

Recommendations for high-risk clinical target volume definition with computed tomography for three-dimensional image-guided brachytherapy in cervical cancer patients

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ABSTRACT

Our purpose was to develop recommendations for contouring the computed tomography (CT)-based high-risk clinical target volume (CTV_{HR}) for 3D image-guided brachytherapy (3D-IGBT) for cervical cancer. A 15-member Japanese Radiation Oncology Study Group (JROSG) committee with expertise in gynecological radiation oncology initiated guideline development for CT-based CTV_{HR} (based on a comprehensive literature review as well as clinical experience) in July 2014. Extensive discussions occurred during four face-to-face meetings and frequent email communication until a consensus was reached. The CT-based CTV_{HR} boundaries were defined by each anatomical plane (cranial–caudal, lateral, or anterior–posterior) with or without tumor progression beyond the uterine cervix at diagnosis. Since the availability of magnetic resonance imaging (MRI) with applicator insertion for 3D planning is currently limited, T2-weighted MRI obtained at diagnosis and just before brachytherapy without applicator insertion was used as a reference for accurately estimating the tumor size and topography. Furthermore, utilizing information from clinical examinations performed both at diagnosis and brachytherapy is strongly recommended. In conclusion, these recommendations will serve as a brachytherapy protocol to be used at institutions with limited availability of MRI for 3D treatment planning.

KEYWORDS: cervical cancer, brachytherapy, high-risk clinical target volume, three-dimensional planning, recommendations

INTRODUCTION

In radiation therapy for uterine cervical cancer, 3D image-guided brachytherapy (3D-IGBT) using magnetic resonance imaging (MRI) or computed tomography (CT) has shown promise for improving local control without increasing the risk of severe complications. Since the publication of the target concept and terms for MRI-based 3D-IGBT by the European Group of Curiotherapy–European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) in 2005, a 90% target dose (D90) delivered to the high-risk clinical target volume (CTV_{HR}) has proved to be a useful dose–volume parameter that correlates with local control [1–3]. However, the CTV_{HR} was originally devised when MRI was used for treatment planning (MRI-based CTV_{HR}); hence, the parameters for CT-based treatment planning (CT-based CTV_{HR}) have not been fully established.

Although MRI is the gold standard for 3D-IGBT for cervical cancer, its global application is still limited. Recent surveys on IGBT for cervical cancer demonstrated that CT is the most commonly used imaging modality for dose specification in clinical practice [4–7]. Brachytherapy for cervical cancer in Japan is rapidly transitioning from 2D to 3D treatment planning. A Japanese questionnaire-based survey conducted in 2012 revealed that 16% of institutes that perform 3D treatment planning primarily use CT; this percentage was expected to increase to 53% over the following 3 years [8]. This survey also revealed that MRI availability for treatment planning is limited in brachytherapy, although utilization of MRI for diagnosis and before commencing brachytherapy is possible at most centers [8].

Clinical outcomes at several Japanese institutions using 3D-IGBT with CT have been reported [9–12]. When physicians contour CTV using CT according to their respective institutional policies, the dose–volume parameters to the target are likely more sensitive because of poorer tumor visualization by CT compared with MRI [13]. Considering the fact that CT is a mainstay for 3D-IGBT in the majority of institutions, the resulting dose uncertainty from such CT-based CTV contouring must be minimized. Therefore, we conducted a multi-institutional study of CT-based CTV_{HR} delineation in order to standardize 3D-IGBT application in regions where the availability of MRI with applicator in place is limited.

MATERIALS AND METHODS

This study was initiated at the volition of the Working Group on Gynecological Tumors committee, a branch of the Japanese Radiation Oncology Study Group (JROSG). The working group consisted of 15 members (from 14 institutes) with expertise in gynecological radiation oncology. Eight institutions used CT as the imaging modality for treatment planning of brachytherapy for cervical cancer, three used both CT and MRI, two used CT and radiography, and one used radiography alone.

During the first meeting, held in July 2014, the background and aims of the multi-institutional collaborative study on CT-based CTV_{HR} were decided. Subsequently, researchers reviewed the international

guidelines (GEC ESTRO and the American Brachytherapy Society) [1, 2, 13, 14] and then devised a timetable for developing recommendations. In the second meeting, held in December 2014, a draft of border definitions for CT-based CTV_{HR} was delivered using actual patient CT images. Afterwards, the details of these definitions were discussed for each anatomical plane (craniocaudal, lateral and anterior–posterior) via e-mail. In the third meeting, in June 2015, cranial and lateral margins were discussed at length, as negotiating these details over email was cumbersome. In the fourth meeting, which was held in July 2015, various issues were discussed, including the use of CT and MR images as references, and definitions of CT-based CTV_{HR}. At the end of August 2015, a consensus was reached on fundamental recommendations, including the image acquisition protocols required for CT-based CTV_{HR}, integration of diagnostic MRI plus information from clinical examinations, and CTV_{HR} border definitions on CT images. The first version was reviewed by two external advisors; the value of MRI and limitations of CT in 3D-IGBT for cervical cancer were updated based on discussions between the external advisors and JROSG members. Finally, the revised recommendations were completed and approved by all members in June 2016.

RESULTS

Definition of CTV_{HR}

In our present recommendations, we defined CTVs according to the imaging modality used when contouring for brachytherapy treatment planning. These included (i) CT-based CTV: CT with applicator insertion [13, 14], (ii) CT-based CTV_{HR}: CT with applicator insertion and MRI just before first brachytherapy [15], and (iii) MRI-based CTV_{HR}: MRI with applicator insertion [1, 2]. For all CTV contouring modalities, clinical examination findings at the time of brachytherapy were also used.

Fundamental policy for delineation

Our recommendations follow the guidelines of MRI-based CTV_{HR} according to the GEC-ESTRO recommendations [1, 2]. The fundamental policy for CT-based CTV_{HR} delineation is to minimize both inter/intraphysician variability of contouring, as well as to reduce the discrepancy in contouring when compared with MRI-based CTV_{HR}. The CT-based CTV_{HR} boundaries are classified by each direction (cranial–caudal, lateral or anterior–posterior) with or without tumor progression beyond the uterine cervix at diagnosis (see the Results subsection below “CT-based CTV_{HR} boundaries”).

Acquisition of CT images

CT with gynecological applicator insertion for planning is performed in the same position as during actual treatment. The scope is set to completely cover the uterus and vagina. Scanning should commence from the level of the uterine fundus 3 cm or more in the cranial direction, and caudally to the level of the vulva. The field of view includes both sides of the pelvic wall, and the slice thickness should be less than 3 mm. In principle, a supine position with the

legs straightened is recommended, since CT images will be compared with MR images obtained at diagnosis or just before brachytherapy. If CT with applicator in place is performed in the lithotomy position, attention may have to be paid to anatomical changes between the CT and MRI positions because the MR images are acquired with straightened legs. CT will be performed at every brachytherapy session. It should be noted that CT and MRI findings are also influenced by image acquisition parameters (e.g. slice thickness, uterine body angle/position that depends on the presence/absence of gynecological applicator placement, contents of the bowel/bladder, and organ movement during the acquisition).

Integration of findings of MR images and clinical information with contouring

CT-based CTV_{HR} contouring based on Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) clinical stage information alone

leads to large overestimation of width and volume compared with MRI-based CTV_{HR} [13, 16]. The use of information from clinical examinations at the time of both diagnosis and brachytherapy is strongly recommended for improving the accuracy of CT-based CTV_{HR} delineation [16]. T2-weighted MR images acquired at diagnosis and just before brachytherapy without applicator should routinely be used as a reference. MRI acquired just before brachytherapy helps not only to evaluate the response to external beam radiation therapy, but also to identify the extent of residual tumors (including parametrial and cranial extensions) and plan suitable gynecological applicator placement (e.g. adding interstitial needles).

Visual integration of the findings of MRI and information from clinical examinations with those of CT images could reduce overestimation of CT-based CTV_{HR} and make it more consistent with MRI-based CTV_{HR}. On the other hand, target transfer from CTV_{HR} delineation on MRI without gynecological applicator insertion before brachytherapy to CT with the applicator inserted at brachytherapy is

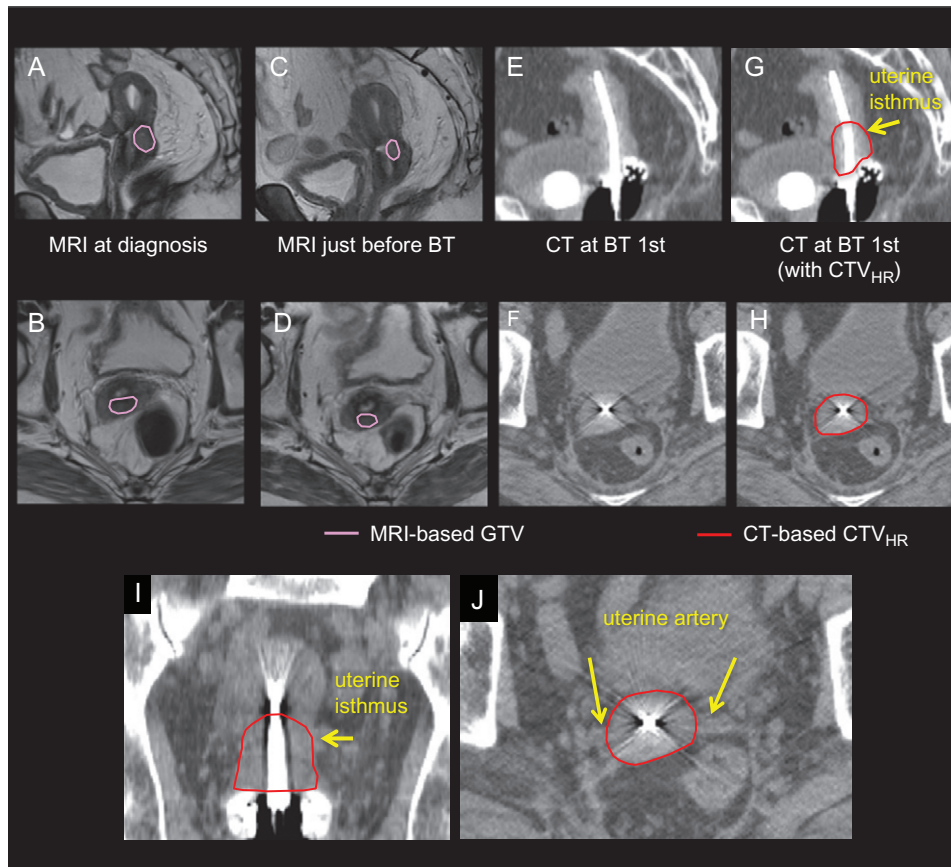


Fig. 1. Caudal, cranial, lateral, anterior and posterior boundaries of a computed tomography (CT)-based high-risk clinical target volume (CTV_{HR}). FIGO Clinical Stage IB1: a case without tumor extension beyond the uterine cervix at diagnosis. T2-weighted magnetic resonance imaging (MRI) in the sagittal plane (A) and transverse plane (B) at diagnosis, and in the sagittal plane (C) and transverse plane (D) just before brachytherapy (BT). A plain CT image in the sagittal plane (E) and transverse plane (F) at the time of first BT, and in the sagittal plane (G) and transverse plane (H) at the time of first BT with CT-based CTV_{HR} contouring. A plain CT image in the coronal plane (I) and transverse plane (J) at the time of first BT with CT-based CTV_{HR} contouring with a landmark at the upper border of the cervix. Gynecological applicators were placed for CT but not for MRI. Pink line = MRI-based gross tumor volume (GTV), red line = CT-based CTV_{HR}, short yellow arrow = uterine isthmus, long yellow arrow = uterine artery.

difficult because large anatomical changes may occur owing to applicator insertion, vaginal packing, and the filling status of the bladder and rectum. Moreover, collection of such image deformations was incomplete because the deformable image registration software is still undergoing improvements. Therefore, the tumor size and topography on MRI just before brachytherapy will be used as the reference in the present recommendations. When complex tumor volumes on MRI without applicator insertion before brachytherapy are visually translated into CT-based CTV_{HR} contouring, there is a potential risk of geographical misses for extensively large tumors with parametrial or adjacent organ involvement [15]. Therefore, greater attentiveness is necessary to minimize such risks in extensively large tumors when determining their sizes and topographies using transverse, coronal and sagittal plane images on MRI.

In principle, the CT-based CTV_{HR} is contoured in the transverse plane image. The uterine axis (perpendicular to the tandem axis) can be used as an index. If available, comparing the position of the uterus between sagittal MR images and sagittal reconstructed CT images is recommended for improving the accuracy of CT-based CTV_{HR} delineation.

In contouring a second CT-based CTV_{HR}, all previous clinical information and MR images acquired just before the first brachytherapy session are integrated into the CT images acquired with applicator insertion at the time of the second brachytherapy. In particular, cervical tumor response at each brachytherapy session, in

terms of size and topography, should be carefully evaluated by clinical examination. The CT-based CTV_{HR} at the first brachytherapy should be referred to. The subsequent CT-based CTV_{HR} is also contoured by the same methods.

CT-based CTV_{HR} boundaries

Caudal boundary

Cases without vaginal invasion at diagnosis. The caudal boundary is defined as cervical tissue at the level of the tandem applicator fringe. Any exophytic tumors (i.e. those that extend into the vaginal cavity) at the time of brachytherapy should be included. CT-based CTV_{HR} contouring excludes applicators inserted (i.e. the fringe of the tandem applicator, ovoid caps, ring applicator, and vaginal cylinder). Vaginal packing material and the vaginal vault are also excluded (Fig. 1).

Cases with vaginal invasion at diagnosis. In addition to the caudal boundary contoured in cases without vaginal invasion (see the subsection “Cases without vaginal invasion at diagnosis”), residual vaginal tumor lesions at the time of brachytherapy are included. The lowest boundary of the vaginal target is determined by referring to either the distance between the caudal edge of the inserted applicator and the caudal edge of the vaginal tumor (for the upper half of the vaginal tumor), or the distance between the external urethral opening and the caudal edge of the vaginal tumor (for the lower half of

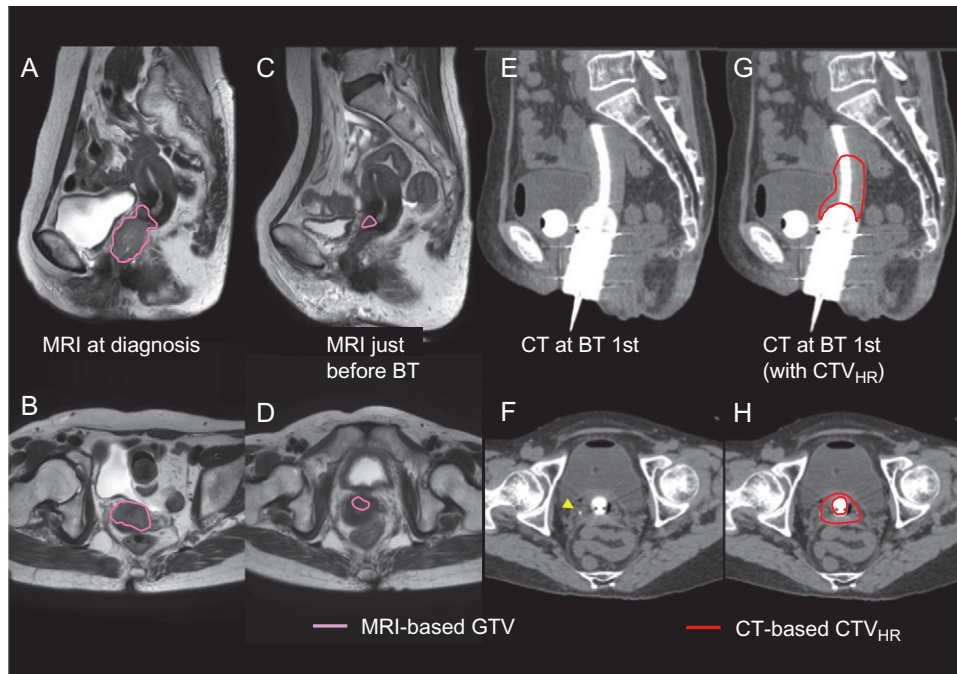


Fig. 2. Caudal boundary of a computed tomography (CT)-based high-risk clinical target volume (CTV_{HR}). FIGO Clinical Stage IIIA: a case with vaginal invasion at diagnosis presented good response at the time of first brachytherapy (BT). T2-weighted magnetic resonance imaging (MRI) in the sagittal plane (A) and transverse plane (B) at diagnosis, and in the sagittal plane (C) and transverse plane (D) before BT. A plain CT image in the sagittal plane (E) and transverse plane (F) at the time of first BT, and in the sagittal plane (G) and transverse plane (H) at the time of first BT with CT-based CTV_{HR} contouring. Gynecological applicators were placed for CT but not for MRI. Pink line = MRI-based gross tumor volume (GTV), red line = CT-based CTV_{HR}, yellow arrowhead = calcification.

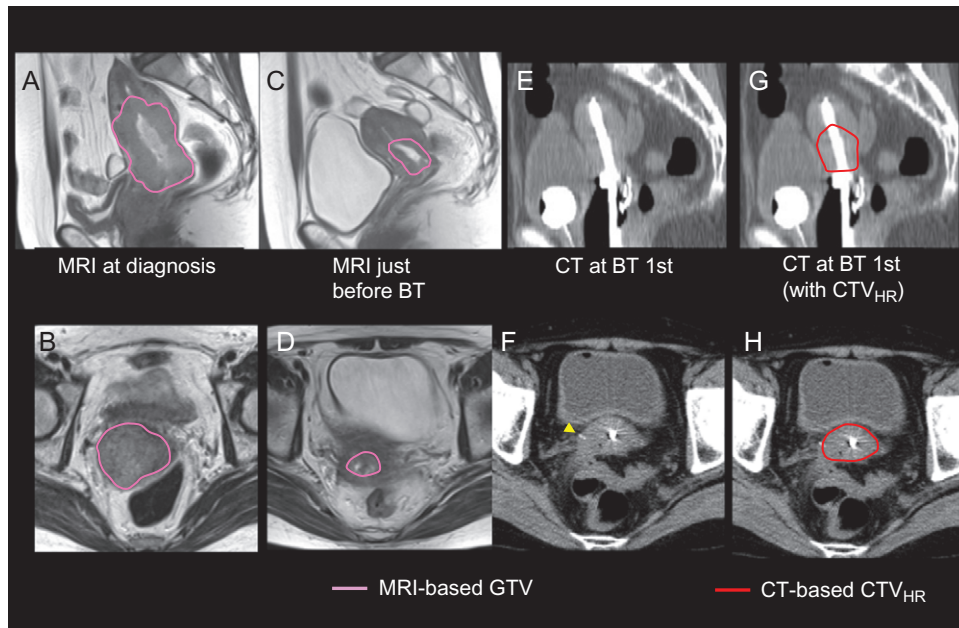


Fig. 3. Cranial boundary of a computed tomography (CT)-based high-risk clinical target volume (CTV_{HR}). FIGO Clinical Stage IIB: a case with uterine corpus invasion at diagnosis showed good response at the time of first brachytherapy (BT). T2-weighted magnetic resonance imaging (MRI) in the sagittal plane (A) and transverse plane (B) at diagnosis, and in the sagittal plane (C) and transverse plane (D) before BT. A plain CT image in the sagittal plane (E) and transverse plane (F) at the time of first BT, and in the sagittal plane (G) and transverse plane (H) at the time of first BT with CT-based CTV_{HR} contouring. Gynecological applicators were placed for CT but not for MRI. Pink line = MRI-based gross tumor volume (GTV), red line = CT-based CTV_{HR}, yellow arrowhead = calcification. Calcification recognized in the periphery of the uterus will be helpful for delineating the border.

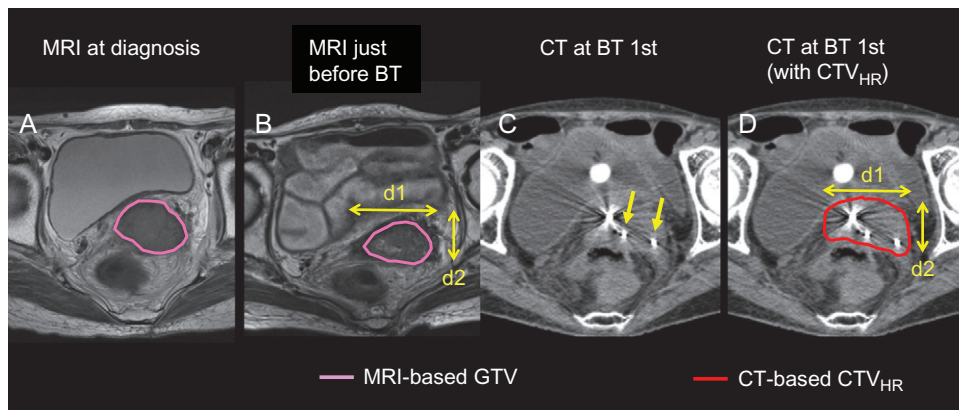


Fig. 4. Lateral boundary of a computed tomography (CT)-based high-risk clinical target volume (CTV_{HR}). FIGO Clinical Stage IIIB: a case with tumor progression to the left pelvic wall at diagnosis presented poor response at the time of first brachytherapy (BT). T2-weighted magnetic resonance imaging (MRI) transverse image at diagnosis (A) and before BT (B). A plain CT transverse image at the time of first BT (C) and at the time of first BT with CT-based CTV_{HR} contouring (D). Gynecological applicators including two interstitial needles were placed for CT but not for MRI. Pink line = MRI-based gross tumor volume (GTV), red line = CT-based CTV_{HR}, yellow arrow = interstitial needle, d1 = width of MRI-based CTV_{HR}, d2 = anteroposterior diameter of MRI-based CTV_{HR}. Tracing the diameter of MRI-based CTV_{HR} (d1 and d2) on the CT image is helpful for minimizing overestimation of the border between CT-based CTV_{HR} and adjacent organs.

the vaginal tumor); both can be confirmed during applicator insertion. The thickness of the vaginal target is defined as the entire vaginal wall, including tumors identified on CT. The thickness and clockwise direction of tumor progression are determined by referring to MR images acquired just before brachytherapy as well as clinical examination findings (Fig. 2).

Cranial boundary

Cases without uterine corpus invasion at diagnosis. The cranial boundary is defined as the upper margin of the uterine cervix at the time of brachytherapy. Contouring starts with the junction of the uterine artery by referring to the upper and lower slices in the transverse plane image or the isthmus of the uterus that correspond to the upper border of the cervix on the serosal side. In most patients, the isthmus of the uterus could be determined based on the sagittal or coronal plane images at the time of brachytherapy. MR images taken just before brachytherapy are useful references. Once the upper border of the serosal side is determined, it will be enclosed at a level 1 cm in the cranial direction in a cone-shaped contour that covers the conical cervical apex along with the uterine cavity (Fig. 1).

Cases with uterine corpus invasion at diagnosis. If the borders of the residual tumor extend beyond the cervix, the cranial boundary is defined as the upper border of the residual tumor at the time of brachytherapy of the uterine corpus; i.e. the upper border of the abnormal signal intensity (including the gray zone), believed to be residual tumor, as detected on MRI just before brachytherapy

(Fig. 3). Contouring starts with the cervical tumor towards the uterine fundus, referring to transverse- and sagittal-plane MR images acquired at diagnosis and just before brachytherapy.

If a residual tumor exists in the cervix or if the tumor has disappeared, the cranial boundary is defined similarly to cases with no corpus invasion at diagnosis, as described above (see the subsection “Cases without uterine corpus invasion at diagnosis”).

Lateral boundary

Cases without parametrial invasion at diagnosis. The lateral boundary is defined as the border between the uterine tissue (soft tissue density on CT) and the surrounding adipose tissue (low density on CT) at the time of brachytherapy. The intestinal tract, adnexa, ascites, and visible linear structures that run laterally (e.g. vessels, nerves and fibrous structures, but not tumor extensions) are excluded. Calcification recognized in the periphery of the uterus on CT images will be helpful for delineating the border in some cases, although it is usually difficult to identify such features on MR images. It is essential to carefully refer to MRI findings at brachytherapy and just before, as well as to clinical examination findings (Fig. 1).

Cases with parametrial invasion at diagnosis. The lateral boundary is defined as the 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 brachytherapy. The lateral border of the CT-based CTV_{HR} should be determined carefully by referring to MR images acquired just before brachytherapy (Fig. 4).

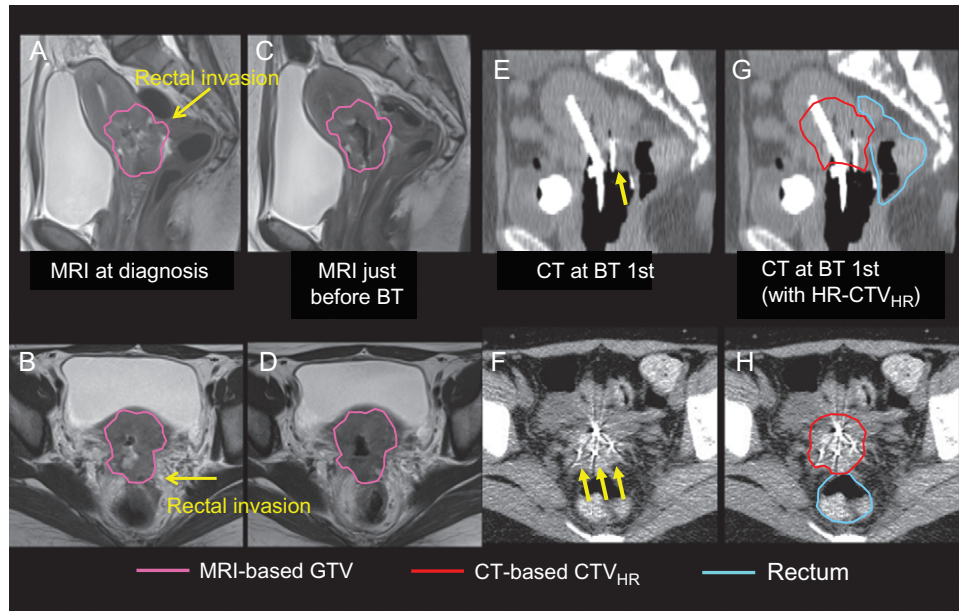


Fig. 5. Posterior boundary of a computed tomography (CT)-based high-risk clinical target volume (CTV_{HR}). FIGO Clinical Stage IVA: a case with invasion of the rectum at diagnosis. T2-weighted magnetic resonance imaging (MRI) in the sagittal plane (A) and transverse plane (B) at diagnosis, and in the sagittal plane (C) and transverse plane (D) before BT. A plain CT image in the sagittal plane (E) and transverse plane (F) at the time of first BT, and in the sagittal plane (G) and transverse plane (H) at the time of first BT with CT-based CTV_{HR} contouring. Gynecological applicators, including three interstitial needles, were placed for CT but not for MRI. Pink line = MRI-based gross tumor volume (GTV), red line = CT-based CTV_{HR}, yellow arrow = interstitial needle.

Posterior boundary

Cases without tumor invasion to the rectum or sigmoid colon wall at diagnosis. The posterior boundary is defined as the border between the uterine tissue at the time of brachytherapy or the residual tumor (soft tissue density on CT), whichever is more posterior, and the adipose tissue (low density on CT). If no adipose tissue is observed, the posterior border of the uterine tissue is determined without including the walls of the rectum, sigmoid colon, and small bowels by referring to the upper and lower slices of the transverse plane image or those of the sagittal plane of the reconstructed images (Fig. 1).

Cases with invasion of the rectum or sigmoid colon wall at diagnosis. Invasion of the rectum or sigmoid colon that is evident at the time of brachytherapy is included (Fig. 5). Tumor progression is determined by referring to MR images (at diagnosis and just before brachytherapy). Other sites in the posterior boundary are handled as described for cases without tumor invasion of the rectum or sigmoid colon wall at diagnosis (see the subsection “Cases without tumor invasion to the rectum or sigmoid colon wall at diagnosis”). Of note, rectum or sigmoid colon wall invasion is confirmed when tumor invasion of the muscle layer is diagnosed independently of mucosal invasion (which is the correct diagnosis criterion of rectal invasion for FIGO Stage IVA tumors).

Anterior boundary

Cases without tumor invasion of the bladder wall at diagnosis. The anterior boundary is defined as the border between the

uterine tissue or the residual tumor (soft tissue density on CT) at the time of brachytherapy, whichever is more anterior, and the adipose tissue (low density on CT). If no adipose tissue is observed, the anterior border of the uterine tissue is determined without including the bladder wall by referring to the upper and lower slices of the transverse plane image or those of the sagittal plane of the reconstructed image (Fig. 1).

Cases with invasion of the bladder wall at diagnosis. The residual bladder invasion that clearly remains at the time of brachytherapy is included (Fig. 6). Tumor progression is determined by referring to MR images acquired at diagnosis and just before brachytherapy. Other sites in the anterior boundary are managed as described in cases without tumor invasion of the bladder wall at diagnosis (see the subsection “Cases without tumor invasion of the bladder wall at diagnosis”). Of note, bladder wall invasion is confirmed when tumor invasion of the muscle layer is diagnosed independently of mucosal invasion (which is the correct diagnosis criterion of bladder invasion for FIGO Stage IVA tumors). When the intestinal tract is close to the anterior uterine tissue, the posterior margin policy for the rectum or sigmoid colon (see the subsection “Cases without tumor invasion to the rectum or sigmoid colon wall at diagnosis”) is applied.

The CT-based CTV_{HR} boundaries described above are shown in Table 1.

DISCUSSION

Several principles of CT-based CTV have been reported; they are based mainly on the consensus of gynecologic radiation oncology

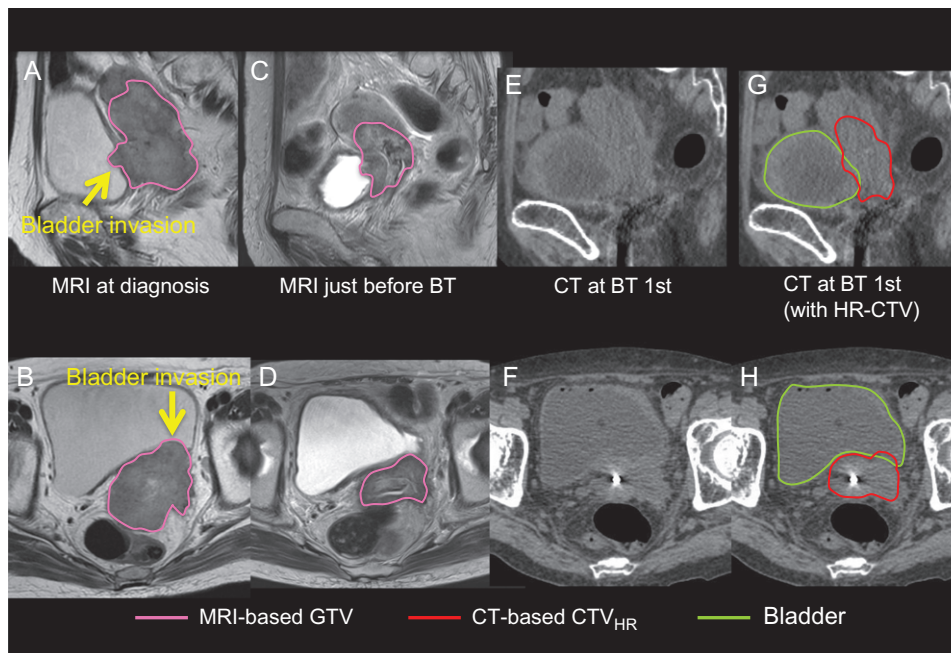


Fig. 6. Anterior boundary of a computed tomography (CT)-based high-risk clinical target volume (CTV_{HR}). FIGO Clinical Stage IVA: a case with invasion of the bladder at diagnosis. T2-weighted magnetic resonance imaging (MRI) in the sagittal plane (A) and transverse plane (B) at diagnosis, and in the sagittal plane (C) and transverse plane (D) just before brachytherapy (BT). A plain CT image in the sagittal plane (E) and transverse plane (F) at the time of BT, and in the sagittal plane (G) and transverse plane (H) at the time of BT with CT-based CTV_{HR} contouring. Gynecological applicators were placed for CT but not for MRI. Pink line = MRI-based gross tumor volume (GTV), red line = CT-based CTV_{HR}.

Table 1. Contouring recommendations for a computed tomography–based high-risk clinical target volume

Direction and tumor extension	Contouring recommendations
1. Caudal boundary	
(a) Vaginal invasion (–)	Contouring commences at the cervical tissue at the level of the tandem applicator fringe. The applicators are excluded, as are the vaginal packing material and vaginal vault.
(b) Vaginal invasion (+)	In addition to ‘1a’, the residual vaginal tumor lesions at the time of brachytherapy are included.
2. Cranial boundary	
(a) Uterine corpus invasion (–)	Defined as the upper margin of the uterine cervix. Contouring starts at the junction of the uterine artery or isthmus. The upper border of the serosal side is enclosed at a level of 1 cm in the cranial direction in a cone-shaped contour, along with the uterine cavity.
(b) Uterine corpus invasion (+)	Defined as the upper border of the residual tumor (i.e. the abnormal signal intensity) as detected on MRI just before brachytherapy of the uterine corpus.
3. Lateral boundary	
(a) Parametrial invasion (–)	Consists of the border between the uterine tissue and surrounding adipose tissue at the time of brachytherapy. The intestinal tract, adnexa, ascites, and visible linear structures that run laterally (e.g. vessels, nerves and fibrous structures) are excluded.
(b) Parametrial invasion (+)	Consists of the border between the uterine tissue or residual tumor and the surrounding adipose tissue at the time of brachytherapy.
4. Posterior boundary	
(a) Rectum or sigmoid colon wall invasion (–)	Defined as the border between the uterine tissue or residual tumor, whichever is more posterior, and adipose tissue.
(b) Rectum or sigmoid colon wall invasion (+)	Invasion of the rectum or sigmoid colon that is evident at the time of brachytherapy is included. Tumor progression is determined by reviewing MR images. Other posterior boundary sites are managed as described in ‘4a’.
5. Anterior boundary	
(a) Bladder wall invasion (–)	Includes the border between the uterine tissue or residual tumor, whichever is more anterior, and the adipose tissue.
(b) Bladder wall invasion (+)	Any residual bladder-invading tumor tissue that is clearly evident at the time of brachytherapy is included. Tumor progression is determined by reviewing MR images. Other anterior boundary sites are managed as described in ‘5a’.
6. General	Clinical examination findings at the time of brachytherapy should be taken into account.

CT = computed tomography, MR(I) = magnetic resonance (imaging).

experts [13, 14]. In these reports, however, MR images acquired before or at brachytherapy were not routinely used for contouring the CT-based CTV. We believe that MRI should be used whenever possible, as it is apparently superior to CT in this regard. In our current recommendations, the intent was to develop a CT-based CTV_{HR} that is as consistent with the MRI-based CTV_{HR} devised by the gynecological (GYN) GEC ESTRO as possible. To our knowledge, our CT-based CTV_{HR} is the first to incorporate MRI (at diagnosis and just before brachytherapy) and clinical examination findings (at diagnosis and brachytherapy) with CT images with applicator in place at brachytherapy.

Cranial boundary

According to the GYN GEC ESTRO recommendation, the cranial boundary of CTV_{HR} is defined as the cranial border of the cervix or a macroscopic residual tumor at brachytherapy [1]. When the cervical tumor does not extend beyond the cervix, the junction of the uterine artery as identified on plane CT images, and/or the isthmus of the uterus as exposed by CT, are useful for determining the upper border of the serosal side.

On the other hand, in cases with uterine body extensions, an inter-observer comparison study on MRI-based CTV_{HR} reported that image quality and window level can result in over- or

underestimation of tumor boundaries, which was the most frequent cause of inter-observer variability during delineation [17]. This study stressed the importance of imaging quality as well as physicians' skill in diagnostic imaging, because MRI (but not CT or clinical examination) can help identify the residual tumor in the uterine body at brachytherapy. In particular, the cranial boundary in CT-based CTV_{HR} appears to be equivalent to MRI-based CTV_{HR} when comparing the reconstructed sagittal CT images with applicator insertion to sagittal MR images acquired just before brachytherapy.

Caudal boundary

The vagina is one of the organs at risk during 3D-IGBT for cervical cancer; it is important to consider the proximal vaginal dose to avoid late vaginal complications [18]. The soft tissue density of the prolapsed vaginal vault may cause overestimation of CT-based CTV_{HR} contouring despite no tumor being present, especially in young patients. Obtaining a baseline distance using MRI before brachytherapy for comparison with CT with applicators in place will be helpful.

For cases with vaginal invasion at diagnosis, adding information from clinical examinations at brachytherapy to imaging data is useful for precisely identifying the vaginal tumor extension. However, it has not been fully decided how physicians should incorporate such clinical information into contouring of the caudal boundary in CT-based CTV_{HR}. The present recommendations proposed the use of the distance between the caudal edge of the inserted applicator and the caudal edge of the vaginal tumor, or the distance between the external urethral opening and the caudal edge of the vaginal tumor, based on clinical examination. Additionally, we recommend the use of thickness and clockwise direction data of tumor progression that can be determined by referring to MR images and clinical examinations at brachytherapy.

Lateral boundary

In a comparison study of MRI-based CTV_{HR} with CT-based CTV for locally advanced cervical cancer, the conformity index of contouring was slightly higher for CT than for MRI in all three tested scenarios, suggesting better distinction on CT between the involved 'gray' region and the non-involvement of the parametria [14]. However, a comparison of MRI and CT for CTV delineation in 3D-IGBT for cervical cancer has revealed that CT-based contouring overestimates the contour width [13]. Therefore, one of the issues discussed during the meetings of experts was how to minimize the difference in width between CT-based CTV_{HR} and MRI-based CTV_{HR}. The first recommendation was to reduce the slice thickness to <3 mm to improve imaging quality. In comparison studies on CTV contouring between CT and MRI, CT slice thickness was reduced from 5 mm in the first study to 1.25 mm in the second study, which likely contributed to improved accuracy in contouring when using CT [13, 14]. Second, we recommended that the lateral border of the CT-based CTV_{HR} should be determined carefully, and MRI findings just before brachytherapy should be referred to. If MRI data with a tandem applicator are available, that would be valuable for measuring the distance between the center of the tandem applicator and the anterior–posterior/left–right borders of the

MRI-based CTV_{HR}. For example, in cases without adipose tissue density between the cervical tumor and adjacent bowels on CT, referring to the distance based on MR imaging just before brachytherapy will be useful for determining the border. Third, we recommended careful exclusion of the visible linear structures that run laterally (e.g. the vessels, nerves and non-tumor fibrous structures); this was previously defined in a consensus-based guideline for CTV of the primary tumor on external beam radiotherapy for intact cervical cancer [19].

Limitations

The GEC-ESTRO defined intermediate risk clinical target volume (MRI-based CTV_{IR}) in their first published recommendations [1]. Certain dosages are usually administered to MRI-based CTV_{IR} that are lower than those used for MRI-based CTV_{HR}. However, clinical data on the dose–response relationship in MRI-based CTV_{IR} are still limited [20]. While the 'CT-based CTV_{IR}' definition and dose prescriptions for 3D treatment planning of brachytherapy are important, this subject is beyond the scope of the current study. Defining CT-based CTV_{IR} and dose prescriptions for 3D treatment planning will be undertaken in a future study.

CONCLUSION

We have developed a set of recommendations aimed at defining the CT-based CTV_{HR} for 3D-IGBT in cervical cancer patients. The recommendations will be introduced into routine practice for 3D-IGBT and will also be used in clinical trials aimed at developing future brachytherapy protocols for institutions where MRI availability for 3D treatment planning is limited.

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CONFLICTS OF INTEREST

None.

CLINICAL TRIAL REGISTRATION NUMBER

Not available.

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