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Risk factors for pelvic and distant recurrence in locally advanced cervical cancer

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ABSTRACT

Objective: Despite the benefits of concomitant radiotherapy and cisplatin for locally advanced cervical cancer, recurrence rates remain high. New treatment strategies such as consolidation chemotherapy and different concomitant chemotherapy combinations have been tested in recent years. Identification of the best candidates for each treatment strategy could optimize results.

Study design: A retrospective review of data from 127 patients with locally advanced cervical cancer (International Federation of Gynecology and Obstetrics Stages IIB–IVA), treated at a single institution from 2005 to 2014. Risk factors for loco-regional and systemic recurrence, and prognostic factors for overall survival (OS) were analysed using Cox regression. Survival of patients treated with consolidation chemotherapy was compared with survival of patients not treated with consolidation chemotherapy in the role cohort and in a propensity-score-matched cohort.

Results: With a median follow-up time of 48.7 months, loco-regional-recurrence-free survival (LRFS), distant-metastasis-free survival (DMFS) and OS at 5 years were 76.6%, 54.0% and 63.0%, respectively. On multivariate analysis, tumour size ≥6 cm was associated with shorter LRFS [hazard ratio (HR) 5.18; 95% confidence interval (CI) 1.45–18.45; $p = 0.011$], and adenocarcinoma (HR 2.48; 95% CI 1.10–5.57; $p = 0.028$) and positive lymph nodes (HR 2.21; 95% CI 1.303–4.72; $p = 0.041$) were associated with shorter DMFS. Tumour size ≥6 cm was associated with shorter OS (HR 2.64; 95% CI 1.09–6.35; $p = 0.031$). Twenty-two patients were treated with consolidation chemotherapy; on univariate analysis, these patients had longer OS compared with patients who were not treated with consolidation chemotherapy ($p = 0.043$). In a propensity-score-matched cohort, patients treated with consolidation chemotherapy had longer DMFS and OS compared with patients who were not treated with consolidation chemotherapy, although the difference was not significant.

Conclusions: Different risk factors are associated with loco-regional and distant metastases in patients with locally advanced cervical cancer, and could potentially lead to particular therapeutic strategies. Although the number of patients treated with consolidation chemotherapy in the study cohort was small, they seemed to live longer and to have better control of distant relapse then patients who were not treated with consolidation chemotherapy.

Introduction

Despite effective preclinical screening and human papillomavirus vaccination, uterine cervical cancer remains a global health problem. Worldwide, there were 528,000 new cases and 266,000 deaths due to cervical cancer in 2012, with a heavier burden in developing countries [1]. In Brazil, cervical cancer is the third most

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common neoplasia in women, with 16,370 new cases expected in 2018 [2].

Radiotherapy with concomitant cisplatin (RTCT) has become the standard treatment for bulky and locally advanced cervical cancer. Several trials have demonstrated reduced local recurrence, distant recurrence and overall survival (OS) with the addition of chemotherapy to radiation [3–8]. However, even with optimized treatment, recurrence rates remain high, with only two-thirds of patients remaining disease-free in the long term. In a Gynecologic Oncology Group (GOG) study, 120 patients treated with RTCT had progression-free survival (PFS) of 60% at 5 years [9], and a Korean study found that patients treated with RTCT had PFS of 67% at 4 years [10]. Despite the fact that local relapse and single-site distant recurrence is potentially curable with salvage treatment, most relapsed patients will succumb to the disease.

A contemporaneous randomized study showed better OS with addition of consolidation chemotherapy after chemoradiotherapy (CRT) for locally advanced patients, mainly due to improved control of metastatic disease (8.1% vs 16.4%) [11]. Another study compared CRT alone with CRT followed by two cycles of adjuvant cisplatin plus paclitaxel for International Federation of Gynecology and Obstetrics (FIGO) Stages IIB–IVA cervical adenocarcinoma. Patients who received adjuvant treatment showed significantly longer disease-free survival, and long-term local and distant tumour control [12].

These studies suggest that treatment intensification could enhance patient outcomes. There is an unmet need to identify prognostic factors to select patients who may benefit from intensified treatment, and which treatment intensification strategy should be pursued in order to improve disease control and spare non-benefiting patients from untoward side-effects. This study aimed to evaluate prognostic factors in patients harbouring locally advanced uterine cervical cancer treated with curative radiotherapy.

Materials and methods

Patients

This study was approved by the Research Ethics Committee at the A.C. Camargo Cancer Center, São Paulo, Brazil. Patients were identified retrospectively from an electronic database. The inclusion criteria were as follows: pathology-confirmed cervical cancer; locally advanced disease (FIGO Stages IIB–IVA); no evidence of metastatic disease on computerized tomography of thorax, abdomen and pelvis; and definitive treatment with radiotherapy starting in the period from January 2005 until May 2014. Patients with metastatic disease, rare histologies (neuroendocrine, sarcoma), or lacking sufficient data regarding date of diagnosis or use of concomitant chemotherapy were excluded.

Treatment

At the study institution, patients with locally advanced disease are treated with external pelvic radiotherapy given as a 1.8-Gy fraction daily, 5 days per week, up to the total dose of 50.4 Gy. After external radiotherapy, patients receive high-dose-rate brachytherapy in four fractions of 7.0 Gy to a total dose of 80 Gy to Point A. Cisplatin at a dose of 40 mg/m^2 is infused weekly during radiotherapy for a minimum of five cycles. Since 2011, the use of consolidation chemotherapy with two cycles of cisplatin 50 mg/m^2 D1 and gencitabine 1000 mg/m^2 D1 and 8 every 21 days for two cycles has been an option, at the discretion of the treating physician.

Clinical data and endpoints

The following data were collected from all patients: age; Eastern Cooperative Oncology Group (ECOG) performance status at the beginning of treatment; histology; tumour size; lymph node status; dose of radiotherapy planned; duration of radiotherapy; use of concomitant chemotherapy; and use of adjuvant chemotherapy. The FIGO stage as identified at gynaecological examination was used. No patient received surgical staging for para-aortic lymph nodes. Patients are routinely staged with abdomen and pelvis computed tomography, magnetic resonance imaging or positron emission tomography.

The primary endpoint was distant-metastasis-free survival (DMFS) and loco-regional-recurrence-free survival (LRFS). The secondary endpoint was OS. DMFS and LFRS were calculated from diagnosis until the identification of distant metastasis and loco-regional relapse, respectively. OS was calculated from diagnosis until death for any reason. Loco-regional relapse was defined as recurrence or progression within the pelvis. Distant relapse was defined as recurrence outside the pelvis.

Statistical analysis

Clinical data were tabulated, and groups who received similar treatments were compared. Chi-squared test and Fisher's exact test were used for comparison of categorical data. Survival curves for LRFS, DMFS and OS were constructed using the Kaplan–Meier method and compared using the log-rank test. A Cox proportional hazards regression model was used for multivariate analysis; all variables with $p < 0.05$ on univariate analysis were included in the multivariate analysis.

In order to evaluate the benefit of consolidation chemotherapy, propensity score matching was performed, and LMFS, DMFS and

Table 1
Clinical characteristics of study patients ($n = 127$).

Characteristic	Frequency (%)
Age (years), median (range)	50.8 (24.3–85.5)
≤60	93 (73.2)
>60	34 (26.8)
ECOG performance status	
0	79 (62.2)
1	30 (23.6)
Histology	
Squamous cell carcinoma	104 (81.9)
Adenocarcinoma	18 (14.2)
Unknown	5 (3.9)
Grade	
1	6 (4.7)
2	48 (37.8)
3	34 (26.8)
Unknown	39 (30.7)
FIGO Stage	
IIB	59 (46.5)
IIIA	4 (3.1)
IIIB	47 (37.0)
IVA	12 (9.4)
IVB	4 (3.1)
Unknown	1 (0.8)
Tumour size (cm), median	5.3
<6	59 (46.5)
≥6	21 (16.5)
Unknown	47 (37.0)
Lymph nodes	
Negative	43 (33.9)
Pelvic	55 (43.3)
Para-aortic	4 (3.1)
Unknown	25 (19.7)
Concurrent chemotherapy	
No	20 (15.7)
Yes	105 (82.7)
Consolidation chemotherapy	
No	94 (74.0)
Yes	21 (18.3)

ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.

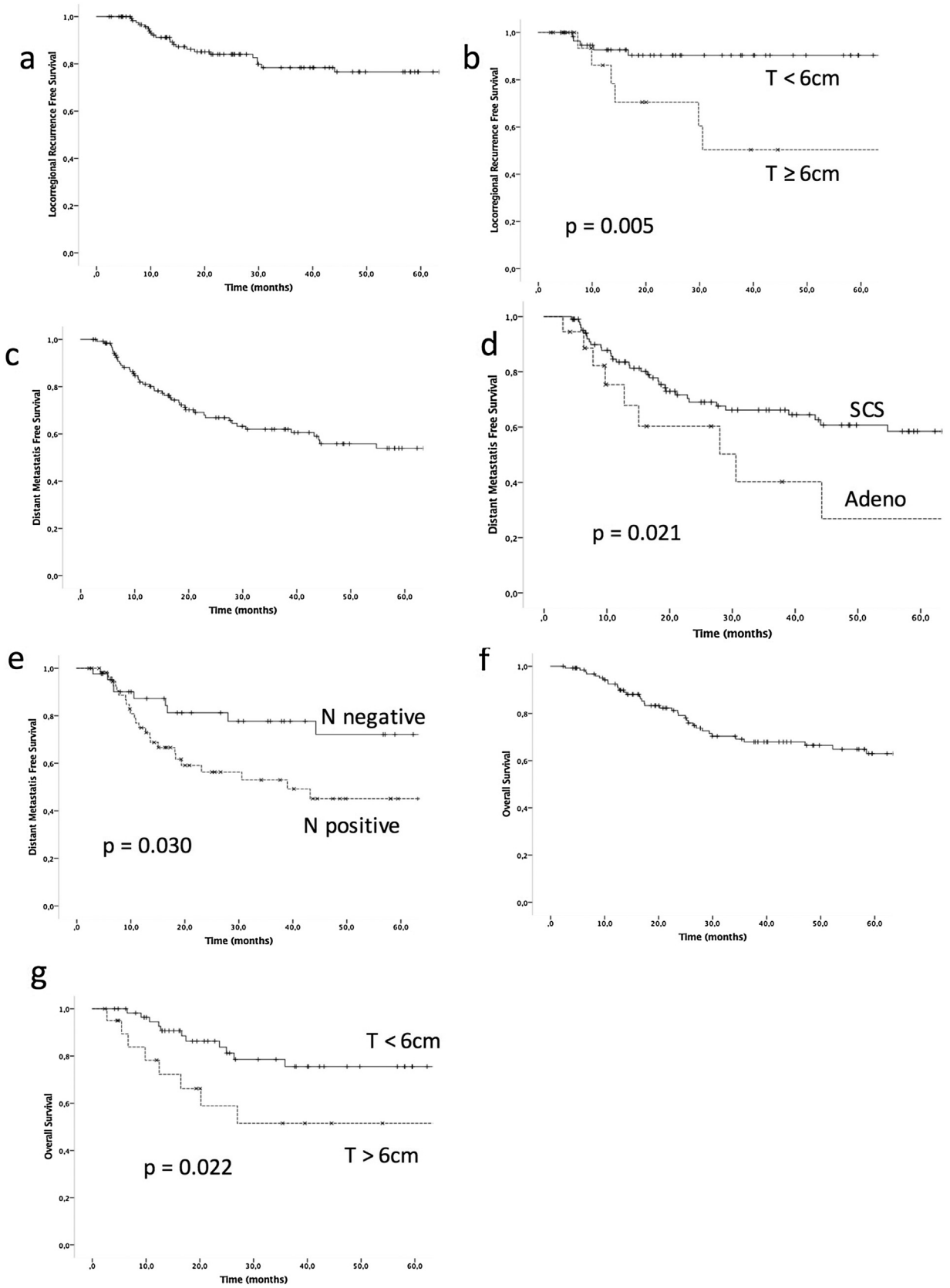

Fig. 1. Loco-regional-recurrence-free survival (LRFS), distant-metastasis-free survival (DMFS) and overall survival (OS). (A) LRFS in the role cohort. (B) LRFS according to tumour size (T). (C) DMFS in the role cohort. (D) DMFS according to histology. (E) DMFS according to lymph nodes (N). (F) OS in the role cohort. (G) OS according to tumour size (T). *p*-values were calculated using log rank test. SCS, squamous cell carcinoma.

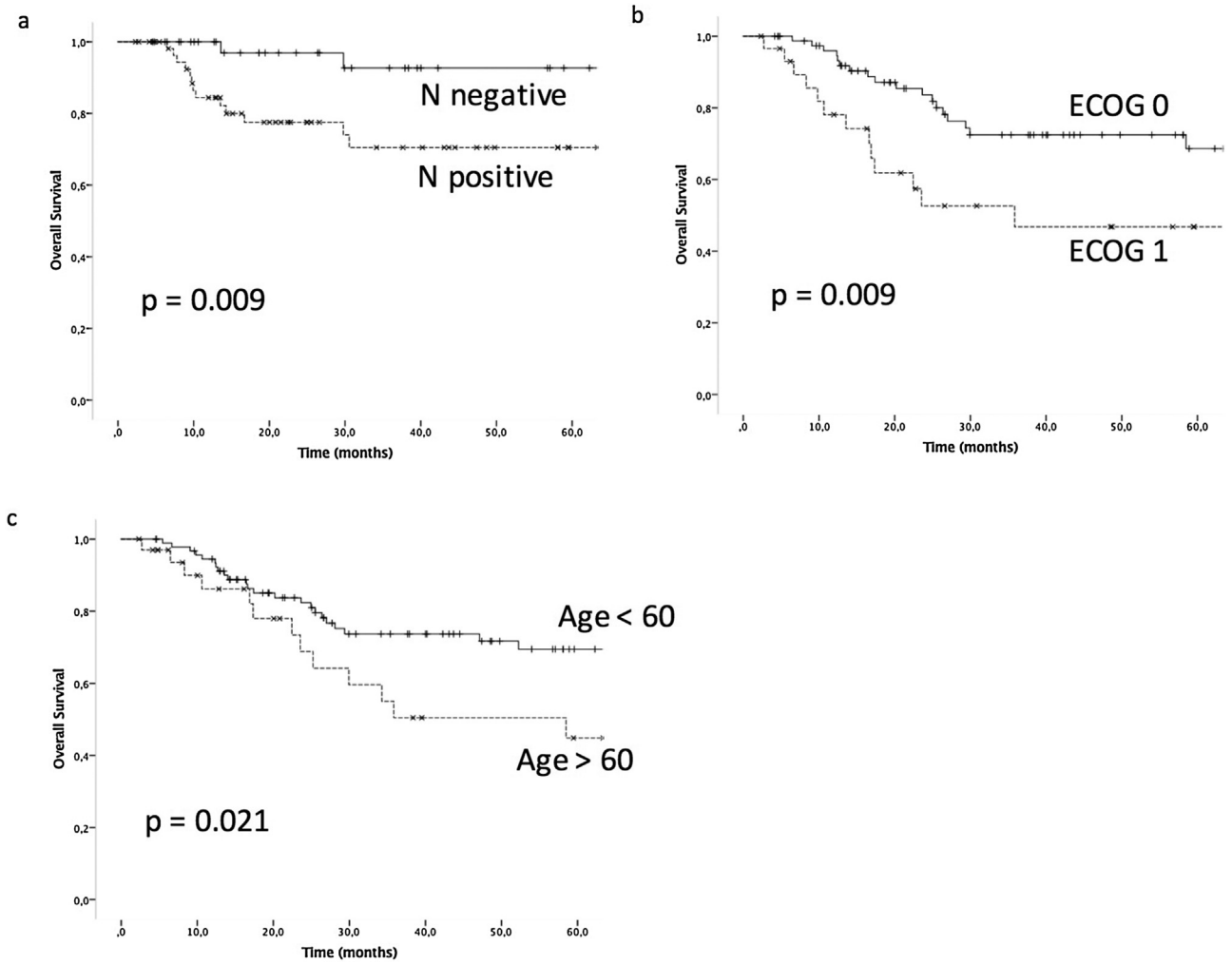

Fig. 2. Loco-regional-recurrence-free survival (LRFS) and overall survival (OS). (A) LRFS according to lymph nodes. (B) OS according to Eastern Cooperative Oncology Group (ECOG) performance status. (C) OS according to age. *p*-values were calculated using log rank test. N, lymph nodes.

OS were compared between patients treated with consolidation chemotherapy and patients who were not treated with consolidation chemotherapy.

One-sided *p*-values <0.05 were considered to indicate significance. All statistical analyses were performed using SPSS Version 21.0 (IBM Corp., Armonk, NY, USA).

Results

One hundred and twenty-seven patients were included in this study. Their clinical and pathological characteristics are summarized in Table 1. Briefly, the median age was 50.8 years, with preponderance of squamous cell carcinoma (81.9%). FIGO Stage IIB was the most common stage (46.5% of cases) and 46.4% of patients had positive lymph nodes. Para-aortic lymph node staging was undertaken by computed tomography in 26 patients (20.5%), by magnetic resonance imaging in 61 patients (48.0%), and by positron emission tomography in 10 patients (7.9%). Thirty patients (23.6%) did not have data on para-aortic staging.

Prognostic factors for loco-regional-recurrence-free survival

After a median follow-up of 48.7 months, 29 (22.8%) patients had loco-regional relapse. LRFS was 78.5% at 3 years and 76.6% at 5 years (Fig. 1A). Univariate analysis for LRFS confirmed that tumour size ≥6 cm and positive lymph nodes were associated with shorter LRFS (Figs. 1B, 2 A and B; also see Table A, online supplementary material). On multivariate analysis, only tumour size ≥6 cm remained independently associated with shorter LRFS [hazard ratio (HR) 5.18; 95% confidence interval (CI) 1.45–18.45; $p = 0.011$] (Table 2).

Prognostic factors for distant-metastasis-free survival

Fifty-one patients (40.2%) had a distant relapse. The most common sites of distant relapse were lymph nodes and lung, followed by bone, peritoneum and liver (Table 3). DMFS was 62.0% at 3 years and 54.0% at 5 years (Fig. 1C). Univariate analysis for DMFS confirmed that adenocarcinoma and positive lymph nodes were associated with shorter DMFS (Fig. 1D and 1E; also see Table B, online supplementary material), and both factors withstood multivariate analysis (increased adenocarcinoma: HR 2.48; 95% CI 1.10–5.57; $p = 0.028$; positive lymph nodes: HR 2.21; 95% CI 1.303–4.72; $p = 0.041$) (Table 2).

Prognostic factors for overall survival

Fifty-five patients had died (30.86%). OS was 67.9% at 3 years and 63.0% at 5 years, and the median has not been reached for the entire population (Fig. 1F). Age >60 years, ECOG performance status >0 and tumour size ≥6 cm were associated with shorter OS

Table 2
Multivariate analysis.

	LRFS[a]		DMFS[b]		OS[c]	
Characteristic	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (years)						
<60	–	–	–	–	1	0.897
≥60	–		–		1.07 (0.38–2.98)	
ECOG performance status						
0	–	–	–	–	1	0.051
≥1	–		–		2.55 (1.00–6.55)	
Histology						
Squamous cell carcinoma	–	–	1	0.028	–	–
Adenocarcinoma	–		2.48 (1.10–5.57)		–	
FIGO Stage						
≤IIB	–	–	–	–	–	–
≥IIIA	–		–		–	
Tumour size (cm)						
<6	1	0.011	–	–	1	0.031
≥6	5.18 (1.45–18.45)		–		2.64 (1.09–6.35)	
Lymph nodes						
Negative	1	0.088	1	0.041	–	–
Positive	6.08 (0.76–48.41)		2.21 (1.03–4.72)	–	–	
Concomitant chemotherapy						
No	–	–	–	–	–	–
Yes	–		–		–	
Consolidation chemotherapy						
No	–	–	1	0.073		
Yes	–		0.38 (0.13–1.09)			

LRFS, loco-regional-recurrence-free survival; DMFS, distant-metastasis-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.
[a] Sixty-seven patients included in the model with 10 events.
[b] Ninety-eight patients included in the model with 33 events.
[c] Eighty-four patients included in the model with 22 events.

Table 3
Sites of disease recurrence.

Recurrence site	Frequency (%)
Pelvic recurrence	29 (22.8)
Distant recurrence	51 (40.2)
Para-aortic lymph nodes	32 (25.2)
Supraclavicular lymph nodes	3 (2.4)
Other lymph nodes	10 (7.9)
Lung	21 (16.5)
Bone	17 (13.4)
Peritoneum	10 (7.9)
Liver	10 (7.9)
Central nervous system	3 (2.4)
Skin and subcutaneous	2 (1.6)
Pleura	1 (0.8)

on univariate Cox regression analysis (Figs. 1G, 2C and D; also see Table C, online supplementary material). On multivariate analysis, only tumour size ≥6 cm remained independently associated with shorter OS (HR 5.18; 95% CI 1.45–18.45; $p = 0.011$) (Table 2).

Role of consolidation chemotherapy

Twenty-two patients were treated with consolidation chemotherapy. In the role cohort, consolidation chemotherapy was not associated with OS on Cox regression, but Kaplan–Meier curves showed that the survival of patients treated with consolidation chemotherapy diverges from the survival of patients not treated with consolidation chemotherapy ($p < 0.05$, log rank test) (Fig. 3).

Patients treated with consolidation chemotherapy were younger and presented with more advanced disease (Table D, see online supplementary material). In order to account for selection bias, propensity score matching of 22 patients who were not treated with consolidation chemotherapy was undertaken with the 22 patients treated with consolidation chemotherapy. In the matched

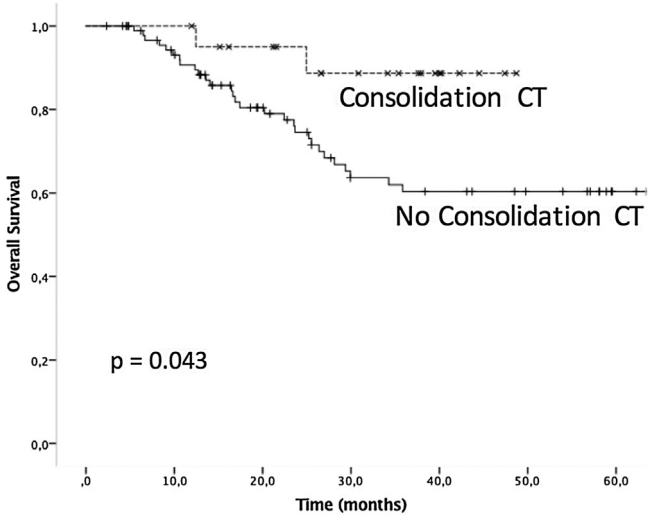

Fig. 3. Overall survival in the subgroup of patients with locally advanced disease according to use of consolidation chemotherapy (CT). *p*-values were calculated using log rank test.

cohort, the consolidation chemotherapy group showed better DMFS (median DMFS 66.1 months vs not reached; $p = 0.233$) and OS (median OS 75.5 months vs not reached; $p = 0.113$), with no difference in LRFS (median not reached in either group; $p = 0.550$), although the differences were not significant (Fig. 4).

Discussion

Cervical cancer remains a disease with high rates of relapse when it is diagnosed at an advanced stage, despite treatment optimization. Therefore, information about prognostic factors is important to

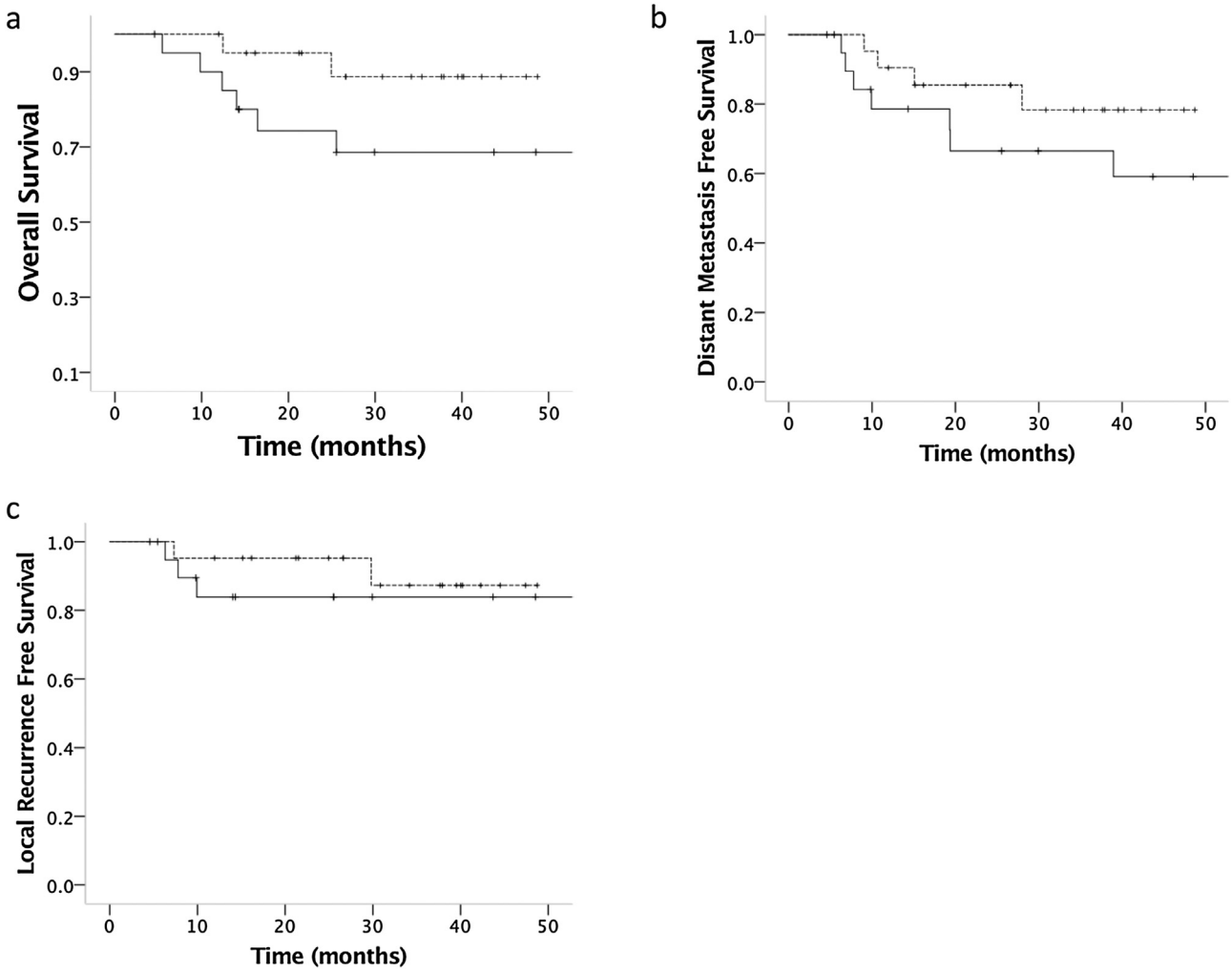

Fig. 4. Survival outcomes according to consolidation chemotherapy in the propensity-score-matched cohort. (A) Overall survival. (B) Distant-metastasis-free survival. (C) Loco-regional-recurrence-free survival. *p*-values were calculated using log rank test.

identify patients who may benefit from new therapeutic strategies. This study analysed prognostic factors for local recurrence, distant recurrence and OS in patients treated with curative radiotherapy. Tumour size ≥6 cm was associated with increased risk of loco-regional relapse, and adenocarcinoma and positive lymph nodes were associated with increased risk of distant relapse. Tumour size ≥6 cm was the only factor associated with worse OS.

According to the study results, tumour size ≥6 cm is a major risk factor for loco-regional relapse, increasing the risk of loco-regional relapse by 5.18 times. Tumour size is a known prognostic factor for early-stage disease. Large clinical tumour diameter was included as a risk factor for use as a criterion to indicate radiotherapy after surgery in cervical cancer [13]. However, few studies have demonstrated a prognostic relationship in patients with more advanced disease in the era of CRT. A retrospective analysis of several GOG trials dealing with external radiotherapy and brachytherapy assessed the risk factors for pelvic recurrence through logistic regression, and their nomogram suggested that FIGO stage and tumour size were the two most important factors related to pelvic recurrence [14]. A Korean series with 397 patients with FIGO Stages IB–IVA cervical cancer treated with CRT confirmed the role of tumour size, histology and age for loco-regional relapse. Notably, FIGO stage was not related to pelvic recurrence [15]. The present study failed to show a clear association between FIGO stage, age or non-squamous histology and loco-regional recurrence on multivariate analysis, which may be related to the sample size of the study or a stronger association between tumour size and loco-regional relapse than between FIGO stage and loco-regional relapse. One recent series identified tumour size as the main factor for PFS, while FIGO stage was not a significant prognostic factor [16]. Notwithstanding this, this study confirmed that tumour size was the most important factor associated with loco-regional recurrence.

This study found that adenocarcinoma and positive lymph nodes were independently associated with shorter DMFS, underscoring the current evidence. Only a few other retrospective studies have examined the risk factors for distant recurrence in locally advanced cervical cancer. The largest of these studies [17] evaluated 549 women with bulky and locally advanced cervical cancer treated with CRT, and also identified pelvic lymphadenopathy and non-squamous cell histology as prognostic factors. They built a nomogram based on Cox regression analysis identifying the following four parameters that were significantly associated with distant recurrence: pelvic and para-aortic nodal positivity on fluorodeoxyglucose positron emission tomography; non-squamous cell histology; and pretreatment serum squamous cell carcinoma antigen levels [17]. Schmidt et al. found that FIGO stage, lymph node status and the extent of tumour regression during treatment were significant predictors for DMFS [18]. A third study found that only serum squamous cell carcinoma antigen levels were associated with distant recurrence [19]. Lymph node metastasis was found to be the most relevant risk factor for distant recurrence in previous studies and the present study.

Approximately 20% of the study sample had adenocarcinoma, in line with several other cohorts. Studies in early-stage cervical cancer showed that adenocarcinoma carries a worse prognosis, with 10–20% lower 5-year survival than squamous cell cancer [20]; this may be related to a higher tendency for metastatic spread [21]. The present study and Kang et al. [17] found that non-squamous histology has a higher risk of distant metastasis in locally advanced disease. Indeed, one positive retrospective study of consolidation chemotherapy in locally advanced disease included adenocarcinoma alone [12].

Tumour size ≥6 cm was the single independent factor associated with OS on multivariate analysis. Although age and ECOG performance status were associated with OS on univariate analysis, tumour size showed the strongest association [22].

Consolidation chemotherapy has been used increasingly at the study institution, and despite the limited number of patients ($n = 22$) treated with consolidation chemotherapy for locally advanced disease, these patients were found to have better OS on univariate analysis. However, this difference was not significant on multivariate analysis. After propensity score matching, consolidation chemotherapy patients had longer DMFS and OS (not significant) and no difference in LRFS. The small number of patients in the matched cohort limits definitive conclusions. This is in accordance with the OS benefit seen in one phase 3 trial [11] and a few retrospective studies [12,23].

The present study has limitations due to its retrospective nature, such as data incompleteness, selection bias and the inherent imbalance between groups in a retrospective cohort study. The authors sought to circumvent such imbalances with the Cox regression analyses. Despite this, all patients were staged and treated according to contemporaneous guidelines, with few (15.7%) patients who were not treated with concomitant cisplatin to radiotherapy, most likely due to impending comorbidities.

A 5-year OS rate of 63.0% is in accordance with phase III trials concerning RTCT [4,6,11,24]. A strength of this study was the prolonged and detailed follow-up with data on recurrence for different sites, allowing the authors to consider this under-evaluated endpoint in detail.

Taken together, the study findings support the hypothesis that locally advanced uterine cervical cancer encompasses a heterogeneous group of diseases. Some patients may have a higher risk of loco-regional relapse, while other patients may have a higher risk of distant relapse, with both mechanisms contributing to unsatisfactory outcomes of currently available treatments. Clear understanding and identification of the risk of relapse in specific sites could provide treatment tailoring using consolidation chemotherapy, newer radiotherapeutic techniques, surgery or even new systemic agents to be used concomitantly to radiotherapy.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2019.01.028.

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