

## Dynamics of high risk clinical target volume reduction during brachytherapy and impact on its coverage in patients with inoperable cervical cancer

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Cervical cancer is the third most common cancer in women worldwide. Standard of care for patients with node positive or locally advanced tumors >4 cm is definitive radiotherapy and concurrent chemotherapy. Brachytherapy is an integral part of definitive radiotherapy for cervical cancer. The aim of the study was to show a dynamics of High Risk Clinical Target Volume (HR-CTV) reduction during Brachytherapy (BT) as a part of definitive treatment (External Beam Radiotherapy /EBRT/ +/- Chemotherapy /ChT/) depending on the initial Gross Tumor Volume (GTV) and its impact on HR-CTV coverage in patients with inoperable cervical cancer. We analyzed the dosimetric data for BT of 54 patients who have had Three Dimensional Planning of BT (3D BT). The Gross Tumor Volume, HR-CTV and organs at risk (OARs) were contoured on the magnetic resonance imaging (MRI), subsequently on the co-registered MRI images with computed tomography (CT). Point A and ICRU 38 rectal and bladder points were defined on reconstructed CT images. Patients were categorized on the basis of whether the 100% isodose line of the point-A prescription dose encompassed the HR-CTV (1st group) or not (2nd group). The 30cc volume has been determined as a cut-off value, which represented the most acceptable value of intermediate size of volumes.

The initial mean value of GTV was 42cc. After completion of EBRT/ChT, the mean GTV was 3.24cc what was 91% reduction rate in relation to the initial value. We followed the dynamics of HR-CTV reduction during BT and have noted its minimal reduction from 24.3cc (mean value) at the time of the first fraction to the 24.1cc before fourth fraction. The mean V100 was 98% and increased with decreasing of the volume size ( $p=0.0063$ , Fisher's exact test). D90 (mean value was 96.3 Gy10) has been correlated with V100 and also, it increased with decreasing of the volume size ( $p=0.0003$ ). The mean D0.1cc and D2cc of rectum doses were 80 Gy3 and 65.6 Gy3, respectively. The mean ICRU rectal dose for all patients was 67.2 Gy3. The mean D0.1cc (99.5 Gy3), D2cc (79.5 Gy3) and ICRU (75.2 Gy3) of bladder doses were acceptable.

Dynamics of HR-CTV reduction during BT was minimal, although, significant reduction of the GTV was achieved after EBRT/ChT. This study revealed that the dose prescription of 7 Gy $\times$ 4 fractions to point A was not sufficient indicator for dose coverage of the HR-CTV. However, dosimetric parameters as V100 and D90 were strong indicators for coverage of HR-CTV which was inversely related to the volume of the target and the extension of tumor. However, dosimetric parameters for rectum and bladder (D0.1cc, D2cc and ICRU) did not show dependence on the target volumes.

*Key words: cervical carcinoma, brachytherapy, 3D planning, dosimetric parameters, magnetic resonance imaging, computed tomography*

Cervical cancer is the third most common cancer in women worldwide; definitive radiation therapy and concurrent chemotherapy is the accepted standard of care for patients with node positive or locally advanced tumors >4 cm. Brachytherapy is an important part of definitive radiotherapy [1]. The current treatment of choice includes EBRT with weekly cisplatin followed by intracavitary BT [2]. Tumor shrinkage during whole pelvic radiation allows for a better geometric

implant leading to excellent local control and survival in patients with early stage disease. However, for patients with bulky disease or with locally advanced stages, locoregional recurrences remain significant leading to a poor survival [3].

Traditionally, as outlined in the International Commission on Radiation Units and Measurements (ICRU) 38 and the 2000 American Brachytherapy Society (ABS) guidelines for cervical cancer, brachytherapy dose was based on

two-dimensional (2D) planning prescribed to a modification of the classical Manchester system point A for target coverage and conventional points for critical organs [4, 5]. However, the doses delivered to tumor and normal tissues from BT are difficult to quantify accurately in conventional BT planning [6].

A modern approach in treatment planning for cervical carcinoma is based on CT sections and on a 3D dose distribution. This allows better assessment of dose distributions in different volumes, such as GTV, CTV, and OARs (rectum, bladder, and intestines). In 2004, guidelines were published for proposing image-based BT for cervical cancer [7]. Recently, recommendations were given for target and OARs delineation and dose prescription on MRI for image based BT in cervical cancer by the GEC-ESTRO [8, 9].

This study was conducted to analyze a dynamics of HR-CTV reduction during BT as a part of definitive treatment (EBRT +/- ChT) depending on the initial GTV and its impact on HR-CTV coverage in patients with inoperable cervical cancer.

## Patients and methods

Between October 2011 and July 2015, 54 patients with biopsy-proven inoperable cervical cancer were enrolled in the prospective study. They underwent radical concurrent chemoradiotherapy consisting of weekly cisplatin plus radiotherapy in the Department of Radiation Oncology at the National Cancer Institute of Slovakia.

All patients were evaluated for staging with routine investigations (blood counts, kidney and liver function test, gynecological examination, CT of thorax and abdomen and diagnostic MRI of the pelvis). The treatment consists of a combination of EBRT with concurrent weekly 40 mg/m<sup>2</sup> cisplatin and high dose rate (HDR) intracavitary BT with or without interstitial needles. The most EBRT was planned with a four-field box technique using a treatment planning system (PrecisePlan), though 5 patients had Intensity Modulated Radiotherapy (IMRT). A total of 45–50 Gy dose (1.8–2 Gy/fraction, daily) was delivered using 18-MV photons. Brachytherapy was performed with a remote HDR afterloading technique with Iridium-192 source. The time between the completion of EBRT/ChT and the first BT application was 7 days. The planned dose per fraction was 7 Gy prescribed to point A, given in 4 fractions, and the BT was delivered twice a week.

All patients underwent tandem and ring high-dose rate BT under general anaesthesia, with a CT/MRI-compatible ring applicator (Nucletron Systems, Veenendaal, The Netherlands) having a tandem length of 4 or 6 cm, a curvature of 45° and a ring diameter of 3 or 3.4 cm (Vienna applicator). Vagina was packed with a gauze to push away the rectum and bladder and to fix the applicator. Before each application, a urinary catheter was inserted and the catheter balloon inflated with contrast media (7 mL) to localize the bladder neck. Patients were encouraged to empty their bowels before a procedure and before the next BT procedures. The probe

for *in vivo* dosimetry has been inserted into the rectum. In addition, eight patients had interstitial needles (range 2–4).

All patients underwent MRI and CT scans followed by contouring on the co-registered images. Before each fraction of BT, all patients had CT but MRI only before the first BT fraction. However, 15 patients had MRI as preplanning. These patients had larger tumor volumes and the preplanning with MRI are used to make decision about addition or not the interstitial needles. MRI was done in the radiodiagnosis department (1.5 Tesla, Siemens). Sagittal, coronal and axial images were obtained, including the tumor, entire cervix, corpus uteri, parametria and vagina. Also, the CT was done in the radiodiagnosis department. No intravenous contrast was used. All MRI and CT slices were transferred via a hospital network to the treatment planning system (Oncentra, Nucletron B.V, The Netherlands).

First, MRI images were obtained followed by the co-registration with CT and contoured for gross tumor volume (GTV), high-risk clinical target volume (HR-CTV), intermediate-risk clinical target volume (IR-CTV) and organ risks (OARs) on Oncentra brachytherapy planning workstation.

The tumor contouring was based on clinical findings and CT/MRI information. The HR-CTV always included the whole of the cervix as per GEC-ESTRO guidelines, and the parametrial and vaginal extensions were included as per the clinical examination at the time of brachytherapy application. The upper limit of the cervix was defined as the conical two slices above the starting of uterine bud, while the endocervical extensions were contoured as suspected clinically. The IR-CTV was contoured based on the adaptation of GEC-ESTRO recommendations with 1 cm margin to HR-CTV. The bladder, rectum and sigmoid were contoured as the outer wall of the organ. Applicator reconstruction was done directly on CT with metallic dummy markers being used as a surrogate for source position. Point A was defined as 2 cm above the superior surface of the ring and 2 cm lateral along the uterine axis. The dose received by at least 90% of the volume (D90) and percentage of volume receiving 100% or more than the prescribed dose (V100) were calculated using cumulative dose–volume histograms (DVHs) of the CTV (HR-CTV). Also, DVHs were evaluated for the dose to 0.1 and 2cc for the OARs. The BT dose was added to the EBRT dose to produce the total equivalent dose in 2 Gy fractions (EQD2) using a  $\alpha/\beta$  ratio of 10 (Gy<sub>10</sub>) for tumor and 3 (Gy<sub>3</sub>) for normal tissues. The dose values for tumor and OARs are reported in the dose/HDR fraction. The 30cc of HR-CTV has been determined as a cut-off value which represented the most acceptable value for intermediate size of volumes.

## Results

The median age of the patients was 51 years (range, 31–78 years). There were 54% of patients (pts) with Stage T2bN1, 11% of pts with Stage T2bN0, 11% of pts with Stage T4N1, 7% of pts with Stage T3bN1, 6% of pts with Stage T2bNx,

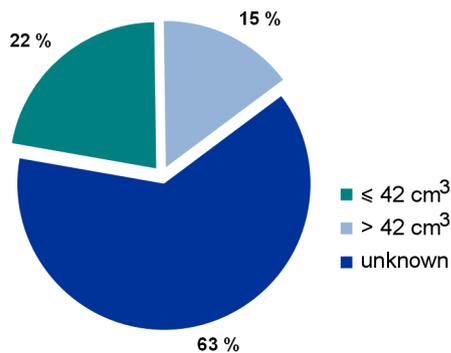


Figure 1. Initial GTVcc (% of pts)

4% of pts with Stage T3aN1, and per 1 patient with Stages T1b1N1, T1b2Nx, T4N0 and T4N2. Patient characteristics are shown in Table 1.

The most patients (63%) received EBRT to a dose of 45 Gy in 25 fractions (range 43.2–50.4 Gy) with concurrent cisplatin-based chemotherapy (mean number of cycles was 5, range 1–6 cycles) followed by four fractions of 7 Gy BT (3 patients had 3 × 7 Gy). Treatment details are shown in Table 2.

Patients were categorized on the basis of whether the 100% isodose line of the point-A prescription dose encompassed the HR-CTV (1st group) or not (2nd group). At the time of the first BT fraction, the dose coverage with 100% at the point A encompassed HR-CTV for 26 patients with a lower volume than 30cc and 9 patients with volumes larger than 30cc. However, 100% dose did not encompass HR-CTV for 13 patients with volumes less than 30cc and for 6 patients with volumes larger than 30cc ( $p=0.7533$ , Fisher's exact test). Also, at the time of the fourth BT fraction, the difference between these two group of pts was not considered to be statistically significant ( $p=0.5490$ ).

Before definitive treatment the mean GTV was 42cc which has been measured using a diagnostic MRI. Most patients had initial GTV above 42cc (63%) (Table 1, Figure 1).

After completion of EBRT/ChT the mean GTV was 3.24cc (range 0.37–20.67cc) which has been measured by MRI for planning, and it was 91% reduction rate in relation to the initial value. The mean GTV before fourth fraction of BT was 2.6cc (range 0.22–19.93cc). We followed dynamics of HR-CTV reduction during BT and a minimal reduction of this volume from mean value of 24.3cc (range 8.9–61.4cc) at the time of first fraction to mean value of 24.1cc (range 6.9–59.1cc) before fourth fraction has been noted.

The mean V100 was 98% (range 75.3–100%) and increased with decreasing of the volume size ( $p=0.0063$ , Fisher's exact test). D90 (mean value was 96.3 Gy<sub>10</sub>/range 71.1–117.3 Gy<sub>10</sub>/) has been correlated with V100 and it also increased with decreasing of the volume size ( $p=0.0003$ ). (Figures 2 and 3).

The mean D0.1cc and D2cc of rectum doses were 80 Gy<sub>3</sub> (range 56.7–97.8 Gy<sub>3</sub>) and 65.6 Gy<sub>3</sub> (range 51.5–73.2 Gy<sub>3</sub>),

Table 1. Patients' characteristics.

Total number of patients		54
Age		mean=51 years (range 31–78)
Staging		Number of pts
T1b1N1		1
T1b2Nx		1
T2bNx		3
T2bN0		6
T2bN1		29
T3aN1		2
T3bN1		4
T4N0		1
T4N1		6
T4N2		1
Histology		
Squamous cell carcinoma		49
Adenocarcinoma		5
Initial tumor volume (cc)		
≤ 30		8 (15%)
>30		34 (63%)
Unknown		12 (22%)

Table 2. Treatment characteristics.

EBRT techniques	Number of pts
Four-field box	49
IMRT	5
Dose	
43.2 Gy (1.8 Gy/fraction daily)	1
45 Gy (1.8 Gy/fraction daily)	34
46 Gy (2 Gy/fraction daily)	5
48.6 Gy (1.8 Gy/fraction daily)	4
50.4 Gy (1.8 Gy/fraction daily)	2
45–46 Gy (1.8–2 Gy/fraction daily)+boost to the residual pelvic lymph nodes with the range of the dose 5.4–16 Gy	8
Concurrent chemotherapy (weekly cisplatin)	
with	53 (mean number of cycles=5 /range1-6/)
without	1
BT (Ring applicator)	
4 × 7 Gy + *interstitial needles (7 pts)	51
3 × 7 Gy + *interstitial needles (1 patient)	3

\*Interstitial needles (range 2–4 needles)

respectively. The mean D0.1cc (99.5 Gy<sub>3</sub>, range 51.9–132.6 Gy<sub>3</sub>) and D2cc (79.5 Gy<sub>3</sub>, range 48.6–91.3 Gy<sub>3</sub>) of bladder doses were acceptable. These DVH parameters were not dependent on the HR-CTV except D0.1cc of rectal doses ( $p=0.0772$ ), although it has been observed that with increasing of the tumor volumes also DVH parameters increased. (Figures 4

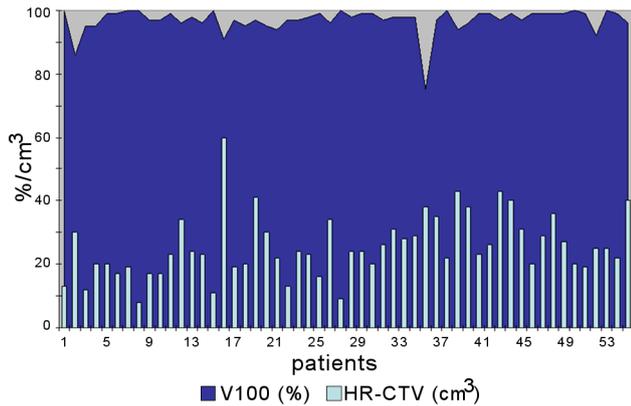


Figure 2. Relationship between V100 and HR-CTV

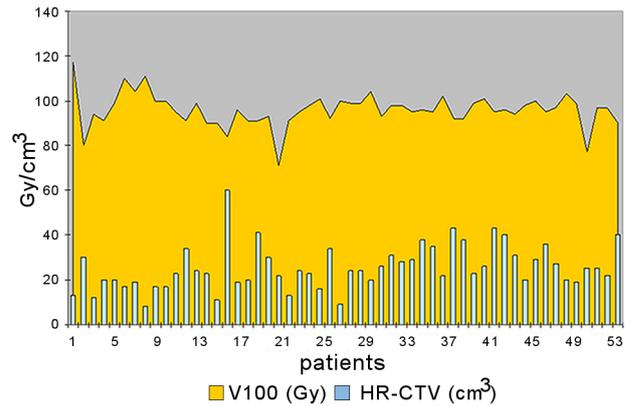


Figure 3. Relationship between D90 and HR-CTV (p=0.0003)

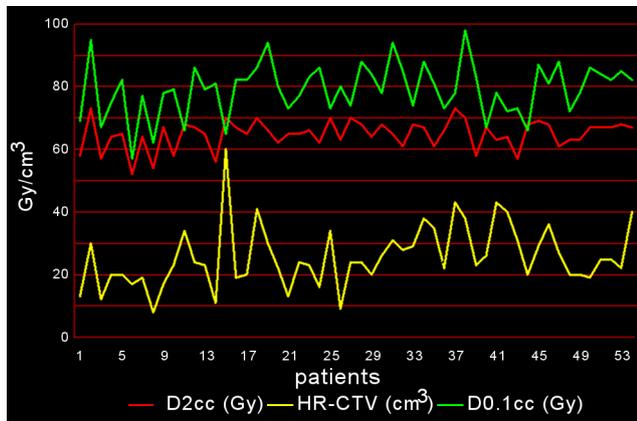


Figure 4. Relationship between D2cc, D0.1cc for rectum and HR-CTV

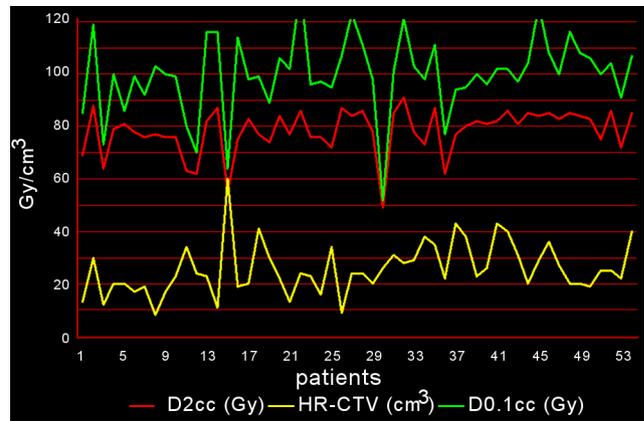


Figure 5. Relationship between D2cc, D0.1cc for bladder and HR-CTV

Table 3. Acute and late toxicity during and after definitive treatment.

Acute toxicity	Number of pts
Without	40
Gastrointestinal (GI)	8
Genitourinary (GU)	1
Unknown	5
<b>Late toxicity</b>	
Without	41
GI	5
GU	3
Combined GI/GU	1
Unknown	4

and 5) The mean ICRU rectal dose for all patients was 67.2 Gy<sub>3</sub> (55.1–77.6 Gy<sub>3</sub>) and the mean ICRU bladder dose was 75.2 Gy<sub>3</sub> (range 49.9–121.8 Gy<sub>3</sub>).

At the time of first control after completion of the definitive therapy (EBRT +/- ChT and BT), 40 pts had complete

tumor regression, 9 patients had residual disease, 2 patients local progression of tumor and 3 patients have not been checked. Among patients with residual disease 4 had initial tumor volume larger than 42cc, 1 patient with tumor volume smaller than 42cc and 4 patients with unknown primary tumor volume. Tumor progression was observed in 1 patient with tumor larger than 42cc and 1 patient with unknown initial tumor volume. Four patients had distant metastases (retroperitoneal lymph nodes, liver, lung, bones, brain) without findings of local tumor. However, 5 patients had distant metastases (retroperitoneal lymph nodes, lung, bones) also with local progression of tumor. Forty patients (74%) have had neither no acute toxicity during their definitive treatment nor 41 pts (76%) late toxicity. Acute and late toxicity are shown in Table 3.

During the mean time follow-up of 10 months (range 2–43), 5 patients died (1 with local tumor progression, 3 with distant metastases and 1 with second malignant disease /non Hodgkin lymphoma – DLBCL/). Four-year disease-free survival (DFS) was 73%, and 4-years overall survival (OS) was 92% in our patients.

## Discussion

Traditionally, the prescribed dose to point A has been used on the basis of ICRU Report 38 (4). However, this prescribed dose point based on two orthogonal X-ray films was not able to visualize the cervical tumor, and there has been uncertainty about whether the whole cervical tumor is covered with the prescribed dose. Recently, the dose to the HR-CTV has also been used as one of the indices presenting the dose to the cervical tumor [8, 9]. In our patients, the 100% isodose line of the point-A prescription dose which sufficiently encompassed or not the HR-CTV did not show dependence on the tumor volumes and there was not a significant difference between these two groups of pts ( $p=0.7533$  for 1st BT fraction and  $p=0.5490$  for 4th BT fraction).

Cervical tumors rapidly decrease in size during EBRT and BT. The time for 50% tumor regression has been reported as 21 days, occurring after 30.8 Gy with concurrent chemoradiotherapy [10, 11]. In our study, the significant regression of GTV has occurred after completion of EBRT/ChT which was 91%. Initially, 63% of our patients had tumor over 42 cc and we have concluded that there was a significant reduction of such large tumors after definitive therapy. However, GTV decreased slightly during BT for additional 3%. Depending on the reduction of GTV, the HR-CTV has been decreased and also, we recorded the minimal reduction of HR-CTV during the BT. We assume that the short duration time of BT was the reason for inexpressive reduction of GTV and consequently HR-CTV.

It is well known that CT alone is inferior to MRI images, and so MRI is taken to be the standard imaging for image-based contouring for brachytherapy [12]. All of our patients had CT before each fraction of BT and MRI before the first fraction. However, 15 patients with larger tumors (above 42cc) had a MRI as a preplanning which has helped us to decide whether to add the interstitial needles for better coverage of HR-CTV. For large tumors, a combined intracavitary and interstitial technique has been shown to improve tumor coverage in these patients.

Dose volume parameters for target volumes can be derived from cumulative dose volume histogram analysis. Although their clinical relevance has not been proven yet, D100 and D90 are suitable for correct plan comparison of all dose rate techniques. V100 describes how closely the intended treatment could be achieved in terms of target coverage, providing information indirectly on the proportion of the underdosed area. For fractionated treatment, however, D90 and V100 are only usable for evaluation after the last fraction, as it uses summed doses of all fractions [9, 13]. It was reported that 2D BT planning achieved lower HR-CTV and dosages to organs at risk (OARs) in patients with big cervical tumors than in those with small tumors. Harmon *et al* demonstrated in their study sufficient tumor coverage with lower doses to OARs in HR-CTV  $D_{90}$  vs. Point A plans in the small lesion group. These improvements were not seen in the

large lesion group, indicating a lesser dosimetric advantage of HR-CTV D90 compared to Point A planning when the cervical lesion is  $>25 \text{ cm}^3$  [14, 15]. However, in our study, as expected coverage of the HR-CTV improves when the plan is optimised to a D90 of 100% of prescription dose rather than prescribing to the A points. The target volume coverage was inversely related to the volume of the target and the extension of tumor.

In fractionated brachytherapy, the location of the high dose region from brachytherapy may not be identical for each fraction. As tumors shrink during the course of radiation, there is a change in tumor volume and configuration over time and consequently, a change in normal tissue topography over time [8]. As organs of interest are hollow, the filling status of the respective organ should be clearly stated, especially for the brachytherapy component. The most constant filling status possible is advised for valid and reliable data collection, especially for the bladder, as this may change within short time periods [9, 16, 17]. Among our patients, dosimetric parameters as D0.1cc, D2cc and ICRU (rectum and bladder) did not indicate dependence on the tumor volume. However, we provided the recommendations for rectal emptiness and constant bladder filling before each fraction which enabled this independence.

Dynamics of HR-CTV reduction during BT was minimal, although, significant reduction of the GTV was achieved after EBRT/ChT. This study revealed that the dose prescription of 7 Gy  $\times$  4 fractions to point A was not sufficient indicator for dose coverage of the HR-CTV. However, dosimetric parameters as V100 and D90 were strong indicators for coverage of HR-CTV which was inversely related to the volume of the target and the extension of tumor. However, dosimetric parameters for rectum and bladder (D0.1cc, D2cc and ICRU) did not show dependence on the target volumes.

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