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Original Research

Neoadjuvant chemotherapy in locally advanced cervical cancer: real-world data from the Cancer Medicines Outcomes Programme (CMOP)

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Objective: To report the outcomes of neoadjuvant chemotherapy (NACT) in patients with locally advanced cervical cancer, we conducted a retrospective study of 126 patients. *Methods*: The electronic chemotherapy prescribing system was used to identify patients from the West of Scotland Cancer Network who received NACT over a 5 year period. Baseline characteristic and treatments details were collected. Association of treatment type and other variables with overall survival (OS) were analysed using Cox proportional hazards model. *Results*: The median follow up was 30 months. Median age was 44 years (interquartile range 34–54), 86% had squamous pathology and 93% had at least International Federation of Gynaecology & Obstetrics (FIGO) stage II disease at diagnosis. 27% had stage IV disease and 30% had para-aortic nodal involvement. NACT regimens consisted primarily of 3 weekly cisplatin/paclitaxel (63%) or carboplatin/paclitaxel (35%). 86% of patients subsequently received chemoradiotherapy (CCRT), 11% radical radiotherapy alone and the remaining patients progressed or defaulted. Three year OS was 61.8% (95% CI (Confidence Interval) 53.4–71.6). Survival was poorer in patients with neutrophil lymphocyte ratio (NLR) $\geq$5 (hazard ratio 2.8 (95% CI 1.32–5.90)) and in those not receiving CCRT (hazard ratio 2.23 (95% CI 1.01–4.91)). *Conclusions*: Three year OS was reasonable considering the advanced nature of the cohort and suggests that NACT is an option for women with bulky cervical cancer.

Keywords

Locally advanced cervical cancer; Neoadjuvant chemotherapy; Chemoradiotherapy; Real-world

1. Introduction

In the UK, cervical cancer accounts for 1% of all cancer deaths in females [1]. Surgery is suitable for early stages but has a limited role in locally advanced disease [2]. Concomitant chemoradiotherapy (CCRT) has been the gold standard treatment for this patient group since 1999 due to the survival advantage demonstrated with CCRT compared to radiotherapy (RT) alone [2]. A UK audit reported a 5-year overall survival (OS) rate of 55% for patients treated with CCRT between 2001–2002 [3]. More recently, the RetroEMBRACE study reported 3 and 5-year OS rates of 74% and 65% respectively, with CCRT (or RT) and image guided brachytherapy (IGBT), indicating the importance of good quality BT [4].

Strategies to improve outcomes further largely focus on additional chemotherapy either in the neoadjuvant [5] or adjuvant [6–8] settings, although the role of surgery post CCRT has also been explored [9, 10]. Despite remarkable results from combined cisplatin/gemcitabine doublet therapy during RT and 4 cycles of adjuvant chemotherapy post CCRT [6], this approach has not been accepted worldwide as a result of concerns over haematological/gastrointestinal toxicity and lack of RT quality assurance. Attempts to replicate the results with an alternative doublet (carboplatin/paclitaxel) indicated that at least one third of women failed to complete 3 adjuvant cycles [8]. The OUTBACK randomised phase III trial has now definitively answered the question of adjuvant chemotherapy and this was shown not to improve OS outcomes [11]. Theoretically, the main drawback of administering further chemotherapy after CCRT (aside from patient compliance and tolerance) is that any residual disease that has persisted beyond CCRT is more likely to be derived from a chemo- and/or radio-resistant clone. Neoadjuvant chemotherapy (NACT) has the advantage of eradicating micro-metastatic disease without having to dose reduce as a consequence of myelosuppression following CCRT, and may lead to reduction in size of the primary tumour, facilitating IGBT. Of course, it is imperative that the delivery of NACT does not compromise the ability of the patient to complete CCRT on schedule. The CXII phase II trial evaluated NACT consisting of weekly paclitaxel and carboplatin chemotherapy before definitive CCRT in 3 UK centres and demonstrated high response rate and 3-year OS of 67%, leading to the development of the international randomised phase III trial, INTERLACE, which is currently recruiting [5].

Within the West of Scotland Cancer Network (WoSCAN), which serves a population of 2.5 million [12], NACT is used as standard of care prior to CCRT for women presenting with "high-risk" cervical cancer. "High-risk" is defined in our institution as inoperable locally advanced disease with at least one of the following risk factors: primary cervical tumour size $\geq$5 cm; multiple pelvic nodes and/or any para-aortic nodes; and/or any node measuring $\geq$1.5 cm. Patients with stage IVB disease restricted to the pelvis (bone, muscle, or omental involvement) are also offered NACT providing all of the disease can be adequately encompassed within a radical RT field.

The Cancer Medicines Outcome Programme (CMOP) aims to better understand treatment outcomes of cancer medicines in the Scottish population [13]. The aim of this CMOP study was to investigate survival outcomes in women receiving NACT for locally advanced cervical cancer within a single institution.

2. Methods

2.1 Patients and methods

A retrospective observational study was performed. The study population consisted of all women with "high-risk" locally advanced cervical cancer who commenced NACT within WoSCAN between January 2012 and December 2016. Exclusion criteria was intent to proceed to definitive surgery. Patients were identified from the chemotherapy electronic prescribing and administration system (CEPAS). Follow up occurred until death, or the end of the study period (February 28, 2018), whichever occurred first.

2.2 Diagnosis

Patients were staged according to International Federation of Gynaecology & Obstetrics (FIGO) 2009. Tumour and/or lymph node size on magnetic resonance imaging (MRI) was defined as maximum width on axial T2-weighted sequences. If MRI was unavailable, maximum cervical tumour width on pelvic examination was recorded. PET-CT was preferred to standard contrast enhanced CT for assessment of distant metastases. Surgical lymph node staging was not performed.

2.3 Data sources

Data were collected from information gathered within CEPAS and ARIA, a radiotherapy management system; Clinical Portal, an electronic application providing sociodemographic information and details of treatment outcomes; and the Acute, Cancer, Deaths and Mental Health (ACaDMe) datamart [14], to obtain death records. Data were entered on a Microsoft Access database and anonymised. Statistical analysis was performed using R software, version 3.3.3 (R Foundation, Vienna, Austria) [15].

2.4 Statistical analysis

Median overall survival (OS) along with 95% Confidence Intervals (CI) were estimated using the Kaplan–Meier (KM) method. For OS and relapse, the date of commencement of NACT served as the start date and February 28, 2018, served as the censor date for those still alive at study end.

Cox proportional-hazard models were used to estimate unadjusted hazard ratios for survival, for the following clinical variables: definitive treatment (CCRT or other); age; baseline performance status (0 versus 1–3); FIGO Stage; para-aortic nodes (yes/no); type (squamous cell carcinoma or other) and grade of pathology (1 versus 2 versus 3); baseline albumin and haemoglobin (lower than normal range versus within normal range); baseline platelets (higher than normal range versus within normal range); Neutrophil lymphocyte ratio (NLR) ($<$5 versus $\geq$5) [16]; Charlson comorbidity index (CCI) score [17]; Scottish Index of Multiple Deprivation (SIMD) (2012) [18]; and NACT regimen (cisplatin/paclitaxel versus carboplatin/paclitaxel versus cisplatin alone). Adjusted models were then created including age and significant variables from univariable analyses ($p < 0.1$).

3. Results

3.1 Baseline characteristics

A total of 126 patients were included in the analysis, and the observed median follow up time was 30 months (Inter quartile range (IQR) 16.4–43.8). The median age was 44 years (IQR 34–54) and the majority (85.7%) had squamous cell carcinoma. 99.2% were staged with either MRI or PET-CT scan (MRI 96.0%, PET-CT 92.1%, both 89.7%). Primary tumour $\geq$5 cm was recorded in 78.6% of patients. Positive pelvic nodes and para-aortic lymph nodes on imaging were identified in 77% and 30% of women, respectively. Over 90% had $\geq$stage II disease and 27% had stage IV disease. Of the stage I patients, 8/9 had FIGO 1B2 disease with primary tumour $\geq$5 cm and 6/9 had nodal involvement. Table 1 shows the baseline characteristics.

3.2 Neoadjuvant chemotherapy

The most common NACT regimen was 3-weekly cisplatin/paclitaxel (62.7%) followed by 3-weekly carboplatin/paclitaxel (34.9%); median number of cycles received was three (IQR 3–4) (Table 2). There were no chemotherapy related deaths.

3.3 CCRT protocol

CCRT was scheduled to commence on day 21 following the final NACT cycle. External beam radiotherapy (EBRT) was CT-planned using 3-D conformal techniques and 45–50 Gy delivered with a 4-field brick, superseded by volumetric arc therapy (VMAT) at the end of 2012. Weekly cisplatin 40 mg/m^2 was administered concurrently for 5–6 weeks. High dose rate (HDR) intracavitary brachytherapy (BT), 24 Gy in 4 fractions prescribed to point A, was incorporated in weeks 5 and 6. After treatment, patients were followed up 3–4 monthly and a pelvic examination was performed. Imaging was requested according to clinician preference and/or at the time of suspected relapse.

Table 1. Baseline characteristics.

Characteristic	Measure	Result
No. patients in study		126
Age (years)	Median (IQR)	44 (34–54)
	Range	22–75
ECOG performance status	0 n (%)	77 (61.1)
	1 n (%)	25 (19.8)
	2–3 n (%)	[a]
	Not available n (%)	22 (17.5)
Pathology	Squamous n (%)	108 (85.7)
	Adenocarcinoma/adenosquamous n (%)	13 (10.3)
	Other/Not available n (%)	5 (4.0)
FIGO Stage (2009)	I n (%)	9 (7.1)
	II n (%)	62 (49.2)
	III n (%)	21 (16.7)
	IV n (%)	34 (27.0)
Stage IVB	n (%)	5 (4.0)
Tumour size prior to NACT (cm)	Median (IQR)	5.8 (5.0–6.8)[b]
	Range	1.3–15.0
Positive para-aortic nodes	n (%)	38 (30.2)
Positive pelvic nodes	n (%)	97 (77.0)
Haemoglobin (g/L)	Median (IQR)	121 (109–132)[c]
	Range	72–152
Platelets ($\times 10^9$/L)	Median (IQR)	367 (307–458)[c]
	Range	124–828
Neutrophils ($\times 10^9$/L)	Median (IQR)	7.3 (5.6–9.7)[c]
	Range	1.7–29.6
Albumin (g/L)	Median (IQR)	34 (30–38)[c]
	Range	20–48
Neutrophil Lymphocyte Ratio (NLR)	$\geq$5 n (%)	39 (31.0)
Charlson Comorbidity Index (CCI) Score	$\geq$1 n (%)	25 (19.8)

[a]Numbers of patients not reported if <5; [b]n = 115; results not available for 11 patients; [c]n = 124; results not available for 2 patients.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology & Obstetrics; NACT, neoadjuvant chemotherapy.

Table 2. Neoadjuvant chemotherapy.

Characteristic (n = 126)	Measure	Result
Neoadjuvant regimen	Cisplatin/Paclitaxel n (%)	79 (62.7)
	Carboplatin/Paclitaxel n (%)	44 (34.9)
	Cisplatin n (%)	[a]
Dose (SACT 1)	Cisplatin $\geq$60 mg/m^2 n (%)	22 (17.5)
	Cisplatin 50 mg/m^2 n (%)	56 (44.4)
	Cisplatin $<$50 mg/m^2 n (%)	[a]
	Carboplatin AUC5 n (%)	35 (27.8)
	Carboplatin $<$ AUC5 n (%)	9 (7.1)
Dose (SACT 2)[b]	Paclitaxel 175 mg/m^2 n (%)	113 (91.9)
	Paclitaxel $<$175 mg/m^2 n (%)	10 (8.1)
Number. of cycles	Median (IQR)	3 (3–4)
	Total range	1–8

[a]Numbers of patients not reported if <5; [b]n = 123.

Abbreviations: SACT, systemic anti-cancer therapy; AUC, Area Under the curve; Dose of SACT is at first cycle; IQR, Interquartile range.

3.4 Definitive therapy

The proportion of patients who proceeded to radical treatment was 96.8% (122/126) with 108 patients (85.7%) receiving CCRT and 14 (11.1%) receiving RT alone. The median time from last cycle of NACT to start of radiotherapy was 27 days (IQR 24–34). The remaining patients defaulted from treatment, had progressive disease and were unable to receive radical treatment, or were lost to follow up. Of the 122 radically treated patients, 116/122 had EBRT plus BT and the remaining 6/122 had EBRT +/– photon boost. BT was not administered to these 6 patients as a result of either patient refusal, compliance or suitability for the procedure. Treatment was completed as planned in 105/122 patients. There was one death during radiotherapy which was unrelated to treatment. Mean EQD2 to point A based on α/β ratio of 10 was 77.2 Gy (range 10–95.9). Median dose to point A of 82 Gy was obtained in 54/122 patients (Table 3).

Table 3. External beam radiation details.

EBRT details	Measure	Result
Patients receiving radical treatment	n (%)	122 (100)
EBRT type	EBRT + IGBT n (%)	116 (95.1)
	EBRT ± photon boost n (%)	6 (4.9)
EBRT dose	≥50 Gy n (%)	90 (73.8)
	45–49 Gy n (%)	27 (22.1)
	<45 Gy n (%)	5 (4.1)
$EQD2_{10}$	Mean	77.2 Gy
	Median	82.0 Gy
	Range	10–95.9 Gy
Completed RT/CCRT within	56 days n (%)	116 (95.1)
	50 days n (%)	112 (91.8)

Abbreviations: EBRT, External beam radiation; CCRT, concurrent chemoradiotherapy; RT, radiotherapy; IGBT, image guided brachytherapy.

Patients who received RT alone or no definitive therapy were older and more likely to have stage IV disease and/or positive para-aortic lymph nodes. See supplementary file (**Supplementary Table 1**) for more details.

3.5 Survival

The Kaplan-Meier plot for OS is shown in Fig. 1. At the study end (median follow up of 30 months), 49 patients had died and the primary cause of death was cervical neoplasm in 90% of cases. There were no treatment related deaths. Median OS was not reached (NR) (95% CI 41.4 months – NR) but the 3-year OS was 61.8% (95% CI 53.4–71.6%).

Using univariable Cox proportional hazard models, the following factors had a significant negative influence on survival: definitive therapy other than CCRT, age, FIGO stage, positive para-aortic nodes, performance status ≥1, baseline albumin and haemoglobin <normal reference range, baseline platelets >normal reference range, NLR ≥5, and CCI score ≥1.

Using multivariable analysis, the factors that remained independently associated with poorer survival were: definitive therapy other than CCRT (Hazard Ratio (HR) 2.23 (95% CI 1.01–4.91) and NLR ≥5 (HR 2.8 (95% CI 1.32–5.90)) (Table 4).

3.6 Relapse and subsequent treatment

Two patients were lost to follow up. Of the remaining 124 patients, 50 (40.3%) had relapsed by the end of the study period, of whom 31 women (25%) went on to receive subsequent treatment. The crude local control rate was 75.8% (30/124 cases with persistent or recurrent cervical disease). The pelvic control rate was 68.5% (39 locoregional failures). Relapse restricted to the pelvis occurred in 21 patients. Isolated distant relapse was documented in 7 patients and in combination with pelvic and/or para-aortic failure in a further 13 patients, resulting in total distant failure rate of 16% (20/124). Of all relapses, 40% (20/50) had distant disease. Five women were salvaged with surgery or radiotherapy, for central pelvis or para-aortic nodal recurrence, respectively. A further 26 patients had treatment with palliative intent.

4. Discussion

4.1 Summary of main results

We report 3-year OS of 61.8% in a cohort of women with very locally advanced cervical cancer who received 3-weekly platinum based NACT prior to CCRT/RT. Both the definitive therapy received following NACT and baseline NLR were found to significantly impact upon survival when adjusted for other potential cofounders. The vast majority of patients proceeded to radical treatment (CCRT 85.7%/RT 11.1%). Distant failure was lower than predicted at 16% but pelvic control was 68.5%.

4.2 Results in the context of published literature

Evidence supporting the use of NACT prior to RT/CCRT is limited, with most data comprising retrospective case studies from India [19–21], or small phase II trials [5, 22–24] that often had short follow up periods and reported response rate rather than survival. Until very recently, there was no randomised evidence available. CIRCE was a two-arm, randomised, open-label phase II trial undertaken within a single centre in Brazil which reported findings in 2019. This study randomised 107 patients to either NACT with 3-weekly cisplatin and gemcitabine followed by CCRT or CCRT alone [25]. Similar to our study, it reported a 3-year OS of 60.7% in the 55 patients who received NACT, although OS was found to be markedly lower compared with those who received CCRT alone (3-year OS 86.8%). CIRCE included predominantly stage IIB and IIIB patients; very few women had stage IV disease. Only 9% in the neoadjuvant arm were recorded as FIGO stage IVA in comparison to 27% stage IV (including 4% stage IVB) in our cohort. Unfortunately, the number of patients who had para-aortic lymph node involvement was not reported as this would have allowed a better comparison with our study. Furthermore, NACT regimen was different with cisplatin/gemcitabine forming the chemotherapy backbone. Extrapolating from OS data comparing various platinum doublets in patients with relapsed and/or metastatic disease [26], the choice of gemcitabine or paclitaxel is unlikely to be a determining factor. Similarly, carboplatin is not

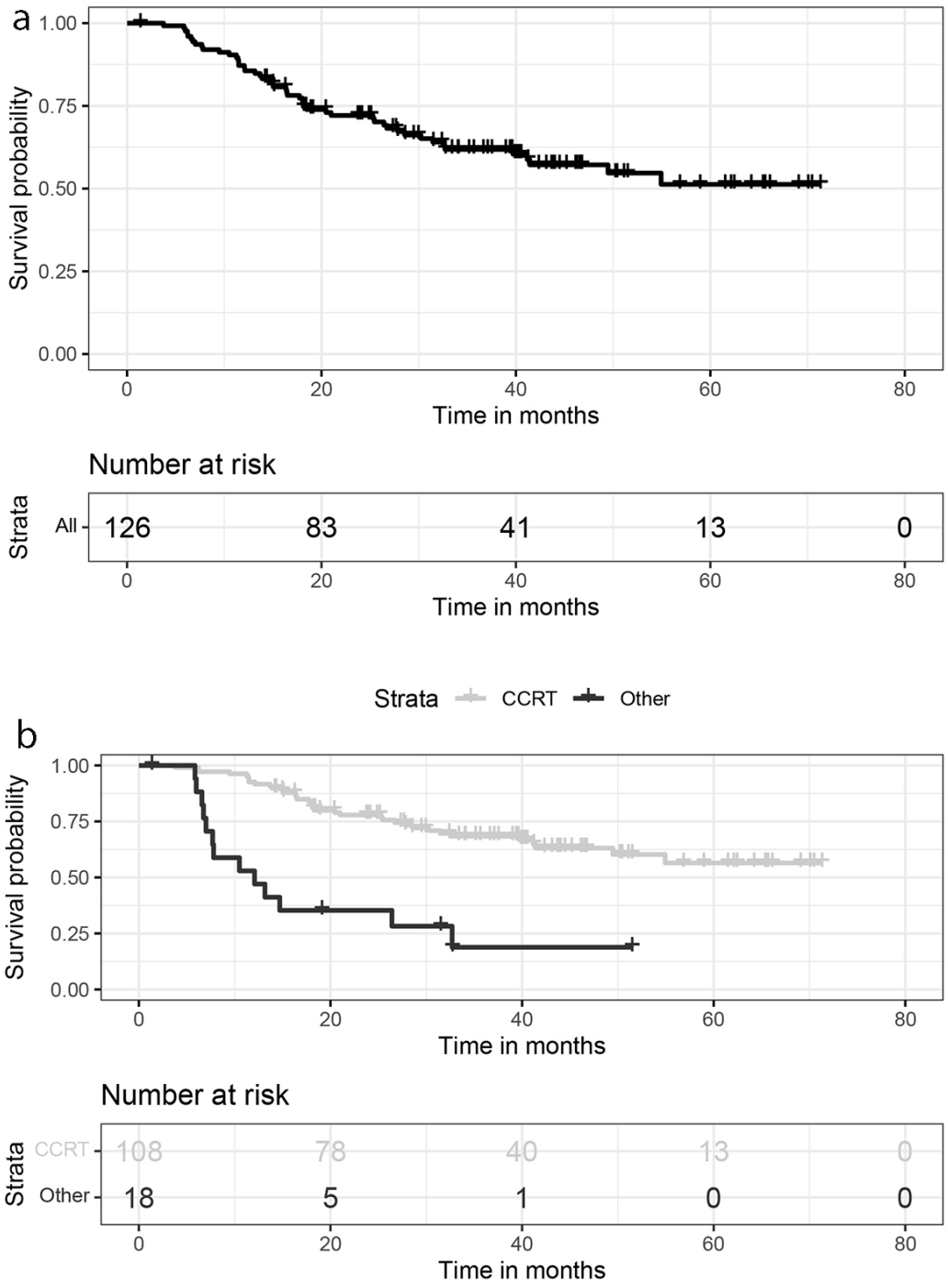

Fig. 1. Kaplan-Meier plots for Survival. (a) Overall survival. (b) Overall Survival by definitive treatment — Concurrent chemoradiotherapy vs. Other. Abbreviations: CCRT, concurrent chemoradiotherapy.

inferior to cisplatin when combined with paclitaxel in the advanced setting [27]. In our population, there was no survival difference detected in those receiving carboplatin/paclitaxel compared to cisplatin/paclitaxel.

Other studies investigating NACT have utilised alternative regimens. The CXII trial [5], for example, used carboplatin and paclitaxel but it was given as six weekly doses in comparison to our study (3-weekly scheduling). The selection of weekly treatment in CXII is based on a historical meta-analysis that suggested dose density and short intervals (<14 days) between chemotherapy may be the key to improve outcomes if NACT is delivered prior to radical treatment for locally advanced cervical cancer, although radical treatment predominantly consisted of RT alone as the data was collated before CCRT was widely accepted [28]. The survival in our study is similar to that reported from CXII, with 3-year OS

Table 4. Overall survival analysis by baseline characteristics & definitive therapy received.

Variable	No. patients	No. deaths	Univariable analysis			Multivariable analysis	
			Unadjusted HR (95% CI)	*p* value	Global *p* value	Adjusted HR (95% CI)	*p* value
Definitive therapy following NACT							
Concurrent chemoradiotherapy	108	36	1		<0.001	1	
Other	18	13	4.66 (2.44–8.89)	<0.001		2.23 (1.01–4.91)	0.047
Age (continuous)	126	49	1.03 (1.01–1.05)[a]	0.008		1 (0.98–1.02)	0.925
ECOG performance status							
0	77	26	1		0.055	1	
1–3	27	15	2.2 (1.16–4.16)	0.016		1.70 (0.8–3.62)	0.167
unknown	22	8	0.97 (0.44–2.13)	0.930		1.13 (0.48–2.64)	0.783
FIGO Stage							
Stage I	9	[b]	1		0.002	1	
Stage II	62	18	2.5 (0.33–18.74)	0.372		1.99 (0.25–15.66)	0.513
Stage III	21	9	4.55 (0.58–35.92)	0.151		2.56 (0.29–22.48)	0.396
Stage IV	34	21	7.42 (1–55.22)	0.050		3.42 (0.41–28.49)	0.255
Para-aortic nodes							
Yes	38	20	1		0.011	1	
No or Not available	88	29	0.46 (0.26–0.82)	0.008		0.64 (0.34–1.22)	0.176
Type of pathology							
Squamous cell carcinoma	108	40	1		0.525	-	
Other	18	9	1.27 (0.62–2.63)	0.514		-	
Grade of pathology							
Grade 1	5	[b]	1		0.619	-	
Grade 2	58	22	0.86 (0.2–3.67)	0.839		-	
Grade 3	40	18	0.92 (0.21–3.99)	0.916		-	
Unknown	23	7	0.54 (0.11–2.61)	0.442		-	
Baseline Haemoglobin (g/L)[c]							
<115 g/L (< lower limit normal)	47	24	1		0.033	1	
115–165 g/L (normal range)	77	24	0.54 (0.31–0.95)	0.032		0.95 (0.44–2.02)	0.884
Baseline Platelets($\times 10^9$/L) [c]							
150–400 $\times$ 10^9/L (normal range)	75	25	1		0.057	1	
>400 $\times$ 10^9/L (> upper limit normal)	49	23	1.74 (0.99–3.07)	0.055		0.89 (0.43–1.85)	0.762

Table 4. Continued.

Variable	No. patients	No. deaths	Univariable analysis			Multivariable analysis	
			Unadjusted HR (95% CI)	*p* value	Global *p* value	Adjusted HR (95% CI)	*p* value
Baseline Albumin (g/L) [c]							
<35 g/L (< lower limit normal)	68	33	1		0.014	1	
35–50 g/L (normal range)	56	15	0.48 (0.26–0.88)	0.018		1.12 (0.5–2.52)	0.787
Neutrophil Lymphocyte Ratio[c]							
<5	85	24	1		<0.001	1	
≥5	39	24	2.93 (1.66–5.16)	<0.001		2.8 (1.32–5.90)	0.007
Charlson comorbidity index score							
0	101	35	1		0.020	1	
≥1	25	14	2.2 (1.18–4.11)	0.013		1.74 (0.77–3.92)	0.179
Scottish Index of Multiple Deprivation (SIMD 2012) [c]							
1	52	21	1		0.931	-	
2	25	10	0.87 (0.41–1.86)	0.725		-	
3	23	10	1.08 (0.51–2.31)	0.834		-	
4	15	[b]	0.67 (0.23–1.95)	0.463		-	
5	9	[b]	1.01 (0.35–2.93)	0.990		-	
Neoadjuvant regimen							
Cisplatin/paclitaxel	79	29	1		0.249	-	
Carboplatin/paclitaxel	44	19	1.63 (0.9–2.95)	0.107		-	
Cisplatin	[b]	[b]	0.72 (0.1–5.31)	0.749		-	

[a] HR for every one year increase in age; [b] Numbers of patients not reported if <5; [c] n = 124, 2 patients with no data available.

Abbreviations: NACT, Neoadjuvant chemotherapy; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology & Obstetrics.

of 61.8% (95% CI 53.4–71.5) versus 67% (95% CI 51–79) with CXII [5]. Although OS was slightly poorer, it is unlikely that 3-weekly treatment is significantly detrimental compared to weekly scheduling as our cohort had poorer prognostic features than the CXII population. The majority of cases in CXII consisted of Stage IIB or IIIB disease with Stage IVA representing only 7% of the study group (Stage IVB was excluded) [5]. Interestingly, the 3-year OS reported within the CCRT arm of CIRCE is higher than that described by the larger multicentre cohort study, RetroEMBRACE, which reported a 3-year OS of 74% using state of the art RT techniques, although only 77% received concomitant chemotherapy [4]. Half of patients in RetroEMBRACE were noted to have Stage IIB disease. Less than 5% had Stage IV disease, including a small number of stage IVB patients (0.7%) [4]. Our local control rate of 75.8% contrasts with 91% at 3 years from RetroEMBRACE [4], suggesting that overall RT dose was suboptimal. However, there were crucial differences in patient characteristics, particularly tumour stage and size. The majority of our patients (almost 80%) had documented primary tumour at diagnosis in excess of 5cm. Local control at 3 years drops from 95% in tumours $<$5 cm to 85% in tumours $\geq$5 cm with an associated reduction in OS from 81% to 66% at 3 years, respectively [4]. Further, most of our patients had involved nodes (77%), contrasting with 40% in RetroEMBRACE. This is pertinent for two reasons — firstly, node positivity influences OS (78% at 3-years in node negative population compared with 67% in node positive population) [4]; and secondly, positive nodes can be a predictor for distant metastases [29, 30]. Allowing for the more advanced nature of our study cohort, the 3-year OS of 61.8%, compares more favourably with the results from RetroEMBRACE. NACT should not be considered as a substitute for effective RT techniques, especially IGBT, and does not appear to augment local control, but NACT may reduce micro-metastases in a group with very high risk disease. The rate of distant relapse in our study was 40% in patients with confirmed recurrence as opposed to 80% in RetroEMBRACE [30], despite the fact that there was a significant variance in node positivity rates at diagnosis.

4.3 Strengths and weaknesses

The main strength of this analysis is the inclusiveness in terms of study participants who received NACT for locally advanced cervical cancer in the era of modern conformal RT planning. However, as a retrospective series, the added benefits of NACT prior to CCRT cannot be evaluated since there was no control arm. The principal limitation of our study is the evolution of RT practice. For instance, the pelvic EBRT dose was increased from 45 Gy to 50 Gy due to concerns over pelvic control rates, and VMAT was introduced in 2012. CT was employed to delineate organs at risk at the time of BT, but dose was prescribed to Point A as per the historical Manchester system. Thus, the recommended ESTRO guideline [31] that stipulates volume based planning was not adhered to. Also, we did not have the facility for combined intracavitary/interstitial BT which was performed in almost 25% patients in RetroEMBRACE [4]. Furthermore, toxicity information relating to both chemotherapy and radiotherapy are not routinely captured electronically in our systems and therefore were unavailable for this study. However, in a prior audit, NACT was found to be reasonably well tolerated [32].

4.4 Implications for practice and future research

As highly developed radiotherapy techniques become increasingly available, and the role of IGBT firmly established in optimising local control, there is a drive to enhance pelvic control rates by characterising elective nodal volumes and implementing simultaneous integrated boost to target involved nodes [33]. It has also been postulated that escalating dose to eradicate nodal burden will reduce distant relapse and/or improve OS. Conversely, some emerging data refutes this [29, 34], suggesting that additional SACT is required. The potential role of adjuvant immunotherapy is currently under investigation in the CALLA trial [35]. As yet, it is unclear whether this will prove to be a successful strategy and, if so, which subgroups will benefit most, as recruitment is likely to continue until 2024. NACT has the advantage of being low cost and readily available. Ultimately, it would be helpful to identify women at highest risk of poor outcome based on clinico-pathological factors and/or molecular markers and direct them to the appropriate therapeutic pathway. The prognostic significance of NLR also warrants further consideration as per previous findings [36], higher baseline NLR was associated with shorter survival.

5. Conclusions

With the exception of low resource units, NACT does not obviate the need for state of the art conformal RT and IGBT combined with concomitant chemotherapy. However, the pattern of failure after optimal CCRT is evolving with increased levels of metastatic disease despite excellent local control. Treatment options remain limited in the event of relapse. NACT does not compromise the ability to tolerate CCRT in the majority of women. It may reduce distant metastases and merits further evaluation in the context of modern CCRT. Until the INTERLACE trial completes accrual, a number of key questions remain unanswered, notably the optimal chemotherapy regimen and scheduling, and whether NACT can provide a survival advantage in locally advanced cervical cancer.

Author contributions

KB, KG, NR, JL, CC, JP, KK, TM, MB, RH, AK, AS conceptualised and designed the study. KB, KG and CC performed the data analysis. KB, KG, JL, JP, KK, MB contributed to the interpretation of the results. KB drafted the paper. KB, KG, NR, JL, MB, JP, KK, TM critically revised the text. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Public Benefit and Privacy Panel for Health and Social Care (1819-0055). Due to the nature of this retrospective clinical effectiveness study, additional ethical approval was not required.

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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://ejgo.imrpress.com/EN/10.31083/j.ejgo4205140.

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