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Reviewing Stereotactic Body Radiation Therapy Boost after Neoadjuvant Chemoradiation as an Alternative to Brachytherapy Boost for Locally Advanced Cervical Cancer

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Abstract

It is generally agreed upon that concurrent chemoradiotherapy (CCRT) is the treatment of choice for locally advanced cervical cancer (LACC). Radiotherapy consists of pelvic external beam radiation therapy (EBRT) and intracavitary brachytherapy (BT) to boost the cervix with coexisting residual tumors. Both of these treatments are administered simultaneously. In developing countries, however, there is a trend toward favoring surgery over other sorts of therapy. This preference can be attributed to several factors, including the fact that surgery is more readily available, socially acceptable, and culturally understood. On the other hand, with the development of more advanced techniques for external beam radiation treatment (EBRT), the usage of brachytherapy (BT), which is intended to boost the cervix in patients diagnosed with cervical cancer (CC), has been steadily decreasing in industrialized countries. The manner in which LACC has been treated as of late has become a contentious issue. In women who have locally advanced CC, we do not have any prospective evidence to support the idea that surgery or current EBRT, or stereotactic body radiation therapy (SBRT), may be substituted for intracavitary BT boost as a treatment option. This study aims to review SBRT as an alternative to brachytherapy following neoadjuvant concurrent chemotherapy and radiation therapy.

Keywords: Brachytherapy Boost; Cervical Cancer; Cervical SCC; LACC; SBRT Boost

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]. Surgery was the only treatment option for CC up to the beginning of the nineteenth century. People held the assumption that cancer had to be completely removed from the body. It has traditionally been emphasized that patients with locally advanced cervical cancer require highly aggressive surgery [3].

Radical chemoradiation is widely considered the gold standard of locally advanced cervical cancer (LACC) treatment. Radical chemo and radiation therapy (RT) consists of pelvic external beam radiation therapy (EBRT) concurrently with weekly chemotherapy followed by intracavitary brachytherapy (BT) boost to the cervix [4]. In the developing world, however, there is a trend toward favoring surgery over other methods of treatment. This preference can be explained by various factors, including the fact that surgery is more readily available, socially acceptable, and culturally understood. On the other hand, as more advanced techniques for EBRT have become available,

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the use of BT to boost the cervix in developed countries has steadily decreased. This is due to the introduction of more advanced treatments, such as intensity-modulated radiation therapy (IMRT) and SBRT. A brief glance back at some of the historical characteristics of SRS and SBRT reveals that SRS achieved tremendous expansion during the late 1980s and early 1990s. Pain syndromes and mobility problems were often the conditions required for this specific form of treatment. In 1987, Sturm et al. were one of the first groups of scientists to indicate that brain metastases might be an indication for SRS. Although SBRT was established around a decade after SRS, it was founded on the same fundamental concepts. SRS operations saw high demand at the Karolinska Hospital in Stockholm. Even though targeting and immobilization issues for sites outside of the brain are much more difficult, radiation oncologist Ingmar Lax and radiation oncologist Henric Blomgren reasoned that similar local control outcomes could be achieved at different body sites with one or a few focally delivered fractions. This was true even if the outcomes were not identical. In 1994, Lax and Blomgren presented their method [5], and the following year, they reported the clinical results of their procedure in 31 patients who had a total of 42 malignant tumors localized in either the liver, the lung, or the retroperitoneum. They were successful in achieving local control in eighty percent of the instances. In 1993, David Larson made a research trip to the Karolinska Hospital in Stockholm, Sweden. He used the method developed by Lax and Blomgren upon his return to his previous institution, where he attended to a total of 150 patients between the years 1993 and 1995. Because of recent advancements in treatment delivery methods (such as intensity-modulated radiotherapy [IMRT] and dynamic-arc treatment) and the availability of highly accurate immobilization and repositioning systems, SBRT is now a viable option for the treatment of relatively small pelvic tumors. In the early 2000s, it was claimed that optimal repositioning for prostate cancer patients might be accomplished using fiducial markers and an inflatable rectal probe. All of the aforementioned created a foundation for subsequent studies on the use of SBRT for cervical cancer and served as an inspiration for a number of studies and clinical trials that investigated the efficacy and toxicity of SBRT for cervical cancer and its effects on survival. SBRT has been adopted as one of the treatment options for recurrent, oligometastatic, and sometimes in up-front settings for gynecologic tumors, either alone or in combination with EBRT. This is the case despite the fact that there have been no randomized controlled trials conducted to evaluate its toxicity effectiveness. SBRT appears to be an acceptable therapeutic option for individuals who are unable to receive intracavitary therapy, according to a number of retrospective clinical findings and retrospective dosimetric analyses. Both Haas et al. [6], and Marnitz et al. [7] utilized the Cyberknife to track the previously implanted gold fiducials in the cervix for the purpose of precise SBRT boost administration. This resulted in a high rate of local control, which was 100% in both cases. Marnitz and colleagues observed a significant rate of treatment-related toxicity, in contrast to the findings that Haas and colleagues found no evidence of G3 or higher toxicity. There is no information published on late toxicity, 3- or 5-year OS, or DFS since the median follow-up period was so short (only 14 months for Haas et al. and six months for Marnitz et al.). This is because the follow-up time was so short. Hsieh et al. reported a 3-year overall survival rate of 46.9% and a 3-year disease-free survival rate of 77.8%, although they also took into consideration a longer total treatment period (the median was 79 days) and patients who had an advanced illness. The first patient we saw had grade 3 diarrhea, and another patient had grade 3 thrombocytopenia while receiving medication. The study had a number of flaws, including the following: no statistical conclusions can be reached as a consequence of the limited number of cases, the retrospective study design, and the short follow-up time; hence, long-term results and close monitoring are required further; Because not all of the patients had fiducial markers implanted, the irradiation margin could not be successfully lowered, even using the image-guided method. This might be the primary explanation for the 33.3% of patients who experienced late G2 rectal toxicity over the course of the trial.

In 2019, O'Donnell et al. [10] published the results of a database evaluation of 15,905 women who were diagnosed with CC. Of these women, 14,394 (or 90.5% of the total) were treated with brachytherapy, 42 (or 0.8% of the total) were treated with SBRT, and 1468 (or 9.2% of the total) were treated with IMRT. Patients treated with brachytherapy as a boost had an average survival time of 99.1 months, patients treated with SBRT as a boost had an average survival time of 30.6 months, and patients treated with IMRT as a boost had an average survival time of 29.8 months. Using Propensity-Matched Analysis, we found no significant difference in overall survival between patients who received an SBRT boost and those who received a brachytherapy boost. In a multivariable analysis, the following factors were found to be significantly associated with decreased overall survival: increasing age, insurance, histology of adenocarcinoma, progression of the disease's FIGO stage, pelvic nodal involvement, presence of distant metastasis, and receiving IMRT rather than brachytherapy. Brachytherapy is a form of radiotherapy that uses small amounts of radiation to treat tumors directly.

The most recent clinical trial, which was carried out in 2020 and reported on by Albuquerque et al. [11], was terminated early due to toxicity concerns (G3/4 toxicity-26.7%). Fifteen patients had whole-pelvis radiation therapy (45 Gy in 25 fractions with SIB to positive nodes), and then 15 patients received SBRT boost therapy (28 Gy/4 fractions) for treatment of their cancer. The local control rate was 70%, which is equivalent to the lower range for standard

Table 1: Outcomes and safty of SBRT boost after WPRT.

Study	N of P.	FIGO stage	Machine	Treatment	Comparison	Median Follow up time	Findings		
							OS	DFS	Toxicity
Haas et al 2012 [6] Retrospective chart review	6	NA	Cyber knife	whole pelvis RT 45–50.4 Gy in 1.8 Gy/fraction followed by SBRT boost (20Gy/5fx or 19.5/3fx)	no	14 months	NA	1-year DFS 100%	G3/4 – NO G2 – NA G1 – 66% (4/6 pt)
Hsieh et al. 2013 [8] A retrospective observational descriptive review	9	IIB to IVA	Tomo-therapy	WPRT followed by SBRT (27-16 Gy/5–9 fractions)	no	13 months (range: 4–40 months)	3-year OS 46.9%	3-years DFS 77.8%	G3 -Diarrhea 11% cytopenia – 11% G2 -Diarrhea – 11%, GU – 11%, cytopenia – 22% G1 – Nausea 100%, Diarrhea -78%, GU – 89%, cytopenia – 89%
Marnits et al 2013 [7] Retrospective observational descriptive review	11	IIB-IIIB	Cyber Knife	WPRT of 50.4Gy with SIB to parametrium 59.36Gy followed by SBRT (30Gy/5 fractions)	no	6 months	NA	NA	G4 – cytopenia – 9% G3 – cytopenia 27%, G2 – Cytopenia -63%, GU – 18%, GI-18% G1 – cytopenia -36%, GU – 81%, GI – 81%, vaginal-100%
Mantz et al 2015 [9] Prospective clinical trial	40	NA	NA	WPRT 45Gy followe by SBRT (40Gy/ 5fx delivered over a 10-day)	no	51 months	NA	2-years DFS 77.5%	NA
O'donnell et al 2018 [10] Retrospective database review	15,905 14,394 (90.5%) BB 42 (0.8%) SBRT 1468 (9.2%) IMRT	I-IVB	NA	WPRT followed by boost – ICB vs IMRT vs SBRT	ICB vs IMRT	NA	Median OS ICB 99.1 Months, SBRT - 30.6 months, IMRT - 29.8 months. With Propensity-Matched Analysis there was no significant difference in overall survival between those who received SBRT boost and those who received a brachytherapy boost (HR = 1.477, 95% CI = 0.746Y2.926, P = 0.263).		
Albuquerqe et al 2020 [11] A Phase II Trial	15	IB2-IVB	NA	whole-pelvis radiotherapy (45 Gy in 25 fractions with SIB to positive nodes) followed by SBRT (28 Gy/4 fractions)	no	19 months	2 years OS 53.3%	2 years DFS 46.7%	G3/4 - 26.7% Study was closed early due to toxicity concerns.

therapy in patients with similarly advanced stage and bulky disease, where the local control rate ranges from 75% to 85%, but lower than what was reported in previous SBRT studies (Table 1). The standard therapy local control rate ranges from 75% to 85%. Because there were so many bulky advanced-stage tumors, a considerable percentage of the study's subjects suffered regional and systemic recurrences of their disease. Within the context of this experiment, these systemic failures, combined with substantial co-morbidities, were a key cause of patient death. In terms of its capability to simulate a BT dose distribution with a steep dose gradient and, as a result, achieve the same treatment outcomes as ICB, at least theoretically, SBRT is the most certain technique among all EBRT modalities. This is because SBRT is the only technique to simulate a BT dose distribution. SBRT makes it possible to provide large doses of chemotherapy directly to the tumor while at the same time preserving as much of the surrounding healthy tissue as is humanly possible. Due to

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the excellent target coverage and OAR-sparing features that SBRT possesses, it has been demonstrated in a few dosimetric trials that it is superior to other treatment methods. However, the question of whether or not a radiobiologically necessary extremely high dosage must be administered within the tumor is still up for discussion and will not be further upon in this study. Even while the BT profile is extremely efficient (an incredibly high dosage distinguishes it within the applicators), it is not capable of competing with the consistency of the EBRT dose over the entirety of the target volume. As a consequence of this, the majority of authors believe that neoadjuvant chemoradiation followed by radical surgery or SBRT may be a viable therapeutic option for patients who have LACC. This belief is not limited to the circumstances in which ICB is unavailable, technically impractical, or rejected. In order to definitively establish or invalidate non-ICB therapeutic choices for cervical cancer, large prospective randomized controlled studies are necessary.

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