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CLINICAL INVESTIGATION **Cervix**

THE AMERICAN BRACHYTHERAPY SOCIETY RECOMMENDATIONS FOR LOW-DOSE-RATE BRACHYTHERAPY FOR CARCINOMA OF THE CERVIX

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Purpose: This report presents guidelines for using low-dose-rate (LDR) brachytherapy in the management of patients with cervical cancer.

Methods: Members of the American Brachytherapy Society (ABS) with expertise in LDR brachytherapy for cervical cancer performed a literature review, supplemented by their clinical experience, to formulate guidelines for LDR brachytherapy of cervical cancer.

Results: The ABS strongly recommends that radiation treatment for cervical carcinoma (with or without chemotherapy) should include brachytherapy as a component. Precise applicator placement is essential for improved local control and reduced morbidity. The outcome of brachytherapy depends, in part, on the skill of the brachytherapist. Doses given by external beam radiotherapy and brachytherapy depend upon the initial volume of disease, the ability to displace the bladder and rectum, the degree of tumor regression during pelvic irradiation, and institutional practice. The ABS recognizes that intracavitary brachytherapy is the standard technique for brachytherapy for cervical carcinoma. Interstitial brachytherapy should be considered for patients with disease that cannot be optimally encompassed by intracavitary brachytherapy. The ABS recommends completion of treatment within 8 weeks, when possible. Prolonging total treatment duration can adversely affect local control and survival. Recommendations are made for definitive and postoperative therapy after hysterectomy. Although recognizing that many efficacious LDR dose schedules exist, the ABS presents suggested dose and fractionation schemes for combining external beam radiotherapy with LDR brachytherapy for each stage of disease. The dose prescription point (point A) is defined for intracavitary insertions. Dose rates of 0.50 to 0.65 Gy/h are suggested for intracavitary brachytherapy. Dose rates of 0.50 to 0.70 Gy/h to the periphery of the implant are suggested for interstitial implant. Use of differential source activity or loading minimizes excessive central dose rates. These recommendations are intended only as guidelines. The responsibility for medical decisions ultimately rests with the treating radiation oncologist.

Conclusion: Guidelines are suggested for LDR brachytherapy for cervical cancer. Practitioners and cooperative groups are encouraged to use these guidelines to formulate their treatment and dose-reporting policies.

Cervix, Brachytherapy, Intracavitary, Interstitial.

INTRODUCTION

The success of radiation therapy requires the delivery of a high radiation dose directly to the tumor while sparing, to some degree, the surrounding normal tissues. Low-dose-rate (LDR) brachytherapy has traditionally been an important component in the overall management of patients with cervical carcinoma. Some institutions are now using high-dose-rate (HDR) brachytherapy. Several studies (including randomized and nonrandomized prospective clinical trials, surveys of published studies, and meta-analyses) have compared HDR brachytherapy to LDR brachytherapy in the management of cervical cancer. These have demonstrated comparable local control, survival, and morbidity (1–13). A discussion of the debate over the use of LDR and HDR brachytherapy to treat cervical cancer is beyond the scope of

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this report. The increased integration of chemotherapy has also affected the practice pattern in cervical cancer.

The curative potential of radiation therapy in the management of carcinoma of the cervix is greatly enhanced by the use of intracavitary brachytherapy (14–17). Although LDR intracavitary brachytherapy has been in use for many years, there is wide variation in its clinical practice (18). Although some dose specification and reporting guidelines exist for gynecologic brachytherapy (ICRU Report 38) (19), they are not widely accepted (20, 21). The American Brachytherapy Society (ABS) has recently issued recommendations for HDR brachytherapy for cervical cancer (22) and felt that specific recommendations should also be provided for LDR brachytherapy for cervical carcinoma. The ABS recognizes that because of the wide variation in clinical practice, it may be difficult to obtain a consensus agreeable to all practitioners.

METHODS AND MATERIALS

Members of the ABS with expertise in LDR cervical brachytherapy performed a literature review and, guided by their clinical experience, formulated specific recommendations and directions for future investigation in LDR cervical brachytherapy. These recommendations were made by consensus opinion and supported by published data whenever possible. In addition, an external multispecialty panel of recognized experts in the field reviewed the consensus recommendations. Revisions were made where indicated. The board of directors of the ABS approved this final report. The definitions of the consensus levels used were similar to those used in previous ABS reports (23), as follows:

ABS levels of consensus opinion for LDR cervical brachytherapy

Level 1. There is uniform panel consensus, based on published literature, that the recommendation is appropriate.

Level 2. Recommendation is based on suggestive evidence, including nonpublished clinical experience. There is no major disagreement among panel members.

Level 3. There is major disagreement among panel members regarding the recommendation.

RESULTS

The results of the deliberation of the panel and the ABS recommendations are given in the following sections. These recommendations were at Level 1 consensus, unless specifically noted to be of Level 2 consensus. None of the recommendations was at consensus Level 3.

Staging recommendations

The ABS recommends the use of the current International Federation of Gynecology and Obstetrics (FIGO) staging definition adopted in 1994 (24). FIGO has made many changes for cervical cancer staging, mostly in the area of microinvasive cancer. The current system includes changes in microinvasive and Stage IB definitions. Imaging modalities allowed for FIGO clinical staging include chest X-ray, intravenous pyelogram (IVP), and barium enema. Cystoscopy, proctoscopy, colonoscopy, biopsy, cervical conization, and examination under anesthesia are also allowed. Lymphangiography, computed tomogram (CT) and magnetic resonance imaging (MRI), and surgical staging may aid in treatment planning, but information from these tests or procedures cannot be used to determine or change the clinical FIGO stage.

The volume of the disease is critical to treatment modality selection, treatment planning, and outcome (17, 25–27). Therefore, in the new FIGO classification, Stage IB cervical cancer was divided into two subgroups to reflect the poorer prognosis associated with larger tumors.

Selection of treatment modalities by stage

FIGO Stage IA

Early invasive cervical carcinoma is usually treated surgically (28–30). The majority of patients are effectively treated by extrafascial hysterectomy or conization, because the risk of recurrence is less than 1% in patients without lymphatic and/or vascular space invasion (LVSI). Patients with contraindications to major surgery can be effectively treated with intracavitary irradiation alone (31).

FIGO Stages IA2 and IB1, IB2 (and small IIA)

The ABS recommends either definitive radiation therapy or radical surgery as the primary treatment for this group of patients, depending on patient variables (e.g., comorbidities, age, patient preference) and the philosophy of the institution, gynecologic oncologist, or radiation oncologist. Therapeutic results of these two modalities are equivalent (32). The ABS recommends that primary therapy should avoid the routine use of both radical surgery and radiation therapy to minimize morbidity related to multimodality therapy (33–35).

Surgical management includes radical hysterectomy with pelvic lymphadenectomy (36, 37). The advantages of radical surgery include a shorter treatment time, less damage to normal tissue, removal of the primary lesion, and a better definition of the true extent of disease spread (surgical staging). Other advantages include preservation of ovarian function and, perhaps, better sexual function. Radical hysterectomy should have a mortality risk of less than 1%. This is likely to exceed the short-term mortality risk of radiation. Other surgical risks include blood transfusion, genitourinary/gastrointestinal (GU/GI) fistulas, and voiding dysfunction.

The advantage of definitive radiotherapy is avoidance of a major surgical procedure and avoidance of the complications associated with postoperative adjuvant radiotherapy in high-risk patients (extensive LVSI, tumor >4 cm). Potential disadvantages of radiation include an increased risk of sexual dysfunction, secondary malignancies, and ablation of ovarian function in premenopausal patients. Nevertheless,

major GU/GI complications are possible with either modality, especially in patients with diabetes, peripheral vascular disease, or long-standing tobacco use. Multiple reports have demonstrated an increase in severe GU/GI complications related to the combination of radical surgery followed by pelvic irradiation (33–35).

There has been no randomized trial in North America comparing definitive radiation therapy to radical hysterectomy. One such trial, performed in Italy on patients with FIGO IB–IIA disease, also included a subgroup of patients who received multimodality therapy. No difference in overall or disease-free survival was observed between patients with radical hysterectomy and those receiving definitive radiation therapy (35). The major complication rate for the surgery group was significantly higher (28%) than that for the radiotherapy group (12%) and highest among the patients receiving multimodality therapy. This study has been criticized for an unusually high rate of adjuvant radiotherapy use (64%) in the surgery group, a high incidence of parametrial disease, a high cut-through rate, and the high complication rate in the surgery-only group.

Stages IB2 through IVA

Radical surgery is appropriate for some patients with Stage IB2 cervical carcinoma. Otherwise, the majority of patients with bulky IB2 disease and more advanced lesions are treated primarily by chemoradiation therapy. Careful attention to disease volume and extent is important for treatment planning and outcome (27, 38, 39).

Treatment modalities

Combined surgery and radiation

Extrafascial hysterectomy after radiation therapy has been advocated for large IB cervical cancer. Most reports have not identified a survival benefit attributable to the addition of the hysterectomy to radiation therapy (40–43). The Gynecology Oncology Group (GOG protocol #71) studied this question in a randomized trial. The adjuvant hysterectomy group experienced a reduced rate of pelvic relapse compared to that seen in the group of patients receiving radiotherapy alone. There was, however, no difference in overall survival between the two groups (44). Because of the increased complications associated with extrafascial hysterectomy and the lack of evidence of any survival benefit, the ABS does not recommend planned radiation therapy and adjuvant hysterectomy.

The use of adjuvant pelvic irradiation after radical hysterectomy and lymph node dissection has been a controversial topic for decades (45–49). Most reports have not shown a survival benefit in patients with risk factors for recurrence. Prognostic factors after radical hysterectomy include lymph node status, tumor size, depth of invasion, and LVSI, with positive pelvic lymph nodes being the strongest predictor of outcome (25, 45, 46, 50).

The ABS recommends adding postoperative radiotherapy for that subgroup of patients that has at least two of the following risk factors for recurrence: (*1*) greater than one-third stromal invasion, (*2*) LVSI, and (*3*) large (>4 cm) tumor diameter. GOG #92 prospectively evaluated node-negative Stage IB cervical cancer treated with radical hysterectomy and pelvic lymphadenectomy (±) pelvic radiotherapy in this subgroup of patients. Those with extracervical spread or positive margins were excluded. There was a statistically significant reduction in the overall recurrence rate in the radiotherapy arm (15% vs. 28%) and an improvement in the recurrence-free rate at 2 years. Adjuvant pelvic radiotherapy after radical hysterectomy reduced the number of recurrences (44% reduction). There was, however, a 6% incidence of Grades 3 and 4 toxicity in that treatment arm compared to 2% in the surgery-only group (51).

The ABS recommends adding postoperative chemoradiotherapy for the subgroup of patients with early-stage cervical cancer that meets at least one of the following criteria: (*1*) positive pelvic lymph nodes, (*2*) positive surgical margins, and (*3*) microscopic involvement of the parametrium. GOG #109 prospectively evaluated concurrent chemotherapy and pelvic radiotherapy or pelvic radiotherapy alone after radical hysterectomy and pelvic lymphadenectomy in this subgroup. Patients in the chemotherapy arm received bolus cisplatin and 96-h continuous infusion of 5-fluorouracil twice during irradiation and two additional courses after radiotherapy was completed. There was a statistically significant improvement in the projected 4-year progression-free interval (63% vs. 80%) and overall survival (71% vs. 81%) in favor of the radiotherapy plus chemotherapy arm (52). The relative risk of death in this group was reduced by 50%.

Concurrent chemoradiation

The ABS recommends the addition of cis-platinum–based chemotherapy during the course of definitive radiotherapy for patients with IB2–IVA disease. Definitive irradiation has been the standard treatment for patients with advanced-stage disease (IIB–IVA), as well as an excellent option for bulky early-stage cervical cancer. Five randomized trials have recently demonstrated significant improvement in local control and survival when concurrent chemotherapy was added to radiation therapy in patients with early-stage disease and high risk for recurrence, as well as in patients with advanced-stage disease (53–59). Four of these studies evaluated concurrent chemotherapy combined with definitive radiotherapy (Table 1).

Radiation therapy recommendations

General recommendations

The Patterns of Care studies have shown that recurrences and complications are decreased when brachytherapy is used in addition to external beam irradiation (EBRT) (14, 60–64). Therefore, the ABS strongly recommends that definitive irradiation for cervical carcinoma include brachytherapy as a component. Precise applicator placement is essential for improved local control and reduced morbidity (17, 64, 65). The outcome of brachytherapy depends in part on the skill and expertise of the operator (18). A small caseload may be insufficient to maintain the skills necessary to perform optimal brachytherapy insertions. It may be

Table 1. Summary of results of chemoradiation therapy for definitive therapy for cervical cancers

Study	FIGO stage	Overall survival	Progression-free survival	Relative risk of progression
Keys *et al.* (53); GOG 123*	IB2			
XRT (control)		74%	63%	
XRT plus weekly CDDP		83%	79%	0.51
Whitney *et al.* (56); GOG 85	IIB–IVA*†			
XRT plus hydroxyurea (control)		43%	47%	
XRT plus CDDP/5-FU		55%	57%	0.79
Rose *et al.* (54); GOG 120	IIB–IVA*†			
XRT plus hydroxyurea (control)		50%	41%	
XRT plus weekly CDDP		66%	62%	0.57
XRT plus hydroxyurea/5-FU/CDDP		67%	61%	0.55
Morris *et al.* (55); RTOG 9001	IB2–IVA			
Extended field XRT (control)		58%	40%	
XRT plus CDDP/5-FU		73%	67%	0.48

Abbreviations: XRT = definitive pelvic radiotherapy; 5-FU = 5-fluorouracil; CDDP = cisplatin.
* Also had adjuvant hysterectomy.
† Negative para-aortic nodes by extraperitoneal laparotomy.

necessary to refer patients to physicians or major medical centers with established brachytherapy expertise (18). Doses given by EBRT, as compared to those given by brachytherapy, depend upon the initial volume of disease, the ability to displace the bladder and rectum, the degree of tumor regression during pelvic irradiation, and institutional practice. Interstitial brachytherapy should be considered for patients with disease that cannot be optimally encompassed by intracavitary brachytherapy. The ABS recommends limiting the total treatment duration to less than 8 weeks when possible. Extending total treatment duration beyond 8 weeks can reduce local control and survival by about 1% per day of prolongation (66–69). Anemic patients should be transfused or receive erythropoietin to maintain the hematocrit level above 30 (Level 2 consensus). Radiation dosage and techniques are discussed later in this report.

External beam therapy

The ABS recommends whole pelvic irradiation with four-field isocentric technique with customized blocking, with all fields treated daily. The ABS recognizes that the pelvic EBRT dose differs from institution to institution and can depend on the stage of disease. Some institutions prefer to limit the whole pelvis dose for patients with early disease and to perform the first intracavitary insertion after 20 Gy, with further EBRT delivered with a central block in place. However, most institutions deliver 40–50 Gy of EBRT to the entire pelvis. Details of EBRT fields are given in standard publications (55, 70, 71). The inferior border should be determined clinically by examining the vaginal extent of tumor. It is very important to identify the distal extension of the tumor at the time of simulation by placing a radiopaque marker on the vaginal wall or by inserting a small radiopaque rod in the vagina. Because of increased probability of metastases in cases with lower vaginal extension, the portals should be modified to cover the inguinal lymph nodes in these patients. The anterior margin of the lateral portal should include the pubis, so as to include the external iliac nodes, and the posterior margin should extend to the sacral hollow to cover the uterosacral ligaments and internal iliac nodes (72). Partial blocking of the sacrum is not recommended.

Some institutions use a midline block for part of the pelvic field irradiation to shield the bladder and rectum to allow a higher dose to be given by brachytherapy. There is no consensus regarding the use of midline blocks. The ABS recommends that, if used, simple rectangular blocks should be 4 cm wide at midplane when intracavitary brachytherapy applicators are used (Consensus Level 2). Alternatively, customized midline blocks based on radiographs taken with similar isocenters and reflecting the isodose distribution of the implant may be considered. When a midline block is inserted before 40 Gy, it should not extend to the top of the pelvic field, because it will shield the common iliac and presacral nodes. When uterosacral ligament involvement is suspected, it is safer to avoid early placement of a midline block, which could potentially shield disease posterior to the implant (72, 73). If EBRT doses greater than 45–50 Gy are to be given, the fields should be coned down after the initial 45–50 Gy to exclude small bowel. An additional parametrial boost may be delivered with reduced portals to bring the EBRT contribution to the pelvic sidewall to approximately 60 Gy when there is persistent parametrial tumor after whole pelvic EBRT. Small bowel should be excluded from this boost volume as much as possible.

If para-aortic node metastases are present, the ABS recommends that the patient be treated with 45 Gy to the para-aortic area, plus a 10–15-Gy boost to enlarged lymph nodes through reduced lateral or rotational portals, along with chemotherapy (74) (Consensus Level 2).

Brachytherapy

Intracavitary applicators

- Manual afterloading Fletcher tandem and colpostats (and their numerous modifications) are used most commonly

(18). Numerous other applicators (e.g., Henschkes) are also available. In addition, low-dose-rate remote afterloading devices, though not commonly available in the United States, are often used in other countries. The clinical, radiobiologic, and physics principles of LDR are the same for both manual and remote afterloading. The size of the applicators, radiation protection features, and, possibly, the ability to limit applicator movement during treatment differ. Discussions of applicator systems are available in standard textbooks (75).

- The ABS does not recommend one applicator system over another. The ABS recommends that the radiation oncologist be familiar with the applicator(s) used.
- Vaginal cylinders can be used in conjunction with an intrauterine tandem to irradiate the vagina when the disease extends from the uterine cervix along the vaginal walls. A vaginal cylinder (without the intrauterine tandem) may be used after a radical hysterectomy if there is a close or positive vaginal margin. A vaginal cylinder is also useful for patients with a very narrow vagina that cannot accommodate the colpostats, if interstitial implant cannot be performed.

Intracavitary insertion techniques

- Insertion of these applicators is often considered a "minor" surgical procedure. It may be advantageous to have an experienced gynecologic oncologist available during insertion for difficult cases.
- The ABS recommends that intracavitary LDR insertions be performed under analgesia/anesthesia to allow examination, insertion, and packing.
- Sequential pneumatic devices (pneumoboots) and low-dose (5,000 units twice daily) s.c. heparin are recommended to prevent deep venous thrombosis.
- Routine antibiotics are prescribed when uterine perforation is suspected.
- The ABS recommends use of two LDR insertions, especially in larger tumors, to allow progressive tumor volume reduction and more effective disease coverage with the second application. The first intracavitary insertion is usually given after delivering 2 to 4 weeks of external beam irradiation as soon as adequate pelvic geometry allows. The second application is usually performed 1 or 2 weeks later such that the entire treatment course is completed within 8 weeks. Every attempt should be made in the second application to replicate the position of the applicators in the first implant, if the geometry was optimal. The ABS recognizes that, in certain circumstances (unreliable patient, excellent geometry, small tumor volume), the brachytherapy could be performed as a single insertion.
- The ABS recommends placing radiopaque markers in the cervix or adjacent normal tissue close to the cervix for radiologic identification of cervical position and to determine the relationship of the vaginal applicators to the cervix.
- A Foley catheter should be placed into the bladder and the balloon filled with 7 cc of radiopaque contrast material.
- It is important to choose an applicator that can optimally treat the disease and can be placed in an anatomically distorted vagina (76). The largest colpostat diameter that can be accommodated in the fornices without displacement should be inserted. The colpostats should fit snugly against the vaginal fornices. The Fletcher minicolpostat or Henschke-type applicator can be used in a narrow vagina that cannot accommodate regular Fletcher colpostats. The use of asymmetrical-sized ovoids is not encouraged in cases of narrow and fibrotic vagina. Interstitial implant is preferred if the vaginal fornix is narrow and fibrotic. Shielded colpostats may help reduce the bladder and rectal doses if the shields are positioned correctly. Practitioners should use the applicator type they are familiar with and recognize that the dose distribution around different applicators is not the same.
- The ABS emphasizes that optimal applicator placement and attention to detail are critical in maximizing local control and minimizing complications (64). Ideally, the tandem and colpostat should be inserted so that the tandem bisects the colpostats on lateral view. The tandem should fall midway between the colpostats and parallel to the body axis on anteroposterior (AP) view. The flange should be at the level of the exocervix as defined by the cervical markers.
- Intraoperative radiographs or fluoroscopy should be obtained to check the applicator position. If these reveal suboptimal applicator position, the implant should be repositioned and repacked. If there is no improvement, a decision must be made whether to change the applicator, accept the insertion (and possibly modify the loading of the tandem and colpostats), or perform an interstitial implant.
- If optimal placement was not achieved in the first insertion, the applicator position, packing, and loading should be adjusted at the second insertion to compensate.
- If the uterine canal is difficult to find, or if perforation is suspected, the ABS recommends the use of ultrasound guidance.
- If a tandem and colpostat applicator cannot be inserted because of vaginal narrowing, the absence of fornices, or vaginal extension of disease, strong consideration should be given to interstitial implantation. Alternatively, a tandem and cylinder applicator may be used, keeping in mind that use of the cylinder results in higher bladder and rectal doses relative to tumor, with a possible increase in complications (76, 77). Additionally, the lower parametrial doses may result in reduced pelvic control.
- The ABS recommends using radiopaque gauze or an inflatable catheter bulb to displace the bladder and rectum away from the applicator to increase the therapeutic ratio.

Localization for dosimetry

The ABS recommends localization using radiographic equipment with high geometric precision (e.g., radiotherapy

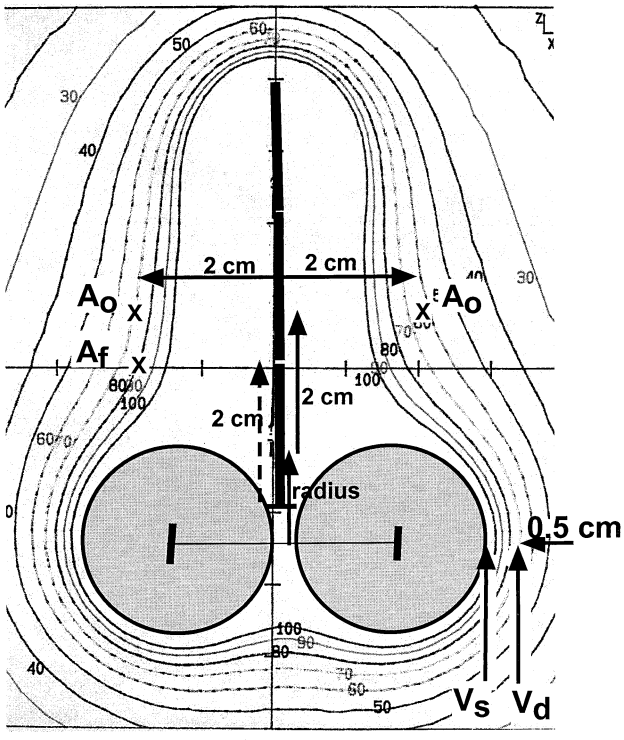

Fig. 1. (Left side) Variations of point A based on definition. The point labeled A_o follows the original definition of 2 cm cephalad from the ovoid surface and 2 cm lateral. The point A_f begins at the flange instead of the ovoid surface. The latter point falls near the rapidly changing gradient in the cephalocaudal direction near the ovoids, whereas the former falls in a region where the dose changes little with changes in the direction along the tandem. (Right side) Recommended reporting points for cervical cancer brachytherapy with a tandem and colpostat: point A, corresponding to the original Manchester definition (A_o); point V_s, on the lateral surface of the ovoid; and point V_d, 0.5 cm deep to point V_s laterally. Reported doses should include the values on *both* the right and left sides for each point.

simulators) or the use of a fiducial jig with standard radiographic equipment. Use of portable X-ray equipment is not recommended because of suboptimal imaging. As discussed later, CT-based and magnetic resonance–based localization allow the correlation of anatomic data with source positioning. The localization method used must be consistent with the requirements of the treatment planning system used at the institution.

Dose specification

1. The ABS recommends specifying the dose for intracavitary applications for treatment of cancer of the cervix to a point equivalent to that used in the classical Manchester System (See Fig. 1). The original definition of the Manchester System (78) found point A by drawing a line connecting the superior aspects of the vaginal colpostats and measuring 2 cm superior along the tandem from the intersection with this line and then 2 cm perpendicular to this in the lateral direction. This point was useful for standardization, because it fell within the portion of the isodose distribution with little cephalocaudal gradient, running mostly parallel to the tandem. The failure of localization radiographs to show the surfaces of the colpostats made implementation of this process difficult, so in 1953, Tod and Meredith changed the procedure to begin at the most inferior point of the sources in the tandem (79). By the construction of the Manchester applicator, these two definitions essentially locate the same point. Use of this latter definition (or a common variant: beginning at the flange abutting the cervical os) with other applicators results in point A locations with a wider variation with respect to the colpostats (80, 81), often with point A falling in a high-gradient region of the isodose distribution. The result of this variation is that two patients with minor differences in the application can receive markedly different amounts of radiation. A location for consistent dose specification point should fall sufficiently superior to the colpostats that the dose distribution runs parallel to the tandem.

   For modern applicators and using radiographic localization, the ABS recommends the following alternative procedure for locating point A, because of the considerations discussed above. Begin by drawing a line connecting the middle of each of the colpostat sources (or the colpostat capsules if the sources are not visible during localization) on the AP radiograph. Then, from the intersection of this line with the tandem, move superiorly along the tandem 2 cm, plus the radius of the colpostats, and then 2 cm perpendicular to the tandem in the lateral directions. The dose shall be calculated and specified to point A on both the right and left. The average of the right and left doses can be taken if a single point A dose is needed.

   For applications using a tandem and vaginal cylinders, point A can be specified using the modified definition. Begin at the flange on the tandem (indicating the external cervical os), travel superiorly along the tandem 2 cm, then laterally perpendicular to the tandem 2 cm (Fig. 2).
2. The ABS recommends reporting the dose at the lateral vaginal surface (mucosa) (points V_s) and at 0.5 cm deep to the vaginal surface (point V_d) and to correlate with clinical outcome. For applications using a tandem and colpostats, the points would fall on a line connecting the centers of each colpostat (Fig. 1). Points V_s and V_d shall be specified separately for the right and left side. The ABS suggests limiting the V_s dose to less than 150% of point A dose (Consensus Level 2).

   For applications using a tandem and vaginal cylinders, there may be several points V_s and V_d (Fig. 2). The first set of points falls 1.25 cm inferior to the external cervical os, indicated by the flange on the tandem, on a line perpendicular to the tandem, with V_s at the cylinder radius from the tandem to the patient's right and left, and V_d 0.5 cm deep to that (Fig. 2). These points approximate the same locations in the vagina as they would with an application using a tandem and medium colpostats and would fall in the middle of a standard 2.5-cm vaginal cylinder segment. They are designated V_{su} and V_{du},

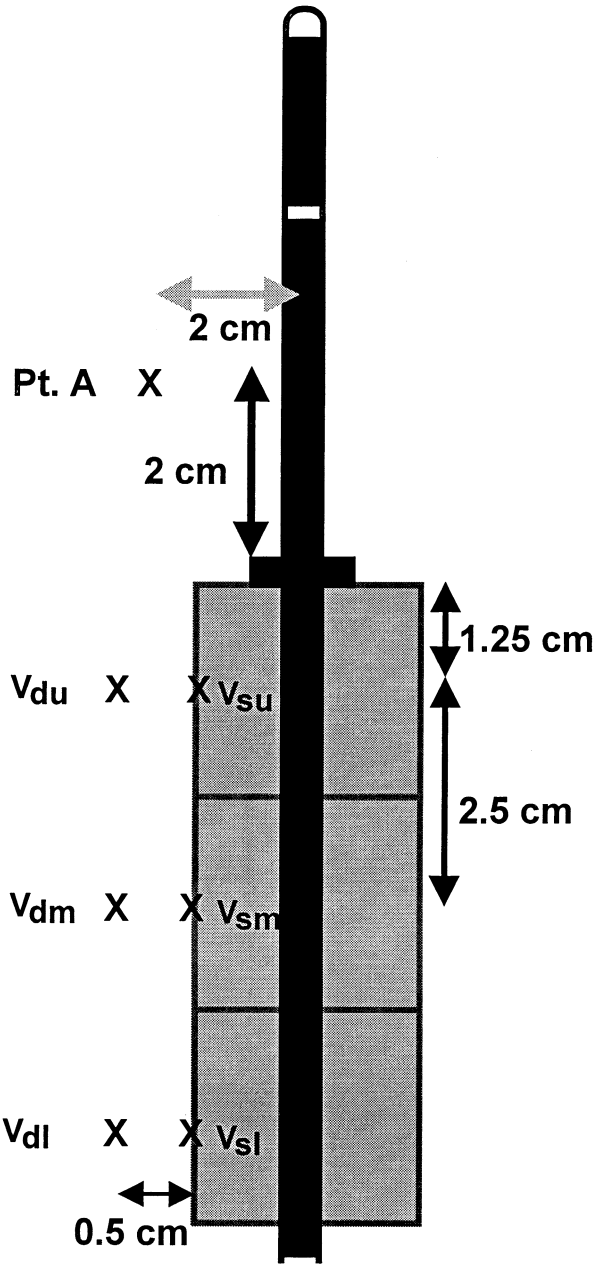

Fig. 2. Dose-reporting points for cervical cancer brachytherapy using a tandem with vaginal cylinders. Point A lies 2 cm cephalad along the tandem from the flange and 2 cm lateral (perpendicular) to the tandem. The upper vaginal dose points fall on the surface of the cylinder 1.25 cm below the bottom of the flange (V_{su}) and 0.5 cm lateral (perpendicular to the tandem) to that (V_{du}). The middle vaginal points fall 2.5 cm inferior parallel to the tandem of the upper points, and the lower vaginal points yet another 2.5 cm inferior.

because these points correspond approximately to the upper third of the vagina.

If the treatment length in the vagina exceeds 4 cm, the dose to a second set of points V_s and V_d shall be calculated. These points are located in the same manner on a line 2.5 cm inferiorly along the tandem to V_{su} and V_{du}, designated as V_{sm} and V_{dm}, for the middle third of the vagina. Treatments including more than 6.5 cm of the vagina shall also specify the dose at a third set of points, V_{sl} and V_{dl}, located on a line 2.5 cm inferiorly along the tandem to V_{sm} and V_{dm}.

3. Nominal bladder point: Practitioners should use the standard ICRU #38 definition for the bladder dose point, with a minor change (19). The bladder point falls on the surface of a Foley balloon filled with 7 cc of iodinated radiographic contrast (diluted if necessary so as not to obscure the localization markers on the AP radiograph) snugged into the trigone of the bladder. The point selected should correspond to the maximum dose on the surface of this balloon. That point may not be the most posterior aspect of the balloon, if it is situated to one side or significantly superior or inferior to the vaginal applicator. It is to be noted that the maximum bladder dose using three-dimensional dosimetry methods is usually higher than the maximum bladder dose obtained by conventional methods (82–84).
4. Nominal rectum point: The standard ICRU #38 definition of rectal point (0.5 cm posterior to the posterior vaginal wall as identified by radiopaque gauze in the vagina) can be used, because it is easy to determine and will maintain standardization with common practice. Additional information regarding the anterior rectal wall may be obtained by injecting a diluted solution of barium contrast into the rectum. Attention should also be given to radiographic visualization and dose to the sigmoid colon, because it may pass close to the tandem. Alternate localization tools, such as lead markers in a catheter or measurement devices, are not recommended, because they often lie much posterior to the anterior wall and therefore result in erroneous low point doses.
5. The dose to the nominal rectal and bladder points should be kept as low as possible, although consistent with delivering appropriate tumor doses. Every effort should be made to keep the bladder dose to $<$90% of point A dose, the total bladder dose below 80 Gy, and the total rectal dose below 75 Gy (Consensus Level 2).
6. Regional lymph nodes: The brachytherapy component of dose to the lymph nodes remains small compared to that from the EBRT. It should be included, nevertheless, in any combined treatment. The ABS recommends calculating the dose to the points defined in ICRU Report 38 as the pelvic wall points. The ABS recommends calling this point PW. Because of the minor contributions of brachytherapy to other nodal locations, other lymph node doses need not be calculated. The ABS does not recommend using the Manchester point B as representative of lymph node locations.

Optimization

Optimization cannot be used to compensate for a substandard applicator positioning. Optimal tandem and colpostat selection and application is essential for an appropriate dose distribution. Conventionally, little optimization has been used in intracavitary applications for cervical cancer, pri-

Table 2. Carcinoma of the uterine cervix: Suggested doses of external beam irradiation and LDR intracavitary brachytherapy*

		External irradiation (Gy)			LDR brachytherapy (Gy)	
Tumor stage	Tumor extent	Whole pelvis	Pelvic wall	Parametrial boost (Gy)	Dose to point A	Total dose to point A (Gy)
IA1		0	0	0	50–60	50–60
IA2 Selected IB1	Superficial ulceration less than 1 cm in diameter or involving fewer than two quadrants	0	0	0	60–70	60–70
IB1		19.8 or 45	50.4 or 45	0	55 or 30–35	75 or 75–80
IB2, IIA,†		45	45	0	40	85
IIB†		45	45	9–15	40	85
III†		45–50	45–50	9–15	40	85–90
IIB, IIIB, IV	Poor pelvic anatomy, patient not readily treated with intracavitary insertions (barrel-shaped cervix not regressing, inability to locate external os)	50	50	9–15	40	90
	Or interstitial	39.6–45	39.6–45	0–15	35–40*‡	75–85*‡

* The panel acknowledges that a range of doses can be suitable, depending on individual patient circumstances.

† The panel acknowledges that the alternative approach is to increase brachytherapy contribution to point A by giving whole pelvic external beam radiotherapy of 19.8 to 30.6 Gy. This is followed by whole-pelvic external beam radiotherapy with a step wedge midline shield for an additional 19.8 to 30.6 Gy and intracavitary brachytherapy to bring point A dose to the recommended level described in the table (71, 131, 132).

‡ The interstitial brachytherapy dose is the ICRU external beam radiotherapy #58 reference dose and not the dose to point A.

marily because manual sources are so few in number and come in limited activities. Low-dose-rate remote afterloaders allow more source positions (eight possible source positions for the equivalent of each manual source position), but only a single strength for each position. Optimization also requires an inverse approach to dosimetry compared to the conventional approach: namely, specifying the doses desired at given locations rather than calculating the doses for a given source configuration. Thus, the optimization approach requires a predetermined understanding of the dose distribution that should be used to treat the target volume. This understanding assumes knowledge of the target. Neither of these is characteristic of intracavitary applications for cervical cancer at the present. Manually afterloaded LDR dose distributions can be modified to a limited extent by using differential source strengths, spacers, and selective changes of the source strengths during the implant. The conventional-shaped dose distributions should be used with typical LDR applications until studies have been performed to determine the actual boundaries of the target tissues.

Dose recommendations for definitive radiation therapy

Recommended doses to point A by stage are listed in Table 2. These guidelines are based on published literature and the experience of the panel members. It must be emphasized that the dose recommendations in Table 2 are intended to serve only as a guide. The ultimate responsibility for the medical decisions rests with the treating physician. Physicians performing brachytherapy need to understand the importance of technique. The recommended LDR dose depends on the whole-pelvic dose delivered. The decision to emphasize the EBRT more than the brachytherapy is contingent upon the initial volume of disease, the ability to displace the bladder and rectum, the degree of tumor regression during pelvic radiation, and institutional practice. It should also be recognized that doses from EBRT and brachytherapy are not biologically equivalent and therefore cannot be mathematically summated. For example, 40 Gy of EBRT plus 40 Gy of brachytherapy will deliver 80 Gy to point A. However, this will not be biologically the same as 20 Gy of EBRT plus 60 Gy of brachytherapy, although 80 Gy will be delivered to point A.

Every effort should be made to keep the total bladder dose below 80 Gy and the total rectal dose below 75 Gy (Consensus Level 2). Clinical situations frequently arise where normal-tissue tolerance is approached or exceeded. Therapeutic strategies to address this clinical dilemma include increasing the EBRT contribution to point A but lowering the total LDR dose, or using an interstitial implant. Because there are uncertainties in the locations of normal-tissue points, some institutions maintain the tumor dose and accept the higher risks of exceeding the nominal normal-tissue tolerance parameters, so as not to compromise tumor control.

Dose recommendations for postoperative radiation therapy after radical hysterectomy

Table 3 summarizes the guidelines for various situations in which postoperative radiation is recommended (51, 52, 85–87).

Table 3. Postoperative radiation therapy for cervical cancer

Tumor status	Whole pelvis (Gy)	Pelvic wall	Tumor boost	Vaginal brachytherapy dose (Gy)	Total vaginal mucosa dose (Gy)
Radiation therapy after simple hysterectomy					
>3-mm invasion, margin clear, nodal status unknown	45–50.4	45–50.4	–	0–15	45–60
Microscopically positive vaginal margins, or LVSI	45–50.4	45–50.4	–	20–30	70–75
Gross residual tumor, or recurrent disease	45–50.4	45–50.4	–	30–35	80
Or with interstitial	45	45	–	30–35*	75–80*
Radiation therapy after radical hysterectomy					
Positive pelvic lymph nodes	45–50.4	45–50.4	–		45–50.4
Deep stromal invasion (≥10-mm or ≥70%, and ≥4-cm tumor) microscopically positive vaginal margins or positive LVSI	50	50	–	20	70
Microscopically positive parametrial or paravesicle margins	45–50.4	50.4	9–15	0	45–60
Gross residual tumor, or recurrent disease	45–50.4	45–50.4	–	30–35	80
Or with interstitial	45	45	–	30–35*	75–80*

* The interstitial brachytherapy dose is the ICRU #58 reference dose and not the dose to vaginal mucosa.
Abbreviation: LVSI = lymphatic and/or vascular space invasion.

Dose recommendations for postoperative radiation therapy after inadvertent simple hysterectomy

Occasionally, a simple or total abdominal hysterectomy is performed, and invasive carcinoma of the cervix is incidentally found in the surgical specimen. It is critical that these patients receive radiation therapy as soon as their postoperative status allows it. The prognosis is worse if postoperative irradiation is not administered when carcinoma is detected after an abdominal or vaginal hysterectomy. Durrance (88) and Andras *et al.* (89) reported survival rates similar to those of patients with an intact uterus when these patients were treated appropriately. The recommended doses of external beam and brachytherapy are presented in Table 3.

Dose reporting for intracavitary brachytherapy

The ABS recommends reporting the following parameters for intracavitary insertions:

1. The prescription, including the prescribed dose to points A, dose rate, implant duration, radionuclide used (usually ^{137}Cs), sources' strengths, and loading pattern;
2. The type of applicator used;
3. Doses to rectal and bladder points;
4. Dose to the pelvic wall, point PW; and
5. Doses to vaginal dose points V_s and V_d.

Quality management

Numerous documents provide general guidelines for treatment planning, dosimetry, and quality management for intracavitary and interstitial brachytherapy. These guidelines also apply to treatment of cervical cancer and should be taken into consideration. These reports may be categorized as follows:

- Dose and Volume Specification for Reporting Interstitial Therapy: ICRU Report 58 (90).
- Dose and Volume Specification for Reporting Intracavitary Therapy in Gynecology: ICRU Report 38 (19). However, this report is currently being revised (20, 21).
- Code of Practice for Brachytherapy Physics: Report of the AAPM Radiation Therapy Committee Task Group 56 (91).
- Quality Assurance of Treatment Planning Systems: Report of AAPM Radiation Therapy Committee Task Group 53 (92).
- Dosimetry of Interstitial Brachytherapy Sources: Report of AAPM Radiation Therapy Committee Task Group 43 (93).
- In addition, many of the ABS recommendations for HDR brachytherapy of the cervix (22) are also applicable to LDR brachytherapy of cervical cancer.

Aspects of quality management directed at preventing treatment errors because of mistakes in the treatment planning become treatment-type specific. Some of the important recommendations of this report are summarized below as they relate to treatment for patients with cancer of the cervix.

The treatment prescription should include the following:

1. A clear designation of the nominal target for the dose specification;
2. A description of the loading of the sources in the applicator, specifying the source strengths;
3. The dose rate for the application; and
4. Duration of the insertion (total dose = dose rate *x* duration).

The treatment plan should be independently reviewed by a physicist or medical dosimetrist not involved with the generation of the treatment plan and the physician and should include checks on the following:

1. That the information on dosimetry input is correct and consistent;

2. That the dose and dose specification location match the treatment prescription and that the treatment prescription follows the institution's protocol for treatment of patients with cancer of the cervix;
3. That the dose distribution achieved matches the desired distribution, given any physical constraints, such as dose-limiting structures;
4. That the reconstructed implant geometry matches radiographic projections;
5. That doses to normal structures remain within tolerances; and
6. That the source strengths and locations match those on the plan.

Part of the review screens the treatment plan for major errors through the use of some objective criteria. The report presents some examples of consistency tests for both the intracavitary and interstitial approaches. These tests compare quantities specific to the patient (such as integrated reference air kerma) with a table of the ranges for the quantity normally encountered with correct treatment plans.

The following measures assist in controlling the quality of the application:

- A visual inspection of applicators before sterilization, to ensure that all components are present and in good working condition;
- A visual inspection of applicators in operating room before insertion to confirm the above;
- Intraoperative ultrasound in the case of a suspected uterine perforation;
- Intraoperative radiograph/fluoroscopy for applicator positioning and modification of applicator position or change of applicator, if necessary.
- Preoperative and postoperative checks to ensure that the correct sources are loaded into the patient at the beginning and unloaded from the patient at the end of the application and correctly accounted for.

Interstitial implantation

Indications

The ABS recognizes that intracavitary brachytherapy is the standard technique for brachytherapy for cervical carcinoma. The ABS recommends use of interstitial brachytherapy for cases in which the use of intracavitary brachytherapy is expected to result in a suboptimal dose distribution. Furthermore, precise needle placement is necessary to fully encompass the tumor while avoiding critical normal structures. Indications for consideration of interstitial implantation for cervical carcinoma include the following:

1. Extensive parametrial involvement,
2. Bulky primary disease,
3. Narrow or distorted vagina,
4. Inability to insert a tandem into the endocervical canal,
5. Post-hysterectomy recurrences, cut-through hysterectomy, or cervical stump presentations,
6. Prior course of radiation therapy to the area of interest,
7. Distal vaginal involvement or extensive vaginal involvement ($>$0.5 cm thick), and
8. Persistent disease after external beam and intracavitary implantation.

Generally, external beam irradiation is given first to reduce the tumor bulk, followed by a single interstitial implant within a week of completion of the external beam irradiation. The dose recommendations are given in Table 2.

Applicators

The ABS recommends the use of a template applicator for interstitial cervical implants. A number of applicators are available. The two most widely used template systems for interstitial implantation of perineal tumors include the Martinez Universal Perineal Interstitial Template (MUPIT) (94–100) and the Syed-Neblett system (101–104). Both have an intracavitary as well as an interstitial component. The ABS acknowledges that the choice of template may vary among institutions.

Insertion

Standard publications provide details of insertion procedures and outcome results (94, 97–116). The following guidelines for interstitial cervical implants are recommended by the ABS.

1. Epidural anesthesia is preferred for needle insertion (117, 118). Epidural anesthesia provides pain control during needle insertion and is also used for postoperative pain management. General endotracheal anesthesia is necessary if laparoscopy or laparotomy is used to guide needle placement. In these cases, effective perioperative pain management can be obtained by patient-controlled analgesia.
2. A pelvic examination under anesthesia is performed to assess the dimensions of the tumor and its relationship to the uterus and other pelvic organs.
3. Intraoperative antibiotics, as well as postoperative antibiotics, are administered during the implant when indicated.
4. Radiopaque markers should be placed in the cervix and/or at the superior and inferior boundaries of the vaginal lesion of interest as reference points for future imaging.
5. Use of a central tandem is controversial and can be associated with central hot spots (104, 105, 108–112) (Consensus Level 2). A guide needle can be inserted into the cervical os (in the center of the vaginal cylinder) if a tandem cannot be placed in the endocervical canal. Careful consideration of differential source strengths and loading patterns in the tandem, on the vaginal surface, and in the remainder of the template positions is essential to minimize complications.
6. Needles should not be placed in direct contact with the vaginal mucosa (104, 105, 109–111) (Consensus Level 2). If needles must be inserted on the surface of the Syed vaginal obturator, a "sleeve" should be placed over the obturator needles, or the needles should be recessed into the obturator grooves to prevent their

direct contact with the vaginal mucosa (119) and lower activity sources used.

7. Closed-tipped needles with a funneled proximal end are used to reduce the risk of infection and to make source loading easier. Plastic flexiguide needles should be used with caution. Bent and broken needle tips have been reported.
8. Needles must be inserted beyond tumor both laterally and in a cephalocaudal direction to adequately cover the tumor volume. Alternatively, differential loading of sources within each needle (with higher activity on each end) can be used.
9. Template holes nearest the bladder and rectum (the 11, 12, 1, 5, 6, and 7 o'clock positions of the 2-cm-radius and 3-cm-radius rings) (112) should not be loaded with active sources in the Syed template unless there is vesicovaginal, rectovaginal septal, or urethral involvement with tumor.
10. Anterolateral needle holes should not be used if interference from the pubic bones causes severe deviation ($>$1 cm) of the needles.
11. Posterior needles should be placed under digital rectal guidance.
12. Needles may be inserted under guidance of fluoroscopy, CT scan, transabdominal ultrasound, transrectal ultrasound, laparoscopy, or laparotomy (115, 120–127). Laparoscopy or laparotomy guidance is especially helpful in post-hysterectomy patients in whom bowel adherence to the vaginal cuff may be repositioned intraoperatively (124, 126) (Consensus Level 2). Preplanning with MRI or CT may be helpful (125).

Localization for dosimetry

The same localization recommendations that apply for intracavitary brachytherapy also apply for interstitial implants. Additional localization considerations for interstitial implants include the following:

- For implants with multiple needles, dummy ribbons with unique sequences of dummy seeds of different sizes that are imaged radiographically while they are loaded in some of the needles greatly help the process of source position reconstruction. To achieve clarity of seed images and optimal accuracy in seed position reconstruction, every attempt should be made to position the patient so that the applicator/needles are parallel to the gantry axis of rotation (i.e., longitudinal axis of the couch).
- The source position reconstruction algorithm should be able to check for patient movement during acquisition of the radiographs and quantify the localization error. Accuracy within 0.2 cm is readily achievable with careful seed location identification and digitization. Failure to achieve this degree of accuracy should prompt reevaluation of the implant geometry reconstruction procedure.

Dose specification

The ABS recommends prescribing the implant dose to the minimum target dose as defined in ICRU Report #58 (90). For these implants, the target is taken as the volume defined by the peripheral needles. The ABS recommends using minimum target dose rates between 0.5 and 0.7 Gy/h. Source strengths to achieve these rates depend on the size of the implant (number of needles and treatment length along the needle), shape of the implant volume, and the spacing between sources. Serious complications have been reported when excessive dose inhomogeneity occurs (103). The maximum significant dose (MSD) can be used to evaluate the dose uniformity. The ABS takes the MSD as the highest isodose curve that encompasses three or more contiguous needles. The ABS recommends that the MSD not exceed 125% of the prescribed dose.

The spacing between source centers may be 0.5 or 1.0 cm. The actual value of source spacing affects the uniformity of the dose distribution. Tests of alternative source spacing for typical implants should be performed to determine which spacing is optimal for a given institution's applicators and techniques. In general, with 1-cm needle spacing, the source strength for interior needles should be about twice that of the peripheral needles.

Sources for the implant can be ordered either before the procedure, based on treatment plans determined by the physician's expectation, or after the procedure, based on dose calculations from localization films. The former has the advantage that the patient need not stay as long in the hospital, whereas the latter allows customization of the source order based upon the actual implant. The ABS deems this to be an institutional preference.

If the tandem is loaded with ^{137}Cs, the obturator surface needles should not be loaded, to prevent central hot spots. The activity of ^{129}Ir in the peripheral needles should be greater (approximately twice) than that of the inner needles.

Optimization

For large implant volumes, using a uniform strength for all sources would produce an unacceptably high dose rate in the middle of the implanted volume. Furthermore, source strengths should be selected in such a manner that the prescribed dose rates fall within the given recommendations. The considerations below assume the use of approximately 3-mm-long ^{192}Ir sources in plastic tubes afterloaded into template needles. The use of radioactive iridium wire, although common in Europe, is rarely encountered in North America.

For all applications, the inner needles (those surrounded by other needles) should use source strengths of approximately one-third to one-half of those in the periphery. Source strength determination along the needle is dependent upon the applicator used. One approach sets all source strengths in a given needle to the same value. In this case, the dose falls below the prescription level within the active length of the needle. Compensation for dose falloff requires inserting the needles beyond the target. The insertion depth must also account for the space between the physical needle tip and the end-most source, usually a distance of 0.7 to 1 cm. The actual extension of the source train beyond the target is obtained from computed isodose distributions. An-

other approach weights the source strengths more heavily on the ends of the needles. In this case, the end sources remain within the target volume, because the treatment isodose surface projects beyond the source train. The actual distance from the center of the end source to the edge of the target is obtained from the computer-generated dose distribution. In general, the end source strength is approximately two to three times that of the sources in the middle of the source train.

Dose reporting

The ABS recommends reporting the following parameters for interstitial implants:

1. The prescription, including the prescribed dose, dose rate, implant duration, radionuclide used, sources' strengths, and loading pattern;
2. The type of applicator used;
3. The volume encompassed by the prescribed isodose surface;
4. The MSD; and
5. Rectal and bladder doses, if assessed.

Quality management

All quality management considerations discussed for intracavitary implants apply to interstitial implants.

Future considerations: Image-based treatment planning

Current imaging technology for intraoperative guidance of applicators and/or needle placement with real-time dosimetry is in its infancy for cervical cancer (128). Applicators that are compatible with the imaging modality must be used (129). With the exception of interstitial brachytherapy of prostate and cervix cancer, for which on-line two-dimensional or three-dimensional transrectal ultrasound devices are available, standard brachytherapy is usually performed without image guidance. In the future, the developments and refinements in imaging technology will heavily influence the practice of brachytherapy (130). Magnetic resonance–based localization and cone beam reconstruction are examples of this trend. Flat-panel technology may replace bulky and cumbersome image intensifiers, improving the quality and speed of image acquisition. Cone beam CT scanners mounted on a C-arm may be used to provide intraoperative applicator or needle guidance. Full three-dimensional dosimetry systems for brachytherapy will allow (*a*) intraoperative evaluation of target volume coverage and dose, (*b*) assessment of normal-tissue dosages, and (*c*) intraoperative assessment of implant quality. It is important to correlate the three-dimensional dosimetry (specifically the isodose line that encompasses the gross tumor volume based on CT or MRI) with tumor control outcome (131–132).

CONCLUSION

The ABS has established guidelines for LDR brachytherapy for cervical cancer. The responsibility for medical decisions ultimately rests with the treating radiation oncologist. Practitioners and cooperative groups are encouraged to use these recommendations to formulate treatment and dose-reporting policies.

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