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Outcomes of treatment for Stage III endometrial carcinoma patients

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Summary

Purposes: To report the outcomes and patterns of failure of Stage III endometrial carcinoma. *Materials and Methods:* Medical records of Stage III endometrial carcinoma patients were retrospectively reviewed. Disease-free survival (DFS) and patterns of failure were reported. Factors to predict pelvic and extra-pelvic recurrences were described. *Results:* Seventy-nine patients with Stage III endometrial carcinoma were included. Most had Stage IIIA (53%) and IIIC disease (33%) with endometrioid cell types (73%). Fifty-five percent of patients received chemotherapy (CMT) alone, 25% received external beam radiation therapy (ERT) alone, 20% received a combination of CMT and ERT. Median follow up time was 47 months. The two-year DFS rate was 78.5%. Pelvic and extra-pelvic recurrences were found in 6.3% and 15.2%, respectively. Major pattern of failure for Stage IIIA was pelvic recurrences, whereas most of Stage IIIC disease failed at the extra-pelvic sites. *Conclusion:* Adjuvant CMT is essential, especially in Stage IIIC disease. Pelvic lymph node dissection appeared to be a significant prognostic factor for pelvic recurrence. Stage IIIC disease, lymphovascular space invasion, gross residual disease after surgery, received ERT alone or sequential CMT/ERT was found to be factor to predict extra-pelvic recurrences.

Key words: Endometrial carcinoma; Stage III; Outcome; Pattern of failure.

Introduction

Endometrial cancer is the most common gynecologic cancer in the developed countries [1]. The incidence is increasing in the developing countries including Thailand [2]. The standard treatment for endometrial cancer is surgery, including at least hysterectomy and removal of adnexal structures. Lymph node evaluation is more selective and tailored to avoid systematic over treatment [3].

Most of the patients have early stage disease (Stage I, II)[4]. Adjuvant treatments were recommended based on risk stratifications regarding adverse risk features [5, 6]. Low risks were opted for surveillance. Intermediate risks were recommended to receive adjuvant radiation therapy, which vaginal brachytherapy (VBT) is comparable to external beam radiation therapy (ERT) for locoregional control and overall survival (OS) [7]. High risks are recommended to receive ERT and/or VBT [3]. Nevertheless, there is no sufficient information to determine the optimal adjuvant treatment in advanced stage (Stage III, IV) endometrial cancer. Systemic therapy is apparently a major treatment for advanced stage patients. However, patients whose disease were limited to the adnexal or uterine serosa (Stage IIIA), or vaginal involvement (Stage IIIB), ERT appeared to be beneficial to control pelvic disease in addition to systemic therapy [8]. ERT was certainly debated for patients with pelvic and para-aortic lymph node metastases for its role to control locoregional disease in addition to systemic CMT[9-15].

The objectives of this study were to report the disease-free survival (DFS) overall survival (OS), and patterns of failure for patients with Stage III endometrial cancer treated at the present institute.

Materials and Methods

A retrospective review of medical records was performed after received an approval by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital. The eligible patients met the following inclusion criteria: 1) surgery with at least removal of uterus and existing adnexal structures, 2) endometrial carcinoma FIGO 2009 Stage III [16], 3) received adjuvant CMT or/and ERT at the present institute, 4) had at least 12 months of follow-up after adjuvant treatment, and 5) no other malignancies diagnosed within five years (except for carcinoma in situ or skin cancer other than melanoma). All patients were treated between 1995 and 2010.

Lymph node dissection was performed if there was at least one of the following findings: 1) high-grade endometrioid carcinoma or serous carcinoma or clear cell carcinoma, 2) large tumor size (> 2 cm in greatest diameter), and 3) myometrial invasion greater than 50% of myometrial thickness, intraoperatively. Tumor staging was defined according to FIGO 2009 surgical staging system [16]. Patients who had only positive peritoneal cytology were excluded from the study, due to conflicting results regarding the significance of positive peritoneal fluid cytology, as a risk factor for tumor recurrence or survival [17]. Adjuvant CMT was composed

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of various regimens, including carboplatin/paclitaxel, carboplatin/doxorubicin, cisplatin/paclitaxel, cisplatin/doxorubicin, and cisplatin/doxorubicin/cyclophosphamide. Adjuvant radiotherapy consisted of ERT and/or VBT. Combination schemes of CMT and ERT were either sequential protocol (CMT/ERT or ERT/CMT) or sandwich protocol (CMT/ERT/CMT).

The data collected from the medical records including age, body mass index, stage, histology cell type, myometrial invasion, lymphovascular invasion, gross residual tumor, adjuvant CMT, and/or ERT. Pathology was all centrally reviewed. Histology cell type was defined according to World Health Organization classification [18], divided into clear cell/papillary serous (CC/PS) and others.

The time to recurrence and time to death were calculated from the date of last adjuvant treatment. The patients were analyzed for their first sites of relapse. The patterns of disease recurrence were defined as pelvic recurrence if they occurred at the vaginal stump or in the pelvic cavity; as extra-pelvic recurrence if they occurred in the abdominal cavity or at the distant organs.

Statistical analyses were performed with Kaplan-Meier curve and Log-rank test to analyze the DFS rate. Cox-proportional hazard model was used to analyze factors that associated with recurrence of the disease.

Results

Between 1995 and 2010, 124 patients were diagnosed with endometrial carcinoma FIGO Stage III. Out of 124 patients, 79 patients met the inclusion criteria. Among these 79 patients, most of the patient (69 patients, 87%) underwent hysterectomy, adnexal removal, and lymph node dissection, while 13% (ten patients) received only hysterectomy and adnexal removal. Forty-five patients were excluded from the study based on the following conditions; 15 patients had ERT as a primary treatment due to inoperable disease or uncontrolled medical conditions, two patients refused to received adjuvant treatments after surgery, seven patients had insufficient follow-up data (lost follow

Table 1. — *Patients' characteristics.*

Characteristics	No. of patients (%)
All patients	79
Age (years)	
< 40	2 (2.5)
40 to < 50	14 (17.7)
50 to < 60	35 (44.3)
60 to < 70	21 (26.6)
≥ 70	7 (8.9)
Body mass index (kg/m^2)	
< 18.5	1 (1.3)
18.5 – 24.99	49 (62.0)
25 – 29.99	22 (27.8)
30	7 (8.9)
Stage	
IIIA	42 (53.1)
IIIB	1 (1.3)
IIIC1	26 (32.9)
IIIC2	10 (12.7)
Histology cell type	
Others	58 (73.4)
CC/PS	21 (26.6)
Myometrial invasion	
< 50% of thickness	30 (38.0)
> 50% of thickness	37 (46.8)
Through serosa	12 (15.2)
Lymphovascular space invasion	
No	52 (65.8)
Yes	27 (34.2)
Gross residual tumor	
No gross residual tumor	72 (91.1)
Yes	7 (8.9)
Adjuvant treatment	
CMT	43 (54.4)
ERT	20 (25.3)
Sequential	9 (11.4)
Sandwich	7 (8.9)

CC = clear cell carcinoma, PS = papillary serous carcinoma, CMT = chemotherapy, ERT = external beam radiation therapy

Table 2. — *Sites of recurrence according to stages of the disease and treatments.*

Stage and treatment	No recurrence	Sites of recurrence			
		Vaginal stump	Pelvic cavity	Abdomen	Distant sites
All Stage III (79)	62 (78.5%)	3 (3.8%)	2 (2.5%)	4 (5.1%)	8 (10.1%)
Stage IIIA (42)					
CMT (24)	21	1	2	-	-
ERT (12)	9	2	-	-	1
Sequential (3)	2	-	-	-	1
Sandwich (3)	3	-	-	-	-
Stage IIIB (1)					
ERT (1)	1	-	-	-	-
Stage IIIC1 (26)					
CMT (12)	10	-	-	-	2
ERT (7)	3	-	-	2	2
Sequential (4)	2	-	-	-	2
Sandwich (3)	2	-	-	1	-
Stage IIIC2 (10)					
CMT (7)	7	-	-	-	-
Sequential (2)	1	-	-	1	-
Sandwich (1)	1	-	-	-	-

CMT = chemotherapy, ERT = external beam radiation therapy.

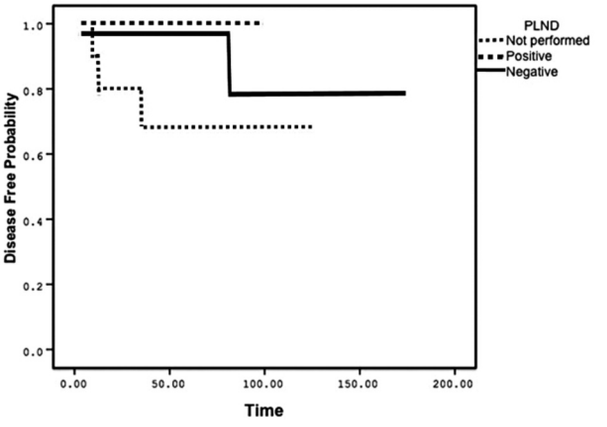

Figure 1. — Pelvic lymph node status: impact on local disease free survival rates. Lymphadenectomy with positive lymph node had a lower probability for pelvic recurrence compared to no lymphadenectomy (p = 0.006). Lymphadenectomy with negative lymph node had a lower probability for pelvic recurrence compared to no lymphadenectomy (p = 0.050). There was no difference in local recurrence probability between positive and negative lymph node groups.

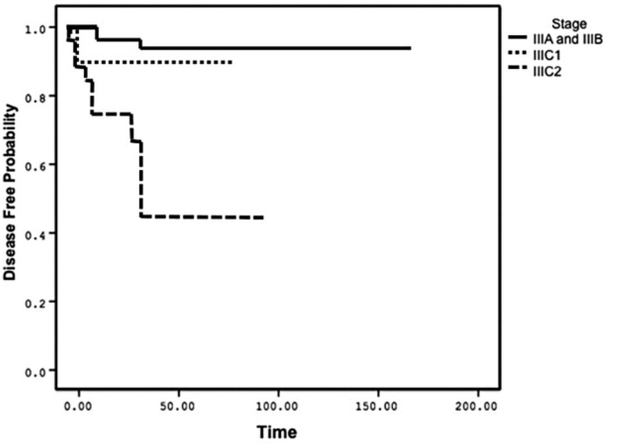

Figure 2. — Stages of the disease: impact on abdominal and distant DFS rates. Stage IIIC1 had a higher probability for abdominal and distant recurrence when compared to Stages IIIA and IIIB (p < 0.001). Stage IIIIC1 was not significantly different in probability for abdominal and distant recurrence when compared to Stage IIIC2. Stage IIIIC2 was not significantly different in probability for abdominal and distant recurrence when compared to Stages IIIA and IIIB.

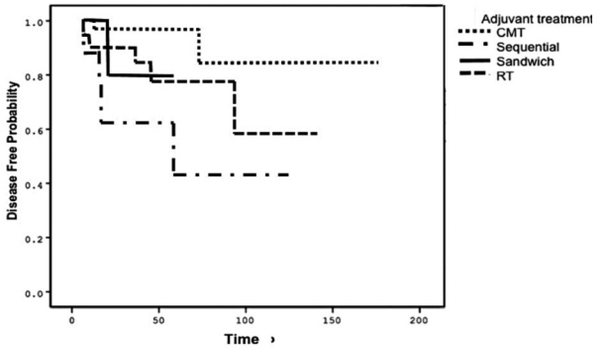

Figure 3. — Adjuvant treatment: impact on abdominal and distant DFS rates. CMT alone had a lower probability for abdominal and distant recurrence when compared to sequential protocol (p < 0.001). CMT alone was not significantly different in probability for abdominal and distant recurrence when compared to RT alone or to sandwich protocol. RT alone was not significantly different in probability for abdominal and distant recurrence when compared to sandwich protocol. Both RT alone and sandwich protocol was not significantly different in probability for abdominal and distant recurrence when compared to sequential protocol.

up or received adjuvant treatments at other hospitals), 12 patients had only positive peritoneal cytology, and nine patients had tumor progress while receiving adjuvant treatment (no disease free interval).

Patients' characteristic are summarized in Table 1. Most of the patients were in FIGO Stage IIIA (53%) and IIIC1 (33%). Only 1% and 13% were in Stage IIIB and IIIC2, respectively. Most of the patients (73%) had endometrioid and mucinous histology. Only 27% had serous and clear cell histology. Adjuvant treatments were prescribed as follows: 55% received CMT alone, 25% received ERT alone, 11% received sequential protocol (CMT/ERT or ERT/CMT), and 9% received sandwich schema (CMT/ERT/CMT).

Median follow-up time was 47 (range 7-176) months. The two-year DFS rate was 78.5% for all patients. Pelvic recurrence was found in 6.3% (5/79) of patients with median time to recurrence at 28.2 (3-81) months. Extra-pelvic recurrence was found in 15.2% (12/79) of patients with median time to recurrence at 20.7 (4-41) months. All patients who had pelvic recurrences were in Stage IIIA disease. Major patterns of recurrences in Stage IIIC disease was extra-pelvic recurrences, irrespective of CMT or ERT (Table 2).

A significant factor to predict pelvic recurrence was an absence of pelvic lymph node dissection on univariable analysis (p = 0.013). Figure 1 shows an impact of pelvic lymph node dissection on local recurrences. However, there was no significant difference of pelvic recurrence between positive or negative pelvic lymph nodes patients. Factors to predict extra-pelvic recurrences on univariable analysis were Stage IIIC (p < 0.001), pelvic lymph node status (p = 0.001), lymphovascular space invasion (p = 0.001), gross residual disease (p = 0.001), and methods of adjuvant treatment (p = 0.009) (Table 3). FIGO Stage IIIC1 disease (HR 9.69, p = 0.010), lymphovascular space invasion (HR 5.24, p = 0.027), gross residual disease after

Table 3. — *Univariable analysis of the impact of prognostic factors on pelvic recurrences and extra-pelvic recurrences at two years.*

Factors	No. of patients	Pelvic recurrences		Extra-pelvic recurrences	
		Event	*p* value	Event	*p* value
All patients	79	5		12	
Age (years)					
≤ 50	21	0	0.625	1	0.104
51-70	52	5		11	
> 70	6	0		0	
Body mass index (kg/m^2)					
< 25	50	3	0.625	11	0.120
≥ 25	22	2		1	
≥ 30	7	0		0	
Histology cell type					
Others	58	5	0.257	8	0.408
CC/PS	21	0		4	
Grade					
1	20	2	0.523	1	0.100
2	27	1		4	
3	32	2		7	
FIGO 2009 staging					
IIIA	42	5	0.201	2	<0.001
IIIB	1				
IIIC1	26	0		9	
IIIC2	10	0		1	
Myometrial invasion					
< 50%	30	2	0.934	2	0.274
> 50%	37	2		8	
Through serosa	12	1		2	
Bilateral salpingo-oophorectomy					
Negative	34	0	0.072	6	0.531
Positive	45	5		6	
Pelvic lymph node dissection					
Not performed	10	3	0.013	0	0.001
Negative	36	2		10	
Positive	33	0		2	
Para-aortic lymph node sampling					
Not performed	35	3	0.710	5	0.854
Negative	33	2		5	
Positive	11	0		2	
Lymphovascular space invasion					
Negative	52	3	0.529	4	0.001
Positive	27	2		8	
Gross residual tumor					
No gross residual	72	5	0.573	9	0.001
Yes	7	0		3	
Adjuvant treatment					
CMT	43	3	0.741	2	0.009
ERT	20	2		5	
Sequential	9	0		4	
Sandwich	7	0		1	

CC = clear cell carcinoma, PS = papillary serous carcinoma; CMT = chemotherapy, ERT = external beam radiation therapy.

surgery (HR 15.34, $p = 0.009$), received ERT alone (HR 16.09, $p = 0.008$), and received sequential CMT/ERT (HR 43.08, $p = 0.001$) were factors to predict extra-pelvic recurrences on multivariable analyses (Table 4). Figure 2 demonstrates the extra-pelvic recurrences, in which patients with Stage IIIC1 appeared to have highest risk of extra-pelvic recurrences and distant metastases. Adjuvant CMT alone had significantly decrease impact on extra-pelvic recurrence and distant metastasis compared to other schemas of treatments (Figure 3). Age, body mass index, cell types, grade, myometrial invasion, ovarian metastasis, and para-aortic lymph node status, were found to be non-significant prognostic factors for both pelvic and extrapelvic recurrences.

Table 4. — *Multivariable analysis of prognostic factors on extra-pelvic recurrence.*

	Abdominal and distant controls		
Factors	HR	95%CI	*p* value
FIGO 2009 staging			
IIIA	1		
IIIB			
IIIC1	9.69	1.713 - 54.866	0.010
IIIC2	8.26	0.575 – 118.62	0.120
Lymphovascular space invasion			
Negative	1		
Positive	5.24	1.208 – 22.753	0.027
Gross residual tumor			
No gross residual disease	1		
Yes	15.34	1.963 – 119.803	0.009
Adjuvant treatment			
CMT	1		
ERT	16.09	2.092 – 123.703	0.008
Sequential	43.08	4.731 – 392.295	0.001
Sandwich	3.29	0.243 – 44.415	0.370

CMT = chemotherapy, ERT = external beam radiation therapy.

Discussion

Surgery is the mainstay treatment for endometrial cancer composed of at least hysterectomy and oophorectomy. Nevertheless, lymph node management is rather controversial. The present authors' prior study for early stage endometrial carcinoma patients showed no benefit of lymph node dissection[19]. Frost *et al.* reported no benefit of lymph node dissection on OS or recurrent free survival (RFS) (hazard ratio: HR=1.07, 95%CI 0.81-1.43; HR=1.23, 95% CI 0.96-1.58 for OS and RFS, respectively) for endometrial carcinoma patients underwent surgery. Also, lymph node dissection provided certain risk of surgery related systemic morbidity and lymphedema/lymphocyst formation (relative risk: RR=3.72, 95%CI 1.04-13.27; RR=8.39, 95% CI 4.06-17.33 for risk of surgery-related systemic morbidity, and lymphedema/lymphocyst formation, respectively [20].

In contrast, a retrospective data of 42,184 patients with endometrial cancer from SEER database from 1988-2003 showed an OS and uterine specific survival benefits of lymph node dissection with HRs of 0.81 ($p < 0.0001$) and 0.78 ($p < 0.0001$), respectively on multivariate analysis. In addition, a removal of > 11 lymph nodes was associated with HRs of 0.74 ($p < 0.0001$) and 0.69 ($p < 0.0001$), respectively [21]. Chan *et al.* also confirmed benefit of lymph node dissection for 2,177 patients with only Stage III endometrioid endometrial carcinoma. Lymph node dissection significant increased five-year disease specific survival (DSS) from 63.1% to 73.8%, ($p < 0.001$) [22]. This study showed the necessity of pelvic lymph node dissection as the patients who underwent lymph node dissection experienced lower rate of pelvic recurrences compared to patients who did not pursue with lymph node dissection. This benefit might be a consequence of advancement of patients with Stage III disease with high likelihood to have nodal metastasis. Surgical removal of nodal metastasis would decrease the bulkiness of disease and diminish the risk of pelvic recurrences.

Adjuvant CMT is an essential treatment for advanced stage endometrial cancer. Adjuvant CMT alone showed more benefit for overall survival than adjuvant pelvic/whole abdominal radiation therapy alone for treating advanced stage endometrial cancer patients [23-25]. In addition, a combination of adjuvant CMT and ERT appeared to have more benefits for locoregional control, PFS and OS than adjuvant ERT alone [26-29]. The present study confirmed the necessity of adjuvant CMT which adjuvant CMT alone provided the most benefits for decreasing extra-pelvic recurrences and distant metastases comparing to other schemas.

CMT regimen contains of doxorubicin/cisplatin based on GOG 107 [30]. The following GOG 163 did not show benefit of paclitaxel/doxorubicin over doxorubicin/cisplatin in terms of response rate, PFS, and OS [31]. GOG 177 showed that paclitaxel/doxorubicin/cisplatin were more effective than doxorubicin/cisplatin for response rate, PFS and OS [32]. However, there was an discordant result of intensification CMT. GOG 184 did not demonstrate a survival benefit of adding paclitaxel to cisplatin/doxorubicin (three-drug regimen) compared to cisplatin/doxorubicin (two-drug regimen). Also, three-drug regimen provided greater toxicities for the patients [33]. GOG 2009 is an ongoing randomized phase III trial of three drugs (doxorubicin/cisplatin/paclitaxel+GCSF) versus two drugs (carboplatin/paclitaxel) in Stage III-IV, recurrent endometrial cancer. Multiple investigators have explored the role of paclitaxel and carboplatin for advanced endometrial carcinoma patients. However, this combination has never been tested in phase III trial. Most of the physicians used this combination based on experienced in ovarian cancer. Yet, the questions remain for the necessity of radiation therapy for Stage III endometrial carcinoma. Whether adding ERT to CMT is controversial. Stage IIIC with pelvic and/or para-aortic lymph nodes is the most common subset of Stage III. Pelvic recurrence rates were reported to range from 19-50% of patients with node positive endometrial cancer who were treated with CMT without ERT [6]. This was suggesting that adjuvant ERT should be combined with systemic CMT in patients with high risk endometrial cancer. Unfortunately, the benefits of adding ERT to CMT were not confirmed in phase III randomized control trial. Most of the evidence were reported in a retrospective studies. There were several retrospective studies that demonstrated a benefit of a combination of CMT and ERT compared with adjuvant CMT alone or ERT alone [34-36].

Klopp *et al.* retrospectively reported a pattern of recurrence of 71 Stage IIIC patients treated with CMT with or without adjuvant ERT. The results showed that adding regional ERT provided better pelvic control (98% *vs.* 61%, *p*

= 0.001), DSS (78% *vs.* 39%, $p = 0.01$) and OS (73% *vs.* 40%, $p = 0.03$)[10]. Secord *et al.* retrospectively reported the outcomes of 265 patients with Stage IIIC endometrial cancer treated with adjuvant CMT, ERT, and both CMT and ERT. Adjuvant therapy with either ERT alone or CMT combined with ERT was associated with improved outcomes for patients with optimally resected Stage IIIC endometrial cancer compared to those treated with CMT alone. Adjuvant CMT alone were at 2.2-fold increase risk of recurrence (95% CI 1.2-4.2, $p = 0.02$) and 4.0-fold increase risk of death (95% CI 1.6-10, $p = 0.004$) [37]. Also, Brown *et al.* confirmed OS benefits when adding ERT to CMT for Stage IIIC endometrial cancer (five-year OS 57% *vs.* 42%, $p = 0.01$, HR=0.44, 95% CI 0.20-0.96, $p = 0.039$)[9]. Booth *et al.* retrospectively reported the outcomes of 22,027 Stage III endometrial cancer patients treated with adjuvant chemoradiation or adjuvant monotherapy (CMT alone or ERT alone). The majority of these patients were in Stage IIIC disease (81%). Although, there were some selection biases for high risk patients to receive a combination of CMT and ERT, the patients who received chemoradiation therapy experienced superior survival outcomes compared with patients who received only adjuvant monotherapy on both univariable (HR=0.66, $p < 0.01$), and multivariable analyses (HR=0.61, $p < 0.01$). Median survivals were 10.3 *vs.* 6.2 years for adjuvant CMT and ERT *vs.* adjuvant monotherapy, respectively [38].

Recently, PORTEC-3 reported the outcomes comparing between adjuvant concurrent chemoradiation followed by adjuvant CMT versus adjuvant pelvic ERT alone. Adjuvant concurrent chemoradiation followed by adjuvant CMT provided better five-years failure free survival (FFS) in patients with Stage III (five-year FFS 69.3% *vs.* 58%, 95% CI 0.45-0.97, $p = 0.032$), however no significant benefit on five-year OS when adding CMT to pelvic ERT (five-year OS 78.7% *vs.* 69.8%, $p = 0.114$). The final results are upcoming. There is an ongoing GOG 258 comparing adjuvant CMT and tumor directed ERT versus adjuvant CMT alone for Stage III-IV endometrial cancer patients. The results are pending.

CMT and ERT sequencing was investigated. Secord *et al.* reported the benefits of sandwich regimens (CMT/ERT/CMT) in 356 patients with locally advanced endometrial cancer. However, given the retrospective nature with low patient numbers and imbalance subtypes, this sequence was not routinely utilized in clinical practice [36]. Given the results of these studies, patients with Stage III disease appeared to have benefits of combining CMT and ERT for locoregional control and OS. ESMO-ESGO-ESTRO recommended to offer adjuvant CMT in combination with ERT, aiming to decrease pelvic recurrence and improve PFS with trend to improve survival [39].

Most of the present patients in Stage IIIC disease received adjuvant CMT alone. The present study showed that the major patterns of failure of Stage IIIC patients were in the abdomen and distant sites. None of Stage IIIC patients failed in the pelvis. These results may be a result of extensive nodal dissection in this study. An absence of pelvic lymph node dissection was found to be a significant factor of pelvic recurrence on univariable analysis in this study. Whereas, majority of the patients with Stage IIIA disease in this study failed in the pelvis despite adjuvant pelvic ERT alone or adjuvant CMT alone. Remarkably, one-fourth of the patients with Stage IIIA disease had unknown pelvic lymph node status. This result should lead to a consideration of giving a combination of CMT and ERT for Stage IIIA endometrial cancer patients rather than adjuvant monotherapy.

There were some limitations in the study given its retrospective nature with relatively small sample sizes and varieties of treatments. However, this study gave a confirmation of a necessity of adjuvant CMT in all Stage III disease. Radiation therapy is rather controversial in this study whether it would add benefits for pelvic and extrapelvic diseases.

The standard treatment for patients with Stage III endometrial carcinoma is surgery, composing of hysterectomy, bilateral oophorectomy, and lymph node dissection/sampling. Pelvic lymph node dissection appeared to be a significant prognostic factor for pelvic recurrence. FIGO Stage IIIC disease, lymphovascular space invasion, gross residual disease after surgery, receiving ERT alone or sequential CMT/ERT, was found to be factor to predict extrapelvic recurrences in this study. Adjuvant CMT is an essential treatment especially for patients with Stage IIIC disease. Adjuvant radiation therapy is rather controversial to add benefit to CMT in this study.

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