Review Article
Imaging-guided brachytherapy for locally advanced cervical cancer: the main process and common techniques

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Abstract: Brachytherapy (BT) delivers integrated boost doses to the central tumor while sparing the surrounding organs at risk (OARs) efficiently. It's a mandatory treatment component for locally advanced cervical cancer (LACC) because it results in excellent overall survival and local control compared with other dose boosting modalities. Currently, BT is undergoing a transition from 2-dimensional (2D) to 3-dimensional (3D) treatment planning. Imaging-guided BT (IGBT) employing computed tomography (CT) or magnetic resonance imaging (MRI) can provide exact individual delineation of target and OARs meanwhile prescribe the dose to the target volume instead of "point A" for X-ray-based BT. There are three main techniques for BT: intracavitary (IC), interstitial (IS), and intracavitary/interstitial (IC/IS) combination. The applicator choice depends on the specific tumor extension. The real-time transabdominal ultrasound (US)-guided applicator placement technique is strongly recommended to ensure ideal applicator positioning. MRI is the ideal standard imaging for BT owing to its superior soft tissue visualization than CT. However, CT-based BT is more often performed because of the availability. In developing countries, US-based BT can be adopted. For treatment planning, the applicator reconstruction is easier on CT than on MRI, because the applicator image is more clearly visible. Individual treatment planning should be performed for every single applicator insertion to ensure dose accuracy. In this review article, we explain the main clinical process and common techniques, including the applicator choice and placement, imaging techniques, target delineation, and treatment planning; asthose will help to improve the efficiency of 3D BT.

Keywords: Imaging-guided, brachytherapy, cervical cancer, process, technique

Introduction

Cervical cancer is the fourth most common cancer in the world, with 527,600 new patients and 265,700 deaths in 2012 [1]; approximately 85% of cervical cancer cases are observed in low- and middle-income countries [2]. External beam radiotherapy (EBRT) with concomitant chemotherapy following brachytherapy (BT) is the standard treatment for locally advanced cervical cancer (LACC) [3-5]. BT, which allows the administration of a relatively high dose to the central tumor while sparing the surrounding normal organs, is an imperative treatment component, as it can improve the tumor local control rate and overall survival [6, 7]. In addition, BT is the only certified strategy that assures a curative dose of 80-90 Gy to the target while controlling the dose to the organs at risk (OARs) within the tolerable dose.

BT was first used for the treatment of cervical cancer over 100 years ago [8]. Since then, several basic systems, including Paris, Stockholm, and Manchester, were developed based on intracavitary BT (IC BT) using the radium radioactive source [9]. The classic Manchester "point A" system, which was determined using 2-dimensional (2D) X-ray imaging but not considering individual anatomy or tumor invision, was introduced in 1938 [10]. The absence of a volumetric concept based on 2D imaging may result in insufficient doses to parametric and/or pelvic tumors with low radiosensitivity to EBRT; conversely, serious radiation-induced damage may occur to the surrounding normal tissue owing to relatively small tumors with good response to EBRT [11]. To avoid "point A" system shortage, the Commission of Radiation Units and Measurements (ICRU) Report 38 proposed the target volume concept for IC BT in

1985, and that an isodose of 60 Gy should cover the reference volume [12]. ICRU Report 38 also specified the ICRU reference bladder and rectum point in the lateral direction but not the reference small bowel and sigmoid colon point [12].

With the development of imaging techniques, Imaging-guided BT (IGBT) with computed tomography (CT) or magnetic resonance imaging (MRI) is widely used currently. 3D BT provides the exact individual delineation of the target and OARs, so it can prescribe the dose to the tumor as well as potentially limit the dose to the OARs. In 2005, the Groupe Europeen de Curie Therapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) published their recommendations for clinical target delineation using MRI, and the gross tumor volume (GTV), high-risk clinical target volume (HR-CTV), and intermediate-risk clinical target volume (IR-CTV) were introduced [13]. In the next year (i.e., 2006), the GEC-ESTRO reported the dose volume parameters of D90% and D100% (i.e., 90% and 100% of the target volume receiving the minimum dose, respectively) [14]. Finally, these concepts were accepted and included in the ICRU Report 89 [15]. Moreover, the results of some clinical trials have showed that 3D BT enhanced the tumor control rate and minimized the treatment-related adverse effects [16, 17].

In this article, we review the importance of BT for LACC while considering the applicator choice and placement, imaging technique, target delineation, and treatment planning for IGBT. We believe that the introduction of the main process and common techniques will be useful for physicians treating cervical cancer with 3D BT.

Brachytherapy is mandatory for the treatment of locally advanced cervical cancer

For LACC, EBRT combined with platinum-based concurrent chemotherapy plus BT is the standard treatment. Yan et al. [18] reported 1926 cervical cancer patients (stage IB2-IVA) received this standard treatment with the median follow-up time of 43.64 months, the 5-year overall survival, 5-year progress-free survival and 5-year local control were 80.80%, 77.4% and 92.6%, respectively. BT plays a very important role in the treatment of LACC, but its

usage has been decreasing over the past decades [5]. The most important reason that contributes to the underutilization of BT seems to be the development of EBRT techniques, such as intensity-modulated radiotherapy (IMRT) and stereotactic body radiation therapy (SBRT); theoretically, these highly conformal techniques especially using inverse planning can deliver the integrated boost dose to the target. However, IMRT cannot replace BT, because BT has a better ability in target dose coverage and OAR sparing than any other EBRT techniques. Some other possible reasons for the decrease in the use of BT include the need for more training and expertise, the increased time and logistical requirement, the lack of adequate imaging and treatment planning techniques, and the absence of a Medicare reimbursement policy. Currently, no prospective randomized clinical trials have compared EBRT boost and BT for dose intensification while treating LACC. However, the results of some retrospective and pattern-of-care studies showed that BT involvement significantly enhanced the local control rate and overall survival of patients with LACC compared with EBRT alone [19, 20]. A final report of the 1973 and 1978 patterns of care studies in the United States included 1558 patients with cervical squamous cell cancer. This study showed that a higher Karnofsky Performance Status (KPS; Stage I and II), older age (Stage I and II), unilateral parametrial involvement (Stage IIB), and unilateral sidewall involvement (Stage III) were mainly pretreatment factors associated with improved pelvic control. However, the application of intracavitary irradiation was the only treatment-related factor associated with increased pelvic control on multivariate analysis. Overall survival was also improved with a much higher dose to point "A" [21]. The results of a recent retrospective study showed better clinical outcomes after BT than after EBRT alone. 220 patients with cervical cancer stage I-IV were included, 134 patients received three or five 6.0 Gy fractions of brachytherapy in addition to the EBRT, whereas 86 patients received EBRT and external boost to the tumor instead of BT with a total dose of 64-72 Gy. The rates of primary complete remission and 5-year cancer-specific survival were significantly enhanced for patients who received BT than those who were treated with external beam boost instead of BT (92.5% vs. 73.3% and 68.5% vs. 35.4%, respectively) [20].

Table 1. The comparison of EBRT combined with BT and EBRT alone

Author/nation	EBRT combined with BT	EBRT alone (IMRT or SBRT)	P
Gill/U.S. [19]			
Patients (n)	6915	739	
Median OS (mouths)	70.9	23.8	<0.01
Karlsson/Sweden [20]			
Patients (n)	134	86	
5-year OS	92.5%	73.3%	<0.0001
5-year CSS	68.5%	35.4%	<0.0001
Han/U.S. [22]			
Patients (n)	4669	2690	
4-year OS	58.2%	46.2%	<0.001
4-year CSS	64.3%	51.5%	<0.001
Logsdon/U.S. [23]			
Patients (n)	641	266	
5-year DSS	45%	24%	<0.0001

Abbreviations: EBRT = external beam radiotherapy; BT = brachytherapy; SBRT = stereotactic body radiotherapy; OS = overall survival; CSS = cancer-specific survival; DSS = disease-specific survival.

A study used the data from the Surveillance, Epidemiology, and End Results (SEER) database of 7359 patients with stage IB2-IVA cervical cancer treated with EBRT between 1988 and 2009. They found that 63% of 7359 patients received BT and the remaining 37% received EBRT alone. The BT utilization rate was 83% in 1988 but only 58% in 2009, with a significant decrease (P<.001). The factors involved in using a higher rate of BT included young age, married women, early diagnosis, and certain SEER regions. Patients who received BT treatment had better 4-year cause-specific survival (64.3% vs. 51.5%, P<.001) and overall survival (58.2% vs. 46.2%, P<.001) than those treated with EBRT alone. BT treatment was independently associated with better cause-specific survival (hazard ratio [HR], 0.64; 95% confidence interval [CI], 0.57-0.71), and overall survival (HR 0.66; 95% CI, 0.60-0.74) [22]. In another study, the authors investigated the trends in BT or IMRT/SBRT boost for 7654 patients with stage IIB-IVA cervical cancer between January 2004 and December 2011 in the U.S. National Cancer Database. Most of patients received brachytherapy (90.3%). However, the BT utilization rate decreased from 96.7% to 86.1%, whereas the use of IMRT and SBRT boost increased from 3.3% to 13.9% in the same period (P<.01). The factors associated with a lower BT use included older age, stage IVA disease, smaller tumor size, later year of diagnosis, lower-volume treatment centers,

and facility type. IMRT or SBRT boost contributed to inferior overall survival (hazard ratio, 1.86; 95% CI, 1.35-2.55; P<.01) compared with BT [18]. These results indicated that BT is a mandatory strategy for treating LACC. The comparison of EBRT combined with BT and EBRT alone is shown in **Table 1**.

Applicator choice

Choosing the appropriate BT applicator is essential for ensuring treatment success. Applicators have evolved over the past century to satisfy variable isotope techniques. Currently, there are three main techniques for cervical cancer BT: intracavitary (IC), interstitial (IS), and intracavitary/interstitial (IC/IS) combination. Different appliactors are used for corresponding BT technique.

IC applicators usually include uterine catheter and vaginal molds. Classic IC applicators include those in the Fletcher family (tandem and ovoids), tandem and ring, and tandem and vaginal cylinder [24-26]. Tandem-ovoids and tandem-ring applicators are usually used for small, superficial and unbiased tumors with no obvious narrowing of the vaginal fornix and vaginal invasion is not serious; the ovoids can fully contact the vaginal fornices, but an appropriate size needs to be selected. An oversized ovoid will cause the displacement of the applicator and lead to insufficient cervical dose distribu-

tion. Compared with the ovoids, the rings have a narrower dose distribution, but the vaginal dose is higher, which is more suitable for narrow vaginal fornix. Tandem-vaginal cylinder is dedicated for vaginal disease without serious lateral parametrial extension; the cylinder can provide high dose for the vagina, but it will also cause relatively high dose for the bladder and rectum. The advantages of IC applicators mainly include simplicity in use, the need for less training for radiologists, and low rate of injury.

IS applicators employing interstitial needles that can be inserted into tumors directly have a great dose advantage for local bulky tumors, serious lateral parametrial extension and/or pelvic involvement, lower vaginal disease or the cervix os can't be entered. The classic IS types include the Syed-Neblett butterfly template and Martinez Universal Perineal Interstitial Template applicator [27, 28]. Some disadvantages of both the perineal templates include the inaccuracy of needle placement because of a relatively large distance between the template and the tumor as well as serious adverse effects owing to the requirement of too many needles. Moreover, needles are usually transplanted once for the whole treatment process, so the patients must keep needles in their body for 2-4 days with a total doses to the tumor volume or reference isodose from the implant range from 25-40 Gy in a low dose rate mode [28]. In our department, IS BT is performed using CT guided free-hand placement of metal needles combining uterine tandem for large-volume cervical cancer (tumor size >5 cm) and/or distal parametrial involvement after EBRT, resulting in excellent dose coverage [29, 30]. For this IS BT technique from our previous work, an intrauterine tandem is implanted into the uterine cavity; then, IS metal needles are inserted into the cervical tumor as well as into the lateral extensions at a depth of approximately 10 mm as a preliminary implantation. Finally, we adjust the direction and depth of the needles repeatedly until all the needles are symmetrically distributed in the tumor at a 1-cm distance from the central axis through multiple CT scans [29]. The final purpose for needles adjustment is to get satisfactory dose distribution for the target volume and OARs in the subsequent treatment planning. Generally, the mean number of CT scans was 2.7±1.3 for every placement of needle, and the mean time was 39.8±9.8 min for each IS implantation [29]. HR-CTV and OAR are always delineated based on CT images. Although T2-weighted MRI is not incorporated into the treatment planning, it is always used as a reference to assess the superior border of tumor if intrauterine involvement is detected; residual parametrial extension was countered based on clinical gynecologic examination results and CT images; In addition, the lowest boundary of the vaginal disease was decided by the result of clinical gynecological examination [30]. Our IS BT technique may be clinically feasible and provide an alternative treatment strategy particularly for clinical facilities with limited resources [29, 30]. However, it requires higher level of operators and needs more experience accumulation. And the long-term clinical results and possible toxicity need be further evaluated.

Combined IC/IS BT with Utrecht and Vienna applicators allows additional needles to be inserted through the ovoids or ring, thereby providing excellent dose coverage for tumors with a difficult topography [31, 32]. The template is fixed with good repeatability and is relatively easy to master. However, IC/IS applicators still have the following defects: the plastic needles used for IC/IS BT cannot be reused. Therefore, IC/IS BT is very expensive especially in developing countries where LACC is highly prevalent. In addition, the IC/IS method may not be useful for some late-stage disease with over two-thirds of the involved parametrium, owing to limitations in the angle of the needles. Nevertheless, some improved IC/IS applicators with some oblique needles (Vienna type 2) or perineal needles (Venice) have been developed to ensure inclusion of distal parametrial and pelvic disease [33]. Recently, the 3D print technique was introduced for treating cervical cancer with BT; applicators including tandem, rings, and needles with proper direction and depth can be designed according to the tumor position and shape before treatment [34]. Therefore, theoretically, this kind of applicator can be customized to obtain individual treatment. Nevertheless, some issues with the technique, such as absence of commercially available treatment planning systems for direct export of a virtual template for 3D printing treatment planning, need to be resolved, and the final clinical outcomes need to be further evaluated.

In addition, the choice of applicators is supposed to match with individual patients to achieve the best dose coverage for the tumor and sparing OARs, which requires physicians to evaluate patients adequately, and could make the choice according to the applicable topography and dosage characteristics of different applicators. Dumane et al. [35] demonstrated a method to meet the OARs constrains by modifying the applicator angle and the ring size between fractions. They introduced two situations. One is to adjust the tandem angle from 30° to 45° at the last two fractions, thereby reducing the bladder dose to meet the constrains. The other is to reduce the rectum dose by choosing a larger diameters ring to keep the rectum away from the applicator origin. In addition to modify the applicators, some new applicators have also been invented. Han et al. [36] introduced a direction modulated brachytherapy (DMBT) tandem applicator, which was designed as a 6 peripheral grooves nonmagnetic tungsten alloy rod and housed by a thin plastic sheath. Compared with the traditional "single channel" tandem, it is equivalent to six channels, which means that the dose distribution can be modulated from multiple directions to highly conformal the target volume, therefore the OARs can be better sparing.

Applicator placement technique

After the appropriate BT applicator is determined, accurate applicator placement is also important for excellent BT planning. Corn et al. [37] investigated BT applicator localization films from 128 patients with LACC. All patients received EBRT followed by one BT application. BT parameters were evaluated based on (a) the distance between the right colpostat source and the distal tandem source, (b) the distance between the left colpostat source and the distal tandem source, and (c) the symmetry of colpostat placement. Eight implants were scored as "ideal" with all three parameters were considered satisfactory; 17 implants were scored as "unacceptable" with none of the parameters were considered satisfactory; 41 implants were scored as "adequate" in all other cases. Ideal and adequate placement of applicator contributed to a significantly improved 5-year local control rate (68% vs. 34%, P = 0.02) and had a strong trend towards improved 5-year survival (60% vs. 40%) compared with unacceptable placements [37]. Optimal placement of the BT

applicator was also the most important prognostic factor of local control.

For bowel preparation, the clear liquids are recommended to be taken the day before implantation. And a soapsuds enema followed by water enema is performed on the procedure day before BT to make sure rectum is clear. A Foley's catheter filled with 7 cm^3 diluted urografin (dilution 1:20) was placed in the bladder. For placement of any type of common applicators including IC, IS, and IC/IS combination technique, patients are usually in the lithotomy position. First, the tandem-a hollow catheter with specific angulation adjusted to the direction of the uterus canal-is placed in the uterine cavity with or without ultrasonography guidance. When real-time transabdominal ultrasound (US) guidance is used during applicator placement, the position and direction of the uterine cavity can be visualized directly; hence, perforation rates of the uterus and misplacement of applicators can be further reduced. When uterine perforation or suspicion occurs, the applicator should be re-implanted and antibiotics should be given prophylactically. Usually, uterine perforation is not a problem, but if the perforation is not found and subsequent treatment is performed, the applicator close to the bladder or bowel can cause serious tissue injury [38]. Therefore, real-time US should be used to avoid perforation for patients with especially challenging anatomy, such as a retroverted uterus, previous perforation, or cervical stenosis. In a systematic review and meta-analysis, researchers analyzed the perforations rate for the insertion of a US-guided applicator during intracavitary BT for cervical cancer. A total of 1757 insertions and 766 patients from 12 studies were included. The pooled perforation rate per insertion was 1.06% (95% CI, 0.41-2.67) with imaging guidance versus 10.54% (95% CI, 6.12-17.57) without imaging guidance (P<.01). In addition, the pooled perforation rate per patient significantly decreased in those treated with US imaging guidance than in those treated without guidance (16.67% versus 2.54%) [39]. The use of transabdominal US also assures that the tandem can be appropriately placed in the uterine cavity prior to obtaining the treatment planning image. This prevents the possibility of tandem resetting and the need for repeated scanning with CT/MRI if there is some problem with the tandem position after the initial CT/MRI scan. After the ini-

tial tandem is placed, the vaginal applicator, most commonly paired ovoids or ring, is placed in the flush cervix or vaginal fornix position. Occasionally, some special paired ovoids or ring with lateral holes, which allow interstitial needles to be inserted, are used for parametrial and pelvic disease. Bladder filling process is performed using 50 mL diluted urografin (dilution 1:20) through a urinary catheter after implantation. Furthermore, vaginal packing is performed with wet gauze to fix the applicators and move the vagina and rectum membrane away from radioactive source.

Imaging technique

Currently, CT-guided and MRI-guided adaptive BT are widely used for cervical cancer. CT-based treatment planning during 3D BT of cervical cancer is more popular, because CT facilities are usually available in most radiation oncology departments. CT imaging provides visualization of both the intact uterus and the OARs, and can be used evaluate the tandem position inserted into the uterus with short scan time. CT-based treatment planning allows practitioners to delineate the OARs and optimize their dose distribution [40]. However, CT is not eligible for accurate delineation of the target volume, because it cannot distinguish the boundary of the cervix, uterus, and vagina clearly, nor can it evaluate the parametrial extension accurately [41]. Therefore, MRI and gynecologic examination are recommended to determine the target contour while performing CT-guided BT [42].

CT has been used for 3D BT for cervical cancer since several decades. In a study that investigated the use of 720 ^{192}Ir high-dose-rate (HDR) BT in 331 patients, the maximum doses to the bladder and rectum during CT-based dosimetry were significantly increased than those obtained on orthogonal radiographs, with average values of 1.44 times, 2.42 times, and 1.37 times for the bladder neck, bladder base, and rectum, respectively. CT-assisted dosimetry was better than orthogonal radiographs, and the estimation of dose volume histograms (DVH) in OARs is more useful in establishing correlations between the dose to normal tissues and complications rather than using single ICRU reference bladder or rectal points [43]. The results of another study showed that "Point A" from orthogonal films resulted in tumor dose uncertainty and underestimation

[44]. The ICRU 38 report also showed that the maximum bladder and rectal doses underestimated the maximum doses to these organs compared with CT [10]. Kang et al. [45] investigated the impact of CT-guided IC BT for late rectal bleeding and local control in patients with cervical cancer. A total of 97 consecutive patients who were treated with CT-based IC BT were included in this study. The patient data were compared with those of a former patient group consisting of 133 individuals treated with conventional 2D BT. There were no significant differences in the overall rectal bleeding rate between the groups (42% for 3D BT vs. 44% for 2D BT), but the rate of severe rectal bleeding was significantly reduced in the 3D BT group (2% for 3D BT vs. 13% for 2D BT; P = .02). A increased local control rate was also observed after 3D BT (98% for 3D BT vs. 81% for 2D BT; P = .02) in patients with tumors >4 cm [45]. CT-based BT may offer better dose distribution to the target tumors and OARs rather than orthogonal radiography, thereby leading to decreased severe toxicity and improved local control.

MRI is the gold standard of imaging during BT for LACC owing to its superior discrimination of soft tissue. It is easier to differentiate tumors from the normal cervix and uterus and to estimate the parametrial involvement compared with CT [46]. The intermediate-to-high signal intensity on T2WI usually represents the tumor area after EBRT [12]. It is particularly noteworthy that clinical examination might be the better option for assessing vaginal infiltration than MRI [47]. Accurate contouring of the tumor allows an adequate dose to cover the target volume as well as potentially limit the dose to the OARs, thus theoretically contributing to increased local control and decreased adverse effects. Nevertheless, it is very difficult to perform MRI during BT for every patient, because of the absence of MRI machines in most radiotherapy centers, the increased costs owing to MRI-compatible applicators, and the need for more time and care for patients. In addition, patients with metal in their bodies or implanted metal applicators are contraindicated for MRI. Generally, MRI should be performed twice at least: at the time of diagnosis before EBRT and at the time of the first BT performed with the BT applicator in place. MRI performed before EBRT is useful because it assists pelvic staging and evaluation of the lymph node involvement,

both of which are used while guiding EBRT boost. Moreover, MRI performed before EBRT could help radiation oncologists to evaluate the clinical feasibility of the BT implant or possible contraindications/anomalies (i.e.: uterus didelphys, uterine fibroids).

Some studies compared the height, width, and thickness of HR-CTV between CT and MRI, and concluded that the height and width on CT were significantly underestimated and overestimated than those observed on MRI, respectively, while the thickness was similar [48-50]. Researchers of one study recommended that if only the CT image is available during BT, the height of the HR-CTV should be at least two-third of the height of the uterus [42]. The delineation of OARs, such as the rectum and bladder, was comparable between CT and MRI [47, 51, 52]. There is still some controversy regarding the dose parameters to target between CT and MRI. Some studies showed no significant difference in D90% HR-CTV between CT and MRI [48, 49, 51, 53, 54]. However, some other studies found that the difference in the width leads to a significant difference in D90% HR-CTV [50, 55]. Rai et al. [50] showed that D90% HR-CTV on CT was less than that on MRI. Dempsey et al. [55] concluded that the D90% HR-CTV significantly decreased if a CT-based treatment plan was shifted to an MRI-based treatment plan. For DVH parameters of OARs, there was no difference between CT and MRI [47, 49, 50].

MRI-guided 3D BT has many advantages, but very few institutions can perform individual MRI-based BT planning for each fraction. Many radiation oncology departments investigated the function of the hybrid CT/MRI mode for BT. Beriwal et al. [56] introduced the hybrid technique with MRI-based BT planning for the first fraction and CT for each of the four subsequent fractions. MRI-based planning was used as the reference for each subsequent CT-based planning. The results of other clinical studies with 44 patients certified the feasibility of this hybrid CT/MRI strategy: 5.0-6.0 Gy × 5 fractions of BT dose. The mean D90% HR-CTV was 83.3 (3.0) Gy. The mean D2cc for the bladder, rectum, and sigmoid colon was 79.7 (5.1) Gy, 57.5 (4.4) Gy, and 66.8 (5.7) Gy, respectively; the 2-year local control, disease-specific and overall survival rates were 88%, 85%, and 86%, respectively [57]. Choong et al. [53] included

76 patients: 49 were treated with the hybrid approach and 27 with the MRI approach. The median follow-up was 41 months (range, 23-71 months). The 3-year local control, overall progression-free survival, and overall survival rates were, respectively, 92.6%, 78.8%, and 77.7% in the hybrid CT/MRI group and 92.2%, 66.3%, and 69.6% in the MRI group. The use of dosimetry and late toxicity rates for OARs were also comparable between the two groups.

US is an alternative imaging guidance modality during BT for LACC. The advantages for US-guided BT include the widely availability, portability, and low cost. And both applicator position and tumor can be observed clearly and real-timely. However, the data related volume based evaluation, treatment planning, and clinical evidence for US-guided BT are still limited [58]. The first report with transabdominal US guided BT planning for cervical cancer is from Van Dyk et al. [59]. A total of 71 patients with LACC were included in this study. The sagittal and axial images of the applicator position that is optimized in the uterus were observed based on transabdominal US, and the applicator geometry is obtained using library based treatment plans on the planning system. Orthogonal films and MRI were also taken with the applicators in situ. The similar target volume (P = 0.11), rectal point (P = 0.8), and vaginal mucosa (P = 0.19) were observed between US based plan and two-dimensional MRI based plan. Local control was 90%. Late bowel morbidity (G3, G4) was <2% [59]. This first reported study using transabdominal US-guided conformal brachytherapy planning indicated agreement between different imaging (MRI/US), and showed an excellent preliminary clinical result. Another study also by Van Dyk et al. [60] measured the distance between the anterior and posterior surface of the uterus at 2.0-cm intervals along the applicator from the external os to the tip of the applicator using transabdominal US and MRI in 192 patients. The differences in the measurements of the cervix layer (<3 mm) and uterus layers (<1.5 mm) were negligible, thereby being clinically acceptable for defining the target volume for BT. They also compared the target volume between US treatment planning and 2D MRI treatment planning, with comparable outcomes (P = .11) [60]. Tharavichitkul E et al. [61] reported the intermediate-term results of trans-abdominal US guided BT in 92 patients with cervical cancer.

Table 2. The advantages and disadvantages of different IGBT methods

Image-guided technology	Advantages	Disadvantages
CT-guided	1. CT facilities are more available in most radiotherapy centers	1. The entire cervical and uterine boundaries can be delineated, but the specific GTV cannot be delineated
	2. Short scan time and convenient	
	3. Low requirements for the applicators and a variety of materials can be used	
	4. The applicators image is clearly visible	
MRI-guided	1. Better soft tissue resolution, especially for the delineation of the tumor tissue	1. Some patients with metal in their bodies cannot undergo MR scanning
		2. The absence of MRI machines in most radiotherapy centers
	2. Differentiate superior border of the tumor, especially the superior border of intrauterine invasion cases	3. It takes more time and increases the cost
		4. The applicator reconstruction is difficult
US-guided	1. It is widely availability, portability, and low cost	1. Lack of treatment planning system
	2. Both the applicator position and tumor are clear	2. Inability to accurately assess tumor volume
	3. Real-time guidance	3. Insufficient clinical evidence

Abbreviations: IGBT = Imaging-guided brachytherapy; CT = computed tomography; MRI = magnetic resonance imaging; US = ultrasound.

The pelvic control, disease-free survival, and overall survival rates were 84.8%, 75%, and 88%, respectively, with median follow-up time of 41.2 months (range 8 to 61 months). 8 patients developed grade 2 gastrointestinal toxicity [61]. Another study investigated the clinical outcomes of transabdominal US-guided BT in 29 patients; the median follow-up was 19 months (range, 17-27 months), and the local control and disease-free survival rates were 93.1% and 86.2%, respectively; One Grade 3 vaginal toxicity was observed [62]. Additionally, trans-rectal US are always used for accurate placement of IS BT needles in the target area as well as avoiding bladder, rectum or uterine perforations due to its ability allowing real time visualization of the catheters. Sharma et al. [63] reported their experience on using of trans-rectal US for IS BT for 25 patients with cervical cancer. Average duration of implant procedure for 40 IS BT procedures was 50 minutes. No needle perforation of bladder or rectum was observed [63]. Their experience indicates trans-rectal US was feasible and effective method for assisting IS needles implantation. Accordingly, US-guided BT maybe a plausible alternative choice for resource-limited institutions in developing countries where LACC is prevalent. However, some work including target volume based evaluation, treatment planning, need to be further investigated. The advantages and disadvantages of different IGBT methods are shown in **Table 2**.

Target delineation and treatment planning

During 3D imaging-guided BT, target delineation is the next step after imaging requirement. In 2005, the GEC-ESTRO decided the terminology and basic concepts for MRI-guided BT [12]. They recommended the basic concepts of MRI-based target volume. GTV-B was defined as the visible and palpable bulk as well as the region of T2 signal intensity (gray zone) on MRI at the time of BT. HR-CTV included the GTVres (residual GTV at BT), the entire cervix and any residual disease, including the involved parametria, uterus, vagina, bladder and rectum, defined as tissue with intermediate-to-high signal intensity on T2WI. IR-CTV was defined as the safety margin of 5-15 mm around the HR-CTV, which was defined according to the extent of tumor shrinkage after EBRT after excluding normal tissue such as the bladder and rectum. For CT-guided BT, the GTV is undetectable owing to its inferior soft tissue discrimination. HR-CTV included the whole cervix and any remaining tumor at the time of BT. The superior border was defined as

a margin of at least 1 cm above the uterine vessels if IV contrast agents were used or the place where the uterus began to enlarge. An approximate 3-cm cranio-caudal height should be contoured for the cervix if it cannot be clearly detected on CT [38]. The IR-CTV is the same for MRI as described above.

For treatment planning of 3D BT, applicator reconstruction is very important for modifying the position and dwelling time of the radioactive resource to ensure adequate dose coverage of the target volume as well as minimum dose to the OARs. The applicator image is very clearly visible on CT but not on MRI. Some nonmetallic applicators, such as plastic and titanium, are eligible for MRI because they do not affect the magnetic field. However, when combined with high-intensity magnets, the titanium needles, especially closely to each other, may be heated and cause the surrounding tissues injury [38]. What's more, these nonmetallic applicators only appear as a black area on MRI, and applicator reconstruction can be less accurate using MRI. Combining CT and MRI may resolve this issue by using MRI to delineate the target and CT to reconstruct the applicator, but this method increases the time and cost as well as causes possible position uncertainty owing to patient transfer and registration error. In addition, applicator reconstruction in MRI can also be performed by using library-based digitalization. The applicators are merged with the collected images according to reference points or based on visible parts of the applicator. Copper sulfate can also be used to visualize plastic applicators; this solution also shows better visualization on T1WI MRI than on T2WI MRI [64]. In addition, MRI markers used to produce signal during MR imaging can also be filled with water/gel.

Individual treatment planning should be performed after each applicator insertion. Davidson et al. [65] compared the DVH parameters for OARs at the time of insertion with those that would have been delivered using the initial plan. They found that the "point" dose to ICRU and D2cc for the bladder and rectum were significantly increased (P<.038) when a single treatment plan was used; the doses to the sigmoid colon and small bowel showed a higher increase. Another study investigated the feasibility of using the first treatment plan for the second insertion during IC/IS BT. Most patients (29 of 44 patients) showed different applicator geometry [66]. Therefore, individual optimization for every single insertion is important when performing IC/IS BT.

GEC-ESTRO recommended the DVH parameters for assessing the dose to the target and OARs for 3D BT. The D90% and D100% represent the minimum dose delivered to 90% and 100% of the GTV, HR-CTV, and IR-CTV. For OARs, the minimum dose to the most irradiated tissue volume (0.1, 1, and 2 cm^3) is defined as D0.1cc, D1cc, and D2cc, respectively [13]. According to American Brachytherapy Society (ABS) recommendation, the HR-CTV D90% should be >80-90 Gy when EBRT and BT are combined. The D2cc should be <75 Gy for the rectum and sigmoid colon and <90 Gy for the bladder [67]. As for EMBRACE II study limits for prescribed dose, the HR-CTV D90% should be >85 Gy when combined with 45 Gy/25 fractions delivered by EBRT, and the OARs limits is same to ABS recommendation. And to reduce the vagina morbidity, especially vaginal stenosis, the EMBRACE II study limits the ICRU rectal-vaginal point dose to <65 Gy [68]. The study results from retroEMBRACE suggest that there is a close correlation between local control and prescribed dose. When HR-CTV D90% ≥85 Gy, the 3-year local control >94% in limited target (HR-CTV<20 cm^3), >93% in medium target (20 cm^3<HR-CTV<30 cm^3) and >86% in large target (30 cm^3<HR-CTV<70 cm^3) [69]. For high dose rate (HDR) BT, We usually perform a dose and fractionation scheme with 6 Gy in 5 fractions in our department; some other departments of radiation oncology may choose different fractionation regimens, such as 7 Gy for 4 fractions, 5 Gy for 6 fractions, and 5.5 Gy for 5 fractions [67]. There is much more variation in fractionation scheme for pulse dose rate (PDR) BT, which simulate the biological effects of low dose rate (LDR) BT [15]. The prescription dose of 40 Gy with a pulse size of 0.5-1.0 Gy/hour is used in French STIC prospective study [70]. The overall treatment time (OTT) for the combination of EBRT and fractionated BT should be limited to 56 days, while much shorter treatment course maybe result in better local tumor control and survival [71].

Summary

Although highly developed EBRT techniques, such as IMRT and SBRT, can deliver the inte-

grated boost dose to the target volume, BT is still an irreplaceable component for treating LACC. Currently, BT has evolved from 2D treatment planning to 3D treatment planning. Before performing BT, the appropriate applicator should be chosen according to tumor characteristics. Moreover, it is better to perform BT using transabdominal US-guided applicators. CT and MRI are common imaging modalities for imaging-guided BT planning. Accurate target delineation and treatment planning is important to ensure treatment success.

Disclosure of conflict of interest

None.

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