



## Review Article

# Why brachytherapy boost is the treatment of choice for most women with locally advanced cervical carcinoma?

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**ABSTRACT**

The standard treatment approach for women with locally advanced cervical carcinoma is definitive radiation treatment with concurrent cisplatin chemotherapy. Radiation treatment is typically external beam radiation therapy to the pelvis followed by intracavitary brachytherapy (BT) boost to the cervix. Numerous studies confirmed very successful outcomes with this approach. In recent years, however, the use of BT to boost the cervix in women with cervical carcinoma was reported to be on the decline. With the advent of advanced external beam radiation therapy techniques, few attempts have been made to substitute the BT boost with stereotactic body radiation therapy or intensity-modulated radiation therapy techniques, but there is a lack of prospective data to justify the routine use of these alternate boost techniques. The aim of this review is to highlight the differences between the use of stereotactic body radiation therapy or intensity-modulated radiation therapy, in lieu of intracavitary BT boost in women with locally advanced cervical cancer, and to argue that BT seems to be truly irreplaceable at the present time and with the knowledge and expertise accumulated to date. © 2015 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

**Keywords:**

Cervical cancer; Radiation therapy; Brachytherapy; Intensity-modulated radiation therapy; IMRT; Stereotactic body radiation therapy; SBRT

**Introduction**

According to the estimated statistics for the year 2015, cervical cancer is the third most common gynecologic malignancy and the third most common cause of death among patients with gynecologic cancers in the United States (1,2). The morbidity and mortality of cervical cancer in developed countries have dramatically decreased over the past 80 years, coinciding with the emergence of successful screening methods and effective treatment of preinvasive lesions (3). In developing countries, however, cervical cancer still constitutes the second most common cause of cancer deaths in women among all cancer types (second only to breast cancer) (4,5). Around 85% of the global burden of cervical cancer occurs in the developing countries, where access to screening remains suboptimal (5).

The standard treatment approach for patients with locally advanced cervical cancer is definitive external beam radiation therapy (EBRT) to the pelvis with concurrent cisplatin chemotherapy (6), followed by brachytherapy (BT) boost to the cervix. With such combined modality approach and with contemporary BT techniques, local control rates are excellent and range between 79% and 96% (7–12), and overall survival rates range from 58% to 80% for patients with International Federation of Gynecology and Obstetrics (FIGO) Stage IB2–IIB cervical carcinoma and up to 50% for patients with Stage III–IVA disease, according to statistics from the American Cancer Society and to contemporary studies (7,8,13). Multiple studies, including Patterns of Care studies, have consistently shown that BT used as boost after EBRT significantly improves survival and that treatment of the central disease (vaginal, cervix, medial parametria) is highly dependent on the dose given by the intracavitary sources through BT (14–18).

However, the use of BT to boost the cervix in women with cervical carcinoma was recently reported to be on the decline (19,20). This trend is not unique to cervical cancer and was also reported in other gynecologic sites, such as the vaginal cancer (21). With the advent of

Received 6 October 2015; received in revised form 23 November 2015; accepted 7 December 2015.

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advanced EBRT techniques, attempts have been made to substitute the BT boost with stereotactic body radiation therapy (SBRT) or intensity-modulated radiation therapy (IMRT) techniques.

The aim of this review was to highlight the differences between the use of SBRT and IMRT, in lieu of intracavitary BT boost in women with locally advanced cervical cancer, and to argue that BT seems to be truly irreplaceable at the present time and with the knowledge and expertise accumulated to date.

## Methods and materials

A search of the literature was conducted using the electronic databases MEDLINE and PubMed with search dates between 1946 and July 2015. No limits for language were applied. Search terms included “cancer of the uterine cervix” (or “uterine cervical neoplasms” as a MeSH term), “brachytherapy,” “intensity-modulated radiation therapy” (“Radiotherapy, intensity-modulated” as a MeSH term), and “stereotactic body radiation therapy” (“Radiosurgery” as a MeSH term). The search was also guided by reference lists of published studies and proceedings of meetings, such as abstracts from the American Society for Radiation Oncology, the European Society for Therapeutic Radiology and Oncology, and the American Brachytherapy Society.

Included studies were clinical studies in which patients with carcinoma of the uterine cervix were selected and were treated with IMRT or SBRT as a boost following EBRT, as part of their definitive treatment. Dosimetric studies, in which SBRT or IMRT plans were devised and compared (or not) with intracavitary or interstitial BT plans, were also included. Studies that included both patients with endometrial cancer and patients with cervical cancer were not excluded. Studies in which patients were treated with IMRT or SBRT, but not as part of their boost treatment, were excluded and studies in which all the patients had recurrent cervical carcinoma. Excluded also were studies in which boost treatment was used in the adjuvant and not in the definitive setting in all the patients.

### *BT and its outstanding legacy of success*

Many decades of success have undoubtedly rendered BT the ultimate form of boost in the definitive treatment for locally advanced cervical carcinoma. Over the past 100 years, BT techniques have evolved tremendously from the Paris system, the Stockholm systems in the 1920s (18), to the predecessors of modern-day BT, the Manchester system in the 1930s, which introduced standard dose calculations using Points A and B (22,23), as well as the Fletcher (M.D. Anderson) system in the 1940s (24). In the 1960s, a search for radium substitute materials such

as  $^{137}\text{Cs}$ ,  $^{125}\text{I}$ , and  $^{192}\text{Ir}$  was undertaken, concomitantly with the development of remote afterloading by Henschke *et al.* (25,26), which allowed for safer BT treatments. The transition from low-dose-rate to high-dose-rate (HDR) BT also led to a relatively easier treatment and improved treatment dose optimization, with improved patients' and operators' convenience, while maintaining similar survival, pelvic recurrence rates, and comparable complication rates (27–29).

Lately, in the past 15 years, the two-dimensional treatment planning has given way to image-based BT (IBBT), CT-based, or MRI-based BT. In 2005, the Gynecological Groupe Europeen de Curietherapie/European Society for Therapeutic Radiology and Oncology group issued recommendations on target delineation using MRI-contoured target and organs at risk (OAR) volumes and on dose–volume parameters to be reported (30,31). IBBT has allowed optimization of prescription dose and limitation of dose to OAR, as well as provided radiation oncologists with the opportunity to adapt the dose, taking into account the different patterns of tumor shrinkage (32). It was therefore possible to move from prescription of dose to the empirical Point A to prescription to a well-defined three-dimensional target, “the sculpted pear,” leading to substantial improvement in target coverage and dose–volume histogram parameters (33–35).

IBBT achieved excellent results, with local control rates of 95–100% at 3 years in limited IB–IIB cervical cancer patients and 85–90% in large IIB/III/IV disease, as reported in a single institutional study conducted in Vienna which included 156 patients (8). A summary of some contemporary studies with excellent local control after BT in women with cervical carcinoma is included in Table 1 (7–12).

The European study on MRI-guided Brachytherapy in locally Advanced Cervical cancer, a multicenter prospective observational study, endorsed by the Groupe Europeen de Curietherapie/European Society for Therapeutic Radiology and Oncology, aims at establishing a benchmark for clinical outcomes with IBBT. Preliminary results were presented at the European Society for Therapeutic Radiology and Oncology meeting in 2012 (36) and at the 2015 American Society for Radiation Oncology meeting (37). Another important advance is the use of positron emission tomography in BT treatment optimization. A systematic review on that topic showed that positron emission tomography–optimized plans displayed better target coverage than conventional plans (38).

The 5-year rates of late Grade 3–4 treatment-related morbidity in recent studies using MRI-based adaptive BT were low and range from only 2–8% for bladder and rectum (7–12) (Table 1). A Nordic study comparing CT-based planning with image-guided adaptive BT demonstrated a 50% reduction in moderate and severe late morbidity when using the latter (39). Technical advances,

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