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American Brachytherapy Society consensus guidelines for interstitial brachytherapy for vaginal cancer

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ABSTRACT

PURPOSE: To present recommendations for the use of interstitial brachytherapy in patients with vaginal cancer or recurrent endometrial cancer in the vagina.

METHODS: A panel of members of the American Brachytherapy Society reviewed the literature, supplemented that with their clinical experience, and formulated recommendations for interstitial brachytherapy for primary or recurrent cancers in the vagina.

RESULTS: Patients with bulky disease (approximately >0.5 cm thick) should be considered for treatment with interstitial brachytherapy. The American Brachytherapy Society reports specific recommendations for techniques, target volume definition, and dose–fractionation schemes. Three-dimensional treatment planning is recommended with CT scan and/or MRI. The treatment plan should be optimized to conform to the clinical target volume and should reduce the dose to critical organs, including the rectum, bladder, urethra, and sigmoid colon. Suggested doses in combination with external beam radiation therapy and summated equivalent doses in 2 Gy fractions are tabulated.

CONCLUSION: Recommendations are made for interstitial brachytherapy for vaginal cancer and recurrent disease in the vagina. Practitioners and cooperative groups are encouraged to use these recommendations to formulate treatment and dose-reporting policies. Such a process will result in meaningful outcome comparisons, promote technical advances, and lead to appropriate utilization of these techniques.

Keywords: HDR; Vagina; Interstitial

Introduction

Primary or recurrent disease in the vagina from cervical, endometrial, or vulvar carcinoma is relatively uncommon (1–3). The initial tumor volume and distribution within the vagina, histologic type and grade, lymphatic vascular invasion, regional lymph node spread, and previous treatment are important determinants of outcome (1, 4–12). Cancers involving the vagina are usually not amenable to curative organ-sparing surgery because of the proximity of the tumor to the rectum, bladder, and urethra. Radiation therapy is currently the most widely used and effective primary treatment for patients with invasive vaginal cancers. Brachytherapy is an integral part of treatment for these tumors to ensure that a curative dose is given to the gross disease (6, 8, 13–21). The brachytherapy technique may be either intracavitary or interstitial depending on the extent, thickness, location, and morphology of the

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disease. Lesions that are very superficial, defined as approximately ≤0.5 cm thick at the time of brachytherapy, may be treated with intracavitary brachytherapy, whereas the remainder of cases should be treated with interstitial brachytherapy.

The rarity of the disease makes the study of vaginal cancer difficult. There have been no prospective randomized trials. Single-institutional studies have shown the long-term efficacy of radiation therapy for both primary and recurrent vaginal cancers (22–29). There have been several reports of interstitial brachytherapy for recurrent endometrial cancer in the vagina, although all are institutional reports. The purpose of this report is to propose guidelines for interstitial brachytherapy that are applicable to primary carcinomas of the vagina and recurrent endometrial or other metastatic cancers involving the vagina. The guidelines discuss safety issues, practice recommendations, and dose considerations, including using both low-dose-rate (LDR) and high-dose-rate (HDR) brachytherapy.

Methods

In 2010, the American Brachytherapy Society (ABS) Board of Directors appointed a group of practitioners having extensive clinical and research experience to provide guidelines for the current practice of interstitial brachytherapy for vaginal cancers. The panel based its recommendations on current guidelines published by medical societies, the published medical literature, and the clinical experience of its members (6, 22, 28–34). Specific recommendations for therapy and recommendations for further investigation were made when there was a consensus. Where major controversy or lack of evidence persists, the ABS declined to make specific recommendations. These guidelines are a statement of consensus of the authors regarding currently accepted approaches to treatment. The suggested dose and fractionation schemes have not been thoroughly tested. Any clinician following these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The ABS makes neither representation nor warranties of any kind regarding their content, use or application, and disclaims any responsibility for their application or use in any way.

In formulating guidelines, it should be noted that variations in approaches to interstitial brachytherapy, as with most medical procedures, are commonplace and may readily fall within accepted and appropriate management of these patients with vaginal cancers. The guidelines 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.

We have categorized these guidelines to cover the following aspects: (*1*) patient evaluation; (*2*) patient selection; (*3*) techniques, contouring, treatment planning, and dose/fractionation; (*4*) postprocedure management and followup care; and (*5*) continuing areas of controversy and future directions in areas where accepted practice is evolving and specific guidelines are not established. This report was reviewed and approved by the Board of Directors of the ABS.

Results

Patient evaluation

Examination under anesthesia is highly recommended to evaluate the extent of disease at presentation, and the findings should be delineated on a diagram for reference at the time of brachytherapy as vaginal mucosal extent is better appreciated on visual examination and bimanual palpation. Placement of fiducial marker seeds to delineate the extent of disease at the time of examination under anesthesia may also assist in defining the target volume for external beam (EBRT) planning and brachytherapy dosimetry. Positron emission tomography (PET) with CT and MRI with vaginal gel or a vaginal marker may be included in the diagnostic workup (35–38). PET/CT provides a better assessment of the lymph nodes compared with CT alone, and MRI helps to define the tumor dimensions, volume, and local extensions of tumor that are needed for brachytherapy procedure and planning. Because of the rarity of vaginal cancer, the rationale for these scans is based on the few available vaginal cancer–specific studies and extrapolation from other gynecologic malignancies.

Patient selection

Patients with primary Stage I–IVA vaginal cancers or recurrent cervical, endometrial, or vulvar carcinoma in the vagina with residual vaginal lesions >0.5 cm thick are potential candidates for interstitial brachytherapy. For patients with significant comorbidities who are at high risk of complications with the prolonged immobilization required for this treatment, the relative benefit of interstitial brachytherapy should be weighed against the risk of complications. The selection criteria should also take into account the available expertise as a well-performed intracavitary technique may produce a better outcome than a poorly performed interstitial technique.

External beam therapy

Most patients with vaginal cancer are treated with a combination of EBRT and brachytherapy because the nature and extent of the disease puts them at risk for lymphatic involvement (39). Patients should receive EBRT with, at a minimum, three-dimensional (3D) treatment planning. The clinical target volume (CTV) should include the gross tumor volume with a 1–2-cm expansion; the entire vagina; the paravaginal area up to the pelvic sidewalls; and

the bilateral pelvic lymph nodes (including the common iliac, external iliac, internal iliac, obturator, and presacral lymph node regions). If the distal one-third of the vagina is involved, the inguinal lymph nodes should also be included (39). The typical dose of EBRT for subclinical (microscopic) disease is 45–50.4 Gy in 25–28 fractions, but some centers prefer to limit the central pelvic dose to lower doses and instead use a midline block to continue sidewall and lymph node treatment to higher doses. Lower central EBRT doses allow a higher brachytherapy dose to be delivered. However caution should be taken with this midline block match technique as it may increase the late long-term side effects, such as ureteral stricture (40).

Chemotherapy

There have been no randomized studies evaluating of the efficacy of chemotherapy in vaginal cancers and, because of the rarity of vaginal cancer, it is unlikely that randomized trials specific to vaginal cancer will ever be done. Two institutions have reported the use of weekly cisplatin for vaginal cancer (41, 42). The similarities in histology, epidemiology, viral association, and natural history between cervical and vaginal cancers permit reasonable extrapolation from the results of trials in patients with cervical cancer (43–46). Based on cervical cancer data, the use of concurrent chemoradiation may be indicated for patients with Stages II, III, or IVA vaginal cancer. The role of concurrent chemotherapy for cuff recurrences of endometrial cancer is not as well defined. Currently, the Gynecologic Oncology Group is conducting a Phase II study (GOG 238) of concurrent weekly cisplatinum with EBRT and brachytherapy for patients with vaginal cuff recurrences treated with definitive radiation therapy (47).

Applicator insertion techniques

The type of the brachytherapy applicator (templates, needles) should be individualized based on the location and extent of the disease. Clinical examination and pretreatment imaging are essential guides to an anatomically correct applicator placement. The procedure is typically done under general or spinal anesthesia, often with placement of an epidural catheter for postoperative pain management (48, 49). The epidural analgesia facilitates adjustments of the applicator at the time of imaging and helps with pain control for the duration of treatment. Fiducial gold, platinum, or carbon fiber marker seeds should be inserted to delineate the residual gross disease (and, if possible, its original extent). Titanium or flexible plastic needles reduce CT simulation artifacts caused by stainless steel needles, facilitate delineation of the target volume, and allow MRI-based planning, if available (50). For apical or upper vaginal lesions, a perineal template with a vaginal cylinder is recommended for placement of needles. Laparoscopy or laparotomy may be considered to help place the needles and avoid inadvertent placement of needles in the small bowel (49–53). If available in the procedure room, transabdominal or transrectal ultrasound, CT scan, or MRI may be used for guidance during placement of needles (30, 31, 54, 55). Use of imaging helps reduce the likelihood of bladder and bowel perforation (56). For mid or distal lesions, either free-hand techniques that allow the physician to palpate the tumor or template-based techniques can be used. For some anterior vaginal lesions, periurethral needle insertion is required, which should be done while avoiding the urethra. Similarly, for posterior lesions, needle insertion into the thin central portions of the rectovaginal septum should be avoided.

Template-based techniques usually yield a spacing of not more than 1 cm between catheters. This same approximate spacing of catheters is recommended for the free-hand technique. Ideally, the target volume should be encompassed with a 1-cm margin beyond the residual gross disease in the lateral, inferior, and superior margins unless limited by normal tissue constraints. This will often yield a peripheral set of catheters in the normal tissue just beyond the target volume. At the conclusion of every interstitial procedure, a digital rectal examination should be performed to ensure that no catheters are perforating the rectum.

Contouring guidelines

Older reports of interstitial brachytherapy used orthogonal radiographs for treatment planning (4, 8). Several studies have shown potential advantages with CT or MRI simulation for gynecologic cancers (32, 57–59). CT imaging permits 3D optimization of dose to the tumor and the adjacent organs at risk. Use of CT scan or, if available, MRI is an excellent method of treatment planning. MRI is better than CT scan for defining the tumor volume, whereas it is equivalent for critical organ definition (33). Some software allows fusing of CT and MRI images to take advantage of the benefit of MRI while performing treatment planning on a CT simulator. The needle positions should be checked and adjusted to optimize their placement during CT or MRI simulation. Needles inadvertently placed in the bladder or rectosigmoid region do not necessarily need to be removed, but they should not be loaded at those locations (60). Critical organs, such as the bladder, rectum, sigmoid, and urethra, should be contoured on the axial scan and during treatment planning. Diluted contrast can be placed into the bladder (5–10 mL Hypaque, 40–60 mL saline) and rectosigmoid region (40–60 mL of diluted barium using a rectal tube that is removed before the CT scan) to help with organ delineation. The entire organ including the wall thickness should be contoured. Furthermore, it is most important to contour accurately the part of the organ closest to the

implant applicator so that accurate critical organ dosimetry (absolute volume rather than percentage of the whole organ) is accomplished.

The CTV is contoured as a separate structure as delineated by either marker seeds, CT scan, or MRI imaging. As the CTV may not be well defined with CT simulation, the combination of clinical findings, fiducial marker seeds, and pretreatment MRI, and PET information provides valuable guidance in contouring the CTV.

Treatment planning

The dose should be optimized to the CTV with the goals of achieving a D_{90} (dose to 90% of CTV) ≥100% of the prescribed dose (i.e., the 100% isodose) and minimizing the dose to normal organs. Normal-tissue dosimetry should include descriptions of dose to volume, such as to 0.1 cm^3, 1 cm^3, and 2 cm^3 of the bladder, urethra, rectum, sigmoid colon, and small bowel, depending on the location of the lesion. The dose distribution should be assessed in representative axial scan images and adjusted, by means of manual or graphical tools, to improve the coverage or normal-tissue sparing. The location and volume of hot spots should be carefully evaluated. This is especially important when using graphical optimization, as unexpected aberrations can occur when this is used without careful consideration. The dwell times should be reviewed to ensure that there are no abnormally high dwell times created by the optimization process. The volume of tissues receiving more than 150% of the prescription dose is limited to the area adjacent to the individual needles or is contained within the vaginal obturator (6). Some of the quality indices suggested by van't Riet (61) and Major et al. (62) can be used to assess conformality and homogeneity. In an ideal case, conformation number = $(CTV_{ref}/V_{CTV}) \times (CTV_{ref}/V_{ref}) = 1$ (less than 1 practically), where CTV_{ref} is the volume of the CTV receiving a dose equal to or greater than the reference dose, V_{CTV} is the volume of CTV, and V_{ref} is the volume receiving a dose equal to or greater than the reference dose. It also includes the unwanted irradiated volume of critical structures outside the CTV receiving a dose equal to or greater than the reference dose. Based on published data, the value of the conformity index is usually between 0.6 and 0.8.

Similarly, the homogeneity index, defined as the fraction of CTV receiving a dose between 100% and 150% of the reference dose, is in the range of 0.6–0.7. The volumetric evaluation of dose distribution should be performed with dose–volume histograms for the target volume and critical organs as part of the optimization process. The total tumor dose (at 2 Gy EBRT per fraction) for should be in the range of 70–85 Gy for CTV (assumed α/β ratio of 10) depending on the tumor location, the extent of disease and the response to EBRT with 2 cm^3 of rectum and sigmoid receiving ≤70 to 75 Gy and the bladder ≤90 Gy (6, 63).

Quality assurance

The policies and procedures assuring appropriate delivery of the planned treatment are part of the Quality Management Program (64–66). All imaging devices, treatment planning systems, and applicators should be commissioned and incorporated in the department's quality assurance program before use. Image-based brachytherapy planning requires particular attention be paid to image quality with an applicator in the field of view (67). Crucial treatment-plan parameters, such as source activity, dwell times, and dose calculations, should be independently checked (68). Catheter reconstruction in the planning system and the associated mapping to the catheters visible at the patient or template surface should be verified. When using a computer-controlled afterloader, accurate transfer of treatment-plan parameters to the treatment machine, and the dwell times for each fraction, should be verified before the delivery of each fraction (69). Individual catheter lengths should be measured. Catheters should be checked before treatment to ensure the implant has not shifted.

Dose recommendations: literature survey

Low dose rate

The published data suggest that the total dose with the combination of EBRT plus brachytherapy to the tumor volume should be between 70 and 85 Gy depending on location and extent of disease (4, 8, 23).

For endometrial cuff recurrences, Curran et al. (4) reported that patients who received ≥60 Gy had significantly better survival and pelvic control rates than did patients who received lower doses. In another study, by Wylie et al. (15), a trend toward better local control (LC) was noted in patients who received ≥80 Gy compared with those who received <80 Gy ($p = 0.07$). In the data from MD Anderson (25), with a median dose of 74 Gy for the entire cohort, patients who received at least 80 Gy had a significantly better LC rate than patients who received <80 Gy ($p = 0.04$), although the radiation dose did not correlate with overall survival. Part of the reason why better LC is observed with higher dose could be because it is difficult to deliver a high dose to larger tumors because of proximity of dose-limiting critical organs.

The LDR literature for vaginal cancer indicates that there is a dose–response relationship between total dose and local tumor control. Chyle et al. (8) noted an increasing risk of local recurrences in patients who received <55 Gy when compared with those receiving >55 Gy (53% vs. 17%). Fine et al. (70) reported local failures in 25%, 33%, and 62% of patients for the administered dose of >75, 60–75, and <60 Gy, respectively. In one of the largest studies, by Frank et al. (15), for patients treated with the combination of EBRT and brachytherapy who were prescribed mean doses of 76 Gy (range, 65–90 Gy), 5-year pelvic disease control rates were 86% for Stage I,

84% for Stage II, and 71% for combined Stages III and IVA. The 5-year risk of complications was 25% in current smokers, 18% in patients who claimed to have quit more than 6 months before radiation therapy, and 5% in patients who had no smoking history ($p < 0.01$).

Depending on EBRT dose, the recommended prescription dose for brachytherapy with LDR would be 25–40 Gy, for a total dose of 70–85 Gy, depending on the tumor location, the extent of disease, and the response to EBRT. The preferred dose rate for LDR brachytherapy is between 35 and 70 cGy/hour.

High dose rate

HDR interstitial brachytherapy has the potential advantages of limiting exposure to caregivers and visitors and increasing the ability to optimize the dose distribution (71, 72). The disadvantages are a lack of consensus on fractionation schedules and limited published data. There have been a few publications on outcome using HDR brachytherapy for vaginal cancers (17, 71–73). Kushner et al. (17) reported on 19 patients treated with the combination of intracavitary and interstitial brachytherapy. In that series, interstitial templates were used in 8 patients. The median HDR dose was 23 Gy (LDR equivalent of 29.8 Gy) after a median EBRT dose of 40 Gy. The 2-year overall survival rate was 66.1%. Three patients, two of whom had interstitial brachytherapy, developed serious and/or late complications, including urethral stenosis, painful vaginal necrosis, and small bowel obstruction. The largest series of HDR brachytherapy for vaginal cancer is from Vienna, reporting on a total of 86 patients with primary vaginal carcinoma treated with HDR (55). Patients with early-stage disease (Stages 0–II) were treated with intravaginal HDR brachytherapy alone ($n = 26/86$), whereas patients with locally advanced disease (Stages II–IV) received HDR brachytherapy combined with EBRT ($n = 55/86$). The prescribed dose per fraction varied from 5 to 8 Gy, with a mean dose of 7 Gy. In that series, although only 8 patients had interstitial brachytherapy, the authors did mention that patients who had incomplete response to EBRT had better LC with interstitial implants. The 5-year recurrence-free survival rates were 100%, 77%, 50%, 23%, and 0% for Stages 0, I, II, III, and IV, respectively. Chronic Grade 3 and 4 side effects for bladder, rectum, and vagina were observed in 1%, 2%, and 4%, respectively. Lieskovsky and Demanes (74) reported on 54 patients with primary vaginal carcinoma treated predominately with interstitial HDR brachytherapy. EBRT consisted of 36 Gy to the pelvis and 50.4 Gy to the pelvic sidewalls with a midline block introduced at 36 Gy. HDR brachytherapy was administered in six fractions of 5.5 Gy to a total dose of 33 Gy. With mean follow-up of 45 months, the crude LC rate was 87% (47/54) and the 5-year overall survival rate for all patients was 52%. There was a 7% incidence of Radiation Therapy Oncology Group Grade 3 late gynecologic morbidity (four cases of vaginal necrosis that resolved completely with hyperbaric oxygen treatment) and a 7% incidence of Grade 4 GI/GU morbidity (one case of a vesicovaginal fistula). In another series of 13 patients with primary vaginal cancer or vaginal recurrence treated with interstitial brachytherapy, Beriwal et al. delivered five fractions twice a day for a total HDR dose of 18.75 Gy over 48 to 56 hours. The reported LC rate was 100% with 2 years of followup (34). One patient had Grade 3 toxicity. The authors suggested that the preferred approach should be a single procedure with twice-a-day fractionation for a total of three to six fractions.

At Brigham and Women Hospital and at the Medical College of Wisconsin, patients receive twice-daily treatment for a total of five to nine fractions (6). The optimal number of implants, fractionation schedule, and dose are by no means certain or established. The suggested doses used for HDR are based on empirical protocols and theoretical equivalence to the LDR brachytherapy parameters as noted above. In addition, the observed and expected morbidity for critical organs in vaginal cancer is thought to be similar to that of cervical cancer where, using 3D image-based dosimetry, it has been shown that doses to critical structures correlate with toxicity. It has been observed and expected that for vaginal cancer involving the posterior or anterior vagina (i.e., close to critical structures), doses to critical structures will be higher and, correspondingly, this may cause higher complication rates. For disease involving the distal vagina in close proximity to the vulva or rectovaginal septum, caution should be exercised and consideration should be given to a lower total dose of 70–75 Gy and/or a lower dose per fraction to reduce the probability complications, in contrast to the upper vagina, which has a much higher tolerance to radiation. Patients who have had poor response to EBRT or have large residual disease may benefit from higher total dose of 80–85 Gy. For these patients, the tolerance doses to critical organs may sometime limit delivery of higher dose. The HDR fractionation schedules noted in the literature or used by expert panelists are presented in Table 1. The number of implant procedures are limited to one or two to minimize the morbidity of repeated procedures with multiple fractions delivered with each implantation procedure.

Postprocedure care

Patients receive subcutaneous heparin, compression stockings, or pneumoboots to decrease the risk of a thromboembolic event. To decrease the risk of a decubitus ulcer secondary to the prolonged immobilization required for LDR and for single-insertion and multiple-fractionation HDR, patients should be placed on an air mattress and, when a template is used, should have Xeroform gauze or a Duoderm pad placed around the edge.

Patients should be treated in a hospital bed and not moved during the hospital stay to decrease the likelihood of needle displacement between fractions. The head of the bed should not be elevated more than 15°. The residual

Table 1
Proposed dose schedules for HDR interstitial brachytherapy in combination with EBRT

Dose of EBRT	HDR dose to CTV (Gy)	EQD2 to CTV	D2 cc per fx to rectum to limit EQD2 to ≤70 Gy
36 Gy/18 fx[a]	5 × 6	72.9	≤4.1
	5.5 × 6	78.0	≤4.1
39.6 Gy/22 fx[a]	5 × 6	76.4	≤3.8
	5.5 × 6	81.5	≤3.8
45 Gy/25 fx	3 × 9	73.6	≤2.55
	3 × 10	76.8	≤2.38
	4.5 × 5	71.5	≤3.75
	5 × 5	75.5	≤3.75
	5.5 × 5	79.8	≤3.75
	7 × 3	74.1	≤5.2
50.4 Gy/28 fx	4.0 × 5	72.9	≤3.25
	4.5 × 5	76.8	≤3.25
	5 × 5	80.9	≤3.25
	7 × 3	79.4	≤4.55

HDR = high dose rate; EBRT = external beam radiation therapy; CTV = clinical target volume; EQD2 = equivalent dose in 2 Gy fractions.
[a] Total pelvic dose to 50.4 Gy with midline block after 36–39.6 Gy.

needle length protruding from the edge of the template and from the perineum should be measured and recorded before each fraction, and repeat imaging with CT scan or fluoroscopy should be done if needle displacement is suspected.

Patients must be placed on radiation precautions with limited visitation if they are receiving LDR treatment. With fractionated HDR treatments, patients may have visits and nursing attendance between their treatments. To prevent bowel movements, patients should have a low-residue diet and scheduled around-the-clock antidiarrheals. The Foley catheter should remain in place throughout the implant. The patient may have intravenous antibiotics during the procedure and may receive a 5-to-7-day course of oral antibiotics. To regain mobility, all patients need appropriate aftercare, which may sometimes include physical therapy.

Followup

All patients should be regularly followed to assess LC and potential side effects of treatment involving the vagina, rectum, bladder, or urethra. The suggested schedule is every 3 months for the first 2 years, every 6 months from Years 3–5, and annually thereafter. Vaginal cytology should be done at each followup visit after the first 3 months. The first followup imaging, including PET scan and/or MRI, can be considered at 3 months after completion of treatments, extrapolating from the cervical cancer data (37). Subsequent imaging schedules have not been established but would, at a minimum, be obtained on an as-needed basis. A vaginal dilator is recommended to decrease the probability of vaginal stenosis. If vaginal ulceration is noted, hydrogen peroxide (50% solution) douching 1–2×/day for 2–4 weeks can be tried. For persistent ulceration or necrosis, hyperbaric oxygen treatment should be considered. The management principles for chronic symptomatic radiation effect on rectum and bladder are similar to those used for patients with cervical cancer treated with brachytherapy.

Continuing controversies and future directions

The heterogeneous fractionation schedules used in small published series by different institutions make it hard to choose any one fractionation schedule over another; this difficulty is reflected in these guidelines. Randomized clinical trials for vaginal cancer are unlikely because of the relative rarity of the disease. Published reports from high-volume single institutions and cooperative registries, therefore, are the best source of data to optimize the treatment of vaginal cancer in future (23, 56, 73–75).

Whether newer modalities such as intensity-modulated radiation therapy and image-guided radiation therapy will be effective alternatives to brachytherapy in some cases needs to be studied. The inherent advantages of brachytherapy, including conformal dose, a localized high-dose volume within the central area of disease, the lack of significant effect of organ motion, and the published outcome data, make brachytherapy the modality of choice at present for most cases. Additionally, the recent trend of integrating 3D imaging into treatment planning has the potential to improve outcome further by improving LC and reducing morbidity.

Conclusion

The preceding ABS 2011 Guidelines summarize recommendations for interstitial brachytherapy for vaginal cancer and recurrent disease in the vagina. Practitioners and cooperative groups are encouraged to use these recommendations to formulate treatment and dose-reporting policies. Such a process will result in meaningful outcome comparisons, promote technical advances, and lead to appropriate utilization of these techniques.

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