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Curative treatment for stage IIIC2 cervical cancer: what to expect?

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ABSTRACT

Background: Since the GOG125 study, treating radically patients with positive para-aortic lymph nodes has been a valid approach. Nevertheless, literature lacks data on how to better treat these patients since they are usually excluded from trials. In this study, we aimed to report the outcomes of patients with advanced cervical cancer and positive para-aortic lymph nodes (PAN) treated in a single tertiary/academic institution and try to identify variables that may impact survival.

Materials and methods: We retrospectively reviewed patients with positive para-aortic lymph nodes treated in our institution. Demographic variables and treatment options were assessed and their impact on overall survival (OS), locorregional control, distant metastasis free survival, and para-aortic lymph node progression was analyzed.

Results: We assessed 65 patients treated from April 2010 to May 2017. Median OS was 38.7 months. Median locorregional and para-aortic progression free survivals were not reached. Median distant metastasis progression-free survival was 64.3 months. Better ECOG performance status ($p > 0.001$), concurrent chemotherapy ($p = 0.031$), and brachytherapy ($p = 0.02$) were independently related to better overall survival.

Conclusion: Patients with current stage IIIC2 cervix cancer may present long term survival. Treating positive PAN cervical cancer patients with concurrent chemoradiation including brachytherapy with curative intent should be standard. Poor PS and more advanced pelvic disease may represent a higher risk for worse outcomes. Distant metastases are still a challenge for disease control.

Key words: cervical cancer; retroperitoneal lymph node; brachytherapy; para-aortic

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Introduction

Para-aortic lymph nodes (PAN) are regional drainage for cervical cancer, but disease affecting these nodes often translates into lower survival [1]. Different surgical cohorts have described the frequency of this finding [2]. Technological advances allowed an increased sensibility in detecting such positive nodes [3], such as the use of fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}FDG-PET-CT scans), but with no impact on survival [3].

Older studies have tested whether prophylactic treatment of theses lymph nodes have an impact on survival, such as the Eastern Organization for Research and Treatment of Cancer (EORTC)

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[4] and the Radiation Therapy Oncology Group (RTOG) 7920 [5]. Others have approached whether patients with positive PAN at diagnosis could be cured. The GOG125 [6], a phase II study, was primarily conducted to determine whether PAN can safely be treated when positive lymph nodes are found. However, these studies used older technology and smaller radiation doses than those currently used for cervical cancer treatment, besides the small sample of only 85 patients in the GOG125. Thus, the question regarding the curability and best approach for these patients remained unsolved.

Patients with positive PAN are often excluded from prospective studies. One of the most important current trials on cervical cancer, the EMBRACE trial, excludes patients with positive retroperitoneal lymph nodes above the L2 vertebrae [7]. In other trials, such as the on-going phase III ANZGOG-0902/GOG0274/RTOG-1174 trial of adjuvant chemotherapy in advanced cervical cancer patients treated with concurrent chemoradiation, positive PAN is an exclusion criterion. On the other hand, the Gynecologic Oncology Group (GOG) and the NRG Oncology are accruing patients with para-aortic disease for a phase I trial which intends to provide radical treatment to these patients, with radiotherapy, concurrent and adjuvant chemotherapy, and brachytherapy [8]. Nevertheless, there is a gap in the literature of prospective good quality trials with this population.

The simple characterization of patients with positive PAN as either curative or palliative candidates has been troublesome. The seventh edition of the American Joint Committee on Cancer (AJCC 7th) [9] shows positive PAN as a metastatic disease, classifying it as stage IV, whereas the 9th edition [10] changes this paradigm and includes PAN positive patients in stage IIIC, differentiating these patients from those with distant metastasis. With that decision, AJCC clearly points positive PAN as a curable disease, even though with a low disease-free survival rate.

In this study, we aimed to report the outcomes of patients with advanced cervical cancer and positive PAN treated in a single tertiary/academic institution and try to identify variables that may impact survival.

Materials and methods

This study was approved by the local ethics committee in April 2021.

We conducted a retrospective study of patients with advanced cervical cancer, current FIGO stage IIIC2 (AJCC any T N2 M0) treated in a university hospital. All patients had biopsy proven cervical cancer and were treated with curative intent. PAN were evaluated by imaging and characterized as positive if larger than 1cm in any diameter in the staging computed tomography (CT). Three-year minimum follow-up was required. Patients with distant metastasis were excluded from analysis.

Radiotherapy (RT) and chemotherapy followed the institutional protocol: 45–50.4 Gy to pelvic and para-aortic fields, with a boost up to 60 Gy to macroscopic nodal disease. If brachytherapy was indicated, 4 fractions of 7–7.5Gy to point A were delivered. If not, a boost on primary site would be done up to 59.4 Gy. Concurrent chemotherapy, when delivered, was with weekly cisplatin (40 mg/m^2).

Demographic and treatment variables were collected. Demographic variables included age, Eastern Cooperative Oncology Group (ECOG) performance status scale, histology, pelvic stage, and the presence of hydronephrosis. Treatment variables included radiotherapy fields and doses, surgical procedures, and chemotherapy, concurrent or not.

Statistical analysis consisted of descriptive and frequencies analysis. Oncological outcomes: overall survival (OS), pelvic disease-free survival (PDFS), paraortic lymph node progression (PANP) and distant metastasis free survival (DMFS) were assessed from the first day of radiotherapy until the event. The Kaplan-Meier method was used for the survival analyses. The log-rank test was used for univariate and Cox regression for multivariate analysis.

This report follows the reporting guidelines of the STROBE [11] statement.

Results

In the study period, 65 patients fulfilled the inclusion criteria and were analyzed. Mean age at diagnoses was 53 years (range 32 to 95 years). Most patients had ECOG performance status of 0 or 1 (83.1%), and squamous cell carcinoma (90.8%). Hydronephrosis was present in 44.6% at diagnosis and 41.5% were stage T4.

Table 1. Demographic and treatment characteristics. The p values stand for the correlation between each variable with brachytherapy treatment group

Patients characteristics	
Age	
< 60 years	45 (69.2%)
≥ 60 years	20 (30.7%)
ECOG	
0–1	54 (83.1%)
2 or more	11 (16.9%)
T stage	
T1 < 4cm	0
T1b2	0
T2a	1 (1.5%)
T2b	28 (43.1%)
T3a	4 (6.2%)
T3b	5 (7.7%)
T4	27 (41.5%)
T4	
No spread	38 (58.5%)
Spread to pelvic organs	27 (41.5%)
Pelvic nodal disease	
No	1 (1.5%)
Yes	64 (98.5%)
Hydronephrosis	
No	36 (55.4%)
Yes	29 (44.6%)
Histology	
Squamous	59 (90.8%)
Adenocarcinoma	4 (6.2%)
Other	2 (3.0%)
Radiation dose	
< 45 Gy	2 (3.0%)
≥ 45 Gy	63 (97.0%)
Para-aortic field	
No	9 (13.8%)
Yes	56 (86.2%)
Chemotherapy (concurrent)	
No	21 (32.3%)
Yes	44 (67.7%)

ECOG — Eastern Cooperative Oncology Group

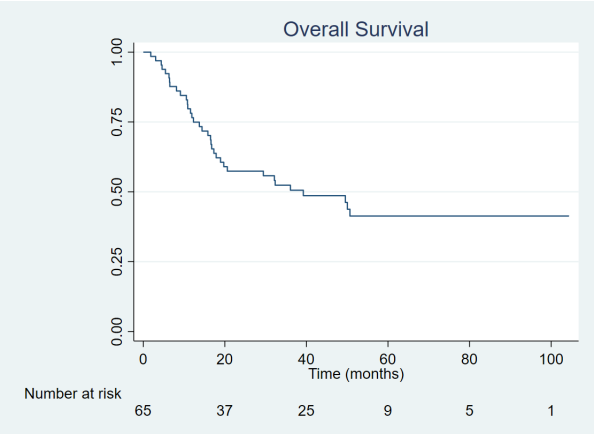

Figure 1. Overall survival (mean 39.2 months)

Radiotherapy and chemotherapy followed the institutional protocol. Only two patients received less than 45 Gy of external beam irradiation and the median RT dose was 57 Gy. Intensity modulation technique (IMRT) was used in only three patients and all the others were treated with 3D external beam radiotherapy technique. Brachytherapy was performed in 44 (67.7%) patients, all with 2D conventional planning. Concurrent chemoradiation was delivered in 44 (67.7%) patients, and 31 (47.7%) received second line chemotherapy. Four (6.2%) patients were submitted to salvage surgery during follow-up. Demographic and treatment characteristics are depicted in Table 1.

With a median follow-up of 30.4 months (1.8 to 102.9 months), median overall survival was 38.7 months (0.43–104.4) with 35 reported deaths (Fig. 1). Pelvic disease and PAN nodes control was achieved in 73.8% and 84.6% of the patients, respectively. Median locoregional progression-free survival and para-aortic progression-free survival were not reached and median distant metastasis-free survival was 64.3 months. Three- and five-year overall survival were 50.6% and 41.3%, respectively. For the other endpoints, three- and five-year rates were both 65.3% for pelvic disease-free survival, 79.6% for paraortic disease free survival, and 59.6% and 54.7%, respectively, for metastasis free survival.

The results of uni- and multivariate analysis regarding overall survival are presented in Table 2. Variables with $p < 0.10$ in the univariate analysis or clinically relevant were selected for the multivariate analysis. Figures 2 and 3 show Kaplan-Meyer curves for different treatment approaches for PAN positive cervical cancer patients. The same analysis was done for pelvic control. Variables that presented significant impact in pelvic control were the presence of hydronephrosis ($p = 0.003$), radiotherapy dose ($p < 0.001$), use of brachytherapy ($p = 0.02$) and concurrent chemotherapy ($p = 0.034$).

Table 2. Univariate and multivariate analysis of variables on overall survival in 65 patients

Variable	Categories	Univariate analysis		Multivariate analysis	
		n (events)	p	p	95% CI
Age	< 60 years ≥ 60 years	24 11	0.96	–	
ECOG	0–1 2–4	25 10	0.00	0.001	0.53–2.21
T4	No Yes	17 18	0.04	0.671	–1.72–1.10
Nodal disease	No Yes	0 35	0.34	–	
Hydronephrosis	No Yes	15 20	0.00	0.303	–0.67–2.16
Histology	Squamous Adenocarcinoma Other	33 1 1	0.41	–	
Radiation dose	< 45 Gy ≥ 45 Gy	2 33	0.00	1.00	–2.75–2.75
Para-aortic field	No Yes	8 27	0.26	–	
Brachytherapy	No Yes	15 20	0.00	0.067	–1.58–0.54
Chemotherapy (concurrent)	No Yes	15 20	0.03	0.031	–1.49– –0.70

CI — confidence interval; ECOG — Eastern Cooperative Oncology Group

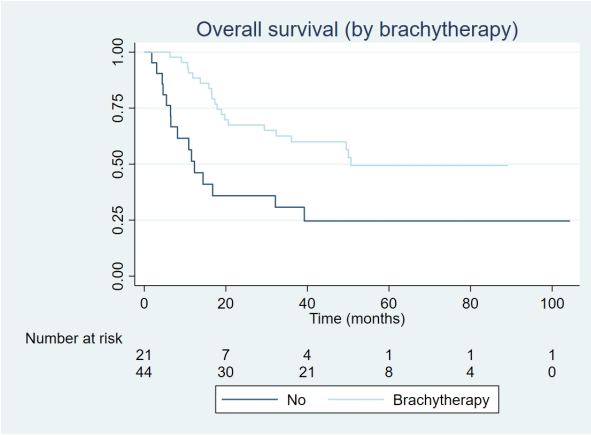

Figure 2. Overall survival by brachytherapy group (mean value was 39.9 months for the brachytherapy group and 22.3 months for no brachytherapy group, p = 0.02)

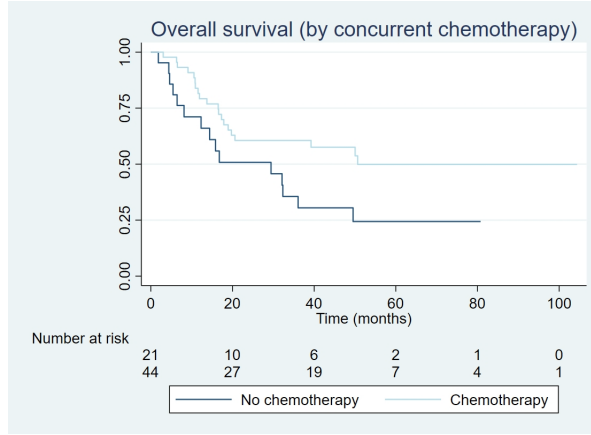

Figure 3. Overall survival by concurrent chemotherapy use (mean value was 37.5 months for those who underwent concurrent chemotherapy and 27.3 months for those that did not, p = 0.034)

Discussion

This is a single center, retrospective study focusing on cervical cancer patients with positive PAN. All 65 patients were treated with curative intent according to the institutional protocol.

We must consider that diagnosis of positive PAN in cervical cancer patients is a concern. The use of CT scans may not be the most efficient way of making this diagnosis. Histologic evaluation of the lymph nodes remains the gold standard to

identify para-aortic extension. Prospective data [12] have already shown the safety and efficacy of surgical staging. The role of imaging only, particularly molecular imaging such as ^{18}FDG-PET scans, is still debatable. Indeed, PET/CT fails to detect approximately 10–15% of patients with para-aortic lymph node metastasis on pathologic staging [13]. Patients with positive pelvic lymph nodes have para-aortic extension in 25–30% of cases, and surgical staging will lead to treatment modification and, probably, to improved para-aortic and distant control, with the potential of avoiding unnecessary radiotherapy to the para-aortic region, even though no impact on survival has been seen [14]. These findings have also been confirmed by the ONCO-GF study [15]. On the other hand, enhancement of imaging performance should be a goal to avoid either unnecessary surgery or irradiation. A recent meta-analysis has shown the high specificity of ^{18}FDG-PET for diagnosing positive PAN in cervical cancer patients, but the sensibility is still low at 70% [16]. In our institution, neither surgery nor ^{18}FDG-PET scans are routinely used for cervical cancer patients staging. All patients had positive PAN defined only by the CT scans according to their size and morphological characteristics. We consider this the major limitation of our study since both false positives and false negatives could be present in our population. Nevertheless, a significant number of our patients had advanced pelvic disease, with pelvic lymph nodes and hydronephrosis, besides T4, that could justify the imaging only criterion for considering positive PAN.

Treating patients with positive PAN can also be a challenge. Some institutions favor prophylactic treatment for PAN [17], strategy not routinely adopted in our institution mainly after risk evaluation, which can be relatively low [18]. Regardless, toxicity is also a concern and have been previously reported [19] in smaller retrospective studies. The impact of intensity modulated radiotherapy (IMRT) or arc therapy in lowering the toxicity rates has been demonstrated in some small studies as well [12–15, 20–22]. In the United States, Osborn et al. (2018) [23], in a study with 103 patients, showed how technology may impact survival on positive PAN cervical cancer patients, particularly the use of ^{18}FDG-PET scans for diagnosis and staging and IMRT technique for treatment. In our cohort, only three patients were treated with (IMRT), all the others with 3D technology. Toxicity was beyond the scope of our study but should not be neglected mostly considering patients irradiated with large fields including the para-aortic nodes. We consider this a limitation of our study. However, only 2 (3%) patients in our study received less than 45 Gy, and median radiation dose was 57 Gy, considering the lymph nodes boost.

Many studies have already been published presenting the outcomes of patients with cervical cancer and positive PAN, most of them with a small number of patients, but with similar results. Back in 1981, Piver et al. [24] published American results on this matter with technology for diagnosis and treatment suitable for that era. More recently, other countries have also published their results, including a Vietnamese [25], Turkish [26], Japanese [27] and Chinese [28] study, all of them with samples smaller than the one presented here. Specifically, regarding Liu et al. (2019) [28], that reported the outcomes of a number of patients (59) similar to our study (65), the three-year overall survival of 52.8% was comparable with 50.6% finding in our cohort.

In the univariate analysis, bad performance status, T4 component, hydronephrosis, lower radiation dose, and no chemotherapy or brachytherapy were related to worse survival. Multivariate analysis selected only performance status, chemotherapy and brachytherapy as significant independent variables related to overall survival.

Almost 70% of our patients were submitted to brachytherapy, which presented a positive impact on overall survival (mean value was 39.9 months for the brachytherapy group and 22.3 months for the non-brachytherapy group, $p = 0.02$). The use of chemotherapy in a similar number of patients (68%) also presented a benefit in survival, together with ECOG performance status (Tab. 2). These findings, however, may just reflect a selection bias for these treatment modalities: patients with better performance, favorable geometry for brachytherapy and able to receive chemotherapy presented better outcomes as expected. The impact on local control provided by brachytherapy in these patients should be better explored, as should be the impact of systemic treatment.

To the best of our knowledge, no study looked specifically at the impact of brachytherapy in this scenario. Indeed, it is part of the standard treatment

Table 3. Univariate analysis for the disease-free survival outcomes

Patients' characteristics	N	PDFS		PaDFS		DMFS	
		Events	p	Events	p	Events	p
Age							
< 60 years	45	13	0.402	9	0.126	15	0.861
≥ 60 years	20	4		1		7	
ECOG							
0–1	54	16	0.702	9	0.981	16	< 0.0001
2 or more	11	1		1		6	
T4							
No	38	7	0.028	4	0.084	10	0.017
Yes	27	10		6		12	
Pelvic nodes							
No	1	0	0.511	0		0	
Yes	64	17		10		22	
Hydronephrosis							
No	36	6	0.005	4	0.091	11	0.037
Yes	29	11		6		11	
Histology							
Squamous	59	15	0.085	9	0.264	20	0.778
Adenocarcinoma	4	0		0		2	
Other	2	2		1		0	
Radiation dose							
< 45 Gy	2	0	-	0	0.900	0	0.900
≥ 45 Gy	63	17		10		22	
Brachytherapy							
No	21	6	0.138	4	0.173	8	0.038
Yes	44	11		6		14	
Chemotherapy (concurrent)							
No	21	7	0.071	7	0.001	8	0.072
Yes	44	10		3		14	

PDFS — pelvic disease-free survival; PaDFS — para-aortic disease-free survival; DMFS — distant metastasis disease free survival; ECOG — Eastern Cooperative Oncolgy Group

even for patients in a more advanced stage. Our findings tend to confirm the benefit of brachytherapy whenever feasible, with a median life-expectancy of 40 months in this cohort and almost 75% of pelvic disease control, 65% in five years.

In our study, 22 (33.8%) patients presented distant metastasis in a median of 64 months, 55% at five years, meaning that long term follow-up is needed in these patients. At least one prospective phase II study has tried to demonstrate the value of neoadjuvant chemotherapy in PAN positive patients, with better results in those with less advanced pelvic disease (Stages IB and II) [29]. A systematic review, including only two randomized controlled trials, evaluated the role of adjuvant chemotherapy for locally advanced cervix cancer (not all patients with positive PAN) [39], yet, with no promising results. Prospective trials assessing the use of current diagnosis and treatment techniques for patients with positive PAN are warranted.

The recent AJCC and International Federation of Gynecology and Obstetrics (FIGO) [31] classifications, translating positive PAN patients from stage IV to potentially curable stage IIIC disease, represent a major change of concept among the scientific community. The discussion on whether a curative approach for these patients is effective can be reinforced by our data, with expected median survival longer than three years. Our results may contribute to newer, prospective studies on the treatment of positive PAN cervical cancer with curative intent.

Conclusion

Patients with current stage IIIC2 cervix cancer may present long term survival. Treating positive PAN cervical cancer patients with concurrent chemoradiation with curative intent should be standard. Brachytherapy is an essential part of the treatment and may directly impact survival. Poor PS and more advanced pelvic disease may represent a higher risk for worse outcomes. Distant metastases are still a challenge for disease control.

Conflict of interests

The authors do not have any conflict of interest to declare.

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Ethics approval and consent to participate

Ethics committee authorization was obtained in the local ethics committee according to Brazilian law and the Declaration of Helsinki. All patients have given written consent to participate.

Consent for publication

The author grants the publisher the sole and exclusive license of the full copyright. The authors guarantee that this manuscript has not been previously published elsewhere. The authors declare that any person named as co-author of the contribution is aware of the fact and has agreed to being so named.

Availability of supporting data

Data on this research is available on request to the corresponding author

Authors contributions

G.M. and V.C. were responsible for study design. H.C. and V.C. were responsible for ethics committee approval. V.C., M.V. and T.A. were responsible for data collection. G.M. has written project's final draft. G.M. was responsible for statistical analysis. H.C. was responsible for overall orientation and manuscript review.

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