Research Journal of Oncology

Open access Research Article

Clinical Outcomes of Various Alternatives to Brachytherapy Boost after Neoadjuvant Chemoradiation for Locally Advanced Cervical Cancer: A Retrospective Cohort Study

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ABSTRACT

Objective: This study aimed to compare the available treatment options for advanced cervical cancer that is reported for the first time in Georgia.

Methods: This study identified and analyzed 43 patients who received definitive treatment. Data were collected, medians and life tables were computed using the product-limit estimate by the Kaplan-Meier method, and the log-rank test was used to assess statistical significance.

Results: The median follow-up period was 33 months. The overall reported loco-regional recurrence was 23.26% (7.14%, 29.41%, 33.33%, and 33.33% in hysterectomy, brachytherapy, Intensity-Modulated Radiation Therapy [IMRT] and Stereotactic Body Radiation Therapy [SBRT]), with the distant failure rates of 14.29%, 35.29%, 44%, and 66%, respectively. The 3-year disease-free survival was the highest in the post-radiation hysterectomy group (86%) compared to brachytherapy, IMRT, or SBRT groups (70%, 55%, and 33%, respectively). The 3-year overall survival was the highest in the SBRT boost group (100%) compared to the hysterectomy, brachytherapy, and IMRT groups (78%, 76%, and 55%, respectively).

Conclusion: Brachytherapy is preferred for treating advanced cervical cancers after external beam radiation and chemotherapy. However, if unavailable, alternatives can give a chance for local control and disease-free survival.

Keywords: Cervical cancer; Uterus cervix; Alternatives of brachytherapy; Neoadjuvant chemoradiation

INTRODUCTION

Cervical Cancer (CC) is a significant global health problem. CC is the fourth most reported type of cancer in females [1]. Approximately 90% of CC-related deaths occur in low and middle-income countries [2]. The early-stage invasive disease can be treated with a high probability of cure, but females with locally advanced CC (LACC) (stage IB2 to IVA) have a higher likelihood of recurrence and metastases. The standard of care for LACC includes conventional External Beam Radiation Therapy (EBRT) and Concurrent Chemotherapy (CTX), followed by Brachytherapy Boost (BB). BB is ideal for treating CC because it delivers a very high radiation dose to the tumor and a much lower dose to the nearby normal tissues [3]. Many patients in developing countries cannot undergo brachytherapy or decline brachytherapy due to medical, financial, access, or social purposes. CC is the fourth most reported cancer in Georgia [4]. Treatment outcomes are poor for several reasons, including the late-stage presentation and incomplete evaluation by current recommendations. Brachytherapy is only available in the capital city, often hours from the patient's residence. Brachytherapy techniques and dosimetry have only recently been updated.

Received:	05-December-2022	**Manuscript No:**	IPRJO-22-15230
Editor assigned:	07-December-2022	**PreQC No:**	IPRJO-22-15230 (PQ)
Reviewed:	21-December-2022	**QC No:**	IPRJO-22-15230
Revised:	26-December-2022	**Manuscript No:**	IPRJO-22-15230 (R)
Published:	02-January-2023	**DOI:**	10.36648/iprjo.6.6.26

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Citation Natelauri E, Kiel K, Natelauri T (2022) Clinical Outcomes of Various Alternatives to Brachytherapy Boost after Neoadjuvant Chemoradiation for Locally Advanced Cervical Cancer: A Retrospective Cohort Study. Res J Onco. 6:26.

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For example, interstitial brachytherapy and magnetic resonance imaging (MRI)-based brachytherapy started in 2019 and are still not covered by universal health care insurance. Chemo-radiation and brachytherapy often have long gaps, which is a detriment to local control. We have seen many patients in everyday practice returning for follow-ups or retreatments that have never been treated with brachytherapy after chemo-radiation. The number of new CC cases in Georgia has ranged from 291 to 357 since the commencement of the cancer registry in 2015. Unfortunately, the 5-year Overall Survival (OS) rate for all stages combined was 56.9%, while the 5-year survival rate on average is 67%-68% in the developed countries [4]. In general, ~25% of CC cases are detected at an early stage and ~13% have metastatic disease. This may be underestimated since staging studies are not always available. Most patients are diagnosed with LACC. A clinical study or even a retrospective analysis of the results of different treatment approaches has never been conducted in Georgia. The national health insurance scheme covers EBRT and CTX. A significant investment was allocated in radiation therapy facilities in the past decade with the introduction of CTX treatment planning and the use of radiation therapy techniques, such as IMRT, Volumetric Modulated Arc Therapy (VMAT), and SBRT. This study aims to evaluate the current state of the art of CC in well-evaluated patients, which should be available to all theoretically. The OS, Disease Free Survival (DFS), Local Failure Free Survival (LFFS), and Distant Failure Free Survival (DFFS) will be compared between available treatment options that deliver definitive treatment. Hypothetically, EBRT or adjuvant hysterectomy could provide comparable or even better outcomes for LACC.

METHODS

Patient Population

This retrospective chart review was approved by the Local Ethic Committee and Review Board of our institution. All patients signed the informed consent. A search of the patient database yielded patients over the age of 18 years with a European Cooperative Oncology Group performance status of ≤ 2 who were treated with radical intent for CC from February 2015 to February 2019. The list was filtered according to exclusion criteria (**Table 1**).

Table 1: Exclusion criteria.

Previous anticancer treatment
Other history of malignancies
ECOG of >2
Early-stage disease
Metastatic disease
Recurrent disease
Age of <18

All patients were required to have histologically proven invasive CC. Pretreatment work-up included a medical history, clinical examination, pelvic (MRI), chest and abdominal Computed Tomography (CT), complete blood count, and liver and renal function measurement. Pelvic MRI and clinical examinations were used to determine the extent of the disease. The staging was mainly performed using whole-body CT. Patient and tumor details were documented. The research team had to review each patient record and assign a The International Federation of Gynecology and Obstetrics (FIGO) 2018 stage to each individual because a new FIGO staging system was introduced in 2018. The chart review included patients who met the criteria for FIGO classification stages IB, IIA, IIB, IIIA, IIIB, or IVA, and patients with metastatic or recurrent diseases were excluded. The patient list was narrowed to include only those who had undergone neoadjuvant chemo-radiation as the initial step in their cancer treatment regimen. Each patient completed and signed an informed consent form regarding their treatment before initiation.

Treatment

All included patients received neoadjuvant chemo-radiation as the first step of treatment (**Figure 1**).

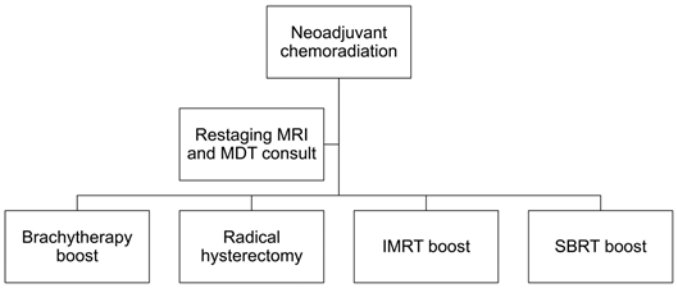

Figure 1: Treatment flow diagram.

Target volume delineation for EBRT was accomplished using simulation CTs and MRIs. Nodal status was evaluated with CT and/or MRI. Nodal positivity was based on nodal architecture and size, and biopsies were not performed. The initial radiation therapy dose was 45 Gy-50 Gy to the whole pelvis, with or without para-aortal nodes, in 25 daily fractions with 1.8 Gy per fraction. A simultaneous integrated boost of 55 Gy-60 Gy (based on size) was delivered to positive nodes. Concurrent cisplatin at 40 ml/m2 was administered weekly to all patients. A restaging MRI was performed with the same protocol as the simulation MRI at 22-23 fractions to evaluate the chemo-radiation response. Patients were reexamined together by an onco-gynecologist and radiation oncologist, and the possibility of surgical resection was assessed. All patients consulted a multidisciplinary team, and all alternatives were discussed. Brachytherapy had always been the preferred treatment method, but alternatives were given, such as surgery if possible or EBRT methods using IMRT or SBRT. In most cases, patients refuse brachytherapy and chose surgery, if surgery was technically possible, as it was a more acceptable and understandable treatment. All patients signed an informed consent form before the next step of treatment. Brachytherapy was performed at a referral institution and was delivered at a high dose rate. Initially (2015-2019), brachytherapy planning was done with two-dimensional (2D) or three-dimensional (3D) planning using CT imaging. The dose was prescribed to Manchester point A in most cases. Similarly, doses to organs at risk were reported as point doses using the International Commission on Radiation Units 38 guidelines. The most commonly prescribed dose was 21 Gy in three fractions delivered over 5-8 days.

Radical surgeries were performed 6-8 weeks after chemo-radiation completion. A radical hysterectomy was performed by

qualified onco-gynecologists using open surgery techniques. No additional radiotherapy or CTX was administered postoperatively. Restimulation CTs and MRIs were performed, and the targets and organ-at-risks were recontoured if EBRT was chosen as a boost, using IMRT or SBRT. The total dose ranged from 60 Gy to 66 Gy for individuals who were treated with an IMRT boost. The SBRT boost dose was 8 Gy-12 Gy in one fraction. Dose constraints to normal tissues mimicked those used for brachytherapy. Decisions regarding the prescribed dose for EBRT boost were made by treating physicians according to safety concerns.

Patients were required to return for follow-up appointments every 3 months. Physicians used imaging studies, especially chest and abdominal CT and pelvic MRI scans, during the first 2 years of follow-up to determine the dates of local and distant failure.

Endpoints and Statistical Analysis

OS, DFS, LFFS, and DFFS were defined as the interval from the start date of radiotherapy to the date of death or until the last follow-up visit, any failure, local failure, or distant failure, respectively. Treatment-related toxicity is beyond the scope of this study. Medians and life tables were computed using the product limit estimate by the Kaplan-Meier method, and the log-rank test was used to assess statistical significance. Statistical analysis was performed using MedCalc statistical software.

RESULTS

During the study period, from February 2015 to February 2019, only 43 patient charts were chosen for analysis for the retrospective review. All 43 patients received neoadjuvant chemo-radiation as the first step of their treatment, as previously described. Additionally, 17 patients were referred for BB after chemo-radiation, 14 underwent a radical hysterectomy, 12 underwent EBRT for the second phase of treatment, 9 received an IMRT boost, and 3 received SBRT. **Table 2** summarizes the patient characteristics.

Table 2: Patient and disease characteristics.

Treatment substitute	BB	AH	IMRT Boost	SBRT
Number of patients	17 (100%)	14 (100%)	9 (100%)	3 (100%)
Median age	62	55	66	67
(Range)	(41-85)	(25-79)	(45-71)	(62-71)
FIGO stage (2018)				
IIB	7 (41%)	4	2	-
IIIA	-	1	2	-
IIIB	-	-	-	-
IIIC1	6 (35%)	4	2	1
IIIC2	2 (12%)	1	1	-
IVA	2 (12%)	4	2	2
Pelvic N+	10 (58%)	9 (64%)	5 (55%)	3 (100%)
Para-aortal N+	4 (23%)	1 (7%)	1 (11%)	0

All 43 patients finished chemo-radiation as planned. No complete radiological responses were reported according to radiological reports of restaging MRI, which were obtained for all patients at 22 or 23 fractions of radiation therapy. All patients have no evidence of progressive disease. Two patients showed stable disease, and both were in the IMRT boost group. The median age of the patients in the radical hysterectomy group was 55 years, which was quite different from the three other groups. The hysterectomy group had the youngest patients, while the SBRT group had the most elderly patients compared to the others in terms of median age. All 14 patients underwent a type III radical hysterectomy in the surgical group. Pelvic lymph node dissection was performed in all patients. Para-aortal node dissection was performed when reported to be pathological on imaging or suspicious intraoperatively and was approved to be metastatic at the frozen section. Two patients had a pathologically complete response (pCR) in the cervix (14.3%), and 12 patients (85.7%) had microscopic residual disease. Of 9 patients with positive nodes, only 1 (11.1%) had a pCR in the regional nodes, and 88.9% showed residual disease in the nodes. Two patients with pCR were previously classified as FIGO 2018 IVa and IIIC1. The median follow-up time was 33 months (12-68 months). The overall local recurrence rate was 23.26% (10/43): 1/15 (7.14%), 5/17 (29.41%), 3/9 (33.33%), and 1/3 (33.33%) in the hysterectomy, brachytherapy, IMRT, and SBRT groups, respectively. The P-value was equivalent to 0.3665 in comparing survival curves with the log-rank test. In total, 32.56% (14 of 43) of the patients failed distantly. The distant failure rates for the hysterectomy, brachytherapy, IMRT boost, and SBRT boost groups were 14.29% (2 patients), 35.29% (6 patients), 44.44% (4 patients), and 66.67% (2 patients), respectively. The P-value was calculated as 0.2709 for distant failure. The 3-year DFS was the highest, accounting for 86% of patients who underwent radical hysterectomy compared to brachytherapy, IMRT, or SBRT (70%, 55%, and 33%, respectively). The 3-year OS was the highest, accounting for 100% in the SBRT group compared to the hysterectomy, brachytherapy, and IMRT groups (78%, 76%, and 55%, respectively). None of the results were statistically significant (p=0.6422 and p=0.4895, respectively) (**Figure 2**).

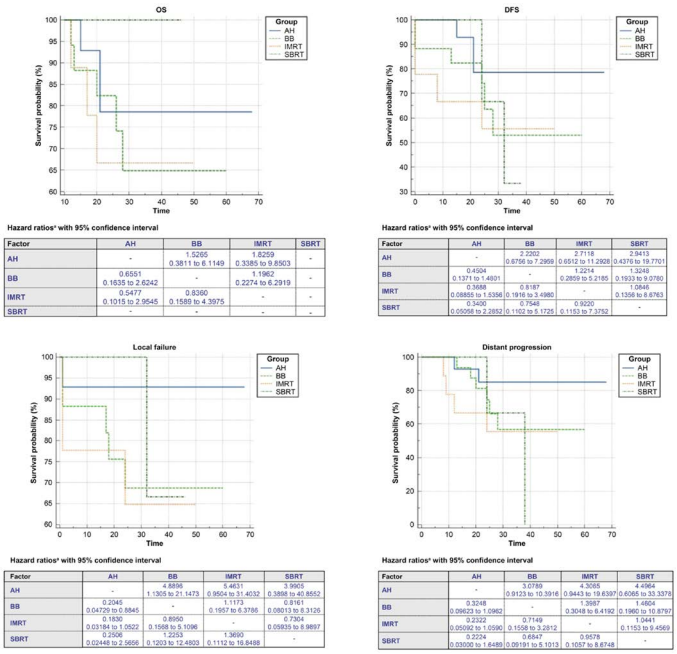

Figure 2: Kaplan-Meier estimates of OS (A)/(P-value: 0.6422), DFS (B)/(P-value: 0.4895), LFFS (C)/(P-value: 0.3665), and DFFS (D)/(P-value:

0.2709).

The median time to local progression was 14.6, 3, 10, and 32 months after BB, surgery, IMRT boost, and SBRT boost, respectively. The median time until distant progression was 18.8, 16, 15.7, and 31 months after BB, radical hysterectomy, IMRT boost, and SBRT boost, respectively.

DISCUSSION

No prospective randomized trials have investigated the alternatives to BB, and none will likely be done. Concurrently, we see different results after retrospective reviews regarding different treatments for advanced CC regarding survival and toxicity. Comparing studies is difficult because of various and evolving study populations, patient evaluation, treatment techniques, and CTX. Some studies used 2D and 3D radiation therapy techniques and other studies used modern IMRT/VMAT techniques for neoadjuvant chemo-radiation. The extent of surgery after radiation in different studies also varied. Some with simple hysterectomy, some with type II hysterectomy, and others with type III or IV hysterectomy looked at sample hysterectomy, others investigated type II hysterectomy, and others investigated type III or IV hysterectomy. Therefore, data to comprehensively analyse and draw meaningful findings are insufficient.

We acknowledge the limitations of our current analysis, which include the small numbers and the retrospective nature, and differences in patient characteristics between the four therapy groups, such as stage distribution, median age, and percentage of positive pelvic or para-aortic nodes. Legitimate concerns could arise about staging quality as we know that Positron Emission Tomography (PET) or PET/CT has high accuracy in detecting LN metastasis in patients with CC compared to CT and MRI because PET/CT and biopsy of suspicious nodes were not employed to assess regional and distant dissemination of the disease [5]. Theoretically, in this review, there could be more patients with FIGO stage IVB than reported. The chart review process revealed that physicians' records suggested that the best responders were treated by hysterectomy as the second phase of their treatment following restaging MRIs. Inadequate responders were referred for brachytherapy or an EBRT boost. The availability and capabilities of brachytherapy in Georgia were quite limited. Interstitial brachytherapy was not accessible before 2019, and MRI-compatible brachytherapy devices did not exist. Modern brachytherapy with MRI guidance, 3D volumetric planning, and accompanying interstitial devices became available in Georgia only after July 2019. None of the patients who participated in the analysis had access to high-quality brachytherapy services. In contrast, surgical teams performing radical hysterectomies were exceptionally skilled and competent. Therefore, patients who underwent hysterectomies experienced better outcomes.

The present study demonstrates that radical hysterectomy after neoadjuvant chemo-radiation was superior to other treatment modalities. Adjuvant surgical resection could improve local control, DFS, and OS because most patients had residual disease after chemo-radiation in the cervical and regional nodes. Therefore, our outcome measures are comparable to the results of the only randomized study published to date by Keys et al., who reported an advantage in terms of local recurrence rate and 5-year DFS in patients treated with an adjuvant hysterectomy versus those treated with radiotherapy and brachytherapy [6]. The selection of patients for hysterectomy was biased toward those with a good radiation therapy response, which biases our outcomes.

SBRT boost, which can mimic the dosimetry of brachytherapy, could be promising in terms of OS. Clinical outcomes following SBRT booster treatment are sparse and inconsistent. Using the National Cancer Database, Gill et al. discovered that IMRT and SBRT had lower OS outcomes than brachytherapy [7], but O'Donnell et al. described identical outcomes between SBRT and BB [8]. However, distant progression could be a reason for further criticism, as well as previously mentioned pathological residual nodal disease identified after radical hysterectomies in SBRT being a promising treatment modality.

CONCLUSION

We acknowledge that radical radiation therapy with concurrent CTX, incorporating EBRT and brachytherapy in combination, is the standard of care. The developing world often has limited resources for treatment. However, many countries have access to different treatment aspects. Our study demonstrates the need for prospective randomized clinical trials to evaluate options for treatment after neoadjuvant CTX when brachytherapy is unavailable to all patients because brachytherapy should only be performed in facilities where experience personnel and required equipment are available. Otherwise, a hysterectomy following neoadjuvant chemo-radiation or SBRT boosting may be more appropriate if high-quality brachytherapy is inaccessible, which is true in a considerable number of places worldwide.

ETHICAL APPROVAL

This retrospective chart review was approved by the Local Ethic Committee and Review Board of our institution.

INFORMED CONSENT

All patients signed the informed consent.

AUTHOR CONTRIBUTIONS

Conception/Design: Eter Natelauri, Krystyna Kiel

Collection and/or assembly of data: Eter Natelauri

Data analysis and interpretation: Eter Natelauri, Krystyna Kiel, Tea Natelauri

Manuscript writing: Eter Natelauri, Krystyna Kiel, Tea Natelauri

Final approval of manuscript: Eter Natelauri, Krystyna Kiel

ACKNOWLEDGEMENT

I would like to thank the people working at EVEX hospitals, Krystyna Kiel Oncology Center, for their encouragement and advice that led to the completion of this paper. I thank my friends for their encouragement and advice. Finally, if not for my family, who supported me all the time, I would never be able to work on this very special project.

CONFLICT OF INTEREST

The author declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article. This research did not receive a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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