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Technical note

Relations between doses cumulated in bone marrow and dose delivery techniques during radiation therapy of cervical and endometrial cancer

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ABSTRACT

Purpose: To compare normal tissue complication probability (NTCP) and average doses in the bone marrow (BM), obtained for five different radiotherapy delivery and planning strategies of cervical and endometrial cancer.
Material/methods: 50 patients were taken to analysis. For each case, 3 different dose delivery techniques were used: 4-field, X15MV, 3DCRT; 7-field, X6MV, IMRT; and 2-arc, X6MV, VMAT. Two optimization scenarios were used for the IMRT and VMAT plans generation: with (+) and without (−) the inclusion of the BM as an optimized structure. Average doses and dose-volume histogram parameters for the PTV, BM, bladder, rectum, bowels and femoral heads were compared. In addition, the BM doses were analyzed with respect to the PTV and/or volume of the BM, and NTCP for the BM were computed.
Results: The dose in PTV for evaluated plans was similar. The worst doses in organs at risk were obtained for 3DCRT. Using the BM during the optimization of IMRT and VMAT reduces an average dose in BM without increasing the doses in the bladder, rectum and bowels. Differences between doses in BM for IMRT(+) and VMAT(+) plans were similar while NTCP was lower for VMAT(+). A correlation between average dose in BM and the volume ratio of BM and PTV was found for each technique.
Conclusion: Using the BM during the optimization of the IMRT and VMAT plans effectively reduces the dose in BM without increasing the dose in the bladder, rectum and bowels. The VMAT(+) plans were characterized by the lowest NTCP.

1. Introduction

Conventional radiotherapy (3DCRT) in gynaecologic malignancies provides high and homogeneous doses to the tumour. Nevertheless, it also leads to large volumes of healthy tissues receiving high dose of radiation, including organs at risk (OARs) that surround the irradiated area. The dose in the OARs significantly limits the total dose that may be administered during a radiation therapy course. However, the recent advances in radiotherapy techniques have removed some of the limitations of gynaecologic radiotherapy.

One of the more spectacular technological achievements is the introduction of intensity modulated radiation therapy (IMRT), which enables a significant reduction of high dose to the area of healthy tissue and OARs while retaining homogeneous distribution in the tumour area. In recent years, volumetric modulated arc therapy (VMAT) techniques have gained popularity as, for a number of clinical cases, they ensure an increase in dose distribution conformity when compared to fixed-beams IMRT [1,2]. VMAT is a rotational approach to fixed-beams IMRT that can be delivered using conventional (C-arm) accelerators with a conventional multi leaf collimator. In the case of gynaecological cancers, both of these technologies can significantly reduce the dose to the OARs such as the bladder, rectum, or intestines [3,4]. This is a consequence of the inclusion of these organs during the optimization of dose distribution [5,6]. As a result, reduction of dose in these organs leads to a reduction of acute gastrointestinal and urinary toxicities [7]. It should be noted that there is also a possibility of dose reduction in the bone marrow, which leads to lower hematological toxicity [8]. Mell et al. [9] and Ahmed et al. [10] show that fixed-beams IMRT effectively reduces doses in the bone marrow in relation to 3DCRT techniques. Kim et al. [11] show superiority of the dose reduction in the bone marrow for treatment realized on Tomotherapy Unit in comparison to fixed-beams IMRT and 3DCRT

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realized on conventional (C-arm) accelerators. Nevertheless, there are still a small number of studies focused on radiotherapy of gynecological cancer where differences between dose distributions in the bone marrow are evaluated for fixed-beams IMRT and VMAT [12,13]. So far, the reduction of doses in the bone marrow was observed for two different scenarios of dose optimization: (1) when optimization implies a deliberate reduction of the dose in the bone marrow and (2) when the bone marrow has not been included as the OAR during optimization. [8–15]. Direct comparisons between these two optimization scenarios for gynecological patients were performed for fixed-beams IMRT [16] and for Tomotherapy [17], and were not yet published for VMAT. Actual status of literature shows that usage of VMAT techniques utilizing strategies of bone marrow sparing in the treatment of cervical and endometrial cancers has not as yet been fully described.

The authors of this study analyzed the dose distributions for patients with postoperative cervical and endometrial cancers that were obtained for IMRT and VMAT and were prepared by two optimization scenarios: with and without the inclusion of the bone marrow as an optimized structure. Regardless of a technique and optimization strategy, dose distribution in the bone marrow is conditioned by the individual patient's anatomy. Therefore, the analyses of correlation between doses in bone marrow and patient's anatomy were performed. Based on obtained dose distributions, modeling of the normal tissue complication probability (NTCP) for the bone marrow and potential hematologic toxicity was performed. The analysis was carried out in the light of the retrospective dose distributions obtained for the four-field technique of the 3DCRT.

2. Material and method

2.1. Patient data and volume definition

The study involved data of 50 patients with cervical or endometrial cancer. All patients underwent planning CT and received 3DCRT treatments (4-field technique, X15 MV) between 2012 and 2013 in our hospital. CT scans (Definition AS, Siemens, Germany) were performed in the supine position (2 mm slice thickness) with a knee and feet support (Combifix; CIVCO Radiotherapy, Coralville, IA, USA).

The clinical target volume (CTV) was defined according to the guidelines presented by Small et al. and included, respectively: upper vagina, parametrial/paravaginal tissues, common, external and internal iliac lymph nodes [18]. If a patient had cervical cancer or endometrial cancer with cervical stromal invasion, presacral lymph nodes were outlined. An 8 mm margin around the lymph nodes and a 12 mm margin around the vagina and paravaginal tissues were applied to generate the PTV. Additionally, the following OARs were delineated: rectum, bladder, femoral heads, bowels and total bone marrow (BM). The rectum was contoured from the anus to the sigmoid flexure. The bowels were contoured from the L4-5 interspace to its lowest extent in the pelvis as an entire bag. Total BM was contoured from the L4 vertebral body to the ischial tuberosities, including the pelvis, L4-5, and sacrum, as described by Rose et al. [19]. Total BM was delineated without specification of functional BM subvolumes [20].

2.2. Treatment techniques

For each patient, X6MV 7-field IMRT and 2-arc VMAT treatment plans were generated, retrospectively, using constraints similar to the ones applied in the RTOG 0418 trial [21]. The protocol specified that the volume of small bowel receiving >40 Gy was limited to <30%; <60% of the rectum was to receive >30 Gy, and <35% of the bladder was to receive >45 Gy. No BM constraints were recommended. For all techniques ICRU-83 plan normalization criteria were followed, with prescription to the median dose [22]. Treatment plans were generated for Varian Clinac-2300C/D (Varian Medical Systems, Palo Alto, CA, USA) using Eclipse treatment planning system ver. 13.6 (Varian Medical Systems, Palo Alto, CA, USA). The analytic anisotropic algorithm with the spatial resolution of 2.5 mm was used for computing dose to the PTV. External beam dose was 50.4 Gy delivered in 28 daily fractions.

For both techniques (fixed-beams IMRT and VMAT), two optimization scenarios were used for the plans generation: without (−) and with (+) the inclusion of the bone marrow as an optimized structure. At first, the scenario (−) was performed. Obtained plan was saved and copied. Based on the copy, the scenario (+) was realized. In the scenario (+) the dose in the BM was reduced as low as possible so as to maintain similar doses obtained in PTV and other OARs for the scenario (−).

2.3. Analysis of the dose distribution

The dose distributions obtained from fixed-beams IMRT and VMAT plans were compared and evaluated in the light of the doses obtained from treatments realized by 3DCRT. In other words, the differences in the dose distribution for the five different plans (fixed-beams IMRT and VMAT with (+) and without (−) BM optimization and 3DCRT) were analyzed. The PTV, bone marrow, bladder, rectum, bowels and femurs were considered in the analysis of the dose distribution.

Two stages of comparison were used. The first stage assumed the qualitative description of the dose distribution on the basis of averaged dose-volume histograms (DVHs). Especially, the dose-volume relations specified during optimizations were analyzed. The analysis of the averaged DVHs allows us to consider general relations of the dose distributions obtained in PTV and OARs for the evaluated techniques. In the second stage, average doses cumulated in PTV, BM, bladder, rectum, bowels and femoral heads obtained from the evaluated plans were compared. In addition, the doses accumulated in BM were analyzed in the light of the volume of PTV and/or BM.

2.4. Normal tissue complication probability (NTCP) for bone marrow

Based on obtained dose distributions, modeling of the NTCP for the bone marrow was performed. The Lyman-Kutcher-Burman-NTCP (LKB-NTCP) [23] with Bazan's method [24] was implemented. The LKB-NTCP model is expressed by the following formulas:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp\left(-\frac{x^2}{2}\right) dx \tag{1}$$

$$t = \frac{D - TD_{50}}{m \cdot TD_{50}} \tag{2}$$

$$TD_{50}(\upsilon) = TD_{50}(1) \cdot \upsilon^{-n} \tag{3}$$

$$\upsilon = \frac{V}{V_{ref}} \tag{4}$$

where, in this study: D is the uniform dose calculated by the generalized equivalent uniform dose (gEUD) formula proposed by Niemierko [25]; TD_{50} is the tolerance dose for a 50% complication probability for uniform doses to the BM; m is a dimensionless parameter to determine the slope of the complication probability according to dose curve; n is the parameter for the volume dependence of the complication probability and V_{ref} is a reference volume