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American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: High-dose-rate brachytherapy

Akila N. Viswanathan[1,*], Sushil Beriwal[2], Jennifer F. De Los Santos[3], D. Jeffrey Demanes[4], David Gaffney[5], Jorgen Hansen[1], Ellen Jones[6], Christian Kirisits[7], Bruce Thomadsen[8], Beth Erickson[9]

[1]*Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*
[2]*Department of Radiation Oncology, University of Pittsburgh School of Medicine, Pittsburgh, PA*
[3]*Department of Radiation Oncology, University of Alabama, Birmingham, AL*
[4]*Department of Radiation Oncology, David Geffen School of Medicine UCLA, Los Angeles, CA*
[5]*Department of Radiation Oncology, Huntsman Cancer Center, University of Utah, Salt Lake City, UT*
[6]*Department of Radiation Oncology, University of North Carolina, Chapel Hill, NC*
[7]*Department of Radiotherapy, Medical University of Vienna, Vienna, Austria*
[8]*Departments of Medical Physics and Human Oncology, University of Wisconsin, Madison, WI*
[9]*Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI*

ABSTRACT

PURPOSE: This report presents an update to the American Brachytherapy Society (ABS) high-dose-rate (HDR) brachytherapy guidelines for locally advanced cervical cancer.

METHODS: Members of the ABS with expertise in cervical cancer formulated updated guidelines for HDR brachytherapy using tandem and ring, ovoids, cylinder, or interstitial applicators for locally advanced cervical cancer. These guidelines were written based on medical evidence in the literature and input of clinical experts in gynecologic brachytherapy.

RESULTS: The ABS affirms the essential curative role of tandem-based brachytherapy in the management of locally advanced cervical cancer. Proper applicator selection, insertion, and imaging are fundamental aspects of the procedure. Three-dimensional imaging with magnetic resonance or computed tomography or radiographic imaging may be used for treatment planning. Dosimetry must be performed after each insertion before treatment delivery. Applicator placement, dose specification, and dose fractionation must be documented, quality assurance measures must be performed, and followup information must be obtained. A variety of dose/fractionation schedules and methods for integrating brachytherapy with external-beam radiation exist. The recommended tumor dose in 2-Gray (Gy) per fraction radiobiologic equivalence (normalized therapy dose) is 80–90 Gy, depending on tumor size at the time of brachytherapy. Dose limits for normal tissues are discussed.

CONCLUSION: These guidelines update those of 2000 and provide a comprehensive description of HDR cervical cancer brachytherapy in 2011.

Keywords: Cervical cancer; Brachytherapy; High dose rate

Introduction

Brachytherapy is an important component in the curative management of carcinoma of the cervix, and significantly improves survival (1, 2). High-dose-rate (HDR) and low-dose-rate (LDR) brachytherapy seem to be relatively equivalent treatments in terms of survival outcomes based on existing retrospective and prospective studies (3–11). Advantages of HDR brachytherapy include opportunities for outpatient treatment, avoidance of exposure to staff from the radiation source, consistent and reproducible applicator positioning, and dose

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In formulating guidelines, it should be noted that variations in approaches to gynecologic brachytherapy, as with most medical procedures, are commonplace and may readily fall within accepted and appropriate management of cervical cancer patients. The guidelines presented are a means to aid practitioners in managing patients, but are not to be viewed as rigid practice requirements that establish a legal standard of care.

* Corresponding author. Department of Radiation Oncology, Brigham and Women's Hospital/Dana-Farber Cancer Institute, 75 Francis Street, ASB 1, L2, Boston, MA 02115. Tel.: c/o ABS +1-703-437-4377; fax: +1-703-435-4390.

E-mail address: abs@americanbrachytherapy.org.

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optimization attained with a variable dwell-time stepping source (3). Virtually all modern clinical trials for cervical cancer allow either HDR or LDR brachytherapy.

The use of HDR brachytherapy for cervical cancer has substantially increased over the past 10 years in the United States and internationally. The most recent Quality Research in Radiation Oncology (formerly Patterns of Care) survey from 2007 to 2009 shows that 62% of surveyed facilities use HDR compared with 13% in the 1996–1999 survey (12). A total of 85% of respondents to surveys in the United States (13) and internationally (14) use HDR brachytherapy. Nevertheless, with HDR brachytherapy, there is a significant variation of the total tumor dose, the dose delivered per fraction and the proportion of tumor dose delivered with external-beam radiotherapy (EBRT) vs. brachytherapy (14).

Given the potential for short- and long-term injury to normal tissues from large HDR doses per treatment, the radiation oncologist must carefully assess and minimize normal-tissue doses administered per fraction, and must calculate the summative total dose of EBRT and brachytherapy. To assess the normal-tissue doses per fraction accurately, computer-assisted tomography or magnetic resonance imaging with the brachytherapy apparatus in place is recommended.

This article will present current concepts in HDR brachytherapy for cervical cancer including three-dimensional (3D) image-based dose-specification methods and review standard practice recommendations.

Methods

Gynecologic radiation oncology experts in the United States were surveyed regarding their willingness to serve as authors for these guidelines. Those responding affirmatively reviewed and updated the 2000 guidelines of the American Brachytherapy Society (ABS) (15). These authors evaluated the relevant literature, identified established and controversial topics via conference calls, and supplemented this information with their clinical experience to formulate the current guidelines. A consensus decision was made to integrate strategies using 3D image guidance when possible. Specific commercial equipment, instruments, and materials are described when necessary. Such identification does not imply recommendation or endorsement by the presenter nor imply that the identified material or equipment is necessarily the best available for these purposes.

This report was reviewed and approved by the Board of Directors of the ABS.

Results

Treatment issues with HDR brachytherapy

External-beam radiation therapy issues related to HDR brachytherapy

Treatment with EBRT and brachytherapy should be completed in less than 8 weeks, as better local tumor control and survival can be expected with relatively shorter treatment courses (16, 17). The HDR brachytherapy may be interdigitated with EBRT to shorten the total treatment duration, with the latter typically given in 1.8-Gy fractions to 45 Gy. Many institutions administer as much EBRT as possible first to minimize the amount of residual disease, ensure that the lymph-node regions of the pelvis receive 5 days of EBRT per week for as long as possible, administer concurrent chemotherapy for a minimum of 5 consecutive weeks, and improve brachytherapy geometry because of tumor shrinkage increasing the distance between the tumor and the organs at risk (OAR). Others facilities elect to administer the first brachytherapy fraction early in the course of EBRT and treat one fraction per week, with brachytherapy not given on the same day as EBRT to minimize treatment duration. For patients with large bulky tumors, commencing the treatment too early and specifying the dose to point A may underdose the tumor volume leading to poor local control (10). In the United States, the most common HDR intracavitary regimen prescribes 2 fractions per week for a total of five fractions (14). The ABS recommends that additional radiation to the parametria/nodes via a boost may be administered on nonbrachytherapy days.

Chemotherapy issues unique to HDR brachytherapy

The ABS recommends the use of concurrent cisplatin-based chemotherapy for patients with adequate renal function. When administering weekly cisplatin, the fifth and sixth dose of chemotherapy may fall during weeks when HDR brachytherapy commences. Although no data support an increase in toxicity (3), given the large fraction sizes used with HDR, the ABS recommends that chemotherapy not be administered on a brachytherapy day but rather on an EBRT day, given the potential for increased complications because of normal-tissue sensitization.

Treatment planning

Optimization issues specific to HDR and pulsed-dose-rate intracavitary brachytherapy

Adequate geometry of the implant is imperative regardless of the simulation method. Incorrect placement of the applicator will negatively impact disease-free survival, and increase rates of local recurrence and, often, toxicity (18). Optimization of brachytherapy will not compensate for poor applicator placement.

A treatment plan should be generated by a qualified physicist or trained brachytherapy dosimetrist in collaboration with the treating radiation oncologist. The term *optimization* refers to the sophisticated process of achieving certain dose values at points or volumes within the implant; it is not the simple generation of a standard dose distribution by using fixed dose points located around the applicator. With conventional LDR brachytherapy, the shape of the dose distribution is hard to customize because of the few sources used (usually three in the tandem and one each

in ovoids) and the limited number of source strengths. HDR and pulsed-dose-rate (PDR) brachytherapy allow more precise shaping of the dose distribution to the extent desired by the radiation oncologist. Some institutions use a squared distribution conforming to the cervix, whereas others use a narrow tapered distribution that extends further into the uterus. Still others attempt to match the physical distribution of the LDR brachytherapy applicators although that produces a very different biologic dose distribution.

Achieving an acceptable dose distribution with HDR and PDR brachytherapy requires both proper insertion of the appliance and a good optimization process. With 3D dosimetry, matching the dose distribution to the high-risk clinical target volume (HR-CTV) while simultaneously avoiding the OAR can be challenging. Two factors complicate the physical aspect of this challenge: throughout the history of cervical brachytherapy, the dose to the tumor, as defined by the HR-CTV, was unknown; and, increasing the weight of a source pushes the dose in all directions, toward OAR and the target. Optimization should be performed with caution by observing changes in the dose, dose/volume parameters, and the spatial dose distribution that results from the modified loading pattern. The exclusive use of dose–volume histogram (DVH)–based parameters to select a source loading is not recommended because substantial and perhaps undesirable changes in the spatial dose distribution may occur. Hot or cold spots in the target region and in noncontoured OAR, such as the vagina, connective tissue, nerves, vessels, or the ureters, may result. Importantly, in 3D imaging, the spatial dose distribution should be analyzed carefully for the location of cold and hot spots within the HR-CTV. Displaying isodose lines higher than 100% may be important to recognize and alter regions of high dose.

Optimization in the 2000 ABS Guidelines referred to setting lateral dose points adjacent to the applicator based on radiographic localization. With 3D imaging, optimization refers to starting with a customary loading of the full length of the tandem and the vaginal applicator (ovoids, ring, or cylinder), then modifying the dwell positions and dwell times to reduce the dose to the OAR and ensure maximum tumor coverage; this results in differences in specification and reporting. For example, a dose of 5.5 Gy may be specified to a 3D-imaging-contoured target of 50-mm width at the level of point A. To fully cover the target, one approach is to define two dose points 25 mm from the tandem and normalize the 100% isodose line to these points. In this case, a dose of 5.5 Gy is specified to the target while the dose at point A will be greater than 5.5 Gy. In daily clinical practice, the planning aims sometimes cannot be achieved because of the dose limits for the OAR. In such cases, the initially planned dose values should be decreased and an optimal compromise reached between tumor and OAR goals.

For the tandem applicator with needles (Fig. 1), evaluation of the spatial dose distribution through the whole implant, including each needle, in addition to DVH values, becomes even more important. The balance of dose delivered through each needle should also be evaluated to avoid undesired high-dose regions in the adjacent tissues, such as the vagina, ureters, connective tissues, and the OAR (19). A reproducible and safe approach is to first optimize dwell time for the intracavitary part of the implant taking into account OAR primarily, without activating the needle positions. The missing coverage of the CTV is compensated for in a second step by fine-tuning the overall dose distribution with activation and direct adjustment of the dwell times in the needles. With inverse or graphical optimization, the dwell times of the intracavitary and interstitial parts should be controlled by the physicist because most optimization algorithms do not take into account the spatial dose distribution. In general, approximately 10–20% of the total dwell time is linked to source positions in the needles, and most of the dose should be delivered through the tandem/ring or tandem/ovoid.

In interstitial brachytherapy, the target volume is typically larger than with intracavitary. The desired dose

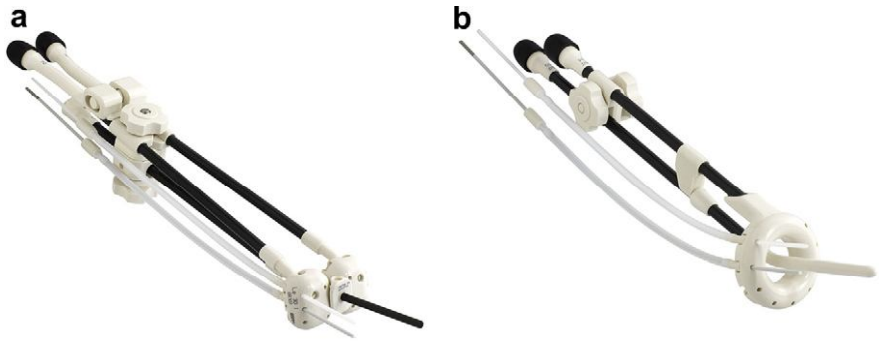

Fig. 1. (a) A tandem and ovoid with interstitial catheters (Utrecht applicator, Nucletron B.V., Veenendaal, Netherlands). The applicator uses interstitial catheters that extend above the ovoids and cover a greater width of the cervix higher up than standard ovoids. (b) A tandem and ring applicator with interstitial catheters inserted (Vienna applicator, Nucletron B.V., Veenendaal, Netherlands). Catheters similar to the Utrecht applicator extend the dose to a greater height and width than without. Only approximately 10% of the dose should be administered through the needles, allowing the majority of the dose contribution to be from the tandem and ovoids.

Table 1
Examples of regimens frequently used in the United States for tandem and ovoid or tandem and ring brachytherapy

EBRT, dose to ICRU 52 point or median dose in case of IMRT	Fractionation to point A (Gy)	EQD2 (Gy) to the tumor (point A dose with $\alpha/\beta = 10$ Gy)[a]	EQD2 (Gy) with 90% of the target dose to the OAR using $\alpha/\beta = 3$ Gy	EQD2 (Gy) with 70% of the target dose to the OAR using $\alpha/\beta = 3$ Gy
25 × 1.8 Gy	4 × 7 Gy	83.9	90.1	74.2
25 × 1.8 Gy	5 × 6 Gy	84.3	88.6	73.4
25 × 1.8 Gy	6 × 5 Gy	81.8	83.7	70.5
25 × 1.8 Gy	5 × 5.5 Gy	79.8	82.6	69.6

ICRU 52 = International Commission of Radiation Units Report 52; IMRT = intensity modulated radiation therapy; EBRT = external-beam radiotherapy; EQD2 = normalized therapy dose; OAR = organs at risk.

[a] For institutions that use radiographic imaging for treatment planning, these doses (e.g., D_{90}) are recorded at point A. For institutions that use computed tomography or magnetic resonance imaging, these doses are recorded covering the target volume or high-risk clinical target volume.

distribution to the central core of an interstitial implant, where needles may lie in close proximity to the tandem sources and the cervical and paracervical tumor, also differs from an intracavitary implant. In contrast, at the periphery of the implant the needles are in close proximity to the OAR and dose is necessarily reduced. During the optimization process, dwell positions and dwell times will be determined to deliver the intended dose. As with all volume implants, one point dose or fraction size cannot adequately describe the implant.

Dose calculations for HDR brachytherapy

The radiobiology of HDR brachytherapy and the use of the linear-quadratic model to convert HDR to LDR doses were discussed in detail in the 2000 ABS recommendations and in recent studies. A worksheet is available for download from the ABS website to facilitate conversion of HDR fractionations into biologically equivalent doses in 2-Gy fractions—normalized therapy doses (NTDs) or EQD2. At the time of this publication, the website is www.americanbrachytherapy.org/guidelines.html. These worksheets, however, are for theoretical guidance and should not replace the empirical observations or judgment of physicians experienced with HDR brachytherapy.

Dose recommendations for HDR brachytherapy

Recommendations for dose depend on the methodology followed for treatment planning. In the United States, the most commonly used regimens are 45 Gy EBRT to the pelvis (possibly with a sidewall boost) with concurrent cisplatin-based chemotherapy and either 5.5 Gy per fraction for five fractions (for patients treated with concurrent chemotherapy who have had either a complete response or have <4 cm of residual disease) or 6 Gy for five fractions (for patients with tumors >4 cm after EBRT). Over the past decade, the most common HDR fraction size used in the United States for all stages of cervix cancer has been 6 Gy for five fractions specified at point A, but concerns have been raised about potential toxicity to the sigmoid colon and rectum in patients treated with chemoradiation (20). As a result, recent clinical trials have included a range of lower fractional doses, such as 5.5 Gy for five fractions. In addition, with the implementation of 3D imaging, although it is recommended to record point A, the imaging allows the physician to specify the 100% isodose line to cover the tumor volume as depicted on imaging, and consider prescription to a DVH parameter such as the D_{90} (the dose received by at least 90% of the volume). Other fractionation regimens are listed in Table 1.

Many institutions use cross-sectional imaging to visualize the cervix and involved regions. In these cases, although the dose to point A should be recorded, the goal should be good coverage (i.e., a D_{90}) of the involved region with EQD2 ≥ 80 Gy for patients with either a complete response or a partial response with residual disease less than 4 cm. For nonresponders or those with tumors larger than 4 cm at the time of brachytherapy, tumor dose escalation to an EQD2 of 85–90 Gy is recommended to either point A or the D_{90} to maximize local control (21, 22). Other fractionation regimens with EQD2 in the range of 80–85 Gy are acceptable, although the larger the fraction size, the higher the risk for normal-tissue toxicity. For the normal tissues, it is recommended that for each fraction of brachytherapy, the DVH values are calculated and the final dose to the bladder, rectum, and sigmoid calculated. Dose limits for the normal tissues are listed in Table 2. The EQD2 limit to the D_{2cc} (the minimum dose in the most irradiated 2 cm^3 normal tissue volume) for the rectum and sigmoid is 70–75 Gy and for the D_{2cc} to the bladder is approximately 90 Gy (23).

Careful consideration should be given to the potential need to boost residual parametrial or lymph-node disease

Table 2
Dose limits to the target and to the organs at risk

Dose specified to	Radiographs	3D imaging
Point A	5 × 5–6 Gy	Variable
D_{90}		≥80–≤90 Gy EQD2
ICRU point bladder	5 × ≤3.7 Gy	
ICRU point rectum	5 × ≤3.7 Gy	
D_{2cc} bladder		≤90 Gy EQD2
D_{2cc} rectum		≤75 Gy EQD2
D_{2cc} sigmoid		≤75 Gy EQD2

EQD2 = normalized therapy dose; 3D = three dimensional.

to higher doses. In HDR brachytherapy, the per-fraction dose to the sidewall may be substantial and therefore patients with small tumors or a complete response with no pelvic-sidewall or lymph-node spread of disease do not require a sidewall boost, whereas those with enlarged lymph nodes should receive a boost with EBRT (24). With each fraction of brachytherapy, the tumor dose is kept relatively constant, although variations in the normal-tissue doses are to be expected with each fraction. The tumor will likely regress over the course of brachytherapy, and therefore, for point A-specified patients, the OAR doses may increase. If treatment to point A results in normal tissues at or beyond the recommended tolerance doses, consideration should be given to 3D target planning. Another option may be to change to an interstitial implant. In some circumstances, it may be necessary to exceed the usual normal-tissue doses to adequately treat the tumor.

HDR interstitial brachytherapy may be delivered by a variety of alternative fractionation schemes (Table 3). There is a paucity of published experience, and the number of implant procedures and the fractions per implant session are not standardized. The HDR fractionation schedules noted in the literature or used by panelists are presented in Table 3. The dose distribution obtained with the combination of intracavitary and interstitial implants is different from that of an intracavitary implant alone, and may require lower EQD2 doses to the HR-CTV than typically delivered with intracavitary brachytherapy. With all cervical brachytherapy, the central tandem delivers a higher central tumor dose compared with the periphery of the target volume and should be placed when a uterus is present, even when needles are used, to prevent a cold spot.

Quality management issues for HDR

The large fraction sizes used for HDR brachytherapy require careful monitoring and quality management (QM), given the potential for toxicity and misadministration. Protocol consistency within an institution will help to avoid errors. Institutions should routinely document insertion, planning parameters including normal-tissue dose, treatment, and followup. A 1998 report from the American Association of Physicists in Medicine addresses QM methods for HDR brachytherapy (25). The recommendations from this report should guide the procedures for any brachytherapy program. QM issues common for all brachytherapy modalities, including treatment planning, treatment delivery systems, applicator commissioning, and periodic checks, will not be addressed in this document. Some aspects of quality assurance directed at preventing errors in treatment planning and delivery that are specific to cervical cancer brachytherapy are summarized below.

Table 3
Examples of potential dose fractionation regimens to consider for template-based HDR interstitial brachytherapy after 45–50.4 Gy of external beam

Dose of EBRT	Brachytherapy dose[a]	EQD2 (Gy) to CTV
45 Gy/25 fractions	3.5 Gy × 9	79.7
	4.25 Gy × 7	79.6
	5 Gy × 5	75.5
50.4 Gy/28 fractions	3 Gy × 9	78.8
	4.5 Gy × 5	76.7

EBRT = external-beam radiotherapy; EQD2 = equivalent dose in 2 Gy/fraction; CTV = clinical target volume; HDR = high-dose-rate.

[a] Twice a day treatments with approximately 6 h between fractions (based on general radiobiologic principles) over 1 week. The nine-fraction regimen is given over 4.5 days in 1 week with one insertion. Other regimens using other doses of external beam and brachytherapy fractionation are also acceptable with consideration of the normal-tissue dose limits and tumor dose.

Verification of treatment plan

The plan should be verified independently by a qualified brachytherapy physicist not involved in the generation of the plan. This verification should at least include the following items:

1. The dose information matches the prescription;
2. The treatment unit, applicator, and radionuclide match the prescription;
3. The applicator and dwell positions are correctly located in the patient (consistent with the imaging modalities used);
4. The reference distance from the treatment device to the most distal dwell position is consistent with the applicator in use; and
5. The individual dwell times and total treatment time are consistent with plans of similar type taking into account the decay of the radionuclide in use. This can be accomplished by performing an independent calculation to a chosen point in the plan, the use of indices or atlases.

Pretreatment verification

Before any treatment is delivered, the pretreatment information should be verified by a qualified physicist. This check should include the following items:

1. The correct patient information has been entered into the treatment device;
2. The per-fraction dose is consistent with the prescription;
3. The dwell times (compensated for radioactive decay), dwell positions, and step size programmed into the treatment device are consistent with the treatment plan; and
4. The channel numbers connected via transfer tubes to the applicator are consistent with the catheter numbers on the plan.

The ABS recommends that radiation oncologists and medical physicists at a facility starting an HDR brachytherapy program for the treatment of patients with cancer of

the cervix should attend courses designed to review HDR practice and QM and spend time learning the procedure at a facility with extensive experience in the treatment modality.

Conclusions

This ABS report recommends that 3D imaging with ultrasound, computer-assisted tomography, or magnetic resonance imaging be performed when feasible to estimate the cervical tumor dimensions and ensure adequate coverage of the tumor. Normal-tissue dosimetry using 3D parameters results in a more accurate reflection of doses administered and may provide more reliable indicators of the risk of toxicity.

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