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Should the Optimal Adjuvant Treatment for Patients With Early-Stage Endometrial Cancer With High-Intermediate Risk Factors Depend on Tumor Grade?

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Objectives: To explore whether the optimal adjuvant treatments for patients with early-stage endometrial cancer with high-intermediate risk (HIR) factors should depend on tumor grade.

Methods: A retrospective analysis of patients with HIR endometrial cancer from 1999 to 2012 was conducted. The adjuvant treatments and survival were evaluated.

Results: A total of 129 patients with HIR were identified, of which 71 had grade 1–2 tumor and 58 had grade 3 tumor. The adjuvant treatment chosen differed significantly between patients with grade 1–2 and grade 3 tumors ($P < 0.001$). Most of the patients (76.1%) with grade 1–2 tumors received no adjuvant treatment; however, chemotherapy alone was the most frequent (75.9%) adjuvant treatment for patients with grade 3 tumors. In the grade 1–2 group, no significant differences in the 5-year progression-free survival (94.1% vs 96.3%; $P = 0.857$) and overall survival (OS) rates (94.1% vs 98.1%; $P = 0.401$), respectively, were observed between patients who received adjuvant treatment (radiation and chemotherapy with or without radiation) and those who did not. For grade 3 disease, patients undergoing adjuvant chemotherapy alone had a favorable outcome with the 5-year progression-free survival rate of 84.4% and the OS rate of 95.5%.

Conclusion: It is logical to speculate that surgery followed by observation might be sufficient for patients with HIR with grade 1–2 tumor. Further prospective trials are required to confirm the issue owing to the limited number of this population. More studies are warranted to clarify the feasibility and efficacy of adjuvant chemotherapy alone in patients with HIR with grade 3 tumor.

Key Words: Endometrial cancer, High-intermediate risk, Adjuvant chemotherapy, Adjuvant radiotherapy

Endometrial cancer is the most common gynecological malignancy in developed countries. In 2014, 52,630 new cases of endometrial cancer, and 8,590 deaths from the disease were reported in the United States.[1] In general, the prognosis for women with endometrial cancer is excellent with approximately 75% of the cases diagnosed with stage I

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disease. Surgical procedures including total hysterectomy (TH) and bilateral salpingo-oophorectomy (BSO) with or without pelvic and/or para-aortic lymphadenectomy are the mainstays of treatment, and most women with early-stage disease can be cured by surgery.

However, a proportion of women will experience recurrence and death despite diagnosis of early-stage disease given the presence of the risk factors, which include diagnosed at an older age, high tumor grade, deep myometrial invasion, lymphovascular space invasion (LVSI), and cervical stromal involvement.[2–4] A series of randomized trials have confirmed that adjuvant radiation can reduce the risk of locoregional recurrence in patients with diagnosis of early-stage disease and presenting high-risk factors; however, it is not sufficient to improve the overall survival (OS).[5,6] Some clinical trials showed that adjuvant chemotherapy significantly improved OS in patients with endometrial cancer compared with adjuvant radiation.[7–9] Nevertheless, most of these studies included patients with not only early-stage disease but also advanced disease.[7,10] Currently, limited data are available on the efficacy of adjuvant chemotherapy patients with early-stage endometrial cancer with high-risk factors.

Patients who were found to have any degree of myometrial invasion with adenocarcinoma of any grade and no evidence of lymph node involvement (International Federation of Gynecology and Obstetrics [FIGO] stages IB, IC, and II [occult]) were considered as a member of intermediate risk group.[6] Gynecologic Oncology Group (GOG) 99 study further divided this group into the low-intermediate risk and high-intermediate risk (HIR) subgroups based on the number of adverse risk factors.[6] In that study, the following criteria were used to classify patients into the HIR group: (1) any age with grade 2–3 tumor, LVSI, and outer-third myometrial invasion, or (2) at least 50 years with any two of the risk factors above, or (3) at least 70 years with any one of the risk factors above. The HIR subgroup represented only one third of the patients entered into that study but accounted for nearly two thirds of the recurrences. A number of patients with early-stage disease and high-risk profiles were classified under the HIR group in subsequent studies.[5,8,11,12] However, a definite standard adjuvant treatment for patients with HIR has not yet been established. Moreover, considering that patients with grade 1–2 tumors had a significantly better outcome than those in the same disease stage with grade 3,[13,14] it is logical to speculate that the optimal adjuvant treatment modality for patients in HIR group could differ depending on the tumor grade.

The aim of this study was to explore whether the optimal adjuvant treatments for patients with early-stage endometrial cancer with HIR factors should depend on tumor grade.

MATERIALS AND METHODS

Inclusion Criteria

We retrospectively reviewed the cases with endometrial cancer who received primary surgical treatment at Sun Yat-sen University Cancer Center from April 1999 to June 2012. The patients with HIR factors were eligible. The risk factors included age in addition to deep (>50%) myometrial invasion, grade 2–3 tumor, and LVSI. In the present study, patients with HIR factors were defined as (1) any age with all 3 additional risk factors, or (2) aged 50 to 70 years with deep myometrial invasion and grade 2–3 tumor, with or without LVSI, or (3) aged 70 years and older having deep myometrial invasion with or without 2 other risk factors. All patients with the histologic type of nonendometrioid adenocarcinoma were excluded from the study.

The clinical data regarding patients' demographics, surgical records, pathologic characteristics, treatment, follow-up, and vital status were extracted from the hospital records. Approval was granted by the institutional review broad before the review of the records.

Treatment

Patients in whom disease was confined to the uterus underwent total hysterectomy (Piver-Rutledge type I) and BSO. Modified radical hysterectomy (Piver-Rutledge type II) and BSO were administered to the patients suspected with cervical involvement. Pelvic lymphadenectomy was performed in patients with risk factors, including grade 3 tumor, deep myometrial invasion, cervical involvement, and enlarged or suspicious nodes. Patients who presented with enlarged common iliac or para-aortic lymph nodes underwent para-aortic lymph node sampling or dissection.

Before 2006, the adjuvant treatment in our department was based on the FIGO guidelines[15] and our clinical experience. A clinical practice guideline was established for our department in 2006. Since then, the adjuvant treatment has been administered according to this well-defined protocol. In general, adjuvant chemotherapy was preferred over adjuvant radiotherapy for patients with endometrial cancer in our department. Since the GOG 122 study was published,[7] which reported that adjuvant chemotherapy resulted in significantly improved progression-free survival (PFS) and OS compared with whole abdominal irradiation in advanced endometrial carcinoma, adjuvant chemotherapy alone has been routinely administered to patients with early-stage endometrial cancer with grade 3 tumor in our department.

Statistical Analysis

Statistical analysis was performed using the SPSS 16.0 software (SPSS Inc, Chicago, IL). The categorical variables were compared using Pearson χ^2 test or the 2-tailed Fisher exact test. Survival time was calculated from the date of diagnosis. The PFSs were censored at the date of first recurrence or death, or the date of last contact with the patients alive without recurrent disease. Overall survival was censored at the date of death or the date of last contact for living patients. Survival curves were calculated using the Kaplan-Meier method and compared by the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model to identify prognostic factors independently associated with survival. Effects were expressed as hazard ratios (HRs) with 95% confidence intervals (CI). Statistical significance was defined as $P < 0.05$.

RESULTS

Patients' Characteristics and Adjuvant Treatments

A total of 129 patients with HIR factors were identified. The median age of patients was 57 years (range, 40–77 years). The patients' characteristics and adjuvant treatments are

TABLE 1. Patient characteristics and adjuvant treatments

Characteristics	No. Patients	%
Age, median (range), yrs	57 (40–77)	
BMI, mean ± SD	24.1 ± 3.6	
Tumor size, cm		
≤2	18	14.0
>2	111	86.0
Tumor grade		
1	1	0.8
2	70	54.3
3	58	45.0
FIGO stage *		
IB	93	72.1
II	36	27.9
LVSI		
Yes	38	29.5
No	91	70.5
Peritoneal cytology		
Positive	5	3.9
Negative	124	96.1
Type of hysterectomy		
I	51	39.5
II	78	60.5
Pelvic lymphadenectomy		
Yes	117	90.7
No	12	9.3
Para-aortic lymph node dissection/sampling		
Yes	28	21.7
No	101	78.3
Median no. pelvic lymph nodes resected (range)	18 (5–39)	
Median no. para-aortic lymph nodes resected (range)	4 (1–28)	
Adjuvant treatment		
EBRT	4	3.1
Chemotherapy alone	55	42.6
Chemotherapy + EBRT	6	4.7
No adjuvant treatment	64	49.6

*FIGO staging 2009

summarized in Table 1. Pelvic lymphadenectomy was performed in 117 (90.7%) of the 129 patients, with a median pelvic lymph node count of 18 (range, 5–39). In the remaining 12 patients (9.3%), the intraoperative assessment showed less than 50% myometrial invasion; however, final pathological evaluation revealed the presence of deep myometrial invasion. Therefore, pelvic lymphadenectomy was not performed in these 12 patients.

Of the 129 patients, 64 (49.6%) had no adjuvant treatment, and 55 (42.6%) received adjuvant chemotherapy alone. Four patients (3.1%) had external beam pelvic radiation therapy (EBRT), which included 2 patients who did not receive pelvic lymphadenectomy, one who presented with deep cervical stromal involvement, and one who underwent type I hysterectomy while having cervical stromal involvement proven by pathological evaluation. Six patients (4.7%) underwent chemotherapy combined with EBRT. The reasons for administering ERBT in addition to chemotherapy to these 6 patients were deep cervical stromal involvement in 5 patients and unknown in one.

Comparison of Patients' Characteristics and Adjuvant Treatments by Tumor Grade

The comparison of patients' characteristics and adjuvant treatments by tumor grade are shown in Table 2. There were more patients aged 60 years and older in the grade 1–2 group than in the grade 3 group (49.3% vs 27.6%; $P = 0.012$). When compared to the patients with grade 1–2 tumor, patients with grade 3 tumor were significantly more likely to have LVSI (50.0% vs 12.7%; $P < 0.001$) and pelvic lymphadenectomy (96.6% vs 85.9%; $P = 0.039$). Most of the patients (76.1%) with grade 1–2 tumor received no adjuvant treatment; however, chemotherapy alone was the most frequent (75.9%) adjuvant treatment for patients with grade 3 tumor. The adjuvant treatment chosen differed significantly between patients with grade 1–2 and grade 3 tumors ($P < 0.001$). There were no significant differences between grade 1–2 and grade 3 tumors with respect to body mass index (BMI), tumor size, stage, and peritoneal cytology.

We performed a subgroup analysis for patients with grade 1–2 tumor. There were no significant differences between patients with grade 1–2 tumor who received adjuvant therapy (radiation and chemotherapy with or without radiation) and patients who did not with respect to age, BMI, tumor size, stage, LVSI, and peritoneal cytology.

Subgroup analysis was also performed in patients with grade 3 disease. The 4 patients who had chemotherapy combined with radiation were excluded given the limited number. In the 44 patients who underwent adjuvant chemotherapy alone, 84.1% (37/44) and 15.9% (7/44) of the patients had stage IB disease and stage II disease, respectively. There was a higher percentage of stage IB disease in patients having adjuvant chemotherapy alone compared to patients who had no adjuvant treatment (84.1% vs 50.0%; $P = 0.019$). No statistical differences were observed between the patients with grade 3 disease who had chemotherapy alone and the patients who had no adjuvant treatment, with regard to age, BMI, tumor size, LVSI, and peritoneal cytology.

TABLE 2. Comparison of patients' characteristics and adjuvant treatments by tumor grade

Characteristics	Grade 1–2 tumor (n = 71)	Grade 3 tumor (n = 58)	P
	No. Patients (%)	No. Patients (%)	
Age, yrs			0.012
<60	36 (50.7)	42 (72.4)	
≥60	35 (49.3)	16 (27.6)	
BMI			0.407
<25	44 (62.0)	40 (69.0)	
≥25	27 (38.0)	18 (31.0)	
Tumor size, cm			0.114
≤2	13 (18.3)	5 (8.6)	
> 2	58 (81.7)	53 (91.4)	
FIGO stage*			0.640
IB	50 (70.4)	43 (74.1)	
II	21 (29.6)	15 (25.9)	
LVSI			<0.001
Yes	9 (12.7)	29 (50.0)	
No	62 (87.3)	29 (50.0)	
Peritoneal cytology			0.491
Positive	2 (2.8)	3 (5.2)	
Negative	69 (97.2)	55 (94.8)	
Pelvic lymphadenectomy			0.039
Yes	61 (85.9)	56 (96.6)	
No	10 (14.1)	2 (3.4)	
Adjuvant treatment			<0.001
EBRT	4 (5.6)	0 (0)	
Chemotherapy alone	11 (15.5)	44 (75.9)	
Chemotherapy + EBRT	2 (2.8)	4 (6.9)	
No adjuvant treatment	54 (76.1)	10 (17.2)	

*FIGO staging 2009

Since most patients with grade 3 tumor received adjuvant chemotherapy alone, we analyzed the chemotherapy regimen in these patients. A total of 163 chemotherapy cycles were administered (median, 4 courses per person). Of the 44 patients with grade 3 tumor receiving adjuvant chemotherapy alone, 29 (65.9%) received paclitaxel (135–175 mg/m^2) and carboplatin (area under the curve [AUC], 5–6), 9 (20.5%) received docetaxel (75 mg/m^2) and carboplatin (AUC, 5–6) or cisplatin (70–75 mg/m^2), 4 (9.1%) had cyclophosphamide (650–750 mg/m^2), doxorubicin (60 mg/m^2), and carboplatin (AUC, 5–6), and 2 (4.5%) received ifosfamide (1.5 g/m^2 days 1–4) and doxorubicin (60 mg/m^2).

Recurrence

Diseases recurred in 16 (12.4%) of the 129 patients, including 6 (4.7%) local recurrences and 10 (7.8%) distant metastases. The median time from surgery to relapse was 12.8 months (range, 1.8–133.7 months).

The sites of initial treatment failure classified according to tumor grade and adjuvant treatments are presented in Table 3. Patients with grade 3 tumor exhibited a significantly higher recurrence rate (11/58 [19.0%]) than those with grade 1–2 (5/71 [7.0%]; $P = 0.041$). The recurrent patterns were similar for both groups. Specifically, the incidences of local recurrence were 1.4% (1/71) in the grade 1–2 group and 8.6% (5/58) in the grade 3 group. Treatment failures were mostly observed at distant sites, with the distant recurrence rates being 5.6% (4/71) and 10.3% (6/58) in the grade 1–2 and grade 3 groups, respectively.

Treatment Outcomes

The median follow-up time was 62.5 months (range, 5.3–183.0 months). The 5-year PFS and OS rates for all patients were 88.6% and 92.7%, respectively. Patients with grade 1–2 tumor had significantly higher 5-year PFS and OS rates than those with grade 3 (95.8% vs 79.3%; $P = 0.024$; and 97.1% vs 86.7%; $P = 0.014$; respectively).

TABLE 3. Sites of initial recurrence according to tumor grade and adjuvant treatments

	All Patients (n =129)	Grade 1–2 Tumor (n = 71)		Grade 3 Tumor (n = 58)		
		No Adjuvant Treatment (n = 54)	Adjuvant Therapy (n = 17)	Chemotherapy Alone (n = 44)	Chemotherapy + Radiation (n = 4)	No Adjuvant Treatment (n = 10)
	No. Patients (%)	No. Patients (%)	No. Patients (%)	No. Patients (%)	No. Patients (%)	No. Patients (%)
No evidence of disease	113 (87.6)	50 (92.6)	16 (94.1)	38 (86.4)	3 (75.0)	6 (60.0)
Recurrence	16 (12.4)	4 (7.4)	1 (5.9)	6 (13.6)	1 (25.0)	4 (40.0)
Local recurrence	6 (4.7)	1 (1.9)	0 (0)	2 (4.5)	0 (0)	3 (30.0)
Vagina	5	1	0	1	0	3
Pelvis	1	0	0	1	0	0
Distant recurrence	10 (7.8)	3 (5.6)	1 (5.9)	4 (9.1)	1 (25.0)	1 (10.0)
Bone	2	0	1	0	1	0
Bone and para-aortic node	1	1	0	0	0	0
Lung	4	1	0	3	0	0
Lung and supraclavicular node	1	0	0	1	0	0
Liver	1	1	0	0	0	0
Malignant pleural effusion	1	0	0	0	0	1

We performed a subgroup analysis for patients with grade 1–2 tumor. In this group, the 5-year PFS rates were 94.1% for patients who had adjuvant treatment (radiation, chemotherapy with or without radiation) and 96.3% for those who did not ($P = 0.857$), respectively. And the 5-year OS rates in the patients who underwent adjuvant treatment and who did not were 94.1% and 98.1%, respectively ($P = 0.401$). After adjusting for age, BMI, tumor size, disease stage, LVSI, and peritoneal cytology, no significant differences in PFS (HR, 0.643; $P = 0.727$) and OS (HR, 0.725; $P = 0.596$) were observed between patients who received adjuvant treatment and those who did not (Table 4).

A subgroup analysis was also performed for patients with grade 3 tumor. The 5-year PFS and OS rates for patients who underwent adjuvant chemotherapy alone were 84.4% and 95.5%, respectively. We did not calculate the survival curve for patients who received chemotherapy combined with radiation owing to the limited number. In these 4 patients who had combined modality treatment, one patient experienced recurrence 6.8 months after surgery and died of the disease 8.7 months later; the 3 other patients remained free of disease after 17.0 to 34.6 months of follow-up. The patients who received no adjuvant treatment had significantly worse 5-year PFS (60.0%; $P = 0.021$) and OS (62.5%; $P = 0.048$) rates when compared with patients who underwent adjuvant chemotherapy alone. The 4 patients with grade 3 tumor were also excluded from multivariate analysis. After adjusting for risk factors, the HRs for PFS (12.323; $P = 0.006$) and OS (10.803; $P = 0.066$) of the patients who received no adjuvant treatment were significantly higher than those of the patients treated with adjuvant chemotherapy alone (Table 4).

DISCUSSION

A series of clinical trials demonstrated that patients with HIR early-stage endometrial cancer could benefit from adjuvant therapy. However, the criteria for defining HIR factors were not consistent among these studies.[5,6,8,11,12] There is no standard adjuvant treatment for patients with HIR as yet. Most previous studies recommended a uniform treatment modality for patients with HIR regardless of the tumor grade. Nevertheless, we found that treatment selection and patient outcome significantly differed among our patients with HIR depending on tumor grade. In our study, the patients with HIR with grade 1–2 tumor had significantly higher 5-year PFS and OS rates than the patients with grade 3 disease. These findings were consistent with previous studies that reported grade 3 tumor was a predictor of adverse outcomes in patients with early-stage endometrial cancer.[13,14]

In the present study, we found no significant difference in both PFS and OS between patients with HIR with grade 1–2 tumor who had adjuvant treatment and who did not. Moreover, the local failure rate in our data for patients with HIR with grade 1–2 tumor who had no adjuvant treatment was only 1.9% (Table 3). Thus far, few studies have reported the survival restricted to patients with HIR with grade 1–2 disease as those shown in our study. In the JGOG study performed by Susumu et al,[8] 190 patients with stage IC (FIGO stage 1988)

TABLE 4. Multivariate Cox regression analysis for PFS and OS according to tumor grade

Variable	PFS			OS		
	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
Grade 1–2 tumor (n = 71)						
Adjuvant treatment modalities						
No adjuvant treatment vs adjuvant therapy	0.643	0.145–6.646	0.727	0.725	0.169–4.062	0.596
Age (≥60 vs <60 years)	3.880	1.433–8.740	0.241	1.933	1.031–5.937	0.484
BMI (≥25 vs <25)	4.018	1.986–9.257	0.225	3.216	1.978–8.814	0.554
Tumor size (>2 vs ≤2 cm)	1.992	0.901–4.537	0.930	2.173	0.816–6.246	0.875
FIGO stage (II vs IB)	0.393	0.097–1.008	0.458	0.983	0.267–4.885	0.614
LVSI (yes vs no)	4.544	2.253–9.676	0.883	2.733	1.125–7.562	0.902
Peritoneal cytology (positive vs negative)	2.782	0.972–6.014	0.965	1.025	0.802–5.245	0.943
Grade 3 tumor (n = 54)						
Adjuvant treatment modalities						
No adjuvant treatment vs chemotherapy alone	12.323	2.049–21.564	0.006	10.803	2.112–22.430	0.066
Age (≥60 vs <60 years)	1.689	0.914–4.318	0.659	1.201	1.014–4.273	0.314
BMI (≥25 vs <25)	1.225	0.923–3.643	0.827	1.873	0.289–4.543	0.684
Tumor size (>2 vs ≤2 cm)	2.163	0.922–5.431	0.262	1.301	0.822–4.225	0.092
FIGO stage (II vs IB)	0.521	0.201–1.316	0.213	0.976	0.224–2.513	0.629
LVSI (yes vs no)	2.429	0.972–6.293	0.298	1.559	0.772–5.174	0.829
Peritoneal cytology (positive vs negative)	4.168	1.299–8.559	0.027	4.133	2.012–8.991	0.022

and grade 1–2 disease had 5-year PFS rates of 87.6% to 94.5% and 5-year OS rates of 90.8% to 95.1%. The survival rates of our patients with HIR with grade 1–2 tumor were comparable to or better than those reported in the study by Susumu et al. Although the results of our study and the JGOG study were not directly comparable given that ours was a retrospective study whereas the JGOG study was a prospective randomized study, it is noteworthy that all of these patients in the JGOG study received adjuvant radiation or chemotherapy, and none with stage II disease accompanied by deep myometrial invasion. A meta-analysis revealed that EBRT did not alter survival in patients with stage IB disease and grade 1–2 tumors (OR, 0.97; 95% CI, 0.69–1.35).[16] In our study, the favorable outcome and low local recurrence rate obtained for this group could be partially attributed to the extensive surgical procedure. All the patients who received type I hysterectomy had 2- to 3-cm vaginal cuff removal. Pelvic lymphadenectomy was performed in 85.9% of the patients in this group. Considering the excellent outcome observed in patients with HIR with grade 1–2 tumor who received no adjuvant treatment in our study, it is logical to speculate that surgery followed by observation might be sufficient for this group of patients. However, the number of patients with grade 1–2 tumor, regardless of having adjuvant treatment or not, was small; and further prospective trials are warranted to confirm the issue in this population. Similar results were reported by Rahatli et al[17] for patients with stage IB disease and grade 1–2 tumor who had a 5-year relapse-free survival rate of 94.4% and an OS rate of 93.1%. Since only 21% of these patients received radiotherapy in that study, it

was thought that surgery alone might be sufficient for patients with early-stage disease and grade 1–2 tumors.

In the present study, we found the patients with HIR with grade 3 tumor had significantly worse outcome than the patients with grade 1–2. There is consensus that adjuvant treatment is essential for these patients with HIR with grade 3 tumor owing to the high risk of recurrence. Nevertheless, the optimal adjuvant treatment for these patients has thus far been unclear. A variety of adjuvant treatment modalities including radiation alone, chemotherapy alone, and radiation combined with chemotherapy have been administered to patients with HIR factors. The GOG 99 study demonstrated that local recurrence was significantly reduced in HIR group patients treated with EBRT compared to those with only observation; however, ERBT did not improve OS in these patients.[6] Since distant recurrence was the primary reason for treatment failure in these patients, the use of systemic chemotherapy was thought to provide better disease control. Susumu et al[8] reported that adjuvant chemotherapy alone achieved significantly higher 5-year PFS and OS rates than EBRT in HIR group patients. The study by Susumu et al is the only study that compares the treatment efficacy of chemotherapy versus radiotherapy in HIR group patients. The 5-year PFS (84.4% vs 83.8%) and OS (95.5% vs 89.7%) rates of our patients with HIR with grade 3 tumors who underwent adjuvant chemotherapy were comparable to those observed in the study by Susumu et al.

Furthermore, some authors recommended a combination of radiation and chemotherapy for patients with HIR to achieve both locoregional and systemic control. The phase 2 trial RTOG (Radiation Therapy Oncology Group) 9708 was

conducted to determine the feasibility of adjuvant EBRT concurrent with cisplatin followed by vaginal brachytherapy (VBT) and 4 additional courses of cisplatin and paclitaxel in patients with endometrial cancer with grade 2 to 3 tumors accompanied by more than 50% myometrial invasion, cervical stromal invasion, or extrauterine disease confined to the pelvis.[18] No recurrence was observed in 13 patients with stages IC, IIA, or IIB (FIGO stage 1988) disease in that study. Excellent locoregional and distant controls were achieved in the RTOG 9708 trial with the combination treatment; however, the number of HIR group patients in this study was limited. Jutzi et al[19] evaluated the efficacy of adjuvant chemotherapy comprising paclitaxel and carboplatin followed by EBRT and VBT in patients with early-stage high risk and observed 1.9% locoregional failures and 7.3% distant recurrences, with 5-year PFS and OS rates of 88.6% and 97.1%, respectively. However, this study had a short follow-up time with a median of 27 months. In another phase 2 trial by Landrum et al,[11] 23 patients with HIR factors who received VBT followed by 3 courses of paclitaxel and carboplatin chemotherapy achieved a 2-year PFS rate of 91% and a 3-year PFS rate of 87%. Indeed, none of the above 3 trials assessing the efficacy of combination treatment had a control group. The accruing phase 3 trial GOG 0249 is comparing VBT followed by 3 cycles of carboplatin and paclitaxel versus pelvic radiation in treating patients with high-risk stage I or stage II endometrial cancer. The forthcoming results will let us know whether VBT combined with chemotherapy is more effective than pelvic radiation.

Adjuvant chemotherapy alone is thought to control distant recurrence better than radiotherapy; however, it may be inadequate to achieve local control.[20,21] Local recurrent rates of 4% to 7% were reported in patients with stage I disease and poor prognostic factors who were receiving surgery followed by radiotherapy,[12,22,23] and up to 4.3% local recurrences were observed in patients with HIR who were treated with radiation combined with chemotherapy.[6,8,11] The local recurrence rate for patients with grade 3 tumor who received adjuvant chemotherapy alone was 4.5% (2/44) in our study, which is comparable to historical data. Moreover, these 2 recurrences were salvageable and alive with no evidence of disease. In our institute, adjuvant chemotherapy was selected more often than adjuvant radiation for patients with endometrial cancer. Since the results of GOG 122 study were published, adjuvant chemotherapy has been routinely administered to patients with early-stage disease and some risk factors in our institute. One of our previous studies suggested that adjuvant chemotherapy alone may be effective and feasible for patients with stage IIIA endometrial cancer, which based only on isolated adnexal involvement.[24] We reported that the 5- and 10-year disease-free survival rates in 67 patients with solitary adnexal involvement who were treated with adjuvant chemotherapy alone were 89.6% and 87.5%, respectively, with only 3% of patients experienced locoregional failure. In the present study, the interesting findings observed warrant further studies comparing adjuvant chemotherapy alone versus adjuvant radiation and combined modality treatment to clarify the feasibility and efficacy of adjuvant chemotherapy alone in patients with HIR with grade 3 tumor.

One of the strengths of our study was that we included a relatively large group of patients with well-defined HIR factors. Pelvic lymphadenectomy was performed in 90.7% of the patients, with a median of 18 pelvic nodes resected. We therefore respected our surgical staging as appropriate. The long follow-up time was another strength of our data. However, our study had some limitations owing to its retrospective nature. First, the patient number was limited, so the results should be interpreted with caution. Especially, the number of patients with HIR with grade 3 tumor who received chemotherapy combined with radiation was too small to make useful conclusion, which could also introduce selection bias. Second, no well-defined postoperative adjuvant treatment protocol could be followed before the year 2006. Third, only 21.7% of the patients had para-aortic lymph node dissection/sampling.

CONCLUSION

For patients with early-stage endometrial cancer with HIR factors, the appropriate adjuvant treatment modality depends on the tumor grade. It is logical to speculate that surgery followed by observation might be sufficient for patients with HIR with grade 1–2 tumor. However, the number of patients with grade 1–2 tumor was small, and further prospective trials are required to confirm the issue in this population. Moreover, it warrants further studies comparing adjuvant chemotherapy alone versus adjuvant radiation and combined modality treatment to clarify the feasibility and efficacy of adjuvant chemotherapy alone in patients with HIR with grade 3 tumor.

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