Does conformal therapy improve dose distribution in comparison to old techniques in teleradiotherapy of cervical cancer patients?

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Received: 14.12.2006
Accepted: 19.08.2008
Subject: original paper

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SUMMARY

BACKGROUND: The use of a combined modality approach – chemotherapy and radiation therapy – in the treatment of patients with cervical cancer is associated with significant toxicity, mainly haematological and gastrointestinal. Conformal radiotherapy has the potential to deliver an adequate dose to the target structures while sparing the normal tissue. Both the radiation dose to the small bowel and the volume are factors known to influence the risk of complications.

AIM: The aim of this study was to determine whether the implementation of conformal modality can reduce the volume of normal tissue included in the RT field.

METHODS AND MATERIALS: 14 cervical cancer patients (FIGO IIB and IIIB) treated with conformal radiotherapy concurrently with cisplatin (40 mg/m^2) administration once a week were analyzed. According to ICRU 50 recommendations target volumes and the organs at risk were contoured on CT slices. For the gross tumour volume (GTV) the tumour of the uterus and cervix was traced. The clinical target volume (CTV) was defined as the vessels and lymph nodes from the obturator level to the aortic bifurcation, presacral region, and upper 1/3 of the vagina. The margin for planning target volume (PTV) was added. The normal tissue region included the small bowel, large bowel and bladder. Using a 3D system and multi-leaf collimator a four-field treatment plan was performed for each patient. All 14 patients were treated with radiotherapy using these conformal 3D plans. Additionally (just for study purposes) for each patient we prepared two simpler plans with (1) two-field: anterior-posterior (A-P) and posterior-anterior (P-A); and (2) four-field box techniques. Dose-volume histograms of target volumes and organs at risk were calculated for each three plans for every patient and compared. Analysis of variance was performed to compute the statistical significance.

RESULTS: There is no statistical difference between doses received by target volumes – in each plan PTV is covered by the 95% isodose. Significantly different volumes of critical organs were included in the treatment field, depending on radiotherapy technique (conformal 3D method vs AP–PA two-field method): rectum 96.82% vs 38.23%, bowels 61.37% vs 30.79%.

CONCLUSION: These data suggest that implementation of conformal radiotherapy can reduce the irradiated volume in all the contoured critical organs, especially the bowels, compared to old techniques.

KEY WORDS: conformal teletherapy, critical organs, cervical cancer

INTRODUCTION

In recent years important changes in the treatment of advanced cervical cancer have occurred due to implementation of modern conformal technologies in radiotherapy and addition of chemotherapy (chemoradiotherapy). The progress in diagnostic imaging (CT, MR), including functional imaging (PET, SPET, SPECT) allows us to improve the precision of definition of tumour volume probably closer to the real tumour dimensions. Computer systems for dose calculation in tumour and healthy tissues integrated with modern linacs create room for methods of dynamic modulation of the radiation beam which may lead to therapeutic index improvement and have the potential for progress of treatment results. The dose delivered to the cervical tumour (GTV) together with the margin of potentially infiltrated tissue (CTV) and physical margin (PTV) is the sum of tele- and brachytherapy doses. The use of conformal radiotherapy allows us to deliver a high dose to the tumour while limiting the dose to the healthy tissues mostly to the bowels, bladder and rectum, considered to be critical structures in cervical cancer radiotherapy. Limiting the volume of healthy tissues seems to be especially important in combining radiotherapy with chemotherapy. Chemotherapy combined with radical radiotherapy is associated with higher toxicity. In a meta-analysis of 17 trials Green et al. [1] found higher haematological toxicity in radiochemotherapy compared to radiotherapy (8 of 16 trials). The authors also found more early gastrointestinal toxicities (G 3–4) in the radiochemotherapy group (9% vs. 4%). The rate of late reactions in the pelvis did not differ [1, 2, 3].

There is therefore increasing concern over adverse radiation effects. In addition, small bowel tolerance remains a key barrier to dose-escalation and potential gains in tumour control. Ways of minimizing the volume of small bowel irradiated are paramount [4].

AIM

The aim of the current analysis was to compare dose distribution in PTV and healthy critical organs using three radiotherapy techniques. Two of them were used in the past in our institution: 1/ two anterior-posterior opposite beams (AP-PA) 2/ the "box" technique in various radiotherapy techniques used in the past and nowadays. The third, conformal technique, is currently used.

MATERIAL AND METHODS

We have analyzed accepted treatment plans of 14 pts diagnosed with cervical cancer in stages IIb-IIIb according to the FIGO classification. Patients were treated in the Dept. of Oncological Gynaecology of the Great Poland Cancer Centre from Jan. to April 2005. The treatment was conformal teleradiotherapy with LDR brachytherapy (2 applications) together with weekly cisplatin 40 mg/m^2. Patients were qualified for treatment after clinical examination, lab tests, imaging tests (USG, CT), and PS assessment (0–2). Patients who needed para-aortal node irradiation were excluded from this study. Planning and delivery of radiotherapy was executed according to the same principles. After simulation (Varis) CT for planning purposes (every 5 mm) was performed. 6 patients additionally had MRI exams followed by MRI/CT fusion. GTV, CTV and PTV were defined with CT as well as critical organs: small and large intestine and urinary bladder. GTV confined primary cervical tumour, CTV1 was GTV plus 0.5 cm margin plus uterine corpus, parametria and 1/3 of the vagina; CTV2 (lymph nodes) was the retroperitoneal space with lymph nodes along the major vessels in the pelvis. PTV was obtained by adding a 1.5 cm margin to CTV1 and a 1.0 cm margin to CTV2. External beam planning was done with v. 6.5 (Varian Medical Systems, Palo Alto, USA).

For every patient a conformal plan was designed using 4 beams encompassing PTV (95–107%) with MLC shaping and this plan was applied for patients' treatment. All 14 patients were treated using the conformal 3D technique described above from Jan. to April 2005.

Two additional plans for each and every patient were prepared only for study purposes. These two plans were not used for treatment. These two "simulation plans" represented older, simpler techniques used in our department in the past. (1) The first was AP-PA (two opposite beams) encompassing the pelvis with the tumour. The inferior border was situated on the lower edge of the obturator foramina, side borders 1.5 cm – 2.0 cm laterally to the pelvic bones, upper border to the upper edge of the fifth lumbar vertebra. (2) The second "simulation plan" ("box") was based on 4 opposite beams, with borders as described for the AP-PA plan except for the anterior border situated on the anterior edge of the pubic symphysis and the posterior border between the second and third sacral vertebra. The beams were modified (enlarged) if the known tumour dimensions (acc. to CT) exceeded assumed borders.

The dose for all 3 techniques was 50 Gy. Dose volume histograms were prepared for target volumes and critical organs. Patients were treated with 20 MV photons delivered with a Varian Clinac 2300CD/S (Varian Medical System, Palo Alto, USA). An 80-leaf collimator was used for shaping portals. In vivo dosimetry was performed for every patient at the beginning and in the middle of radiotherapy course, portal images being done every week. In case of change of irradiation parameters (such as significant weight loss) patients were re-planned (it occurred in 5 pts). These second plans were not considered in the analysis (the second plan at the earliest was prepared after 26 Gy). The three-plan comparative analysis was based on comparison of mean doses (variance analysis) in the target volumes (GTV, CTV, PTV) and in critical organs: bladder, small intestine, rectum.

RESULTS

The analysis revealed that in every patient the PTV was covered by the 95% isodose and max. dose did not exceed 107% in the PTV as per ICRU criteria. In three patients (28%) planned with 3D technique it was necessary to broaden the lateral portals (box technique) by 1cm-1.5cm in order to avoid geographical miss. In Table 1 mean doses Dm (%) (for the group of 14 patients) in CTV1, CTV2 and PTV using the three techniques, conformal technique, box technique and AP-PA technique, are presented.

In the next table (Table 2) the proportion of critical organs receiving the dose prescribed for the PTV (50 Gy) are presented (mean % values with standard deviation for the group of 14 patients). The volume of organs at risk differs significantly between analyzed patients (different capacity), which explains the high SD value.

The irradiated volumes (doses) were compared (variance analysis – ANOVA). In the table 3a, 3b, and 3c p values for the variance test are presented. Techniques were compared each to each, e.g. in the table 3a p value for the comparison of the rectum volume irradiated with box technique vs. 4 conformal portals is 0.09 – hence the volumes do not differ significantly ($p=0.09$); in the table 3b p value for the comparison of small intestine volume irradiated with box technique vs. 4 conformal portals is 0.039 – hence the volumes differ significantly ($p<0.05$).

Table 1. Mean doses Dm (%) in CTV1, CTV2 and PTV with the use of three techniques: conformal technique, box technique and AP-PA technique

	CTV1		CTV2		PTV	
Technique	**Dm [%]**	**SD**	**Dm [%]**	**SD**	**Dm [%]**	**SD**
2 portals AP-PA	102.06	0.77	101.98	0.80	101.93	0.80
box	101.58	0.55	102.01	0.57	102.11	0.52
4 conformal portals	101.60	0.57	101.97	0.55	101.98	0.54

Table 2. The proportion of critical organs' volume receiving the dose prescribed for the PTV (50 Gy)

	Rectum		Small intestine		Bladder	
Technique	**V [%]**	**SD**	**V [%]**	**SD**	**V [%]**	**SD**
2 portal AP-PA	96.82	9.11	61.37	10.41	97.27	9.71
box	58.59	25.38	48.98	19.88	96.06	12.91
4 conformal portals	38.23	25.72	30.79	16.23	80.64	11.65

Table 3. p values for the variance test comparing the mean rectum, small intestines and bladder volumes irradiated with the dose 50 Gy with three different methods (AP-PA, 4 box and 4 conformal)

	AP-PA	4 box	4 conformal
Rectum			
AP-PA		0.000	0.000
4 box	0.000		0.090
4 conformal	0.000	0.090	
Small intestine			
AP-PA		0.250	0.000
4 box	0.250		0.039
4 conformal	0.000	0.039	
Bladder			
AP-PA		0.993	0.003
4 box	0.993		0.006
4 conformal	0.003	0.006	

CONCLUSIONS

1. There were no statistically significant differences in the mean dose in target volumes (CTV1, CTV2, PTV) using the three techniques.

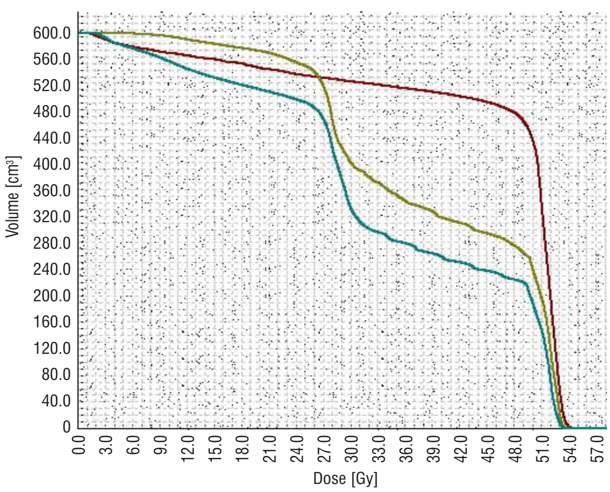

Fig. 1. DVH for bowels in three compared techniques: AP-PA (red), box (green), conformal (blue). A significant reduction of intestine volume irradiated with conformal and box technique is seen compared to AP-PA radiotherapy, especially in the dose range 30 Gy – 50 Gy.

2. There were significant differences ($p<0.05$) in dose distributions in critical organs between the techniques. The smallest volumes of critical organs were irradiated using the 4-portal conformal technique. The greatest volume of rectum and bladder was irradiated using the AP-PA technique.

3. Using a 3D technique allowed us to avoid geographical miss in 4 patients.

DISCUSSION

The AP-PA technique was used for many years in our institution. The AP-PA technique covers the target area with a homogeneous dose, but at the expense of considerable risk of toxicity for large PTV volumes encompassing critical organs. The risk of complications is even higher with combination of radiotherapy and chemotherapy. The small intestine is subject to the greatest toxicity both early and late. The total dose (including the dose from brachytherapy) and the irradiated volume of the intestines contribute to the rates of toxicities. Roesce et al. reported a correlation between "clinically significant" toxicity and the volume of small bowel receiving 90 and 100% of the prescription dose – they reported 28% incidence of clinically significant acute toxicity [5]. Here we have shown that the simple AP-PA technique significantly increases the irradiated volumes of rectum, bladder and intestine compared to box and 3D conformal radiotherapy. The box technique allows the irradiated volumes of critical organs, especially bowels, to be reduced, but is associated with the risk of geographical miss (in our study 28%, which correlates with data in the literature) [6, 7]. Therefore conformal radiotherapy seems to be optimal, for it enables 3D definition of the tumour and critical organs and then conforming the fields with MLC according to the PTV shape. For the whole group analyzed treatment planning was done using CT. Only in 6 patients was MR done additionally with subsequent CT-MR fusion for planning purposes. MR-based planning was more accurate, especially for defining the primary tumour and infiltration of the parametria. MR should be used for planning wherever possible and should be standard in all patients.

Mobility of internal organs in our patients is not easy to follow and not even well known in contrast to e.g. prostate movements.[2] PTV was created by adding 1.5 cm to CTV1. As Buchali et al.[8] described, the internal mobility of the uterine corpus depends on bladder and rectum filling and ranges from 3 mm to 15 mm in an up-and-down direction and 0 mm to 9 mm in a forward-backward direction. Huh et al. have also shown a difference in uterine volume and angle during the whole treatment course (more than 1 cm and 30 degrees). In order to get PTV 1 cm was added to CTV2. Because of the proximity of bone margins it was assumed that the internal mobility of lymph nodes and vessels is lower than the mobility of the uterine corpus (L. Van de Bunt et al.)[9].

Another important issue is the day-to-day reproducibility of the patient's position on the linac couch for the large fields used with no efficient immobilization available and frequent obesity of the patient. In order to minimize this problem these patients require multiple verification films and simulation checks – deviations of <6 mm for the field position were considered acceptable. Nowadays in our centre "belly boards" are available which enable us to minimize the intestine volume irradiated; however, the belly board does not solve the problem of target and critical organ motion [4, 6, 10, 11].

The IMRT technique is hoped to be able to minimize critical organ irradiation [1, 2, 12], but it was not used in this study.

Our analysis confirmed quantitatively that conformal planning minimizes the volume of irradiated healthy tissues, as it was assumed when we introduced this technique into practice in our institution. The answer to the question of what is the impact of statistically significant minimization of irradiated volume of healthy tissues on the rate of radiation side effects in patients requires longer follow-up and a larger group of patients. The results of this study encouraged us to implement the IMRT technique for gynaecological cancer treatment in a large group of patients, and we are waiting for the follow-up results.

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