

# Brachytherapy in the treatment of cervical cancer: a review

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**Abstract:** Dramatic advances have been made in brachytherapy for cervical cancer. Radiation treatment planning has evolved from two-dimensional to three-dimensional, incorporating magnetic resonance imaging and/or computed tomography into the treatment paradigm. This allows for better delineation and coverage of the tumor, as well as improved avoidance of surrounding organs. Consequently, advanced brachytherapy can achieve very high rates of local control with a reduction in morbidity, compared with historic approaches. This review provides an overview of state-of-the-art gynecologic brachytherapy, with a focus on recent advances and their implications for women with cervical cancer.

**Keywords:** cervical cancer, brachytherapy, image-guided brachytherapy

## Introduction

Cervical cancer is the third-most common cancer among women worldwide, with an annual incidence of 530,000 cases and 250,000 deaths. In the developing world, it is the second leading cause of cancer death among women.<sup>1,2</sup> Its incidence in developed countries has (fortunately) decreased by 70% over the past 50 years, with the adoption of improved screening methods in cervical cytology.<sup>3</sup> Additional reduction in its incidence is anticipated with the implementation of human papilloma virus vaccine, which targets the high-risk subtypes most responsible for cervical cancers.<sup>4</sup>

For women who develop locally advanced cervical cancer, the standard of care has evolved from external beam radiation therapy (EBRT) alone, to EBRT plus brachytherapy, to combined EBRT plus brachytherapy with concurrent chemotherapy.<sup>5,6</sup> The external beam portion of treatment encompasses treatment to the pelvic lymph nodes, parametria, and primary tumor, to a dose adequate to control microscopic disease. The addition of brachytherapy serves to boost the gross tumor, and improves disease control and survival.<sup>7-11</sup> The addition of chemotherapy serves predominantly as a radiosensitizer, resulting in improvements of about 5% in overall survival.<sup>5</sup>

Brachytherapy involves the application of a radioactive source in close proximity to the tumor. It takes advantage of the inverse-square law, whereby radiation dose is inversely proportional to the square of the distance from the source. In practical terms, this allows for a very high dose to the tumor with relative sparing of the surrounding normal structures. Brachytherapy is the only demonstrated method of providing the high dose required to control cervical cancer (>80 Gray [Gy]), without causing undue side effects.

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The aim of this review is to explore current best practice and state-of-the-art developments in cervical cancer brachytherapy, including patient selection, applicator selection, operative technique, and radiation treatment planning. It is intended for those with a general interest in the treatment of cervical cancer. A detailed analysis of historical approaches to brachytherapy and treatment planning is beyond the scope of this review.

## Patient evaluation and staging

In general, all women with locally advanced cervical cancer – International Federation of Gynecology and Obstetrics (FIGO) stage IB2-IVA – should be considered for brachytherapy as part of their definitive treatment management. The initial work-up should include a cervical biopsy for histopathologic diagnosis. As per FIGO recommendations, an examination under anesthesia should be performed to determine clinical stage. This includes a pelvic exam, sigmoidoscopy, and cystoscopy. Initial bloodwork should include a complete blood count, basic metabolic panel, liver function tests, and evaluation of renal function. In cases of hydronephrosis and/or hydroureter from direct tumor extension toward the pelvic sidewall or ureteral obstruction from metastatic lymphadenopathy, ureteral stents or nephrostomy tube placement may be indicated, to relieve significant obstruction prior to therapy.

Although not included as part of routine FIGO staging, additional imaging at diagnosis can provide valuable information to guide prognosis, determine management, and assist in treatment planning.<sup>12</sup> For locally advanced disease, pelvic magnetic resonance imaging (MRI) and positron emission tomography-(PET) computed tomography (CT) should be obtained at diagnosis when possible. T2-weighted pelvic MRI is superior to clinical exam or CT, for determining the initial disease extent, with overall staging accuracy estimated between 75%–96%.<sup>13–15</sup> Compared with CT, MRI has superior soft tissue resolution. It has been shown to better detect tumor extent, parametrial involvement, and invasion of surrounding organs. In a series of patients, staged with MRI, followed by surgery, MRI staging accuracy was 81%.<sup>16</sup> Obtaining an MRI at diagnosis also aids the radiation oncologist in treatment planning, for both EBRT and brachytherapy.

PET-CT provides complementary information at the time of diagnosis. It is the superior imaging method for lymph node detection, with a sensitivity and specificity of >99% for metastatic lymph nodes of >5 mm.<sup>17</sup> Kidd et al have shown PET-staged lymph nodes to be highly prognostic of progression-free survival, independent of FIGO stage.<sup>18</sup>

Following staging evaluation, patients who proceed with definitive radiation treatment will have a planning CT simulation prior to the start of their EBRT. This is a simulation of how the patient will be set up and treated daily during the course of their EBRT. Patients are typically simulated in the supine position, with some type of immobilization device for the pelvis and/or lower extremities. Often, intravenous contrast will be used to help better delineate the pelvic vasculature, and some physicians also use oral contrast to improve delineation of the bowel. Patients are commonly asked to have a comfortably full bladder for the simulation and daily treatments, as this helps displace the bowel from the pelvis, thereby reducing dose and (ultimately) toxicity to the bowel. Prior to the simulation, patients should also have marker seeds implanted into the lowest extent of disease, to ensure that the inferior field border of the external beam radiation field adequately encompasses the most distal extent of disease. A discussion of the pros and cons of using a three-dimensional (3D) conformal “4-field box” technique (versus using intensity modulated radiation therapy) for treating the pelvis is beyond the scope of this review.

EBRT to the pelvis is generally delivered daily, Monday to Friday, for 5 weeks (25–28 treatments). Concurrent chemotherapy (most commonly, weekly bolus cisplatin 40 mg/m<sup>2</sup>) is begun at Day 1 of radiotherapy. Cisplatin should be given before radiation, on the day the patient receives both treatments. Ideally, chemotherapy is given at the beginning of the week, rather than the end. It should not be given on the same days as brachytherapy. EBRT, also, should not be given on the same day as brachytherapy.

Brachytherapy treatments are either interdigitated with EBRT (generally, starting no earlier than week 3 of treatment) or are given after EBRT is completed. Starting brachytherapy later in the treatment course allows for maximal tumor shrinkage, thus allowing for smaller brachytherapy treatment volumes. Ultimately, the most critical part of deciding when to start brachytherapy is the monitoring of treatment response, through regular pelvic examinations during the course of EBRT. At each visit, the remaining disease extent should be clearly documented and, ideally, drawn on a diagram. Each individual's treatment response will determine the appropriate time and method to initiate brachytherapy. Patients undergoing concurrent chemotherapy should also have bloodwork measured weekly, especially prior to brachytherapy implants. In the setting of neutropenia, brachytherapy implants should be delayed until it has resolved.<sup>19</sup>

It is well established that the overall treatment time of EBRT and brachytherapy should be less than 8 weeks, for patients treated with radiotherapy alone. Beyond this duration, local control and survival has been shown to decrease by ~1% per day.<sup>20–23</sup>

## High dose rate brachytherapy versus low dose rate brachytherapy

When starting the brachytherapy component of treatment, one must first decide on whether to use high dose rate (HDR) or low dose rate (LDR) brachytherapy. Historically, cervical brachytherapy used exclusively LDR sources. Treatments were delivered over 1–2 fractions, with treatment times of (typically) 1–3 days, requiring prolonged patient immobilization. LDR brachytherapy is delivered at a point A dose rate of <0.4 Gy/hour, typically using the cesium-137 isotope.

Since the early 2000s, there has been increasing adoption and utilization of HDR, as opposed to LDR. Eighty-five percent of respondents to a recent American Brachytherapy Society (ABS) survey reported having HDR at their institution.<sup>24</sup>

With HDR, a remote afterloading technology allows a small iridium source attached to the end of a cable to be robotically driven through multiple channels, stopping at predetermined points (dwell positions) for varied lengths of time.

HDR brachytherapy is delivered at a point A dose rate of >12 Gy/hour, primarily using the iridium-192 isotope. The advantages of HDR include the precise positioning of the source, infinitely variable dwell times and dwell positions – allowing for “dose sculpting” – shorter treatment times (minutes versus days), and the protection of health care personnel from radiation exposure.<sup>25–27</sup> Overall clinical outcomes and toxicities are felt to be similar with both HDR and LDR.<sup>25</sup>

A third type of treatment, not commonly used in the United States, is known as pulsed-dose rate (PDR) brachytherapy. This hybrid form of treatment uses an HDR source and remote afterloader to mimic the radiobiologic effects of LDR treatment,<sup>28,29</sup> which is accomplished by deploying the source for a brief period of time, hourly, over a prolonged treatment delivery period (2–3 days). PDR has potential radiobiologic advantages, but it requires prolonged patient immobilization and hospitalization. It remains in use at several key academic centers, but patients treated with PDR represent only a small proportion of all cervical cancer patients who are treated with brachytherapy.

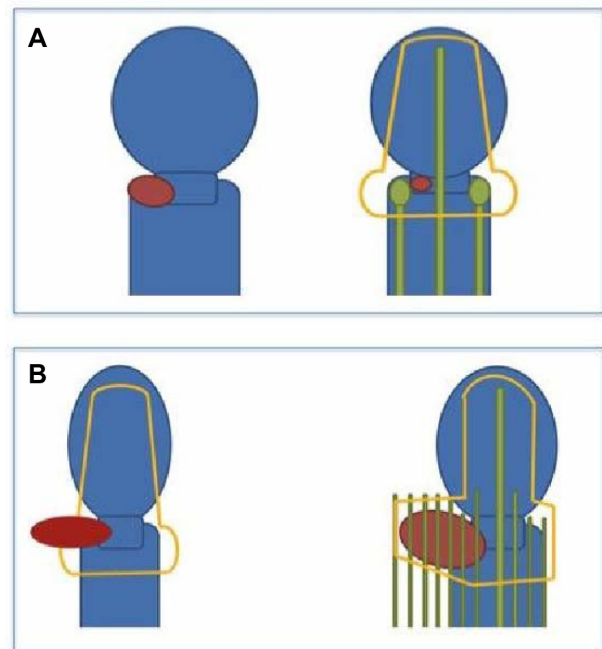
## Applicator selection

Brachytherapy for cervical cancer can be performed using an intracavitary, interstitial, or combination approach. Intracavitary brachytherapy involves placing the radioactive source using an applicator, through the vaginal cavity, and can treat the upper vagina, cervix, and uterus. In interstitial brachytherapy, catheters (small tubes) are placed in and around residual disease, using a transperineal/vaginal approach.

The choice of technique depends primarily on disease extent and anatomy (Figure 1). It is imperative to consider which approach should be used, starting at the time of diagnosis. There are few centers with true expertise in interstitial brachytherapy and the early recognition of a patient who needs this type of treatment allows for appropriate coordination of care.<sup>19</sup>

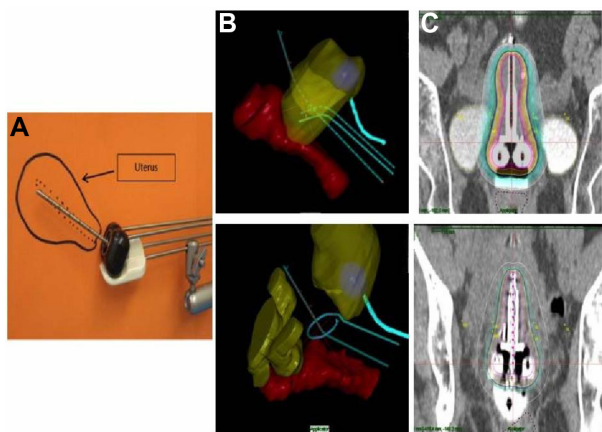
## Intracavitary brachytherapy

Intracavitary brachytherapy remains the most commonly practiced form of brachytherapy for cervical cancer.<sup>30</sup> A wide variety of commercially available applicators exists for intracavitary brachytherapy. Two of the most common include variations on the Tandem and Ovoid (T&O) or Tandem and Ring (T&R) design (Figure 2). The T&O consists of a tandem,



**Figure 1** Selecting intracavitary versus interstitial brachytherapy.

**Notes:** (A) the red tumor at the time of diagnosis (left) reduces to a small size, and the green tandem and ovoids fit appropriately, so that the orange distribution of radiation dose adequately encompasses the residual disease. (B) a large red tumor at the time of diagnosis does not respond well, so an interstitial approach with multiple (green) little tubes is used to cover the full extent of residual disease, which would not have been possible using an intracavitary approach.



**Figure 2** Examples of an intracavitary implant.

**Notes:** (A) the tandem, extending to the top of the uterine fundus. The ovoids are located at the level of the cervical os, and a white rectal paddle is noted posterior to the ovoids. The apparatus is held in place by a base plate. (B) three-dimensional rendering of the tandem and ovoid (top) and tandem and ring (bottom) in relation to the rectum and bladder. (C) coronal CT slice of the distribution of radiation using a tandem and ovoids (top) and tandem and ring (bottom).

**Abbreviation:** CT, computed tomography.

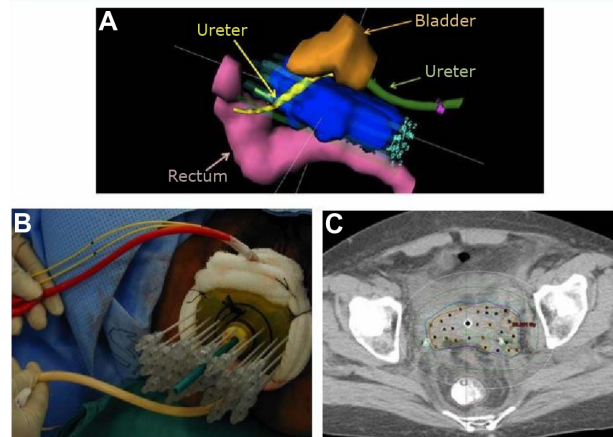
an intrauterine tube placed through the cervix to the level of the uterine fundus, and two ovoids (colpostats) that are placed on either side of the cervix in the lateral vaginal fornices. The T&R also consists of a tandem, and utilizes a ring that sits on either side of the cervix. There are some differences in ease of use and distribution of radiation dose between these two applicators. However, both result in similar outcomes. So, the decision to use one over the other is mostly user-dependent.

These brachytherapy procedures are performed as outpatients, when using HDR, and as inpatients, when using LDR.

## Interstitial brachytherapy

Interstitial brachytherapy utilizes a transperineal template, through which several hollow tubes are inserted directly into tissues (Figure 3). A tandem and central vaginal cylinder are incorporated into the template. Commonly used templates include the Syed-Neblett template and the Martinez Universal Perineal Interstitial Template.

Interstitial brachytherapy has been characterized as the treatment of choice when intracavitary applicators are deemed unsuitable. Recognized indications for interstitial brachytherapy include large tumors, lower vaginal involvement, lateral extension of disease (beyond the reach of intracavitary applicators), and ill-fitting intracavitary applicators (which may result from an effaced cervix or narrow vaginal fornices).<sup>19,26</sup> Patients who have had a supracervical hysterectomy and who develop cancer in the cervical stump should also be considered for interstitial implants. Template-based interstitial methods are (ultimately) the most flexible form of



**Figure 3** Examples of an interstitial implant.

**Notes:** (A) three-dimensional rendering of the organs at risk, in relation to the brachytherapy catheters and radiation dose cloud. (B) a completed implant. (C) axial CT slice showing the distribution of radiation dose achievable with an interstitial implant.

**Abbreviation:** CT, computed tomography.

gynecologic brachytherapy, and can be used for the widest variety of clinical scenarios.

Hybrid applicators have also been developed that allow for several interstitial catheters to be placed in combination with a T&R or T&O applicator.<sup>31,32</sup> These applicators allow for many fewer needles to be placed, but offer a much more restricted spatial distribution, compared with a template. Conversely, these applicators are potentially less user-dependent, and are more amenable to day procedures than are template-based approaches.

## Applicator placement

The placing of an intracavitary applicator can be performed either in the operating room or a procedure suite at a clinic. Some practitioners prefer the patient to be kept under general anesthesia for the insertion process. Other practitioners perform the procedure under either conscious sedation or local anesthesia. Some physicians place a Smit sleeve into the cervical os at the time of the first applicator insertion. This allows the cervical os to be easily identified and dilated, allowing easier insertion of the tandem at subsequent treatments.<sup>33,34</sup>

For the procedure itself, a Foley catheter is placed in the bladder. A speculum is then placed, to visualize the cervix. If marker seeds were not placed at the time of EBRT, then seeds should be placed in at least two locations in the cervix (eg, 11:00 and 2:00). A single tooth tenaculum can then be used on the anterior lip of the cervix, to provide counter traction when trying to sound the uterus, and later for inserting the tandem. It is important that this be done carefully, so as not

to perforate the uterus. Based on the length and curvature of the uterus, one then selects an appropriate tandem to insert. Many physicians now use either transabdominal or transrectal ultrasound to ensure appropriate placement of the tandem, rather than relying on fluoroscopy alone.<sup>35</sup>

After the tandem has been inserted, the ovoids/ring can be placed. It is important to select the largest ovoids/ring that can fit in the fornices, to ensure the best dose differential between the tumor and normal tissues. After the applicator is in place, it must be stabilized, and the rectum and bladder should be displaced from the applicator as much as possible. Two-inch gauze packing, with a radiopaque lining, is commonly used to accomplish this. The radiopaque lining allows one to view the packing using X-ray. One must be cautious to not displace the ovoids/ring inferiorly from the os during this process. This is the most technique-dependent portion of the procedure, and tends to be the most uncomfortable part for the patient. An alternative to using gauze packing – which appears to be more consistent between insertions and more comfortable – is using balloon-type vaginal packing.<sup>36</sup> After packing is complete, it is important to verify that the applicator is in the proper position. Most commonly, an anteroposterior and lateral X-ray are taken, to ensure the appropriate positioning of the tandem relative to the ovoids/ring, cervical os, and packing.

The technique for interstitial brachytherapy is more involved, as it requires the insertion of multiple small, hollow tubes to encompass the residual disease. The procedure is done in the operating room, with either general anesthesia or some combination of spinal/epidural and sedation. There are multiple techniques available to guide the placement of the catheters, including laparoscopic assistance (to ensure the bowel is not perforated), fluoroscopic guidance, ultrasound guidance, CT guidance, and MRI guidance. A discussion of the pros and cons of each of these techniques is beyond the scope of this review.

Performing brachytherapy implants is a user-dependent skill. Like other surgical procedures, high-volume centers demonstrate superior outcomes, and poor quality implants result in less-desirable patient outcomes.<sup>37–39</sup> It is alarming that reductions in cause-specific and overall survival have been noted with decreasing utilization of brachytherapy for cervical cancer patients in the United States.<sup>40</sup> As cervical cancer is a rare disease in the United States, it is important that teams taking care of these women maintain an adequate volume of cases, as brachytherapy technique is a critical part of ensuring ideal outcomes for these patients.

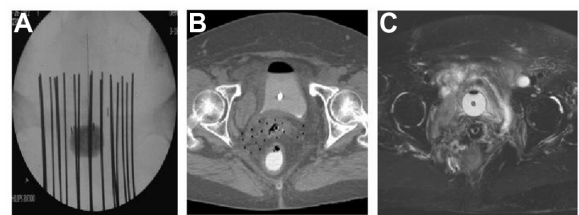
## Treatment planning/dosimetry

### Determining the appropriate treatment target volume

Ideally, following the completion of applicator insertion, a simulation is performed using an MRI or CT scan. Traditionally, this has been done using plain film X-rays only, but one can quickly appreciate the limitations of this. On X-rays, you have limited ability to see the actual tumor and the organs at risk (rectum, bladder, and sigmoid). This necessitates prescribing to points in two dimensions rather than being able to prescribe to 3D volumes, as can be done with CT and MRI images (Figure 4).

The International Committee on Radiation Units and Measurements' Report 38 (ICRU38) outlines the most commonly applied conventions for prescribing dose to points.<sup>41</sup> The radiation dose should be prescribed to point A – a point located 2 cm superior to the cervical os, and 2 cm lateral, along the plane perpendicular to the intrauterine tandem.<sup>19,42</sup> Point A derives from the Manchester system, and was defined by Tod and Meredith in a paper that detailed the nature and course of radiation necrosis following radium-based brachytherapy.<sup>43</sup> They noted that, following radiation, there was necrosis at the paracervical vessels. They defined point A within this paracervical triangle (commonly thought of as where the ureter crosses the uterine artery) as a point of limiting tolerance. As improvements in imaging from X-ray to CT/MRI occurred, studies by Potter et al and Narayan et al demonstrated that defining point A using plain films often results in point A lying inside or outside the uterus, thereby under- or overdosing the true volume of interest.<sup>44,45</sup> This discrepancy could contribute to local failures and/or complications.

Beyond just adequately dosing the tumor, the limitations of a two-dimensional (2D) approach also extend to constraining the dose to normal tissues (bladder, rectum, sigmoid). Based on ICRU38, organs at risk doses are calculated based on surrogate



**Figure 4** Examples of brachytherapy.

**Notes:** (A) X-ray. (B) axial CT slice. (C) axial MRI slice. One can see the increasing amount of anatomic detail that is apparent on MRI, compared with the other imaging modalities.

**Abbreviations:** CT, computed tomography; MRI, magnetic resonance imaging.

points. The bladder point is defined as the surface of the foley catheter balloon (filled with 7 cc contrast medium), to represent the maximal dose to the bladder. The rectal point is specified as 0.5 cm posterior to the vaginal wall, directly posterior to the center of the ovoids or the ring applicator. Studies using 3D imaging demonstrate that the ICRU38 organs at risk points do not always accurately estimate the true highest dose to the organ at risk, and that using 3D contouring of the entire organ at risk is necessary to accurately determine maximum doses.<sup>46</sup>

While the use of ICRU38 reference points provides a useful standard practice for cervical brachytherapy, the incorporation of 3D imaging into brachytherapy practice has clear advantages. The GEC-ESTRO working group released a series of recommendations, beginning in 2005, which sought to establish a common language and set of parameters for 3D image-(MRI) based treatment planning.<sup>12,47–49</sup> These recommendations introduced new fundamental concepts to gynecologic brachytherapy. While the key concepts from these recommendations are presented here, practitioners are referred directly to these papers for reference.

Rather than prescribing to a point, the working group suggested prescribing to a high-risk clinical target volume (HR-CTV). They define this volume as the area of gross residual disease at the time of brachytherapy. It includes the gross disease at the time of implant (determined on T2-weighted MRI), the entire cervix, and any areas clinically suspicious for residual disease (palpable abnormalities or indurations) or suspicious on imaging (residual “gray zones” on T2 MRI). The optimal dose to the HR-CTV remains undefined, though it is commonly prescribed to the same dose as would have been prescribed to point A (generally, >80 Gy).

They also define a second volume called the intermediate risk clinical target volume (IR-CTV). It includes the HR-CTV, the gross disease at diagnosis, plus an additional margin of 5–15 mm, based on the clinical situation. The IR-CTV should receive more than 60 Gy, through dose contributed by EBRT and brachytherapy.

The GEC-ESTRO recommendations promote an adaptive brachytherapy strategy; that is, a volume-based treatment approach, whereby the target is modified with each brachytherapy fraction, based on response to treatment. Ideally, an MRI is obtained (with the applicator in place) with each fraction. Where logistic and financial challenges prohibit this approach, an alternative strategy is to obtain an MRI with the first fraction, and CT for subsequent fractions.<sup>50</sup> CT-based determination of cervical volumes is known to be inferior to MRI-based determinations, and so using MRI as much as possible is thought to be best.<sup>51</sup>

The GEC-ESTRO guidelines also suggest several parameters to describe target dose coverage. These include D90 and D100 (the dose delivered to 90% and 100% of the volume), as well as V100 (the volume receiving 100% of the prescription dose). The combined total dose from EBRT and brachytherapy can be calculated using a linear quadratic model to determine the equivalent dose in 2 Gy fractions (EQD2). It is important to understand that the doses from EBRT and brachytherapy using HDR are not additive. For example, a patient who receives 45 Gy EBRT, followed by 6 Gy  $\times$  5 fractions of HDR, does not receive a total dose of 75 Gy but an EQD2 of 84.3 Gy. Sample worksheets to conduct these calculations are available from the ABS website.<sup>52</sup>

For organs at risk, GEC-ESTRO recommendations suggest reporting the dose for the most exposed 0.1 cc, 1.0 cc, and 2.0 cc (D0.1cc, D1cc, and D2cc), of the rectum, sigmoid, and bladder.

As data regarding optimal treatment volumes evolve, recording the dose to point A (and taking care not to under dose point A) is still recommended. Internationally, prescription to point A remains the norm. But practice is rapidly shifting away from prescriptions based solely on ICRU reference points, to volume-based prescriptions.<sup>30</sup>

## Determining the appropriate dose and fractionation scheme

After determining what volume or point to prescribe to, one must select a dose fraction scheme (how many treatments, and the size of the dose, per treatment). A variety of dose/fractionation schedules are used in clinical practice for HDR brachytherapy. The most common fractionation schedules in the United States are 5–6 Gy  $\times$  5 fractions. However, shorter regimens are also in use, including 7 Gy  $\times$  4, 8 Gy  $\times$  3, and 10 Gy  $\times$  2.<sup>53,54</sup> Hesitation for adopting higher doses per fraction comes from studies which suggest higher rates of complications with doses >7 Gy per fraction.<sup>55</sup> Intracavitary brachytherapy fractions are typically delivered 1–2 times per week. For template-based interstitial implants, the entire treatment is commonly done during one insertion, given the complexities involved with proper placement of the brachytherapy catheters. Fractions may be delivered twice-daily, separated by 6 hours, with the total brachytherapy course delivered over 2–3 days.

Direct comparisons between dose/fractionation schedules for cervical brachytherapy are limited.<sup>56–58</sup> The European study on MRI-guided brachytherapy (EMBRACE) is a multicenter trial (sponsored by GEC-ESTRO) that will prospectively assess MRI-guided cervical brachytherapy.

A variety of brachytherapy prescriptions will be used at the discretion of individual institutions. Therefore, the results of this study will provide the best information yet on the merits of different fractionation options, in the era of adaptive, image-guided brachytherapy.

In the absence of convincing outcomes data, most fractionation schemes are influenced by practicalities and resource constraints. Fewer insertions are associated with less anesthesia, less chance for operative complications, less demand for operating room time, shorter overall treatment time, with the potential for less repeat imaging and lower use of treatment planning resources. The potential disadvantages include requirements for inpatient care, prolonged patient immobility and its attendant risks, and uncertainty associated with applying a single treatment plan for multiple fractions.

Finally, interstitial and intracavitary brachytherapy have not been compared using similar fractionation schedules; however, slightly lower doses are recommended by the ABS, when using interstitial approaches.<sup>53</sup> This is mostly related to issues with meeting rectal constraints when treating larger volumes, as is often the case with interstitial brachytherapy.

## Clinical outcomes using image-guided brachytherapy

Early series using advanced, image-guided adaptive brachytherapy have shown major improvements in both local control and reduced normal tissue toxicity.<sup>59,60</sup> One of the first studies to compare 2D versus 3D planning was the French STIC study.<sup>61</sup> In the cohort of patients treated with EBRT plus chemotherapy followed by brachytherapy, at 24 months, local relapse-free survival was 74% and 79%, while grade 3–4 toxicity rates were 23% versus 3% in the 2D versus 3D groups, respectively. There was also an improvement seen in overall survival: 65% versus 74%. Similar improvements with image-guided brachytherapy were presented in a series of 156 patients from Vienna.<sup>60</sup> At 3 years, overall local control was 95% (98% for tumors 2–5 cm, and 92% for tumors >5 cm). Cancer-specific survival rates at 3 years were 83% for stage IB, 84% for stage IIB, and 52% for stage IIIB. Grade 3–4 toxicities were low, at around 8%. The same group also showed a strong dose–effect relationship for local control, with local control rates >90% being associated with HR-CTV D90 of >86 Gy.<sup>62</sup> Similar importance of the D90 was presented at ESTRO 2013, on retro-EMBRACE data (patients with MRI- or CT-guided 3D treatment prior to the start of the EMBRACE study).<sup>63</sup> It was demonstrated

that in 592 patients (with a median follow-up of 31 months) that a D90 to the HR-CTV of >92 Gy resulted in an overall local control rate of 95%. Ultimately, the EMBRACE study will provide us with definitive data regarding the true value of image-guided brachytherapy.

Outcomes for template-based interstitial brachytherapy cannot be directly compared to intracavitary or hybrid intracavitary/interstitial treatments, because of differences in patient selection. Moreover, individual interstitial series are highly varied, in terms of patient selection, size, and treatment technique. Pinn-Bingham et al reported the largest series of HDR interstitial brachytherapy for cervical cancer.<sup>64</sup> One hundred and sixteen women were treated with 50.4 Gy EBRT and two applications of HDR to a dose of 36 Gy. About 60% of patients also received interstitial hyperthermia. At a median follow-up of 35.1 months, the clinical locoregional control rate was 85%, and the 5-year disease survival rate was 60%. Approximately 13% of patients had late grade 3 toxicities. While this study utilized CT-based planning, it did not use the GEC-ESTRO definitions of HR-CTV, nor did it report D2cc doses to organs at risk. In addition the use of hyperthermia and the timing of the implants make generalization and comparison of these results challenging.

## Toxicity

Despite the limitations in 2D brachytherapy planning, toxicity can be reliably correlated to dose based on ICRU points.<sup>65–69</sup> With the introduction of 3D-based planning, volume-based dose parameters have been investigated, and also appear to provide clinically meaningful correlation with toxicities.

Early investigations demonstrated a clinical correlation between rectal dose volume and toxicity.<sup>70,71</sup> The most consistently validated organ at risk parameter has been the D2cc rectum. Georg et al prospectively studied 141 cervical cancer patients treated with image-guided adaptive brachytherapy in combination with EBRT, with or without chemotherapy.<sup>59,72</sup> At a median follow-up of 51 months, the 5-year actuarial side effect rate for the rectum was 12%, using the LENT-SOMA scoring system. Using a cut-off D2cc of >75 Gy, overall late rectal side effects were 20% versus 5%, and 12% versus 4%, for grade  $\geq 2$  rectal toxicity. A 10% rate of grade  $\geq 2$  rectal toxicity was associated with a D2cc of >78 Gy. A study of 51 women with a variety of gynecologic malignancies (including recurrences), treated with interstitial brachytherapy at Brigham and Women's Hospital, demonstrated that a 10% risk of grade  $\geq 2$  rectal toxicity correlated with a D2cc of >62 Gy.<sup>73</sup> These studies had important differences in design, population, toxicity scoring, follow-up, and treatment

method, but nonetheless, illustrate a clear correlation between rectal D2cc and toxicity.

Dose–volume relationships have also been shown to correlate with late bladder toxicities. Georg et al showed a correlation for all dose volume histogram points (D0.1cc, D1cc, and D2cc) and ultimately suggested a cut-off of D2cc <100 Gy, which corresponded to 9% versus 13% rates of grade 0–1 versus grade 2–4 toxicity.<sup>59</sup>

No clear correlation between dose–volume and toxicity has been determined for the vaginal mucosa, sigmoid, urethra, or ureters.

Overall, in the era of image-guided brachytherapy, later grade  $\geq 3$  rectal, bowel, and bladder toxicity rates are typically in the  $\leq 10\%$  range. Ongoing prospective trials (and the ABS) suggest limiting the D2cc rectum to <70–75 Gy, D2cc sigmoid to <75 Gy, and D2cc bladder to <90 Gy.<sup>53</sup> Moving forward, consistency in toxicity scales is required, for comparison between series as well as for improved reporting of patient-reported morbidity.

## Alternatives to brachytherapy

The possible disadvantages of brachytherapy include that it is invasive, resource-intensive, can be technically challenging, and is ideally performed in women who have a good performance status. Investigators have started to publish early experiences of using an EBRT technique called stereotactic body radiation therapy (SBRT), as a substitute for brachytherapy in patients who are not deemed appropriate brachytherapy candidates. SBRT still delivers radiation from outside, as in standard EBRT, but at a much higher dose per fraction. It is typically completed in five or fewer sessions. Its goal is to noninvasively mimic the dose distribution that can be achieved with HDR brachytherapy. Dosimetric studies have shown these methods to provide good target coverage, and doses to organs at risk similar to brachytherapy, but clinical data is very limited.<sup>74–77</sup> At the current time, techniques such as SBRT, in place of brachytherapy, should only be performed in clinical trials.

## Conclusion

Progress from 2D- to 3D-based imaging and treatment planning for cervical cancer brachytherapy has improved local control, reduced toxicity, and improved overall survival for women. Further data from 3D-based techniques is accumulating, and results from the EMBRACE trial will provide strong evidence regarding the true merits of this approach. This is indeed an exciting time for brachytherapy.

## Disclosure

The authors report no conflicts of interest in relation to this work.

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