TITLE:

NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED CERVICAL CARCINOMA –A ROLE IN PATIENTS WITH PARAAORTIC LYMPH NODE INVOLVEMENT? A 10-YEAR INSTITUTIONAL EXPERIENCE

1st author: Dr Harshani Miranda Green BSc MBBS MRCP FRCR

Address:

University College London Hospitals NHS Foundation Trust (UCLH)

1st floor Central

250 Euston Road

London

United Kingdom

NW1 2PG

E-mail: Harshani.green@nhs.net

Co-authors (3):

2nd author: Nicholas Counsell

Department: Cancer Research United Kingdom & University College London Cancer Trials Centre

Institution: University College London (Address: CRUK & UCL Cancer Trials Centre, University College London, 90 Tottenham Court Road, London,UK. W1T4TJ)

County: United Kingdom

E-mail: Nicholas.counsell@ucl.ac.uk

[SENIOR AUTHOR] and 3rd Author: Dr Mary McCormack PhD FRCR (UCLH)

Department: Clinical Oncology

Institution: University College London Hospitals NHS Foundation Trust, University College London.

City: London

County: United Kingdom

Address:

University College London Hospitals NHS Foundation Trust (UCLH)

1st floor Central , 250 Euston Road, London, United Kingdom. NW1 2PG

E-mail: mary.mccormack2@nhs.net

4th author: Dr Amy Ward MBBS MRCP MSc FRCR (UCLH)

Department: Clinical Oncology

Institution: University College London Hospitals NHS Foundation Trust (Address 1st floor Central, 250 Euston Road, London, UK. NW1 2PG)

City: London

County: United Kingdom

Amy.ward4@nhs.net

Acknowledgements

Thank you to Joni Ainsworth for contributing to data collection.

MMC acknowledges support from UCL Biomedical Research Centre.

Competing Interests

None

Funding

None

Ethics and approvals

Patients with paraaortic lymph nodes were offered this treatment following on from the CX2 trial data. No ethics was required. All patients still received standard of care treatment but with additional chemotherapy. This retrospective study received local institutional approval.

Word Count: 2789 (excluding title page, abstract, references, figures and tables)

Abstract

Background

Overall survival (OS) and progression-free survival (PFS) with concomitant chemoradiotherapy for locally advanced cervical carcinoma has been described as 66% and 58% respectively at 5 years. Paraaortic lymph node involvement significantly increases risk of relapse and death. The role of additional chemotherapy in these patients is as yet undefined.

Methods

We reviewed patients with FIGO 2014 stage IB1–IVA cervical carcinoma who received extended-field radiotherapy in addition to standard pelvic chemoradiotherapy with or without neoadjuvant chemotherapy, at University College London Hospital (January 2007 – January 2018). Patients in open clinical trials were excluded.

Results

Overall, 47 (15.8% of 298 eligible patients) patients with pelvic and/or paraaortic lymph node-positive cervical carcinoma received extended-field radiotherapy. 19 (40.4%) had both neoadjuvant chemotherapy (all received 6 cycles) and extended-field radiotherapy (median 44 days), 28 (59.6%) patients received extended-field radiotherapy alone (median 43 days). All patients completed radical radiotherapy within 49 days.

We observed evidence that patients receiving neoadjuvant chemotherapy and extended-field radiotherapy had a lower risk of death (median follow-up 4.8 years, 3

deaths) compared to extended-field radiotherapy-alone (median follow-up 3.0 years, 11 deaths, HR=0.27, 95% CI: 0.08-1.00; p=0.05). 3-year OS rates were 83.3% (95% CI: 66.1-100) and 64.6% (95% CI 44.6-84.6) respectively. A PFS benefit was seen (HR 0.25, 95% CI: 0.08-0.77; p=0.02), with 3-year PFS-rates of 77.8% (95% CI: 58.6-97.0) and 35.0% (95% CI: 14.0-56.0) respectively.

Conclusions

Our institutional experience suggests that the use of additional systemic therapy before chemoradiotherapy benefits women with locoregionally advanced (FIGO 2018 IIIC2) cervical cancer. Neoadjuvant chemotherapy was associated with longer OS and PFS, without compromising definitive extended-field chemoradiation.

Keywords: Locally advanced cervical cancer, paraaortic lymph node, extended field radiotherapy, neoadjuvant chemotherapy

1. Introduction

1.1 Overview

Cervical cancer is a significant global health problem. It is the second most common cancer in women in low- and middle-income countries and fourth most common cancer in high-income countries,[1]. Chemoradiation was established as the standard of care for The International Federation of Gynaecology and Obstetrics (FIGO) stage IB-IVA two decades ago following 5 large randomised controlled trials (RCTs) and an announcement by the National Cancer Institute (NCI),[2]. An individual patient data meta-analysis from 13 trials confirmed concomitant chemotherapy is beneficial over radiotherapy alone, with improvements of 6% (from 60% to 66%) and 8% (from 50% to 58%) in 5-year overall survival (OS) and disease-free survival respectively,[3]. However, a significant proportion of women relapse and die from their disease.

The prognostic importance of nodal involvement has recently been recognised by FIGO with the incorporation of nodal status in the revised 2018 staging system,[4]. For many years, there were no standardised approaches to managing patients with positive paraaortic lymph nodes. Recent European Society of Gynaecological Oncology (ESGO) guidelines recommend that patients with paraaortic lymph node metastases, or those at high-risk of microscopic involvement, are treated with extended-field chemoradiation,[5]. A retrospective review of 175 patients with pathology-proven paraaortic lymph nodes receiving extended-field radiotherapy reported a median OS of just 23.4 months; the majority died within 3 years,[6]. The authors highlighted current limitations of treatment and the need for more effective therapy.

1.2 Extended-field radiotherapy

A systematic review and meta-analysis of RCTs investigating prophylactic paraaortic lymph node radiotherapy identified 4 RCTs involving over 1,000 patients,[7-12]. Extended-field radiotherapy significantly reduced paraaortic lymph node failure-rate (Hazard Ratio (HR) 0.35, 95% Confidence Interval (CI): 0.19–0.64; p<0.01) and the incidence of distant metastases (HR 0.69, 95% CI: 0.50–0.96; p=0.03). There was a trend towards a decrease in cancer-related deaths (Odds Ratio 0.68, 95% CI: 0.45–1.01; p=0.06) with extended-field radiotherapy in two studies that published cancer-specific survival,[7]. A 2018 Cochrane Systematic Review highlighted that 3 of these studies did not use concurrent chemotherapy, which is now considered substandard treatment,[9-16]. These RCTs were also during an older era of imaging with no modern MRI or PET-CT. It discussed one chemoradiotherapy study of 74 participants, which reported a probable decreased risk of death from extended-field chemoradiation *versus* pelvic chemoradiation (HR 0.37, 95% CI: 0.14 to 0.96),[14]. The authors concluded that modern high-quality RCTs are required,[13].

1.3 Neoadjuvant chemotherapy

Neoadjuvant chemotherapy before radiotherapy is not a new concept and has been the subject of many trials with conflicting outcomes. A meta-analysis of 18 trials, divided according to chemotherapy cycle-length, demonstrated a HR of 1.25 (5-year survival detriment of 8% from 45% to 37%) for trials with cycle intervals >14 days and a HR of 0.83 (5-year survival benefit of 7% from 45% to 52%) for those with cycle lengths ≤14 days,[17]. The Cx2 trial, a single arm phase II study in 46 patients with locally advanced cervical cancer, explored this concept further with dose-dense weekly chemotherapy schedules of carboplatin/paclitaxel for 6 weeks followed, without delay, by radical pelvic/extended-field chemoradiation. The key differences

here were the use of dose-dense schedules incorporating a taxane and eliminating the gap between chemotherapy and definitive chemoradiotherapy. This confirmed that the approach was feasible with manageable toxicity whilst not compromising chemoradiotherapy,[18]. Within Cx2 (median follow-up=39.1 months), 5 patients had positive paraaortic lymph nodes; 3 were alive and disease-free at the time of analysis,[18].

The INTERLACE trial is a phase III RCT comparing 6 weeks of carboplatin/paclitaxel chemotherapy followed by chemoradiotherapy with chemoradiotherapy alone in women with locally advanced cervical cancer,[19]. To date 436 patients have been randomised out of a target of 500 and is expected to complete accrual within the next 12 months. The OUTBACK trial of adjuvant chemotherapy after chemoradiotherapy has recently reported,[20,21]. There was no difference in 5-year overall survival with additional chemotherapy given following chemoradiation,[21].

A recent phase II trial of neoadjuvant chemotherapy randomised patients with locally advanced cervical cancer to either three cycles of neoadjuvant chemotherapy with 3-weekly cisplatin/gemcitabine followed by chemoradiation (n=55) or chemoradiotherapy alone (n=52),[22]. After a median follow-up of 31.7 months, 3-year progression-free survival (PFS)-rates were 40.9% in neoadjuvant chemotherapy arm and 60.4% in the chemoradiotherapy arm (HR 1.84; 95% CI: 1.04-3.26; p=0.033). Neoadjuvant chemotherapy was associated with shorter OS (3-year OS-rate, 60.7% *versus* 86.8%; HR 2.79; 95% CI: 1.29-6.01; p=0.006). The interval between neoadjuvant chemotherapy and chemoradiation may have allowed for tumour repopulation, potentially contributing to the detriment in survival observed. No patients received extended-field radiotherapy,[22].

A phase II study of 37 women with FIGO 2009 stage IB1-IVA cervical cancer with positive paraaortic and/or pelvic lymph nodes, treated with 2 cycles of neoadjuvant 3-weekly cisplatin and paclitaxel chemotherapy followed by extended-field chemoradiation, reported 3-year OS and PFS-rates of 70.1% and 48.5% respectively,[23,24]. The regime was shown to be feasible with acceptable toxicity,[23]

1.4 Study aim

Subsequent to Cx2, all medically fit patients with paraaortic lymph node involvement were treated with neoadjuvant chemotherapy followed by extended-field chemoradiation. This paper reports on the outcome of a cohort of paraaortic lymph node-positive patients treated with neoadjuvant chemotherapy followed by extended-field chemoradiation compared with patients treated with extended-field chemoradiation without neoadjuvant chemotherapy. Patients treated within the INTERLACE trial were excluded.

2. Materials and Methods

Patients with FIGO 2014 stage IB1–IVA cervical carcinoma treated with curative intent at our centre between January 2007 and January 2018 were identified through our brachytherapy database,[25]. Clinical records were reviewed; patient characteristics, treatment details and outcome data were recorded. Patients treated with extended-field radiotherapy were identified and data including age, histology, nodal status, use of concurrent chemotherapy, neoadjuvant chemotherapy, radiological response and toxicity were recorded.

All patients received 50.4Gray (Gy) in 28 fractions (f) over 5.5 weeks to a planned pelvic volume using a 3D-conformal four-field technique plus intracavitary high-dose rate brachytherapy (15Gy in 2f or 21Gy in 3f from June 2010). A boost of 5.4Gy in 3f over 3 days using parallel-opposed fields was considered for involved pelvic nodes, parametrial involvement or pelvic sidewall extension. Patients treated with extended-field received 45Gy in 25f over 5 weeks to the paraaortic lymph nodes using parallel-opposed or a three-field technique. The conventional pelvic field extended from the top of L5 to the bottom of the obturator foramen or 2 cm below the lowest level of disease and laterally 1.5 cm beyond the bony pelvis. The lateral fields extended from the anterior border of the symphysis pubis to the S2/3 interspace posteriorly. Fields were modified to take account of available information from pre-treatment magnetic resonance imaging (MRI) scans and examination under anaesthesia to ensure adequate tumour coverage. For extended-field, the superior field border was at T12/L1 and the inferior border at L4/5.

All patients were considered for cisplatin 40mg/m^2 weekly. Neoadjuvant chemotherapy consisted of 6 weeks of carboplatin AUC2/paclitaxel 80mg/m^2 on days 1, 8, 15, 22, 29 and 36. Generally, neoadjuvant chemotherapy was only considered for those patients with radiologically enlarged paraaortic lymph nodes diagnosed after September 2012 following activation of INTERLACE protocol. Patients with positive paraaortic lymph nodes were excluded from the trial. Prior to this date, patients with positive paraaortic lymph nodes were treated with standard extended-field chemoradiation. Those deemed at risk of microscopic paraaortic lymph node involvement (multiple positive pelvic lymph nodes/common iliac lymph nodes) were

treated with extended-field chemoradiation without neoadjuvant chemotherapy. Haematological, bowel and bladder toxicity were graded using NCI Common Toxicity Criteria for Adverse Events (CTCAE version 4.0).

Patients were reviewed weekly on treatment. Patients were transfused where necessary to maintain a Haemoglobin of ≥11.5g/dl. Patients were assessed post-neoadjuvant chemotherapy with MRI/CT after 3-6 cycles. Response to chemoradiotherapy was assessed 12 weeks post-treatment with MRI. Post-treatment images were formally compared to pre-treatment MRI by a radiologist; assessing response at all sites of disease. RECIST criteria was only used for patients within a clinical trial. Patients received follow-up 3-monthly for the first 2 years, 6-monthly until year 5 and annually thereafter.

Analyses of this case series are predominantly descriptive. The primary endpoints of interest were OS and PFS, measured from the date of diagnosis until death from any cause, date of progression for PFS, or censored at the date last seen. OS and PFS are described using Kaplan-Meier plots and rates at 3- and 5-years; comparisons by treatment group (extended-field radiotherapy and/or neoadjuvant chemotherapy) are exploratory in nature, HRs were estimated using univariable Cox regression with a 5% two-sided test of significance. Response rates are also presented, with 95% exact binomial CIs, unknown responses were included in the denominator to provide conservative estimates (i.e. assumed no response).

3. Results

350 patients with FIGO 2014 IB1–IVA cervical carcinoma treated with curative intent between January 2007 and January 2018 were identified. Those with small cell or clear cell histopathology, paediatric patients and palliative-intent treatment were excluded (n=10). 305 patients (89.7%) received chemoradiotherapy, 29 patients (8.5%) had contraindications to cisplatin, and 6 patients (1.8%) had missing chemotherapy data. 62 patients (18.2%) were in a clinical trial; 20 patients on Cx2 protocol and 42 on INTERLACE protocol. Excluding INTERLACE patients, as the trial is still running, 298 patients were evaluated and 13.8% (41/298) received neoadjuvant chemotherapy.

Overall, 15.8% (47/298) of patients received extended-field radiotherapy in addition to standard pelvic chemoradiotherapy. Of 47 patients treated with extended-field radiotherapy, 19 (40.4%) received neoadjuvant chemotherapy for involved paraaortic lymph nodes (neoadjuvant chemotherapy/extended-field group). The majority (18/19, 94.7%) of these patients received concurrent chemotherapy with definitive radiotherapy; 8 (42.1%) patients had paraaortic lymph node surgery to confirm nodal involvement and 6 of these had debulking of involved nodes prior to neoadjuvant chemotherapy.

The remaining 28 of 47 patients (59.6%) received extended-field radiotherapy without neoadjuvant chemotherapy (extended-field alone group). This group included those treated prophylactically (paraaortic lymph node-negative but positive pelvic nodes, n=9, 32.1%), but also patients with positive-paraaortic lymph nodes (n=19, 67.9%). 25 of 28 (89.3%) received concurrent chemotherapy. 16 (57.1%) patients had paraaortic

lymph node surgery confirming nodal involvement and 13 of these had debulking surgery. 2 patients received four cycles of adjuvant carboplatin/paclitaxel chemotherapy.

All neoadjuvant chemotherapy/extended-field patients completed 6 cycles (6 weeks) of neoadjuvant chemotherapy; 84.2% completed ≥5 cycles of concurrent cisplatin [see *Table 1*]. There was no difference in the median radiotherapy overall treatment time between the groups (neoadjuvant chemotherapy/extended-field; 44 days versus 43 days extended-field alone; maximum overall treatment time 49 days). The response rate (complete/partial), assessed at 12 weeks post-treatment, was 78.9% (95% CI: 54.4-93.9) in neoadjuvant chemotherapy/extended-field group and 75.0% (95% CI: 55.1-89.3) in extended-field alone group [see *Table 1*].

Table 1: Descriptive statistics of treatment, response and toxicity for patients receiving neoadjuvant chemotherapy/extended-field radiotherapy

	Neoadjuvant chemotherapy/Extended-field (n=19)	**Extended-field alone (n=28)**
Median Age years/(range)	45 (25-69)	52 (26-72)
Paraaortic lymph node (PALN) positive	18 (94.7%)	19 (67.9%)
Paraaortic lymph node negative, Pelvic node positive	1 (5.3%)	9 (32.1%)
Nodal Diagnosis		
Imaging	11[a] (57.9%)	12 (42.9%)
FDG PET CT	4 (21.1%)	11 (39.2%)
Laparoscopic PALN or pelvic nodal sampling/surgery:	8 (42.1%)	16 (57.1%)
Of these, number having debulking surgery	6	13
Total: Surgical PALN diagnosis or FDG PETCT	11 (57.9%)	23 (82.1%)
Neoadjuvant chemotherapy (n)		
Median weeks	6 (6-18[b])	-
Dose modifications	0	-
Neoadjuvant chemotherapy Radiological response		
Complete response	0	-
Partial response	13 (68.4%)	-
Stable disease	1 (5.3%)	-
Progression	0	-
Unknown	5 (26.3%)	-
Median radiotherapy overall treatment time (days)	44	43
Admissions	4 acute, 4 elective	3 acute, 0 elective
Concurrent chemotherapy	18	25
Median number cycles	5 (3-6)	5 (0-7[c])
Completed ≥ 5 cycles	16 (84.2%)	22 (78.6%)
Chemoradiation Radiological response		
Complete response	14 (73.7%)	18 (64.3%)[d]
Partial response	1 (5.3%)	3 (10.7%)
Stable disease	0	2 (7.1%)
Progression	2 (10.5%)	4 (14.2%)[d]
Unknown	2 (10.5%)	1 (3.6%)
Acute Toxicity		
Bladder		
≥Grade 3	0	0
Grade 2	0	2 (7.1%)
Bowel		
≥Grade 3	0	2 (7.1%)
Grade 2	6 (31.6%)	2 (7.1%)
Haematological		
≥Grade 3	4 (21.1%)	1 (3.6%)
Grade 2	4 (21.1%)	2 (7.1%)
Unknown	3 (15.8%)	3 (10.7%)
Late Toxicity		
Bladder		
≥Grade 3	1 (5.3%)	3 (10.7%)
Grade 2	4 (21.1%)	1 (3.6%)
Bowel		
≥Grade 3	3 (15.8%)	4 (14.2%)
Grade 2	2 (10.5%)	1 (3.6%)
Unknown	1 (5.3%)	2 (7.1%)
Relapse	**4 (21.1%)**	**15 (53.6%)**
Locoregional	1	3
Distant	3[e]	12[e]
Status at last follow-up		
Alive	**16 (84.2%)**	**17 (60.7%)**
Alive with progression	1 (5.3%)	5 (17.9%)
Died	**3 (15.8%)**	**11 (39.3%)**
Died with progression	3 (15.8%)	10 (35.7%)
Median (interquartile range) follow-up (years)	**4.8 (3.4-7.7)**	**3.0 (2.3-6.6)**

[a] 1 patient had enlarged paraaortic nodes by CT criteria, negative PA node dissection, pelvic nodal dissection not done but treated with high suspicion of risk with neoadjuvant chemotherapy/extended-field
[b] 1 patient had 18 weeks as on initial diagnosis, not felt to be radically treatable
[c] 1 patient commenced cisplatin 1 week prior to radiotherapy and hence was treated with 7 cycles
[d] 2 additional patients had local pelvic control, but one had a new retrocrural node and one developed lung metastases and hence were included under 'progression.'
[e] 2 patients had mixed locoregional and distant relapse in each group

Median follow-up for the neoadjuvant chemotherapy/extended-field group was 4.8 years (interquartile range (IQR): 3.4-7.7) and 3.0 years (IQR: 2.3-6.6) for extended-field alone. There was evidence of a benefit in terms of OS and PFS for neoadjuvant chemotherapy/extended-field (n=19, 3 deaths, 4 progressions/deaths) versus extended-field alone (n=28, 11 deaths, 16 progressions/deaths), with a HR=0.27 (95% CI: 0.08-1.00, p=0.05) for OS and a HR=0.25 (95% CI: 0.08-0.77; p=0.02) for PFS respectively [see *Figure 1*]. 3-year OS- and PFS-rates for neoadjuvant chemotherapy/extended-field were 83.3% (95% CI: 66.1-100) and 77.8% (95% CI: 58.6-97.0) compared with 64.6% (95% CI: 44.6-84.6) and 35.0% (95% CI: 14.0-56.0) respectively for extended-field alone. 5-year OS and PFS rates for neoadjuvant chemotherapy/extended-field were 83.3% (95% CI: 66.1-100) and 77.8% (95% CI: 58.6-97.0) versus 43.1% (95% CI: 15.3-70.9) and 35.0% (95% CI: 14.0-56.0) for extended-field alone.

For the entire patient cohort of eligible patients (N=298), 3-year OS- and PFS-rates were 79.4% (95% CI: 74.1-84.7) and 67.3% (95% CI: 61.4-73.2) respectively [see *Figure 2a, 2b*], 5-year OS and PFS rates were 75.5% (95% CI: 69.6-81.4) and 63.8% (95% CI: 57.5-70.1) respectively. Median follow-up was 4.7 years (IQR: 2.3-7.1). *Figure 2c and 2d* show stratification by stage. CTCAE Grade ≥3 chemoradiation late bowel and bladder toxicity rates were 8.5% and 5.9% respectively.

There was some evidence of a trend towards worse outcome in patients requiring extended-field radiotherapy compared to those not requiring extended-field radiotherapy; OS and PFS HRs were 1.68 (95% CI: 0.93-3.06; p=0.09) and 1.57 (95%

CI: 0.96-2.57; p=0.07) respectively. 3- and 5- year OS rates for patients requiring extended-field were 72.9% (95% CI: 59.2-86.6) and 64.1% (95% CI: 47.4-80.8).

Figure 3a shows OS for all neoadjuvant chemotherapy patients with or without extended field radiotherapy (n=41) versus no neoadjuvant chemotherapy (n=239) HR=0.65 (95% CI: 0.29-1.43, p=0.28). *Figure 3b* shows PFS for neoadjuvant chemotherapy (n=40) versus no neoadjuvant chemotherapy (n=237) HR=0.51 (95% CI: 0.26-1.02, p=0.06).

4. Discussion

4.1 Summary of Main Results

This 10-year single-institution case-series has demonstrated favourable results for the addition of dose-dense weekly neoadjuvant carboplatin and paclitaxel chemotherapy, to extended-field chemoradiation, in patients with paraaortic lymph node-positive locally advanced cervical cancer. This treatment approach is feasible and shows no evidence of detriment to definitive chemoradiation.

4.2 Results in the Context of Published Literature

Our 5-year OS/PFS rates for patients with locally advanced cervical cancer of 75.5% and 63.8% respectively, are comparable with those in the published literature but with a longer median follow-up (4.7years),[3,26]. In the retroEmbrace series, the OS for node positive/advanced disease patients at 3- and 5- years was 64% and 49%

respectively; it is unclear what proportion received extended-field radiotherapy,[26,27]. In our series, the 3- and 5-year OS rates for paraaortic and or pelvic node-positive disease were 72.9% and 64.1% respectively. In other published studies, 3-year OS rates for paraaortic lymph node-positive disease vary from 33% to 61%,[28-31] and 62-73% for pelvic node positive disease,[28,32]. Thus, confirming that a significant proportion of these patients succumb to their disease. In our small series of 19 patients treated with dose-dense weekly chemotherapy followed by extended-field chemoradiation, there was some evidence of a marked improvement in OS with a HR of 0.27 (95% CI: 0.08-1.00, p=0.05) and in PFS with a HR of 0.25 (95% CI: 0.08-0.77, p=0.02). The corresponding 3-year OS and PFS rates were 83.3% and 77.8%; these rates were maintained at 5 years.

Overall, 21.1% of patients in neoadjuvant chemotherapy/extended-field group relapsed compared with 53.6% in extended-field alone group. The 3 deaths observed in the neoadjuvant chemotherapy/extended-field group occurred in the first 2 years post-diagnosis and those alive without early relapse appear to survive long-term; hence similar 3-year and 5-year OS rates. In the extended-field alone group, deaths continued with time from diagnosis and 10 of 11 deaths followed disease progression; with an OS-rate drop from 64.6% at 3 years to 43.1% at 5 years [see *Figure 1*]. Relapses were mainly distant in both groups highlighting the potential of neoadjuvant chemotherapy in controlling micro-metastatic disease.

All patients who received neoadjuvant chemotherapy completed all cycles and proceeded with chemoradiotherapy in week 7. The response rate (complete/partial) assessed at 12 weeks post-treatment were similar; 78.9% in neoadjuvant

chemotherapy/extended-field group and 75% in extended-field alone group. The neoadjuvant approach did not compromise definitive chemoradiotherapy with all patients in both cohorts completing treatment in <50 days. Neoadjuvant chemotherapy did not negatively impact the ability to deliver concomitant cisplatin with both cohorts receiving a median of 5 cycles and 84.2% ≥5 cycles in the neoadjuvant chemotherapy arm. In CX2, only 80% completed all 6 cycles of the same neoadjuvant chemotherapy regimen with 50% completing ≥5 cycles of cisplatin,[18]. This likely reflects experience gained using this approach and fewer treating clinicians.

As anticipated, the patients who received neoadjuvant chemotherapy/extended-field experienced higher acute haematological toxicity rates (Grade ≥3 21.1%) compared to those treated with extended-field radiotherapy without neoadjuvant chemotherapy (Grade ≥3 3.6%). In the Cx2 study, severe acute haematological toxicities were reported in 20% during neoadjuvant chemotherapy and 52% during chemoradiotherapy,[18]. Singh *et al* reported 28.5% Grade ≥3 neutropenia during neoadjuvant chemotherapy and 29% during chemoradiotherapy,[33]. Late toxicity was not significantly affected by neoadjuvant chemotherapy.

4.3 Strengths and Weaknesses

The results are all the more provocative given that those who received neoadjuvant chemotherapy were likely in a poorer prognostic group with more advanced nodal disease than those in the comparator arm and thus suggest that patients with advanced node-positive disease may benefit from intensification of systemic treatment.

This study is limited mainly by the small numbers of pelvic and/or paraaortic lymph node-positive patients; nevertheless, it does demonstrate again that this approach is feasible and can benefit especially high-risk patients. The other weaknesses are common to such retrospective case series, in particular the database was not designed specifically for the study and the potential for unknown confounding factors with regards to treatment choice.

4.4 Implications for Practice and Future Research

There is minimal literature on the use of neoadjuvant chemotherapy in paraaortic lymph node-positive locally advanced cervical cancer. This study highlights the potential for improved outcomes with additional systemic treatment in such patients. The INTERLACE trial, a randomised phase III study addressing this approach, is ongoing and has almost completed accrual (460/500 patients) [19].

5. Conclusions

Our institutional experience suggests that the use of additional systemic therapy before chemoradiotherapy may benefit women with locoregionally advanced (FIGO 2018 IIIC2) cervical cancer. Neoadjuvant chemotherapy was associated with longer OS and PFS without compromising definitive extended-field radiotherapy.

6. References

1. Bray F, Ferlay J, Soerjomataram I, Siegel R, Torre M, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36

cancers in 185 countries. *Ca Cancer J Clin* 2018; 68:394–424. https://doi.org/10.3322/caac.21492

2. National Cancer Institute. Chemotherapy plus radiation improves survival (press release). Bethesda, MD: *National Cancer Institut*e. https://www.cancernetwork.com/view/chemotherapy-plus-radiation-improves-survival-patients-cervical-cancer 1999 [accessed 9 October 2021].

3. Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. *Cochrane Database Syst Rev.* 2010 Jan 20;2010(1)CD008285. https://doi.org/10.1002/14651858.CD008285

4. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri*. Int J Gynaecol Obstet* 2018; 143 Suppl 2: 22-36 https://doi.org/10.1002/ijgo.12611

5. Cibula D, Pötter R, Planchamp F, Avall-Lundqvist E, Fischerova D, Haie-Meder C et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology Guidelines for the Management of Patients With Cervical Cancer. *Virchows Arch.* 2018 Jun;472(6):919-36. https://doi.org/10.1007/s00428-018-2362-9

6. Perry L, Mathews C, Nugent E, Farrell R, Zorn K, Moore K. Outcomes of Cervical Cancer and Positive Para-aortic Lymph Nodes in the Modern Era of

Chemoradiation. *Int J Gynecol Cancer* 2014; 24:564-9. https://doi.org/10.1097/IGC.0000000000000093

7. Sapienza LG, Gomes MJL, Calsavara VF, Leitao Jr M, Baiocchi G. Does para-aortic irradiation reduce the risk of distant metastasis in advanced cervical cancer? A systematic review and meta-analysis of randomized clinical trials. *Gynecol Oncol.* 2017;144(2):312–7. https://doi.org/10.1016/j.ygyno.2016.11.044

8. Lin SY, Tsai CS, Chang YC, Ng K, Chang TC, Kao WH et al. The role of pretreatment FDG-PET in treating cervical cancer patients with enlarged pelvic lymph node (s) shown on MRI: a phase 3 randomized trial with longterm follow-up. *Int J Radiat Oncol Biol Phys* 2015;92(3):577–85. https://doi.org/10.1016/j.ijrobp.2015.02.027

9. Rotman M, Choi K, Guse C, Marcial V, Hornback N, John M. Prophylactic irradiation of the para-aortic lymph node chain in stage IIB and bulky stage IB carcinoma of the cervix, initial treatment results of RTOG 7920. *Int J Radiat Oncol Biol Phys* 1990;19(3):513–21. https://doi.org/10.1016/0360-3016(90)90475-y

10. Rotman M, Pajak TF, Choi K, Clery M, Marcial V, Grigsby P et al. Prophylactic extended-field irradiation of paraaortic lymph nodes in stages IIB and bulky IB and IIA cervical carcinomas. Ten-year treatment results. *JAMA.* 1995 Aug 2;274(5):387-93.

11. Chatani M, Matayoshi Y, Masaki N, Narumi Y, Teshima T, Inoue T. Prophylactic irradiation of para-aortic lymph nodes in carcinoma of the uterine cervix. A prospective randomized study. *Strahlentherapie Und Onkologie* 1995; 171(11):655–60.

12. Haie C, Pejovic MH, Gerbaulet A, Horiot J, Pourquier H, Delouche J et al. Is prophylactic para-aortic irradiation worthwhile in the treatment of advanced cervical carcinoma? Results of a controlled clinical trial of the EORTC radiotherapy group. *Radiot and Oncol* 1988;11(2): 101–12.

13. Thamronganantasakul K, Supakalin N, Kietpeerakool, Pattanittum P, Lumbiganon P. Extended-field irradiation for locally advanced cervical cancer. *Cochrane Database of Systematic Reviews* 2018(10): CD012301 https://doi.org/10.1002/14651858.CD012301.pub2

14. Asiri MA, Tunio MA, Mohamed R, Bayoumi Y, Alhadab A, Saleh R et al. Is extended-field concurrent chemoradiation an option for radiologic negative paraaortic lymph node, locally advanced cervical cancer?. *Cancer Management and Research* 2014;6:339–48. https://doi.org/10.2147/CMAR.S68262

15. Morris M, Eifel PJ, Lu J, Grigsby P, Levenback C, Stevens R et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *New England Journal of Medicine* 1999;340 (15):1137–43. https://doi.org/10.1056/NEJM199904153401501

16. Eifel PJ, Winter K, Morris M, Levenvack C, Grigsby P, Cooper J et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of Radiation Therapy Oncology Group trial (RTOG) 90-01. *J Clin Oncol.* 2004;22(5):872–80. https://doi.org/10.1200/JCO.2004.07.197

17. Tierney J, Neoadjuvant Chemotherapy for Cervical Cancer Meta-analysis Collaboration (NACCCMA) Collaboration, Rydzewska L, and Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group. Neoadjuvant chemotherapy for locally advanced cervix cancer. *Cochrane Database of Systematic Reviews* 2004(2):CD001774. https://doi.org/10.1002/14651858.CD001774.pub2

18. McCormack M, Kadalayil L, Hackshaw A, Hall-Craggs M, Symonds R, Warwick V et al. A phase II study of weekly neoadjuvant chemotherapy followed by radical chemoradiation for locally advanced cervical cancer. *Br J Cancer* 2013;108:2464–9. https://doi.org/10.1038/bjc.2013.230

19. McCormack et al. (NCT01566240) INTERLACE: A phase III multicentre trial of weekly induction chemotherapy followed by standard chemoradiation versus standard chemoradiation alone in patients with locally advanced cervical cancer. https://clinicaltrials.gov/ct2/show/NCT01566240 [accessed 1 January 2021]

20. Mileshkin L, Narayan K, Moore K, Rischin D, Trimble E, Stockler M et al. (NCT01414608) A phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: Outback (ANZGOG0902/GOG0274/RTOG1174). https://clinicaltrials.gov/ct2/show/NCT01414608 [accessed 1 January 2021].

21. Mileshkin L, Moore K, Barnes E, Gebski V, Narayan K, Bradshaw N et al. Adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: The randomized phase III OUTBACK Trial (ANZGOG 0902, RTOG 1174, NRG 0274). *J Clin Oncol* 2021 39:18_suppl, LBA3-LBA3 https://doi.org/10.1200/JCO.2021.39.15_suppl.LBA3

22. da Costa S, Bonadio R, Gabrielli F, Aranha A, Dias Genta M, Miranda V et al. Neoadjuvant Chemotherapy With Cisplatin and Gemcitabine Followed by Chemoradiation Versus Chemoradiation for Locally Advanced Cervical Cancer: A Randomized Phase II Trial. *J Clin Oncol.* 2019 Aug 26:JCO1900674. https://doi.org/10.1200/JCO.19.00674

23. Shimoji Y, Nagai Y, Toita T, Ariga T, Heianna J, Nakasone T et al. A Phase II Study of Neoadjuvant Chemotherapy Followed by Extended Field Concurrent Chemoradiotherapy for Para-aortic Lymph Node Positive Cervical Cancer. *Anticancer Research* 2020; 40 (6) 3565-70. https://doi.org/10.21873/anticanres.14346

24. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet.* 2009 May;105(2):103-4. https://doi.org/10.1016/j.ijgo.2009.02.012

25. FIGO Committee on Gynecologic Oncology. FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. *Int J Gynaecol Obstet.* 2014;125(2):97-8. https://doi.org/10.1016/j.ijgo.2014.02.003

26. Sturdza A, Potter R, Fokdal L, Haie-Meder C, Tan L, Mazeron R et al. Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. *Radiother Oncol 2016;120(3):428-33.* https://doi.org/10.1016/j.radonc.2016.03.011

27. Pötter R, Tanderup K, Kirisits C, Leeuw A, Kirchheiner K, Nout R et al. The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. *Clin Transl Radiat Oncol.* 2018 Jan 11;9:48-60 https://doi.org/10.1016/j.ctro.2018.01.001

28. Vargo JA, Kim H, Choi S, Sukumvanich P, Olawaiye A, Kelley J et al. Extended field intensity modulated radiation therapy with concomitant boost for lymph node positive cervical cancer: analysis of regional control and recurrence patterns in the positron emission tomography/computed tomography era. *Int J Radiat Oncol Biol Phys* 2014;90(5):1091–8. https://doi.org/10.1016/j.ijrobp.2014.08.013

29. Small W Jr, Winter K, Levenback C, Iyer R, Gaffney D, Asbell S et al. Extended-field irradiation and intracavitary brachytherapy combined with cisplatin chemotherapy for cervical cancer with positive para-aortic or high common iliac lymph nodes: results of ARM 1 of RTOG 0116. *Int J Radiat Oncol Biol Phys.* 2007 Jul 15;68(4):1081-7. https://doi.org/10.1016/j.ijrobp.2007.01.026

30. Small W, Winter K, Levenback C, Iyer R, Gaffney D, Asbell S et al. Extended-field irradiation and intracavitary brachytherapy combined with cisplatin and amifostine for cervical cancer with positive para-aortic or high common iliac lymph nodes: Results of arm II of Radiation Therapy Oncology Group (RTOG) 0116. *Int J Gynecol Cancer* 2011;21:1266-75. https://doi.org/10.1016/j.ijrobp.2007.01.026

31. Grigsby PW, Heydon K, Mutch DG, Kim R, Eifel P. Long-term follow-up of RTOG 92-10: Cervical cancer with positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys* 2001;15:982-7. https://doi.org/10.1016/s0360-3016(01)01723-0

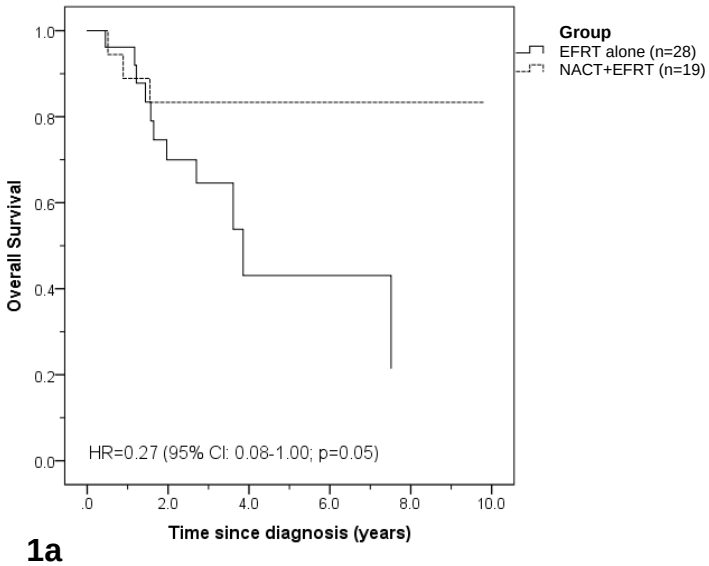
32. Liang JA, Chen SW, Hung YC, Yeh L-S, Chang W-C, Lin W-C et al. Low-dose, prophylactic, extended-field intensity-modulated radiotherapy plus concurrent weekly cisplatin for patients with stage IB2-IIIB cervical cancer, positive pelvic lymph nodes, and negative para-aortic lymph nodes. *Int J Gynecol Cancer* 2014;24:901-7. https://doi.org/10.1097/IGC.0b013e31829f4dc5

33. Singh R, Chander S, Mohanti B, Pathy S, Kumar S, Bhatla N et al. Neoadjuvant chemotherapy with weekly paclitaxel and carboplatin followed by chemoradiation

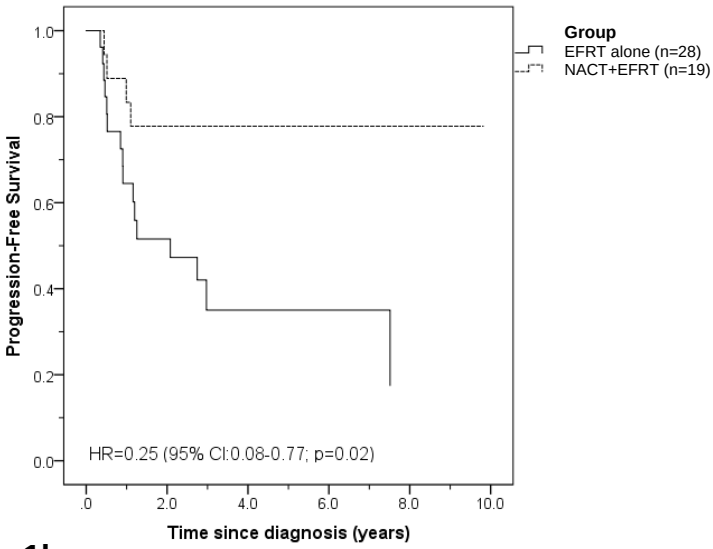
in locally advanced cervical carcinoma: a pilot study. *Gynecol Oncol* 2013;129:124–8. https://doi.org/10.1016/j.ygyno.2013.01.011

10. FIGURES

FIGURE 1



1a

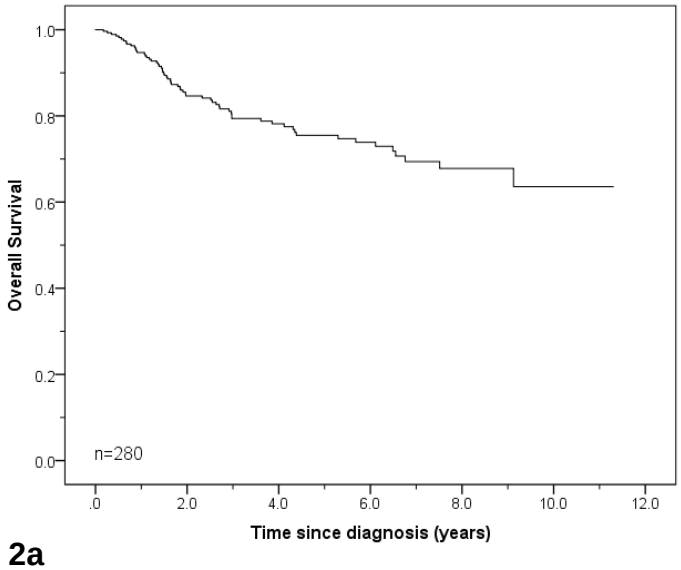


1b

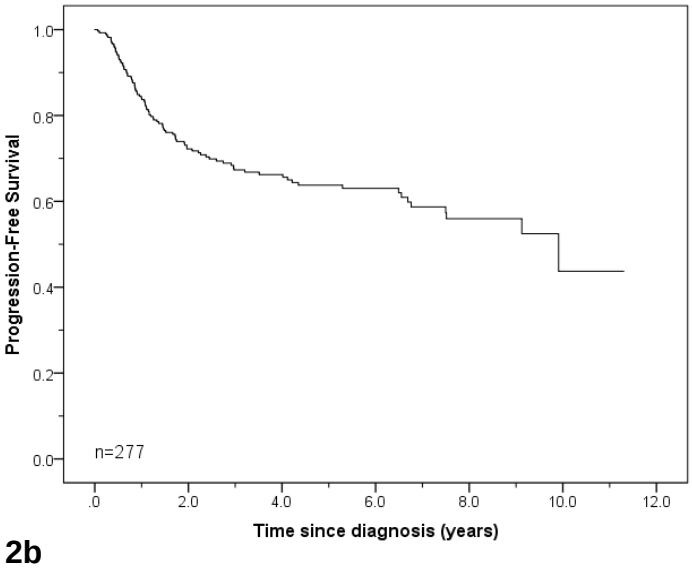
	Median follow-up	3-year OS (95% CI)	5-year OS (95% CI)	3-year PFS (95% CI)	5-year PFS (95% CI)
EFRT alone (n=28)	3.0 years	64.6% (44.6-84.6)	43.1% (15.3-70.9)	35.0% (14.0-56.0)	35.0% (14.0-56.0)
NACT+EFRT (n=19)	4.8 years	83.3% (66.1-100)	83.3% (66.1-100)	77.8% (58.6-97.0)	77.8% (58.6-97.0)

Figure 1: Kaplan-Meier curves of OS [1a] and PFS [1b] comparing neoadjuvant chemotherapy/extended-field group/NACT+EFRT (n=19, 3 OS events, 4 PFS events) versus extended-field alone group/EFRT (n=28, 11 OS events, 16 PFS events).

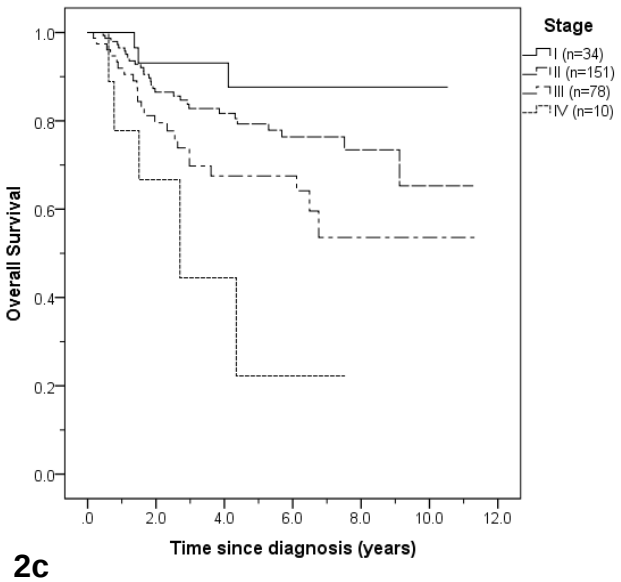
FIGURE 2



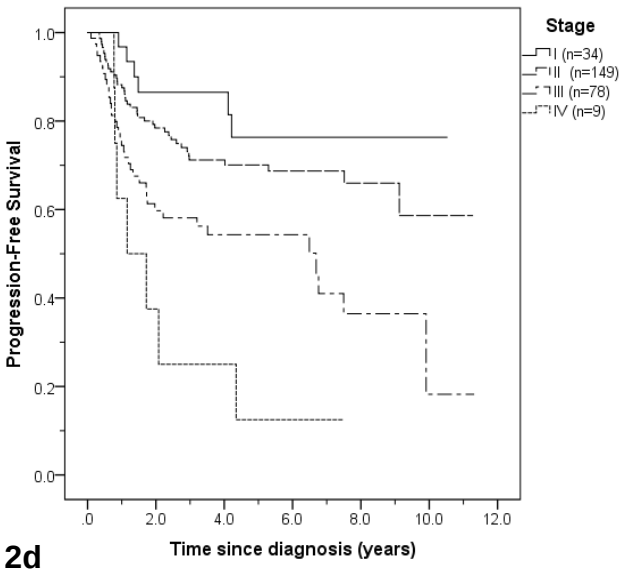
2a



2b



2c

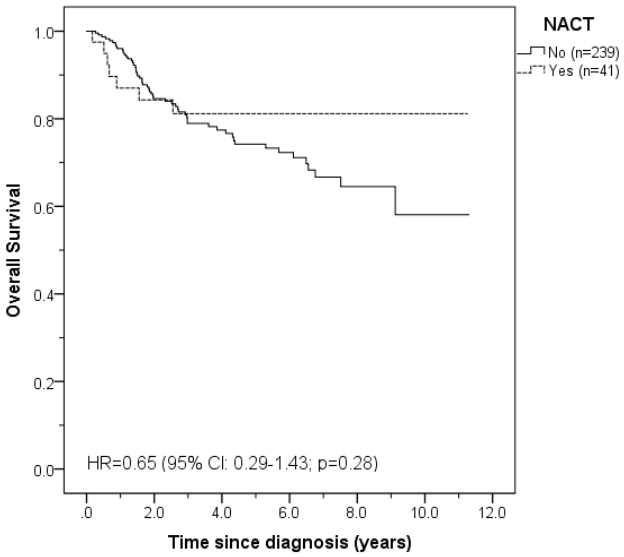


2d

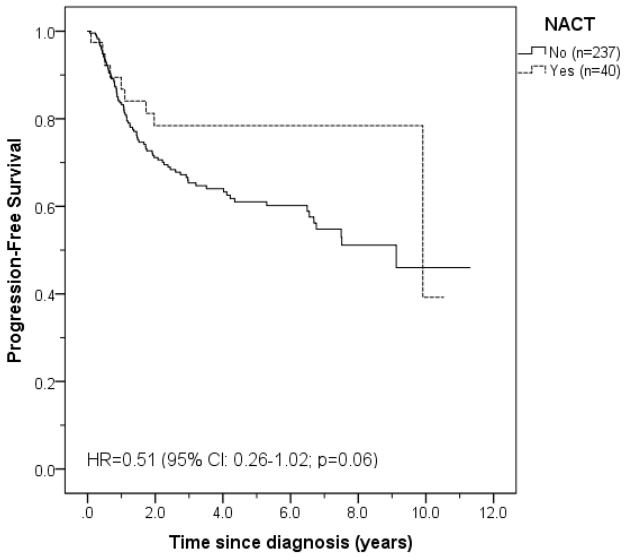
	Median follow-up	3-year OS (95% CI)	5-year OS (95% CI)	3-year PFS (95% CI)	5-year PFS (95% CI)
All patients (n=298)	4.7 years	79.4% (74.1-84.7)	75.5% (69.6-81.4)	67.3% (61.4-73.2)	63.8% (57.5-70.1)

Figure 2: Kaplan-Meier curves of OS [2a] and PFS [2b] for this 10-year institutional case-series of patients with locally advanced cervical cancer treated with radical chemoradiotherapy or radical radiotherapy (excluding INTERLACE patients, N=298 where available), and by FIGO stage (OS, 2c; PFS, 2d).

FIGURE 3



3a



3b

Figure 3: Kaplan-Meier curves of OS [3a] and PFS [3b] comparing neoadjuvant chemotherapy versus no neoadjuvant chemotherapy for all radically-treated locally advanced cervical cancer patients (excluding INTERLACE patients, N=298 where available). Median follow-up for neoadjuvant chemotherapy patients was 5.0 years and 4.6 years for patients who did not receive neoadjuvant chemotherapy.