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Original Research

Sequential Chemoradiation versus Radiation for the Adjuvant Treatment of Stage III Endometrioid Adenocarcinoma of the Uterus

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Summary

Purpose of Investigation: The optimal adjuvant therapy for women with Stage III endometrial cancer following surgical staging is controversial. Post-operative sequential chemotherapy followed by external beam radiotherapy is the standard treatment for Stage III uterine cancer at our institution since 2006. We aim to analyse the survival outcomes in this group of patients comparing with the historical group of patients who received radiation only. *Materials and Methods:* This is a retrospective single-institution analysis of patients with surgical Stage III endometrioid adenocarcinoma of the uterus treated at KK Women's and Children's Hospital from 2000 to 2010. *Results:* Ninety-six patients with surgical Stage III endometrioid endometrial cancer who received postoperative adjuvant therapies were identified; 43% (n = 41) received chemotherapy followed by radiotherapy, 57% (n = 55) received radiotherapy only. The 2 groups were well balanced with regard to age, ECOG performance status, tumour size, myometrial invasion, lymphovascular invasion, peritoneal cytology status and debulking status. At a median follow up of 62.5 months (range: 4 -164), the 5-year overall survival (OS), cancer-specific survival (CSS) and disease-free survival (DFS) were not significantly different. Following adjustment for age, disease stage, tumour grade, residual disease, tumour size and nodal status, the adjusted hazard ratios for DFS, CSS and OS for those treated with chemoradiation were not significantly better than those treated with radiation only. *Conclusion:* In this single institution retrospective analysis of Asian patients with surgical Stage III endometrioid endometrial cancer, there was a trend towards sequential chemotherapy followed by radiation having better OS and CSS over radiation alone but this did not reach statistical significance.

Key words: Endometrial cancer; Chemotherapy; Radiotherapy.

Introduction

Endometrial cancer remains the most common gynaecologic malignancy in women with 319,600 new cases and 34,700 deaths worldwide and incidence of endometrial cancer in the developed world is on the rise [1]. Majority of patients present early and have an excellent prognosis with 5-year survival rates ranging from 85-90% for Stage I and 80% for Stage II disease [2]. However, patients with Stage III disease have a much poorer outcome with 5-year survival decreasing to 50-65%, with more than half the total number of deaths arising from advanced disease [2, 3]. Adjuvant management of Stage III endometrial cancer following surgery remains controversial. The optimal management of this group of patients has yet to be defined. External beam pelvic radiation therapy (EBRT) is indicated to maximize pelvic control, but there is no prospective data to suggest that it improves overall survival. Historically, adjuvant radiotherapy to the whole abdomen and pelvis was found to decrease recurrence [4], however these small and mostly retrospective series also found that the majority of them relapsed distally, paving the way for chemotherapy trials [5].

Systemic chemotherapy has been shown to improve survival outcomes in stage III and IV endometrial cancer compared to whole abdominal irradiation in a prospective phase III randomized controlled trial by the Gynaecologic Oncology Group (GOG) [6]. However, patients who received chemotherapy had a higher pelvic relapse rate (18%). In view of these findings, there has been significant interest in integrating both chemotherapy and radiation therapy in the treatment of this group of patients in order to optimize both local and distant disease control. Several authors have reported that the combined modality of treatment for women with endometrial cancer yielded superior outcomes compared to single modality treatment. This includes 2 phase III randomized trials, the NSGO/EORTC and the MaNGO-ILIADE III [7]. These two studies investigated the role of adjuvant sequential chemotherapy followed by radiation versus radiation alone in 540 women with operated endometrial cancer [7]. The pooled analysis of these two trials demonstrated that the combined modality treatment improves progression-free survival (HR 0.63; p = 0.009) but not overall survival (HR 0.69; p = 0.07). Majority of pa-

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Table 1. — *Clinical and Tumour Characteristics.*

	CT followed by RT (n = 41)		RT only (n = 55)		*p* value
	No.	%	No.	%	
Age (years)					
Median	51.4 (34-66)		54.8 (30-85)		0.302
FIGO Stage					0.261
IIIA	11	27	17	31	
IIIB	0	0	3	5	
IIIC	30	73	35	64	
High/Low Grade					0.006
G1&G2	27	66	49	89	
G3	14	34	6	11	
Residual Disease					0.574
Yes ($\leq$ 1 cm)	1	2.5	1	2	
Yes ($>$ 1 cm)	1	2.5	1	2	
No	39	95	53	96	
Myometrial nvasion (%)					0.782
$<$ 50	13	32	16	29	
$\geq$ 50	28	68	39	71	
Vascular Invasion					0.5
Present	29	71	34	62	
Absent	12	29	20	36	
Missing data	0	0	1	2	
Peritoneal Washing					0.169
Positive	11	27	7	13	
Negative	26	63	44	80	
Not done	4	10	4	7	
Tumour Size (cm)					0.144
Mean (95% CI)	5.5 (4.6-6.4)		4.6 (3.8-5.4)		
Pelvic Lymph Node Dissection					–
Yes	41	100	55	100	
No	0	0	0	0	
Pelvic Lymph Node Involvement					0.822
Yes	27	66	35	64	
No	14	34	20	36	
Para-aortic Lymph Node Dissection					0.12
Yes	15	37	8	15	
No	26	63	47	85	
Para-aortic Lymph Node Involvement					0.065
Yes	5	67	0	0	
No	10	33	8	100	
ECOG at Diagnosis					0.117
0	34	85	52	95	
1	6	15	3	5	
2	0	0	0	0	
3	0	0	0	0	
Recurrence					0.413
Total Number	6	100	13	100	
Loco-Regional	1	17	2	15	
Distant	2	33	4	31	
Distant and Loco-Regional	3	50	7	54	

tients in this study had early stage cancer, with only 19% of patients with Stage III disease. This study, like many other studies, included heterogenous patient population with various disease stages and histological subtypes [7].

Since 2006, sequential chemotherapy followed by radiation (C-RT) has been the standard of care for women with Stage III endometrial cancer following comprehensive surgical staging in our institution. Prior to 2006, our patients were treated with single-modality radiation (RT) treatment only. In this single-institution retrosepctive review, we aim to determine if the outcomes of surgical Stage III (FIGO 1988) endometrial cancer patients treated with adjuvant C-RT were better than those treated with RT only. We have limited our study to patients with exclusively endometrioid adenocarcinoma histology, as these tumours may be biologically different from the non-endometrioid tumours [8].

Material and Methods

Institutional Review Board approval was obtained from Singhealth and a single-institution retrospective analysis was performed on patients diagnosed with Stage III uterine cancer in KK Women's and Children's Hospital (KKH) between January 2000 to December 2010. The gynaecology oncology database in KKH was utilized to identify patients with surgical Stage III disease. Only pure endometrioid adenocarcinoma was included in the analysis. All histology specimens were reviewed by two pathologists. Casenotes were reviewed and information was extracted and recorded using Microsoft Excel. The standard surveillance practice in our hospital was to review patients every 3 months for the first 3 years, then every 6 months for the next 2 years and annually thereafter.

Statistical analysis was performed using IBM SPSS Statistics software package (Version 19). Various statistical methods such as ANOVA, Pearson Chi-square test were used to compare differences between the groups analyzed. Significant p-value was taken as < 0.05. The Kaplan-Meier model and Log Rank tests were used to compare unit variables among the 2 groups and graphs were plotted to compare the disease-free survival (DFS), cancer-specific survival (CSS) and overall survival (OS). Cox proportion hazard model was used for multivariate analysis.

Results

Patient characteristics

A total of 120 patients with surgical Stage III pure endometrioid endometrial cancer were identified in our institution between 2000 to 2010. Adjuvant C-RT has replaced RT as the standard treatment for Stage III endometrial cancer at our institution since 2006. Of the 120 patients, majority (96/120) received C-RT (34%) or RT only (46%); 3% (4/120) received adjuvant chemotherapy only and 17% (20/120) did not receive any adjuvant treatment. Stage IIIA (FIGO 1988) patients with positive peritoneal cytology alone without serosal or adnexal involvement were thought to have better prognosis. This select group of patients was excluded from our analysis.

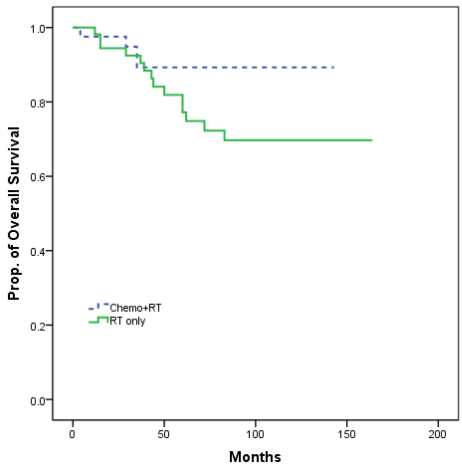

Figure 1. — Overall survival of patients with stage III endometrioid. adenocarcinoma of uterus treated with adjuvant C-RT or RT only. $p = 0.102$.

Our analysis will focus on the 96 patients who were treated with C-RT (n = 41) between 2006 to 2010 and RT (n = 55) between 2000 and 2005. Patient and tumour characteristics are summarized in Table 1. The median age was 51.4 years (range 33-66) in the C-RT group and 54.8 years (range 30-85) in the RT group ($p = 0.302$). Majority (96%) were debulked to no residual disease. Almost all the patients underwent pelvic lymphadenectomy (94/96; 98%); 66% in the C-RT and 64% in the RT group had pelvic nodal disease ($p = 0.682$). Twenty-four percent (23/96) of the patients had para-aortic lymphadenectomy in addition to pelvic lymphadenectomy. Twelve percent of the patients treated with C-RT had disease in the para-aortic lymph nodes compared with 0% of those treated with RT ($p = 0.009$). In patients who received C-RT compared to those who received RT, grade 3 tumours were more prevalent (34% *vs.* 11%; $p = 0.006$). The dosage of chemotherapy and radiation given to the few patients with residual disease post surgery was the same as patients with no residual disease. The two treatment groups were otherwise well-balanced with regard to age, ECOG performance status, tumour size, myometrial invasion, lymphovascular invasion, peritoneal cytology status and debulking status (Table 1).

Adjuvant Therapy

Forty-one of the 96 (43%) patients were treated with C-RT and 55 (57%) with RT. All of the patients who were treated with chemotherapy received a platinum-based regimen (41/41; 100%). The most common regimen was carboplatin and paclitaxel (25/41; 61%) followed by cisplatin and doxorubicin (12/41; 29%); 10% received cisplatin with gemcitabine or cisplatin with etoposide. The median number of chemotherapy cycles administered was 6 (range 1-7). The chemotherapy completion rate was high with 85%

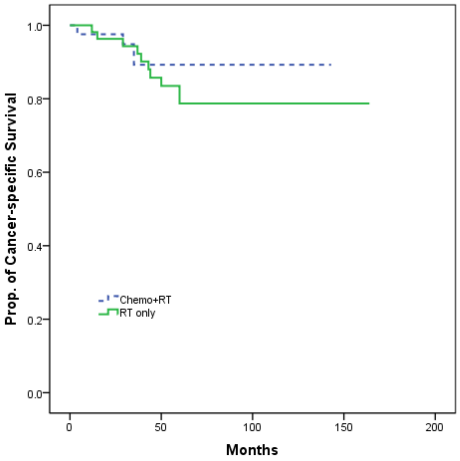

Figure 2. — Cancer-specific survival of patients with stage III endometrioid. adenocarcinoma of uterus treated with adjuvant C-RT or RT only. $p = 0.302$.

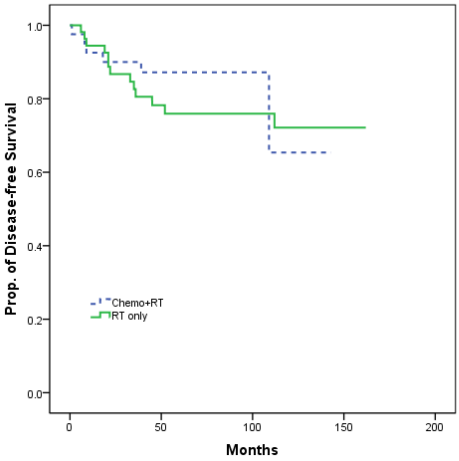

Figure 3. — Disease-free survival of patients with stage III endometrioid. adenocarcinoma of uterus treated with adjuvant C-RT or RT only. $p = 0.445$.

(35/41) completing the six cycles of planned treatment. The chemotherapy treatments were well tolerated. Adverse effects of chemotherapy were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) grading system. Peripheral neuropathy was the main toxicity in the patients who received carboplatin and paclitaxel (Grade 2 16% (4/25); Grade 34% (1/25)). The incidence of febrile neutropenia and Grade 4 nephrotoxicity was 10% (4/41) and 2% (1/41) respectively, all of which occurred in patients who received cisplatin-based treatments. There were no treatment related deaths. Following chemotherapy, the pelvic EBRT dose was given at a standard dose of 45 Gy to 50.4 Gy in 25 to 28 fractions, and vaginal vault brachytherapy was given at a dose of 10 Gy in 2 fractions. Extended field RT was administered to patients with disease in the para-aortic lymph nodes.

55 patients (57%) received RT alone. The dosage of radiation therapy is described as above. In this group, of those who had para aortic nodal dissection done (8/55; 15%), none of them had positive para aortic nodes therefore only EBRT and vaginal vault brachytherapy were administered.

Treatment Outcomes

The median follow-up was 67.5 months (4-164 months); 62 months (4-143 months) in the C-RT group and 83 (4-164 months) months in the RT group ($p = 0.054$). The OS was 82.1% for all patients at 5 years.

The 5-year OS between the two groups was not significantly different; 89.3% and 77.2% ($p = 0.102$) for C-RT and RT respectively (Figure 1). The 5-year CSS was similar between the two treatment groups (89.3% for C-RT *vs.* 78.7% for RT; $p = 0.302$) (Figure 2). There was a trend towards C-RT having better OS and CSS over RT however this did not reach statistical significance.

A total of 19 patients had disease recurrence (20%). 6 of the 41 (15%) patients treated with C-RT and 13 of the 55 (24%) treated with RT had recurred. There was no significant difference in the DFS between the two treatment groups; the 5-year DFS was 87.2% and 75.9% in the C-RT and RT groups respectively ($p = 0.445$) (Figure 3), and overall DFS was 80.7%. The majority of the recurrences involved both loco-regional and distant sites (10/19; 53%), while 16% (3/19) were loco-regional and 31% (6/19) were distant (Table 1). The pattern of relapses were similar between the two treatment groups ($p = 0.413$); the rates of distant relapses were not lower in patients treated with C-RT (Table 1).

Proportional hazard modelling was used to adjust for tumour characteristics and assess treatment efficacy (Table 2). Following adjustment for age, disease stage, tumour grade, residual disease, tumour size, nodal status, there were no significant differences in the DFS (HR 0.87; 95% CI 0.26-2.92; $p = 0.822$), CSS (HR 0.97; 95% CI 0.22-4.20; $p = 0.967$) or OS (HR 0.73; 95% CI 0.19-2.94; $p = 0.666$) between those who received C-RT compared to those treated with RT. Tumour grade, pelvic or para-aortic nodal disease were not significant survival indicators. Patients with IIIA (FIGO 1988) disease had similar DFS and OS as those with IIIC disease, but with improved CSS (HR 20.1; 95% CI 1.02-395.96, $p = 0.05$). Patients with IIIB (FIGO 1988) disease had improved OS and CS compared to those with IIIA disease (HR 7.80; 95% CI 1.09-56.12, $p = 0.04$ and HR 13.2; 95% CI 1.37-126.50, $p = 0.03$ respectively). Age was an independent predictor for survival; patients older than 60 years had a 42.5 fold increased risk of death (95% CI 4.6-392.1; $p = 0.001$) than patients who were 60 years or younger, but no increased risk of cancer-related death or disease recurrence (Table 2). The presence of residual disease after full surgical staging was also an independent predictor for survival with HR of 42.5 (95% CI 4.6-392.1; $p = 0.001$) for OS and HR 30.3 (95% CI 1.9-470.5; $p = 0.015$)

Table 2. — *Multivariable cox proportional hazards analysis for disease-free, cancer-specific and overall survival.*

Variable	Overall Survival		Cancer – Specific Survival		Disease Free Survival	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Adj. Treatment						
RT only	1		1		1	
Chemo followed by RT	0.737 (0.185, 2.942)	0.666	0.970 (0.224, 4.196)	0.967	0.870 (0.260, 2.917)	0.822
Histology Grade						
G1 & G2	1		1		1	
G3	1.695 (0.475, 6.041)	0.416	1.725 (0.393, 7.569)	0.47	1.554 (0.405, 5.968)	0.521
Stage						
IIIA	1		1		1	
IIIB	7.807 (1.086, 56.116)	0.041	13.183 (1.374, 26.500)	0.025	4.500 (0.676,29.931)	0.12
IIIC	11.908 (0.802, 76.720)	0.072	20.122 (1.023, 95.965)	0.048	2.385 (0.137, 1.422)	0.551
Residual Disease						
No	1		1		1	
Yes	42.521 (4.612,392.065)	0.001	30.264 (1.947,470.482)	0.015	1.207(0.026,55.567)	0.923
Pelvic Lymph Node Involvement						
No	1		1		1	
Yes	0.105 (0.009, 1.191)	0.069	0.102 (0.009, 1.185)	0.068	0.366 (0.026, 5.117)	0.455
Para-aortic Lymph Node Involvement						
No	1		1		1	
Yes	0.000 (0.000, -)	0.979	0.000 (0.000, -)	0.984	1.017 (0.016,65.034)	0.994
Unknown	1.066 (0.198, 5.750)	0.941	0.769 (0.128, 4.617)	0.774	0.893 (0.215, 3.702)	0.876
Tumour Size	1.054 (0.866, 0.281)	0.601	1.044 (0.842, 1.294)	0.695	1.070 (0.884, 1.295)	0.49
Age Group						
≤ 60	1		1		1	
> 60	42.521 (4.612, 92.065)	0.001	3.510 (0.948, 12.995)	0.06	2.492 (0.820, 7.574)	0.107

for CSS, with no difference in DFS (Table 2).

A subgroup Kaplan-Meier analysis was undertaken to determine which patients may benefit from the addition of chemotherapy to the treatment regimen (Table 3). Patients with Stage IIIA disease or grade 3 tumours did not preferentially benefit from the combined treatment. In patients with nodal disease, both pelvic and para-aortic, there was a trend towards improved survival outcomes in the C-RT group however numbers were small and it did not reach statistical significance.

Discussion

To date, our study is amongst the largest reported institutional series of patients with Stage III endometrioid endometrial cancer. This study primarily evaluates treatment outcomes of patients treated with sequential chemotherapy and radiation and those patients who received single modality radiation treatment. We have limited our study to patients with surgical Stage III endometrial cancer with endometrioid adenocarcinoma histology only.

In this study, C-RT had good tolerability but failed to improve the 5-year DFS, CSS and OS over single-modality RT. Although there was a trend towards improved OS and CSS in the C-RT group, our patients who received RT did not under-perform; in fact they had excellent survival outcomes with a 5-year DFS of 75.9% and OS of 77.2% that are comparable to other series of Stage III endometrial cancer treated with radiation that reported 5-year DFS and OS rates ranging between 67-76% [9-11].

However, the two treatment groups in our study were imbalanced with regard to tumour grade; more patients in the C-RT group had grade 3 tumours. Klopp *et al.* reported that grade 3 endometrioid tumours were independent predictors of adverse survival [10] which may confer an unfavourable outcome in the C-RT group. The prognostic significance of tumour grade in Stage III endometrioid endometrial cancer is however far from clear. In contrast to the findings by Klopp *et al.*, grade 3 disease was not an independent predictor of inferior survival in our study and in the study by Lee *et al.* [11].

The lack of survival benefits with combined modality treatment in our study is consistent with the findings of Secord and colleagues [12]. Their large retrospective series of women with Stage IIIC endometrial cancer failed to demonstrate a survival benefit in women treated with

Table 3. — *Univariable analysis for disease-free, cancer-specific and overall survival.*

Variable	5 Years Disease Free Survival Rate (%)			5 Years Cancer Specific Survival Rate (%)			5 Years Overall Survival Rate (%)		
	Chemo + RT	RT only	*p* value	Chemo + RT	RT only	*p* value	Chemo + RT	RT only	*p* value
Stage									
IIIA	80.8	80.4	0.969	90	87.1	0.8	90	81.3	0.349
IIIB	-	-		-	-	-		-	
IIIC	86.2	78.5	0.683	88.9	80.1	0.526	88.9	80.1	0.327
Histology Grade									
G1&G2	92.3	74.9	0.106	91.7	83.4	0.229	91.7	76.5	0.108
G3	69.8	83.3	0.597	84.4	83.3	0.929	84.4	83.3	0.367
Pelvic Lymph Node Involvement									
No	77.9	72.7	0.788	85.1	76.3	0.677	85.1	72	0.326
Yes	88.3	78.5	0.434	91.3	80.1	0.352	91.3	80.1	0.221
Para-aortic Lymph Node Involvement									
No	75	85.7	0.7	87.5	85.7	0.994	87.5	85.7	0.994
Yes	75	-	-	100	0	-	100	0	-
Unknown	88.5	74.3	0.216	88.5	77.7	0.39	88.5	76	0.164

chemotherapy and radiation compared to radiation alone. These findings, however, contradict that of several prospective and retrospective studies which have reported the superiority of the multimodality treatment over single modality radiation treatment in endometrial cancer [6, 7, 13]. However, many of these studies involved heterogenous patient groups. Investigators often studied patients with Stage III disease together with either high-risk early stage (Stage I and II) disease [7] or with Stage IV disease [6, 13], despite their very different prognoses. The extent of surgical staging also varies, for example, less than 30% of patients in the NSGO/EORTC and the MaNGO-ILIADE III study underwent pelvic lymphadenectomy [7]. Moreover, endometrioid and non-endometrioid subtypes are often included in the same studies [7, 13, 14] despite their marked molecular differences according to study findings by the Cancer Genome Atlas Research Network (TCGA) [8]. Papillary serous endometrial cancers share genomic features with ovarian high grade serous cancers with the propensity for peritoneal spread [15]. It is thus postulated that these cancers are more likely to benefit from chemotherapy than the endometrioid cancers though the benefit of chemotherapy in this subtype still remains unclear. In subgroup analyses of two large randomized studies, the NSGO 9501/EORTC 5591 and MaNGO-ILIADE III trials suggested that the benefit of adjuvant chemotherapy was limited to patients with endometrioid tumours rather than the serous or clear cell tumours (HR 0.83; 95% CI 0.42-1.64; $p = 0.59$) [7]. The recently published PORTEC-3 study reported that the non-endometrioid tumours derived similar failure free-survival benefit from chemo-radiation when compared to the endometrioid tumours [16]. However, as these analyses were unplanned small subgroup analyses, no definite conclusions can be drawn on the efficacy of adjuvant chemotherapy for serous or clear cell cancers.

For studies limited to the endometrioid endometrial cancers with patient population more akin to our study, the MaNGO-ILIADE III is a phase III randomized study of patients with Stage IIB and III endometrioid adenocarcinoma endometrial cancer. Patients were randomized to receive shorter courses of chemotherapy comprising of three cycles of cisplatin and doxorubicin chemotherapy followed by radiation treatment or radiation alone. The study showed that the combined treatment failed to improve the progression-free survival (HR 0.61; $p = 0.10$) or the OS (HR 0.74; $p = 0.41$) [7]. However, the study only managed to recruit 157 of the planned 300 subjects thus making the interpretation of the study results difficult. A retrospective series by Lee LJ and colleagues of 66 patients with Stage IIIC endometrioid endometrial cancer, reported that the combined chemotherapy and radiation therapy independently predicts for improved DFS and OS (HR 0.12, 95% CI 0.03-0.49; $p < 0.01$; HR 0.20, 95% CI 0.05-0.75, $p = 0.02$) compared to radiation [11]. The combined treatments involved heterogenous treatment regimens and the decision to add chemotherapy to radiation was at the discretion of the treating clinician. At our institution, combined treatment is routinely offered since 2006 thereby minimizing the patient selection bias of selecting out the fitter patients for the combined treatment and the consequent improved outcomes in patients treated with this modality.

We performed a sub-analysis of survival and treatment outcomes for patients with Stage IIIA and IIIC disease as patients with adnexal involvement may have different treatment or survival outcomes compared to those with nodal involvement. We found that only the CSS differed between

the Stage IIIA and IIIC patients, with no differences in OS and DFS (Table 2). In our study, no particular subgroup of Stage III patients (IIIA/IIIB/IIIC) appeared to benefit from the addition of chemotherapy to radiation (Table 3). This is consistent with the results of the Korean KROG 13-17 study by Yoon *et al*, which concluded that there was no survival benefit in Stage IIIC1 and IIIC2 cancers with either treatment modality [17]. Conflicting results from Lum *et al.* suggests survival benefit from use of adjuvant chemoradiation for Stage IIIA patients, however they included non-endometrioid histology subtypes in their retrospective study, which may account for the differing results [14]. Our results also showed that high grade tumours (Grade 3) did not preferentially benefit from the addition of chemotherapy.

In this study, advancing age independently predicts for inferior OS; women above the age of 60 had a 42.5 fold increased risk of death compared to their younger counterparts and presence of residual disease after full surgical staging also independently negatively predicts for poorer OS and CSS, which is consistent with the majority of reports [11]. Grade 3 disease, tumour size, myometrial invasion, lymphovascular invasion, positive peritoneal cytology and nodal involvements did not independently predict for DFS, CSS or OS.

Limitations of our study

The retrospective nature of this study has the inherent biases of other retrospective studies. As the study spanned over a ten-year period, stage migration issues, changes in surgical practices (such as increased number of para-aortic lymphadenectomy from 2009) and radiation techniques (such as shifting from conventional 2D planning to 3D planning) over time might have resulted in changes in management of patients. Our sample size is also limited due to our selection of only Stage III endometrioid endometrial cancer patients for the study. The increased availability and advances in imaging technology over time may introduce survival bias by excluding patients with metastatic disease and may also result in earlier detection of recurrences.

Strengths of our study

The strengths of this single institution study ensures the homogeneity of surgical, radiation and chemotherapy treatments. Combined modality treatment has been routinely offered to patients in our centre since 2006, which thus minimizes the selection biases or clinician preferences.

The optimal sequencing of the treatment regimens in endometrial cancer is still under investigation. Clinicians have looked into "sandwich" regimens [13, 18, 19] or administering pelvic radiation before chemotherapy [16, 20, 21]. Onal *et al.* concluded that the "sandwich" regimen conferred superior OS over the sequential regimen in stage IIIC endometrial carcinoma (74% *vs.* 56%, $p = 0.03$) [19].

The final analysis of RTOG 9708 suggests good outcomes with use of combination treatment regime consisting of radiation plus cisplatin, vaginal brachytherapy followed by cisplatin and paclitaxel [20]. The recently published PORTEC-3 investigated a different sequencing of combination therapy. This large randomized phase III study recruited patients with Stage I and Stage II high-risk and Stage III endometrial cancer of both endometrioid and non-endometrioid histological subtypes and randomized patients to either the combination treatment of two cycles of cisplatin chemotherapy given concurrently with radiation followed by four cycles of carboplatin and paclitaxel chemotherapy or radiation. However, less than 60% of patients in this study had undergone pelvic lymphadenectomy. Consistent with our study findings, the PORTEC-3 reported that in patients with Stage III cancers, combination treatment failed to improve the OS (78.7% *vs.* 69.8%, $p = 0.114$). The study did however demonstrate an 11% improvement in 5-year failure-free survival (69.3% *vs.* 58%, $p = 0.032$) of the combination treatment group compared to those who received the standard-arm treatment of pelvic RT [16].

Summary

In summary, in our single institution retrospective study of Asian women with surgical Stage III endometrioid endometrial cancer, there was a trend towards C-RT having better OS and CSS over RT alone but this did not reach statistical significance. The lack of statistically significant OS benefit is consistent with the findings of other large randomized studies. Combination chemotherapy and radiation treatment in Stage III endometrial cancers at best only improved the DFS compared with radiotherapy [7, 16, 17]. The added toxicities of these additional treatment modalities to improve cancer control need to be weighed against the lack of OS improvements. It is clear that not all patients with Stage III endometrial cancer will benefit from adjuvant combination treatment. Future clinical trials should integrate molecular classifiers to enable the risk stratification and study of adjuvant treatment efficacy. The Cancer Genome Atlas Network Research (TCGA) identified four prognostic subgroups based on the POLE mutation, p53 and MSI status [8]. Molecular classifiers such as ProMISE (Protective Molecular Risk Classifier for Endometrial Cancer) and the classifier developed by the Leiden/Translational Research in Postoperative Radiation Therapy for Endometrial Cancer (TransPORTEC) team that are based on the TCGA study show great potential as tools to stratify patient risk in early stage endometrial cancers [22, 23]. The development of molecular classifiers for advanced endometrial cancers are urgently required and we eagerly await future results.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board (IRB) of Singhealth, Singapore under approval number 2014/837/B. Due to its retrospective nature, approval for waiver of informed consent was sought and permitted during the analysis of data for this study.

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Conflict of Interest

All authors have no conflict of interest to declare.

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