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Cervix cancer brachytherapy

Inter-observer comparison of target delineation for MRI-assisted cervical cancer brachytherapy: Application of the GYN GEC-ESTRO recommendations

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ABSTRACT

Background and purpose: To investigate the inter-observer variation of target contouring when using the GYN GEC-ESTRO recommendations for MR image-guided brachytherapy (IGBT) for cervical cancer.

Materials and methods: Nineteen cervical cancer patients, treated by radiotherapy at the Institut Gustave Roussy (IGR) in France ($n = 9$) or at the Medical University of Vienna (AKH) in Austria ($n = 10$) were included in this study. IGBT was used for all patients. Two radiation oncologists, one from IGR and the other from AKH, outlined the target volumes on MRI at the time of brachytherapy according to the GYN GEC-ESTRO recommendations. The absolute, common and encompassing volumes and their conformity indices (CIs) were assessed for the GTV, HR CTV and IR CTV. D90 and D100 for each volume were assessed. Visual evaluation was made to assess the reasons for the most frequent inter-observer differences.

Results: The mean volumes of GTV and HR CTV did not differ significantly between the observers, $p > 0.05$. Significant differences were observed only for the mean volumes of the IR CTV of both centres, $p < 0.05$. CIs ranged from 0.5 to 0.7. DVH-parameter analyses did not reveal any statistical differences, except for the D100 for the GTV at AKH, and the D90 for the IR CTV at IGR, $p < 0.05$. Underlying reasons for inter-observer differences included image contrast adjustment and neglecting to consider anatomical borders.

Conclusions: The results of this inter-observer study show that the application of the GYN GEC-ESTRO recommendations for IGBT contouring at two different institutions with two different traditions for applicators, CTV assessment, MR image acquisition and dose prescription is feasible, and it produces acceptable inter-observer variability.

Magnetic resonance (MR) image-guided brachytherapy (IGBT) for locally advanced cervical cancer enables individualised adaptation of the application technique and the dose distribution [1–6]. The dose to the target can be escalated, and the organs at risk (OARs) are spared [7–12]. With the application of IGBT the conformity increases, but the method still depends on the ability of the radiation oncologist to identify and to delineate to a high degree of accuracy the target structures.

To minimize uncertainties and to establish a common language internationally, the Gynaecological (GYN) European Group of Curietherapie (GEC) – European Society for Therapeutic Radiology and Oncology (ESTRO) Working Group issued recommendations for the definition of targets with high and intermediate risks for recurrence (High Risk Clinical Target Volume – HR CTV, Intermediate Risk Clinical Target Volume – IR CTV) [13–14]. To prove the feasibility of implementation of these recommendations and to assess any outstanding uncertainties, a number of contouring workshops and inter-observer studies have been performed by the Working Group [15–19]. During these contouring workshops, it has been observed that when inexperienced observers initially apply the contouring recommendations, the level of conformity is low: CI of 0.1–03 [15].

With regard to inter-observer studies, applying the GYN GEC-ESTRO recommendations for cervical cancer IGBT, the following three results were found: (1) Two investigations performed in a multi-institutional setting, showed good volumetric and dosimetric agreement [16–17]. (2) A comparison between MR and Computed Tomography (CT) imaging modalities revealed no significant differences in volume sizes and Dose–Volume

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Histogram (DVH) parameters for the OARs, but for target volumes, CT-based contouring significantly ($p < 0.05$) overestimated the contour width when compared to Magnetic Resonance Imaging (MRI) [19]. This was also reflected in significant variations for the values of D90, D100 and V100 of the HR CTV [19]. (3) In an investigation estimating the agreement between HR CTV outlines delineated by two observers on transverse (T) and para-transverse (PT) MR images, inter-observer and inter-planar conformity indices were high: 0.7–0.8 [18]. Inter-observer variation and inter-planar topographic variation of DVH parameters were not significant, $p > 0.05$. Contouring difficulties were significantly lower ($p < 0.05$) in the para-transversal plane [18].

The current inter-observer investigation was performed before the initiation of a phase II multi-centre trial (EMBRACE) studying IGBT in patients with locally advanced cervical cancer. The aim was to prove the feasibility of the application of the GYN GEC-ESTRO recommendations for contouring, when applied in two institutions with different philosophies for defining CTV and for dose prescription, the Medical University of Vienna (AKH) and the Institut Gustave Roussy in Villejuif (IGR), see Table 1. These centres represent two different traditions for the application of tandem-ring and mould applicators, and for CTV assessment: HR CTV and IR CTV, and dose prescription 85+ Gy and 60+ Gy.

Materials and methods

Patients and treatment

A total of 19 patients with biopsy proven cervical cancer, treated by radiotherapy at the AKH ($n = 10$) or at the IGR ($n = 9$), were included in this study. The patients were randomly selected, and the requirement for their inclusion was the use of IGBT for biopsy proven locally advanced cervical cancer. Fédération Internationale de Gynécologie Obstétrique (FIGO) stage distribution was as follows: IB1 = 1, IIA = 2, IIB = 9, IIIB = 6, IVA = 1. The mean patient age was 55 (±13) years. Bilateral, unilateral and no parametrial involvement were present in 11, 5 and 3 patients, respectively. The distal vagina was invaded in four and proximal vagina in five patients. Fourteen patients had squamous cell, four adenocarcinoma, and one adenosquamous cancer.

At both AKH and IGR, the initial clinical assessment of local tumour stage was performed by two independent examiners, a radiation oncologist and a gynaecologist. Pre-treatment staging evaluation, in addition to FIGO staging requirements, included abdominopelvic CT, pelvic MRI, and in some patients laparoscopic lymph node staging (AKH) or Positron Emission Tomography (PET) scanning (IGR).

The treatment at AKH consisted of 3D conformal CT-based External Beam Radiotherapy (EBRT) (45–50 Gy in 25–28 fractions) ± concomitant Cisplatin chemotherapy (40 mg/m^2 weekly), followed by high dose rate IGBT. Insertions were performed using an MRI compatible, Stockholm-based, tandem-ring applicator (Nucletron®). In locally advanced disease, additional interstitial catheters were inserted, if indicated. Four fractions of 7 Gy were prescribed to the HR CTV. The total dose to the HR CTV from EBRT and brachytherapy was 84–89 Gy (EQD2) [4,13,20].

Table 1
Features at the two institutions (AKH, IGR).

	AKH	IGR
MRI device	0.2 T	1.5 T
Application technique	Tandem ring ± interstitial	Mould applicator
Target tradition	HR CTV (related to point A)	IR CTV (related to 60 Gy reference volume)
Dose prescription	85+ Gy EQD2 to HR CTV	60 Gy EQD2 to IR CTV

A total of 7/9 patients at IGR underwent 3D conformal CT-based EBRT (45–50 Gy in 25–28 fractions), ± concomitant Cisplatin chemotherapy (40 mg/m^2 weekly), followed by low dose rate IGBT. Insertions were performed using an MRI compatible individualised and moulded applicator with two intravaginal sources designed according to tumour shape and extension, and one intrauterine source. A dose of at least 10–15 Gy was prescribed to the IR CTV [13]. The remaining two patients were treated by preoperative low dose rate brachytherapy alone of 60 Gy, prescribed to the IR CTV [13]. Descriptions of the procedures of applicator reconstruction, treatment planning and dose prescription for both centres are given in the previous reports, published by Kirisits [4] and Gerbaulet [21].

MRI technique

At both institutions, an MRI scan was obtained for every patient before EBRT and at the time of brachytherapy when the patient was in supine position with the applicator in place. At AKH, MRI was performed using a pelvic surface coil with a 0.2 T low field system (Siemens Magnetom Open-Viva®), in the transverse (i.e., perpendicular to the body axis), para-sagittal, para-coronal and para-transverse orientations. The image acquisition protocol has been described in detail by Dimopoulos et al. [22].

In IGR, MRI scans were obtained with a 1.5 T device (GE Excite®) with a pelvic-phased array coil. Images were generated in the transverse and para-sagittal orientations. A fast spin–echo technique with a repetition time of 3350 ms and an echo time of 120 ms for T2-weighted images was used. The displayed field of view was 30 × 30 cm^2 and data collection was performed with a matrix of 224 × 256 pixels. The slice thickness was 3 mm without an intersection gap. Glycerine-filled catheters were placed inside the intrauterine and the intravaginal catheters, before the scan was performed in order to enable their visualisation on the MR images. Axial images were obtained from the level above the uterine fundus to the inferior border of symphysis pubis below any vaginal tumour extension. Sagittal images were obtained between the internal obturator muscles.

Subsequently, all the transverse MRI scans were transferred to a treatment planning system (TPS) for contouring. In AKH, this was the PLATO TPS (Version 14.3, Nucletron®, Veenendaal, The Netherlands) and in IGR, the Dosigray Imago (Version 1.0, Dosisoft, Cachan, France).

Contouring

The Gross Target volume (GTV), HR CTV and IR CTV were delineated by two radiation oncologists, observer 1 at AKH (OBS-1) and observer 2 at IGR (OBS-2), using their current practice and following the recommendations of the GYN GEC-ESTRO working group [13]. Definitions of target volumes, including definitions of *bright areas* and *grey zones* have been described in detail previously [13,14,22]. OBS-1 and OBS-2 had four years and one year of experience in the field of MRI-based gynaecological brachytherapy, respectively.

After treatment, the complete MRI datasets were exchanged between the two centres, and contouring was repeated by the second observer. The Dosigray imago TPS (Version 1.0, Dosisoft, Cachan, France) used at IGR for contouring provides an auto-margin tool. This was occasionally used by OBS-2 for the generation of the IR CTV by adding a margin to the HR CTV. The PLATO TPS (Version 14.3, Nucletron®, Veenendaal, The Netherlands) used for contouring at AKH does not include such a tool.

To facilitate the delineation procedure, complete MRI datasets were available on DICOM viewer software (eFilm Workstation, version 1.5.3, Copyright ©2001. eFilm Medical Inc., Toronto, Canada).

The delineation process was based not only on the MRI data, but also on clinical drawings with the clinical information assessed at the time of diagnosis and at the time of brachytherapy. Both observers kept the contouring time within reasonable time limits (<30 min), simulating real clinical conditions.

For each of the AKH patients, the MRI scan from a single high dose rate brachytherapy fraction was selected randomly, whereas for the IGR patients, the MRI scan from the single low dose rate fraction was used.

To perform volumetric and DVH analysis, the contoured MRI data sets with the treatment plans were transferred to an Oncentra® Brachy TPS (Nucletron, Veenendaal, The Netherlands).

Volumetric analysis

The volume computations were performed by the TPS. For each MRI scan, the sizes of target volumes as delineated by both observers were then compared. For the three resulting pairs of contours, a common volume (defined as the largest volume common to a pair of outlines) and an encompassing volume (defined as the smallest volume encompassed by a pair of outlines) were calculated. The same calculation method was used for all patients using the TPS Boolean operator tools.

To study the volumetric inter-observer agreement, a CI was determined. A variety of definitions for CI exist. Our analysis of volumetric agreement was based on the work of Rasch et al. [23]. The concept of a conformity index (CI) defined as the ratio between the common and encompassing volume of a given pair of contours was introduced. Perfectly overlapping volumes are indicated by CI = 1, and as the agreement decreases CI tends towards zero.

Topographic analysis

In order to perform qualitative topographic analysis, delineated pairs of contours were analysed by the two observers and their colleagues during joint discussions, rather than relying on only CI correspondence. Reasons for discrepancies were identified and their frequencies determined.

DVH analysis

To perform dosimetric analysis, the IGBT plans created for the treatment of the 19 patients were analysed in accordance with the recommendations of the GYN GEC-ESTRO working group [13,14]. For each of the AKH patients, the plan from a single high dose rate brachytherapy fraction selected randomly for contouring was used for the calculation of the DVH parameters. For the IGR patients, the plan from the single low dose rate fraction was used for DVH analysis.

A total of 114 cumulative DVHs were generated (2 observers × 3 target volumes × 19 patients). DVH analyses included the volume of the target, and the minimum dose delivered to 90% (D90) and 100% (D100) of the volume of interest. Altogether, 228 values for D90 and D100 were calculated. For the AKH patients, these doses were calculated for study purpose only and not for actual treatment, since the total high dose rate brachytherapy doses were extrapolated from the single fraction studied. All dose values were biologically normalised to an equivalent dose of 2 Gy per fraction (EQD2) based on the linear quadratic model (LQ-model) with $a/b = 10$ Gy for the GTV, HR CTV and IR CTV [20].

Statistical analysis

All continuous numerical variables were presented as mean values with ranges and standard deviations. The variations in volumetric data and DVH parameter were assessed using a Wilcoxon signed rank test, and a value of $p < 0.05$ was considered significant. SPSS software (version 11.0.1. for Windows, Copyright© SPSS Inc. 1989–2001, Chicago, IL) was used for the analyses.

Results

Volumetric analysis

The mean volumes of the GTV, HR CTV and IR CTV are given in Table 2. No overall pattern for a given observer can be demonstrated for the three target volumes. For the GTV and the HR CTV, the results are reasonably similar for both observers. Significant differences between the mean volumes of the outlined pairs of contours were seen for the IR CTV at both centres, $p < 0.05$.

The sizes of the common and encompassing volumes necessary for calculating the conformity indices are given in Tables 3 and 4. The values of CI for all three volumes were similar for both AKH and IGR. The reasonably high values of CI between 0.5 and 0.7 for the individual centres indicate consistency between the observers in both centres (Table 3). When the data are combined (Table 4), the CIs are either 0.6 or 0.7.

Topographic analysis

For the GTV, the most frequent cause of inter-observer variability (7/19 patients) was associated with variability in the manual adjustments of the window levels and window widths of the MR images. This effect was particularly pronounced in the caudal portions of the GTV. The second most common observation (6/19 patients) was related to the regions of high signal intensity surrounding the cervical canal, representing fluid and/or mucous. These were interpreted as macroscopic visible tumour masses and were included in the GTV by one of the observers. In the two cases with the poorest volumetric agreement for the delineation of the GTV (CI = 0.1 and CI = 0.3), image quality was the decisive factor. An additional uncertainty appeared to be linked to the areas of the cervix and the corpus depicted with an inhomogeneous high-to-intermediate signal intensity on T2-weighted images. The extent of inclusion of these regions differed between the observers in 3/19 patients.

For the HR CTV, a different degree of weighting of the clinical information for the extent of vaginal and parametrial involvement

Table 2
Mean contoured volumes for target structures.

Structure	Volume (cm^3) mean (range)			Volume (cm^3) mean (range)		
	AKH, $n = 10$			IGR, $n = 9$		
	OBS-1	OBS-2	p value	OBS-1	OBS-2	p value
GTV	18 (3–43)	**17** (1–41)	$p > 0.05$	5 (2–11)	5 (2–10)	$p > 0.05$
HR CTV	53 (13–96)	**50** (12–97)	$p > 0.05$	**26** (15–59)	29 (13–51)	$p > 0.05$
IR CTV	**118** (43–199)	142 (53–222)	$p < \mathbf{0.05}$	**86** (51–182)	102 (63–178)	$p < \mathbf{0.05}$

Measurement results by observers OBS-1 and OBS-2 for contoured volumes in 10 patients from AKH and nine patients from IGR. The lowest volume assessment for a given contour for each OBS-1 and OBS-2 pair and significant p values (<0.05) are given in bold type.

Table 3
Common and encompassing volumes and associated conformity indices for AKH and IGR.

Structure	Volume (cm^3) mean (range) and CI			Volume (cm^3) mean (range) and CI		
	AKH, $n = 10$			IGR, $n = 9$		
	Common	Encompassing	CI	Common	Encompassing	CI
GTV	14 (1–39)	20 (3–45)	**0.6** (0.3–0.9)	3 (1–7)	7 (3–15)	**0.5** (0.1– 0.7)
HR CTV	42 (10–83)	59 (16–108)	**0.7** (0.5–0.8)	20 (11–14)	35 (18–67)	**0.6** (0.4–0.7)
IR CTV	111 (40–187)	147 (54–228)	**0.7** (0.6–0.8)	73 (41–152)	114 (67–208)	**0.6** (0.5–0.7)

The mean CIs for a given contour for AKH and IGR are given in bold type.

Table 4
Common and encompassing volumes and associated conformity indices for both centres combined.

Structure	Volume (cm^3) mean (range) and CI Combined results from both centres, $n = 19$		
	Common	Encompassing	CI
GTV	9 (1–39)	14 (3–45)	**0.6** (0.1–0.9)
HR CTV	31 (10–84)	47 (16–108)	**0.7** (0.4–0.8)
IR CTV	92 (40–187)	127 (54–228)	**0.7** (0.5–0.8)

The mean CI for a given contour is given in bold type.

was revealed to be the cause of inter-observer variability in the three patients with the lowest conformity indices, CI = 0.4. Differences with regard to the cranial border of the HR CTV were observed, when the conical shape of the cranial border of the cervix was ignored (5/19 patients). In these patients, a margin was added either to the visible cervix in the absence of *bright* areas or *grey zones* (3/19 patients), or to the GTV in the direction of the uterine corpus (2/19 patients). In three of these patients, the visibility of the uterine zonal anatomy was lost.

For the IR CTV, the use of the TPS auto-margin tool for the generation of an IR CTV without any subsequent manual editing of the generated contours, in particular in regions where the OARs (bladder, rectum and sigmoid) are involved, was the cause of inter-observer variation in 7/19 patients. Similar findings were observed at the pelvic side wall, located approximately 5–10 mm medially to the internal obturator muscle in 2/19 patients (Fig. 1). Variability in outlining the caudal border of the IR CTV was observed, and appeared to be mainly associated with differences in the amount of intravaginal applicator/packing included in the IR CTV. However, there did not appear to be any systematic differences in contouring between the two observers. Finally, we noted that ignoring the cranial boundary of the parametrial space was associated with inter-observer variability in 3/19 patients.

DVH analysis

The inter-observer mean values of D90 and D100 are given in Tables 5 and 6. DVH-parameter analyses did not reveal any statistical differences, except for the D100 for the GTV at AKH, and the D90 for the IR CTV at IGR, $p < 0.05$.

Discussion

One of the most frequent factors contributing to inter-observer variability in any target delineation study is the lack of a strict protocol [24–31]. Contouring guidelines have been proposed and applied by several working groups for different tumour sites [13,32–35]. In IGBT of cervical cancer, the GYN GEC-ESTRO working group recommendations provide a sound basis for such a protocol [13,16–18].

To date, there have been few inter-observer studies for the delineation of target volumes with cervical cancer [16–19,24,25].

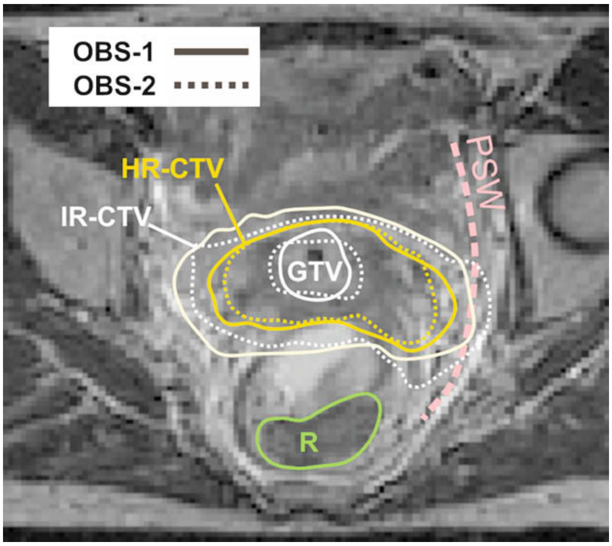

Fig. 1. Axial T2-weighted MR image of a patient with cervical cancer FIGO IIIB at the time of brachytherapy with the applicator in place. The patient was treated at IGR with EBRT + concomitant Cisplatin chemotherapy, followed by low dose rate IGBT. The contours of observer 1 (OBS-1) are indicated by the solid lines and those of observer 2 (OBS-2) by dotted lines. Small inter-observer variability was assessed for the lateral extension of the GTV and HR CTV contours. The anatomic boundary of the pelvic side wall (PSW-dotted line), which is located ~5–10 mm medial to the internal obturator muscle, was neglected by OBS-2 during IR CTV delineation. However, CIs were 0.4 for the GTV and 0.6 for both the HR CTV and IR CTV contours. The mean differences for the D90 for the GTV, HR CTV and IR CTV were 4, 2 and 1 Gy EQD2, respectively. R, rectum.

Some of these studies were in the setting of EBRT, and in the absence of contouring guidelines [24,25]. For example, Weiss et al. compared the CTV, as delineated by seven different specialists. They obtained CIs of 0.1–0.6 [24], whereas our results gave CIs of 0.5–0.7.

In a study involving delineation of the prostate, Rasch et al. reported on the level of contouring concordance between three observers across two different imaging modalities (CT and MRI). The mean ratios of encompassing/common volume for the inter-observer and inter-modality comparisons were approximately 1.6 and 2.4, respectively (corresponding to CIs of 0.6 and 0.4) [23]. In a study of tangential breast irradiation, Struikmans et al. found a mean inter-observer CI of 0.87 and 0.56 for delineation of whole breast CTV and boost CTV, respectively [36].

However, even if guidelines are strictly followed by experienced observers, complete agreement between the measured contours cannot be expected to be achieved due to the possibility of small random errors by the observers: However, systematic errors can be reduced by education and by strictly following the contouring protocol and/or guidelines.

The observers of this study, since they had one and four years experience with MRI-based contouring for cervical cancer brachytherapy, and since they were coming from centres that contributed

Table 5
Mean D90 and D100 values for AKH patients.

Structure	D90 (Gy) mean (range)			D100 (Gy) mean (range)		
	OBS-1	OBS-2	*p* value	OBS-1	OBS-2	*p* value
GTV	118 (82–164)	133 (79–209)	$p > 0.05$	87 (61– 135)	100 (58–173)	$p <$ **0.05**
HR CTV	86 (64–105)	89 (67–111)	$p > 0.05$	67 (55–83)	66 (54–79)	$p > 0.05$
IR CTV	66 (57–79)	67 (58–76)	$p > 0.05$	55 (49–61)	55 (49–64)	$p > 0.05$

Measurement results by observers OBS-1 and OBS-2 for D90 and D100 values (mean and range) of 10 patients from the AKH. The D90 and D100 are in equivalent dose in 2 Gy fractions (EQD2, / = 10). Significant *p* values (<0.05) are given in bold type.

Table 6
Mean D90 and D100 values for IGR patients.

Structure	D90 (Gy) mean (range)			D100 (Gy) mean (range)		
	OBS-1	OBS-2	*p* value	OBS-1	OBS-2	*p* value
GTV	96 (52–123)	102 (55–144)	$p > 0.05$	77 (42–99)	80 (43–108)	$p > 0.05$
HR CTV	70 (35–99)	68 (43–97)	$p > 0.05$	58 (26–79)	57 (33–79)	$p > 0.05$
IR CTV	58 (28–78)	54 (30–66)	$p <$ **0.05**	49 (21–64)	48 (21–58)	$p > 0.05$

Measurement results by observers OBS-1 and OBS-2 for D90 and D100 values (mean and range) of nine patients from the IGR. The D90 and D100 are in equivalent dose in 2 Gy fractions (EQD2, / = 10). Significant *p* values (<0.05) are given in bold type.

to the development of the protocol, have to be considered as experienced. The question has been raised whether similar results can be achieved by less experienced observers. It is well recognized that there is a learning curve, and formal training, as is offered regularly by teaching courses and workshops of the GYN GEC-ESTRO group, is advisable. Relying on the experience from teaching and from the EMBRACE dummy run contouring evaluation, formal training and contouring experience of at least six months and/or 30 patients are recommended to participating centres prior starting the MRI-based approach.

With the increasing size of an outlined volume, inter-observer variability was found to increase in our study. The largest differences observed in terms of absolute volume size were for the IR CTV, with significant differences for both centres, $p < 0.05$, see Table 2. However, the CIs for the IR CTV were higher than or equal to the CIs of GTV or HR CTV, see Tables 3 and 4. This finding indicates that despite the difference in absolute volumes, the impact of inter-observer variability on the encompassing and common volumes was rather limited and associated with high CIs. Nevertheless, this demonstrated a high degree of topographical agreement between observers for the IR CTV.

According to the GEC-ESTRO contouring recommendations, extracervical tumour extension, such as pathological residual tissue in the parametria defined by palpable induration and/or residual grey zones of intermediate signal on T2-weighted MR images, has to be included into the HR CTV [13]. Hence, both the clinical and the MRI findings have to be translated into the HR CTV contours.

Documentation of the clinical findings with drawings, especially with regard to the degree of parametrial and vaginal extension [14], is essential for the contouring procedure. In the study, contouring was based not only on MRI findings, but also on clinical findings as documented on clinical drawings created at the time of diagnosis and at the time of brachytherapy. Nevertheless, topographical analysis showed that the weighing of multiple sources of clinical information, particularly regarding the extent of parametrial and vaginal invasion, was different between the observers, and appeared to be a significant cause of inter-observer variability in the three patients with the lowest conformity indices, CI = 0.4. Our results emphasise that the translation of the clinical information available into the HR CTV contours represents a key uncertainty in HR CTV contouring.

It must be emphasised that for the definition of the IR CTV, a detailed mental integration of the pre-treatment clinical and MRI data with the situation at the time of IGBT appears of vital importance, since regions which are perhaps partly without macroscopically visible tumour have to be outlined [13]. To identify these areas, the initial anatomy and pathology have to be superimposed on the brachytherapy MR images with the applicator in place. We believe that for this challenging procedure, standardised training for observers is essential.

The imaging modality used, CT or MRI, is of high importance for the delineation procedure [19,37]. For tumours of the brain, Ten Haken et al. claimed that the degree of inter-observer variability in volume definition is of the same order of magnitude as differences in volume definition, which are obtained between CT and MRI [37]. A comparison of MRI and CT for target delineation in IGBT of cervical cancer has revealed that CT-based contouring overestimates a contour width and results in significant variations in D90 and D100 values for the HR CTV [19].

In the present study, which exclusively used MRI because of its superior soft tissue depiction quality for target delineation, inter-observer agreement was good. Nevertheless, image quality and window level can result in overestimation or underestimation of tumour boundaries and thereby increase inconsistencies of target volume definition among observers [38].

The ability to discriminate the lower portions of the bright GTV was associated with variability in the often necessary manual adjustments of the window levels and window widths, and decreased significantly with dark window levels. Thus, intra- and inter-observer image windowing differences may occur in the same patient. In our study, this was the most frequent cause of inter-observer variability for the delineation of the GTV (7/19 patients). However, we believe that standard pre-defined window levelling parameters do not result in the same contrast quality in all patients, and are therefore not universally applicable. In addition to image windowing, other factors including patient movement and bowel peristalsis influenced image quality.

A precise knowledge of anatomical landmarks of the pelvic side walls, parametria and the cervix are essential for the delineation of the boundaries of the target volumes (Fig. 1). In our study, inter-observer variability in the definition of target volumes was seen due to uncertainties in the identification of certain anatomical borders. This was particularly seen in 10 contour pairs, five of which involved the cranial cervix, three involved the upper parametria, and two involved the pelvic side walls.

The use of the TPS auto-margin tool for the generation of IR CTVs, without any subsequent manual editing of the generated contours, was the cause of noticeable inter-observer variation in 7/19 patients. Of note, the use of auto-contouring tools is not described in the GYN GEC-ESTRO contouring recommendations. It seems important to minimise these variations by the manual editing of contours.

In elderly patients, imaging with a low field MR device can be characterized by the absence of typical uterine zonal anatomy on T2-weighted images [39]. As a consequence, during brachytherapy and after EBRT, there is often a lack of sufficient contrast between the uterine cervix and the uterine corpus. In such cases, other landmarks such as the level of the uterine artery and the conical shape of the cervix can be used to identify and delineate the upper boundary of the HR CTV [13,19,39]. It should be noted that the upper borders of the parametrial space are also indicated by the uterine arteries [19,39].

Insufficient coverage of the brachytherapy target volume has been correlated to persistent disease and increased rates of pelvic relapse [40–42]. Appropriate tools to accurately measure target coverage are DVH parameters. In IGBT for cervical cancer, when using DVH parameters, favourable results for local control are obtained [9]. In the present study, significant differences between observers were obtained for the D100 of the GTV at AKH, and the D90 of the IR CTV at IGR ($p < 0.05$, see Tables 5 and 6).

Of note the mean difference of the D90 of IR CTV was 4 Gy, which represents some seven percent of the total dose applied to this target volume. With reference to the D100 of the GTV, it is believed that due to the steep dose gradient, small spikes in the contour can cause large deviations in the D100 [4,14]. Therefore, the differences observed in our study might be largely attributed to small inter-observer variations for this small-sized target.

Conclusions

This inter-observer study was performed prior to the initiation of a phase II multi-centre clinical trial (EMBRACE) involving IGBT for patients with locally advanced cervical cancer. The results show that the application of the GYN GEC-ESTRO recommendations for IGBT contouring at two different institutions with two different traditions for applicators (tandem-ring, mould), CTV assessment (HR CTV and IR CTV), MR image acquisition (0.2 T, 1.5 T) and dose prescription (85+ and 60 Gy) is feasible, and produces acceptable inter-observer variability.

This study supports the applicability of the GYN GEC-ESTRO recommendations in experienced centres. Inter-observer variability can be reduced by formal training. In addition, variability can be reduced by taking into account the uncertainties described in this study.

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