Gynecologic Oncology 176 (2023) 10–15

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Simultaneous integrated or sequential boost to clinically involved lymph nodes in patients with locally advanced cervical cancer treated with definitive chemoradiotherapy

Alper Kahvecioglu, M.D., Ezgi Gurlek, M.D., Fazli Yagiz Yedekci, PhD., Sezin Yuce Sari, M.D., Assoc. Prof., Melis Gultekin, M.D., Prof. *, Ferah Yildiz, M.D., Prof.

Hacettepe University, Faculty of Medicine, Department of Radiation Oncology, Ankara, Turkey

HIGHLIGHTS

- Dose escalation to the clinically involved lymph nodes by modern radiotherapy techniques provides excellent nodal control.
- Combined use of simultaneous integrated and sequential boost techniques is feasible.
- The dose contribution of brachytherapy should be kept in mind prior to additional dose prescription to the lymph nodes.

ARTICLE INFO

Article history:
Received 12 May 2023
Received in revised form 20 June 2023
Accepted 23 June 2023
Available online 4 July 2023

Keywords:
Boost
Cervical cancer
Chemoradiotherapy
Lymph nodes
IMRT
VMAT

ABSTRACT

Objective. The optimal treatment of metastatic lymph nodes (LNs) in locally-advanced cervical cancer (LACC) is controversial. With the widespread use of modern radiotherapy (RT) techniques, it is become possible to perform dose escalation in clinically involved LNs. This study aimed to evaluate the oncologic outcomes of dose escalation to the involved LNs with the simultaneous-integrated (SIB) or sequential boost (SEB) techniques as a part of definitive chemoradiotherapy (CRT) for patients with LACC.

Methods. The data of 47 patients treated with definitive CRT with either a SIB or SEB technique to the metastatic LNs between 2015 and 2021 were retrospectively analyzed. All patients received 50.4 Gy/28 fractions of external-beam RT and 28 Gy/4 fractions of brachytherapy.

Results. The number of boosted LNs was 146. The median size of the LNs was 2 cm (range, 1–5 cm). The median cumulative equivalent dose in 2-Gy fractions for the LNs was 64.2 Gy (range, 57.6–71.2 Gy). During the median 30 months of follow-up (range, 14–91 months), no boosted LNs recurred and the local control (LC) rate was 100%. The 2-year overall, disease-free, local recurrence-free, and distant metastasis-free survival rate was 83.1%, 70.5%, 77.5%, and 74.4%, respectively. In multivariate analysis, the non-squamous cell histology was the only negative independent prognostic factor for DFS and DMFS. Treatment was well tolerated without any serious acute toxicity. Serious late toxicity developed in three (6%) patients as ureteral stenosis, rectal bleeding and pelvic fracture in one patient each.

Conclusions. RT dose escalation provides excellent LC for the clinically involved LNs, even for bulky ones, with a low toxicity profile. Routine LN dissection may not be necessary. However, randomized trials are needed to determine the optimal treatment approach.

1. Introduction

The standard treatment of locally-advanced cervical cancer (LACC) is definitive chemoradiotherapy (CRT) followed by brachytherapy (BRT). However, regional recurrences (RRs) are important failure patterns after definitive treatment and local control (LC) of the metastatic lymph nodes (LNs) should be one of the most important goals beside the primary tumor [1].

* Corresponding author at: Hacettepe University Oncology Institute, Department of Radiation Oncology, 06100 Sıhhiye, Ankara, Turkey.
E-mail addresses: alperkahvecioglu@hacettepe.edu.tr (A. Kahvecioglu), ezgi.gurlek@hacettepe.edu.tr (E. Gurlek), yagiz.yedekci@hacettepe.edu.tr (F.Y. Yedekci), sezin.yuce@hacettepe.edu.tr (S.Y. Sari), melisgultekin@hacettepe.edu.tr (M. Gultekin), fyildiz@hacettepe.edu.tr (F. Yildiz).

https://doi.org/10.1016/j.ygyno.2023.06.020
0090-8258/

According to the revised 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system, patients with pelvic and para-aortic LN metastases are staged as IIIC1 and IIIC2, respectively [2]. The optimal treatment approach to the metastatic LNs is controversial. While LN-dissection (LND) may be an option for bulky LNs, dose escalation with modern radiotherapy (RT) techniques such as intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) is another promising alternative. There are no randomized trials comparing LND and dose escalation with RT; however, in retrospective series, very high LC rates were reported with LN boost [3–5].

The simultaneous integrated boost (SIB) technique allows the simultaneous delivery of varying doses as lower fraction dose to the whole lymphatic region and higher dose to the involved LNs within the same fraction. On the other hand, in the sequential boost (SEB) technique, an additional dose is applied to the LNs after the whole course of external beam RT (EBRT). The most prominent advantage of SIB is that it does not prolong the overall treatment time (OTT). The advantage of SEB on the other hand is the ability to deliver the additional dose to the shrunken LN volume after EBRT. Additionally the dose contribution from BRT can also be taken into account in the SEB technique. Although both techniques have their own advantages and disadvantages, there is no study showing the superiority of one technique over the other. In addition, literature about the combined use of SIB and SEB is scarce. In this study, we examined the outcomes and toxicity profile of patients that underwent dose escalation for the clinically involved LNs with a SIB and/or a SEB technique.

2. Methods

2.1. Patient population

Medical records of 51 patients who underwent definitive CRT with a LN boost for LACC between 2015 and 2021 in our department were retrospectively analyzed. Fourty-seven patients who completed definitive treatment and had ≥ 3 months of follow-up were included in this study. Patients with stage IVB disease and treated with RT techniques other than IMRT/VMAT were excluded and all patients included in this study received either IMRT or VMAT techniques of RT. No patients underwent LND and the involved LNs were radiologically identified by magnetic resonance imaging (MRI) and/or positron emission tomography/computed tomography (PET/CT). LNs with a short axis > 1 cm, contrast enhancement and/or restricted diffusion were considered clinically involved on the MRI whereas on PET/CT, LNs with an 18-fluoro-deoxy-glucose (FDG) uptake higher than the liver were accepted clinically involved. This study was approved by the institutional ethics board (GO 23/306) and conducted in compliance with the principles of the Helsinki declaration.

2.2. Treatment

Currently, we determine the RT fields according to the ongoing EMBRACE-II protocol [6]. According to this protocol, the internal/external iliac, presacral and obturator lymphatics (small pelvis) in low-risk and this small pelvis with addition of common iliac (CI) lymphatics (large pelvis) are being treated in intermediate risk patients. In high-risk patients with either CI LN metastasis or ≥ 3 suspicious pelvic LNs, the para-aortic field is treated electively concurrent with the large pelvis (EFRT). For patients with suspicious para-aortic LN metastasis, EFRT is routinely applied. In EFRT, the clinical target volume (CTV) included paraaortic-paracaval lymphatics starting from the level of renal pelvis+large pelvis in addition to primary tumor, whole uterus, parametriums and at least upper part of the vagina. However, since the study included former patients, elective para-aortic irradiation was not applied for all patients with ≥ 3 pelvic LNs in this study but to all patients with a positive CI LN.

The CT simulation (sim-CT) was performed with a 2.5-mm slice thickness using intravenous contrast. MRI and PET/CT images were fused with the sim-CT images for target volume delineation. All patients were treated with 50.4 Gy in 28 fractions EBRT with a concurrent weekly platinum-based chemotherapy, followed by a 28 Gy in 4 fractions high-dose-rate CT-guided three dimensional BRT (3DBRT). Recommendations of GEC-ESTRO working group were followed for BRT planning [7]. For SIB technique, the boost dose was defined to the initial volume of the LNs whereas for SEB technique, a new sim-CT was performed following the end of 50.4 Gy EBRT, and the boost dose was defined for the volume of the shrunken LNs. Target volumes and the dose constraints for EBRT are summarized in supplementary Table S1 [6]. The dose per fraction in the SIB group was either 2Gy/fr to a total dose of 56 Gy or 2.14–2.28 Gy/fr to a total dose of 60–64 Gy in the involved LNs. The other parts of the CTV was treated with 1.8 Gy/fr. In the SEB technique, all the CTVs were treated with 1.8 Gy/fr first followed by a boost dose of 2 Gy/fr to the LNs. We use Linear Quadratic formula in order to calculate the total equivalent dose in 2 Gy per fraction (EQD2) using the $\alpha/\beta = 10$ Gy for the tumor and $\alpha/\beta = 3$ Gy for the organs at risk (OARs). The dose contribution to the LNs from BRT was also considered during plan evaluation. For LNs in close proximity to the cervix, a SIB technique was not applied as the dose contribution of BRT would be significant and the SEB dose was calculated taking into account the BRT doses. For LNs far away from the cervix as CI and para-aortic LNs, an initial SIB dose was prescribed. For patients receiving an initial SIB dose to the LNs, we decided whether to apply an additional SEB dose after the BRT contribution was calculated. Although it varies according to the LN size and OAR doses, we aimed to reach ≥ 60 Gy in EQD2 to the involved LNs.

In our institutional protocol, the weekly cisplatin dose is 40 mg/m^2 for all patients receiving pelvic EBRT. On the other hand, for patients receiving an EFRT, our institutional policy is to administer a cisplatin dose of 25 mg/m^2. Patients who cannot tolerate cisplatin received weekly carboplatin at a dose of area-under-curve (AUC) = 2. No patients received neoadjuvant or adjuvant chemotherapy.

2.3. Follow-up

At the end of treatment, patients were monitored every three months during the first two years, every six months for the next three years, and annually thereafter. Three months after the definitive treatment, the first response was evaluated by a gynecological examination together with an MRI and PET/CT. In the next follow-ups, gynecological examination was repeated and imaging techniques were only added in case recurrence was suspected.

2.4. Statistical analysis

Statistical Package for the Social Sciences version 23.0 (IBM, Armonk, NY, USA) was utilized for analyses, including descriptives, overall survival (OS), disease-free survival (DFS), local-regional recurrence-free survival (LRRFS) and distant metastasis-free survival (DMFS). All time-related events were calculated from the completion of treatment to the last follow-up, death, or recurrence whichever came first. LR was defined according to the Response Evaluation Criteria in Solid Tumors criteria [8]. RR was defined as a pelvic and/or para-aortic LN recurrence. DM was defined based on radiologic findings performed in case of clinical suspicion. The Kaplan-Meier method was used for the survival analysis and the log-rank test for the comparisons. Age, histology, number of involved LNs, LN localization, presence of CI LN metastasis, LN volume and size, maximum-standardized-uptake-value (SUVmax) of the involved LNs, cumulative EQD2 dose to the LNs and OTT were included in the univariate analysis according to the median value of numeric and to the dichotomization of categorical variables. The potentially significant covariates following univariate analyses with significant contribution to the survival estimation ($p < 0.10$)

were preserved in the final multivariate model. The Cox proportional hazards model was used for the multivariate analysis. Hazard ratios with 95% confidence interval (CI) were reported. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline patient, tumor and treatment characteristics

The patient, tumor and treatment characteristics are presented in Table 1. A total of 146 LNs were boosted. The median LN EQD2 was 64.2 Gy (range, 57.6–71.2 Gy). The dose distribution images of a patient are presented in Fig. 1.

3.2. Treatment results

Three months after the completion of treatment, 45 (96%) patients had a complete response (CR) and two (4%) had a partial response (PR) in the boosted LNs. Patients with a PR were evaluated in the gynecological oncology tumor board and were decided to be followed without additional treatment. At the sixth month after treatment, CR was obtained in all residual LNs.

Median follow-up was 30 months (range, 14–91 months). There was no recurrence in any of the 146 boosted LNs during the follow-up period and the LC rate was 100%. The 1- and 2-year rate of OS was 93.1% and 83.3%, DFS was 84.2% and 70.5%, LRRFS was 90.8% and 77.5%, and DMFS rate was 84.5% and 74.4%, respectively. There was one LR (i.e., at the cervix), two RR (i.e., para-aortic LN out of RT field), six DM, and one LR + DM. Both LRs were treated with systemic therapy due to unresectable tumors. In the two patients with a RR, both had ≥ 3 pelvic metastatic LNs at diagnosis. One of these patients was treated with para-aortic CRT after chemotherapy. Following salvage treatment, she had a CR and is still being followed-up without disease. The other patient was recommended a LND which she refused and was applied chemotherapy. In one patient with a solitary supraclavicular LN metastasis, 40 Gy in five fractions of stereotactic body RT was applied after chemotherapy and a CR was obtained in the follow-up. The other five patients with DM were all polymetastatic and chemotherapy was applied to all. Following CRT, hysterectomy was performed in one patient due to a suspected LR, but chronic inflammation was reported at pathological evaluation.

3.3. Prognostic factors

The results of univariate analysis are summarized in Table 2. In multivariate analysis, the non-SCC histology was found the only negative independent prognostic factor for DFS (hazard ratio [HR]: 13.6, 95% confidence interval [CI]: 1.3–13.4, $p = 0.025$) and DMFS (HR: 14.4, 95% CI: 1.3–14.9, $p = 0.025$).

3.4. Toxicity

Treatment was well tolerated without severe acute toxicity. The most common grade 1–2 acute toxicity was nausea and vomiting

Table 1
Patient, tumor and treatment characteristics.

	SIB (n, %)	SEB (n, %)	SIB + SEB (n, %)	All patients (n, %)	*p*
Age (med)	53 y (range, 31–76 y)	48 y (range, 29–80 y)	44 y (range, 38–62 y)	51 y (range, 29–80 y)	0.57
Tumor Histology					0.09
Squamous cell	24 (92)	14 (100)	6 (86)	44 (94)	
Adenosquamous	2 (8)	0 (0)	0 (0)	2 (4)	
Undifferentiated	0 (0)	0 (0)	1 (14)	1 (2)	
FIGO 2018 Stage					0.7
IIIC1r	18 (69)	10 (72)	6 (86)	34 (72)	
IIIC2r	7 (27)	3 (21)	0 (0)	10 (22)	
IVA	1 (4)	1 (7)	1 (14)	3 (6)	
Initial imaging					0.3
PET/CT	1 (4)	1 (7)	1 (14)	3 (6)	
MRI and PET/CT	25 (96)	13 (93)	6 (86)	44 (94)	
Involved LNs					
Number (med)	3 (range, 1–11)	3 (range, 1–6)	2 (range, 1–8)	3 (range, 1–11)	0.9
Size (med)	2 cm (range, 1–5 cm)	1.7 cm (range, 1–4 cm)	2.5 cm (range, 1.5–4.5 cm)	2 cm (range, 1–5 cm)	0.6
Volume (med)	2.7 cc (range, 1.15–15.8 cc)	2.6 cc (range, 1.3–5.6 cc)	3.5 cc (range, 1.8–14 cc)	2.8 cc (range, 1.15–15.8 cc)	0.08
SUVmax (med)	4.5 (range, 2–11)	6 (range, 3–11)	4 (range, 3–12)	5 (range, 2–12)	0.9
Location of involved LNs					0.2
Pelvic only without CI LNs	11 (42)	10 (72)	1 (14)	22 (47)	
Pelvic only with CI LNs	7 (27)	2 (14)	3 (43)	12 (25)	
Pelvic and PA LNs	8 (31)	2 (14)	3 (43)	13 (28)	
EBRT field					0.1
Pelvic	11 (42)	10 (72)	1 (14)	22 (47)	
Pelvic and PA	15 (58)	4 (28)	6 (86)	25 (53)	
Concurrent CHT					0.09
Cisplatin	26 (100)	11 (79)	7 (100)	44 (94)	
Carboplatin	0 (0)	3 (21)	0 (0)	3 (6)	
LN boost dose (med)	60 Gy (range, 56–64 Gy)	59.4 Gy (range, 54.4–60.4 Gy)	62 Gy (range, 60–66 Gy)	60 Gy (range, 54.4–66 Gy)	0.1
Fraction number of EBRT	28 (range, 28–28)	32 (range, 31–33)	31 (range, 30–32)	31 (range, 28–33)	0.5
Dose contribution of BRT* (med)	4 Gy (range, 0–9.6 Gy)	4.6 Gy (range, 1–8 Gy)	2.2 Gy (range, 0–6 Gy)	3.6 Gy (range, 0–9.6 Gy)	0.7
LN cumulative EQD2 (med)	64.2 Gy (range, 57.6–71.2 Gy)	63.2 Gy (range, 57.7–68.4 Gy)	68 Gy (range, 62.3–70.2 Gy)	64.2 Gy (range, 57.6–71.2 Gy)	0.07
OTT (med)	7 w (range, 6–8 w)	7 w (range, 6–9 w)	8 w (range, 7–9 w)	7 w (range, 6–9 w)	0.4
Response evaluation**					0.9
MRI	0 (0)	3 (21)	0 (0)	3 (6)	
PET/CT	1 (4)	1 (7)	1 (14)	3 (6)	
MRI and PET/CT	25 (96)	10 (72)	6 (86)	41 (88)	

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics, LN = lymph node, PET/CT = positron emission tomography/computed tomography, MRI = magnetic resonance imaging, SUVmax = maximum standardized uptake value, EBRT = external beam radiotherapy, CHT = chemotherapy, SIB = simultaneous integrated boost, SEB = sequential boost, BRT = brachytherapy, EQD2 = equivalent dose in 2-Gy fractions, PA = para-aortic, n = number, y = years, w = weeks, med = median.

* To the involved lymph nodes.

** Three months after treatment.

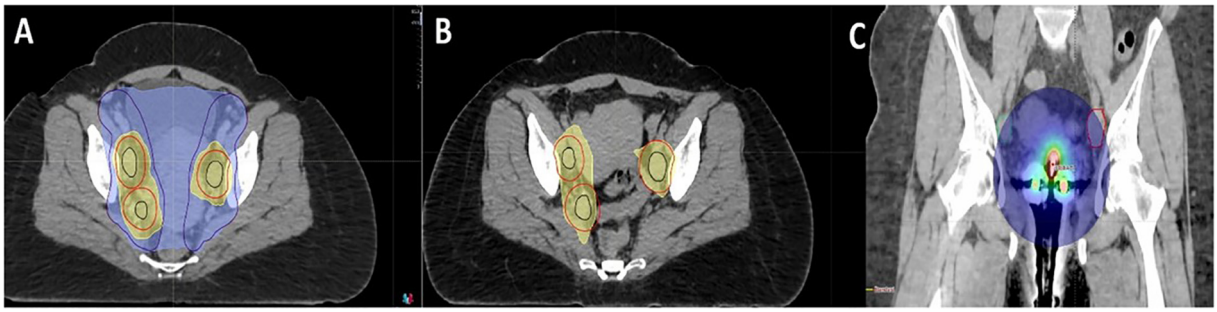

Fig. 1. Dose distribution of a patient treated with SIB (A) + SEB (B) techniques. An additional SEB dose was decided after calculating the dose contribution of BRT to the boosted LNs (C).

($n = 18$), followed by diarrhea ($n = 16$), and cystitis ($n = 10$). The rates of acute toxicities were not significantly different between SIB vs. SEB vs. SIB and SEB groups (Table 3). The most common grade 1–2 late toxicity was vaginal stenosis ($n = 6$). Late ≥ grade 3 toxicity was observed in three (6%) patients (i.e, 1-ureteral stenosis, 1-rectal bleeding, 1-pelvic fracture). The patient that developed ureteral stenosis, a total EQD2 of 64 Gy with a SIB technique was applied to involved LNs. The ureter was within the PTV of the boosted LN in a small portion along its tracing. The creatinine level of patient increased to 7 mg/dL in the sixth month after CRT and decreased to 1.4 mg/dL after a double J stent was placed. In the patient with rectal bleeding, toxicity developed seven months after CRT. The cumulative rectal dose was compatible with the recommendations (D2cc = 67.3 Gy) but a colonoscopy revealed a rectal ulcer [9]. She was treated medically but succumbed to DM. In the third patient, a CT was performed due to back pain 11 months after CRT and insufficiency fractures due to RT in the sacral and lumbar vertebrae were detected. Due to her medical comorbidities, surgery could not be performed and the patient was treated with vasodilators and analgesics.

4. Discussion

Our findings indicate that LN boost via modern RT techniques such as IMRT/VMAT provides excellent LC with minimal toxicity for patients with LACC. Although the residual LNs were observed on the MRI and/or PET/CT in 4% of patients three months following treatment, all of them disappeared at the sixth month. Similar to the recommendations in the EMBRACE-I study, patients with residual LNs did not require any treatment but were followed closely for recurrence [10].

Table 2
Results of univariate analysis.

Variable	2y OS	*p*	2y DFS	*p*	2y LRRFS	*p*	2y DMFS	*p*
Age								
<51 years ($n = 24$, 51%)	87%	0.197	73.2%	0.264	74.2%	0.697	82.7%	0.540
≥51 years ($n = 23$, 49%)	80%		69%		79%		67%	
Histology								
SCC ($n = 44$, 94%)	84.7%	0.287	73%	***0.011***	78.6%	0.457	77%	***0.005***
Non-SCC ($n = 3$, 6%)	66.7%		33%		66.7%		33%	
N of Metastatic LNs								
<3 ($n = 22$, 47%)	85.1%	0.476	75.7%	0.38	78.3%	0.521	82%	0.290
≥3 ($n = 25$, 53%)	80.4%		67.7%		75.6%		66.8%	
Location of Metastatic LNs								
Pelvic ($n = 35$, 75%)	85.8%	0.075	78%	***0.012***	81%	***0.04***	84%	***0.004***
Pelvic + PA ($n = 12$, 25%)	75%		50%		67%		50%	
CI LN Metastasis								
Present (n = 25, 53%)	67%	***0.009***	51%	***0.038***	61%	***0.018***	51%	***0.011***
Absent (n = 22, 47%)	100%		89%		94%		92%	
CI LN Metastasis*								
Present ($n = 12$, 35%)	53%	***0.009***	48%	***0.04***	50%	***0.043***	50%	0.066
Absent ($n = 22$, 65%)	100%		89%		94%		96%	
Volume of Metastatic LNs								
<2.8 cc (n = 22, 47%)	90.5%	0.624	74%	0.33	81.3%	0.95	75.2%	0.265
≥2.8 cc ($n = 25$, 53%)	79.6%		71.3%		70.8%		77%	
Size of Metastatic LNs								
≤2 cm (n = 25, 53%)	87%	0.322	74%	0.396	75.6%	0.308	78%	0.210
>2 cm (n = 22, 47%)	82.7%		70.8%		80.6%		74.8%	
SUVmax of Metastatic LNs								
≤5 ($n = 29$, 62%)	88.2%	0.983	71.8%	0.621	82.6%	0.77	77.7%	0.423
>5 (n = 18, 38%)	80.7%		71.4%		85.7%		72%	
Cumulative EQD2 Dose to LNs								
≥64.2 Gy (n = 24, 51%)	88.2%	0.136	70%	0.153	86%	0.3	80%	0.327
<64.2 Gy (n = 23, 49%)	78.3%		60.8%		67.2%		68.9%	
Cumulative EQD2 Dose to LNs								
>60 Gy ($n = 28$, 85%)	88%	0.893	78%	0.485	82%	0.652	85%	0.707
≤60 ($n = 7$, 15%)	82%		78%		80%		80%	
OTT								
≤7 weeks (n = 28, 7%)	88%	0.702	82%	0.256	82.5%	0.759	88.5%	0.104
>7 weeks ($n = 7$, 15%)	75%		64.3		75%		65%	

Abbreviations: OS = overall survival, DFS = disease-free survival, LRFS = locoregional recurrence-free survival, DMFS = distant metastasis-free survival, SCC = squamous cell carcinoma, N = number, LN = lymph node, PA = para-aortic, CI = common iliac, SUVmax = maximum standardized uptake value, EQD2 = equivalent dose in 2-Gy fractions, OTT = overall treatment time.

* For the 34 patients with pelvic LNs only.

Table 3
Toxicities of treatment groups.

Toxicity	SIB (n, %)	SEB (n, %)	SIB + SEB (n, %)	All (n, %)	*p*
Acute (≤ Grade 2)					
Nause and vomiting	8 (30)	7 (50)	3 (43)	18 (38)	0.8
Diarrhea	6 (23)	6 (42)	4 (57)	16 (34)	0.3
Radiation cystitis	4 (15)	4 (28)	2 (28)	10 (21)	0.9
Radiation proctitis	2 (7)	2 (14)	0 (0)	4 (8)	0.09
Anemia	4 (15)	2 (14)	1 (14)	7 (15)	0.6
Leukopenia	5 (19)	2 (14)	1 (14)	8 (16)	0.8
Trombocytopenia	2 (7)	0 (0)	0 (0)	2 (4)	0.07
Acute (≥ Grade 3)	0 (0)	0 (0)	0 (0)	0 (0)	N/A
Late (≤ Grade 2)					
Vaginal stenosis	2 (7)	3 (21)	1 (14)	6 (13)	0.5
Radiation proctitis	1 (3)	0 (0)	0 (0)	1 (2)	0.2
Late (≥ Grade 3)					
Ureteral stenosis	1 (3)	0 (0)	0 (0)	1 (2)	0.08
Radiation proctitis	1 (3)	0 (0)	0 (0)	1 (2)	0.4
Pelvic fracture	0 (0)	0 (0)	1 (14)	1 (2)	0.4

Abbreviations: SEB = sequential boost, SIB = simultaneous integrated boost, n = number, N/A = not available.

Both MRI and PET/CT are critical for staging in LACC. However, although the specificity of PET/CT is high, its sensitivity is low for detecting occult LN metastasis. The false-negative rates of up to 20% have been reported in the para-aortic region [11]. Therefore, the extent of the disease is thought to be determined more accurately by surgical staging. However, the role of LND is controversial due to its lack of survival benefit and the risk of postoperative toxicity [1]. In the randomized UTERUS-11 study, laparoscopic surgical staging was compared with CT and MRI staging [12]. Although the authors reported similar survival rates for both techniques, an up-staging was reported in one third of patients after laparoscopic LND. However, the fact that PET/CT was not performed for staging in this study is a serious limitation. In addition, the authors underlined surgical staging did not cause a delay in starting CRT. However, in some series, it has been reported that LND can delay the onset of CRT due to postoperative morbidity, which has a negative impact on survival [13].

Metastatic LNs are recommended to be managed in a multidisciplinary approach in LACC [14]. Moreover, considering the false-negative rates of PET/CT, particularly in the para-aortic region, elective para-aortic irradiation is becoming increasingly popular. In our study elective para-aortic RT was applied to 13 stage IIIC1 patients all of whom had positive CI LNs, and six of whom had a total of ≥ 3 involved pelvic LNs. During the follow-up, none of these patients recurred at the para-aortic field. On the other hand, pelvic RT alone was performed in eight patients with ≥ 3 involved pelvic LNs without positive CI LNs, and para-aortic recurrence was observed in two (%25) of them. Therefore, risk adapted elective para-aortic irradiation appears to be a promising alternative to surgical staging. The long-term results of the prospective EMBRACE-II study are pending and will provide better quality information on this subject.

Dose escalation can be applied in LNs with a SIB or SEB technique. In the SIB technique, while the larger target volume receives fraction doses of 1.8–2 Gy, higher fraction doses can be delivered simultaneously to smaller volumes, such as the suspicious LNs. The most prominent advantage of SIB is that it does not prolong the OTT and the boosted LNs are also benefited from concurrent chemotherapy. On the other hand, the advantages of SEB is to deliver an additional dose to the shrunken LN volume after EBRT, and the dose contribution from BRT can also be taken into account. Although there is no study in the literature comparing SIB and SEB techniques, retrospective studies showed that dose escalation with both techniques are effective for nodal control [4,5,15,16].

Metastatic LNs after EBRT also receive varying doses during BRT, according to their locations. However, these doses are usually low about 2–6 Gy, and BRT does not contribute an additional dose to superiorly located LNs such as the para-aortic LNs [17]. In our findings, the boosted LNs received a median 3.6 Gy during BRT. When calculating the total dose achieved with EBRT in clinically involved LNs, the dose contribution of BRT should be kept in mind prior to additional dose prescription, particularly for the LNs in the lower pelvis.

It is well-known that there is a strong dose-response relationship in the involved LNs in LACC. In the study of Bacorro et al. [17], the LN volume and dose were independent prognostic factors for nodal control, and it increased with > 57.5 Gy LN dose. In the presence of macroscopic disease, a total 60–66 Gy EQD2 are recommended depending on the size and location of the LNs [1,15]. In our study, a median EQD2 of 64 Gy was applied although it varied depending on factors such as OAR doses and the locations of LNs. When the required doses for pelvic LNs can be achieved with SIB and BRT, SEB may not be required. On the other hand, SEB can be considered in LNs in the para-aortic region, since the contribution of BRT would be insignificant. As a standard protocol in our center, we currently take the decision of SEB dose to pelvic LNs by taking into account the dose contribution of BRT after EBRT ± SIB and we aim to reach ≥ EQD2 of 60 Gy.

In the retrospective studies on dose escalation, LN boost was stated a safe technique, and the rates of grade ≥ 3 late toxicity were 0–12% [3–5]. In our findings, the rate of ≥ grade 3 late toxicity was found 6%. However, within this 6% late toxicity rate, only the patient with ureteral stenosis developed toxicity due to the application of a LN boost. In the other two patients, we interpreted the cause of toxicity as CRT and BRT, not the LN boost. Therefore, we can consider the grade ≥ 3 late toxicity rate directly due to LN boost was only 2%.

We applied a cisplatin dose of 25 mg/m^2 in order to increase the tolerance to the treatment without a need for treatment breaks due to the toxicity in patients who need EFRT. There are several trials in the literature regarding the efficacy of low dose cisplatin in the treatment of LACC used concomittantly with RT. [18,19] The median number of concomittant chemotherapy cycle with this approach in our patients was 6 and there were no patients that necessitated a break in the treatment. The regional control rate in these patients was 100% and only 5% developed either local progression or recurrence.

The prognostic factors for oncologic outcome observed in our study were similar to the literature as the histopathology and LN metastasis being the most important factors [20]. There are studies showing that SUVmax of the primary tumor is a prognostic factor in LACC patients treated with definitive CRT [21–23]. However, SUVmax of the metastatic LNs was not found prognostic in our study, most probably due to our excellent nodal control.

Although SIB or SEB is used alone for dose escalation in most previous studies, our study also included the combination of them and the dose contribution of BRT to the involved LNs was taken into account when calculating the total dose. Considering our 100% LC rate in boosted LNs, we think that the application of dose escalation through modern RT

techniques would increase nodal control without causing serious toxicity and may prevent unnecessary surgical interventions such as LND or surgical removing the bulky LNs. In addition, combined use of SIB and SEB techniques may provide a higher dose prescription to the clinically involved LNs. Although, our study has a high LC rate with LN boost, it has limitations of having retrospective design, small number of patients, and short time of follow-up.

In conclusion, RT dose escalation to the clinically involved LNs in patients with LACC yields an excellent LC rate, even in very large LNs. However, prospective randomized studies comparing surgical excision and RT boost are needed for clarifying the optimal management.

Funding

None.

Consent to publish

All the authors give consent to publish.

Financial disclosures

None.

Ethical approval and consent to participate

This study was approved by the institutional ethics board (GO 23/306, 18.04.2023) and conducted in compliance with the principles of the Helsinki declaration.

Previous presentation

The preliminary results of this study was presented at 'ASTRO 2022 annual meeting' as an e-poster and published as an abstract at International Journal of Radiation Oncology, Biology, Physics (DOI: https://doi.org/10.1016/j.ijrobp.2022.07.1244).

CRediT authorship contribution statement

Alper Kahvecioglu: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Ezgi Gurlek:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation. **Fazli Yagiz Yedekci:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation. **Sezin Yuce Sari:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Melis Gultekin:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Ferah Yildiz:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

None.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2023.06.020.

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