

ORIGINAL RESEARCH

Determination of prognostic factors and optimal adjuvant therapy in patients with FIGO stage III endometrial cancer—a multi-institutional cohort study

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Abstract

Background: This study aimed to identify prognostic factors and assess which high-risk subgroups would benefit the most from the combination of chemotherapy and radiotherapy in patients with stage III endometrial cancer. **Methods:** A retrospective analysis was conducted with a cohort of 294 patients diagnosed with stage III endometrial cancer. All of whom underwent comprehensive surgical staging and adjuvant treatment between 2009 and 2021. **Results:** The median follow-up period was 42 months. Age over 60 years, substage IIIC2, and high grade or non-endometrioid histology were associated with poorer cancer-specific and overall survival (OS), though only age over 60 emerged as an independent adverse prognostic factor. Across the full cohort, survival did not differ significantly by adjuvant treatment modality. However, among patients aged over 60 years, adjuvant radiotherapy alone was associated with the lowest 5-year OS (42.3%), compared to chemotherapy alone (53.4%) and combined chemoradiotherapy (68.7%). In multivariate analysis, patients in this age group who received radiotherapy alone had significantly worse OS compared to those who received combined chemotherapy and radiotherapy (hazard ratio (HR) 3.15, 95% confidence interval (CI): 1.05–9.47, $p = 0.04$). **Conclusions:** The result of this real-world, multi-institutional cohort study showed that age over 60 years was a poor prognostic factor for stage III endometrial cancer patients. Combining adjuvant chemotherapy with radiotherapy was associated with the best survival outcomes, but this was only significant for patients aged over 60 years. Further prospective investigations of adjuvant therapies are warranted.

Keywords

Adjuvant therapy; Elderly; Endometrial cancer; Prognostic factor; Stage III

1. Introduction

Endometrial cancer (EC) is the fifth most common cancer among Taiwanese women, with approximately 3500 newly diagnosed cases in 2022 [1]. Most EC patients (over 70%) are diagnosed at an early stage, with a 5-year survival rate exceeding 90%. However, patients with advanced-stage EC (stage III–IV) have poorer outcomes. The standard management approach for stage III EC involves staging surgery, including hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy, with or without para-aortic lymphadenectomy, followed by post-operative adjuvant treatment. Nevertheless, the choice of the optimal adjuvant treatment regimen remains a matter of debate. Current options include radiotherapy (RT), chemotherapy (CT), and a combination of both (CT + RT). The Post Operative Radiation Therapy in Endometrial Carcinoma 3 (PORTEC-3) trial provided evidence supporting the use of CT + RT (two cycles of cisplatin during

RT, followed by four cycles of paclitaxel plus carboplatin) over RT alone for stage III EC, with better failure-free survival and a marginal benefit in overall survival (OS) [2]. In contrast, the Gynecologic Oncology Group-258 (GOG-258) trial compared CT + RT (using the same regimen as the PORTEC-3 trial) to CT alone (six cycles of paclitaxel plus carboplatin) in patients with stage III–IVA EC with a median follow-up of 10 years, and the results showed no significant difference in OS or recurrence-free survival between the two adjuvant treatment regimens [3, 4].

In current clinical practice, CT + RT often involves sequential or sandwich methods, differing from the regimen used in the PORTEC-3 and GOG-258 trials. Consequently, several recent retrospective studies have assessed the real-world benefits of adjuvant CT + RT with these sequential or sandwich methods, suggesting that such treatment may indeed offer improved survival benefits compared to CT alone [5–7]. Given the substantial heterogeneity among patients with stage III EC,

whether it is appropriate to apply the same adjuvant treatment approach to all patients is still under debate [8]. In addition, although the molecular classification of EC provides important prognostic information, it remains unclear which adjuvant treatment is most suitable for certain molecular subtypes of EC. Therefore, this study aimed to identify significant prognostic factors for patients with stage III EC and evaluate which high-risk subgroups would benefit the most from adjuvant CT + RT treatment.

2. Materials and methods

2.1 Data source

The data analyzed in this study were retrieved from Chang Gung Research Database (CGRD), which contains the original medical records from four medical institutes around Taiwan: Keelung Chang Gung Memorial Hospital (CGMH), Linkou CGMH, Chiayi CGMH, and Kaohsiung CGMH. According to the National Cancer Registry in Taiwan, about 20% of all EC patients are treated in these four medical institutes. The CGRD is a de-identified database that, in addition to primary electronic medical records, includes a cancer registry with data on the date of cancer diagnosis, stage, treatment modality, and date of death. The Institutional Review Board of CGMH approved this study (IRB No.: 202201469B0). The requirement for written informed consent was waived by the Ethics Committee as the data were retrospectively retrieved from a de-identified database, and the study population was treated or diagnosed according to routine clinical practice.

2.2 Patient selection

Patients diagnosed with 2009 International Federation of Gynecology and Obstetrics (FIGO) stage III EC between January 2009 and December 2021 were recruited for this retrospective analysis. All patients underwent total hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy with or without paraaortic lymphadenectomy, and they were staged according to the FIGO 2009 staging system [9]. Stage IIIA was defined as tumor invasion of the uterine serosa and/or adnexae; IIIB as vaginal and/or parametrial involvement; IIIC1 as pelvic lymph node metastasis; and IIIC2 as para-aortic lymph node metastasis. Due to the small number of FIGO stage IIIB cases (only 3.56% in our study), analyzing survival with stages IIIA, IIIB, and IIIC separately would reduce statistical power, particularly for stage IIIB. To address this limitation and ensure more meaningful analysis, we combined stages IIIA and IIIB. This approach is supported by prior studies, as the prognostic outcomes of stages IIIA and IIIB are more similar to each other than to stage IIIC [6, 8]. Grouping these stages enables a more balanced sample size and enhances the robustness of survival analysis. Patients who were staged using the FIGO system prior to the 2009 version, those who received incomplete surgical staging, those who received neoadjuvant treatment (including RT and CT), and those who were followed up for fewer than 90 days were excluded. In addition, patients who refused to receive any adjuvant treatment, those who received only adjuvant RT of a total dose of less than 4500 cGy (centigray), and those who received only adjuvant CT of

fewer than 4 cycles were also excluded from this study, as these inadequate treatment may have compromised survival outcomes [10, 11].

2.3 Covariates and outcomes

Clinicopathological characteristics were collected directly from CGRD, including age at diagnosis, FIGO substage, histologic type, histologic grade, status of lympho-vascular space invasion (LVSI), the number of dissected lymph nodes during staging surgery, and the number of positive lymph nodes in those with stage IIIC EC. Adjuvant treatment regimens were classified as RT alone, CT alone, or CT + RT. Patients who received adjuvant CT of 4 or more cycles and adjuvant RT of a dose less than 4500 cGy were classified into the CT alone group. Patients who received adjuvant CT of fewer than 4 cycles and adjuvant RT of a dose of 4500 cGy or more were classified into the RT alone group. All patients who received CT were treated with a platinum-based regimen, typically combined with paclitaxel, doxorubicin, or ifosfamide.

The primary outcome of interest was OS, defined as the period from the date of staging surgery to the date of death from any cause. Cancer-specific survival (CSS) was defined as the time from the date of staging surgery to the date of death from EC.

2.4 Statistics

Clinicopathological variables were compared among various adjuvant treatment regimens using the chi-square or Fisher's exact test. Univariate and multivariate Cox regression analyses were conducted to assess the potential impact of age, FIGO substages, histology, grade, LVSI status, the number of dissected lymph nodes, the number of positive lymph nodes, and adjuvant treatment regimens on survival outcomes in both the overall cohort and subgroups by calculating the hazard ratio (HR) and corresponding 95% confidence interval (CI). Kaplan-Meier analysis was used to assess survival, and the log-rank test was used to compare differences in survival among adjuvant treatment groups. A *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1 Baseline characteristics of the patients

A total of 294 patients were eligible for analysis (Fig. 1), with baseline characteristics summarized in Table 1 by adjuvant treatment type. Most patients received RT alone (*n* = 135, 45.9%), followed by CT alone (*n* = 84, 28.6%) and combined CT + RT (*n* = 75, 25.5%). The median age at diagnosis was 55 years (interquartile range (IQR): 50–61). The majority were stage IIIC (73.5%) with endometrioid histology (69.7%). LVSI was more frequently positive in the RT and CT + RT groups than in the CT group. No significant differences were noted among the three groups in terms of age, FIGO substage, histology, tumor grade, lymph node dissection, number of

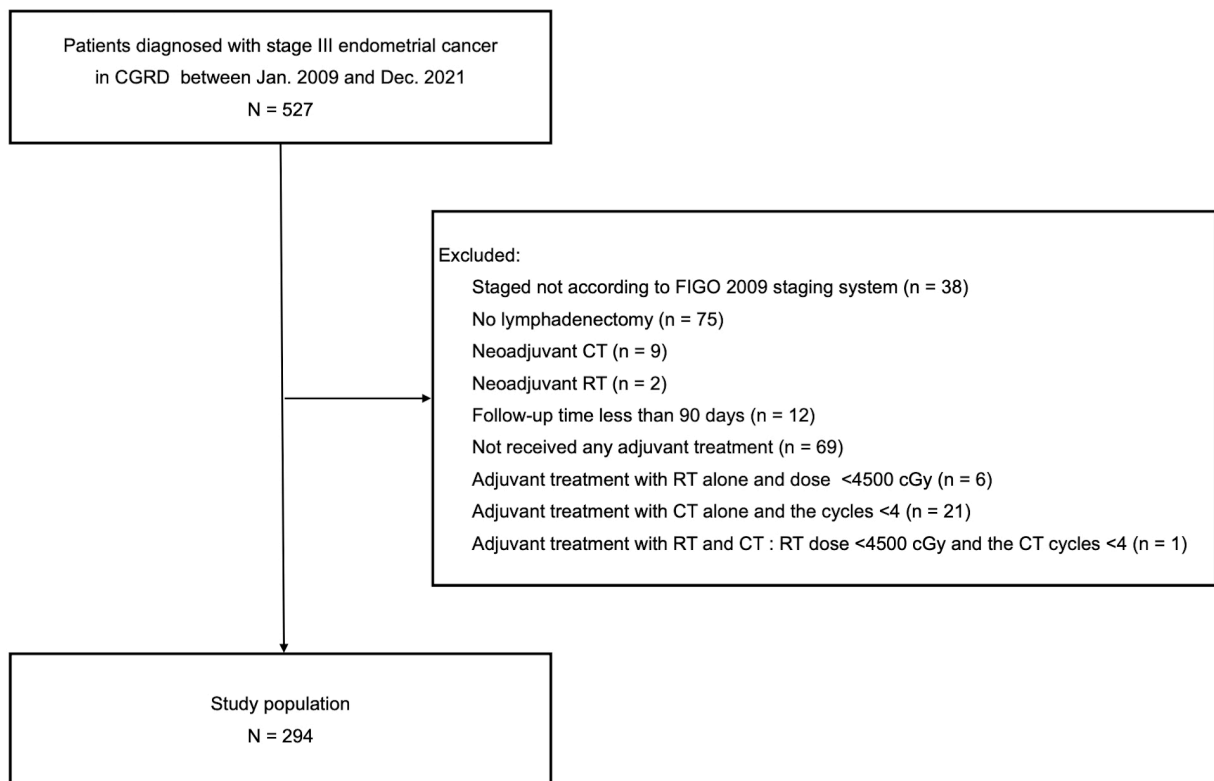


FIGURE 1. Flowchart of patient selection. CGRD: Chang Gung Research Database; FIGO: International Federation of Gynecology and Obstetrics; CT: chemotherapy; RT: radiotherapy.

TABLE 1. Baseline characteristics of the patients.

Variable	Total	RT		CT		CT + RT		p-value
	n	n	(%)	n	(%)	n	(%)	
	294	135	(45.9)	84	(28.6)	75	(25.5)	
Age (yr)								
≤60	216	99	(73.3)	64	(76.2)	53	(70.7)	0.733
>60	78	36	(26.7)	20	(23.8)	22	(29.3)	
FIGO stage								
IIIA/IIIB	78	44	(32.6)	21	(25.0)	13	(17.3)	0.061
IIIC1	131	53	(39.3)	35	(41.7)	43	(57.3)	
IIIC2	85	38	(28.2)	28	(33.3)	19	(25.3)	
Histologic type and grade ¹								
Endometrioid Grade 1–2	140	66	(48.9)	42	(50.0)	32	(42.7)	0.467
Endometrioid Grade 3	58	32	(23.7)	11	(13.1)	15	(20.0)	
Non-Endometrioid	86	33	(24.4)	28	(33.3)	25	(33.3)	
Lympho-vascular space invasion								
Negative	52	35	(25.9)	9	(10.7)	8	(10.7)	<0.001
Positive	108	68	(50.4)	5	(6.0)	35	(46.7)	
Unknown	134	32	(23.7)	70	(83.3)	32	(42.7)	
Number of dissected lymph nodes								
1–20	66	34	(25.2)	12	(14.3)	20	(26.7)	0.102
>20	228	101	(74.8)	72	(85.7)	55	(73.3)	

TABLE 1. Continued.

Variable	Total		RT		CT		CT + RT		p-value
	n		n	(%)	n	(%)	n	(%)	
	294		135	(45.9)	84	(28.6)	75	(25.5)	
Number of positive lymph nodes ²									
0	78		44	(32.6)	21	(25.0)	13	(17.3)	0.104
1–5	156		70	(51.9)	42	(50.0)	44	(58.7)	
>5	59		21	(15.6)	21	(25.0)	17	(22.7)	
Total dose of radiotherapy									
<5040 cGy	33		23	(17.0)	N/A		10	(13.3)	N/A
≥5040 cGy	177		112	(83.0)	N/A		65	(86.7)	
Disease status									
No recurrence	209		94	(69.6)	64	(76.2)	51	(68.0)	0.195
Regional metastasis	13		3	(2.2)	6	(7.1)	4	(5.3)	
Distant metastasis	48		28	(20.7)	7	(8.3)	13	(17.3)	
Persistent disease	24		10	(7.4)	7	(8.3)	7	(9.3)	

RT: radiotherapy; CT: chemotherapy; CT + RT: chemotherapy and radiotherapy; FIGO: International Federation of Gynecology and Obstetrics; N/A: not applicable; cGy: centigray.

^{1,2}Due to missing data, the sum of category counts may be less than the total number of patients included in the analysis.

positive nodes, or recurrence rate/pattern. Radiation dose was comparable between the RT and CT + RT groups, with ≥5040 cGy administered in 83.0% and 86.7% of patients, respectively.

3.2 Prognostic factors and impact of adjuvant treatment modality on survival

The median follow-up time was 42 months (interquartile range: 21.6 to 84 months), and the 5-year CSS and OS rates in the overall cohort were 82.0% and 79.6%, respectively. In addition, the 5-year OS rates were 81.3%, 79.8% and 78.5% with adjuvant CT + RT, CT, and RT, respectively, and the 5-year CSS rates were 81.3%, 81.0% and 83.0%. There were no significant differences in survival outcomes between the different adjuvant modalities.

Univariate analysis revealed that age over 60 years, substage IIIC2, and grade 3 endometrioid/non-endometrioid histology were associated with worse CSS and OS. However, in the multivariate analysis, only age over 60 years was an independent factor for poor CSS (HR 2.90; 95% CI: 1.72–4.91) and OS (HR 3.13; 95% CI: 1.91–5.13). The results of both univariate and multivariate analyses indicated that the type of adjuvant treatment modality was not a significantly prognostic factor in the overall cohort (Table 2).

3.3 Subgroup analysis

To investigate the impact of different adjuvant treatment modalities on the OS of high-risk patients with stage III EC, we performed Cox regression analyses stratified by age, histology, grade, and substage. In multivariate analysis, the impact of different adjuvant treatment modalities on OS

was generally insignificant across most of the subgroups (Supplementary Tables 1,2,3,4,5,6) except in patients aged over 60 years. In this group, although the choice of adjuvant therapy modality did not significantly influence CSS, it had a noticeable impact on OS (Supplementary Table 2). The 5-year CSS rates were 68.7%, 53.4%, and 51.5% for patients aged over 60 who received adjuvant CT + RT, CT, and RT, respectively (Fig. 2A), and the 5-year OS rates were 68.7%, 53.4% and 42.3% (Fig. 2B). In the multivariate analysis, the patients aged over 60 years who received adjuvant RT had a significantly worse OS compared to those who received adjuvant CT + RT (HR 3.15, 95% CI: 1.05–9.47, $p = 0.04$) (Fig. 3).

4. Discussion

In this study, we found that age over 60 years, substage IIIC2, and grade 3 endometrioid/non-endometrioid histology were adverse prognostic factors in patients with stage III EC. Among these factors, only age over 60 years remained independently significantly associated with CSS and OS in multivariate analysis. In general, the survival outcomes were comparable between the different adjuvant treatment modalities. However, for the patients aged over 60 years, CT + RT was associated with the highest OS rate compared to the use of CT or RT alone. Our findings are novel and the first to suggest that aggressive adjuvant treatment does not compromise the survival benefits in older patients.

Numerous prognostic factors have been associated with unfavorable survival outcomes in patients with stage III EC, including older age, high-grade histology, non-endometrioid histology, and substage IIIC2 [8, 12, 13]. Consistent with

TABLE 2. Univariate and multivariate analyses for cancer-specific survival and overall survival of the entire cohort.

Variable	Cancer-specific survival (N = 294)						Overall survival (N = 294)					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	Crude HR	95% CI	<i>p</i> -value	Adjusted HR	95% CI	<i>p</i> -value	Crude HR	95% CI	<i>p</i> -value	Adjusted HR	95% CI	<i>p</i> -value
Age (yr)												
≤60	Ref			Ref			Ref			Ref		
>60	3.37	(2.03–5.60)	<0.0001	2.90	(1.72–4.91)	0.0001	3.43	(2.13–5.52)	<0.0001	3.13	(1.91–5.13)	<0.0001
FIGO Stage												
IIIA/IIIB	Ref			Ref			Ref			Ref		
IIIC1	1.46	(0.67–3.16)	0.3416	1.11	(0.49–2.48)	0.8022	1.10	(0.56–2.16)	0.7822	0.90	(0.44–1.83)	0.7713
IIIC2	3.50	(1.66–7.38)	0.0010	2.01	(0.87–4.61)	0.1004	2.59	(1.36–4.93)	0.0039	1.58	(0.76–3.30)	0.2210
Histologic type and grade												
Endometrioid G1–2	Ref			Ref			Ref			Ref		
Endometrioid G3 & Non- Endometrioid	1.95	(1.14–3.33)	0.0143	1.40	(0.79–2.46)	0.2478	1.91	(1.15–3.14)	0.0116	1.47	(0.87–2.49)	0.1534
LVSI												
Negative	Ref			Ref			Ref			Ref		
Positive	2.78	(1.07–7.20)	0.0355	1.90	(0.69–5.22)	0.2141	2.12	(0.93–4.83)	0.0736	1.58	(0.65–3.82)	0.3110
Unknown	2.28	(0.88–5.91)	0.0899	1.85	(0.67–5.10)	0.2333	1.86	(0.82–4.22)	0.1367	1.74	(0.73–4.18)	0.2138
Number of dissected lymph nodes												
1–20	0.78	(0.41–1.50)	0.4517	0.84	(0.42–1.68)	0.6165	0.82	(0.45–1.50)	0.5256	0.86	(0.45–1.64)	0.6465
>20	Ref			Ref			Ref			Ref		
Adjuvant treatment												
RT	0.81	(0.43–1.50)	0.4976	1.02	(0.54–1.93)	0.9497	1.01	(0.56–1.84)	0.9624	1.26	(0.68–2.32)	0.4606
CT	0.99	(0.50–1.94)	0.9703	0.94	(0.43–2.10)	0.8884	1.04	(0.54–2.03)	0.9017	0.94	(0.44–2.04)	0.8793
CT + RT	Ref			Ref			Ref			Ref		

HR: hazard ratio; 95% CI: 95% confidence interval; Ref: reference; LVSI: lympho-vascular space invasion; RT: radiotherapy; CT: chemotherapy; CT + RT: chemotherapy and radiotherapy; FIGO: International Federation of Gynecology and Obstetrics; *p*-values less than 0.05 are presented in bold.

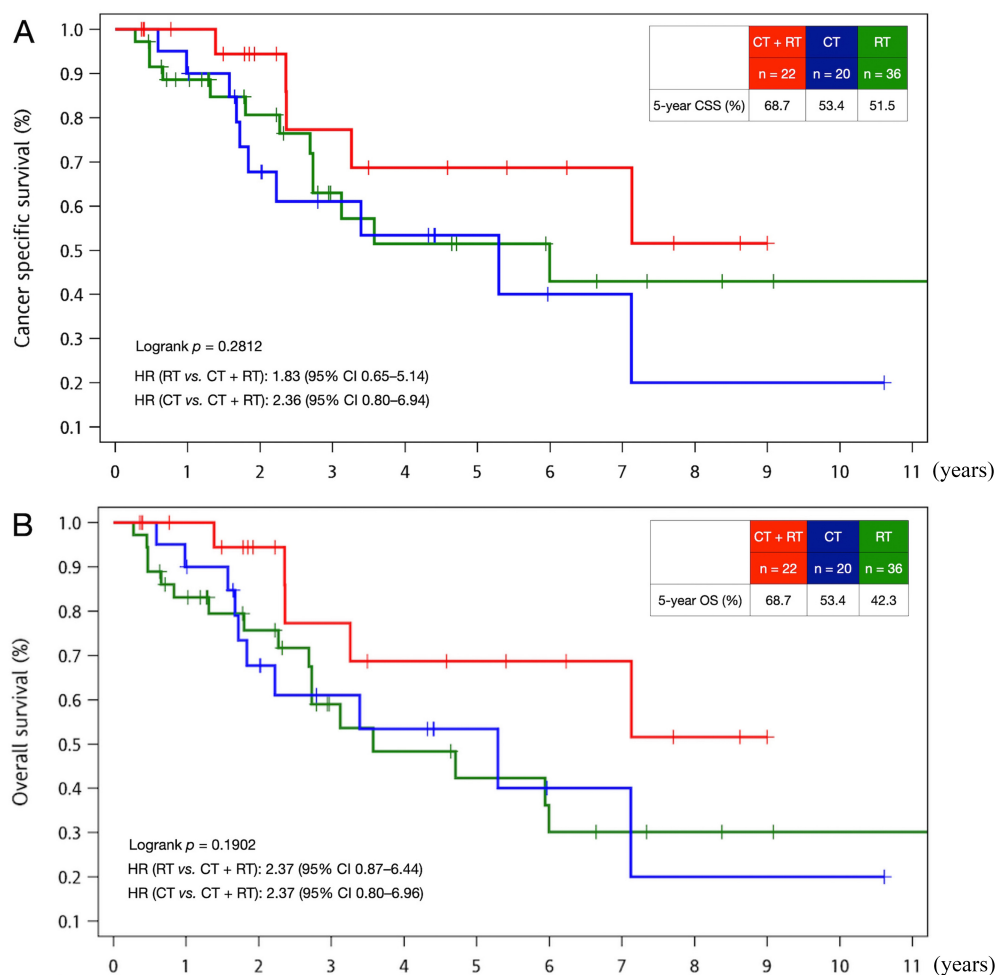


FIGURE 2. Kaplan-Meier curves for cancer-specific survival (A) and overall survival (B) in stage III EC patients aged over 60. HR: hazard ratio; RT: radiotherapy; CT: chemotherapy; CT + RT: chemotherapy and radiotherapy; CI: confidence interval; CSS: cancer-specific survival; OS: overall survival.

previous findings, we also found that older age was the most significant independent factor associated with lower OS. Previous studies investigating the optimal adjuvant modality for patients with stage III EC have primarily focused on substage and histologic type. A meta-analysis of 15 retrospective studies and a randomized controlled trial (GOG-258) on stage III EC reported that adjuvant CT + RT was generally associated with superior OS outcomes compared to adjuvant CT alone, particularly in patients with stage IIIC; however, the findings were based on pooled data with high heterogeneity [7]. In our analysis, different adjuvant treatment modalities did not significantly impact survival in the overall cohort of stage III EC patients, even in subgroup analyses specifically focusing on the high-grade/non-endometrioid histology group and the stage IIIC2 group. This inconsistency may be due to differences in the characteristics of stage III EC across individual studies, including differences in the rate of lymphadenectomy and specific adjuvant modality regimens.

Older age is known to be a significant independent adverse prognostic factor for survival outcomes in EC patients [14]. However, research on the optimal adjuvant treatment for older patients with stage III EC is limited. Data from GOG protocols

249, 209, and 229L showed that even though older EC patients generally have a higher incidence of aggressive disease and are more likely to require adjuvant treatment, only about half of the patients receive the recommended adjuvant treatment [15].

A German study demonstrated that the rate at which physicians did not recommend indicated adjuvant treatments increased with patient age. Importantly, the study found that this disparity was not due to patient refusal, but rather to physician recommendations [16]. Additionally, a recent review highlighted treatment gaps in older patients with EC, noting that they tend to receive less aggressive treatment—particularly adjuvant CT and RT—compared to younger patients with the same histological stage. The authors suggested that the poorer survival outcomes in older patients are largely attributable to the underutilization of adjuvant therapies [17].

Our study emphasizes the survival benefits of aggressive adjuvant treatment for older EC patients, as the results showed that the patients over 60 years with stage III EC who underwent complete staging surgery and adjuvant CT + RT had a significant improvement in OS. However, the improvement in CSS was only marginal. This discrepancy may be attributed to potential misclassification of the cause of death, where

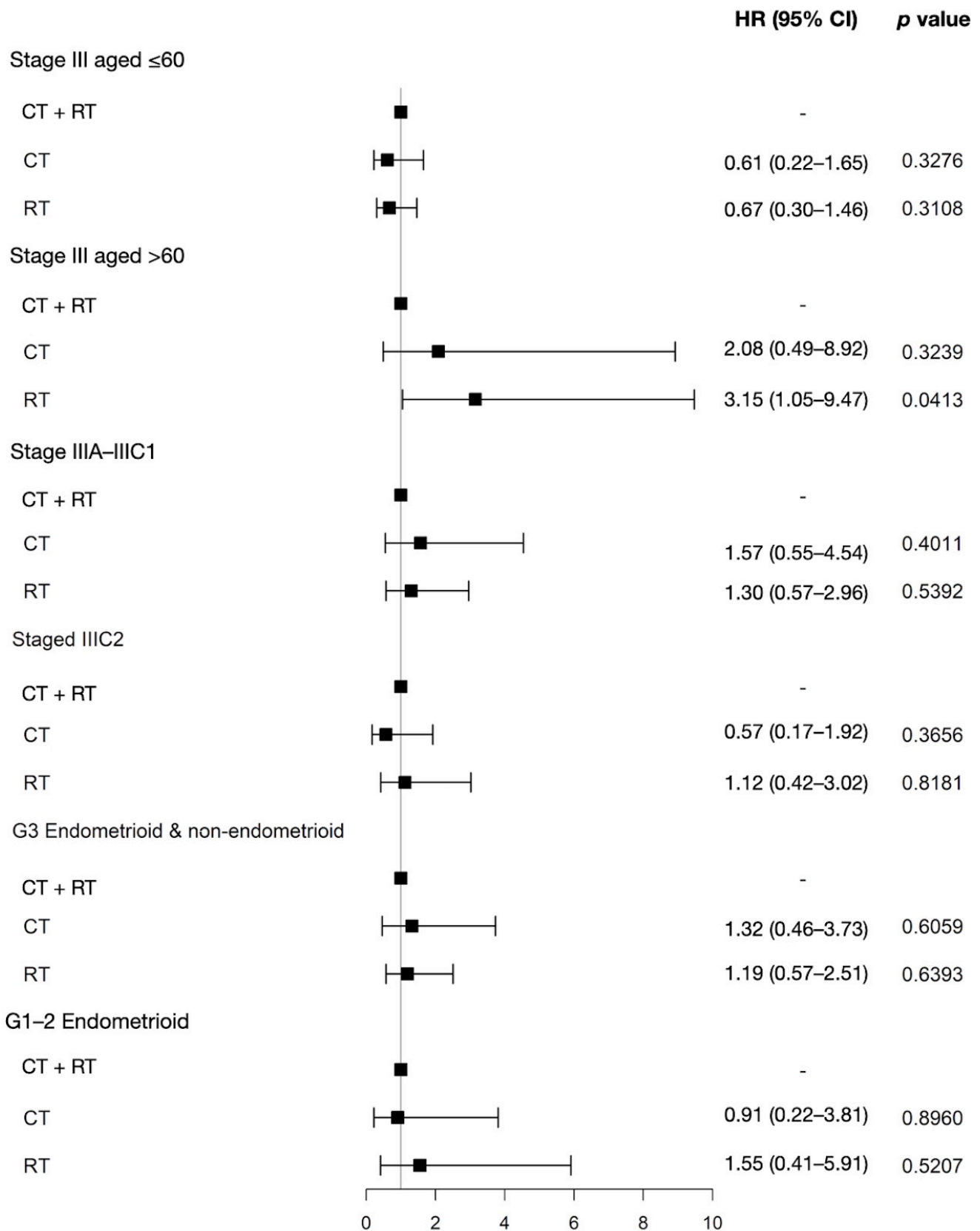


FIGURE 3. Forest plot demonstrating hazard ratios (HR) and 95% confidence intervals (CI) for adjuvant treatment effects on overall survival across subgroups according to multivariate Cox regression analysis. The HRs with 95% CIs are represented by black square and error bars. CT + RT: adjuvant chemotherapy and radiotherapy; CT: adjuvant chemotherapy alone; RT: adjuvant radiotherapy alone.

cancer may have contributed to but not been the sole cause of death, thereby complicating the assessment of cancer-related mortality [18]. Although adjuvant CT + RT is associated with a higher rate of adverse events [2, 3], it improved OS in the older patients with advanced EC in our study, particularly compared to adjuvant RT alone. This finding suggests that age should not be the sole barrier to aggressive adjuvant therapy in older patients. Instead, a comprehensive frailty assessment should guide treatment decisions to ensure that older patients receive appropriate care.

The molecular analysis of the PORTEC-3 trial indicated that patients over 60 years old had a higher prevalence of p53-abnormal tumors compared to other molecular subtypes. While this suggests a possible association between older age and p53-abnormal tumors, it only indirectly indicates an increased prevalence in this age group. In addition, the PORTEC-3 trial reported that adjuvant CT + RT improved recurrence-free survival and OS in patients with p53-abnormal tumors in the high-risk EC population. Although these findings align with our results, they do not directly support our conclusions [19].

This study has several strengths. First, it is the first study to demonstrate a significant survival benefit from adjuvant CT + RT in older patients with stage III EC. Second, the heterogeneity of our study cohort was relatively low. We recruited patients who underwent complete staging surgery with lymphadenectomy and excluded stage IIIA cases with solely positive peritoneal cytology. These clear criteria helped to minimize variability in the study population. Third, we performed multivariate analysis considering key prognostic factors to assess the survival impacts of various adjuvant treatment modalities.

However, certain limitations also need to be addressed. First, some subgroup analyses were performed with a small sample size (the older subgroup included only 78 patients: CT + RT, $n = 22$; CT, $n = 20$; RT, $n = 36$). As a result, the statistical power may be limited, and the findings should be interpreted cautiously. Second, the grouping strategy in this study was based on the completion of full-dose adjuvant treatments (CT cycles ≥ 4 ; RT dose ≥ 4500 cGy). Therefore, the findings may not be generalizable to older patients with a high comorbidity burden who cannot tolerate full-dose treatment. This limitation should be taken into account when interpreting the treatment efficacy across different groups. Third, because certain clinical variables, such as performance status, were not initially included in the CGRD database, we were unable to analyze the impact of the Charlson Comorbidity Index on survival. Fourth, due to the de-identified nature of the database, we were unable to retrieve detailed information for patients with unknown LVSI status. Given that 45.6% of the patients had an unknown LVSI status, accurately assessing its impact on survival was not possible in this study. In addition, the distribution of patient characteristics across different adjuvant treatment groups may have been influenced by the non-randomized allocation inherent in retrospective studies. Finally, we did not investigate the impact of The Cancer Genome Atlas (TCGA) molecular classification on EC survival outcomes, although TCGA classification plays an increasingly critical role in optimizing future treatment strate-

gies [20, 21]. Recently, the European Network for Gynaecological Oncological Trial groups (ENGOT)-en11/KEYNOTE-B21 trial reported that adding immune checkpoint inhibitors to adjuvant CT with or without RT for high-risk EC patients led to a significant improvement in disease-free survival, but only in the deficient mismatch repair group [22]. The most appropriate adjuvant treatment beyond CT and RT for older patients still requires further investigation.

5. Conclusions

In summary, the results of this study showed that age over 60 years was an independent adverse prognostic factor in patients with stage III EC who underwent comprehensive staging surgery with lymphadenectomy. However, the patients aged over 60 years who received adjuvant CT + RT had better OS compared to those who received adjuvant CT or RT alone. These results indicate that advanced age should not be the sole barrier to aggressive adjuvant therapy. Further prospective investigations of adjuvant therapies, including immune checkpoint inhibitors, are warranted to confirm these findings.

AVAILABILITY OF DATA AND MATERIALS

The data contained within this article are available.

AUTHOR CONTRIBUTIONS

SWH, HCF and HL—conceptualization; writing review and editing. CHW and SMY—methodology and software. SWH, YCO, HCF and HL—investigation. YCO and SMY—formal analysis. SWH, YCO and SMY—writing original draft preparation. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No.: 202201469B0). The requirement for written informed consent was waived by the Ethics Committee as the data were retrospectively retrieved from a de-identified database, and the study population was treated or diagnosed according to routine clinical practice.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at <https://oss.ejgo.net/files/article/2011678183210795008/attachment/Supplementary%20material.docx>.

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