Results of External Beam Parametrial Boost for Advanced Cervical Cancer

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Abstract

Introduction Even though largely used, external beam parametrial boost concurrent with brachytherapy for advanced cervical cancer is consensual and lacks prospective evidence.

Objective To assess the impact of external beam parametrial boost on cancer control and toxicity.

Materials and Methods The present research is a retrospective, single, institutional study of patients with locally advanced cervical cancer with parametrial involvement.

Results The charts of 247 patients with parametrial invasion treated with concurrent chemoradiation and brachytherapy were assessed. The mean follow-up was 48.2 months. Median overall survival (OS), local progression-free survival (LPFS), and distant progression-free survival (DPFS) were not reached. Overall survival, LPFS, and DPFS at 3 years were 81.4%, 87.4%, and 83.4%, respectively. The mean OS for patients receiving parametrial boost and those that did not receive was 47.4 months and 46.8 months, and the mean LPFS was 43.9 months and 44.0, respectively. There were no differences regarding acute ($p = 0.662$) or late ($p = 0.923$) toxicity between groups. There were 6 deaths due to treatment, all in the parametrial boost group.

Conclusion External beam parametrial boost should be carefully and not routinely considered. There is a lack of good evidence on the matter, and prospective studies should be designed regarding parametrial boost, perhaps with interstitial brachytherapy and not external beam.

Keywords
- brachytherapy
- radiotherapy
- uterine cervical neoplasms

Introduction

Even though external beam parametrial boost (EBPB) for cervical cancer with parametrial invasion has been used for a long time, its impact is still unknown. In 1983, Hamberger et al.[1] described the possible association with toxicities. For a long time, though, the prescription of EBPB was recommended. The American Brachytherapy Society (ABS) favored EBPB in its 2012 version.[2] Current publications still describe the use of EBPB,[3] but ongoing trials omit the boost, at least with external beam radiation.[4]

Objective

The present article investigates the role of EBPB in a single university center retrospective cohort. It aims to describe the

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use of EBPB, correlations with other demographics and treatment variables, and its impact on outcomes.

Materials and Methods

We retrospectively assessed patients diagnosed with locally advanced cervical cancer that were treated with radical radiotherapy from 2013 to 2019. All patients had biopsy-proven carcinoma of the cervix and parametria invasion by physical exam in the first clinical consultation by physical exam or proven invasion on staging magnetic resonance imaging (MRI). Survival was assessed from the beginning of radiation treatment. All patients were staged with thorough physical exam and thorax, abdomen, and pelvis computed tomography (CT) scans. Pelvic MRI was desirable, but not mandatory. There was no surgical lymph nodes sampling. The patients were treated according to the institutional protocol. All patients underwent 3D conformal radiotherapy for the whole pelvis in the dose of 45 Gy delivered in 25 fractions. Patients with no parametrial invasion detected on physical examination but suspected or positive in the MRI could receive 50.4 Gy in 28 fractions to the whole pelvis and no EBPB. When indicated, EBPB was delivered through conventional 3D technique, with anteroposterior opposed fields with a 4-cm wide midline block. Brachytherapy was delivered after the third week or at the end of pelvic irradiation, according to local geometric feasibility. Both conventional 2D point-based planning and image-guided (CT or MRI) 3D planning (image-guided brachytherapy – IGBT) were used. Four fractions of 7 to 7.5 Gy to point A or to the high-risk clinical target volume (HR-CTV) were prescribed.[5] The EBPB was initiated the end of whole pelvis irradiation and with at least the delivery of the first brachytherapy fraction. The prescribed dose was 9 to 14 Gy in 5 to 7 fractions. Patients with positive lymph nodes in the para-aortic region were treated with extended-field to cover that region. As per institutional protocol, no patient was treated electively to the para-aortic region. Concomitant chemotherapy was delivered weekly 40 mg/m^2 cisplatin for 5 to 6 cycles. External beam radiation therapy and chemotherapy were not given on the day of brachytherapy. Induction chemotherapy was prescribed for a few patients during the studied period either due to an institutional protocol or to expected delays in the beginning of radiotherapy (RT).

The statistical analysis consisted of descriptive and frequencies analysis. Patients were divided into two groups, with or without EBPB. A comparison between groups was performed using the Fisher's exact test. Survivals outcomes were assessed from the beginning of radiation treatment with the Kaplan-Meier method. The Log-rank test was used for univariate analysis, and Cox regression test for multivariate analysis. The Stata (StataCorp LLC, College Station, TX, USA) software, version 18, was used for the analysis, and the significance level was set at 5% ($p \leq 0.05$).

The present study was approved by the local ethics committee in April 2021, and it follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines for reporting retrospective cohorts.[6]

Results

The charts of 247 patients with cervical cancer diagnosis treated with curative intent from January 2013 to July 2019 were retrospectively reviewed.

The mean age at diagnosis was 49.7 years (range: 20–86). Most patients presented good Eastern Cooperative Oncology Group (ECOG) performance status (95.5%) and squamous cell carcinoma histology (88.7%). The median tumor size was 5.3 cm (2.1–10.7). Besides parametrial involvement, 55.9% presented enlarged pelvic and/or paraortic lymph nodes classified as positive by imaging (CT or MRI) (stages IIIC and IVA) (►**Table 1**). Most patients were treated according to the institutional protocol, with 87.4% receiving parametrial boost as described. The median time between the beginning of treatment and the final brachytherapy session was 9.4 weeks (range: 6.2–16.4 weeks). For 75 patients (30.4%), brachytherapy began during EBRT treatment; and for only 9 (3.6%), it exceeded 10 days. Parametrial boost did not affect the total duration of the treatment ($p = 0.63$). A comparison between the group that received EBPB and the one that did not is presented in ►**Table 1**. The presence of hydronephrosis ($p = 0.029$) and the use of conventional 2D planning brachytherapy ($p < 0.001$) were correlated with prescription of EBPB.

With a mean follow-up of 48.2 months (2.7–112.3 months), 91 (36.8%) deaths were reported. Median overall survival (OS), local progression-free survival (LPFS), and distant progression-free survival (DPFS) were not reached. Overall survival, LPFS, and DPFS at 3 years were 81.4%, 87.4%, and 83.4%, respectively. There were 91 (36.8%) deaths reported. We assessed whether treatment time correlated with OS, LPFS, and DPFS and treatment time shorter than 10 weeks positively impacted OS ($p = 0.03$) but not LPFS ($p = 0.62$), nor DPFS ($p = 0.64$). Kaplan-Meyer curves for patients that received and did not receive parametrial boost for LPFS can be seen in ►**Fig. 1**.

A univariate analysis on survival can be seen in ►**Table 2**. The EBPB did not impact survival. The factors that impacted OS and LPFS were selected for the multivariate analysis, so the EBPB was not selected. For the multivariate analysis, only variables that were significant ($p < 0.05$) on univariate analysis were selected, and the results can be seen in ►**Table 3**. In the multivariate analysis, performance and hydronephrosis were independent factors that correlated with OS. Distant metastasis-free survival (DMFS) was impacted by hydronephrosis as well, but also, paradoxically, by the dose of the EBPB, even though the use of EBPB itself did not impact it.

The correlation between EBPB and toxicity was evaluated, and it is summarized in ►**Table 1**. The dose of EBPB also did not impact toxicity, neither acute ($p = 0.662$) nor late ($p = 0.923$). There were 6 reported deaths due to treatment, all in the parametrial boost group. All cases of grade-5 toxicity were observed in those patients who were operated on due to acute abdominal pain from bowel toxicity

Table 1 Comparison between the groups that did and did not receive parametrial boost

Demographics	Parametrial boost		*p*
	No N = 31 (12.5%)	Yes N = 216 (87.5%)	
Age (years): ≤ 60; > 60	26 (83.9%); 5 (16.3%)	165 (76.4%); 51 (23.6%)	0.352
ECOG: 0–1; 2–4	31 (100%); 0	205 (94.9%); 11 (5.1%)	0.199
Histology: Squamous cell; Adenocarcinoma; Other	27 (87.0%); 2 (6.5%); 2 (6.5%)	192 (88.9%); 22 (10.2%); 2 (0.9%)	0.064
Tumor size (cm): ≤ 5; > 5	12 (38.7%); 19 (61.3%)	109 (51.9%); 101 (48.1%)	0.170
Hydronephrosis: Yes; No	1 (3.2%); 30 (96.8%)	41 (19.0%); 175 (81.0%)	**0.029**
Primary FIGO stage: IIB–IIIA; IIIB–IVA	13 (41.9%); 18 (58.1%)	104 (48.2%); 112 (51.8%)	0.51
Nodal disease: Yes; No	19 (61.3%); 12 (38.7%)	119 (55.1%); 97 (44.9%)	0.516
Treatment			
EBRT dose: 45 Gy; 50.4 Gy	23 (74.2%); 8 (25.8%)	214 (99.1%); 2 (0.9%)	< **0.0001**
Para-aortic RT: Yes; No	6 (19.3%); 25 (80.7%)	25 (11.6%); 191 (88.4%)	0.221
Nodal boost: Yes; No	5 (16.1%); 26 (83.9%)	20 (9.3%); 196 (90.7%)	0.236
Brachytherapy: Conventional; IGBT	17 (54.8%); 14 (45.2%)	182 (84.3%); 34 (15.7%)	**0.0001**
Brachytherapy dose (to point A): ≤ 7 Gy; > 7 Gy	17 (54.8%); 14 (45.2%)	82 (38.0%); 134 (62.0%)	0.073
Chemotherapy (neoadjuvant): Yes; No	4 (12.9%); 27 (87.1%)	53 (24.5%); 163 (75.5%)	0.151
Chemotherapy (concurrent): Yes; No	31 (100%); 0	211 (97.7%); 5 (2.3%)	0.392
Total treatment duration: ≤ 10 weeks; > 10 weeks	24 (77.4%); 7 (22.6%)	159 (73.6%); 57 (26.4%)	0.638
Toxicities			
Acute GI:			
0–2; 3–4	31 (100%); 0	211 (97.7%); 5 (2.3%)	0.309
Acute GU: 0–2; 3–4	31 (100%); 0	209 (96.8%); 7 (3.2%)	0.392
Acute (any): 0–2; 3–4	29 (93.6%); 2 (6.5%)	197 (91.2%); 19 (8.8%)	0.662
Late GI: 0–2; 3–4; 5	26 (83.9%); 5 (16.1%); 0	187 (86.6%); 25 (11.6%); 4 (1.8%)	0.589
Late GU: 0–2; 3–4; 5	28 (90.3%); 3 (9.7%); 0	183 (84.7%); 31 (14.4%); 2 (0.9%)	0.665
Late (any): 0–2; 3–5	23 (74.2%); 8 (25.8%)	162 (75.0%); 54 (25.0%)	0.923

Abbreviations: EBRT, external beam radiation therapy; ECOG, Eastern Cooperative Oncology Group performance status scale; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics) staging system; GI, gastrointestinal; GU, genitourinary; IGBT, image-guided brachytherapy (three-dimensional); RT, radiotherapy.
Note: The *p*-values stand for the correlation between each variable and the parametrial boost treatment group.

(perforation, blockage, or both) or ureteral obstruction with the need of open surgery intervention after failed double J catheterization and with no findings of disease relapse. Patients with doubtful disease relapse and those that did not undergo surgery to confirm disease relapse were not considered grade-5, but grade-4 toxicity. The only variable that correlated with toxicities was the prescription of higher dose in the brachytherapy treatment (30 Gy to either point A or HR-CTV). It correlated with any late ($p < 0.001$) but not acute ($p = 0.16$) toxicity.

Discussion

Consistently, EBPB is not associated with better survival. Our results are in accordance with this finding. In addition, hydronephrosis presented great impact on survival and disease control in our series, like in other large retrospective studies and systematic reviews that consistently show this trend.[7–9] Hydronephrosis consistently impacts survival, and it has been independently assessed comparing to stage and renal function.[10] Usually, EBPB is associated with more advanced stages, which could be a confounding factor, but

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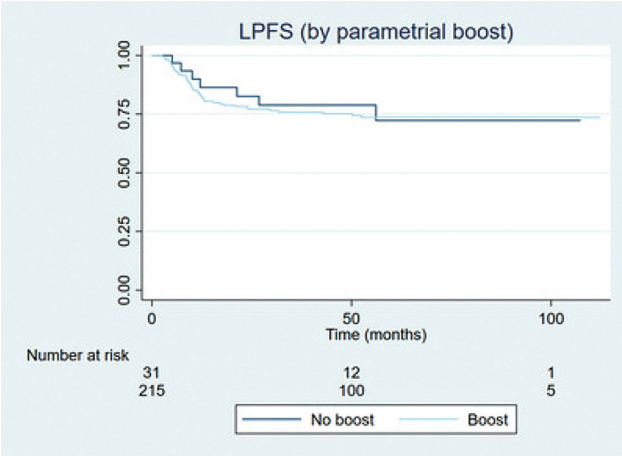

Fig. 1 Local progression-free survival (no median values reached; $p = 0.53$).

not in this cohort, even though it was associated with hydronephrosis. Therefore, hydronephrosis should be regarded as a confounding factor since in our sample more patients with it underwent EBPB ($p = 0.029$). The use of EBPB on patients that did not have parametrial invasion is a curious fact, possibly associated with dubious descriptions on staging images and inconsistences between images and physical examination. The conclusion of the findings in the present study, and in the literature, is that EBPB does not increase disease control.

Increased toxicity is expected with EBPB. Parametrial boost delivered with a similar technique as the one used in our institution (4 cm midline shielding) increased the rate of proctitis, mostly related to higher doses in a large patient cohort.[11] The authors suggested that incomplete midline shielding of the upper rectum might have been the cause. Thus, attempts to try to lower the bowel doses should be

Table 2 Univariate analysis of survival outcomes

Patient characteristics	N	OS			LPFS			DMFS		
		Median	Events	*p*	Median	Events	*p*	Median	Events	*p*
Age: ≤ 60 years; > 60 years	191; 56	91.5; NR	76; 16	0.18	NR; NR	50; 8	0.08	NR; NR	55; 19	0.61
ECOG: 0–1 ≥ 2	236; 11	NR; 19.0	84; 8	< 0.001	NR; 29.6	54; 4	0.09	NR; 62.0	71; 3	0.52
Histology: Squamous cell; Adenocarcinoma; Other	219; 24; 4	91.5; NR; 63.5	83; 7; 2	0.78	NR; NR; 56.1	49; 8; 1	0.51	NR; NR; NR	65; 8; 1	0.94
Tumor size (cm); ≤ 5; > 5	12;7 120	NR; 79.6	41; 48	0.18	NR; NR	24; 34	0.09	NR; NR	35; 37	0.48
Hydronephrosis: Yes; No	42; 205	22.0; NR	30; 62	< 0.001	42.8; NR	16; 42	< **0.01**	25.4; NR	22; 52	< **0.01**
Primary FIGO stage: IIB–IIIA; IIIB–IVA	117; 130	NR; 91.5	27; 65	0.56	NR; 42.8	16; 42	0.55	NR; NR	19; 55	0.73
Nodal disease: Yes; No	138; 109	79.6; NR	61; 31	**0.01**	NR; NR	35; 23	0.37	NR; NR	48; 26	**0.02**
EBRT dose: 45 Gy; 50.4 Gy	237; 10	NR; NR	89; 3	0.77	NR; NR	55; 3	0.59	NR; NR	73; 1	0.23
Parametrial boost: Yes; No	216; 31	NR; NR	82; 10	0.58	NR; NR	51; 7	0.79	NR; NR	68; 6	0.17
Parametrial dose: ≤10 Gy; > 10 Gy	176; 71	91.5; 77.1	58; 25	0.96	NR; NR	35; 17	0.98	NR; NR	55; 13	**0.02**
Para-aortic irradiation: Yes; No	31; 216	49.4; 91.5	16; 76	**0.04**	NR; NR	6; 52	0.80	70.2; NR	13; 61	**0.04**
	25; 222	91.5; NR	10; 82	0.98	NR; NR	7; 51	0.61	74.2; NR	10; 64	0.44

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Table 2 (*Continued*)

Patient characteristics	N	OS			LPFS			DMFS		
		Median	Events	*p*	Median	Events	*p*	Median	Events	*p*
Nodal boost: Yes; No										
Brachytherapy: Conventional; IGBT	199; 48	91.5; NR	77; 15	0.83	NR; NR	46; 12	0.66	NR; NR	65; 9	0.20
Brachytherapy dose: $\leq$ 7 Gy; $>$ 7 Gy	99; 148	NR; 79.6	33; 59	0.17	NR; NR	19; 39	0.12	NR; NR	30; 44	0.71
CT (neoadjuvant): Yes; No	57; 190	77.1; NR	25; 67	0.34	NR; NR	15; 43	0.67	NR; NR	22; 52	0.18
CT (concurrent): Yes; No	242; 5	NR; 24.1	89; 3	0.06	NR; NR	57; 1	0.72	NR; NR	72; 2	0.25
Treatment duration: $\leq$ 10 weeks; $>$ 10 weeks	183; 64	NR; 72.4	61; 28	**0.03**	NR; NR	40; 15	0.62	NR; NR	52; 19	0.64

Abbreviations: CT, chemotherapy; DMFS, distant metastasis-free survival; EBRT, external beam radiation therapy; ECOG, Eastern Cooperative Oncology Group performance status scale; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics) staging system; IGBT, image-guided brachytherapy (3D); LPFS, local progression-free survival; NR, not reached; OS, overall survival.
Note: The median values are expressed in months.

made. In our cohort, no statistically significant differences were found between the boost and no boost groups regarding toxicity. In addition, the incidence of grades-3 and -4 toxicity doubled in the EBPB group ($p > 0.05$). These findings do not indicate that EBPB should not be used, but dose to organs at risk (OAR) must be a concern since it reflects on toxicity.

The use of EBPB is historical. In 2012, the ABS[2] guidelines for cervical cancer brachytherapy still recommended its use,

Table 3 Uni and multivariate analyses for overall and distant metastasis-free survivals

Variable	N	DMFS				OS			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		Median	*p*	*p*	95%CI	Median	*p*	*p*	95%CI
ECOG: 0–1; $\geq$ 2	236; 11	NR; 62.0	0.09	-	-	NR; 19.0	$<$ **0.001**	**0.03**	0.06–1.72
Hydronephrosis: Yes; No	42; 205	25.4; NR	$<$ **0.001**	$<$ **0.001**	0.57–1.64	22.0; NR	$<$ **0.001**	$<$ **0.001**	0.69–1.66
Nodal disease: Yes; No	138; 109	NR; NR	**0.02**	0.052	-0.04–1.07	79.6; NR	**0.01**	0.10	-0.07–0.86
Parametrial dose: $\leq$ 10 Gy; $>$ 10 Gy	176; 71	NR; NR	**0.02**	**0.02**	0.08–1.31	77.1; 91.5	0.96	-	
Para-aortic RT: Yes; No	31; 216	70.2; NR	**0.04**	0.32	-0.32–0.97	49.4; 91.5	**0.04**	0.06	-0.23–1.09
Treatment duration: $\leq$ 10 weeks; $>$ 10 weeks	183; 64	NR; NR	0.64	-	-	NR; 72.4	**0.03**	0.48	-0.31–0.65

Abbreviations: 95%CI, 95% confidence interval; DMFS, distant metastasis-free survival; ECOG, Eastern Cooperative Oncology Group performance status scale; NR, not reached; OS, overall survival; RT, radiotherapy.
Note: The median values for survival are expressed in months.

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and again in 2019, the same institution recommended that low and middle-income countries use EBPB.[12] Another publication from the ABS in the same year[13] highlighted the need to define how brachytherapy doses may impact lymph node or parametrial boosts, which is important mainly when integrated external beam boost or interstitial implants are not available. Thus, this is still a debatable subject. But as of 2019, the ABS does not formally recommend the use of EBPB in its guideline.

In the conventional brachytherapy era, EBPB is prescribed for patients with parametrial involvement. Jamora et al.[14] correlated EBPB indication with more advanced stages (IIIB) and the use of concurrent chemotherapy. A survey from the Gynecological Cancer Intergroup from 2012[15] reported the use of brachytherapy throughout the world and the consistency of prescription. In the survey, some institutions reported the use of parametrial boost. No more details regarding the boost were provided. Nevertheless, even in the conventional brachytherapy era, EBPB was associated with increased toxicity, but not better outcomes.[11] Even with the use of enhanced tools for diagnosis of compromised parametrium, better coverage cannot be associated with improved outcomes.[16] No prospective randomized study yet was designed to answer this question.

In the era of IGBT, EBPB has become more controversial. In dosimetric studies, the use of EBPB is not associated with improved coverage of the target volume but to increased dose to OAR.[17] Less-than-optimal staging and lack of brachytherapy (intracavitary or interstitial) were associated with a higher indication of EBPB in a multicentric study.[18] The delivery or not of the boost did not influence the outcomes, but the better technology and improvement of target definition in the more recent period was highly associated with better outcomes. The development of interstitial brachytherapy for parametria coverage, which does increase dose to target without increasing OAR dose,[19] affected the use of EBPB in newer clinical trials. The RetroEMBRACE study[20] described great results without the use of EBPB, with fewer toxicities, such as gastrointestinal (7%) and genitourinary (5%). In the EMBRACE trial,[21] there is a report for disease recurrence on positive parametrial nodes (16%), but external beam boost to those same nodes did not improve disease control. Afterwards, the EMBRACE II trial did not allow external beam boost to parametrial nodes but not to the parametria themselves. Parametria should be treated, when indicated, with interstitial brachytherapy. In fact, in a systematic review of interstitial brachytherapy for cervical cancer, 60% of the patients had stage IIIB disease or higher and yet, a local control rate of 79% was found. The local control seemed to correlate with the dose delivered to the tumor, while toxicity rates were similar to those of other cervical cancer series using 3D image-based brachytherapy.[22]

The current is a retrospective study; thus, by its own nature, it has method-related biases, such as registration and selection biases. Nevertheless, this study is a considerably large retrospective cohort of a large, single-center academic hospital. Although there has been long-time interest in comparing EBPB to other boosts, this issue has not been addressed by any comparative study to our knowledge, which makes our data new and important to guide new prospective research and guidelines.

It is important to highlight the global trend in prospective trials to include an interstitial IGBT boost to the parametria. The EMBRACE II prospective trial actively suggests the use of interstitial boost and describes its protocol. In cervical cancer, attempts to replace brachytherapy by dose escalation with high technology external beam irradiation (stereotactic body radiotherapy – SBRT) have been made. Dosimetric studies compared SBRT to conventional brachytherapy and defended the technique.[23] A phase-I trial was designed to obtain the best dose for the use of SBRT.[24] Nevertheless, retrospective studies with small samples have shown that SBRT results for control are worse than older technologies of brachytherapy.[25] In the USA, nation-wide assessments showed that this substitution can be very detrimental. In the current study, the use of external beams was associated with larger lesions and smaller treatment centers. The impact of brachytherapy, however, was larger than the impact of concurrent chemotherapy.[26] The rationale that can be drawn from these studies is that the impact of brachytherapy for cervical cancer is superior to that of external beam. Considering parametrial boosts, an interstitial brachytherapy boost should be considered a better option than an external beam design for future trials.

Conclusion

External beam parametrial boost was not associated with improved survival in the current study but presented a trend to increase toxicity. External beam parametrial boost should not be used routinely, and its indication and dose should be balanced with the potential risk of complications and the expected disease control. Since most prospective trials in the modern era do not use EBPB and are reporting favorable outcomes, new studies should investigate the role of parametrial boost with interstitial brachytherapy.

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03582818.9.0000.0065.

Clinical Trials
None.

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Conflict of Interests
The authors have no conflict of interests to declare.

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