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Original Research

Impact of different adjuvant treatment approaches on survival in stage III endometrial cancer: A population-based study

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Abstract ***Background:*** Patients with International Federation of Gynaecology and Obstetrics (FIGO) stage III endometrial cancer (EC) have a substantial risk of adverse outcomes. After surgery, adjuvant therapy is recommended with external beam radiotherapy (EBRT), chemotherapy (CT) or both EBRT and CT. Recent trials suggest that EBRT + CT is superior to EBRT or CT alone but also results in more toxicity. We have compared the outcome of different adjuvant treatments in a population-based cohort to identify subgroups that benefit most from EBRT + CT.

Methods: All patients diagnosed with FIGO stage III EC and treated with surgery in 2005–2016 were identified from the Netherlands Cancer Registry. The primary outcome was overall survival (OS); associations with adjuvant treatment were analysed using Cox regression analysis.

Results: Among 1241 eligible patients, EBRT + CT was associated with a better OS than CT (hazard ratio [HR] = 1.84, 95% confidence interval [CI] = 1.34–2.52) and EBRT alone (HR = 1.37, 95% CI = 1.05–1.79). In stage IIIC, there was a significant benefit of

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EBRT + CT compared with CT or EBRT alone. In stage IIIA–B, there was no difference between EBRT + CT or EBRT alone. In endometrioid EC (EEC) and carcinosarcomas, EBRT + CT was associated with a better OS than CT or EBRT alone. For uterine serous cancers, there was no survival benefit of EBRT + CT over CT. In all analysis by stage and histology, any adjuvant treatment was superior to no adjuvant therapy.

Conclusions: In this population-based study, adjuvant EBRT + CT was associated with improved OS compared with CT or EBRT alone in FIGO stage IIIC EC, EEC and carcinosarcoma. This suggests that application of EBRT + CT in stage III should be further stratified according to these subgroups.

1. Introduction

Endometrial cancer (EC) is the most common gynaecological malignancy in developed countries, affecting approximately 380,000 women annually worldwide [1]. While most patients are diagnosed with early-stage disease and have a favourable prognosis, for those with extrauterine disease (stage III–IV), there is a high risk of recurrence and poor outcomes [2,3]. Primary treatment of EC consists of hysterectomy and bilateral salpingo-oophorectomy with additional lymphadenectomy in case of clinical suspicion of extended disease [4,5]. The appropriate adjuvant treatment strategy for patients with stage III disease is still under debate, resulting in widespread variation in application of external beam radiotherapy (EBRT), chemotherapy (CT) and EBRT + CT [6–11]. Recently, two randomised controlled trials have evaluated the benefit of combining CT with EBRT: the PORTEC-3 study compared EBRT + CT with EBRT alone in a population of 660 high-risk patients with EC that included 295 patients with stage III disease, reporting a significant survival benefit for EBRT + CT, with a 5-year overall survival (OS) of 78.5% in the EBRT + CT group and 68.5% in the EBRT group [12]. The GOG-258 study randomised 715 patients with stage III EC to EBRT + CT or CT alone and observed a non-significant difference in progression-free survival of 59% for patients treated with EBRT + CT versus 58% in patients treated with CT alone [13]. Data of this trial on OS are not yet presented. In both studies, treatment-related morbidity was higher for combined treatment than for EBRT or CT alone [13,14].

Patients included in trials are often younger and have less comorbidities than the patient population in a gynae-oncology outpatient clinic, which challenges translation of results from randomised clinical trials into clinical practice [15,16]. As advanced age and higher comorbidity scores are associated with adverse outcomes in treatment of EC, it is relevant to investigate the optimal use of adjuvant CT and radiotherapy (RT) in patients with International Federation of Gynaecology and Obstetrics (FIGO) stage III EC [17,18]. Population-based research can be used to identify subgroups of patients that profit most from adjuvant CT, EBRT or EBRT + CT. Therefore we analysed a population-based cohort of patients with stage III EC to compare the outcomes of different adjuvant treatment approaches in a large population-based cohort including all patients with stage III EC diagnosed between 2005 and 2016 in the Netherlands.

2. Materials and methods

2.1. Data collection

Data were retrieved from the Netherlands Cancer Registry (NCR), which contains clinicopathologic characteristics of all patients diagnosed with cancer from 1989 onwards in the Netherlands. Data of all consecutive patients diagnosed with FIGO 2009 stage III EC between 1st January 2005 and 31st December 2016 were requested. Patients were excluded for analysis if they received neoadjuvant CT, did not undergo surgery, received adjuvant brachytherapy only, or had residual tumour after surgery. The NCR is linked to the Municipal Personal Records Database to obtain information on vital status of patients in the registry. For our analyses, the information concerning vital status was available up to 31st January 2019. Data on age, FIGO stage, histology, tumour grade, surgical and adjuvant treatment including number of positive lymph nodes, and number of surgically removed lymph nodes were obtained from the NCR database. Data with regard to adjuvant therapy were categorised into the following groups: no adjuvant therapy, EBRT, CT and EBRT + CT.

2.2. Outcome

The primary outcome was OS in relation to adjuvant treatment strategies after correction for covariates. Within the different treatment strategies, survival was compared for patients with and without lymph node

metastasis, i.e. stage IIIA–B versus stage IIIC, and patients with endometrioid EC (EEC), uterine serous cancer (USC) and carcinosarcoma histology.

2.3. Statistical analyses

Baseline patient and tumour characteristics were compared for adjuvant treatment strategies. OS was measured from the date of diagnosis until the date of death or last follow-up. Impact of adjuvant treatment on OS was estimated using Kaplan–Meier analyses and log-rank tests. Univariable and multivariable Cox regression analyses were performed for OS including age, grade, histological subtype, stage, i.e. IIIA–B and IIIC, and number of removed lymph nodes. The number of removed lymph nodes was categorised into 0, 1–10, 11–20 and >20 [19]. Variables that were significant in univariable analysis ($P < 0.10$) were included in multivariable Cox regression analysis. Subsequently, subgroup Cox regression analyses were performed for stage and histological subtypes. Data analysis was performed using STATA statistical software, version 14.2. A P-value of <0.05 was considered statistically significant.

3. Results

3.1. Patient and tumour characteristics

A total of 1850 patients with EC were diagnosed with stage III disease in 2005–2016. After exclusion of patients without surgery ($n = 214$), residual disease ($n = 325$), neoadjuvant CT ($n = 33$) and only vaginal brachytherapy ($n = 37$), 1241 patients were included for analysis (Table 1). The mean age at diagnosis was 67.0 years (standard deviation = 10.7), and the majority of patients were diagnosed with endometrioid histology ($n = 837$). Most patients were diagnosed with stage IIIA (50.2%) or IIIC (40.1%), and only a minority was diagnosed with stage IIIB (9.6%). Adjuvant treatment was applied to 79.2% ($n = 983$) of the patients and consisted of EBRT for 52.4% ($n = 650$), CT for 12.7% ($n = 158$) or EBRT + CT for 14.1% ($n = 175$). In patients with stage IIIA–B disease, no lymph nodes were removed in 80.1% ($n = 595$) patients; in 13.9% ($n = 103$) patients, ≤20 nodes were removed and in 6.1% ($n = 45$), >20 nodes were removed. For patients with stage IIIC disease, all patients had at least one lymph node removed, with 69.9% ($n = 348$) patients

Table 1
Baseline characteristics of patients ($n = 1241$) with FIGO stage III EC between 1st January 2005 and 31st December 2016.

Variable	Total	EBRT	CT	EBRT + CT	None
	$n = 1241$	$n = 650$	$n = 158$	$n = 175$	$n = 258$
Age (SD)	67.0 (10.7)	66.5 (10.5)	65.8 (8.2)	62.9 (9.5)	71.4 (11.9)
Age					
<60 years	319 (25.7)	174 (26.8)	28 (17.7)	61 (34.9)	56 (21.7)
60–69 years	410 (33.0)	214 (33.3)	78 (49.4)	66 (37.7)	52 (20.2)
70–79 years	347 (30.0)	186 (28.6)	48 (30.4)	45 (25.7)	68 (26.4)
>80 years	165 (13.3)	76 (11.7)	4 (2.5)	3 (1.7)	82 (31.8)
FIGO stage					
IIIA	624 (50.2)	365 (56.2)	45 (28.5)	56 (32.0)	158 (61.2)
IIIB	119 (9.6)	71 (10.9)	17 (10.8)	10 (5.7)	21 (8.1)
IIIC1–2	498 (40.1)	214 (32.9)	96 (60.8)	109 (62.3)	79 (30.6)
Histology					
Endometrioid	837 (67.4)	536 (82.5)	30 (19.0)	90 (51.4)	181 (70.2)
Serous	210 (16.9)	44 (6.8)	82 (51.9)	51 (29.1)	33 (12.8)
Clear-cell	55 (4.4)	26 (4.0)	12 (7.6)	4 (2.3)	13 (5.0)
Carcinosarcoma	139 (11.2)	44 (6.8)	34 (21.5)	30 (17.1)	31 (12.0)
Grade					
I	218 (17.6)	135 (20.8)	7 (4.4)	25 (14.3)	51 (19.8)
II	325 (26.2)	221 (34.0)	12 (7.6)	28 (16.0)	64 (24.8)
III	599 (48.3)	262 (40.3)	114 (72.2)	109 (62.3)	114 (44.2)
Unknown	99 (8.0)	32 (4.9)	25 (15.8)	13 (7.4)	29 (11.2)
Number of nodes removed					
0	608 (49.0)	358 (55.1)	42 (26.6)	43 (24.6)	165 (64.0)
1–10	232 (18.7)	116 (17.8)	39 (24.7)	30 (17.1)	47 (18.3)
>10	401 (32.3)	176 (27.1)	77 (48.7)	102 (58.3)	46 (17.8)
Number of positive nodes					
0	755 (60.8)	440 (67.7)	62 (39.2)	66 (37.7)	187 (72.5)
1–9	452 (36.4)	200 (30.8)	84 (48.0)	105 (60.0)	63 (24.4)
10–19	23 (1.8)	5 (0.8)	11 (7.0)	2 (1.1)	5 (1.9)
≥20	11 (0.9)	5 (0.8)	1 (0.6)	2 (1.1)	3 (1.2)

Variables are displayed as number (%) or mean (standard deviation).
EC, endometrial cancer; SD, standard deviation; CT, chemotherapy; EBRT, external beam radiotherapy; FIGO, International Federation of Gynaecology and Obstetrics.

having ≤20 nodes removed and 30.1% (n = 150) having >20 nodes removed.

3.2. Survival

Five-year OS for all patients with FIGO stage III EC stratified by adjuvant treatment regimen is shown in Fig. 1. The 5-year OS rates were 0.61 (95% confidence interval [CI] = 0.53–0.69) for patients treated with EBRT + CT; 0.55 (95% CI = 0.51–0.59) for patients treated with EBRT alone; 0.39 (95% CI = 0.32–0.47) for patients treated with CT alone and 0.35 (95% CI = 0.29–0.41) for patients who received no adjuvant therapy. After multivariable Cox regressions with correction for other covariates including age, histology, grade, stage and number of lymph nodes removed, EBRT + CT was significantly associated with improved survival compared with CT alone (hazard ratio [HR] = 1.50, 95% CI = 1.09–2.04, P = 0.014), EBRT only (HR = 1.72, 95% CI = 1.30–2.27, P < 0.001) and no adjuvant treatment (HR = 2.89, 95% CI = 2.15–3.88, P < 0.001, Table 2). Other covariates, such as age less than 70 years, low-grade disease and endometrioid histology, remained independently associated with improved OS as well, except for performance of lymph node dissection (only >20 nodes removed was associated with improved OS) and positive lymph nodes (stage IIIC).

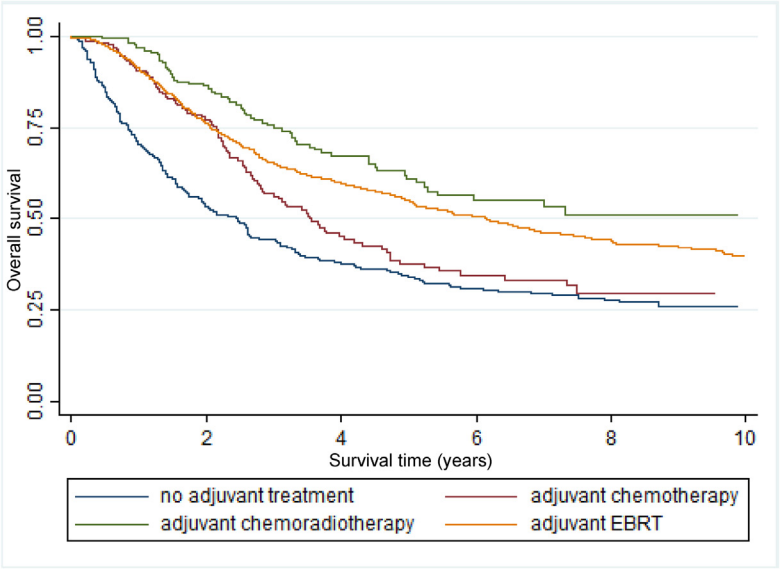
3.3. Subgroup analysis on FIGO stage

To investigate whether EBRT + CT was equally beneficial for patients with stage IIIA–B disease versus stage IIIC disease, subgroup Cox regression analyses were performed (Fig. 2, Supplementary Tables 1–2). Among patients with stage IIIA–B disease, all adjuvant therapies (EBRT + CT, CT, EBRT) were associated with improved outcomes when compared with no adjuvant treatment (P-values < 0.01). EBRT + CT was not superior compared with CT or EBRT alone.

For patients with stage IIIC disease, EBRT + CT was significantly associated with improved survival compared with CT (HR = 1.76, 95% CI = 1.22–2.54, P = 0.003), EBRT (HR = 1.74, 95% CI = 1.17–2.59, P = 0.007) and no adjuvant treatment (HR = 4.32, 95% CI = 2.91–6.43, P < 0.001).

3.4. Subgroup analysis based on histology

To investigate the impact of EBRT + CT on different histological subtypes, Cox regression analyses were performed for EEC, USC and carcinosarcomas (Fig. 2, Supplementary Tables 3–5). Clear-cell carcinomas were not analysed separately because of the low number of cases (n = 55). For patients with EEC (n = 837), EBRT + CT was significantly associated with improved survival compared with CT (HR = 2.04, 95% CI = 1.08–3.84, P = 0.028), EBRT (HR = 1.60, 95%



Numbers at risk

EBRT+chemotherapy	171	152	134	96	70	52	41	28	21	15
EBRT	595	496	427	361	310	264	221	193	163	129
Chemotherapy	144	122	88	63	46	37	29	20	14	10
None	183	139	116	91	80	70	64	57	51	47

Fig. 1. Kaplan–Meier analysis of overall survival stratified by adjuvant treatment regimen. EBRT, external beam radiotherapy.

Table 2
Cox regression analysis of overall survival of patients ($n = 1241$) with FIGO stage III EC between 1st January 2005 and 31st December 2016.

Variables	Univariable Cox regression	P-value	Multivariable Cox regression	P-value
Adjuvant treatment				
None	2.47 (1.86–3.27)	<0.001	2.89 (2.15–3.88)	<0.001
EBRT	1.37 (1.05–1.79)	0.019	1.72 (1.30–2.27)	<0.001
CT	1.84 (1.34–2.52)	<0.001	1.50 (1.09–2.06)	0.014
EBRT + CT	–	–	–	
Age				
<70 years	–	–	–	–
≥70 years	2.45 (2.11–2.84)	<0.001	2.12 (1.82–2.47)	<0.001
Grade				
I	–	–	–	–
II	1.66 (1.26–2.20)	0.001	1.64 (1.24–2.16)	0.001
III	3.20 (2.49–4.12)	<0.001	2.99 (2.27–3.94)	<0.001
Unknown	2.95 (2.12–4.12)	<0.001	2.26 (1.59–3.22)	<0.001
Histology				
Endometrioid	–	–	–	–
Non-endometrioid	1.93 (1.66–2.25)	<0.001	1.33 (1.10–1.62)	0.004
FIGO stage				
IIIA–B	–	–	–	–
IIIC1–2	1.24 (1.07–1.44)	0.005	1.29 (0.99–1.68)	0.051
Number of removed nodes				
0	0.85 (0.70–1.03)	0.089	1.12 (0.84–1.48)	0.437
1–10	–		–	–
11–20	1.02 (0.80–1.29)	0.893	0.92 (0.72–1.17)	0.494
>20	0.71 (0.55–0.92)	0.010	0.73 (0.56–0.94)	0.015

EC, endometrial cancer; CT, chemotherapy; EBRT, external beam radiotherapy; FIGO, International Federation of Gynaecology and Obstetrics.

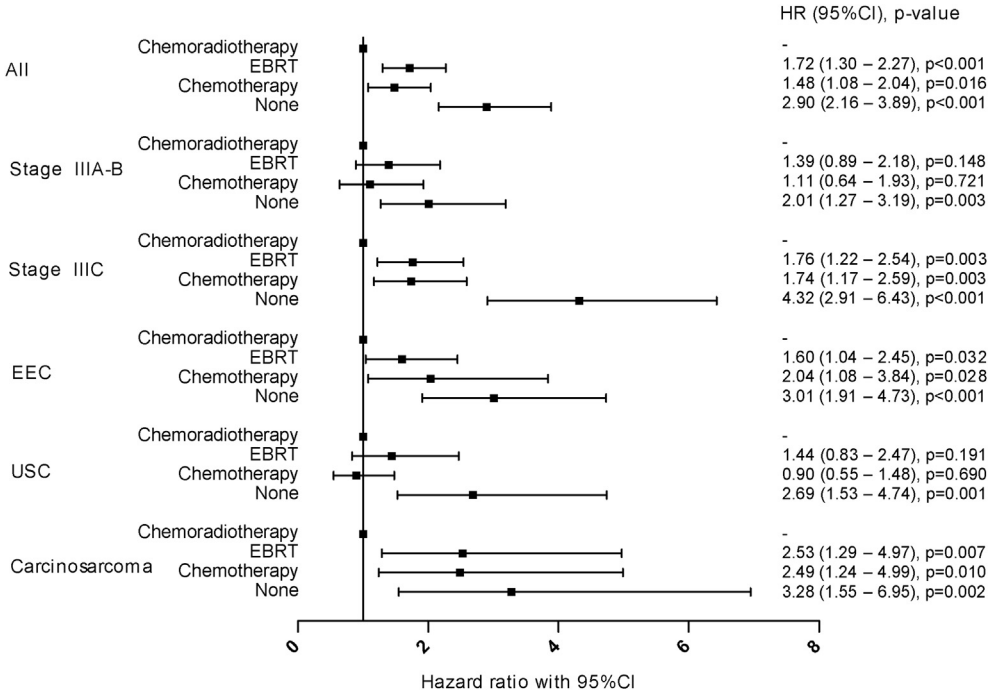


Fig. 2. Multivariable Cox regression analysis for overall survival (OS) of the complete cohort and relevant subgroups. The hazard ratios with 95% confidence intervals are depicted by the black line. EBRT, external beam radiotherapy; EEC, endometrioid type endometrial cancer; USC, uterine serous cancer; CI, confidence interval; HR, hazard ratio.

CI = 1.04–2.45, P = 0.032) and no adjuvant treatment (HR = 3.01, 95% CI = 1.91–4.73, P < 0.001).

In USCs ($n = 210$), EBRT + CT was associated with improved survival compared with no adjuvant treatment (HR = 2.68, 95% CI = 1.53–4.71, P < 0.001), but not when compared with CT or EBRT alone.

Among carcinosarcomas ($n = 139$), EBRT + CT was significantly associated with improved survival

compared with CT only (HR = 2.49, 95% CI = 1.24–4.99, P = 0.010), EBRT only (HR = 2.53, 95% CI = 1.29–4.97, P = 0.007) and no adjuvant treatment (HR = 3.28, 95% CI = 1.55–6.95, P = 0.002).

4. Discussion

In this population-based study, we have shown that the administration of adjuvant CT, EBRT or EBRT + CT is associated with improved OS compared with no adjuvant therapy in stage III EC, with the highest impact for EBRT + CT. After stratification for stage, EBRT + CT resulted in a better OS than EBRT or CT alone in FIGO stage IIIC EC, but not in stage IIIA and IIIB disease. Stratification for histology showed that administration of EBRT + CT resulted in a better OS than EBRT and CT in EEC and carcinosarcoma. In USCs, no difference in impact of EBRT + CT, CT alone and EBRT alone was found. These results indicate that EBRT + CT should be applied selectively, taking into account the substantial comorbidity of this treatment, with 25% of patients experiencing persistent sensory neurological symptoms after EBRT + CT [14].

Our results are in line with the results of the phase III randomised controlled trial PORTEC-3 study, in which the use of EBRT + CT was associated with an improved survival compared with EBRT in a subgroup of patients with stage III disease [12]. The GOG-258 study compared the use of EBRT + CT with CT in stage III–IVA EC. Published data on the failure-free survival in 736 patients with stage III–IVA EC showed no added value of EBRT + CT over CT, but the data on OS require further maturation, hampering comparison with this study [13].

We have investigated the impact of adjuvant therapy in several subgroups. First, we analysed subgroups stratified by stage. Two large retrospective population-based studies performed in the United States compared the impact of adjuvant therapy on OS in patients with stage IIIC EC [20,21]. Wong et al. [20] found improved survival from adjuvant therapy among 6720 patients with stage IIIC EC identified from the National Cancer Database (NCDB). The largest impact was found in patients treated with EBRT + CT, which is in line with our results. Xiang et al. [21] identified 13,270 patients with stage III–IVA EC from the NCDB to compare EBRT + CT with CT alone. Subgroup analyses showed that patients with stage IIIC EEC (especially stage IIIC2) benefited from EBRT + CT, whereas no significant effect was seen in patients with stage IIIA–B EC. These results are in line with our data in which we found a significant improvement in patients with stage IIIC disease, but not in patients with stage IIIA–B disease. The lack of significant differences in outcomes between adjuvant treatment strategies in stage IIIA–B disease discourages the use of standard EBRT + CT in these patients. It also highlights the importance of adequately identifying patients with stage IIIC disease as these patients benefit from adjuvant EBRT + CT. In our study, the majority of patients with stage IIIA–B disease did not undergo lymphadenectomy. Interestingly, in those who underwent extensive lymphadenectomy (>20 nodes), the outcome was significantly better than that in those without extensive lymphadenectomy. This highlights the relevance of proper staging to determine adjuvant therapy. No prospective trials have investigated the effect of EBRT alone in patients with stage III EC. Interestingly, we have found a survival benefit of applying EBRT only in this group of patients.

Second, we explored the impact of adjuvant therapy on different histological subtypes. For USCs, we observed no difference in impact of EBRT + CT compared with EBRT and CT alone. This is in accordance with the results of a population-based study by Rauh-Hain et al. [22] among 2188 patients with stage III–IV USC. The PORTEC-3 study did observe a benefit for EBRT + CT over EBRT alone in patients with serous histology. However, the PORTEC-3 study did not only include patients with stage III serous carcinoma (39/105) but also included those with low-stage disease. Our results however indicate that the benefit of EBRT + CT disappears if only patients with stage III serous carcinoma are included. In carcinosarcomas, EBRT + CT was associated with superior OS compared with CT, EBRT or no adjuvant therapy. A previous population-based study reported that CT with or without RT had significant survival advantages among 3353 patients with stage III–IV carcinosarcomas [23]. For the first time, we report that EBRT + CT is superior to CT alone in these patients. The benefit of adding EBRT to CT in treatment of carcinosarcomas could be explained by the observation that carcinosarcomas spread through lymph vessels rather than via the haematogenous route, with most recurrences observed in the pelvis rather than in distant sites [24–26].

In the future, the treatment of stage III EC might be further optimised based on the four groups with distinct molecular signature and prognosis as identified by the Cancer Genome Atlas (TCGA) [27]. Currently, no prospective study has validated the TCGA classification as a guide for cancer therapy yet. However, the group of tumours that lack the ability to repair DNA mismatches (MMR-D group) can be treated with the checkpoint inhibitor pembrolizumab with promising results in initial studies among patients with progressive disease after standard treatment [28,29]. Further studies will determine how this affects the adjuvant treatment of stage III EC.

We noticed that the OS rates in our study were lower than those in the recently published studies. The lower OS than that in the PORTEC-3 study could be related to inclusion of highly selected groups of patients in

randomised controlled trials, resulting in underrepresentation of patients with advanced age or poor performance status [15,30]. This is illustrated by the higher age in our population-based study than that in the PORTEC-3 study (67.0 vs. 62.4 years, respectively) and the higher comorbidity rates (47% for hypertension and 14% for diabetes mellitus in our cohort vs. 35% and 14% in PORTEC-3, respectively). For patients with stage IIIC disease, Wong et al. [20] found superior survival rates compared with our study. Unfortunately, the histological subtypes were not reported in the study of Wong et al. [20], hampering direct comparisons between both cohorts. Possibly, the extent of lymphadenectomy could have influenced the outcomes as independent impact of extensive lymphadenectomy (>20 nodes removed) on OS was shown in this study. Finally, the sequence and dosage of RT and CT could have impacted the OS of EBRT + CT. Exploratory analysis shows that there is no difference in the number of cycles and the type of CT administered to patients in the EBRT + CT group (75%) compared with those in the CT group (84%). In this study, it is not clear whether all patients received EBRT + CT according to the PORTEC-3 schedule (upfront EBRT with two cycles of concurrent cisplatin followed by four cycles of carboplatin/paclitaxel) or if other protocols were followed. A recent study among 5795 patients with EEC reported that administration of CT before EBRT might result in a better outcome in stage III–IV disease [31–33].

The present study has several limitations. Differences in data completeness across the study period could have influenced the analyses. Although the total number of included patients was substantial, the total number of patients was limited in some subgroup analyses stratified by histology. In addition, as patients were included before and after 2009, some were staged according to the FIGO 1988 staging system. We were unable to exclude patients with stage IIIA disease based on positive peritoneal cytology. The impact of the adjusted FIGO classification for stage IIIA was illustrated by data of the Surveillance, Epidemiology and End Results (SEER) database and showed that a small percentage of patients (2.6%) were downstaged, without difference in survival between the FIGO 1998 and 2009 classification system. Therefore, it is unlikely that this would have altered our results. Finally, the non-randomised allocation of adjuvant treatment has influenced the distribution of patient characteristics in different treatment groups. Therefore, results of the Kaplan–Meier analysis and the absolute 5-year survival rates have to interpreted with caution.

To conclude, in this population-based study, we show that adjuvant EBRT + CT is associated with improved OS compared with CT or RT in stage IIIC EC, especially in EEC and carcinosarcoma. For USCs, there was no survival benefit of EBRT + CT over CT or RT. This suggests that application of EBRT + CT in stage III EC could be further stratified according to these subgroups.

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Conflict of interest statement

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.04.012.

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