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REVIEW

Cervix Cancer Brachytherapy: Target Volume Determination

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SUMMARY

Concurrent chemoradiotherapy followed by brachytherapy (BRT) is the standard treatment for patients with locally advanced cervical cancer. Today, three-dimensional (3D) image-guided BRT (3D-IGBT) is the new standard. It improves local control, increases overall survival, and minimizes toxicity. Magnetic resonance imaging (MRI), ultrasound (US), computed tomography (CT), and positron emission tomography (PET)/CT can be performed in 3D-IGBT. In cervical cancers, MRI is considered the gold standard imaging modality. It also has been implemented into the cervix 3D-IGBT because of the excellent soft tissue contrast with clear definition of target volumes and easily identified organs at risk (OARs). This review summarizes imaging and volume definitions in 3D-IGBT of cervical cancer.

Keywords: Brachytherapy; cervix carcinoma; contouring; imaging; target volume.

Introduction

External beam radiotherapy (EBRT) with concurrent cisplatin-based chemotherapy followed by brachytherapy (BRT) is the standard treatment for patients with locally advanced cervical cancer.[1-3] Dose escalation and greater sparing of the surrounding organs at risk (OARs) can be achieved by using BRT technique, resulting in increased survival rates and reduced toxicity.[4] According to the Surveillance, Epidemiology, and End Results database, a significant survival advantage was observed in patients treated with EBRT and BRT compared with that in EBRT alone.[5]

Based on the improved dosimetric parameters and clinical outcomes in several studies, three-dimensional (3D) image-guided BRT (3D-IGBT) became the new standard in cervical cancer.[6-10] Target volumes and OARs can be delineated more accurately with 3D-IGBT. It accounts for the changes in tumor configuration during treatment or the changes in the position of the OARs as a result in the changing tumoral topography. Considering the volume and location of the tumor, dose can be increased in large residual tumors or more OARs can be protected in small residual tumors. Thus, local control and survival rates are improved, and morbidity is decreased.[6,11,12] However, 3D-IGBT requires a high level of experience, and it is often time consuming and expensive.

3D-IGBT in cervical cancer follows a standard six-step process: sedation and analgesia, pelvic examination and applicator insertion, imaging, contouring of target volumes and OARs, applicator reconstruction, and treatment planning and plan evaluation. This article summarizes imaging and volume definitions in 3D-IGBT of cervical cancer.

Imaging in Cervical Cancer

In cervical cancer, magnetic resonance imaging (MRI), ultrasound (US), computed tomography (CT), and positron emission tomography (PET)/CT are preferred imaging modalities.

In the evaluation of cervical cancers, MRI is considered the gold standard imaging modality. Tumor size and configuration have been proven to be more

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appropriately assessed by MRI than any other imaging procedure. It is used for staging, treatment planning, monitoring of treatment response, and follow-up. Better image quality; excellent soft tissue contrast; and better uterine, para-uterine tissues, cervix, and tumor differentiation are the most important advantages compared to CT.[13,14] MRI can also be used to perform functional imaging. Diffusion-weighted (DW) MRI has been applied to evaluate the cellular density and membrane integrity. Dynamic contrast-enhanced (DCE) MRI has been applied to evaluate the tumor microvasculature and perfusion (hypoxia).[14-16]

In particular, MRI has been implemented into the cervix 3D-IGBT procedure because of the excellent soft tissue contrast with clear definition of target volumes and easily identified OARs (Fig. 1). We can also assess the adequacy of the application and the presence of perforation.[17] All patients with cervical cancer should undergo MRI at diagnosis and at least just before the first fraction of BRT in addition to clinical examination for treatment planning.[17] Most commonly, 3T MRI is used for diagnostic imaging, and 0.2–1.5 T MRI is used for BRT planning. Multiplanar (transvers, sagittal, coronal, and oblique image orientation) T2-weighted (T2W) images with pelvic surface coils have been considered as the gold standard for delineating the topography of the tumor and the OARs. The use of an intracavitary coil is not recommended because it alters normal pelvic anatomy. Bowel preparation is optional prior to the MRI imaging. However, antiperistaltic agents, such as glucagon, are commonly used to minimize artifacts from bowel movements in BRT planning.[13] Vaginal contrast (e.g. US gel, gadolinium) allows for more accurate determination of vaginal extension, and it improves the ability to determine the extent of bladder or rectal invasion, if present.[17]

When using MRI for BRT planning as a radiation oncologist, we need to know 1) normal uterine cervix anatomy, 2) cervicouterine junction, and 3) topography and extension of parametrium.[18] The cervix, approximately 2–3 cm long, is the lowest part of the uterus situated between the endometrial cavity and vagina. It consists of fibromuscular structure and has supravaginal (endocervix) and vaginal (ectocervix) parts. The endocervical canal has high-signal intensity (hyperintense), cervical stroma has low signal intensity (hypointense), and smooth muscle has intermediate signal intensity in non-contrast T2W images.[19] The upper limit of the cervix extends to the uterine corpus like cone shaped, which corresponds to 5 mm above where the uterine arteries enter the uterus in non-contrast T2W images. On MRI, the parametrium appears as the fat signal intensity and extends anteriorly to the bladder, posteriorly to the perirectal or mesorectal fascia, medially to the tumor or cervical ring, and laterally to the pelvic wall or the medial edge of the internal iliac and obturator veins. Disruption of cervical stromal ring corresponds to the parametrial involvement on MRI (Fig. 1).[19]

Transabdominal US is usually used during the insertion procedure to assist the proper placement of an intrauterine applicator, in particular the suspicion of uterine perforation or in the presence of retrovert or excessive antevert uterus.[20] However, this technique is highly operator dependent. The role of US in contouring and treatment planning are areas of active investigation.[21,22] When used in conjunction with CT-based planning, it has also been shown to be equivalent to MRI-based planning.[23]

The CT scan may also be used in cervical cancer to verify applicator placement, and it ensures that the uterus has not been perforated (Fig. 2). However, soft tissue contrast is poor, and tumor extension is not truly assessed with this technique. Limitations of CT in 3D-IGBT can be eliminated by gynecological examination and MRI immediately before BRT.[24-27]

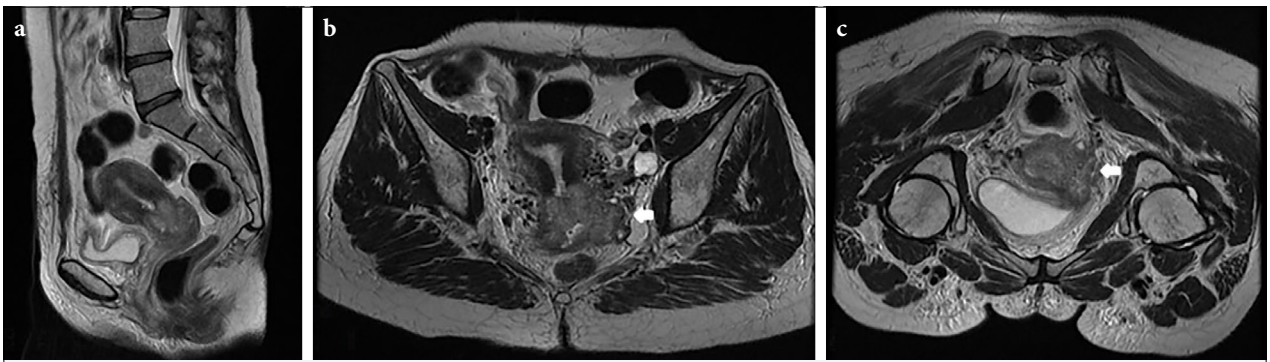

Fig. 1. A patient with a stage IIB cervical cancer with left parametrial involvement (white arrow). Sagittal (a), axial (b), and coronal (c) images of the T2W MRI showing cervical mass with normal uterus.

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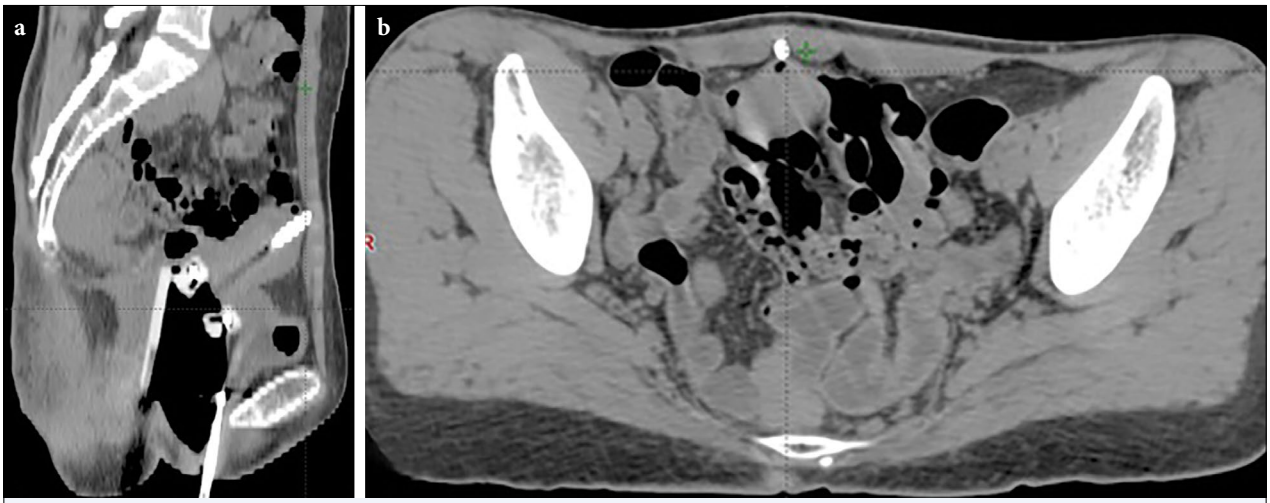

Fig. 2. Sagittal (a) and axial (b) CT images in a 34-year-old woman with stage IB2 cervical cancer show an uterine perforation at first fraction of BRT.

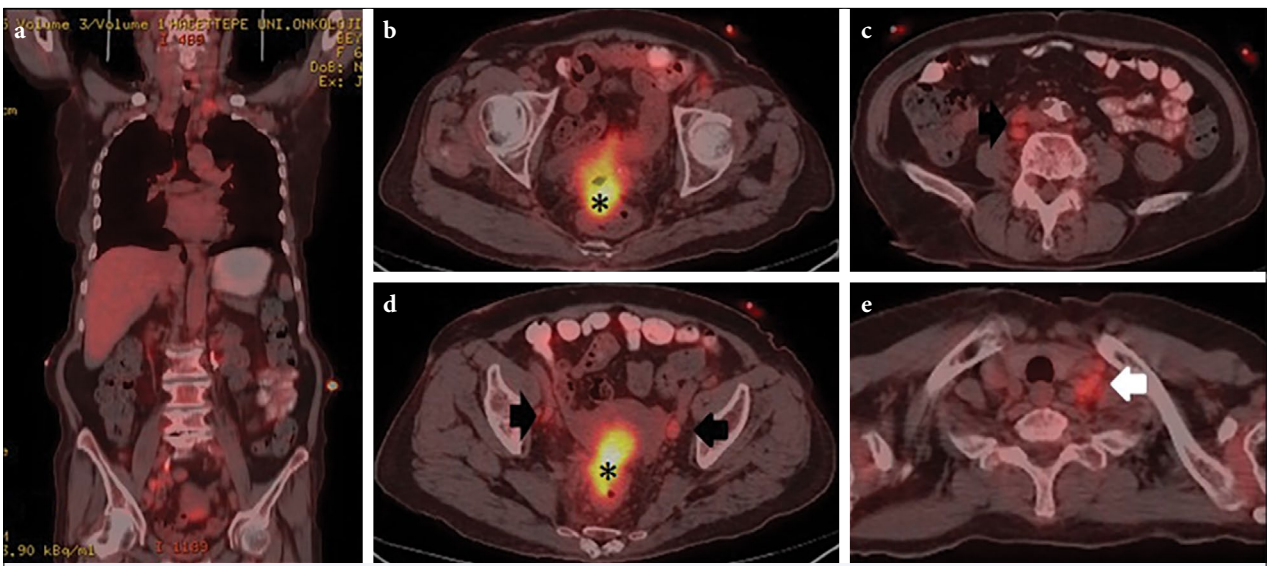

Fig. 3. Coronal (a) and axial (b-e) PET/CT images in a 70-year-old woman with a cervical mass (*) and supraclaviculary (white arrow), pelvic, and para-aortic lymph node metastases (black arrow) at diagnosis.

PET/CT is a functional imaging technique that provides metabolic information. It has been widely used in the evaluation of lymph node or distant metastases at diagnosis in cervical cancer (Fig. 3). It can also be used for RT treatment planning, predicting outcome, and assessing treatment response and surveillance.[28]

Target Volume Determination in BRT

The most important source of uncertainty in the 3D-IGBT procedure is related to the target volume delineation with a mean relative standard deviation of 8%–10% for the gross tumor volume (GTV) and high-risk (HR) clinical target volume (CTV), resulting in cumulative whole-treatment uncertainty of ±5 Gy.[29-31] Accurate delineation of target volumes has a direct impact on clinical outcomes, because an inadequate coverage of the GTV and CTV increases the rate of local recurrence.[32]

Target volume determination in 3D-IGBT is performed according to the gynecologic examination and MRI findings at diagnosis and at BRT. The Group Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) recommendations were developed to use a common

language for 3D-IGBT.[29,33] The first and most important step in target volume assessment is based on clinical examination.[26] As tumor configuration and topography change significantly during EBRT, repetitive gynecological examination is required.[34] GTV, vaginal extension of disease and parametrial involvement should be assessed in every examination, and 3D clinical drawings should be made.

3D-IGBT can be applied in three different ways: 1) MRI can be performed in each BRT fraction with an applicator in place, 2) MRI can be performed with an applicator in place only in the first BRT fraction combined with CT for succeeding fractions, and 3) MRI can be performed before BRT without an applicator in place and fusion can be performed with CT images. Pötter et al. showed that MRI without applicator before BRT had no additional benefit in stage IB tumors but sufficient and useful in limited stage IIB and IIIB cases.[35] In patients with large tumors and severe parametrial involvement, MRI should be performed with applicator.

a. MRI-Based Contouring

MRI is the gold standard technique for delineation of target volumes in 3D-IGBT. Target volume definitions are made in accordance with the GEC-ESTRO and the International Commission on Radiation Units and Measurements (ICRU) 89 recommendations.[29,33] MRI with T2W sequences is required at diagnosis and at time of BRT with the applicator in place. BRT applicators, which are considerably more expensive than metallic ones, must be MRI compatible (plastic or titanium).

MRI-based assessment of GTV and CTV was to be performed in para-axial, para-sagittal, and para-coronal planes, supplemented by 3D clinical drawings. GTV, CTV, and OARs are contoured according to the clinical examination and MRI at diagnosis and at (each) time of BRT. Primary tumor-GTV includes macroscopic tumor extension at diagnosis (GTV-Tinit) and at time of BRT (GTV-Tres), as represented by high-signal intensity (hyperintense) masses relative to the healthy cervix on T2W images. CTV includes GTV and subclinical disease. Three CTVs are defined according to tumor load and hence to the risk of recurrence: an HR-CTV with a residual macroscopic disease, an intermediate-risk CTV (IR-CTV) with a residual microscopic disease, and a low-risk CTV (LR-CTV) including potential microscopic tumor spread. HR-CTV includes the areas that correspond to major risk of local recurrence at time of each BRT application (HR-CTVB1, HR-CTVB2, etc.). The GTV during BRT, the entire cervix, the extracervical extension and the gray zones in parametria, uterine corpus, vagina or rectum and bladder on MRI are included in HR-CTV. IR-CTV (IR-CTVB1, IR-CTVB2, etc.) carrying a significant microscopic tumor load encompasses HR-CTV with a safety margin of craniocaudally 1–1.5 cm, anterioposteriorly 0.5 cm, and laterally 1 cm. It is contoured based on macroscopic tumor extension at diagnosis. No safety margin is added if there is no rectal or bladder involvement. No safety margins are added for HR-CTV or PTV.

MRI-based 3D-IGBT requires a high level of experience, and it is often time consuming and expensive.[29,33]

b. CT-Based Contouring

Although MRI with the applicator in place is the "gold standard" technique for 3D-IGBT, MRI units are not available in many radiation oncology department or they are mostly located far from the institution.[36] The CT scans are widely available than MRI, and could be used more frequently for logistic reasons in BRT planning.[25]

For CT-based contouring, the tumor size and topography should routinely be used as a reference on T2W MRI at diagnosis and just before BRT without applicator (Fig. 4). In HR-CTV contouring, all clinical information and MRI findings just before BRT are integrated into the CT images with applicator in place.

To date, there are several guidelines published for CT-based 3D contouring in cervical cancer BRT.

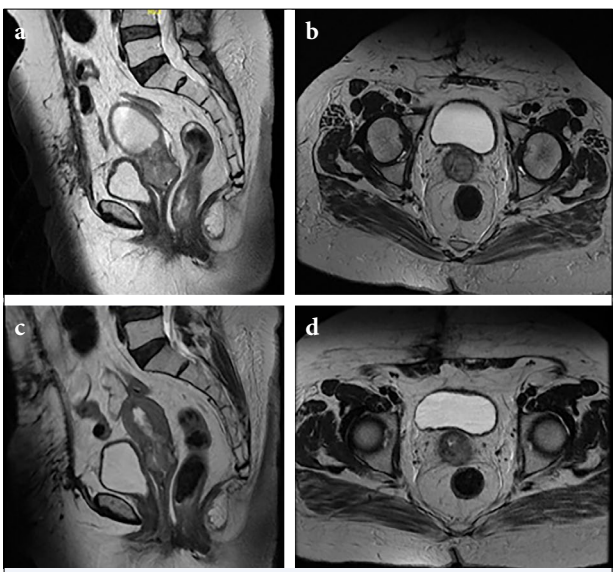

Fig. 4. Sagittal and axial T2W MR images in a 59-year-old woman with stage IIB cervical cancer at diagnosis (a, b) and at the time of BRT (c, d) without applicator.

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[24,37] In 2007, Viswanathan et al. compared the CT-based and MRI-based contours of 10 patients with stage IIA–IIIB cervical cancer to assess the validity of CT-based contours using GEC-ESTRO MRI definitions.[24] All patients underwent both CT and MRI at time of BRT with the tandem and ring applicator in place. On CT-based contouring, the superior border of the cervix and the lateral border of the parametrium were not clearly defined. Also, the cervix and its lateral extension of parametrial tissues were contoured wider than MRI contour. It resulted in a decrease in the D100 and D90. No statistically significant differences were found in the dose for the OARs.

In 2014, Viswanathan et al. compared the CT-based and MRI-based contours in local advanced cervical cancers, and generated a 95% consensus volume.[37] Online contouring atlases for 3D-IGBT are available for instruction at http://www.nrgoncology.org/Resources/ContouringAtlases.aspx. In this study, 23 gynecologic radiation oncology expert from the Radiation Therapy Oncology Group contoured same three cervical cancer cases: stage IIB, near-complete response; stage IIB, partial response; and stage IB2, complete response. All patients had a 3T MRI at diagnosis, an MRI and a CT performed at the time of BRT (within an hour of applicator insertion), and clinical drawings. When CT and MRI volumes were compared, the mean tumor volume was larger on CT than on MRI for all three cases. Among physicians' contours, CT had a higher level of agreement. There was no statistically significant difference in D90 or D2cc OARs comparing CT to MRI. The lowest concordance between CT and MRI contours was found for a patient with a stage IIB cervical cancer with a near-complete response to chemoradiotherapy. The highest concordance between CT and MRI contours was found for a patient with a stage IB2 cervical cancer with a complete response. The concordance between CT and MRI contours was good in a patient with a stage IIB disease with a partial response. According to this study, patients with no parametrial extension at diagnosis and with a good response to EBRT are least likely to benefit from the use of MRI. On the contrary, patients with a large tumor at diagnosis with parametrial extension and with a near-complete response are most likely to benefit from the use of MRI.

In 2017, Ohno et al. published recommendations for contouring the CT-based HR-CTV for 3D-IGBT for cervical cancers.[38] In this study, 15 gynecologic radiation oncology experts from the Japanese Radiation Oncology Study Group defined CT-based HR-CTV boundaries in cranial–caudal, lateral, or anterior–posterior planes. To minimize the difference in width between CT-based HR-CTV and MRI-based HR-CTV, they recommended to 1) reduce the slice thickness to <3 mm, 2) determine the lateral border carefully, and 3) exclude the visible linear structures that run laterally (e.g. the vessels, nerves and non-tumor fibrous structures).

All these HR-CTV contouring guidelines for CT are summarized in Table 1.

The superior extent of the cervix cannot be clearly determined by CT. However, it encompasses the average cervical height of 3 cm. If intravenous (IV) contrast material is given, the superior extent of the cervix corresponds to the cervicouterine junction where the uterine vessels abut to the cervix. It can be delineated as the superior border of the HR-CTV. MRI immediately before or at BRT may help to accurately determine the superior border of the HR-CTV. If MRI is not available, HR-CTV should include a minimum two-thirds of the uterine height.[26] It is also critical to avoid unnecessarily contouring uninvolved parametrial tissue. The inferior border of the HR-CTV is more accurately delineated based on gynecologic examination with 3D clinical drawings at diagnosis and at BRT. On CT, borders of tumor, cervix, and parametrium could not be distinguished; and GTV cannot be delineated. HR-CTV includes the entire cervix and any notable residual tissue at parametrium, uterus, vagina, rectum, and bladder. If adjacent organ invasion is present, region of tumor invasion into adjacent organ should be contoured. IV contrast is not mandated. However, when the contrast material is given to the bladder or rectum, the cervix can be more clearly defined. When IR-CTV is contouring, 1 cm safety margin is added around

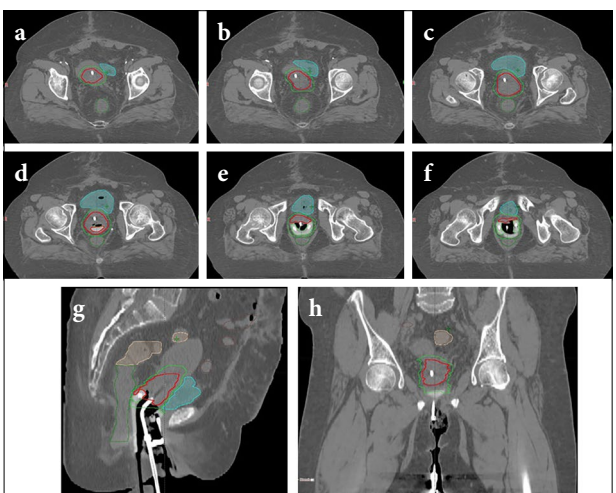

Fig. 5. CT-based HR-CTV and IR-CTV volumes in a same patient with residual disease at time of BRT. Axial (a-f), sagittal (g), and coronal (h) images. Red line=HR-CRV, green line=IR-CTV, cyan=bladder, dark green=rectum, pink=sigmoid.

Table 1 HR-CTV contouring guidelines for CT

	Viswanathan AN et al. (2007)[24]	Viswanathan AN et al. (2014)[37]	Ohno T et al. (2017)[38]
Inferior	Upper level of the applicator or lowest part of the vaginal extension	Starts from ring or ovoid level Tissue inside the central ring or to the level of the ovoids should be contoured If there is an involvement at the time of BRT, vaginal tissue adjacent to the ring should be contoured	Cervical tissue at the level of the tandem applicator fringe Contour exophytic tumors extending to the vaginal cavity at the time of BRT Applicators, vaginal packing, and vaginal vault are not included If vaginal invasion at diagnosis, residual vaginal tumor at the time of BRT and entire vaginal wall should be contoured
Superior	If IV contrast is given, the level where the uterine vessels abut the cervix or where the uterine tissue/cavity begins Additional two slices are contoured around tandem superiorly with decreasing diameter (to include conical cervical apex) Cervical height should be measured (~3 cm)	The level where the uterus begins (internal os), contour the next 1 cm as a cone shaped Cervical height ~3 cm	Starts at the junction of the uterine artery or serosal side of the uterine isthmus, contour the next 1 cm as a cone shaped If uterine corpus invasion at diagnosis, abnormal signal intensity (gray zone) on MRI just before BRT should be contoured
Lateral	If inner half of the parametrium is involved laterally contour ≤2 cm from edge of cervix If outer half of the parametrium is involved laterally contour >2 cm from edge of cervix Contour parametrium throughout the entire cervix	Parametrial extension (gray/white on the CT) should be included (similar density to the cervix)	Border between the uterine tissue or residual tumor (soft tissue density on CT) and surrounding adipose tissue (low density on CT) at the time of BRT Bowel, adnexa, ascites, and visible linear structures (e.g. vessels, nerves and fibrous tissues) that run laterally are not included. Calcifications at the periphery of the uterus can determine the lateral border
Anterior			Border between the uterine tissue or residual tumor at the time of BRT and the adipose tissue If there is no adipose tissue, bladder wall is not included If there is an invasion to the bladder wall at the time of BRT, residual bladder invasion should be contoured For invasion of the bladder, muscle layer invasion should be confirmed
Posterior			Border between the uterine tissue or residual tumor at the time of BRT and the adipose tissue If there is no adipose tissue, the walls of the rectum, sigmoid colon, and small bowels are not included Involved rectum or sigmoid colon walls at the time of BRT should be contoured For invasion of the rectum or sigmoid colon wall, muscle layer invasion should be confirmed

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HR-CTV, and it is modified by tumor extension at diagnosis. IR-CTV should include the parametrial, uterosacral, and vaginal disease at diagnosis. If there is no involvement, the contour should not extend to the bladder, sigmoid, rectum, and pelvic bones. Figure 5 shows CT-based target volumes.

Conclusion

We conclude that contouring guidelines should be considered in 3D-IGBT for cervical cancers. The MRI-based BRT with applicator in place is the gold standard technique, especially in patients with large tumors and parametrial involvement. The CT scans are adequate for OARs delineation, but the cervix cannot be assessed clearly and CT-based target contours significantly wider than with MRI. Gynecological examination and MRI immediately before BRT can eliminate limitations of CT. It should be kept in mind that 3D-IGBT requires considerable time and high level of experience.

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