ELSEVIER

Brachytherapy 11 (2012) 33−46

BRACHYTHERAPY

American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: General principles

Akila N. Viswanathan[1,*], Bruce Thomadsen[2],
American Brachytherapy Society Cervical Cancer Recommendations Committee

[1]*Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*
[2]*University of Wisconsin, Madison, WI*

ABSTRACT

PURPOSE: To develop brachytherapy recommendations covering aspects of pretreatment evaluation, treatment, and dosimetric issues for locally advanced cervical cancer.

METHODS: Members of the American Brachytherapy Society (ABS) with expertise in cervical cancer brachytherapy formulated updated recommendations for locally advanced (Federation of Gynecology and Obstetrics Stages IB2−IVA) cervical cancer based on literature review and clinical experience.

RESULTS: The ABS recommends the use of brachytherapy as a component of the definitive treatment of locally advanced cervical carcinoma. Precise applicator placement is necessary to maximize the probability of achieving local control without major side effects. The ABS recommends a cumulative delivered dose of approximately 80−90 Gy for definitive treatment. The dose delivered to point A should be reported for all brachytherapy applications regardless of treatment-planning technique. The ABS also recommends adoption of the Groupe Européen Curiethérapie-European Society of Therapeutic Radiation Oncology (GEC-ESTRO) guidelines for contouring, image-based treatment planning, and dose reporting. Interstitial brachytherapy may be considered for a small proportion of patients whose disease cannot be adequately encompassed by intracavitary application. It should be performed by practitioners with special expertise in these procedures.

CONCLUSIONS: Updated ABS recommendations are provided for brachytherapy for locally advanced cervical cancer. Practitioners and cooperative groups are encouraged to use these recommendations to formulate their clinical practices and to adopt dose-reporting policies that are critical for outcome analysis.

Keywords: Cervical cancer; Brachytherapy; Guidelines

Introduction

The American Brachytherapy Society (ABS) endorses the use of brachytherapy as an integral component of the definitive treatment of locally advanced cervical cancer. Several studies have shown decreased recurrence rates and increased survival when brachytherapy is a component of treatment (1−4). Patients selected for brachytherapy may have any stage of cervical cancer. In particular, brachytherapy is indicated after external beam for all cases of locally advanced disease (Stages IB2−IVA); brachytherapy alone may be used as primary treatment for those with earlier stage disease (IA−IB1). For cervical cancer patients with a medical contraindication to brachytherapy, the physician should document in the medical record the specific reasons why brachytherapy is not considered feasible for the patient.

Received 25 March 2011; received in revised form 3 July 2011; accepted 8 July 2011.

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

The American Brachytherapy Society Cervical Cancer Recommendations Committee for high dose rate includes Sushil Beriwal, MD; Jennifer De Los Santos, MD; D. Jeffrey Demanes, MD; Beth Erickson, MD; David K. Gaffney, MD; Jorgen Hansen, MS; Ellen Jones, MD; Christian Kirisits, ScD; and for low dose rate/pulse dose rate, the Committee includes Indra J. Das, PhD; Patricia Eifel, MD; Susan A. Higgins, MD; Anuja Jhingran, MD; Larissa Lee, MD; William Small Jr, MD; Aaron Wolfson, MD.

* Corresponding author. Department of Radiation Oncology, Brigham and Women's Hospital, 75 Francis Street, ASB 1, L2, Boston, MA 02115. Tel.: +1-703-234-4078; fax: +1-703-435-4390.

E-mail address: abs@americanbrachytherapy.org.

1538-4721/$ - see front matter
doi:10.1016/j.brachy.2011.07.003

The skill and expertise of the radiation oncologist and proper applicator placement are critical determinants of dose specification (5) and outcome (6–8). A report from the Radiotherapy Oncology Group found that unacceptable measures of brachytherapy implant quality, such as asymmetry or displacement of the ovoids from the cervix, resulted in higher rates of local recurrence (9). Centers with limited experience in treating patients with an intact cervix should refer such patients to physicians or medical centers with established brachytherapy expertise for optimal outcomes (10–12).

General recommendations common to all forms of brachytherapy for locally advanced cervical cancer will be reviewed in this report. Separate recommendations specific for low-dose-rate (LDR)/pulse-dose-rate (PDR) and high-dose-rate (HDR) cervical brachytherapy follow this article.

Methods

The 2000 ABS recommendations were revised by members of the ABS with expertise in gynecologic brachytherapy. The literature was reviewed to identify peer-reviewed articles, organizational guidelines, and clinical-trial data. The new recommendations also address image-guided treatment planning and delivery, and recommended reporting parameters for quality assurance. Specific commercial equipment, instruments, and materials are described for necessary procedures. Such identification does not imply recommendation or endorsement by the presenter nor imply that the identified material or equipment is the best available for these purposes. The specific recommendations were established by consensus opinion of the authors, with the support of the published literature when available. Where major controversy or lack of evidence persists, the ABS declines to make specific recommendations. This report was reviewed and approved by the Board of Directors of the ABS.

Results

Pretreatment evaluation

Staging recommendations

The ABS recommends careful documentation of disease extent and volume, as defined by physical examination and imaging studies, before the initiation of external-beam radiation therapy (EBRT) and at the time of brachytherapy. The ABS recommends the use of the International Federation of Gynecology and Obstetrics (FIGO) staging definition most recently revised in 2009 (13). Modifications include the subdivision of Stage IIA by tumor size ($\leq$4 cm vs. $>$4 cm) based on published evidence of its prognostic importance (14–18). Preinvasive lesions (Stage 0) are no longer included in the FIGO staging system. Cervical cancer remains a clinically staged disease, although the use of diagnostic imaging is recommended and surgical-pathologic findings, such as lymphovascular invasion, should be reported.

Imaging

When available, the ABS recommends the use of cross-sectional imaging, such as magnetic resonance imaging (MRI) or computed tomography (CT), to obtain measurements of tumor size, volume, and extent of disease. When compared with clinical examination, pelvic MRI is a more sensitive method for the detection of parametrial involvement and estimation of tumor size (19, 20). MRI also provides more detailed views of uterine and cervical anatomy that may guide subsequent sounding of the uterine canal for brachytherapy. CT imaging, a less sensitive tool but widely available, can estimate cervical diameter and afford meaningful clinical information. For nodal evaluation, positron emission tomography (PET) has become the standard clinical staging tool for the detection of pelvic and para-aortic lymph node metastasis. The Centers for Medicare and Medicaid Services approved coverage for the use of PET in the initial staging evaluation of cervical cancer in 2005. The finding of pelvic and/or para-aortic lymph node involvement may be used to guide clinical decisions related to radiation treatment planning, such as the field size and delivered dose. Lymph node staging by PET has also been shown to be an important prognostic factor for recurrence and survival (21). Surgical staging before definitive chemoradiotherapy is also an acceptable approach to detect intra-abdominal disease and for pathologic assessment or debulking of pelvic and/or para-aortic lymph nodes (22).

Treatment modalities

External-beam radiation

For patients with disease confined to the pelvis, the standard EBRT fields are directed to the pelvis using a four-field isocentric technique with customized blocking to a total dose of 45 Gy. For patients with nodal disease involving the high common iliac nodes or para-aortic chain, an extended treatment field is recommended. Details of the EBRT fields used in the management of cervical cancer are described elsewhere (22, 23). In the setting of pelvic nodal or parametrial disease, additional dose may be delivered by anterior posterior:posterior anterior (AP:PA) fields using a midline block, three-dimensional (3D) conformal radiotherapy or intensity-modulated radiation therapy (IMRT). The ABS recommends a combined dose of 60–70 Gy to enlarged lymph nodes. The cumulative dose delivered by EBRT and brachytherapy must be carefully integrated during treatment planning to avoid significant overexposure to midline structures, particularly the ureters and rectum. 3D conformal radiotherapy or IMRT may also be used for a nodal boost in the para-aortic region to minimize dose to small bowel (24–27). Normal-tissue constraints and

dose reporting for the small bowel and kidneys are described in the Quantitative Analyses of Normal-Tissue Effects in the Clinic review (28, 29). Although IMRT is becoming more widely available, the use of IMRT in the definitive treatment of cervical cancer has not yet been validated, given concerns about target definition, inter- and intrafraction motion, and tumor regression during treatment (30–35).

Concurrent chemotherapy

The National Comprehensive Cancer Network Practice Guidelines (2010) state that the primary treatment for locally advanced cervical cancer is definitive radiotherapy with concurrent cisplatin-based chemotherapy delivered as a single agent or in combination with fluorouracil (22). Delivery of concurrent cisplatin was shown to reduce local recurrence and improve overall survival in five randomized trials (23, 36–41), leading to a National Cancer Institute alert in 1999. The ABS recommends concurrent cisplatin-based chemotherapy for patients with adequate renal function, or consideration of carboplatin (42–45) and/or paclitaxel (46, 47) for those not able to receive a cisplatin-based regimen. The most commonly used regimen in the United States is weekly cisplatin, 40 mg/m^2, ideally administered 1 h before EBRT (48), although several institutions use cisplatin and 5-FU chemotherapy given in two doses, approximately 3 weeks apart (39).

The ABS recommends that laboratory testing with a complete blood count, including differential and chemistries, be done weekly during chemotherapy in addition to the weekly assessment of clinical symptoms. This is particularly important for patients who require pelvic and para-aortic nodal fields, which encompass a greater volume of bone marrow.

Treatment duration

The total treatment duration of EBRT and brachytherapy should be limited to less than 8 weeks, as prolonged treatment duration leads to a decrease in local control and survival of approximately 1% per day (49–52).

Brachytherapy

Preimplant patient evaluation

Table 1 lists a preprocedure and procedural checklist reflecting the key elements in preparing for the implant. Before the first brachytherapy procedure, the patient should have a gynecologic examination during which time the physician will assess the anatomy, the remaining tumor, and medical factors, and decide which brachytherapy applicator is best suited to the patient's anatomy. Patients should have appropriate medical evaluations and a preprocedure anesthesia assessment, which may require meeting with an anesthesiologist to assure that adequate sedation can safely be provided to optimize patient comfort and safety. Depending on the type of procedure and anesthesia used, instructions on fasting, bowel preparation, and preoperative testing, including laboratory studies, electrocardiogram, and chest X-ray, should be clearly provided. Patients requiring anticoagulant medication for a medical condition must be carefully evaluated. Anticoagulation testing should be done before the procedure. Based on careful consideration, anticoagulant medication may be held before the procedure. Patients on bed rest overnight should remain on subcutaneous low-dose heparin as prophylaxis for thromboembolic events (53, 54); in addition, compression stockings and sequential calf-compression devices may be considered.

For patients with absolute neutrophil counts less than 500 mm^3, the brachytherapy applicator is not placed until the counts recover. Bone marrow stimulation may be expedited with timely administration of growth factors to prevent treatment delays. Blood-count depression, acute gastrointestinal toxicity, and disturbance of fluids and electrolytes can limit anesthesia options. Timely administration of fluids, potassium and magnesium, as well as antidiarrhea and nausea regimens, can help to prevent treatment prolongation during both EBRT and brachytherapy.

Table 1
Checklists listing items recommended as part of the preprocedural and procedural process

Preprocedural checklist
☐Initial history and physical examination
Gynecologic examination with documentation of examination kept in chart.
Laboratory values before chemotherapy administration:
☐Complete blood count with differential,
☐Creatinine and blood urea nitrogen, and
☐Sodium, potassium, glucose, liver function tests.
☐Diagnostic staging studies.
☐Anesthesia assessment.
☐Medication assessment (query about anticoagulants).
☐Bowel preparation information reviewed.
☐Day before instructions given to patient (e.g., nothing by mouth after midnight).
Procedure checklist
☐Consents present in the chart.
☐IV access obtained.
☐Anesthesia administered.
☐Examination under anesthesia at the time of brachytherapy:
☐Document disease extension in drawing.
☐Dilation of cervical os; ultrasound use if insertion is difficult.
☐Smitt sleeve placement if preferred.
☐Applicator placement.
☐Caution that applicator does not slip.
☐Packing.
☐Imaging (CT, MRI, plain radiographs).
☐Prescription.
☐Treatment planning.
☐Documentation of OAR (sigmoid, rectum, bladder) doses in chart.
☐QA checks.
☐Treatment delivery.
☐Dictation of treatment administered.
☐Applicator removed.
☐Posttreatment care:
☐Followup scheduled.

IV = intravenous; CT = computed tomography; MRI = magnetic resonance imaging; OAR = organs at risk.

Applicator selection

Careful thought regarding which applicator will be most appropriate for the patient begins at the time of the patient's initial evaluation. Over the course of EBRT, regular examinations allow the physician to monitor tumor response and also provide valuable information as to which brachytherapy applicator may ultimately provide the best fit. The radiation oncologist should be familiar with the applicators used and select the appropriate applicator based on optimal coverage of the tumor.

Patients with an intact uterus should have a tandem placed; if the patient had a prior supracervical hysterectomy, a short tandem may be placed and consideration given to an interstitial implant. Interstitial brachytherapy is also recommended for extensive cervical cancer (55) and, if the patient has an intact uterus, an intracavitary tandem should be placed with the interstitial catheters to adequately dose the superior aspect of the cervix and uterus (8).

A variety of applicators are available for the treatment of cervical cancer, including tandem and ovoids, tandem and ring, tandem and cylinder, and tandem and ovoid or ring with guides for interstitial needles (interstitial catheters will be described below). It is important to be familiar with the selected applicator and to be sure that the components of the applicator fit correctly, that is, tight to the cervix and snugly into the available lateral fornices. The relationship to the adjacent normal structures must be understood.

- *Interstitial*: poorly fitting intracavitary applicators, large lesions, and lower vaginal involvement are indications for interstitial methods.
- *Tandem and cylinder* is typically reserved only for cases with upper vaginal stenosis causing narrowing and an inability to place ovoids or a ring, or for cases with superficial disease involving the lower vagina (outside the range of the other applicators) that is less than approximately 5 mm thick. The practitioner should recognize that the dose distribution of a tandem and cylinder may be significantly different from that of the tandem and ovoid applicator, resulting in higher doses to the bladder and rectum and concomitantly lower dose to the parametrial tissues.
- *Tandem and ring* applicator results in a slightly narrower distribution than ovoids, and may result in a higher vaginal dose. The tandem and ring technique is ideal for patients who have shallow vaginal fornices.
- *Tandem and ovoids* may be preferable for cases with a barrel-shaped cervix. The largest ovoid that can be placed snugly into the fornices should be used. Oversized ovoids can result in displacement of the applicator down the vagina, which causes the quality of the dosimetry to deteriorate and leads to undesirably low doses to the cervix. A cervical flange is used in most cases to prevent perforation and to confirm tandem depth. It should be in direct contact with the cervix or the plastic (Smitt; Nucletron, Veenendaal, the Netherlands) sleeve. With some applicators, the relationship between the flange and the ovoids will vary according to the anatomy of the cervix, whereas with other applicators the relationship is fixed. With an effaced or flattened cervix, the ovoids will be lower and with a long ectocervix they will be higher up in relation to the external cervical os or sleeve. The ovoids preferably should be lateral to the cervical os and tucked snugly into the lateral fornices. Fletcher-Suit ovoids provide a wider surface area on the cervix and some practitioners prefer them to the Henschke ovoids that may fit readily into the fornices but deliver higher doses to the upper vaginal wall, rectum, and bladder.
- *Tandem and ring or ovoids with short interstitial needles* (for HDR or PDR) may be preferable for patients with large, bulky tumors, to cover the depth of the cervix and reduce the dose to the organs at risk (OAR), including the rectum, bladder, and sigmoid (56, 57).

Anesthesia

A comfortable and cooperative patient is required for an optimal brachytherapy procedure. Patient discomfort will hinder placement of the applicator and impair normal-tissue displacement; this in turn may lead to suboptimal application, and cause potential psychologic distress for the patient. Insertion of intracavitary applicators is considered a minor surgical procedure. In addition, the procedure is typically serial and a painful or unpleasant experience may inhibit the patient from completing the recommended therapy and decrease the quality of medical care. In an international survey of gynecologic cancer experts, the types of analgesia administered for cervical cancer brachytherapy included general (46%), spinal (27%), intravenous conscious sedation (28%), and/or oral pain medication (14%) (58).

Intracavitary HDR brachytherapy is most commonly administered to ambulatory patients in a day surgery (outpatient) fashion. For HDR, some institutions place a Smitt sleeve under general or spinal anesthesia, then use either intravenous conscious sedation, a paracervical block or oral medications for subsequent fractions; other institutions administer spinal or general anesthesia for every HDR fraction. For LDR or PDR, the applicator is usually inserted one or two times, and each insertion is performed under general, spinal, or epidural anesthesia to allow for a thorough examination, applicator insertion, and packing.

Epidural anesthesia is useful for patients who remain as inpatients while the applicator remains in place for several days. The interstitial brachytherapy procedure is typically done under general or spinal anesthesia, often with placement of an epidural catheter for postoperative pain management. The epidural analgesia facilitates adjustments of the applicator at the time of imaging and also helps to keep pain under control during the hospitalization required for the treatment.

Applicator insertion

Intracavitary applicators: To obtain the best possible dose distribution to the cervix and at-risk tissues, applicator placement must be optimal. The patient should first be placed in the dorsal lithotomy position in stirrups. A bimanual examination may then be performed, noting any residual nodularity, the cervix size, and the size of the fornices.

A rectal tube may also be placed before a sterile preparation or at the end of the applicator placement procedure to remove air and insert 20–30 mL of diluted barium contrast into the rectum and sigmoid colon for visualization of the anterior rectal wall. The vagina and perineum may be prepared with a sterilizing solution and draped with sterile towels. A Foley catheter may be inserted into the bladder and the balloon inflated with dilute contrast material per International Commission on Radiation Units and Measurement (ICRU) recommendations (59). A sterile speculum or a set of right-angle retractors is inserted into the vagina for adequate visual examination of the cervix.

The applicator insertion procedure begins by placement of a uterine sound. Placing a tenaculum on the cervix controls the position of the cervix and provides countertraction that may aid in insertion. The uterine sound is advanced to the uterine fundus. A clamp or ring forceps may be attached to the sound at the level of the os. The sound is then extracted and the inserted distance is measured by the position of the clamp. If the sound does not enter the uterus easily, ultrasound is useful for guiding and confirming correct placement (60–63). For best ultrasound visualization of pelvic anatomy, the bladder should be filled with approximately 200 cc of saline. An abdominal or transrectal transducer may be used. Perforation rates can be minimized through experience and by the use of ultrasound guidance. If ultrasound is not available, CT confirmation of appropriate localization of the tandem is recommended.

Uterine perforation typically occurs in the posterior cervix but it may also occur at the fundus; therefore, a proper understanding of the uterine size, position, and flexion (e.g., anteversion, retroflexion) may be helpful in avoiding such occurrences. If a uterine perforation occurs or is suspected, the applicator should be removed and reinserted to obtain proper positioning, and broad-spectrum intravenous antibiotics should be administered during the hospitalization for LDR or PDR cases. Oral antibiotics, such as trimethoprim-sulfamethoxazole, may be used during the hospitalization for uncomplicated insertions. Perforation per se usually is not problematic if identified and corrected by repositioning the applicator correctly before treatment. However, an unrecognized perforation with subsequent radiation treatment delivery with the tandem outside the uterus and close to or in the bowel or bladder may result in significant normal-tissue radiation exposure and toxicity. If the applicator cannot be properly positioned, the patient should be referred to a center with 3D-imaging capability for image-guided insertion or consideration of an interstitial implant.

On completion of uterine sounding and depth determination, the cervical canal may be serially dilated depending on the tandem diameter. Either the tandem or, for HDR or PDR cases, a plastic sleeve may be inserted through the cervical canal into the uterine cavity and the tandem inserted through the center of the sleeve. The plastic sleeve keeps the cervical os open between fractions and eliminates the need for dilation with subsequent fractions. However, in some cases the sleeve may be difficult to insert; therefore, some physicians prefer serial dilations. A Smitt sleeve has a radio-opaque ring at the base, visible on radiographs and CT. For institutions that use radiographic imaging, placement of fiducial seeds that mark the location of the cervical os and areas of disease extension at the time of brachytherapy is recommended. Once dilation is complete, the tandem is inserted, preferably to the uterine fundus. The distance from the flange to the tip of the tandem is the same as the depth to which the uterus was sounded. Applicator sets include tandems with various degrees of curvature. The selection of tandem curvature must be compatible with patient anatomy, but in general it should be noted that tandems with moderate curvature are less likely to give a high dose to the sigmoid colon at levels above the rectal packing or rectal retractor.

For tandem and ovoid or tandem and ring applicator insertions, the bladder and rectum must be displaced away from the radiation source using packing. Packing material containing a radio-opaque thread enhances visualization of the vaginal walls on subsequent imaging. For those using gauze for packing, separate anterior and posterior packs avoid entangling the applicator in packing at the time of removal. An alternative type of packing using a balloon instead of gauze may be considered. One typically starts with the rectal packing, given the lower dose tolerance of the anterior rectal wall, then balances insertion of the anterior bladder pack, sometimes initiating placement of the bladder packing while inserting the rectal pack to ensure as much packing as possible is placed for both anterior and posterior aspects. Gauze packing may be placed using fingers or forceps, starting at the superior level of the applicator, ensuring that the packing does not cross over the top of the applicator and displace it from the cervix. Some applicators come with a built-in ''rectal'' retractor, and require separate bladder packing after insertion of the rectal retractor. Displacement must be performed for each fraction to minimize the OAR doses. With the mould technique, no packing is necessary, as the mould by itself expands the vaginal walls.

Particularly for cases for which CT or MRI simulation is planned, the bladder is completely drained, the bladder catheter is clamped, and about 30–60 mL of dilute contrast is inserted and retained to provide contrast of the bladder lumen; after imaging the clamp is removed. Before imaging, radio-opaque localization markers are placed into the applicator. For HDR, external fixation devices can decrease applicator movement; these may include fixation

to the table, a perineal bar or a base plate and clamp device (''brachy board'' or ''applicator base plate''). Use of this immobilization device allows one to adjust and stabilize the position of the tandem midline in the pelvis. The applicator should be placed in the midline position on a frontal view to equally weight the dose to the pelvic lymph nodes and parametria, the ICRU pelvic wall points (59), or point B and to avoid overdosing lateralized rectosigmoid, bladder, or ureters. The tandem should be near the transverse midline of the pelvis and positioned approximately midway between the bladder and the rectum in the sagittal plane. If patients must be moved between the times of applicator placement, imaging, and treatment delivery (especially if changing tables), the applicator may be temporarily detached from the clamp to prevent the risk of perforation. Patient movement should be minimized during transfer by using an appropriate sliding board or other specifically designed device for holding the applicator in as stable a position as possible. After movement, the applicator position should be assessed at least visually, or radiographically if possible, and repositioned as needed to maintain the tandem in the upright position midline in the pelvis. In addition, the apparatus should be checked after movement and, if inferior displacement occurs, the applicator should be repositioned snugly against the cervix, ensuring that packing has not moved over the ovoids or ring.

Interstitial brachytherapy: Interstitial brachytherapy is a complex, multistep procedure with special dosimetric advantages and patient management requirements. In certain clinical situations, such as bulky lesions, a narrow vaginal apex, inability to enter the cervical os, extension to the lateral parametria or pelvic sidewall, and lower vaginal extension, interstitial brachytherapy can achieve better dose distribution than intracavitary methods and may be the treatment of choice for some cases (55). In addition to interstitial needles, a tandem should be placed whenever possible to dose the cervix, uterus, and parametrial tissues adequately (8). If a tandem cannot be placed because of loss of the endocervical canal, positioning and loading of the central needles must be considered carefully to avoid a central cold spot. The ABS Committee believes that cure of cervical cancer requires some degree of inhomogeneity of dose at the center of both intracavitary and interstitial implants. Attention to proper needle placement is necessary to fully encompass the tumor while avoiding the OAR. The clinical advantages of interstitial over intracavitary brachytherapy can be offset by complications if needles are inadvertently inserted into the OAR and treatment ensues.

Similar to the intracavitary insertion process, the patient is examined and a vaginal and perineal preparation are followed with appropriate sterile draping. Fiducial gold or platinum marker seeds may be inserted to delineate the residual disease in the cervix and parametria and to mark selected locations, such as the distal extent of the disease in the vagina, if present, or the top of the uterine fundus. Sutures should be placed into the cervix or deeply into the lateral vagina to be used as countertraction during needle insertion. Titanium or flexible plastic needles are preferred as they reduce CT simulation artifacts caused by stainless steel needles and also allow MRI-based planning. Care must be taken when using titanium needles with high-strength magnets as heating can occur around the needles and cause tissue injury, particularly if the needles are in contact with each other because of convergence.

Perineal templates should be used as they help to maintain needle geometry and thus improve dose distribution. These include the Syed template (64), with concentric circles designed for vaginal coverage; the MUPIT applicator (65), with diverging needles aimed toward the parametrial tissues; or customized variations available in individual institutions. Another interstitial approach, referred to as a combined intracavitary/interstitial, involves insertion of interstitial needles through special guides in the more traditional appearing intracavitary ring or ovoid applicators. The main part of the delivered dose results from loading in the intrauterine and vaginal applicators, whereas needles are used to shape, fine tune, and enlarge the treated volume. These applicators for combined intracavitary and interstitial brachytherapy can be used to improve lateral coverage by an additional 10 mm when compared with intracavitary applicators alone (57, 66).

If available in the procedure room, image guidance during the insertion of the applicator with ultrasound, fluoroscopy, CT, or MRI helps to determine the depth of insertion, facilitates adjustment of needle position to improve conformality of dose, and avoids inadvertent needle placement into the OAR. Imaging during the procedure may result in the need for fewer needles and minimize the potential for poorly placed needles or insertion into normal organs.

Laparoscopy may be used; laparoscopic visualization during interstitial brachytherapy can provide useful information regarding the location of catheter tips relative to the peritoneal space and loops of small bowel, and reveal bleeding from traumatized vessels. The needles should cover the length of the cervix and beyond and rest within the endopelvic fascia and the uterine and cervical tissues involved with tumor. The risk of small-bowel, sigmoid, ureteral, and vascular injury increases if needles are not correctly advanced into the pelvic tumor. To avoid needles within the urethra, bladder, rectovaginal septum, or rectum, the template holes at 6 and 12 o'clock are not used unless tumor has invaded these structures. Needles placed in the bladder or rectosigmoid should be removed, if feasible, immediately after insertion unless the patient has tumor invading the normal tissue (Stage IVA disease). If the needles cannot be removed, they should be kept in place for the duration of the implant but not loaded with radioactive sources. Such a determination can be made both during the image-guided procedure and during 3D image-based dosimetry.

The decision of the dose rate (HDR, PDR, or LDR) to be used with interstitial implants must be considered. HDR and PDR allow for computerized optimization of each dwell position, whereas with LDR, source strengths are usually limited to 6–10 strength bins. HDR will result in large doses per fraction to the normal tissues that could increase long-term toxicity. HDR interstitial typically includes the time and labor associated with treating the patient twice a day. The recommended whole-pelvic EBRT doses are similar to those used for intracavitary HDR. Chemotherapy given before an interstitial implant must be properly timed to avoid blood-count depression and other problems that would make the procedure more risky.

Imaging

The ABS recommends localization using radiographic equipment with high geometric precision (e.g., radiotherapy simulators to obtain plain film, CT, or MRI images). CT- and MR-based localization allows for correlation of anatomic data with source positioning. Image-based volumetric information by CT or MRI requires contiguous slice acquisition with slice thickness of 1–5 mm. The localization method must be consistent with the requirements of the treatment-planning system used at the institution. It is expected that the institution has a periodic quality assurance program for the CT and MR scanners to avoid or minimize image distortion. Proper fusion software should be available if multiple imaging modalities are used for planning purposes.

Volumetric imaging

The use of 3D imaging has resulted in more accurate contouring of the tumor, cervix, uterus, and normal tissues such as the bladder, rectum, and sigmoid. MRI has been reported to be the best modality for demonstrating normal anatomy of the female pelvis and delineating tumors of the uterus and uterine cervix (67, 68). Studies have shown that the regression of cervical tumors can be documented with MRI (69). Particularly in patients with advanced or deeply infiltrating tumors, the specific signal intensities of gynecologic tissue allow for distinct separation on T1- and T2-weighted images, including the cervix (low T1, low T2), parametrium (high T1, high T2), and cervix tumor (low T1, high T2) (70, 71). Fat-suppressed T2-weighted images can be particularly useful. CT has been used in evaluating disease extent for cancer of the cervix, but it does not provide adequate delineation of the tumor because of poor tissue contrast and lack of anatomic detail (72). CT scanning, compared with MRI, overestimates the lateral dimensions of the cervix (68).

The resolution of PET is insufficient to permit accurate contouring delineation, but it is an area of research (73). PET–CT scans, however, should be available for pretreatment diagnosis and to follow the course of the disease. Regardless of the imaging modality used, the geometry of the applicator placement should be assessed by the physician before the patient leaves the table and adjustments made immediately, followed by a final set of images demonstrating acceptable placement.

Ultrasound imaging

Ultrasound may be used not only to guide tandem insertion but also to assist with cervix delineation (74, 75).

Radiographic imaging

For facilities that do not have 3D imaging available, radiographic images should be obtained during the procedure and the applicator repositioned immediately if the images indicate poor placement. Proper placement of the applicator has been shown to significantly improve local control and disease-free survival (76).

The criteria for an adequate implant regardless of imaging modality used include the following:

- The tandem should bisect the ovoids on an AP and lateral image.
- On a lateral image, the ovoids should not be displaced inferiorly from the flange (cervical stop) and should be as symmetrical as possible (should overlap one another).
- The tandem should be approximately one-half to one-third the distance between the symphysis and the sacral promontory, approximately equidistant between a contrast-filled bladder and rectum-sigmoid.
- The superior tip of the tandem should be located below the sacral promontory within the pelvis (77).
- Radio-opaque packing will be visible on radiographic images and should be placed anterior and posterior to the ovoids, with no packing visible superior to the ovoids. Superior packing represents an unwanted inferior displacement of the applicator and indicates the need to repack properly before source loading.

Imaging for interstitial implants

Recent studies have demonstrated not only the feasibility of using CT or MRI simulation for treatment planning for interstitial brachytherapy but its superiority to plain films (78–81). Treatment planning using CT or MRI should be done for interstitial brachytherapy as the treatment volume is large and the needles fall in close proximity to the OAR. The OAR should be accounted for in planning to reduce the risk of complications.

Contouring

Advances in image guidance for applicator insertion and treatment planning have resulted in 3D tissue contouring guidelines (68, 82–84), a new dosimetric nomenclature (85) and initial reports indicating improved outcomes (86–88). The Groupe Europeen Curietherapie-European Society of Therapeutic Radiation Oncology (GEC-ESTRO)

contouring guidelines (82) have influenced practice internationally, with 32% of surveyed experts reporting that they specify dose using the GEC-ESTRO nomenclature and a 3D image-based approach (58). Contouring guidelines exist for both MRI- (82) and CT-based (68) imaging, with most practitioners in the United States using CT. U.S. and international surveys demonstrate that approximately 55% of institutions obtain a CT simulation after brachytherapy applicator insertion (58, 89).

After insertion of the tandem and vaginal applicators, the target volumes and normal-tissue structures should be delineated on images in the treatment-planning computer. For institutions that use MRI, the defined target volumes should include the gross tumor volume, the high-risk clinical tumor volume (HR-CTV) of the cervix plus tumor extension at the time of brachytherapy, and the intermediate-risk CTV of the cervix plus tumor extension at the time of diagnosis. Normal-tissue structures that should be contoured include the bladder, rectum, and sigmoid. For CT-based treatment planning, the width of the cervix and any parametrial extension should be contoured as the HR-CTV (68). The superior border of the cervix should extend at least 1 cm above the uterine vessels identified by intravenous contrast or the location where the uterus begins to enlarge. If CT anatomy does not permit identification of the cervix, a height of approximately 3 cm should be contoured for the cervix, with the caveat for CT-planned cases that the entire length of the tandem should be treated, as precise determination of the superior extent of disease is not feasible.

The terminology used in the GEC-ESTRO guidelines should be applied to interstitial cases. For interstitial brachytherapy, the gross tumor volume may not be as apparent as with an intracavitary applicator, as the needles may distort visualization of the tumor. Therefore, an MRI obtained immediately before insertion may be helpful to determine the location of residual disease. Portions of the HR-CTV may also be distorted by the applicator, in which case the physician must contour the apparent region at risk and overestimate the HR-CTV to ensure adequate coverage of the disease. All regions of suspected gross residual disease, based on clinical examination and preimplant imaging, and of adjacent tissue involvement, such as the parametrial tissues or vaginal tissues, should be included, similar to the recommendations for tandem and ring or tandem and ovoid implants. For physicians starting a 3D-imaging practice, participation in an image-guided brachytherapy workshop is recommended.

Prescription

A treatment prescription should contain sufficient information to generate a treatment plan for delivering the brachytherapy intended by the responsible radiation oncologist. It should at least include the following items:

1. The target, target dose, dose per fraction, and the fractionation plan.
2. The type of isotope and source used for delivery of the treatment.
3. The treatment plan, including:
   a. The dose distribution to the target and
   b. The critical organs and their dose limits.
4. The applicator type and size features.

Treatment planning

Treatment planning and dosimetry should be performed every time applicators are inserted to assess doses to the target and normal tissues, even if fixed-geometry applicators are used. Failure to perform dosimetry can result in exceeding the normal-tissue tolerance of the OAR because of differences in applicator positioning and organ motion between applications.

Target dose specification with volume imaging

Dose–volume parameters for reporting with 3D imaging have been defined in the GEC-ESTRO recommendations and practitioners are referred to that publication for details (7). The dose should be prescribed such that the prescribed dose covers 90% of the HR-CTV (i.e., equals the D_{90}) and reaches the threshold levels indicated in Table 2 of the ABS Cervical Cancer Brachytherapy Guidelines Part II: HDR. Optimization, discussed below, facilitates achieving this goal while holding the dose to the OAR to tolerance levels as described in the volumetric treatment-planning section.

Target dose specification with radiographic imaging

When using radiographs, no target volume can be delineated. Instead, treatments based on radiographs specify the dose to point A, as originally defined in the Manchester System (90) as 2 cm cephalad along the tandem from the apices of the vaginal fornices and 2 cm perpendicularly lateral to the tandem. The previous ABS recommendation for HDR cervical brachytherapy gave details for finding point A (called point H in that report). The failure of the vaginal fornices to show on radiographs and rotations makes it impossible to determine point A on the images (9). The 2011 ABS recommendation is that point A should be determined as follows. On the treatment-planning computer, connect a line through the center of each ovoid or the lateral-most dwell position in a ring. From the point on the tandem where this line intersects, extend superiorly the radius of the ovoids (Fig. 1) or for the rings (Fig. 2) move superiorly to the top of the ring and then move 2 cm along the tandem. Define point A on each side as 2 cm laterally on a perpendicular line from this point on the tandem. For tandem and cylinders, begin at the flange or seeds marking the os and

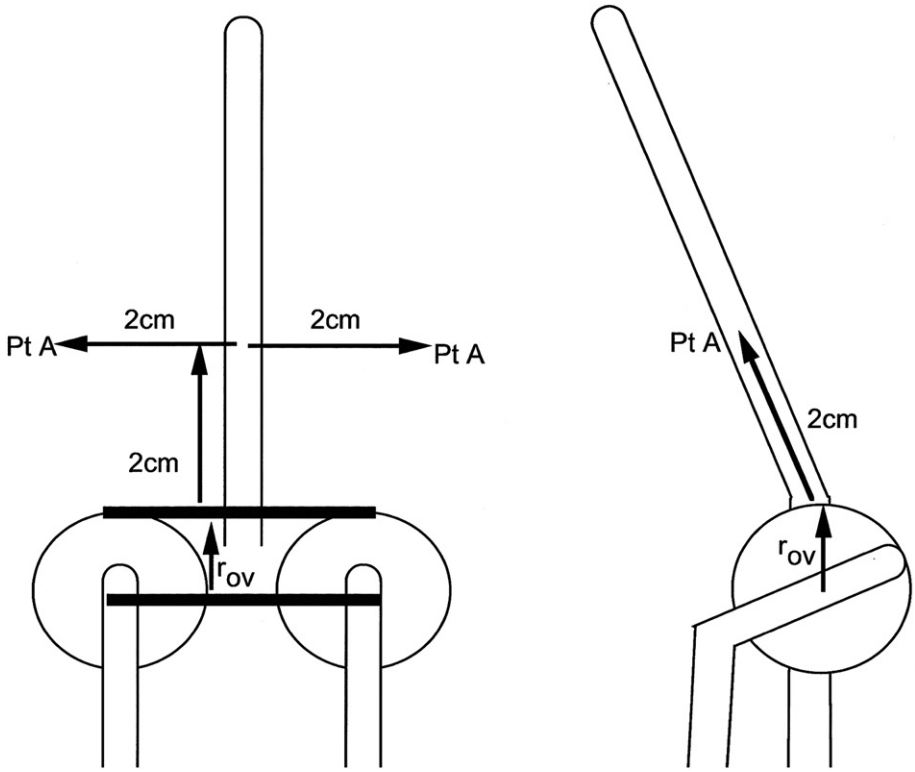

Fig. 1. Point A, for a tandem and ovoid applicator, with reference to the superior surface of the ovoids. On the treatment-planning computer, connect a line through the center of each ovoid. From the point on the tandem where this line intersects, extend superiorly the radius of the ovoids, r_{ov}, then add an additional 2 cm along the tandem. Define point A on each side as 2 cm laterally on a perpendicular line from this point on the tandem.

move 2 cm superiorly along the tandem and 2 cm laterally on a perpendicular line (Fig. 3). The previous report, based on Potish *et al.* (91), demonstrated that the practice of finding point A relative to the flange on the tandem for tandem and ovoid cases produced inconsistent dose specifications and should not be used.

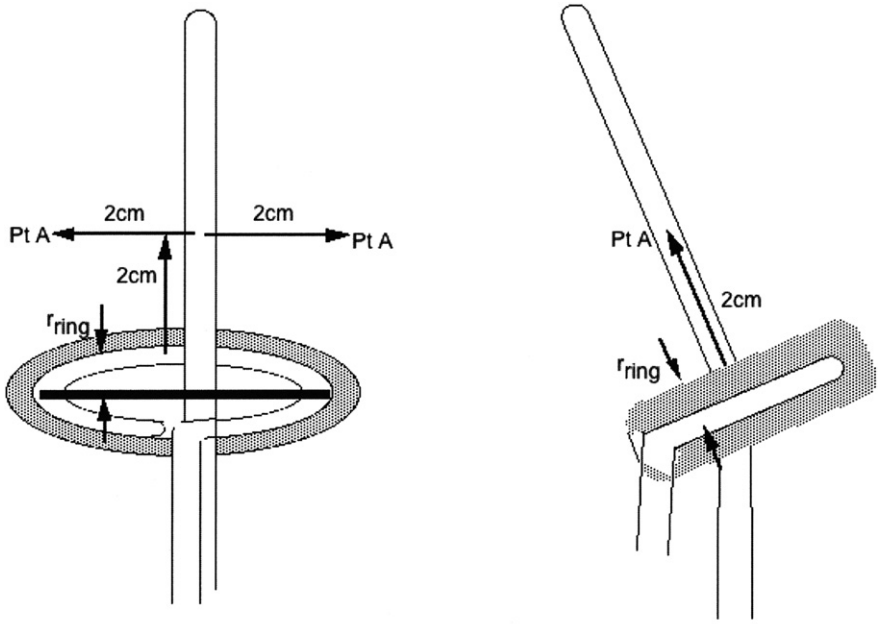

Fig. 2. Point A, for a tandem and ring applicator, with reference to the superior surface of the ring. On the treatment-planning computer, connect a line through the center of the lateral-most dwell position in a ring. From the point on the tandem where this line intersects, extend superiorly the superior thickness of the ring cap, r_{ring}, and then move 2 cm along the tandem. Define point A on each side as 2 cm laterally on a perpendicular line from this point on the tandem.

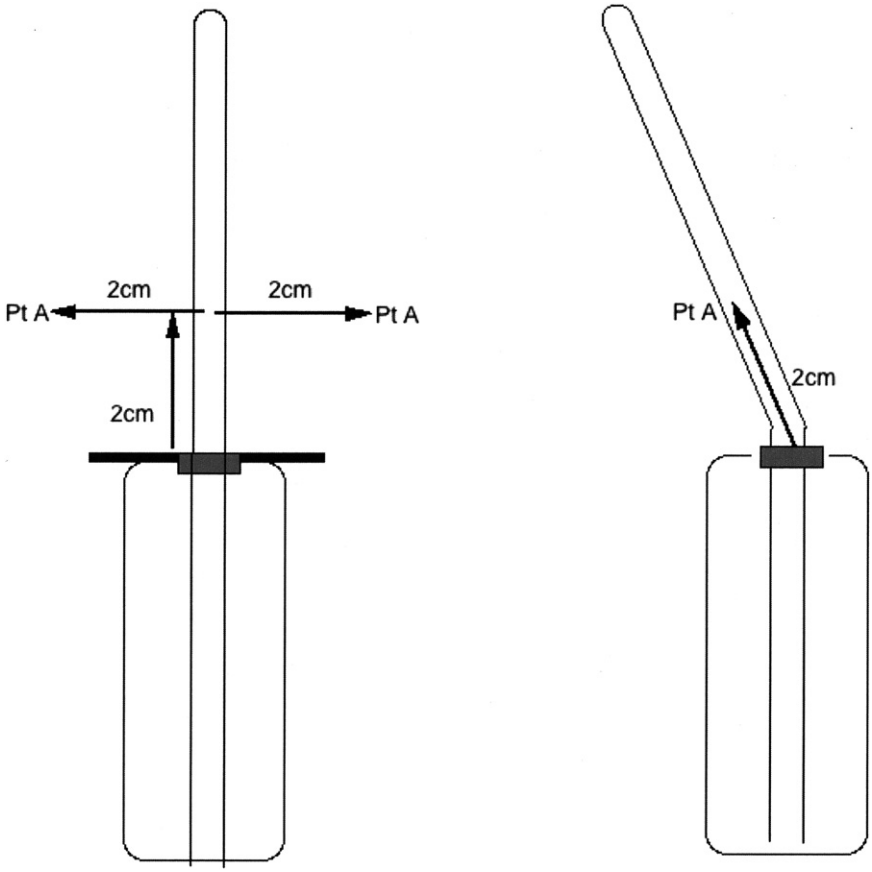

Fig. 3. Point A depicted on a tandem and cylinder applicator. Begin at the tip of the cylinder marking the os and move 2 cm superiorly along the tandem and 2 cm laterally on a perpendicular line.

OAR specification with volumetric imaging

When using volume imaging, dose–volume histograms describe in a reproducible way the dose distribution of the OAR. The use of a single parameter to describe a heterogeneous dose to OAR, however, is challenging. The most predictive quantity has yet to be established, which is why the reporting recommendations suggest three quantities to characterize the dose distribution for the OAR. The dose to 2 cc of an organ ($D_{2\ cc}$) can be useful during dose planning and for evaluating toxicities (92). The parameter $D_{0.1\ cc}$ is recommended for reporting, as it is indicative of the maximum dose. The $D_{5\ cc}$ of the organ wall may be related to toxicity, but when contouring for this quantity, the contour must be limited to the organ wall and not include the contents. Useful limits for $D_{2\ cc}$ to the sigmoid and rectum (70–75 Gy) and to the bladder (90 Gy) are shown in Table 2.

OAR specification with radiographic imaging

The ICRU Report 38 definition for the bladder point is on the surface of a Foley balloon filled with 7 cc of iodinated radiographic contrast (diluted so as not to obscure the localization markers on the AP radiograph) situated at the trigone of the bladder (93). Studies with CT simulation, however, have noted that the ICRU Report 38 bladder point is not likely indicative of the highest dose to the bladder (94). For those that do not have 3D-imaging capability, a point located 1.5 cm above the ICRU bladder point may be more representative of the actual bladder dose.

The ICRU Report 38 definition of the rectal point is 0.5 cm posterior to the posterior vaginal wall, directly posterior to the center of the ovoids or ring. A small amount of diluting barium contrast with air helps visualize the anterior rectal wall and the sigmoid colon (which often lies in close proximity to the tandem). Alternate localization methods, such as lead markers in a catheter or direct dose measurement devices, are not recommended because they often lie posterior to the anterior wall and therefore result in erroneously low point doses. As with the bladder, studies have shown that the ICRU Report 38 rectal point may not indicate the maximum rectal dose, but the differences are usually less than with the bladder point (94). Contrast can be very useful for imaging the sigmoid but it is often difficult to define the corresponding dose points on both the AP and lateral images.

Dose to the regional lymph nodes is highly variable and inconsistent and depends on patient anatomy, applicator position, the lymph nodes selected for dose calculations

(obturator, internal iliac, external iliac), and other factors. A rough approximation of the dose to the lymph nodes is 10–30% of the total brachytherapy dose (LDR) or fractional dose (i.e., 0.6–1.8 Gy of a 6-Gy fraction for HDR) (95, 96). The ABS Committee does not have specific recommendations regarding recording the lymph node doses. The practitioner may choose to calculate the dose to the points defined in ICRU Report 38 as the Pelvic Wall Points for reporting.

Recommended reporting

The ABS recommends reporting the following parameters for intracavitary insertions:

1. The type of applicator used;
2. The prescription, including a description of the dose per fraction and total dose to designated points or a limited target volume, such as the HR-CTV or point A;
3. The dose to point A;
4. Total reference air kerma of the radionuclide used (usually ^{192}Ir). For reference purposes, 1 mgRaeq = 7.24×10^{-6} Gy of total reference air kerma;
5. Loading pattern (dwell pattern and dwell times);
6. D_{90}, D_{100}, and V_{100} for HR-CTV if image-based planning is used; in addition, the V_{150} and V_{200} may be included for interstitial brachytherapy;
7. The doses to the ICRU rectal and bladder points and/or, if volume-based dosimetry is performed, the $D_{0.1\ cc}$ and $D_{2\ cc}$, to the OAR and the $D_{5\ cc}$ if the organ wall is contoured for OAR per GEC-ESTRO guidelines;
8. Isodose distributions in the following planes:
   - Sagittal including the tandem,
   - Oblique frontal coronal through point A and the middle of the vaginal sources, and
   - Axial through the vaginal sources with isodose lines;
9. The dose at the lateral vaginal mucosa and 0.5 cm deep to the vaginal surface (97). For LDR applications, the vaginal points for tandem and ovoid (Fig. 4) should fall along the plane of the center of the colpostats and should be limited to less than 120–150% of point A dose. Vaginal dose should also be reported for cylinder applications 1.25 cm inferior to the external cervical os along the vaginal surface and at 0.5 cm depth (Fig. 5).

Documentation

Each fraction for each procedure must be documented by a note present in the medical record. Example of such notes are available at the ABS Web site: www.americanbrachytherapy.org/guidelines.html.

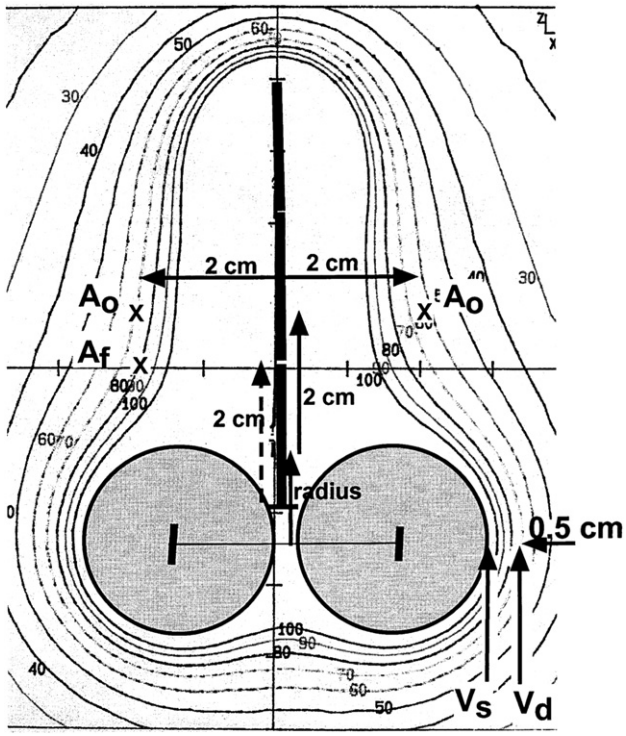

Fig. 4. The vaginal points for tandem and ovoid should fall along the plane of the center of the colpostats and should be limited to less than 120–150% of point A dose.

Followup

Routine followup with a radiation oncologist and gynecologic oncologist is strongly encouraged. It should include a pelvic examination and papanicolaou (PAP) smear every

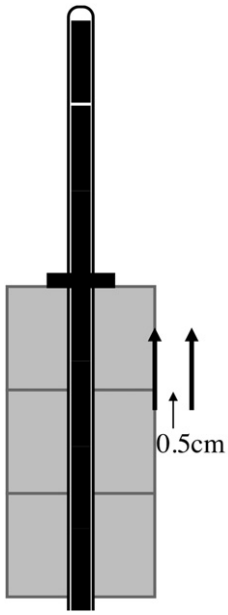

Fig. 5. Vaginal dose should also be reported for tandem and cylinder applications 1.25 cm inferior to the external cervical os along the vaginal surface and at 0.5 cm depth (Fig. 2).

3 months for 2 years after the completion of brachytherapy, then every 6 months for the next 3 years and annually thereafter.

Followup should also include radiologic imaging, such as a PET scan, 3 months after completion of radiation for patients at high risk for persistent or recurrent disease (98). Routine surveillance imaging may help to detect an asymptomatic recurrence that can potentially be salvaged (99).

Conclusion

The ABS has established recommendations for locally advanced cervical cancer that incorporate the use of image-based treatment planning. Practitioners and cooperative groups are encouraged to use these recommendations to formulate treatment and dose-reporting policies.

References

[1] Lanciano RM, Won M, Coia LR, *et al*. Pretreatment and treatment factors associated with improved outcome in squamous cell carcinoma of the uterine cervix: A final report of the 1973 and 1978 patterns of care studies. *Int J Radiat Oncol Biol Phys* 1991;20: 667–676.

[2] Hanks GE, Herring DF, Kramer S. Patterns of care outcome studies. Results of the national practice in cancer of the cervix. *Cancer* 1983; 51:959–967.

[3] Coia L, Won M, Lanciano R, *et al*. The Patterns of Care Outcome Study for cancer of the uterine cervix. Results of the Second National Practice Survey. *Cancer* 1990;66:2451–2456.

[4] Montana GS, Martz KL, Hanks GE. Patterns and sites of failure in cervix cancer treated in the U.S.A. in 1978. *Int J Radiat Oncol Biol Phys* 1991;20:87–93.

[5] Potish RA. The effect of applicator geometry on dose specification in cervical cancer. *Int J Radiat Oncol Biol Phys* 1990;18:1513–1520.

[6] Perez CA, Breaux S, Bedwinek JM, *et al*. Radiation therapy alone in the treatment of carcinoma of the uterine cervix. II. Analysis of complications. *Cancer* 1984;54:235–246.

[7] Corn BW, Hanlon AL, Pajak TF, *et al*. Technically accurate intracavitary insertions improve pelvic control and survival among patients with locally advanced carcinoma of the uterine cervix. *Gynecol Oncol* 1994;53:294–300.

[8] Viswanathan AN, Cormack R, Rawal B, *et al*. Increasing brachytherapy dose predicts survival for interstitial and tandem-based radiation for stage IIIB cervical cancer. *Int J Gynecol Cancer* 2009;19: 1402–1406.

[9] Viswanathan A, Moughan JW, Small J, *et al*. The quality of cervical-cancer brachytherapy implantation and the impact on local recurrence and disease-free survival in RTOG Prospective Trials 0116 and 0128. *Int J Radiat Oncol Biol Phys* 2010;75:S86.

[10] Erickson B, Eifel P, Moughan J, *et al*. Patterns of brachytherapy practice for patients with carcinoma of the cervix (1996-1999): A Patterns of Care study. *Int J Radiat Oncol Biol Phys* 2005;63: 1083–1092.

[11] Eifel PJ, Moughan J, Erickson B, *et al*. Patterns of radiotherapy practice for patients with carcinoma of the uterine cervix: A patterns of care study. *Int J Radiat Oncol Biol Phys* 2004;60:1144–1153.

[12] Eifel PJ, Moughan J, Owen J, *et al*. Patterns of radiotherapy practice for patients with squamous carcinoma of the uterine cervix: Patterns of care study. *Int J Radiat Oncol Biol Phys* 1999;43:351–358.

[13] Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. *Int J Gynaecol Obstet* 2009;105:107–108.

[14] Perez CA, Grigsby PW, Nene SM, *et al*. Effect of tumor size on the prognosis of carcinoma of the uterine cervix treated with irradiation alone. *Cancer* 1992;69:2796–2806.

[15] Horn LC, Fischer U, Raptis G, *et al*. Tumor size is of prognostic value in surgically treated FIGO stage II cervical cancer. *Gynecol Oncol* 2007;107:310–315.

[16] Quinn MA, Benedet JL, Odicino F, *et al*. Carcinoma of the cervix uteri. FIGO 6th Annual Report on the results of treatment in gynecological cancer. *Int J Gynaecol Obstet* 2006;(95 Suppl. 1):S43–103.

[17] Eifel PJ, Jhingran A, Levenback CF, *et al*. Predictive value of a proposed subclassification of stages I and II cervical cancer based on clinical tumor diameter. *Int J Gynecol Cancer* 2009;19:2–7.

[18] Lowrey GC, Mendenhall WM, Million RR. Stage IB or IIA-B carcinoma of the intact uterine cervix treated with irradiation: A multivariate analysis. *Int J Radiat Oncol Biol Phys* 1992;24:205–210.

[19] Hricak H, Gatsonis C, Coakley FV, *et al*. Early invasive cervical cancer: CT and MR imaging in preoperative evaluation—ACRIN/-GOG comparative study of diagnostic performance and interobserver variability. *Radiology* 2007;245:491–498.

[20] Mitchell DG, Snyder B, Coakley F, *et al*. Early invasive cervical cancer: Tumor delineation by magnetic resonance imaging, computed tomography, and clinical examination, verified by pathologic results, in the ACRIN 6651/GOG 183 Intergroup Study. *J Clin Oncol* 2006; 24:5687–5694.

[21] Kidd EA, Siegel BA, Dehdashti F, *et al*. Lymph node staging by positron emission tomography in cervical cancer: Relationship to prognosis. *J Clin Oncol* 2010;28:2108–2113.

[22] NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer. v.1; 2010.

[23] Morris M, Eifel PJ, Lu J, *et al*. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med* 1999;340:1137–1143.

[24] Esthappan J, Chaudhari S, Santanam L, *et al*. Prospective clinical trial of positron emission tomography/computed tomography image-guided intensity-modulated radiation therapy for cervical carcinoma with positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys* 2008;72:1134–1139.

[25] Gerszten K, Colonello K, Heron DE, *et al*. Feasibility of concurrent cisplatin and extended field radiation therapy (EFRT) using intensity-modulated radiotherapy (IMRT) for carcinoma of the cervix. *Gynecol Oncol* 2006;102:182–188.

[26] Beriwal S, Gan GN, Heron DE, *et al*. Early clinical outcome with concurrent chemotherapy and extended-field, intensity-modulated radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2007;68:166–171.

[27] Salama JK, Mundt AJ, Roeske J, *et al*. Preliminary outcome and toxicity report of extended-field, intensity-modulated radiation therapy for gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2006;65:1170–1176.

[28] Kavanagh BD, Pan CC, Dawson LA, *et al*. Radiation dose-volume effects in the stomach and small bowel. *Int J Radiat Oncol Biol Phys* 2010;76:S101–S107.

[29] Dawson LA, Kavanagh BD, Paulino AC, *et al*. Radiation-associated kidney injury. *Int J Radiat Oncol Biol Phys* 2010;76:S108–S115.

[30] van de Bunt L, van der Heide UA, Ketelaars M, *et al*. Conventional, conformal, and intensity-modulated radiation therapy treatment planning of external beam radiotherapy for cervical cancer: The impact of tumor regression. *Int J Radiat Oncol Biol Phys* 2006;64:189–196.

[31] van de Bunt L, Jurgenliemk-Schulz IM, de Kort GA, *et al*. Motion and deformation of the target volumes during IMRT for cervical cancer: What margins do we need? *Radiother Oncol* 2008;88: 233–240.

[32] Taylor A, Powell ME. An assessment of interfractional uterine and cervical motion: Implications for radiotherapy target volume definition in gynaecological cancer. *Radiother Oncol* 2008;88:250–257.

[33] Collen C, Engels B, Duchateau M, *et al*. Volumetric imaging by megavoltage computed tomography for assessment of internal organ

motion during radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2010;77:1590–1595.

[34] Beadle BM, Jhingran A, Salehpour M, *et al*. Cervix regression and motion during the course of external beam chemoradiation for cervical cancer. *Int J Radiat Oncol Biol Phys* 2009;73:235–241.

[35] Chan P, Dinniwell R, Haider MA, *et al*. Inter- and intrafractional tumor and organ movement in patients with cervical cancer undergoing radiotherapy: A cinematic-MRI point-of-interest study. *Int J Radiat Oncol Biol Phys* 2008;70:1507–1515.

[36] Keys HM, Bundy BN, Stehman FB, *et al*. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med* 1999; 340:1154–1161.

[37] Rose PG, Ali S, Watkins E, *et al*. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: A Gynecologic Oncology Group Study. *J Clin Oncol* 2007;25:2804–2810.

[38] Rose PG, Bundy BN, Watkins EB, *et al*. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999;340:1144–1153.

[39] Eifel PJ, Winter K, Morris M, *et al*. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: An update of radiation therapy oncology group trial (RTOG) 90-01. *J Clin Oncol* 2004;22:872–880.

[40] Whitney CW, Sause W, Bundy BN, *et al*. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: A Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol* 1999;17: 1339–1348.

[41] Stehman FB, Ali S, Keys HM, *et al*. Radiation therapy with or without weekly cisplatin for bulky stage 1B cervical carcinoma: Follow-up of a Gynecologic Oncology Group trial. *Am J Obstet Gynecol* 2007;197:e1–e6.

[42] Corn BW, Hernandez E, Anderson L, *et al*. Phase I/II study of concomitant irradiation and carboplatin for locally advanced carcinoma of the uterine cervix: An interim report. *Am J Clin Oncol* 1996;19:317–321.

[43] Higgins RV, Naumann WR, Hall JB, *et al*. Concurrent carboplatin with pelvic radiation therapy in the primary treatment of cervix cancer. *Gynecol Oncol* 2003;89:499–503.

[44] Dubay RA, Rose PG, O'Malley DM, *et al*. Evaluation of concurrent and adjuvant carboplatin with radiation therapy for locally advanced cervical cancer. *Gynecol Oncol* 2004;94:121–124.

[45] Cetina L, Garcia-Arias A, Uribe Mde J, *et al*. Concurrent chemoradiation with carboplatin for elderly, diabetic and hypertensive patients with locally advanced cervical cancer. *Eur J Gynaecol Oncol* 2008;29:608–612.

[46] Addeo D, Blank S, Muggia F, *et al*. Concurrent radiotherapy, paclitaxel and dose escalating carboplatin in the treatment of cervical cancer—a phase I study. *Anticancer Res* 2008;28:3143–3146.

[47] Lee MY, Wu HG, Kim K, *et al*. Concurrent radiotherapy with paclitaxel/carboplatin chemotherapy as a definitive treatment for squamous cell carcinoma of the uterine cervix. *Gynecol Oncol* 2007; 104:95–99.

[48] Pearcey R, Brundage M, Drouin P, *et al*. Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. *J Clin Oncol* 2002;20:966–972.

[49] Girinsky T, Rey A, Roche B, *et al*. Overall treatment time in advanced cervical carcinomas: A critical parameter in treatment outcome. *Int J Radiat Oncol Biol Phys* 1993;27:1051–1056.

[50] Perez CA, Grigsby PW, Castro-Vita H, *et al*. Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. *Int J Radiat Oncol Biol Phys* 1995;32:1275–1288.

[51] Petereit DG, Sarkaria JN, Chappell R, *et al*. The adverse effect of treatment prolongation in cervical carcinoma. *Int J Radiat Oncol Biol Phys* 1995;32:1301–1307.

[52] Lanciano RM, Pajak TF, Martz K, *et al*. The influence of treatment time on outcome for squamous cell cancer of the uterine cervix treated with radiation: A patterns-of-care study. *Int J Radiat Oncol Biol Phys* 1993;25:391–397.

[53] Jhingran A, Eifel PJ. Perioperative and postoperative complications of intracavitary radiation for FIGO stage I-III carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2000;46:1177–1183.

[54] Lanciano R, Corn B, Martin E, *et al*. Perioperative morbidity of intracavitary gynecologic brachytherapy. *Int J Radiat Oncol Biol Phys* 1994;29:969–974.

[55] Viswanathan AN, Erickson B, Rownd J. Image-based approaches to interstitial brachytherapy. In: Viswanathan A, Kirisits C, Erickson B, Potter R, editors. *Gynecologic radiation therapy: novel approaches to image-guidance and management*. 1st ed. Berlin: Springer; 2011. p. 247–259.

[56] Dimopoulos JC, Kirisits C, Petric P, *et al*. The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: Clinical feasibility and preliminary results. *Int J Radiat Oncol Biol Phys* 2006;66:83–90.

[57] Jurgenliemk-Schulz IM, Tersteeg RJ, Roesink JM, *et al*. MRI-guided treatment-planning optimisation in intracavitary or combined intracavitary/interstitial PDR brachytherapy using tandem ovoid applicators in locally advanced cervical cancer. *Radiother Oncol* 2009;93: 322–330.

[58] Viswanathan AN, Creutzberg C, Craighead P, *et al*. International Brachytherapy Practice Patterns: A Survey of the Gynecologic Cancer Intergroup (GCIG). *Int J Radiat Biol Phys* 22 Dec 2010; Epub ahead of print.

[59] Kubo HD, Glasgow GP, Pethel TD, *et al*. High dose-rate brachytherapy treatment delivery: Report of the AAPM Radiation Therapy Committee Task Group No 59. *Med Phys* 1998;25:375–403.

[60] Davidson MT, Yuen J, D'Souza DP, *et al*. Optimization of high-dose-rate cervix brachytherapy applicator placement: The benefits of intraoperative ultrasound guidance. *Brachytherapy* 2008;7:248–253.

[61] Mayr NA, Montebello JF, Sorosky JI, *et al*. Brachytherapy management of the retroverted uterus using ultrasound-guided implant applicator placement. *Brachytherapy* 2005;4:24–29.

[62] Sahinler I, Cepni I, Oksuz DC, *et al*. Tandem application with transvaginal ultrasound guidance. *Int J Radiat Oncol Biol Phys* 2004;59: 190–196.

[63] Rush S, Gottesman R, Lovecchio J. The use of intraoperative transabdominal ultrasound in gynecologic brachytherapy. *Int J Radiat Oncol Biol Phys* 1991;21:1107.

[64] Syed A, Puthawala AA, Neblett D, *et al*. Transperineal interstitial intracavitary "syed-neblett" applicator in the treatment of carcinoma of the uterine cervix. *Endocuriether Hypertherm* 1986;2:1–13.

[65] Martinez A, Cox RS, Edmundson GK. A multiple-site perineal applicator (MUPIT) for treatment of prostatic, anorectal, and gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 1984;10:297–305.

[66] Kirisits C, Lang S, Dimopoulos J, *et al*. The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: Design, application, treatment planning, and dosimetric results. *Int J Radiat Oncol Biol Phys* 2006;65:624–630.

[67] Mayr NA, Tali ET, Yuh WT, *et al*. Cervical cancer: Application of MR imaging in radiation therapy. *Radiology* 1993;189:601–608.

[68] Viswanathan AN, Dimopoulos J, Kirisits C, *et al*. Computed tomography versus magnetic resonance imaging-based contouring in cervical cancer brachytherapy: Results of a prospective trial and preliminary guidelines for standardized contours. *Int J Radiat Oncol Biol Phys* 2007;68:491–498.

[69] Mayr NA, Magnotta VA, Ehrhardt JC, *et al*. Usefulness of tumor volumetry by magnetic resonance imaging in assessing response to radiation therapy in carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1996;35:915–924.

[70] Schoeppel SL, Ellis JH, LaVigne ML, *et al*. Magnetic resonance imaging during intracavitary gynecologic brachytherapy. *Int J Radiat Oncol Biol Phys* 1992;23:169–174.

[71] Olpin J, Tempany C. Imaging of gynecologic malignancies. In: Viswanathan A, Kirisits C, Erickson B, Potter R, editors. *Gynecologic radiation therapy: novel approaches to image-guidance and management*. 1st ed. Berlin: Springer; 2011. p. 3–18.

[72] Schoeppel SL, LaVigne ML, Martel MK, *et al*. Three-dimensional treatment planning of intracavitary gynecologic implants: Analysis of ten cases and implications for dose specification. *Int J Radiat Oncol Biol Phys* 1994;28:277–283.

[73] Lin LL, Mutic S, Low DA, *et al*. Adaptive brachytherapy treatment planning for cervical cancer using FDG-PET. *Int J Radiat Oncol Biol Phys* 2007;67:91–96.

[74] Erickson B, Foley WD, Gillin M, *et al*. Ultrasound guided transperineal interstitial implantation of pelvic malignancies: Description of the technique. *Endocuriether Hypertherm* 1995;11:107–113.

[75] Van Dyk S, Narayan K, Fisher R, *et al*. Conformal brachytherapy planning for cervical cancer using transabdominal ultrasound. *Int J Radiat Oncol Biol Phys* 2009;75:64–70.

[76] Viswanathan AN, Moughan J, Small W, *et al*. Quality of cervical cancer brachytherapy implantation in RTOG prospective trials. *Int J Radiat Oncol Biol Phys* 2009;75:S86–S87.

[77] Katz A, Eifel PJ. Quantification of intracavitary brachytherapy parameters and correlation with outcome in patients with carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2000;48:1417–1425.

[78] Eisbruch A, Johnston CM, Martel MK, *et al*. Customized gynecologic interstitial implants: CT-based planning, dose evaluation, and optimization aided by laparotomy. *Int J Radiat Oncol Biol Phys* 1998;40:1087–1093.

[79] Erickson B, Albano K, Gillin M. CT-guided interstitial implantation of gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 1996;36: 699–709.

[80] Viswanathan AN, Cormack R, Holloway CL, *et al*. Magnetic resonance-guided interstitial therapy for vaginal recurrence of endometrial cancer. *Int J Radiat Oncol Biol Phys* 2006;66:91–99.

[81] Erickson B, Albano K, Gillin M. Magnetic resonance imaging following interstitial implantation of pelvic malignancies. *Radiat Oncol Invest* 1996;2:298–300.

[82] Haie-Meder C, Potter R, Van Limbergen E, *et al*. Recommendations from gynaecological (GYN) GEC-ESTRO working group (I): Concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. *Radiother Oncol* 2005;74:235–245.

[83] Potter R, Haie-Meder C, Van Limbergen E, *et al*. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol* 2006;78:67–77.

[84] Nag S, Erickson B, Thomadsen B, *et al*. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2000;48: 201–211.

[85] Kirisits C, Potter R, Lang S, *et al*. Dose and volume parameters for MRI-based treatment planning in intracavitary brachytherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2005;62:901–911.

[86] Potter R, Dimopoulos J, Georg P, *et al*. Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. *Radiother Oncol* 2007;83:148–155.

[87] Dimopoulos JC, Lang S, Kirisits C, *et al*. Dose-volume histogram parameters and local tumor control in magnetic resonance image-guided cervical cancer brachytherapy. *Int J Radiat Oncol Biol Phys* 2009;75:56–63.

[88] Sturdza AE, Potter R. Clinical outcomes of 3d based external beam radiation and image guided brachytherapy. In: Viswanathan A, Kirisits C, Erickson B, Potter R, editors. *Gynecologic radiation therapy: novel approaches to image-guidance and management*. 1st ed. Berlin: Springer; 2011. p. 263–282.

[89] Viswanathan AN, Erickson BA. Three-dimensional imaging in gynecologic brachytherapy: A survey of the American Brachytherapy Society. *Int J Radiat Oncol Biol Phys* 2010;76:104–109.

[90] Tod M, Meredith W. Treatment of cancer of the cervix uteri-a revised ''Manchester method''. *Br J Radiol* 1953;26:252–257.

[91] Potish R, Gerbi B, Engler GP. *Dose prescription, dose specification, and applicator geometry in intracavitary therapy.* Madison, WI: Medical Physics Publishing; 1995.

[92] Georg P, Lang S, Dimopoulos JC, *et al*. Dose-volume histogram parameters and late side effects in magnetic resonance image-guided adaptive cervical cancer brachytherapy. *Int J Radiat Oncol Biol Phys* 2011;79:356–362.

[93] ICRU 38. *Dose and volume specification for reporting intracavitary therapy in gynecology.* Bethesda, MD: ICRU 38; 1985.

[94] Pelloski CE, Palmer M, Chronowski GM, *et al*. Comparison between CT-based volumetric calculations and ICRU reference-point estimates of radiation doses delivered to bladder and rectum during intracavitary radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2005;62:131–137.

[95] Lee LJ, Sadow CA, Russell A, *et al*. Correlation of point B and lymph node dose in 3D-planned high-dose-rate cervical cancer brachytherapy. *Int J Radiat Oncol Biol Phys* 2009;75:803–809.

[96] Gebara WJ, Weeks KJ, Jones EL, *et al*. Carcinoma of the uterine cervix: A 3D-CT analysis of dose to the internal, external and common iliac nodes in tandem and ovoid applications. *Radiother Oncol* 2000;56:43–48.

[97] Nag S, Chao C, Erickson B, *et al*. The American Brachytherapy Society recommendations for low-dose-rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2002;52:33–48.

[98] Schwarz JK, Siegel BA, Dehdashti F, *et al*. Association of posttherapy positron emission tomography with tumor response and survival in cervical carcinoma. *JAMA* 2007;298:2289–2295.

[99] Singh AK, Grigsby PW, Rader JS, *et al*. Cervix carcinoma, concurrent chemoradiotherapy, and salvage of isolated paraaortic lymph node recurrence. *Int J Radiat Oncol Biol Phys* 2005;61:450–455.