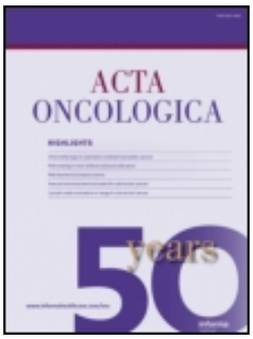

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ORIGINAL ARTICLE

High-risk clinical target volume delineation in CT-guided cervical cancer brachytherapy: Impact of information from FIGO stage with or without systematic inclusion of 3D documentation of clinical gynecological examination

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Abstract

Purpose. The aim of the study was to improve computed tomography (CT)-based high-risk clinical target volume (HR CTV) delineation protocols for cervix cancer patients, in settings without any access to magnetic resonance imaging (MRI) at the time of brachytherapy. Therefore the value of a systematic integration of comprehensive three-dimensional (3D) documentation of repetitive gynecological examination for CT-based HR CTV delineation protocols, in addition to information from FIGO staging, was investigated. In addition to a comparison between reference MRI contours and two different CT-based contouring methods (using complementary information from FIGO staging with or without additional 3D clinical drawings), the use of standardized uterine heights was also investigated. *Material and methods.* Thirty-five cervix cancer patients with CT- and MR-images and 3D clinical drawings at time of diagnosis and brachytherapy were included. HR CTV_{stage} was based on CT information and FIGO stage. HR $CTV_{stage+3Dclin}$ was contoured on CT using FIGO stage and 3D clinical drawing. Standardized HR CTV heights were: 1/1, 2/3 and 1/2 of uterine height. MRI-based HR CTV was delineated independently. Resulting widths, thicknesses, heights, and volumes of HR CTV_{stage}, HR $CTV_{stage+3Dclin}$ and MRI-based HR CTV contours were compared. *Results.* The overall normalized volume ratios (mean± SD of CT/MRI_{ref} volume) of HR CTV_{stage} and HR $_{stage+3Dclin}$ were 2.6 (± 0.6) and 2.1 (± 0.4) for 1/1 and 2.3 (± 0.5) and 1.8 (± 0.4), for 2/3, and 1.9 (± 0.5) and 1.5 (± 0.3), for 1/2 of uterine height. The mean normalized widths were 1.5 ± 0.2 and 1.2 ± 0.2 for HR CTV_{stage} and HR $CTV_{stage+3Dclin}$, respectively ($p < 0.05$). The mean normalized heights for HR CTV_{stage} and HR $CTV_{stage+3Dclin}$ were both 1.7 ± 0.4 for 1/1 ($p < 0.05$.), 1.3 ± 0.3 for 2/3 ($p < 0.05$) and 1.1 ± 0.3 for 1/2 of uterine height. *Conclusion.* CT-based HR CTV contouring based on FIGO stage alone leads to large overestimation of width and volume. Target delineation accuracy can systematically improve through incorporation of additional information from comprehensive 3D documentation of repetitive gynecological examination in the contouring protocol, and thus help to improve the accuracy of dose optimization in settings with limited access to imaging facilities at the time of brachytherapy. If CT information is only available, minimum 2/3 of uterine height may be a good surrogate for the height of HR CTV.

Cervical cancer is the third most common female cancer in women and is the second highest cause of female cancer mortality worldwide [1–3]. The invasive cervical cancer is highly prevalent in developing countries, where it accounts for 15% of female cancers [4]. Especially in these countries it is difficult to apply the most modern techniques for brachytherapy (BT) planning.

Three-dimensional (3D) image-based BT planning in cervical carcinoma started to increase with the availability of computed tomography (CT)/magnetic resonance imaging (MRI)-compatible applicators, treatment planning systems, and guidelines [5–7], which allow conformal planning and adaptation of dose to target volumes and organs at risk (OARs) [8,9]. Recent reports indicate that image-guided BT

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may improve local control and decrease treatment-related morbidity [10].

MRI is considered the best imaging modality for assessing cervical tumor extent compared with CT [11,12]. For parametrial invasion and advanced disease there is reasoned indication that MRI assessment may be significantly better for staging of cervical carcinoma compared to clinical assessment [13]. The brachytherapy group of the European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) provided recommendations for MRI-guided BT in cervix cancer including definitions for: gross tumor volume (GTV), high-risk clinical target volume (HR CTV) and intermediate-risk CTV (IR CTV) [6,7].

Assessment of cervical cancer on CT is limited, as tumor dimensions and invasion of uterine corpus or parametria may not be detected accurately. In a multicentric study by ACRIN/GOG, MRI proved significantly better than CT for tumor visualization and detection of parametrial invasion of cervical cancer [14]. CT allows limited quantitative estimation of tumor regression during radiotherapy and cannot distinguish between normal tissue and residual disease [15]. Some studies reported that CT-based contouring is feasible for OARs but may overestimate the target volume as recognition of tumor and surrounding normal tissue is often not possible [16,17]. There are currently no widely agreed upon guidelines for CT-guided BT especially if MRI is not available at diagnosis or at time of BT [16].

However, there is a long tradition of clinical gynecologic examination (CGE) in cervical cancer, which represents the gold standard of FIGO stage definition [18]. Clinical findings can be documented on diagrams with schematic drawings in all body orientations and a speculum view [6,19]. According to MRI-CT pathologic studies, the value of CGE seems to be comparable to MRI regarding stage allocation [20]. For these reasons, CGE has been highlighted in the GEC-ESTRO Recommendations on MRI-guided BT as a complementary tool for stage allocation and tumor spread in clinically accessible regions (cervix, vagina, parametria) [7,12].

The aim of our study was to evaluate different approaches of CT-based HR CTV delineation, for clinical settings where no access to MRI facilities is available for BT treatment planning. We investigated if and to what extent a systematic inclusion of precise 3D documentation of CGE in a purely CT-based delineation protocol, compared to FIGO stage information alone [18], can improve CT-based target contouring. As tumor length cannot be assessed on CT, the value of using different standardized uterine heights was investigated. For quality assessment of the CT-based HR CTV contours, MRI-based HR CTV delineation was used as a reference.

Material and methods

This study was designed to compare CT-based HR CTV delineation using information from FIGO stage with or without 3D documentation of CGE with a reference of MRI-based HR CTV delineation regarding total volume, width, height and thickness of HR CTV (Figure 1).

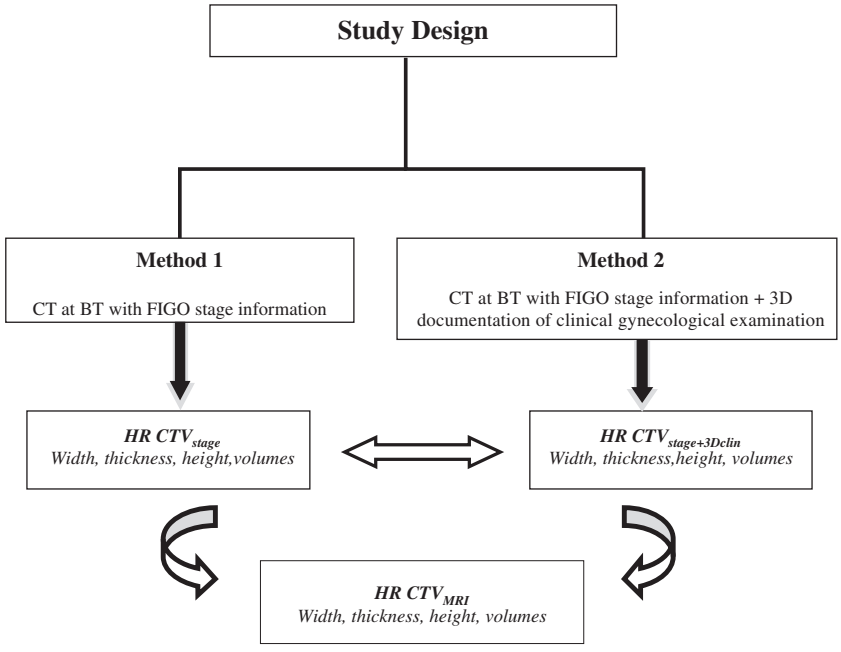

Figure 1. Study design.

Patients and treatment

Thirty-five patients with cervix cancer were retrospectively selected from our overall patient cohort (n = 165, 2001–2008) on the basis of availability of both CT and MRI with applicator in place and full 3D documentation (diagram drawings) representing CGE [10].

All patients had biopsy-proven cervical cancer [FIGO stages IB (8), IIB (18), and III (9)]. They received definitive chemoradiotherapy (45–50 Gy EBRT) with curative intent. All patients were treated with 4 fractions of MRI-guided BT to achieve a total D90 for HR CTV of ≥ 85 Gy EQD2 ($\alpha/\beta = 10$ Gy). CT/MRI-compatible tandem-ring applicators with (17) or without (18) interstitial needles were used (Nucletron Systems, Veenendaal, The Netherlands). Institutional imaging protocols for MRI and CT acquisition with applicator in place have been previously described [15,16].

Clinical examination and 3D documentation with diagram drawing

The CGE was performed by an expert radiation oncologist and included vaginal inspection, palpation and transrectal examination. Accurate documentation of clinical findings was done by drawing on a specific standard diagram (Figure 2A) developed within the framework of the Gyn GEC-ESTRO recommendations [6] and further adapted for the EMBRACE study (available at https://www.embracestudy.dk).

MRI and HR CTV contouring

T2-weighted MRI studies after BT applicator placement were generated in 5 mm slice intervals. The HR CTV_{MRI} was contoured according to the Gyn GEC-ESTRO recommendations [6,7] using PLATO/Oncentra Masterplan (OMP) workstations (Nucletron, Veenendaal, The Netherlands), by an expert gynecological radiation oncologist (RP, AS).

CT imaging and HR CTV contouring

The CT images at time of BT with applicator in place were generated in 4 mm slice intervals. The CT scanner is a conventional multislice CT scanner (Somatom plus S, Siemens, Erlangen, Germany) [6]. CT scans were performed using contrast agents for

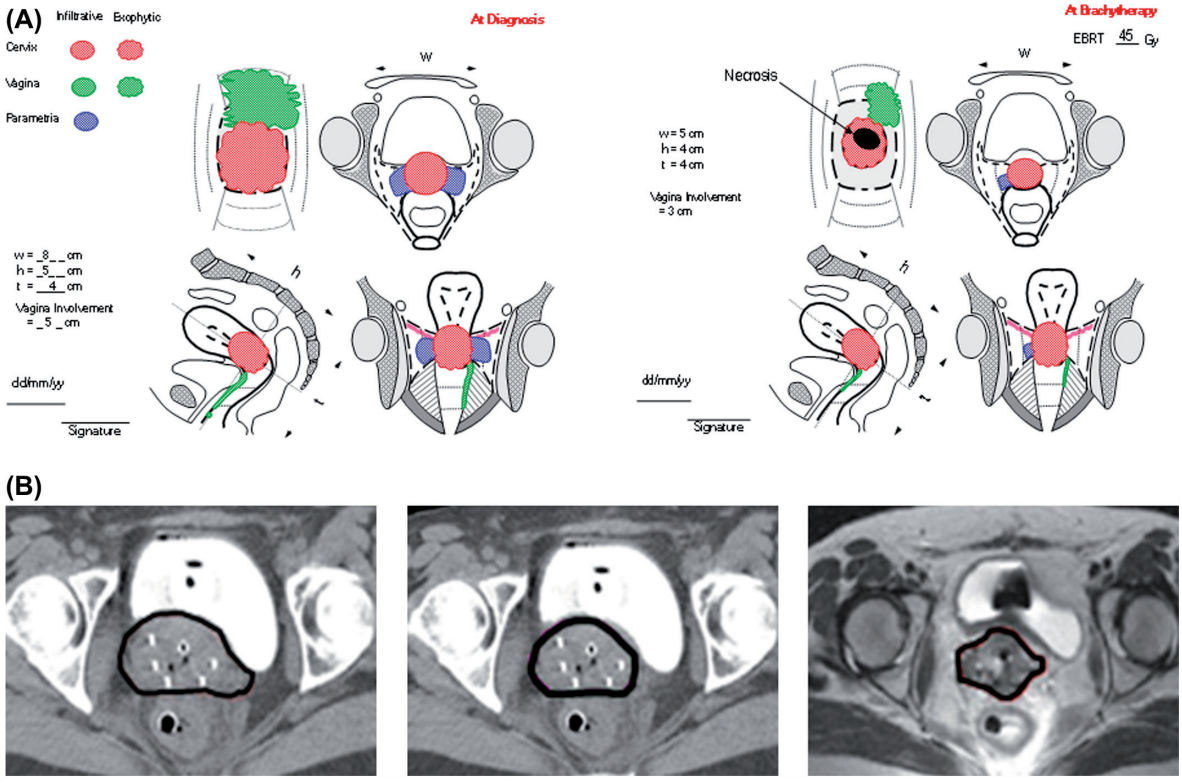

Figure 2. A) 3D clinical drawing of CGE for patient with large tumor in whole cervix with bilateral parametrial disease and vaginal infiltration along anterior and left wall reaching the lower third of vagina (FIGO stage IIIA) at diagnosis, Residual tumor after radiochemotherapy at time of BT was still in whole cervix with a central necrosis extending up to the right mid-parametrium and in the anterior-left upper third of vaginal wall. B) HR CTV delineation for the same patient on transverse CT section through the low cervix region with tandem applicator and interstitial needles: CT-based HR CTV_{stage}, CT-based $HRCTV_{stage+3Dclin}$ and MRI-based HR CTV_{MRI}.

bladder only. Contouring was done without knowledge of MRI findings by another expert radiation oncologist (NH) on an OMP workstation (Nucletron, Veenendaal, The Netherlands). HR CTV_{stage} was delineated using information on FIGO stage only. HR $CTV_{stage+3Dclin}$ was delineated by the same observer, taking additionally into account 3D documentation of CGE, as depicted on the clinical diagrams (Figure 2A).

As cranial tumor extension cannot be accurately assessed by FIGO, CGE or CT, in advanced disease, a standardized approach was chosen. Uterine height was measured on CT (sagittal plane) from the most cranial part of uterine fundus to most caudal slice of cervical tissue (at ring level). The height of HR CTV_{stage} and HR $CTV_{stage+3Dclin}$ were contoured using three different standardized uterine heights: 1/1, 2/3 and 1/2 of the uterus. These heights were investigated to assess which one would correspond best to the height as individually assessed from MRI (height of HR CTV_{MRI}) . For each patient six CT-based HR CTVs were designed: 1) HR CTV_{stage} with 1/1, 2/3, 1/2 uterine height; and 2) HR $CTV_{stage+3Dclin}$ with 1/1, 2/3 and 1/2 uterine height.

HR CTV_{stage} volumes were contoured on CT based on information of FIGO stage [18] and preliminary CT-based contouring guidelines [7]. For stage IB, HR CTV_{stage} encompassed the whole cervix as seen on CT. In FIGO stage IIB, HR CTV_{stage} included the entire cervix and parametria on both sides irrespective of the CT findings (as accurate distinction between tumor and parametrium and invasion of parametria may not always be detected accurately on CT). For stage IIIA, HR CTV_{stage} included the entire cervix, and the whole parametria if involved (Figure 2). In stage IIIB the entire cervix and both parametria to the pelvic side wall were contoured, respecting anatomical boundaries.

HR $CTV_{stage+3Dclin}$ volumes were contoured on CT with integration of information from 3D documentation of precise CGE at the time of BT. For stage IB the entire cervix seen on CT with dimensions comparable to CGE was contoured. In IIB, HR $CTV_{stage+3Dclin}$ encompassed cervix and residual parametrial extension according to dimensions and location identified by CGE. For IIIA (Figure 2), HR $CTV_{stage+3Dclin}$ included cervix, involved parametria and vagina at the time of BT. In IIIB, HR $CTV_{stage+3Dclin}$ included the entire cervix, and residual parametrial disease as described in the clinical drawings (Figure 2B).

Evaluation

Three-dimensional parameters, i.e. maximum height, thickness, and width, were measured for each HR CTV. The height of CT-based HR CTV indicates the cranio-caudal diameter assessable on mid-sagittal view along the uterine axis. The thickness was measured as the largest anteroposterior diameter on axial view. The width is the largest transverse diameter, measured on axial view. The volumes of all HR CTVs calculated by the treatment planning system were recorded for each patient.

The resulting 3D parameters of HR CTV_{stage} and HR $CTV_{stage+3Dclin}$ were compared with each other, and also with HR CTV_{MRI} (Figure 1). Width, height, and volume parameters for HR CTV_{stage} and HR $CTV_{stage+3Dclin}$ were normalized to corresponding HR CTV_{MRI} reference values, and resulting CT/MRI ratios were reported, e.g. volume ratio $VR_x = V_x / V_{HR\ CTV\ MRI}$, where x stands for HR CTV_{stage} or HR $CTV_{stage+3Dclin}$. For comparison between the different HR CTV volume parameters a paired Wilcoxon-rank test was performed. P-values < 0.05 were considered significant.

Results

Thirty-five patients with cervical cancer were evaluated. The mean values and standard deviations of height, width, thickness and volume of HR CTV_{stage}, HR $CTV_{stage+3Dclin}$ and HR CTV_{MRI} are listed in Table I. All parameters are reported as mean $\pm$ 1

Table I. Mean, standard deviations and ranges of volume, height, width, and thickness of HR CTV_{stage}, HR $CTV_{stage+3Dclin}$ and HR CTV_{MRI}.

Parameters (mean ± SD [range])	Height (cm)	Width (cm)	Thickness (cm)	Volume (cm^3)
HR CTV_{stage} 1/1 uterine height	6.6 ± 1.5 [4.0–10.8]	6.2 ± 0.8 [4.8–7.9]	3.9 ± 0.5 [2.9–4.8]	82 ± 27 [38–164]
HR CTV_{stage} 2/3 uterine height	5.1 ± 1.3 [3.2–9.2]	*	*	71 ± 23 [32–149]
HR CTV_{stage} ½ uterine height	4.3 ± 1.1 [2.8–8.4]	*	*	60 ± 20 [28–131]
HR $CTV_{stage+3Dclin}$ 1/1 uterine height	6.6 ± 1.5 [4.0–10.8]	5.4 ± 0.6 [4.2–6.5]	3.7 ± 0.5 [2.3–4.6]	66 ± 23 [32–141]
HR $CTV_{stage+3Dclin}$ 2/3 uterine height	5.1 ± 1.3 [3.2–9.2]	*	*	56 ± 20 [27–127]
HR $CTV_{stage+3Dclin}$ 1/2 uterine height	4.3 ± 1.1 [2.8–8.4]	*	*	47 ± 17 [21–111]
HR CTV_{MRI}	4.1 ± 1.5 [2.0–8.0]	4.4 ± 0.7 [3.0–5.7]	3.2 ± 0.6 [2.0–4.1]	34 ± 15 [12–73]

*Asterisks indicate that width and thickness values are independent of uterine height. The heights for the two different CT-based HR CTV groups are identical when the same uterine standard length is used.

standard deviation (SD). Statistically significant differences between the volumes of HR CTV_{stage} and HR $CTV_{stage+3Dclin}$ (each with 1/1, 2/3, 1/2 of uterine height) were found ($p < 0.05$). The volumes of HR CTV_{stage} and HR $CTV_{stage+3Dclin}$ were significantly larger ($p < 0.05$) than the volumes of HR CTV_{MRI} irrespective of chosen uterine height (Figure 3). The contouring of 1/1 uterine height for HR CTV_{stage} and HR $CTV_{stage+3Dclin}$ resulted in significantly larger volumes. The mean normalized volumes (CT/MR volume ratio) of HR CTV_{stage} and HR $CTV_{stage+3Dclin}$ were 2.6 ± 0.6 and 2.1 ± 0.4. The place and extent of parametrial infiltration was not detectable on CT in more than 60% of cases.

The widths of the CT-based HR CTVs were larger than the widths of HR CTV_{MRI}. The differences between the normalized widths of both HR CTV_{stage} (1.5 ± 0.2) and HR $CTV_{stage+3Dclin}$ (1.2 ± 0.2), and HR CTV_{MRI} (1) were statistically significant (Figure 4), as well as the difference between the mean normalized widths of HR CTV_{stage} and HR $CTV_{stage+3Dclin}$. The overestimation of the widths of HR CTV volumes contoured on CT was decreased by adding CGE information (Table II). No statistically significant differences were noticed in regard to thickness (Table II).

For patients with stage IB (8/35), the mean height ratio (CT height/MRI height) of HR CTV_{stage} and HR $CTV_{stage+3Dclin}$ including 1/2 uterine height was 1.1 ± 0.1. For patients with stage IIB and III (27/35), heights of CT-based HR CTVs including 1/2 uterine height were smaller than the heights of HR CTV_{MRI} in 10 patients (six stage IIB and four stage III). The height of CT-based HR CTV including 2/3 uterine height was slightly smaller than the height of HR CTV_{MRI} in three patients (two stage IIB and one stage III). These three patients had extensive intrauterine tumor infiltration at time of BT and the whole intrauterine tandem lengths had to be loaded to achieve sufficient dosimetric coverage of the original HR CTV_{MRI}.

Discussion

In order to evaluate the potential improvement of a fully CT-based delineation protocol, for settings without access to MRI at the time of brachytherapy, the use of information based on FIGO stage with/without adding precise documentation of gynecological findings was investigated in this study. The quality of the CT-based HR CTV contours was assessed by comparison with the gold standard, i.e. MRI-based target delineation. The results indicate a clear advantage of CT contouring when taking into account precise information from CGE. The volumes of HR CTV_{stage} were statistically significantly larger than those of HR $CTV_{stage+3Dclin}$, as contours based on FIGO stage alone lead to a large overestimation, especially of target width. The importance of CGE became most evident in width assessment and was not very pronounced for HR CTV thickness. The place and extent of parametrial infiltration was not

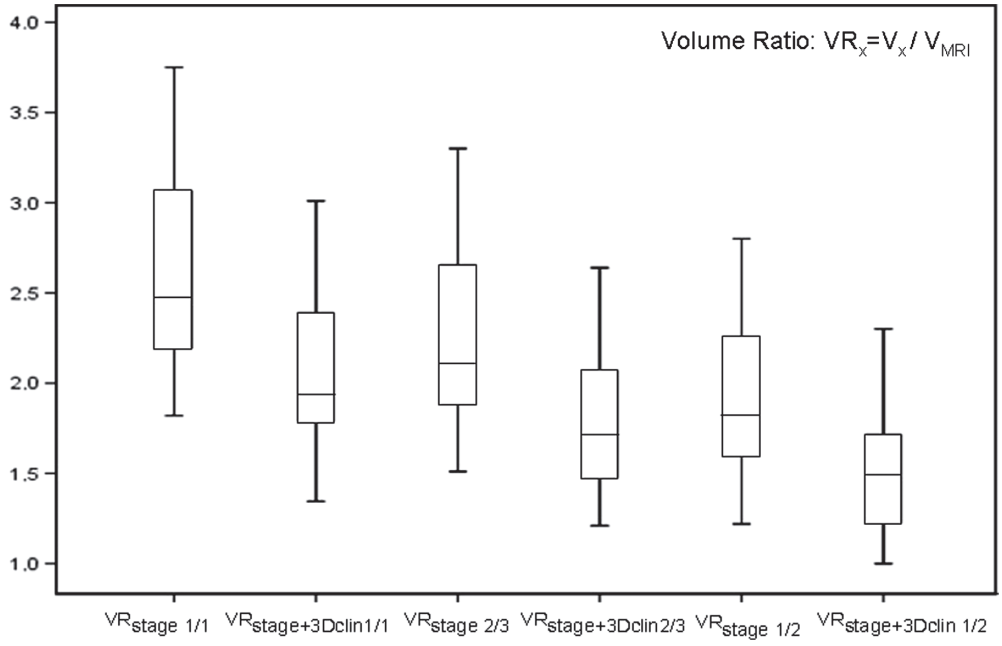

Figure 3. Significant decrease of the volume ratios (VR) of HR CTV by adding of CGE diagrams, for all standardized uterine lengths (1/1, 2/3, 1/2) used in the study. VR_{stage} is the volume ratio of HR CTV_{stage}/HR CTV_{MRI} and $_{VRstage+3Dclin}$ is the volume ratio of CT-based HR $CTV_{stage+3Dclin}$/HR CTV_{MRI}.

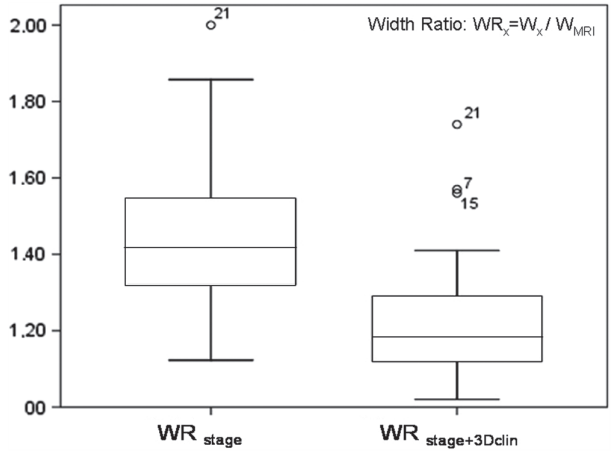

Figure 4. Significant decrease of the width ratio (WR) of HR CTV by adding of CGE diagrams. WR_{stage} is the width ratio of CT-based HR CTV_{stage}/HR CTV_{MRI} and $_{WRstage+3Dclin}$ is the width ratio of CT-based HR $CTV_{stage+3Dclin}$/HR CTV_{MRI}.

detectable on CT in more than 60% of cases. The protocol had foreseen delineation of the whole parametria in case of FIGO stage information alone. This conservative approach provides upper limits for the overestimation of CT-based HR CTV volumes in case of very limited additional information.

Our study showed that HR CTV_{stage} and HR $CTV_{stage+3Dclin}$ volumes based on standard heights are significantly larger than HR CTV_{MRI} volume, overestimating mainly the width and using standard heights. These findings are in agreement with other reports [16,17] and are due to the inferior soft tissue contrast of CT which does not allow identification of macroscopic tumor. The comprehensive information of disease spread based on clinical examination may contribute to reduce the inaccurate CT-based volume determination (in particular in width). This is shown by the present study by an improved conformity, through width and volume reduction, when comparing contouring based on gynecologic information with FIGO stage information only. CT-based HR CTV contouring should always be based on CGE [documented on a specific diagram (Figure 2A)]. This procedure is recommended by the GEC ESTRO even when MRI is available [6,7,12], and also formed the basis of the CT-MRI study by Viswanathan et al. [16]. Additional improvement most likely would be gained if the same person doing the gynecological examination is also doing the contouring, which was not the case for this study.

Several studies compared CT-guided BT with conventional BT and demonstrated that CT-based planning is superior to conventional planning, improving conformity of target coverage [21]. Shin et al. [21] used pre-treatment MRI to detect evidence of intrauterine tumor extension. The macroscopic residual cervical tumor was delineated on CT images with information of CGE and pre-treatment MRI.

Our study tried additionally to assess the potential of using various standard uterine heights for CT-based HR CTV height determination. The height of the individual uterine tumor invasion could not be assessed in the study population, as neither CT nor CGE are capable of assessing uterine tumor invasion in cervix carcinoma. Therefore a standardized approach was investigated by contouring three different uterine heights (whole, 2/3 and 1/2 of uterus). Excessively large volumes were observed in patients with stage IB where such extensive contouring seems to be unnecessary. The very pronounced volume effect of choosing a standard height of 2/3 or 1/1 of the uterine corpus presents the major difference compared to results in a former study [16]. In the latter, an assumed dome shaped cranial cervix border was contoured based on CT information.

As a conclusion of the present study, the CT-based contouring guidelines as suggested earlier by Viswanathan et al. [16] have to be taken with caution, regarding the superior border of the HR CTV. According to these recommendations the cranial border of the HR CTV should be delineated at the level where uterine vessels first appear, or to a point where the uterine cavity appears. Then two slices of

Table II. Mean and standard deviations of the CT/MRI width ratios ($WR_{x=}$ W_x/W_{MRI}) thickness ratios ($TR_{x=}$ T_x/T_{MRI}) for all HR CTV_{stage} and HR $CTV_{stage+3Dclin}$, and heights ratios ($HR_{x=}$ H_x/H_{MRI}) for all standard uterine heights used for both CT-based contour types, grouped by different FIGO stages.

		FIGO stage			
	x	IB (n = 8)	IIB (n = 18)	III (n = 9)	All (n = 35)
CT/MR width ratio WR_x	HR CTV_{stage}	1.5 ± 0.3	1.4 ± 0.1	1.4 ± 0.2	1.5 ± 0.2
(mean± SD)	HR $CTV_{stage+3Dclin}$	1.3 ± 0.2	1.2 ± 0.1	1.2 ± 0.2	1.2 ± 0.2
CT/MR thickness ratio TR_x	HR CTV_{stage}	1.2 ± 0.1	1.3 ± 0.2	1.1 ± 0.1	1.2 ± 0.2
(mean± SD)	HR $CTV_{stage+3Dclin}$	1.2 ± 0.1	1.2 ± 0.2	1.1 ± 0.1	1.2 ± 0.1
CT/MR height ratio HR_x	1/1 uterine height	1.7 ± 0.2	1.9 ± 0.2	1.7 ± 0.6	1.7 ± 0.4
(mean± SD)	2/3 uterine height	1.3 ± 0.1	1.5 ± 0.2	1.3 ± 0.4	1.3 ± 0.3
	1/2 uterine height	1.1 ± 0.1	1.2 ± 0.2	1.1 ± 0.4	1.1 ± 0.3

contour around the tandem superiorly were added to cover the cervical apex. However, it is clearly recognized in literature that for cranial tumor extension assessment, CT alone is insufficient [14].

According to findings of the present study there may be a geographical miss in 10–35% of cases with advanced disease when defining the cranial border of HR CTV at 2/3 or 1/2 of the uterine height. Therefore, any tailoring of this border should be avoided, if only CT is available, except in cases of very limited disease. If MRI is not available, our recommendation is, consequently, to include most of the height along the uterine cavity into the HR CTV in advanced stages. A straightforward approach for CT-based treatment planning is to keep the full loading of intrauterine tandem length up to its tip as planning aim according to traditional practice.

The potential dosimetric benefit of our improved CT-based target structures has not been assessed in the present study. Overall, the reported DVH parameters for CT-based target structures are expected to underestimate systematically the dose to the corresponding MRI-based HR CTV, which is usually smaller according to present and former findings [17], in particular in regard to height and width. The impact of volume on the D90 HR CTV for standard dose planning and dose prescription to point A was presented by Tanderup et al. [22]. For example, increasing the HR CTV volume from 30 to 45 cm^3 decreases the D90 by more than 20%.

Overall, our study shows that CT-based contouring can be significantly improved by careful integration of comprehensive CGE at diagnosis and at time of BT, in particular for appropriate width. The height of the HR CTV should be determined by applying standard heights. If only CT information is available (no MRI), the selection of at least two thirds of the uterine cavity as standard height will include most of the potential cranial tumor extension for advanced disease. The results presented here, are based on a medium-size cohort of patients who were evaluated retrospectively. Therefore, these findings need to be validated within a larger (multi-institutional) prospective trial. The use of most modern, contrast enhanced techniques might further improve the quality of CT-based contouring in general. As another alternative to CT and MRI, modern ultrasound techniques, adapted for treatment planning, might be used in the future [23–25].

While MRI remains the gold standard for contouring HR CTV for 3D IGABT, CT-based delineation of HR CTV may be applied in situations with limited imaging resources. However, to arrive at a clinically acceptable accuracy such CT-contouring always has to be based on a comprehensive 3D documentation of repetitive gynecologic examination.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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