BRACHYTHERAPY

Task Group/Practice Parameter

American Brachytherapy Society: Brachytherapy treatment recommendations for locally advanced cervix cancer for low-income and middle-income countries

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ABSTRACT

PURPOSE: Most cervix cancer cases occur in low-income and middle-income countries (LMIC), and outcomes are suboptimal, even for early stage disease. Brachytherapy plays a central role in the treatment paradigm, improving both local control and overall survival. The American Brachytherapy Society (ABS) aims to provide guidelines for brachytherapy delivery in resource-limited settings.

METHODS AND MATERIALS: A panel of clinicians and physicists with expertise in brachytherapy administration in LMIC was convened. A survey was developed to identify practice patterns at the authors' institutions and was also extended to participants of the Cervix Cancer Research Network. The scientific literature was reviewed to identify consensus papers or review articles with a focus on treatment of locally advanced, unresected cervical cancer in LMIC.

RESULTS: Of the 40 participants invited to respond to the survey, 32 responded (response rate 80%). Participants were practicing in 14 different countries including both high-income (China, Singapore, Taiwan, United Kingdom, and United States) and low-income or middle-income countries (Bangladesh, Botswana, Brazil, India, Malaysia, Pakistan, Philippines, Thailand, and Vietnam). Recommendations for modifications to existing ABS guidelines were reviewed by the panel members and are highlighted in this article.

CONCLUSIONS: Recommendations for treatment of locally advanced, unresectable cervical cancer in LMIC are presented. The guidelines comment on staging, external beam radiotherapy, use of concurrent chemotherapy, overall treatment duration, use of anesthesia, applicator choice and placement verification, brachytherapy treatment planning including dose and prescription point, recommended reporting and documentation, physics support, and follow-up. © 2016 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords: Cervix cancer; Brachytherapy; Global oncology; Low-resource setting; Consensus guidelines

Introduction

Cervical cancer is a large and growing problem in low and middle-income countries (LMIC). Cervical cancer is the fourth most common cancer diagnosed in women worldwide with nearly 530,000 cases diagnosed in 2012 (1). Of these, nearly 85% occurred in LMIC. The burden is disproportionately large in LMIC in part due to limited screening, lack of the human papilloma virus (HPV) vaccination, and co-infection with viruses predisposing to HPV infection, such as human immunodeficiency virus (HIV). In addition to the high burden of disease, a disproportionate number of cervical cancer deaths—nearly 90%—occur in LMIC (1). Due to lack of screening and public health awareness of cancer symptomatology, many women present with advanced stage disease (2). Timely access to appropriate cancer care may also be limited in many LMICs (3).

Cervical cancer treatment is stage dependent and often includes surgical resection, chemotherapy, radiotherapy, or a combination of these treatments (4). Cervical cancer is curable, even with locally advanced disease, and therefore the importance of stage-appropriate treatment cannot be underestimated. For locally advanced disease, concurrent chemoradiotherapy followed by brachytherapy has been the standard of care in the United States since the late 1990s when several clinical trials showing an improvement in survival with the addition of chemotherapy were published (5–8).

Brachytherapy is an essential part of cervical cancer treatment, as it allows the cervical tumor to be treated with very high-dose radiotherapy, while providing protection to the bladder, rectum, and sigmoid colon. Many studies have demonstrated improvements in local control and survival when incorporating brachytherapy as part of cervical cancer treatment paradigm (9–12). However, brachytherapy administration requires investment in equipment, as well as skills and expertise on the part of the radiation oncologist, physicist, and treatment team. Poor-quality brachytherapy implants have been shown to result in higher local recurrence (13). In the United States, most patients with intact cervical cancer receive brachytherapy as part of their cancer management plan (14). In countries that lack external beam facilities, brachytherapy alone may be the only curative option available. Brachytherapy advances in recent years have focused on using advanced imaging such as magnetic resonance imaging (MRI) to improve tumor localization and enhance treatment planning. However, high-quality brachytherapy can be delivered even in the absence of advanced imaging modalities (15).

The American Brachytherapy Society (ABS) has previously published articles on proper brachytherapy administration for locally advanced cervical cancer (16, 17). However, these guidelines are not intended for use in LMIC with limited radiotherapy resources. Given the high burden of cervical cancer in these countries, as well as the disproportionately poor outcomes from cervix cancer (18), there is an urgent need to improve treatment availability and delivery. The International Atomic Energy Agency has issued a primer for radiation oncologists on management of cervical cancer in resource-limited settings (19). In addition, the National Comprehensive Cancer Network and the American Society for Clinical Oncology have issued guidance of management of cervix cancer in resource-limited settings (20, 21), however, these do not address brachytherapy specifically. The ABS aims to provide recommendations for brachytherapy administration for cervical cancer in resource-limited settings.

Methods

The 2012 ABS recommendations were reviewed by clinicians with expertise in radiotherapy and brachytherapy administration in LMIC. A survey was developed to identify practice patterns at the authors' institutions and was also extended to participants of the Cervix Cancer Research Network meeting held in Bangkok, Thailand in January, 2016. Of the 40 participants invited to respond to the survey, 32 responded (response rate 80%). The survey represents 14 different countries including both high-income (China, Singapore, Taiwan, United Kingdom, and United States), and low- or middle-income countries (Bangladesh, Botswana, Brazil, India, Malaysia, Pakistan, Philippines, Thailand, and Vietnam). Furthermore, the scientific literature was reviewed to identify consensus papers or review articles with a focus on treatment of locally advanced, unresected cervical cancer in LMIC. Recommendations for modifications to existing guidelines were reviewed by the panel members. The specific recommendations outlined in this article represent the consensus opinion of the panel members. This report was reviewed and approved by the Board of Directors of the ABS.

Results

Staging

The ABS recommends appropriate staging, defined as documentation of disease extent and volume. In addition to clinical examination, imaging modalities such as computed tomography (CT), MRI, and positron emission tomography (PET)/CT can be useful to understand the full extent of local and distant disease. However, in many resource-constrained settings, advanced imaging modalities are not available. Many centers use ultrasound for staging when cross-sectional imaging is not available. Clinical staging using the International Federation of Gynecology and Obstetrics (FIGO) version 2009 is appropriate. The FIGO staging system incorporates disease extent gleaned from clinical examination, cystoscopy, and proctoscopy/sigmoidoscopy when bladder or rectal

Table 1
Modifications from ABS 2012 consensus guidelines for practice in resource-limited settings (RLSs)

	ABS 2012 consensus guideline recommendation	Guideline modification for RLSs
Total treatment time (EBRT + brachy)	8 weeks	No modification
Concurrent chemotherapy	Weekly, cisplatin-based chemotherapy × 5—6 weeks Weekly testing of CBC including differential and chemistries	Concurrent chemotherapy: most often weekly cisplatin; however, other agents may be used such as 5-FU or paclitaxel
Imaging	Use 3D imaging (CT, ultrasound, and/or MRI) to obtain measurements of tumor size, volume, and extent of disease. PET for lymph node evaluation	Use 3D imaging if available (CT, ultrasound, or MRI)
Anesthesia	Sedation to general anesthesia	If sedation or general anesthesia are not available, oral pain medication plus anxiolytic can be used
Optimization	Start with customary loading of full tandem and vaginal applicator then modify dwell positions/times to reduce dose to OAR and ensure maximal tumor coverage	Start with customary loading of full tandem and vaginal applicator then modify dwell positions/times to reduce dose to OAR and ensure maximal tumor coverage. In some settings, library plans may be used
Prescription point	Volume or point A	No modification
EQD2 conversion worksheet	Yes	Yes, if 3D planning available
Dose	45 Gy external beam to whole pelvis followed by 5.5—6 Gy × 5 (most commonly used regimen in the United States); EQD2 80—90 depending on response to CRT. Technique for EBRT is 4-field with custom blocking. 60—70 Gy to enlarged lymph nodes	40—45 Gy external beam to whole pelvis and a minimum EQD2 of 80 Gy; 4-field plan with blocking preferred, but 2-field plan can be used
OARs	DVH values calculated for each fraction, so final dose of bladder, rectum, sigmoid is calculated	DVH or point doses encouraged. ICRU 38 bladder and rectum should be <75 Gy. D2cc for bladder and rectum should be < 90 and 75 Gy, respectively.
Boosts	Pelvic sidewall and involved lymph nodes	Pelvic sidewall and involved lymph nodes, if 3D planning available
Protocol consistency	Documentation of insertion, planning parameters including normal tissue dose, treatment, and f/u	No modification
Verification of treatment plan	Verified by brachytherapy physicist not involved in planning - Dose matches prescription - Treatment unit, applicator, radionuclide match prescription - Applicator and dwell positions correctly located in patient - Reference distance from treatment device to most distal dwell position is consistent with applicator in use - Individual dwell times and total treatment time consistent with plans of similar type, taking radionuclide decay into account	Performed by one experienced practitioner - Dose matches prescription - Treatment unit, applicator, radionuclide match prescription - Applicator and dwell positions correctly located in patient - Reference distance from treatment device to most distal dwell position is consistent with applicator in use - Individual dwell times and total treatment time consistent with plans of similar type taking radionuclide decay into account
Pre-treatment verification	Checked by physicist - Correct patient information entered into treatment device - Per-fraction dose consistent with prescription - Dwell times (compensated for radioactive decay), dwell positions, and step size programmed into treatment device consistent with plan - Channel numbers connected via transfer tubes to applicator are consistent with catheter numbers of plan	Checked by one experienced practitioner - Correct patient information entered into treatment device - Per-fraction dose consistent with prescription - Dwell times (compensated for radioactive decay), dwell positions, and step size programmed into treatment device consistent with plan - Channel numbers connected via transfer tubes to applicator are consistent with catheter numbers of plan
Procedure checklist	- Consent in chart - IV access obtained - Anesthesia administered - Examination under anesthesia - Dilation of cervical os - Smit sleeve placement preferred - Applicator placement - Packing - Imaging (CT, MRI, plain radiographs) - Prescription—generally 5.5 Gy × 5 fractions - Treatment planning - Documentation of OAR doses - QA checks - Treatment delivery	- Consent in chart - Anesthesia or oral pain medication/anxiolytic administered - Examination under anesthesia - Dilation of cervical os - Applicator placement - Packing preferred - Image verification of applicator placement. Use ultrasound or plain films if CT or MRI not available. - Prescription—hypofractionated regimens acceptable - Treatment planning - Documentation of OAR doses - QA checks - Treatment delivery - Documentation of treatment administered

(Continued)

Table 1 (*continued*)

	ABS 2012 consensus guideline recommendation	Guideline modification for RLSs
	- Documentation of treatment administered - Applicator removed - Post-treatment care including follow-up	- Applicator removed - Post-treatment care including follow-up when feasible
Applicator types	Interstitial Tandem and cylinder Tandem and ring Tandem and ovoids Tandem and ring or ovoids with short interstitial needles	Tandem and ovoids Tandem and cylinder Tandem and ring Tandem and ring or ovoids with short interstitial needles
Applicator insertion	- Dorsal lithotomy position - Rectal tube - Foley catheter - Uterine sound - Ultrasound guidance if needed - Antibiotics for uterine perforation - Cervical dilation with Smit sleeve placement - Packing/retractors - Bladder contrast	- Dorsal lithotomy position - Cervical dilation - Foley catheter - Uterine sound - Ultrasound guidance if needed - Antibiotics for uterine perforation - Packing/retractors encouraged
Prescription	- Target, target dose, dose per fraction, fractionation plan - Type of isotope, source used for delivery of treatment - Treatment plan including dose distribution and critical organ dose limits - Applicator type and size features	No modification
Treatment planning	Should be performed for each fraction	Ideally performed for each fraction
Recommended reporting and documentation in medical record	- Type of applicator used - Prescription including dose per fraction and total dose to designated points - Dose to point A - Total reference air kerma of radionuclide used - Loading pattern (dwell pattern and times) - D90, D100, V100 if image-based planning used - Dose to ICRU rectal and bladder points - Isodose distributions in sagittal, coronal, and axial planes - Dose at lateral vaginal mucosa and 0.5 cm depth - Patient identification performed - Transfer tube inspection performed - Patient set-up verified - Application position verified - Prescription reviewed and signed by treating physician - Radiation safety check by physicists performed	- Type of applicator used - Prescription including dose per fraction and total dose to designated points - Dose to point A - Dose to ICRU rectal and bladder points - Patient identification performed - Transfer tube inspection performed - Patient set-up verified - Application position verified - Prescription reviewed and signed by treating physician - Radiation safety check by trained personnel performed
Follow-up	Pelvic examination and Pap smear every 3 months for 2 years, then every 6 months for 3 years, and then annually thereafter. PET/CT 3 months after treatment	Pelvic examination at 3 months, then every 6–12 months until year 3, and then annually thereafter.

CBC = complete blood count; CRT = chemoradiotherapy; DVH = dose volume histogram; EBRT = external beam radiotherapy; CT = computed tomography; ICRU = International Commission on Radiation Units; MRI = magnetic resonance imaging; OAR = organs at risk; PET = positron emission tomography.

invasion is suspected. When available, cross-sectional imaging and information from pathologic staging should be incorporated into treatment decision-making. Recommendations for imaging in resource-limited settings are provided in Table 1.

Recommendation

Histopathologic confirmation of cervical cancer diagnosis is necessary. Clinical staging should be completed as per FIGO version 2009 using clinical examination, cystoscopy and/or proctoscopy/sigmoidoscopy for concern of bladder or rectal invasion based on clinical symptoms, transabdominal ultrasound for evaluation of the kidneys and/or pelvic or para-aortic lymphadenopathy, transrectal ultrasound for evaluation of parametrial invasion, and chest x-ray for distant metastatic disease evaluation. If available, advanced imaging with CT, PET/CT, or MRI can be used to characterize disease extent; although the results of these studies will not change clinical stage, the information should be incorporated into treatment planning.

External beam radiotherapy

For locally advanced disease confined to the pelvis, the ABS recommends external beam radiation using a four-field isocentric technique with custom blocking to a dose of

45 Gray (Gy) in 1.8 Gy fractions. In our survey (Table 2), we found that many centers are either using hypofractionation or dose reduction with regimens such as 40 Gy in 2 Gy per fraction or dose escalating to 50—50.4 Gy in 1.8—2 Gy per fraction. Most centers have the capacity to use CT for simulation and treatment planning; however, not all centers have custom blocking or multileaf collimators to block normal structures. When possible, custom blocking is recommended to reduce normal tissue toxicity; however, midline block is not recommended due to the potential to underdose the gross tumor.

Adequate dose delivery to the primary tumor and pelvic lymph nodes is crucial; therefore, every attempt should be made to reach a target dose of 45 Gy in 1.8 Gy fractions. Although hypofractionation may be entirely appropriate for definitive radiotherapy and may improve resource utilization and clinical workflow, data demonstrating the safety and efficacy of this approach are limited. One study of 17 patients treated with palliative intent using 20—25 Gy in five fractions has been reported. Response rates and control of symptoms including bleeding and pain were high, and toxicity was limited; however, patients were not treated with definitive intent (22). Another prospective study from Nigeria compared 50 Gy administered in 15 fractions three times a week to 50 Gy in 25 fractions administered daily. They found similar local control and overall survival; however, late toxicity was higher in the patients that underwent hypofractionation (23). Prospective clinical trials to study hypofractionation in this setting are in development (24).

Recommendation

The recommended external beam radiotherapy (EBRT) dose is 45 Gy in 1.8 Gy fractions or 40 Gy in 2 Gy fractions. Hypofractionated regimens are not recommended at this time. A 4-field technique is optimal; however, a 2-field approach can be used if needed in a patient without large anterior to posterior separation. Custom blocking should be used when available; however, an acceptable alternative is use of corner shields to reduce dose to the bladder, rectum, and small bowel. The use of a midline block is not recommended. CT-based planning is strongly encouraged. For centers without CT-based planning, field design should be based on bony landmarks as seen on fluoroscopy.

Chemotherapy

The ABS recommends administration of concurrent chemoradiotherapy on the basis of several randomized clinical trials showing an improvement in overall survival. For small tumors less than 4 cm in size, radiotherapy alone can be administered at the discretion of the treating physician. Concurrent weekly cisplatin is the most commonly used regimen in the United States, however alternative options include cisplatin administered every 3 weeks, cisplatin and 5-FU administered every 3 weeks, or weekly carboplatin, paclitaxel, and/or hydroxyurea (21). Sequential treatment (radiotherapy followed by chemotherapy) may improve local control and overall survival as compared to radiotherapy alone but is not as effective as concurrent chemoradiotherapy (25). The proportion of patients in our surveyed centers receiving concurrent chemotherapy with radiotherapy ranged from 60% to 95%. In some centers, concurrent chemotherapy is initiated but not always administered during all 5 weeks of radiotherapy. All centers administering chemotherapy were able to check weekly laboratory results to monitor for hematologic toxicity.

Recommendation

Concurrent cisplatin-based chemotherapy is recommended while administering EBRT. For small tumors (<4 cm in size), chemotherapy can be used at the discretion of the treating physician. If cisplatin is not available, alternative chemotherapy regimens can be used. At a minimum, white blood cell count should be checked during chemoradiotherapy. If concurrent chemotherapy cannot be administered due to patient performance status, medical comorbidities including obstructive uropathy or lack of availability of chemotherapy, radiotherapy alone is appropriate. Radiotherapy should not be delayed to administer concurrently with chemotherapy.

Overall treatment duration

The ABS recommends total treatment duration of 8 weeks for external beam radiotherapy and brachytherapy, as a 1% per day decrease in local control, and survival has been noted with extended treatment courses (26—29). In our surveyed centers, 80%—98% of patients are able to complete their course within 8 weeks. Every attempt should be made to complete treatment in the 8-week time frame; however, treatment with EBRT and brachytherapy should still be administered even if treatment prolongation is required to accomplish this. More modern data suggest that the addition of chemotherapy to radiotherapy and the use of high dose rate (HDR) brachytherapy instead of low dose rate (LDR) brachytherapy may reduce the effect of treatment prolongation (30, 31).

Recommendation

Every attempt should be made to complete radiotherapy treatment (EBRT + brachytherapy) in an 8-week time frame. With very large primary tumors, it may be beneficial to complete EBRT before initiation of brachytherapy to allow for maximal tumor shrinkage and optimal implant geometry. In these cases, brachytherapy treatments should be scheduled twice weekly if possible.

Anesthesia

Medication for pain control is recommended to allow for optimal applicator placement. Various types of pain control including general anesthesia, spinal anesthesia, intravenous conscious sedation, and/or oral pain medication are

Table 2
Survey responses

Question	Response
General information	
Number of countries represented	15
Number of cases per year	Mean 229
	Median 140
	Range 6−1000
Number of radiation oncologists	Mean 5
	Median 4
	Range 1−18
Number of physicists	Mean 7
	Median 5
	Range 1−16
Number of dosimetrists	Mean 3
	Median 1
	Range 0−8
Number of oncology nurses	Mean 6
	Median 4
	Range 0−30
Number of medical assistants	Mean 4
	Median 3
	Range 0−20
Management paradigms	
Diagnostic evaluation/staging[a]	92% CT
	38% ultrasound
	71% MRI
	21% PET/CT
Proportion receiving concurrent CRT	60%−100%
Weekly laboratory results reviewed	100%
Proportion completing CRT in ≤8 weeks	80−98%
EBRT dose/fractionation	3% 30 Gy in 15 fractions (2 Gy/fraction)
	13% 40 Gy in 20 fractions (2 Gy/fraction)
	31% 45 Gy in 25 fractions (1.8 Gy/fraction)
	6% 46 Gy in 23 fractions (2 Gy/fraction)
	13% 50 Gy in 25 fractions (2 Gy/fraction)
	28% 50.4 Gy in 28 fractions (1.8 Gy/fraction)
	6% Other
Brachytherapy practices	
Anesthesia use	9% No anesthesia
	25% Oral or inhaled medications
	66% IV/spinal/general
Prescription point	33% Point A
	25% Volume
	21% Combination
	21% Varies depending on case
Brachytherapy dose/fractionation	4 Gy × 6 fractions
	5.5 Gy × 5 fractions
	6 Gy × 4 fractions
	6.5 Gy × 4 fractions
	6 Gy × 5 fractions
	7 Gy × 3 fractions
	7 Gy × 4 fractions
	8 Gy × 3 fractions

(Continued)

Table 2 (*continued*)

Question	Response
EQD2 conversion worksheet used	58% Yes
	30% No
	12% Other
Brachytherapy verification by physicist not involved in planning	54% Yes
	42% No
	4% Other
Ultrasound guidance routinely used	29% Yes
	38% No
	33% Other (i.e., when placement is difficult)
Uterus sounded	83% Yes
	17% No
Smit sleeve placed	4% Yes
	88% No
	8% Other (i.e., used occasionally)
Foley catheter	96% Yes
	4% No
Bladder contrast used	75% Yes
	25% No
Packing or retractors used	97% Yes
	3% No
Image verification	23% X-ray
	3% Ultrasound
	64% CT
	10% MRI
Treatment planning before each fraction	92% Yes
	8% No
Organ-at-risk dose reporting	33% Point dose
	29% Volume-based dose
	38% Both

CRT = chemoradiotherapy; EBRT = external beam radiotherapy; CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography.

[a] Answer choices are not mutually exclusive.

considered acceptable by the ABS. In our survey study, we found that nearly all centers used some form of anesthesia, ranging from oral pain medication and anxiolytics to general anesthesia. Patients receiving general anesthesia should be evaluated by an anesthesiologist or practitioner with expertise in sedation.

Recommendation

Pain control using general or spinal anesthesia, or IV conscious sedation, is recommended with oversight of anesthesiology. If these modalities are not available or the patient is considered high risk for IV anesthesia, an oral pain medication and anxiolytic should be provided before brachytherapy insertion. Suboptimal pain control can lead to poor applicator placement and resulting poor dose distribution.

Applicator choice, insertion, and placement verification

There are several choices for applicators including tandem and cylinder, tandem and ring, tandem and ovoids, one of the above plus interstitial needles, or interstitial

application. In our survey, all centers using brachytherapy have tandem and ovoids, tandem and cylinder, or tandem and ring; however, the availability of interstitial implants was limited. Most centers are using Foley catheters during implant placement; however, rectal tube use is uncommon. In most centers in our survey, the uterus was sounded for each intracavitary application. Smit sleeves were not routinely used; therefore, the cervical OS was dilated for each fraction. All centers used either retractors or radio-opaque contrast-soaked materials to pack the bladder and the rectum away from the implant.

After insertion, applicator placement was confirmed by orthogonal x-rays, CT, or MRI. Two centers reported using transabdominal or transrectal ultrasound to verify placement of the applicator. Among centers using MRI, the majority use MRI for the first fraction only. Proper applicator placement is critical; however, some centers have no imaging capability for confirmation of applicator placement. In these centers, the use of fixed applicator configurations and library-based treatment plans can minimize the need for imaging (15). If 2D imaging is available, radio-opaque applicators should be used, and imaging should be performed to verify applicator geometry and identify points of interest (point A, bladder point, rectal point). Criteria for adequate implant placement are as described in the ABS guidelines: (16, 17)

- 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
- 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.

The use of transabdominal and transrectal ultrasound for confirmation of applicator placement, as well as treatment planning, may be comparable to CT and MRI in experienced hands (32−37). Once the applicator has been placed, transabdominal ultrasound can be used to define the target volume in the sagittal and axial planes. These ultrasound images can then be imported in the treatment planning system for radiotherapy planning. Advantages of using transrectal ultrasound for imaging include cost effectiveness and near universal availability.

Recommendation

A variety of applicators can be used depending on patient anatomy and tumor geometry. The uterus should be sounded before insertion to avoid uterine perforation. Ultrasound should be used to guide tandem placement if insertion is challenging, and in cases where other cross-sectional imaging is not performed to confirm placement in the uterus. Some form of retractors or radio-opaque contrast-soaked gauze to pack the bladder and the rectum should be used. In centers without imaging capability, fixed geometry applicators should be used with plan selection from a library of available options. If 2D imaging or 3D imaging is available, CT and/or MRI compatible, radio-opaque applicators should be used.

Treatment planning

Advances in imaging have allowed for 3D tumor and normal tissue contouring for treatment planning. Initial reports have indicated excellent outcomes from this approach (38−40). The GEC−ESTRO guidelines have provided a detailed approach to contouring which is used by many clinicians (41). In many low-resource settings where 3D imaging, and in some cases 2D imaging, is not possible at the time of applicator placement, volume-based contouring is not realistic. In addition, 3D planning is more costly and time-consuming. In our survey, some centers prescribed to point A as was historically done using the Manchester system (42). Most centers describe using a combination of point A, and volume-based planning where plans are devised according to point A prescriptions and modified if 3D imaging shows disease extending outside the high-dose region or dose to organs at risk exceeds tolerance.

Dose fractionation varied considerably by center. Many centers prescribed 21 Gy in three fractions (7 Gy per fraction) if administered with concurrent chemotherapy; otherwise, 28 Gy in four fractions for radiotherapy alone. Some centers reported using 27.5 Gy in five fractions (5.5 Gy per fraction). With the exception of 21 Gy in three fractions, these dose fractionation schemes corresponded to an EQD2 of 80−85 Gy. Given the high throughput in many centers in resource-limited environments, delivering three instead of five fractions is often more realistic and allows for treatment of a higher number of patients. However, late toxicity may be increased as number of fractions decreases (37). Many but not all centers use the EQD2 worksheet to calculate dose to the high-risk CTV and normal structures. It should be noted that the EQD2 worksheet used to calculate dose can be used with either 2D or 3D planning.

If 3D imaging capabilities are available, adherence to the GEC−ESTRO guidelines and use of an high risk CTV (HR-CTV) is encouraged. For brachytherapy planning, gross tumor volume (GTV), clinical target volume (CTV), and organ-at-risk structures should be contoured, and the dose volume histogram for each structure should be reviewed, along with the 3D isodose line or dose cloud visualization tools.

Recommendation

If 2D imaging is available, radio-opaque applicators should be used, and imaging should be performed to verify applicator geometry and identify points of interest (point A, bladder point, rectal point). If 3D imaging is available, volume-based planning can be performed. Another commonly used and acceptable alternative is planning to point A with modifications in loading made based on tumor volume and organ-at-risk doses. The use of CT imaging for treatment planning is strongly encouraged in centers with CT simulators. Common dose fractionation includes 8 Gy × 3, 7 Gy × 4, 6 Gy × 5, or 5.5 Gy × 5. In most cases, the minimum EQD2 should be 80 Gy. Small or rapidly responding tumors may require lower radiotherapy doses.

Recommended reporting and documentation

At many centers, the reporting recommended by ABS may need to be modified. At a minimum, the following items should be reported and documented in the patient's chart:

- Patient identification performed
- Transfer tube inspection performed
- Patient set-up verified
- Application position verified
- Prescription reviewed and signed by treating physician
- Radiation safety check by physicists performed

Physics support

In prior publications, the ABS has recommended that two physicists not involved in the treatment of the patient and with specialization in brachytherapy planning evaluate the treatment plan before treatment administration. In our survey, most centers reported having one physicist with brachytherapy experience and/or expertise. In some centers, therapists with brachytherapy expertise provide quality-assurance checks. The ABS recommends that quality assurance be performed on every fraction administered to every patient. A ''best practices'' checklist should be developed and followed at each treating center.

Recommendation

Each fraction of brachytherapy administered should have quality assurance performed by at least one physicist, therapist, dosimetrist, or physician with training in brachytherapy quality-assurance paradigms and/or familiarity with the IAEA guidance on quality assurance. Even if treatment planning is not performed for each fraction delivered, quality assurance should still be performed before treatment delivery.

Follow-up recommendations

Follow-up frequency following the completion of chemoradiation is crucial to rule out disease recurrence and to manage treatment toxicity. In our survey, follow-up practices varied by region. Some centers follow-up at 3 months with a CT, MRI, and/or PET CT scan and subsequent clinical examinations thereafter. In other centers, follow-up is rarely performed. Follow-up can be challenging due to very high clinic throughput of new and on-treatment patients, as well as logistic challenges with patient transport. The ABS recommends follow-up for disease surveillance and toxicity assessment when possible. Three-dimensional imaging may be helpful for symptoms but is not required for routine surveillance.

Recommendation

Follow-up can be difficult in resource-limited environments due to constraints on physician time, patient availability, and resources for imaging. Nonetheless, follow-up is critical to catch early recurrences and address treatment toxicity. Follow-up clinical examination should be performed 3 months after the completion of chemoradiotherapy. If advanced imaging is available, it can be performed at this time period; however, this is not mandatory. After the initial follow-up visit, patients should be seen back every 6 months when feasible for a period of 3—5 years. In the absence of specific concerning symptoms or examination findings, imaging is not required at these follow-up visits.

Conclusion

The use of brachytherapy is an integral component of treatment for locally advanced, intact cervical cancer, the burden of which is disproportionately large in LMIC. The ABS has made recommendations for guidelines modification that are appropriate for use in resource-limited settings. Importantly, no one set of guidelines can uniformly fit all LMIC. There is likely to be substantial variation between high-income countries and LMIC—as well as variation between LMIC—in health beliefs, access to care, health environment, infrastructure, technology, and availability of physicians and support personnel required to successfully treat cervical cancer (43).

Importantly, several issues of high relevance to radiotherapy delivery in LMIC were outside the scope of this focused manuscript. Access to radiotherapy equipment and technology, including maintenance of existing machines and regular machine upgrades, was not discussed but is an important component to high-quality radiotherapy service. Additionally, training of personnel using brachytherapy equipment was not covered in this manuscript. Several training guidelines and programs are currently in existence through the IAEA, as well as partnerships between cancer centers in HIC and LMIC; however, improvement is needed in this area as well.

Extrapolating research and treatment paradigms from HIC for application in LMIC can sometimes be

problematic. In addition to investment in cancer control programs, an evidence base generated in LMIC is urgently needed to uniquely address issues related to cancer care in resource-limited environments. As this evidence base evolves, these guidelines can be expanded.

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