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PET/CT-based dose-escalated definitive radiotherapy in cervical cancer: a single-institution series

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ABSTRACT

Background: The objective was to evaluate clinical outcomes and toxicity of patients with cervical cancer treated by radiotherapy with dose escalation in involved lymph nodes based on positron emission tomography/computed tomography (PET/CT) staging.

Materials and methods: Retrospective cohort study involving locally advanced cervical neoplasms treated with definitive radiotherapy. Volumetric modulated arc therapy (VMAT), image-guided radiotherapy (IGRT), and registration of PET/CT were employed in all. Involved lymph nodes were given higher doses simultaneously.

Results: Between February 2012 and September 2023, there were 37 patients, with median age of 48 (range 27–91) years. Almost 70% were stages III/IVA. Two-thirds were given retroperitoneal irradiation. The mean delivered doses to primary tumor and to involved lymph nodes were, respectively, 52.5 Gy, and 62.5 Gy. The 10-year rates of overall survival, event-free survival, local-recurrence-free survival, and metastasis-free survival were, respectively, 76%, 50%, 91%, and 82%. There were 13 and 2 cases of gastrointestinal toxicity grades II and III, respectively. Grades II and III of genitourinary toxicity were seen respectively in 7 and 3 patients. On univariate analysis, age was related to local recurrence-free survival (LRFS); standard uptake values (SUV) was related to event-free survival (EFS); lymph node dose was related to overall survival (OS), and EFS; primary tumor dose was directly related to EFS, albeit inversely to the likelihood of grade > II gastrointestinal toxicity. Retroperitoneal irradiation improved LRFS, and rates of grade > II gastrointestinal toxicity. On multivariate analysis, SUV remained an independent predictor of EFS; lymph node dose was an independent predictor of OS, and age was an independent predictor of lymph node recurrence.

Conclusion: Dose escalation radiotherapy (RT) based on PET/CT for cervical cancer may be feasible and safe. Further robust study results are needed.

Keywords: cervical cancer; radiotherapy; ^{18}F-FDG PET/CT

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Introduction

Gynecological neoplasms, primarily involving cervix and uterine body, are highly prevalent worldwide [1, 2]. Therapeutic planning hinges on staging and histological type. Locally advanced tumors are typically managed with multimodal therapy. Lymph node involvement remains a key prognostic factor, and its treatment efficacy varies based on the type of employed radiotherapy [3].

Hence, studies were conducted to assess the benefits of concurrent dose escalation in compromised lymph nodes [4]. However, this treatment has only become feasible upon radiotherapy technical evolution – intensity-modulated beams (IMRT), image-guided radiotherapy (IGRT) [5–7] — enabling precise radiation beam conformation, while minimizing doses to healthy organs [8]. Furthermore, the co-registration of different imaging methods have improved accuracy [9], including PET/CT, which might lead to potential changes in radiotherapy fields, such as including the retroperitoneum in cases initially not intended for such treatment [10]

This study aims to assess clinical outcomes and toxicity profile of gynecologic cancer patients treated with modern radiotherapy, incorporating dose escalation based on the initial PET/CT.

Materials and methods

This study received approval from the Research Ethics Committee of the Teaching And Research Institute of the Sírio-Libanês hospital (São Paulo, Brazil). It is a retrospective cohort study involving patients with locally advanced uterine cervix cancer treated with definitive or adjuvant radiotherapy, along with systemic treatments. Volumetric modulated arc therapy (VMAT), an advancement in IMRT, was employed, featuring a concomitant boost in visualized gross disease areas through the registration of PET/CT on the planning tomography. The inclusion of brachytherapy, surgery, or systemic therapies was based on specific treatment indications. The analysis period spanned from February 2012 to September 2023.

In terms of radiotherapy, all patients underwent a pretreatment CT-based simulation. PET/CT fusion with the simulation CT was performed, considering suspected lesions with standard uptake values (SUV) over 2.5 as metabolically active disease. Cases with gross common iliac, or retroperitoneal lymph node involvement received radiation to the retroperitoneum. Patients with indication for brachytherapy underwent high-dose-rate intracavitary 3D-brachytherapy using an iridium-192 source and Fletcher afterloading applicators, typically administered twice weekly under general anesthesia.

Our group utilized the quadratic linear model to determine equivalent doses in conventional fractionation, respecting tissue response coefficients to treatment (alpha-beta relationship) [11].

Patients who did not complete the proposed radiotherapy protocol, and those with insufficient follow-up data for analysis were excluded.

Study variables were age, pathology, FIGO staging, PET/CT data, treatment-related factors (type of radiotherapy, prescribed dose, brachytherapy, surgery, systemic therapy, timing of treatments), and follow-up details (date of last contact, status, date until event, type of event, degree of gastrointestinal and genitourinary toxicity during follow-up). We scored toxicities according to the Common Terminology Criteria for Adverse Events (CTCAE) [12].

Data collection involved two researchers reviewing physical and electronic records, with outcomes considered from the end of radiotherapy treatment, focusing on local, regional, and distant recurrence. Local failures were defined as any evidence of active disease (confirmed by biopsy) in cases of intact uterus, regional failures were those in pelvic or retroperitoneal lymph nodes, and distant disease was considered in visceral, brain, bone, lymph node metastases beyond the pelvis or retroperitoneum.

Statistical analysis

Qualitative variables will be summarized using frequency and percentage, and quantitative variables using mean, standard deviation, median, minimum, maximum, and the number of valid observations. For group comparisons with qualitative variables, we will use a Chi-square test or Fisher's Exact test. For quantitative variables, the parametric t-student test, or non-parametric Mann-Whitney test will be employed. Survival outcomes will be assessed through Kaplan Meier method, and variable comparison through Log-rank test. Multivariate analysis will require linear regression test. Significance level is set at 5% ($p \leq 0.05$), and statistical analysis will be performed using the Stata™ statistical program.

Results

Patients characteristics

A total of 37 patients were included, with at least one month follow-up. The median age was 48 (range, 27–91) years. Table 1 shows patient characteristics.

Overall, there were five deaths during the period, all cancer-related. In addition, there were other 13 cancer-related events. Among them, one patient

Table 1. Patient characteristcs

Characteristc		N	%
2018 FIGO staging	IIB	10	27.03
	IIIA	1	2.70
	IIIB	14	37.84
	IIIC	10	27.03
	IVA	2	5.41
Surgery	"Adjuvant"	5	13.51
	No surgery	32	51.35
Pathologic subtype	Adenocarcinoma	14	37.84
	Squamous cell carcinoma (SCC)	18	48.65
	Other	5	13.51
Site	Uterine cervix	32	86.49
	Endocervix	5	13.51
Concurrent systemic treatments	Yes	37	100.00
Retroperitoneal irradiation	Yes	15	67.57
	No	12	32.43
Brachytherapy receipt	Yes	26	70.27
	No	11	29.73
Initial PET/CT use for radiotherapy planning	Yes	37	100.00
Initial PET/CT SUV for primary tumor	Up to 5	10	27.03
	> 5	27	72.97
Initial PET/CT SUV for lymph nodes	Up to 5	12	32.43
	> 5	25	67.56
Characteristc		**Median**	**Range**
Brachytherapy	Number of fractions	4	3–4
	Dose per fraction [Gy]	7	7–7.5
	Total dose [Gy]	28	21–28
Delivered doses to pelvis (plus/minus retroperitoneum)	Number of fractions	25	20–30
	Dose per fraction [Gy]	1.8	1.6–2.1
	Total dose [Gy]	45	41.4–50.4
	EQD2/10 [Gy]	44.25	40.71–50
Doses delivered to uterus and parametria	Number of fractions	25	20–30
	Dose per fraction [Gy]	2	1.8–2.25
	Total dose [Gy]	52.5	44–56.25
	EQD2/10 [Gy]	52.76	44.73–58.3
Doses delivered to bulky lymph nodes	Number of fractions	25	20–30
	Dose per fraction [Gy]	2.5	2.2–2.7
	Total dose [Gy]	62.5	50–72.8
	EQD2/10 [Gy]	65.1	52.08–72.92

FIGO — International Federation of Gynecology and Obstetrics; PET/CT — positron emission tomography/computed tomography; SUV — standard uptake value; Gy — Gray; EQD2/10 — equivalent dose for conventional fractionation (2 Gy/day) with tissue response coefficient of 10 (alpha-beta ratio)

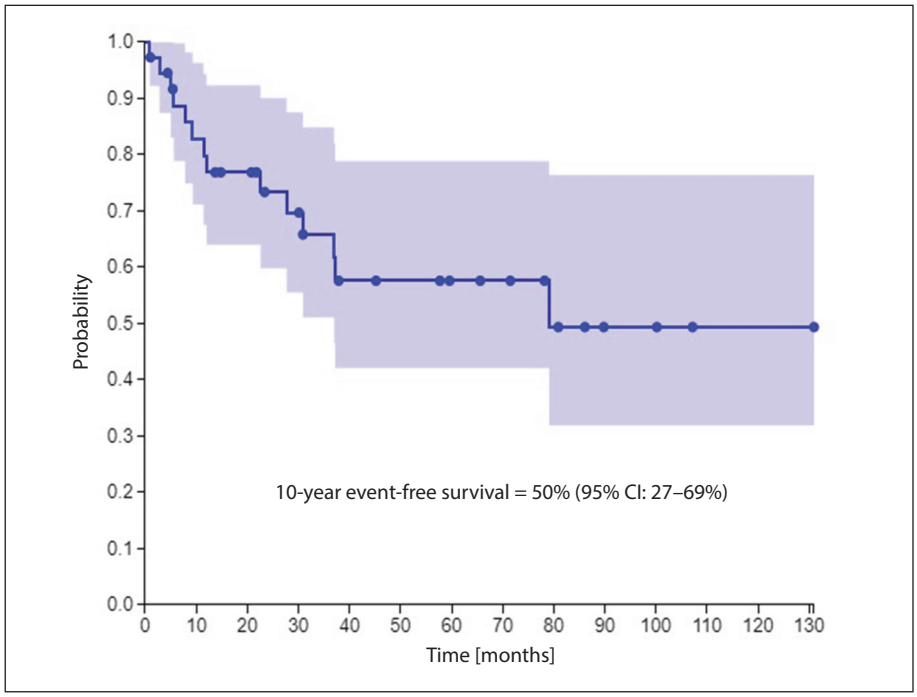

Figure 1. Overall survival. CI — confidence interval

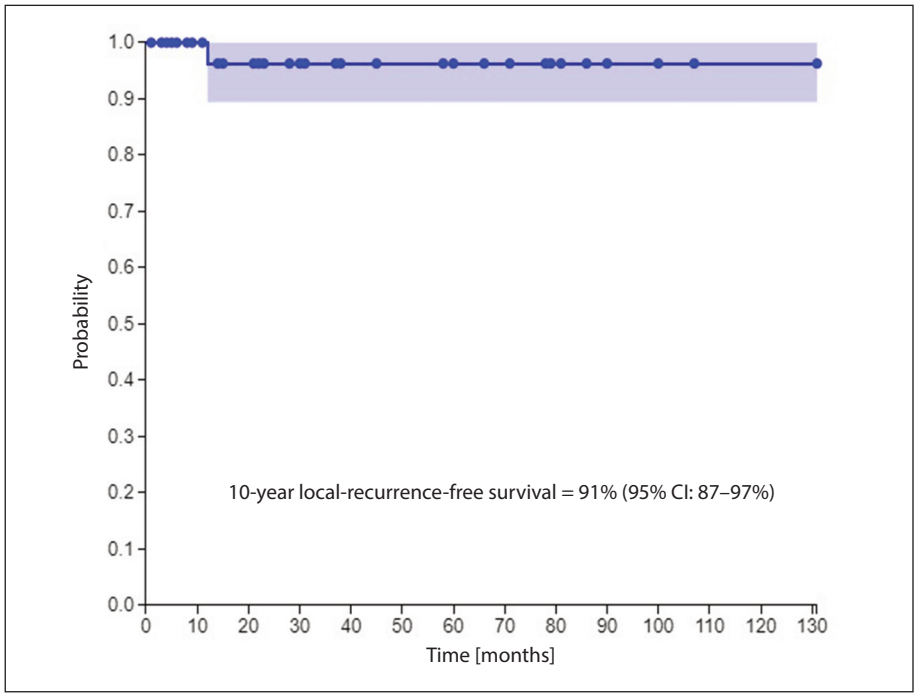

Figure 2. Event-free survival. CI — confidence interval

presented local recurrence, two cases evolved with lymph node metastases, and 11 cases presented metastatic disease as their first cancer-related event.

Figure 1 illustrates the overall survival outcome. Within a median follow-up time of 30 (6–131) months, the 10-year overall survival was 76% (95% CI: 54–89%).

Figure 2 shows the event-free survival outcome. The 10-year event-free survival was 50% (95% CI: 27–69%).

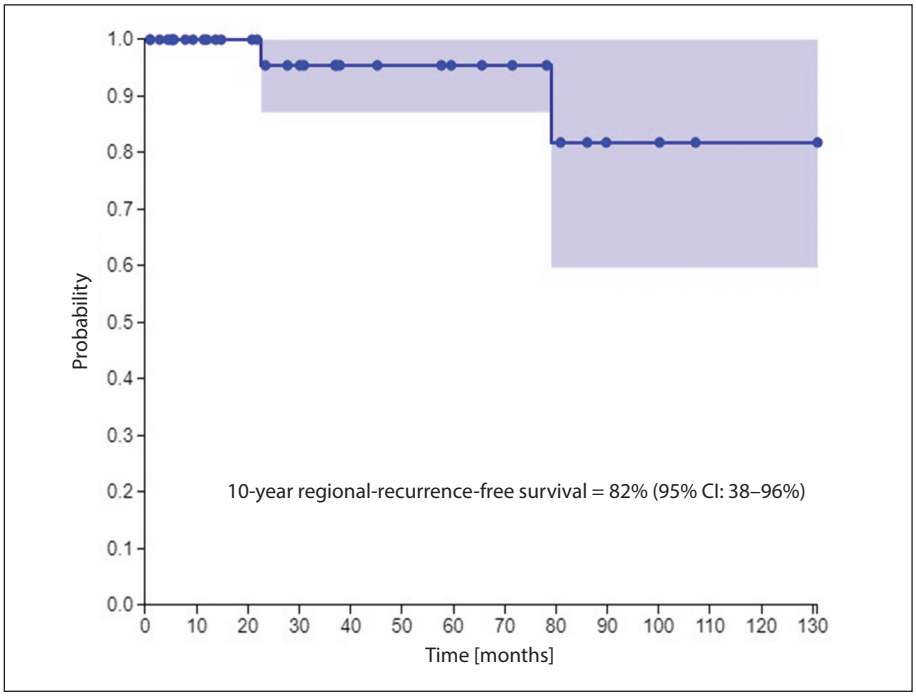

Figure 3. Local-recurrence-free survival **[The same figure]**

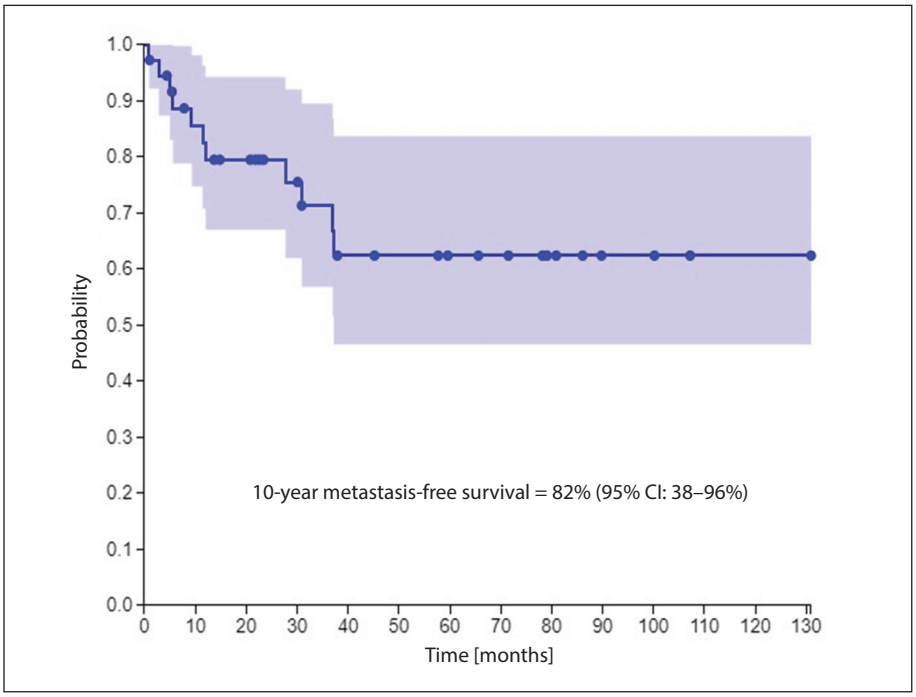

Figure 4. Metastasis-free-survival. CI — confidence interval

Figure 3 illustrates the actuarial local-recurrence-free survival. The 10-year local-recurrence-free survival was 91% (95% CI: 87–97%).

Figure 4 illustrates the metastasis-free-survival. At 10-year follow-up, the rate was 82% (95% CI: 38–96%). It is important to note that some cases had more than one event subsequent to the first one, but were kept on follow-up. Treatments used in these patients varied but, in general, cases of local and regional recurrence underwent surgery plus

Table 2. Univariate and multivariate analyses

Univariate Analysis (p-values for T, Fisher, or Mann-Whitney tests)						
		Event-free-survival	Overall Survival	Regional-recurrence-free survival	GI Toxicity > grade II	GU Toxicity > grade II
Clinical Stage	Up to IIB *vs* > IIB	0.9	0.9	0.8	0.9	0.9
Age	Up to 50y *vs* > 50y	0.82	0.73	0.0001	0.99	0.1
SUVprimary	< 5 *vs* > 5	0.004	0.5	0.37	0.06	0.9
SUVlymph node	< 5 *vs* > 5	0.09	0.36	0.26	0.15	0.99
Lymph node doses EQD2/10 [Gy]	< 60 *vs* > 60	0.04	0.002	0.9	0.9	0.47
Uterus and parametria doses EQD2/10 [Gy]	< 54 *vs* > 54	0.02	0.5	0.9	0.01	0.09
Pelvic doses EQD2/10 [Gy]	< 45 *vs* > 45	0.22	0.2	0.99	0.9	0.11
RT to Retroperitoneum	No *vs* yes	0.12	0.36	0.04	0.03	0.99
Multivariate analysis (p-value for Linnear regression test)						
SUVprimary	< 5 *vs.* > 5	0.04	–	–	–	–
Uterus and parametria doses EQD2/10 (Gy)	< 54 *vs.* > 54	-	0.63	–	0.4	–
Lymph node doses EQD2/10 (Gy)	< 60 *vs.* > 60	0.05	0.02	–	–	–
Age	Up to 50y *vs* > 50y	–	–	0.004	–	–
RT to Retroperitoneum	No *vs* yes	–	–	0.1	0.36	–

GI — gastrointenstinal; GU — genitourinary; SUV — standard uptake value; Gy — Gray; PTVEQD2/10 — equivalent dose for conventional fractionation (2 Gy/day) with tissue response coefficient of 10 (alpha-beta ratio); RT = radiotherapy

or minus systemic and radiation therapy, whereas cases of metastatic disease were given systemic therapies, according to tumor subtype and patient's condition at that time.

Regarding rates of gastrointestinal toxicity, we observed that 11 cases had grade I, 13 cases had grade II, and two cases had grade III toxicities, including one who had a rectovaginal fistula. There were no cases of grade IV toxicity. The remaining patients (n = 11) did not present significant gastrointestinal toxicity scores.

Concerning genitourinary toxicity, there were 14 cases without any toxicity, whereas 13 cases had grade I, seven cases had grade II, and three cases had grade III toxicities, including 3 who had significant ureteral stricture.

An exploratory analysis of outcomes was carried out. Table 2 illustrates main findings after univariate analysis. Following the variables analyzed, age (cut-off 50 years) was significantly related to recurrence-free-survival; the SUV of the primary tumor — SUVp — (cut-off 5) was correlated with event-free survival; the dose received by the lymph nodes (cut-off 60 Gy) was correlated with overall, and event-free survival; the dose received by the uterus and parametria (54 Gy cut-off) was directly related to event-free survival, albeit inversely to the rate of grade > II gastrointestinal toxicity. Irradiation of the retroperitoneum improved recurrence-free-survival, but was adversely related to rates of grade > II gastrointestinal toxicity.

Table 2 also depicts multivariate analyzes. The SUVp remained an independent predictor of event-free survival; the dose received by the lymph nodes was an independent predictor of overall survival, and age remained an independent predictor of lymph node recurrence.

Discussion

Summary of main results

This study has demonstrated the safety and efficacy of dose-escalation treatment in areas of bulky disease for patients with gynecological neoplasms undergoing curative-intent therapy. The incorporation of modern radiotherapy techniques improved delivery of different dose gradients [13], with PET/CT registration. Notably, we identified the SUVp as a prognostic biomarker for patient outcomes.

The combination of these strategies endorsed good low toxicity rates, and effectiveness. A note-

worthy finding supporting this observation was the occurrence of only one case of retroperitoneal lymph node recurrence in a patient initially treated with pelvic radiotherapy (without retroperitoneal inclusion in the radiation fields). This aligns with findings from other studies, indicating retroperitoneal recurrence rates of around 10% [14]. Even in series with dose escalation in areas of gross disease and with formal inclusion of the retroperitoneum without the use of PET/CT — such as the study by Biplab et al. [15] — failure rates in the retroperitoneum were around 7%, but acute toxicity and late was relevant.

Results in the context of published literature

This study revealed 40% and 27% of gastrointestinal and genitourinary toxicities grade > II, respectively. These data are somewhat similar to those observed by two meta-analyses evaluating definitive treatment for cervical tumors [16, 17]. Their rates of gastrointestinal and genitourinary toxicities grades > II were 55% and 35%, respectively, in spite of having used conventional radiotherapy. When comparing our data with randomized studies evaluating IMRT [18], our toxicity rates were higher — gastrointestinal, and genitourinary toxicities grades > II, respectively, of 21% and 7%, even though in such study there was no concomitant boost in grossly positive lymph nodes. In another study [19], conventional radiotherapy were compared to VMAT. In the latter, a boost dose was simultaneously delivered to affected lymph nodes. Disease control rates were preliminary, but with a trend towards VMAT cases, and toxicities rates were also lower in favor of VMAT. Similar to what the aforementioned study (and other studies [20–21]) found in our study, although we did not make a comparison with a historical series, we were also able to observe improved outcomes.

The disease control rates in our study were in line with what other investigators found, as shown in Table 3. While some studies did not find radiotherapy dose as an independent predictor of outcomes [23], others mitigate such association. Whitney et al. [24]. found an inverse relationship between failure rates and dose range. Kato et al. [25], found an association between dose escalation in lymph nodes and improved local control. These results were relatively replicated by Shewalkar et al. [26], although in this study, dose escalation was performed sequentially.

The lymph node control is an important prognostic factor. The dose received by the lymph nodes comes "only" from external-beam radiotherapy as there is an insufficient contribution of brachytherapy [27] to achieve adequate total doses in these lymph node areas. Some studies, such as Macchia et al. [28] evaluating patients undergoing radiochemotherapy in the preoperative context showed that complete pathological response rate in lymph nodes submitted to treatment with escalating doses was around 85%. In our study, five patients were referred for surgery after definitive treatment (data not shown), but none of them had active disease in lymph nodes.

The aim of controlling primary and regional disease with definitive treatment needs to be balanced against low likelihood of toxicities [29]. IGRT allows checking the position of the patient and internal organs before treatment [30]. It is possible to identify, for example, differences in organ filling between doses. In addition to the use of VMAT [31], the association of IGRT gave us the guarantee that the planning objectives were carried out during the treatment, and also surrogates low rate of toxicities. In addition to the risk of toxicities, the pursuit for adequate lymph node control must also be weighed against a potential increase in toxicities in scenarios of lymph node failure, where patients often undergo surgery in irradiated areas [32], which can lead to a greater risk of postoperative complications. If they are not eligible for surgery, these patients often receive further courses of radiotherapy. Although ablative techniques are used (such as stereotactic body radiotherapy [33], or intraoperative radiotherapy [34]), it will also incur the scenario of re-irradiation, under a weak substrate of current literature.

Strengths and weaknesses

According to Table 3, only two studies — ours and Chung et al. [10] — proposed the dose escalation in gross lymph nodes simultaneously with the main treatment [35]. Our results, while comparable to theirs, revealed unprecedented insights: the SUVp was independently related to event-free survival, and the EQD2/10 (equivalent dose in 2 Gy fractions, with alpha-beta relationship of 10 Gy) of lymph node disease was also recognized as an in-

Table 3. Studies' comparisons

Study	Year	Study type	N	Site	EBRT	EBRT type	IGRT	Brachy	CT	Surgery	Pelvic dose	LN dose	EQD 2/10 LN	PET/CT plan	GI toxicity	GU toxicity	OS	DFS	RFS	Obs
Kato S	2006	Retrosp	44	cerv	Yes	C-ion	No	Yes	Yes	Various	50 Gy	68 Gy	72.8 Gy	No	N = 8 (G3)	N = 5 (G3)	40% @ 5y	Not reported	79% @ 5y	Sequential boost
Macchia G	2010	Retrosp	32	cerv	Yes	3d + VMAT	No	No	Yes	Adjuvant	45 Gy	50 Gy	55 Gy	No	N = 15 (G2)/ N = 6 (G3)/ N = 1 (G4)	N = 4 (G2)	92% @ 2y	68% @ 2y	63.5% @ 2y	Concurrent boost
Marnitz S	2010	Retrosp	40	cerv	Yes	Tomo-therapy	No	Yes	Yes	Various	50 Gy	60 Gy	58 Gy	No	20% G2 /2.5% G3	None	Not reported	Not reported	Not reported	Sequential boost
Khosla FD	2013	Retrosp	25	cerv	Yes	Vmat	No	Yes	Yes	Upfront	46 Gy	63–70 Gy	79 Gy	No	N = 11 (G2)/ N = 2 (G3)	N = 2 (G2)	67% @ 3y	74% @ 3y	76% @ 3y	Sequential boost
Wakatsuki M	2014	Retrosp	22	cerv	Yes	C-ion	No	Yes	Yes	Various	40 Gy (13 fr)	15 Gy (5 fr)	72 Gy	No	None G > 1	N = 2 (G2)	50% @ 5y	68.2% @ 5y	Not reported	Sequential boost
Wakatsuki M	2014	Prosp	58	cerv	Yes	C-ion	No	Yes	Yes	Various	36 Gy (12 fr)	60 Gy (20 fr)	74 Gy	No	N = 2 (G3)	N = 5 (G3)	38.1% @ 5y	68% @ 5y	Not reported	Sequential boost
Hegazy MW	2016	Retrosp	20	cerv	Yes	VMAT	Yes	Yes	Yes	Various	45 Gy	55 Gy	60 Gy	No	39% G1	19% G2	Not reported	Not reported	Not reported	Sequential boost
Chung YL	2016	Retrosp	72	cerv	Yes	VMAT	Yes	Yes	Yes	Various	45 Gy	60 Gy	60 Gy	Yes	N = 7 (G3)	N = 3 (G3)	69.1% @ 5y	50% @ 5y	Not reported	Concurrent boost
Gogineni E	2020	Retrosp	77	cerv	Yes	3D	No	Yes	Yes	Various	50 Gy	66 Gy	69 Gy	No	13% G > 2	None	Not reported	Not reported	Not reported	Sequential boost
Shewalkar B	2022	Prosp	52	cerv	Yes	VMAT	No	Yes	Yes	Various	50 Gy	70 Gy	67 Gy	No	N = 6 (G3)	N = 3 (G3)	Not reported	Not reported	Not reported	Sequential boost
Scharl S	2022	Retrosp	19	cerv	Yes	VMAT	Yes	Yes	Yes	Various	45 Gy	60 Gy	60 Gy	Yes	Not reported	Not reported	Not reported	Not reported	Not reported	Concurrent boost
Lee HC	2023	Prosp	88	cerv	Yes	VMAT	Yes	Yes	Yes	Various	50 Gy	60 Gy	58 Gy	Yes	N = 6 (G2)/ N = 2 (G3)	N = 7 (G2)	93.6% @ 30 m	82.8% @ 30 m	89.4% @ 30 m	Sequential boost
Present study	2023	Retrosp	37	both	Yes	VMAT	Yes	Yes	Yes	Various	45 Gy	66 Gy	69 Gy	Yes	N = 15 (G2 and 3)	N = 10 (G2 and 3)	76% @ 10 y	50% @ 10 y	82% @ 10 y	Concurrent boost

Cerv — cervix; C-ion — carbon-ion radiotherapy; CT — chemotherapy; DFS — Disease-free Survival; EBRT — external-beam radiotherapy; EQD2/10 — equivalent dose for conventional fractionation (2Gy/day) with tissue response coefficient of 10 (alpha-beta ratio);G — grade; Gy — Gray; OS — Overall Survival; RFS — Recurrence-free Survival; SUV — standard uptake value; VMAT — volumetric modulated arc therapy

dependent predictor of overall survival. It is known that the SUVp of patients with cervical tumors is an independent predictor of prognosis [36, 37], and it is also known that there is a dose-response relationship with disease control, as commented above. Our study somehow "associated" that information through our outcomes.

On the other hand, this is a small, and retrospective study of non-consecutively treated cases, within a single institution, without any comparison with a control group or historical series. Therefore, some bias inherent to this type of publication must be taken into account.

Implications for practice and future research

Our results might constitute a background for the same treatment strategy in our next patients. Further studies are needed to tailor treatments, especially when we find independent predictor variables of outcomes. Ideally, they should be considered in prospective studies as patient selection criteria.

Conclusions

The findings of this small, retrospective study suggest that radiotherapy with dose escalation based on PET/CT appears to be viable considering the good results and low rates of toxicity related to the treatment. Some variables that predict risk of toxicities or survival influenced our results. All promising results observed deserve validation in robust cohorts with longer follow-up.

Conflict of interests

Authors declare no conflict of interests.

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