Sequential chemotherapy-radiotherapy as adjuvant treatment of high-risk endometrial carcinoma: a retrospective review of the Manchester experience

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Objective: The optimum sequencing of adjuvant treatment in patients with high-risk endometrial cancer remains contentious. Here, we report the outcomes of women treated in Manchester, United Kingdom, where sequential chemotherapy-radiotherapy is the standard adjuvant treatment approach for these patients. *Methods*: A retrospective analysis was carried out on 106 consecutive patients referred for adjuvant treatment of high-risk endometrial cancer in 2014 and 2015. High-risk endometrial cancer was defined as: International Federation of Gynaecology and Obstetrics (2009) stage I grade 3 endometrioid carcinoma with deep myometrial invasion and/or lymphovascular space invasion, stage II–III endometrioid carcinoma, or any other histological subtype with stage I–III disease. Adjuvant treatment included carboplatin (AUC5) and paclitaxel (175 mg/m^2) every 21 days for 4/6 cycles, followed by external beam pelvic radiotherapy (40 Gy in 20 fractions#) or vaginal brachytherapy (28 Gy in 2 fractions#) or both. Primary outcome measures were recurrence free survival (RFS), overall survival (OS) and treatment-related toxicity. *Results*: Seventy-nine percent of patients were treated with sequential chemotherapy-radiotherapy. After a median follow-up of 64.4 months, 5-year RFS was 70% (95% CI 60.8–80.6%) and 5-year OS was 71.4% (95% CI 62.3–81.7%). Single modality adjuvant therapy was given for patient choice or contra-indications to treatment. Patients tolerated sequential treatment well; 96% of patients completed all treatment and 20% of patients had ≥grade 3 adverse events. *Conclusions*: Sequential chemotherapy-radiotherapy as adjuvant treatment for high-risk endometrial cancer was tolerable and was associated with survival outcomes consistent with recent international phase III clinical trials.

Keywords

Endometrial cancer; Chemotherapy; Radiotherapy; Brachytherapy

1. Introduction

Endometrial cancer is the fourth most common cancer affecting women in the United Kingdom [1] with prevalence increasing due to obesity and an ageing population [2]. Patients usually present with early stage, low-risk disease and have 5-year survival rates of 95% with surgical management alone [2, 3]. However, 15% of patients present with high-risk disease, that carries an increased risk of cancer progression and death [2]. High-risk features of endometrial cancer include a non-endometrioid histology, endometrioid histology with stage II–III disease, or endometrioid histology with stage I disease, high grade differentiation and invasion into surrounding structures [2, 4].

For patients presenting with high-risk disease, adjuvant treatment is recommended after primary debulking surgery. However, the most effective adjuvant treatment strategy is under contention. Adjuvant radiotherapy reduces pelvic recurrence but does not impact on overall survival (OS) [5], whereas adjuvant chemotherapy prevents distant recurrence and improves progression-free survival (PFS) and OS [5, 6]. Subsequent trials have investigated outcomes of combination chemotherapy-radiotherapy regimens. The outcomes of these studies show inconsistent benefits of combined modality treatment administered under varying schedules compared to chemotherapy or radiotherapy alone [7–10]. The PORTEC-3 trial used a combination chemoradiotherapy regimen of cisplatin (50 mg/m^2, week 1 and week 4) alongside external-beam pelvic radiotherapy followed by further chemotherapy with carboplatin (AUC5, every 21 days) and paclitaxel (175 mg/m^2, every 21 days) for 4 cycles [4]. Results showed that in patients with high-risk endometrial cancer combination chemoradiotherapy gave a significant improve-

ment in 5-year OS (81.4% vs 76.1%, HR 0.70, $p = 0.034$) and failure free survival (76.5% vs 69.1%, HR 0.70, $p = 0.016$) compared to external-beam pelvic radiotherapy alone [9]. On the other hand, the GOG258 trial showed no significant difference in survival outcomes in patients with stage III/IVA endometrial cancer treated with a comparable chemoradiotherapy regimen compared to chemotherapy alone [10]. A recent retrospective study showed that patients with FIGO stage III endometrial cancer had a prolonged OS with 'sandwich modality' treatment (HR 0.33, 95% CI 0.20–0.53, $p < 0.0001$) [11].

Synthesis of evidence into one management strategy for adjuvant treatment of high-risk endometrial cancer has proven a controversial issue, which is reflected in national and international guidelines [2, 3]. Due to this, we felt that it was important to evaluate the outcomes of patients with high-risk endometrial cancer treated at a large cancer centre in Manchester, United Kingdom, where a consistent policy of utilising sequential platinum-based chemotherapy followed by external-beam pelvic radiotherapy +/- vaginal brachytherapy has been adopted.

2. Methods

A retrospective cohort study was conducted at The Christie NHS Foundation Trust, Manchester, United Kingdom, of consecutively treated patients with high-risk endometrial cancer. Approval was given by the Quality Improvement and Clinical Audit Committee to carry out the study and obtain access to patient electronic medical records.

In order to allow adequate follow-up, patients included were those referred to the gynaecological medical oncology team, after primary surgery and multi-disciplinary team discussion, with high-risk endometrial cancer between the 1 January 2014 and 31 December 2015. High-risk endometrial cancer was defined as: International Federation of Gynaecology and Obstetrics (FIGO) 2009 [12] stage I endometrioid carcinoma with grade 3 differentiation and deep myometrial invasion and/or lymphovascular space invasion, stage II–III endometrioid carcinoma, or any other histological subtype with stage I–III disease [2, 4]. Patients were excluded if referred for neo-adjuvant treatment, with synchronous ovarian cancer or with stage IV disease.

Surgery included total hysterectomy, bilateral salpingoopherectomy, +/- pelvic and para-aortic lymph node dissection +/- omentectomy. The adjuvant treatment offered to patients comprised of 4 or 6 cycles of carboplatin (AUC5) and paclitaxel (175 mg/m^2) chemotherapy every 21 days and sequential radiotherapy with external beam pelvic radiotherapy (40 Gy in 20 fractions#) alone or followed by vaginal brachytherapy (19 Gy in 1 fraction#) or vaginal brachytherapy alone (28 Gy in 2 fractions#). Radiotherapy was given by specialist gynaecological clinical oncologists and the majority of vaginal brachytherapy was delivered using Pulsed Dose Rate equipment.

Standard follow-up consisted of 3-monthly review for 2 years followed by 6-monthly review until 5 years after treatment had been completed. Follow-up consisted of clinical assessment of symptoms and physical examination, with computed tomography (CT) or magnetic resonance imaging (MRI) imaging performed at clinician discretion.

Demographic data at time of referral was obtained from the electronic oncology notes. The primary outcomes of the study are recurrence free survival (RFS) and overall survival (OS). RFS is recorded from the date of surgery to the date of radiological evidence on CT or MRI of recurrent disease or death from any cause, whichever occurred first. OS is recorded from the date of surgery to the date of death as documented in the electronic medical notes. The patient was censored if neither primary outcome was reached. Treatment-related toxicity was also a primary outcome of the study. Adverse events were assessed retrospectively and categorised according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 criteria [13], including each event of peripheral sensory neuropathy of grade 2 or above, any grade drug reaction, and any other adverse event of grade 3 or above.

Categorical data is presented as number or percentage and continuous data is presented as mean (range) or median (range). Kaplan-Meier statistics were used to generate survival curves. Log-rank tests were used to assess for differences between groups, with a p-value < 0.05 deemed significant.

3. Results

One hundred and fifty-nine patients with newly diagnosed endometrial cancer were referred to the gynaecological medical oncology team between 1 January 2014 and 31 December 2015; 37 patients were excluded for stage IV disease, 7 patients were excluded for diagnosis of synchronous ovarian cancer, 4 patients were excluded for referral for neo-adjuvant treatment and 5 patients were excluded as they did not fit the criteria for high-risk disease. The remaining 106 patients were included in the study and followed up for a median of 64.4 months (range 2.1–77.3 months).

The median age of patients was 67 years (range 33–82) and 45% of patients were obese. The majority of patients had endometrioid histology (48%), but 20% of patients had carcinosarcoma histology. Only 13% of patients had p53 status documented, with 9% of patients having a p53 mutation (Table 1).

3.1 Adjuvant treatment

Seventy-nine percent of patients were treated with sequential chemotherapy-radiotherapy (n = 84); 7.5% (n = 8) received chemotherapy alone and 8.5% (n = 9) received radiotherapy alone. Five percent (n = 5) of patients received no adjuvant treatment. The main reasons why patients received single modality treatment was patient choice (n = 9), co-morbidities (n = 6), or if multi-modality treatment was not deemed appropriate by the clinician for the patient's disease (n = 7).

Table 1. Patient demographics in all patients and in patients within each treatment group, represented as percentage (number of patients), unless otherwise stated.

	All patients (n = 106)	Sequential chemotherapy-radiotherapy (n = 84)	Chemotherapy (n = 8)	Radiotherapy (n = 9)	No adjuvant treatment (n = 5)
Age at diagnosis					
Median (years)	67	66.5	68	68	80
Range (years)	33–82	33–82	51–79	53–79	49–80
<60 years	24% (25)	25% (21)	25% (2)	11% (1)	20% (1)
60–69 years	39% (41)	39% (33)	25% (2)	56% (5)	20% (1)
≥70 years	38% (40)	26% (30)	50% (4)	33% (3)	60% (3)
Eastern Cooperative Oncology Group performance status					
0	39% (41)	37% (31)	63% (5)	44% (4)	20% (1)
1	51% (54)	60% (50)	13% (1)	22% (2)	20% (1)
2	7% (7)	2% (2)	25% (2)	22% (2)	20% (1)
3	4% (4)	1% (1)	0	11% (1)	40% (2)
Comorbidities					
Type II Diabetes	17% (18)	17% (14)	0	44% (4)	0
Hypertension	11% (12)	35% (29)	25% (2)	67% (6)	57% (4)
Cardiovascular	9% (10)	7% (6)	13% (1)	22% (2)	14% (1)
High cholesterol	16% (17)	15% (13)	0	33% (3)	14% (1)
Body mass index (BMI)					
Median (BMI)	29.1	29.7	29	28.9	19.4
Range (BMI)	17.7–51.7	17.7–51.7	28.6–43	21–34.6	16.3–22.5
<18.5	2% (2)	1% (1)	0	0	20% (1)
18.5–24.9	19% (20)	20% (17)	0	22% (2)	20% (1)
25–29.9	29% (31)	30% (25)	50% (4)	22% (2)	0
30–39.9	34% (36)	36% (30)	25% (2)	44% (4)	0
≥40	11% (12)	13% (11)	13% (1)	0	0
Not documented	5% (5)	0	13% (1)	11% (1)	60% (3)
International Federation of Gynaecology and Obstetrics (2009) stage					
Ia*	18% (19)	19% (16)	13% (1)	11% (1)	20% (1)
Ib	19% (20)	21% (18)	13% (1)	0	20% (1)
II	18% (19)	12% (10)	25% (2)	67% (6)	20% (1)
IIIa	21% (22)	23% (19)	0	22% (2)	20% (1)
IIIb	7% (7)	6% (5)	13% (1)	0	20% (1)
IIIc1	16% (17)	18% (15)	25% (2)	0	0
IIIc2	2% (2)	1% (1)	13% (1)	0	0
Histology					
Endometrioid	45% (48)	45% (38)	38% (3)	56% (5)	40% (2)
Carcinosarcoma	20% (21)	20% (17)	25% (2)	0	40% (2)
Serous	15% (16)	17% (14)	0	22% (2)	0
Clear cell	7% (7)	6% (5)	13% (1)	11% (1)	0
Mixed histology	9% (10)	8% (7)	13% (1)	11% (1)	20% (1)
Undifferentiated/Dedifferentiated	4% (4)	4% (3)	13% (1)	0	0
International Federation of Gynaecology and Obstetrics Histological Grade					
1	9% (10)	8% (7)	25% (2)	11% (1)	0
2	17% (18)	13% (13)	25% (2)	33% (3)	0
3	64% (68)	6% (56)	25% (2)	56% (5)	100% (5)
Other	1% (1)	1% (1)	0	0	0
Mixed	1% (1)	0	13% (1)	0	0
Not documented	8% (8)	7% (7)	13% (1)	0	0
Myometrial invasion					
<50%	40% (42)	38% (32)	13% (1)	67% (6)	60% (3)
>50%	52% (55)	54% (45)	63% (5)	33% (3)	40% (2)

Table 1. Continued.

	All patients (n = 106)	Sequential chemotherapy-radiotherapy (n = 84)	Chemotherapy (n = 8)	Radiotherapy (n = 9)	No adjuvant treatment (n = 5)
Lymphovascular space invasion					
Present	66% (70)	52% (58)	75% (6)	33% (3)	60% (3)
Cervical stroma involvement					
Present	38% (40)	35% (29)	38% (3)	67% (6)	40% (2)
P53 status					
P53 mutation	9% (10)	12% (10)	0	0	0
Wildtype	2% (4)	5% (4)	0	0	0
Not documented	87% (92)	83% (70)	100% (8)	100% (9)	100% (5)
Surgery					
TAH + BSO	36% (38)	35% (29)	50% (4)	22% (2)	60% (3)
TAH + BSO + lymph node dissection	37% (39)	37% (31)	25% (2)	56% (5)	20% (1)
TLH + BSO	20% (21)	20% (17)	13% (1)	22% (2)	20% (1)
TLH + BSO + lymph node dissection	8% (8)	8% (7)	13% (1)	0	0
Number of nodes removed					
Median (number)	9	9	6	10	10
Range (number)	1–39	1–32	4–12	7–39	Not applicable

*All defined as high-risk endometrial cancer due to histology—all have histology other than endometrioid.

Ninety-five percent of patients (n = 80) were able to complete sequential chemotherapy-radiotherapy. Four patients whose planned management included sequential chemotherapy-radiotherapy were not referred for adjuvant radiotherapy following completion of chemotherapy; 3 patients had developed progressive disease upon completion of chemotherapy and 1 patient had become too unwell for referral for radiotherapy. These patients were included in the sequential chemotherapy-radiotherapy group to allow an 'intention-to-treat' analysis.

Eighty-nine percent of patients were treated with 4 or 6 cycles of carboplatin (AUC5) and paclitaxel (175 mg/m^2) every 21 days. There is no clear guidance in National Comprehensive Cancer Network or European Society for Medical Oncology guidelines about the number of cycles to be offered therefore practice was clinician led based on stage of disease [2, 3]. Patients whose planned treatment included 6 cycles of chemotherapy (n = 50) had a higher stage of disease at diagnosis; 84% of patients had at least stage 3a cancer. The remaining 42 patients received 4 cycles of chemotherapy, of whom most had stage 1 disease (87%). Two patients received weekly carboplatin (AUC2) and paclitaxel (60 mg/m^2) treatment due to patient preference in one case and deterioration in performance status in the other. Single agent carboplatin (AUC5) was offered to patients (n = 6) due to co-morbidities which prevented the use of paclitaxel, such as peripheral neuropathy and previous cardiovascular morbidity. Two patients received pegylated liposomal doxorubicin in combination with carboplatin, instead of paclitaxel; one to avoid alopecia, and the other because of immediate hypersensitivity to paclitaxel.

Radiotherapy included external beam pelvic radiotherapy alone (48%), vaginal brachytherapy alone (25%) or combination external beam pelvic radiotherapy followed by vaginal brachytherapy (27%). The majority of patients receiving external beam pelvic radiotherapy were treated with 40 Gy in 20 fractions (81%) or 45 Gy in 25 fractions (13%). Vaginal brachytherapy was delivered as a dose of 19 Gy in 1 fraction if preceded by external beam pelvic radiotherapy or 28 Gy in 2 fractions if used alone (50% and 46% respectively). Two patients underwent High Dose Rate brachytherapy; one receiving it alone as 22 Gy in 4 fractions and one receiving 15 Gy in 3 fractions after external beam pelvic radiotherapy.

3.2 Toxicity

A total of 19 patients (18%) had grade 3 or worse adverse events during treatment. Of patients receiving sequential chemotherapy-radiotherapy 20% (n = 17) of patients had grade 3 or worse adverse events, compared to 13% (n = 1) of patients receiving chemotherapy alone and 11% (n = 1) of patients receiving radiotherapy alone.

The majority of adverse events recorded occurred during chemotherapy (90%), with 42% of those being grade 2 or above peripheral sensory neuropathy. Grade 3 or more adverse events during chemotherapy included myelosuppression, infection, vomiting and diarrhoea (Table 2). Grade 3 pulmonary embolism during chemotherapy occurred in 4% of patients (n = 4). One patient had grade 3 atrial fibrillation leading to grade 4 ischaemic colitis and another had a grade 3 cerebrovascular accident within 30 days of receiving chemotherapy treatment. Dose reduction of carboplatin

Table 2. Incidence of adverse events during treatment represented by number (percentage).

Incidence grade 3 or 4 toxicity	Chemoradiotherapy group (n = 84)			Chemotherapy group (n = 8)	Radiotherapy group (n = 9)
	Total	During chemotherapy	During radiotherapy		
Anaemia	1 (1%)	1 (1%)	0	0	0
Neutropenia	3 (4%)	3 (4%)	0	1 (13%)	0
Febrile neutropenia	1 (1%)	1 (1%)	0	1 (13%)	0
Thrombocytopenia	1 (1%)	1 (1%)	0	0	0
Nausea/Vomiting	3 (4%)	2	1 (1%)	0	1 (11%)
Diarrhoea	7 (8%)	3 (4%)	4 (5%)	0	1 (11%)
Pulmonary embolism	3 (4%)	3 (4%)	0	1 (13%)	0
Cardiovascular accident	1 (1%)	1 (1%)	0	0	0
Atrial fibrillation	0	0	0	1 (13%)	0
Ischaemic colitis	0	0	0	1 (13%)	0
Lung infection	3 (4%)	3 (4%)	0	0	0
Reduced renal function/AKI	2 (2%)	2 (2%)	0	0	0
Electrolyte disturbance	1 (1%)	1 (1%)	0	0	0
Myalgia	3 (4%)	3 (4%)	0	0	0
Other infection	2 (2%)	2 (2%)	0	0	0
Grade 2 or above neuropathy	24 (29%)	24 (29%)	0	1 (13%)	0
Any grade drug reaction	3 (4%)	3 (4%)	0	1 (13%)	0

Adverse events not listed in the table due to no incidences of grade 3 or more events include constipation and deranged liver function.

and/or paclitaxel was required in 25% of patients (n = 23) and early discontinuation of paclitaxel alone or both carboplatin and paclitaxel was required in 14% (n = 12) of patients. There were no treatment-related deaths.

The main grade 3 or above adverse events during radiotherapy treatment were nausea/vomiting (2%) and diarrhoea (5%) (Table 2). One patient had to discontinue external beam pelvic radiotherapy prematurely due to G3 diarrhoea so received 33 Gy of planned 40 Gy and could not proceed to vaginal brachytherapy.

3.3 Outcomes

At an average of 64.4 months follow-up, 37 patients (35%) had developed recurrent disease or had died. Twenty-seven (25%) had radiological evidence of recurrence. Thirty-three patients (31%) had died; with cause of death attributed to endometrial cancer in 24 patients (23%). Seven patients who died had no evidence of disease progression prior to death, and no cause of death could be determined from electronic oncology notes or from contact with their last registered GP.

Patients who received sequential chemotherapy-radiotherapy (n = 84) had a 5-year RFS of 70% (95% CI 60.8–80.6%) and 5-year OS of 71.4% (95% CI 62.3–81.8%). Patients who received chemotherapy alone (n = 8) and radiotherapy alone (n = 9) had a 5-year RFS of 62.5% (95% CI 36.5–100%) and 55.6% (95% CI 31–99.7%), respectively, and a 5-year OS of 87.5% (95% CI 67.3–100%) and 55.6% (95% CI 31–99.7%), respectively. Patients who did not receive adjuvant treatment (n = 5) had a 5-year RFS of 40% (95% CI 13.7–100%) and a 5-year OS of 60% (95% CI 29.3–100%). There was no statistically significant difference in RFS (p = 0.39) or OS (p = 0.17) outcomes between treatment groups (Fig. 1).

Patients with stage III disease treated with sequential chemotherapy-radiotherapy had a 5-year RFS and a 5-year OS of 64.9% (95% CI 51.7–81.6%). Those that were not treated with sequential chemotherapy-radiotherapy had a 37.5% 5-year RFS (95% CI 15.3–91.7%, p = 0.13) and a 62.5% 5-year OS (95% CI 36.5–100%, p = 0.87) (Fig. 1).

Patients presenting with stage I/II disease, compared to those presenting with stage III disease, had a better 5-year RFS (71.9% [95% CI 61.1–84.7%] vs 60.3% [95% CI 48.0–75.9%]) and 5-year OS (75.7% [95% CI 65.4–87.6%] vs 64.5% [95% CI 52.3–79.6%]) (Fig. 2). In addition, patients presenting with type I disease compared to those with type II disease, had an improved 5-year RFS (72.3% [95% CI 60.6–86.4%] vs 62.0% [95% CI 50.7–75.9%]) and improved 5-year OS (81.3% [95% CI 70.9–93.1%] vs 61.8% [95% CI 50.4–75.8%]) (Fig. 2).

4. Discussion

Women with high-risk endometrial cancer are at risk of developing both local and distant disease recurrence after initial surgical management. It is logical to consider adjuvant treatment strategies to reduce the incidence of both of these events, but the best way to deploy these modalities is unclear. The two most recently reported phase III trials, PORTEC-3 and GOG258, have evaluated upfront combined cisplatin-radiotherapy followed by 4 cycles of carboplatin-paclitaxel chemotherapy in their investigational arm with differing results. This approach delays the commencement of systemic therapy and appears to reduce the tolerability of chemotherapy, which may in turn impair the eradication of micrometastatic disease. One alternative approach that may address these issues is to administer adjuvant chemotherapy followed by radiotherapy (sequential therapy). Here, we describe a consecutive series of women treated in Manch-
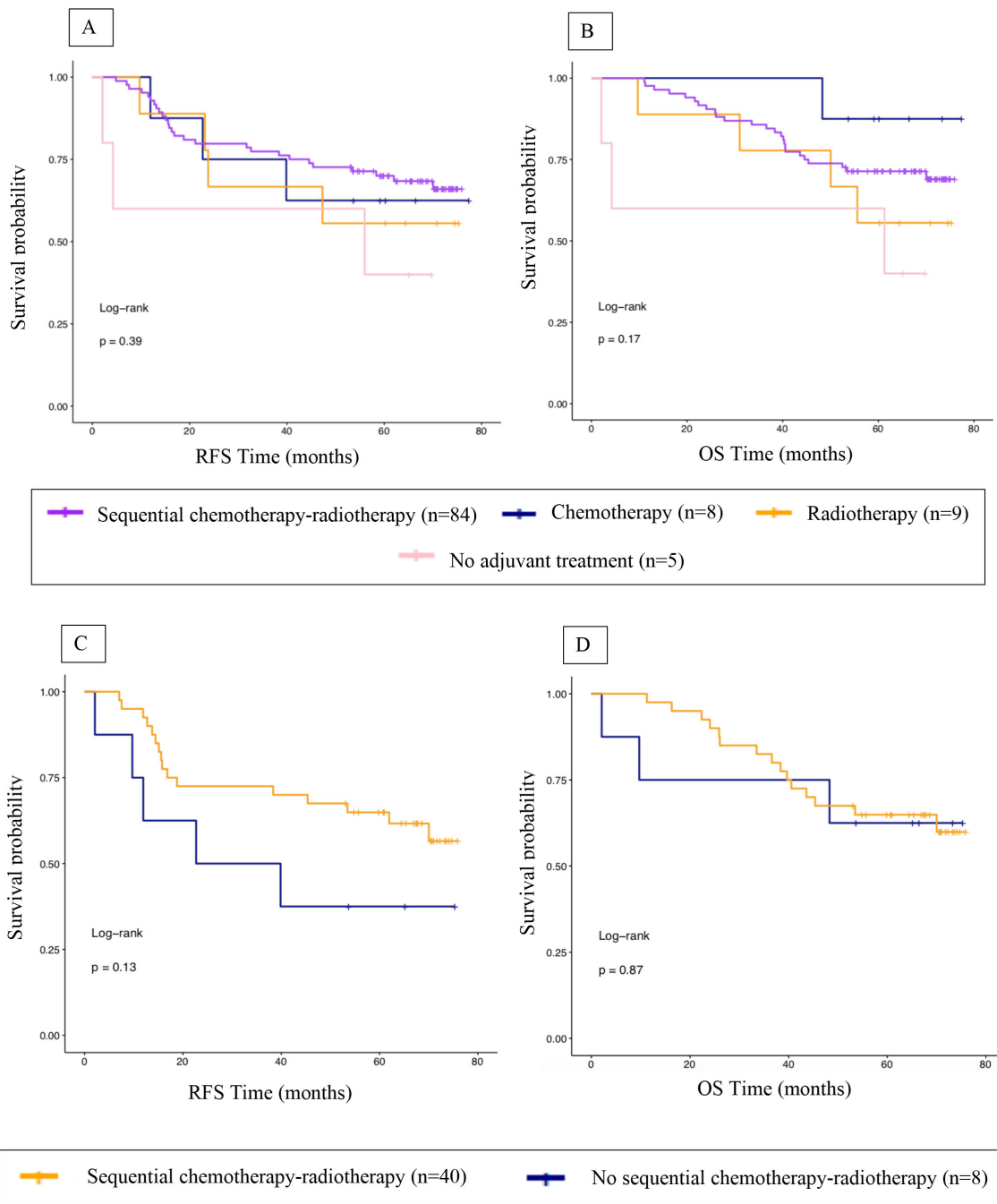
Fig. 1. 5-year recurrence free survival (RFS) and 5-year overall survival (OS) curves based on treatment received. (A) Kaplan-Meier Curve to show 5-year RFS in all patients based on treatment received. (B) Kaplan-Meier Curve to show 5-year OS in all patients based on treatment received (Number of patients: sequential chemotherapy-radiotherapy = 84, chemotherapy = 8, radiotherapy = 9, no adjuvant treatment = 5). (C) Kaplan-Meier Curve to show 5-year RFS in patients with stage III disease treated with sequential chemotherapy-radiotherapy compared to those that were not treated with sequential chemotherapy-radiotherapy. (D) Kaplan-Meier Curve to show 5-year OS in patients with stage III disease treated with sequential chemotherapy-radiotherapy compared to those that were not treated with sequential chemotherapy-radiotherapy (Number of patients: sequential chemotherapy-radiotherapy = 40, no sequential chemotherapy-radiotherapy = 8).

ester, United Kingdom, where sequential chemotherapy-radiotherapy is the standard adjuvant treatment approach for high-risk endometrial cancer.

The demographic characteristics of this series broadly match the general patient population with endometrial can-

cer who are aged over 60 years, have a high body mass index (BMI) and typically present with endometrioid histology [2]. However, our population is older than that reported in recent phase III trials (66 years old compared to 62 years old for PORTEC-3 and 60 for GOG258), has more patients
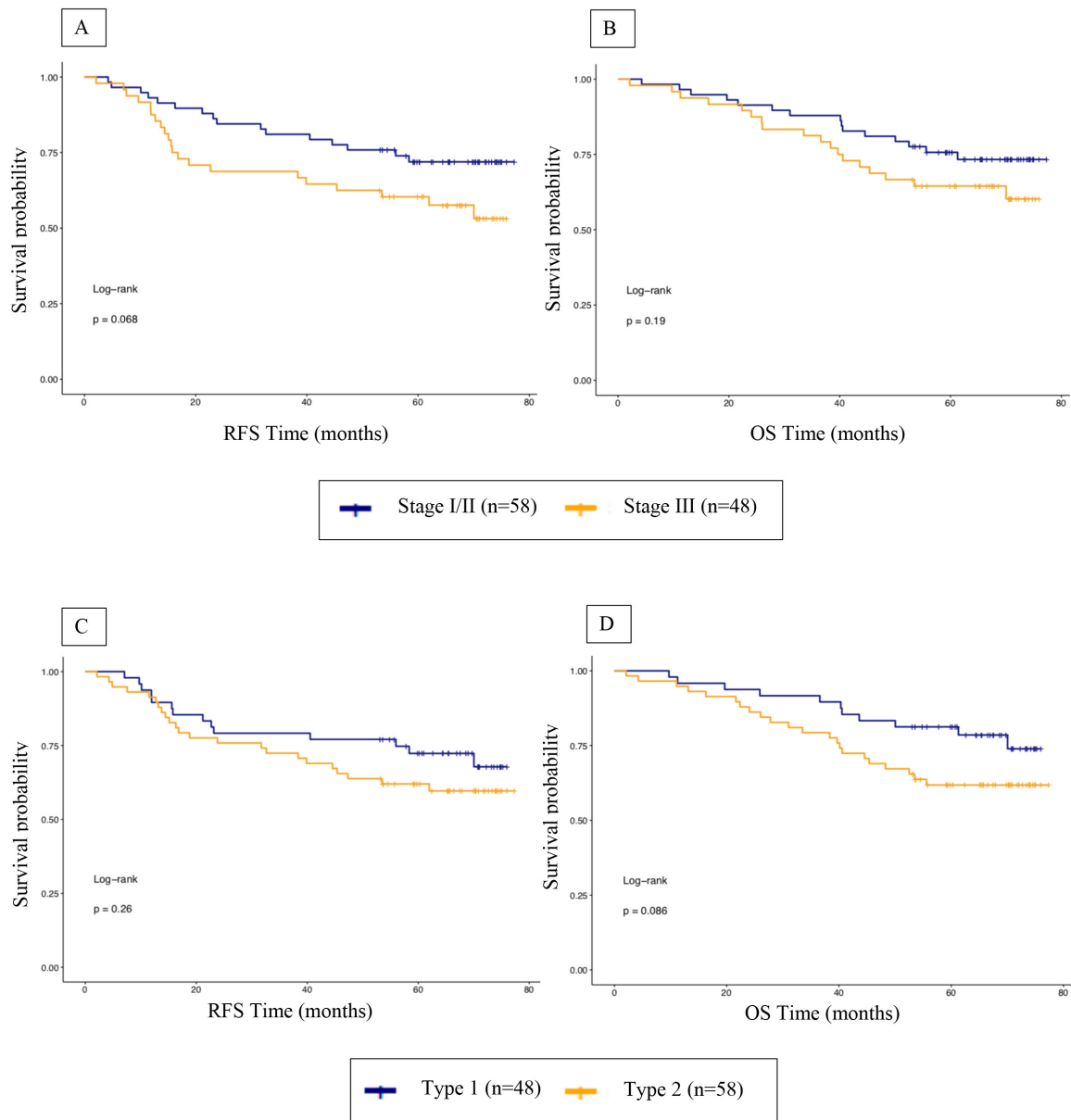
A

B

Stage I/II (n=58) — Stage III (n=48)

C

D

Type 1 (n=48) — Type 2 (n=58)

Fig. 2. 5-year recurrence free survival (RFS) and 5-year overall survival (OS) curves based on stage and type of disease. (A) Kaplan-Meier Curve to show 5-year RFS based on stage of disease. (B) Kaplan-Meier Curve to show 5-year OS based on stage of disease (Number of patients: stage I/II = 58, stage III = 48). (C) Kaplan-Meier Curve to show 5-year RFS based on type of disease. (D) Kaplan-Meier Curve to show 5-year OS based on type of disease (Number of patients: type I = 48, type II = 58).

with moderate performance status (Eastern Cooperative Oncology Group performance status 2) and has a higher proportion of women with non-endometrioid cancers [4, 10]. Notably, 19% of our cases had been diagnosed with endometrial carcinosarcoma which is higher than cases reported in recent phase III and large retrospective studies [9–11]. All of these factors are associated with worse outcomes. Despite this, our data show that outcomes for patients receiving sequential chemotherapy-radiotherapy are comparable to those reported in the investigational arms from the PORTEC-3 and GOG258 trials. For patients with stage III cancer, recurrence free survival was 64.9% is our series compared to

failure-free survival of 70% in PORTEC-3 and relapse-free survival of 59% in GOG258 [9]. Five-year overall survival was greater in the whole combined chemoradiotherapy population in PORTEC-3 trial compared to our study (81.4% compared to 71.4%), which may reflect the poorer underlying prognosis of our patient group [9].

We found that patients treated with sequential chemotherapy-radiotherapy were able to tolerate treatment better than those receiving chemoradiotherapy in PORTEC-3 and GOG258. More of our patients were able to complete chemotherapy; 95% completed all planned cycles compared to 79% in PORTEC-3 and 75% in the combined

arm of GOG258 [4, 10]. There were also fewer grade 3 or worse adverse events in patients receiving combination treatment (18% versus 60% in PORTEC-3) [4]. This suggests that sequential chemotherapy followed by radiotherapy may be more tolerable with similar efficacy to a concomitant administration regimen.

This study adds to recently published phase III trials but providing real-world data from a major cancer centre. This study reports outcomes of all-comers, rather than those selected by strict eligibility criteria. However, a limitation of our study includes the small number of patients receiving single modality adjuvant treatments precluding comment on the impact of chemotherapy or radiotherapy alone. Further data are needed from a larger number of patients to determine more accurate outcomes in these groups.

In addition, only a small percentage of our patients had documented p53 immunohistochemical analysis of their tumours (14%, n = 17). This number was too small to allow us to determine if patients with cancers harbouring p53 mutations had significantly different survival or response to adjuvant therapy to those that were p53 wildtype. Based on the recent findings from the PORTEC-3 trial, the presence of a p53 mutation is shown to be a poor prognostic factor and those with tumours high in p53 mutation responded better to chemoradiotherapy compared to radiotherapy alone [14]. This highlights the need to incorporate simple molecular profiling prospectively to allow risk stratification in clinical trials and potentially guide routine clinical management decisions in high risk endometrial cancer.

We have no quality-of-life data in this study and it could be argued that sequential chemotherapy-radiotherapy does prolong the length of treatment which might impact on patient-perceived quality of life despite less adverse effects.

5. Conclusions

In conclusion, this retrospective study has highlighted that the administration of sequential chemotherapy-radiotherapy in patients with high-risk endometrial cancer was associated with international levels of survival and that this treatment is tolerable and safe in the majority of patients. This approach warrants incorporation into future molecularly stratified clinical trials in high-risk endometrial cancer.

Author contributions

RDMahmood is the first author and contribution includes planning the study, collection and interpretation of the data, and writing up of the manuscript. ARC oversaw the entire project, made substantial amendments to the manuscript and approved the final manuscript. TD performed the statistical analysis of the data. RDMorgan, NM, CM, JH, GCJ, LB, KH, JL, EJC and RJE were all involved in the care of patients that were included in the study and all had significant input in substantive revisions of the manuscript. All authors have approved the final manuscript.

Ethics approval and consent to participate

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Conflict of interest

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