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Original article

Vaginal dose de-escalation in image guided adaptive brachytherapy for locally advanced cervical cancer

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ABSTRACT

Purpose: Vaginal stenosis is a major problem following radiotherapy in cervical cancer. We investigated a new dose planning strategy for vaginal dose de-escalation (VDD).

Materials and methods: Fifty consecutive locally advanced cervical cancer patients without lower or middle vaginal involvement at diagnosis from 3 institutions were analysed. External beam radiotherapy was combined with MRI-guided brachytherapy. VDD was obtained by decreasing dwell times in ovoid/ring and increasing dwell times in tandem/needles. The aim was to maintain the target dose (D90 of HR-CTV $\geqslant$ 85 Gy EQD2) while reducing the dose to the surface of the vagina to <140% of the physical fractional brachytherapy dose corresponding to a total EQD2 of 85 Gy.

Results: The mean vaginal loading (ovoid/ring) was reduced from 51% to 33% of the total loading with VDD, which significantly reduced the dose to the vaginal dose points ($p < 0.001$) without compromising the target dose. The dose to the ICRU recto-vaginal point was reduced by a mean of 4 ± 4 Gy EQD2 ($p < 0.001$), while doses to bladder and rectum (D^3_{2cm}) were reduced by 2 ± 2 Gy and 3 ± 2 Gy, respectively ($p < 0.001$).

Conclusions: VDD significantly reduces dose to the upper vagina which is expected to result in reduction of vaginal stenosis.

 Radiotherapy and Oncology xxx (2016) xxx–xxx

Vaginal mucosa is exposed to high radiation doses in the upper vagina and to intermediate doses in the mid and lower vagina during radiotherapy (RT) for locally advanced cervical cancer. RT induces vaginal morbidity and causes a wide spectrum of short- and long-term side effects, e.g. vaginal stenosis, telangiectasia shortening, adhesions, dyspareunia, and dryness which have an impact on the patient's quality of life [1–4]. Patients may progressively develop vaginal related morbidities and sexual dysfunction throughout the first years post RT which may persist thereafter [5]. The probability of having vaginal morbidity of grade 2 or more (G $\geqslant$ 2 (through the first two years after treatment has been reported to be 29% [6]. The most frequently reported vaginal side effect is vaginal stenosis with actuarial probability rates for G $\geqslant$ 2 at two years of 22% [6].

The direct method for reducing RT induced vaginal morbidity is by delivering less radiation dose to the vaginal mucosa. It has been suggested to limit the vaginal mucosal doses to 140–150% of point A dose [7,8], although this is not supported by clinical evidence. There is altogether lack of validated vaginal dose constraints and little knowledge about the implication of vaginal dose reduction on target dose. With vaginal mucosal dose limited to 140% or less of point A dose, the probability of developing severe late vaginal morbidity has been reported to be 20.2% for patients treated with RT alone [2]. Addition of concomitant chemotherapy with vaginal mucosal dose of $\leqslant$125% of point A dose increased the probability to 35.1% [2].

The dose point which has been known as the "ICRU rectum point" has recently been re-labelled into the "ICRU recto-vaginal point" according to the ICRU report 89 [9]. This change of nomenclature is due to the fact that the ICRU rectum point is in fact a good surrogate for dose to the upper vagina. In this paper, the "ICRU recto-vaginal point" nomenclature will be used. A recent analysis suggested that doses to the ICRU recto-vaginal point correlate with the probability of G $\geqslant$ 2 vaginal morbidity [10]. This relationship between dose and effect is a strong motivation to consider dose optimisation which spares vaginal mucosa and decreases the dose to the ICRU rectal point.

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This planning study explores the possibilities of vaginal dose de-escalation during BT in locally advanced cervical cancer patients with 3D MRI guided BT. We propose a planning strategy which aims to decrease the vaginal loading. We quantify the effect through utilisation of vaginal dose reporting points including the ICRU recto-vaginal point. The hypothesis was that by changing the loading pattern it is possible to de-escalate the doses delivered to the vaginal mucosa and to the ICRU recto-vaginal point without compromising the HR-CTV D90.

Material and methods

Fifty patients, enrolled in the prospective "An IntErnational Study on MRI-guided BRachytherapy in locally Advanced CErvix Cancer" (EMBRACE, www.embracestudy.dk), were included from 3 institutions which used different applicators and dose rates. Patients without vaginal involvement in the middle or lower part were consecutively included in the present analysis. Twenty patients were included from Aarhus University Hospital treated with tandem and ring applicator (TR), and pulsed dose rate (PDR) BT. Ten patients from Vienna Medical Center were treated with TR and HDR BT. Twenty patients from Utrecht Medical centre were treated with tandem and ovoid applicator (TO), with HDR (eleven patients) or PDR (nine patients). Intracavitary BT (IC BT) was used in 37 patients, and combined intracavitary/interstitial BT (IC/IS BT) in 13 patients. Four HDR BT fractions were delivered in 21 patients and 2 PDR BT fractions in 29 patients. External beam radiotherapy (EBRT) doses were 45–50 Gy/25–30 fx. MRI guided BT was optimised according to a planning aim of D90 HR-CTV $\geqslant$ 85 Gy EQD2 for the total EBRT and BT contribution. Organ at risk (OAR) constraints were 90 Gy for bladder D^3_{2cm}, and 70–75 Gy for rectum, sigmoid, and bowel (total EQD2). Vaginal dose points were not considered during optimisation of the clinically delivered plans (non-VDD plans). BT imaging, contouring, reconstruction, and reporting were done according to the GEC ESTRO guidelines [11–14].

Vaginal dose reporting was based on multiple points allowing for comprehensive evaluation of the dose to the whole vagina [8,15]. Lateral vaginal dose points were inserted at the surface of the vaginal applicator (0 mm) and at 5 mm depth; anterior and posterior vaginal points were placed at 5 mm depth. For reporting the dose in the mid/lower region of the vagina, we positioned 2 points: the posterior inferior border of the symphysis pubis (PIBS) and PIBS + 2 which is 2 cm cranial to the PIBS. Both points were placed along the tandem [15] Fig. 1.

The starting point for dose planning was a standard plan with point A dose normalisation of 85 Gy (total EBRT and brachytherapy dose). Intracavitary and interstitial optimisation was performed by manual adaptation of dwell times. The loading of needles was controlled by an overall rule to load the needles by less than 10–20% of the dwell time loading used in tandem in a standard plan. Only when needles were located within the GTV or far from the border of the CTV_{HR}, it was allowed to exceed this rule of loading.

Vaginal dose de-escalation (VDD) was performed by decreasing dwell times in ovoid/ring and increasing the loading in tandem/needles, Fig. 2. The VDD plan was optimised with the 1st priority to deliver HR-CTV D90 similar to the delivered plan (non-VDD). The 2nd priority of the VDD plan was to keep the dose to the vaginal mucosa lower than 140% of the physical fractional BT dose corresponding to 85 Gy total EBRT and brachytherapy dose. E.g. in a fraction schedule of 4 times 7 Gy BT the 140% isodose is 10 Gy. The maximum dose degradation allowed in the VDD plans for HR-CTV D90 was 3 Gy if the non-VDD plan had delivered HR-CTV D90 of $\geqslant$90 Gy EQD2, 2 Gy when 85 Gy EQD2 < HR-CTV D90 < 90 Gy EQD2 and 0 Gy difference when HR-CTV D90 for the non-VDD plan was $\leqslant$85 Gy EQD2.

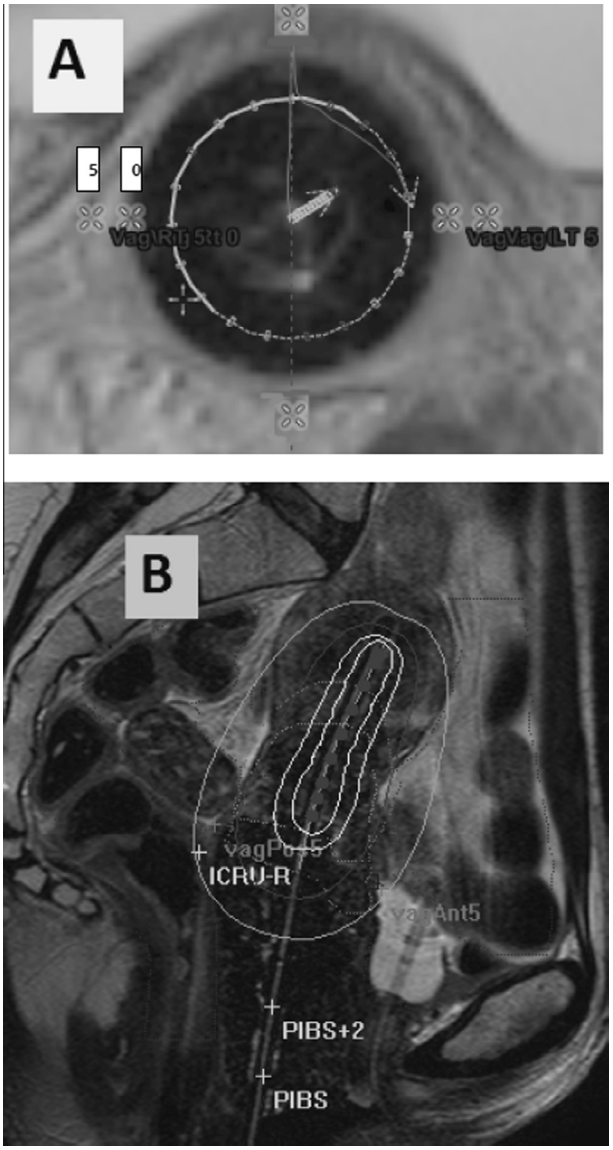

Fig. 1. (A) A transverse MRI section at the level of ring applicator showing cross marks of the vaginal points. Lateral vaginal dose points were inserted at the surface of the vaginal applicator (0 mm) and at 5 mm depth; anterior and posterior vaginal points were placed at 5 mm depth. (B) a sagittal MRI section showing placement of ICRU recto vaginal point (ICRU-R), the posterior inferior border of the symphysis pubis (PIBS) and PIBS + 2 points along the tandem applicator.

Doses were reported in total EBRT and BT EQD2 dose using the linear quadratic model (α/β = 3 Gy for OARs, α/β = 10 Gy for tumour, T½ = 1.5 h) [12]. VDD optimisation and analysis of the DVH parameters were done for the first BT fraction (BT1) only. The comparison between the two scenarios was based on BT1 multiplied by the number of fractions the patient received (4 HDR, 2 PDR). Furthermore, the total TRAK and the vaginal TRAK were calculated and the ratio of the vaginal TRAK to the total TRAK was compared between both plans. Paired and unpaired *t*-tests were applied to determine significant differences. Significance level was set 2-sided at 5%.

Results

For the included patients, the median clinical tumour width at diagnosis was 50 mm [25–100 mm] and at BT1 35 mm [10–70 mm]. The FIGO stage distribution was IB 24%, IIA 4%, IIB 56%, IIIB

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