	-	-	-	Died without recurrence after 11 mos
3	54	2	+	-	28.8 mos	Paraaortic	Recurrence was surgically excised. Alive with no evidence of disease after 44 mos
4	55	3	-	Intravaginal brachytherapy	38.3 mos	Peritoneum	Died with disease after 73 mos
5	53	2	-	-	9 mos	Vaginal cuff and inguinal lymph nodes	Died with disease after 39 mos

node metastases (and stage III disease thereof) and benefit of additional treatment in this heterogeneous population might be confined to these higher stage patients. PPLND might also have some therapeutic value and reduce the benefit of any further treatment. The same situation is also applicable for adjuvant chemotherapy. In the combined analysis of the NSGO/EORTC and MaNGO/ILIADE trials, significant benefit of chemotherapy was demonstrated in the NSGO/EORTC trial where LND was performed in less than 20% of the patients but not in the MaNGO trial where LND was performed in nearly half of the patients (Hogberg et al., 2010). Our study is retrospective, none of the patients received chemotherapy and 13 patients (21%) received radiotherapy (mostly brachytherapy). RT was offered to all patients with stage IB grade 2-3 disease but only 21% accepted. Low number of the patients and lack of pre-specified criteria for tailoring treatment preclude any comparison of outcomes between treatment modalities. Second, most of our patients had grade 1 or 2 disease. Only 6.5% of the patients had grade 3 disease. Nevertheless, given the low number of recurrences compared to the pertinent literature after 46 months of follow up, we propose that not all patients with stage IB disease need treatment particularly if they have grade 1-2 disease and extensive lymph node dissection is performed. A recent retrospective study demonstrated 3 year cumulative failure rate of 5.4% in patients with grade 1-2 disease and 29% in those with grade 3 disease, most of the recurrences being distant and fatal (Long et al., 2012). Therefore, grade seems to be the most important factor in making treatment decisions in stage IB disease. Lymphovascular invasion was also found to be associated with high recurrence rate (25%) among patients with stage IB-IIA endometrial cancer (Sukumaran et al., 2011).

In conclusion, patients with stage IB grade 1-2 disease in our study have relatively low recurrence rates although majority of them received no adjuvant treatment. All our patients had comprehensive staging surgery including systemic lymphadenectomy, which eliminated those patients with micrometastatic disease in lymph nodes or other sites (occult stage III patients) from the cohort and might have a role in the low recurrence rate obtained. Vaginal brachytherapy alone may be a treatment option given the encouraging effect on local recurrence and low morbidity rate (Nout et al., 2012). Patients with grade 3 disease were under represented in our cohort but particularly distant failure rates are high in the literature and systemic therapy might be justified for these high risk patients.

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