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Original article

Multicentre evaluation of a novel vaginal dose reporting method in 153 cervical cancer patients

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ABSTRACT

Background and purpose: Recently, a vaginal dose reporting method for combined EBRT and BT in cervical cancer patients was proposed. The current study was to evaluate vaginal doses with this method in a multicentre setting, wherein different applicators, dose rates and protocols were used.

Material and methods: In a subset of patients from the EMBRACE study, vaginal doses were evaluated. Doses at the applicator surface left/right and anterior/posterior and at 5 mm depth were measured. In addition, the dose at the Posterior–Inferior Border of Symphysis (PIBS) vaginal dose point and PIBS±2 cm, corresponding to the mid and lower vagina, was measured.

Results: 153 patients from seven institutions were included. Large dose variations expressed in EQD2 with $\alpha/\beta = 3$ Gy were seen between patients, in particular at the top left and right vaginal wall (median 195 (range 61–947) Gy/178 (61–980) Gy, respectively). At 5 mm depth, doses were 98 (55–212) Gy/91 (54–227) Gy left/right, and 71 (51–145) Gy/67 (49–189) Gy anterior/posterior, respectively. The dose at PIBS and PIBS±2 cm was 41 (3–81) Gy, 54 (32–109) Gy and 5 (1–51) Gy, respectively. At PIBS+2 cm (mid vagina) dose variation was coming from BT. The variation at PIBS−2 cm (lower vagina) was mainly dependent on EBRT field border location.

Conclusions: This novel method for reporting vaginal doses coming from EBRT and BT through well-defined dose points gives a robust representation of the dose along the vaginal axis. In addition, it allows comparison of vaginal dose between patients from different centres. The doses at the PIBS points represent the doses at the mid and lower parts of the vagina. Large variations in dose throughout the vagina were observed between patients and centres.

The current standard treatment for locally advanced cervical cancer (FIGO stage ⩾IB2) is definitive radiotherapy combined with chemotherapy as a radiosensitizer. The radiotherapy consists of a combination of external beam radiotherapy (EBRT) to the pelvis, followed by an image-guided adaptive brachytherapy (IGABT) boost to the cervical tumour and its local extension (=high risk CTV (CTV_{HR})). Nowadays, the planning aim of brachytherapy (BT) is to give a least 85 Gray (Gy) to the CTV_{HR} D_{90}, without exceeding the dose constraints for the organs at risk. This aim is often challenging and needs adaptation of the standard loading pattern traditionally prescribed to point A often combined with additional interstitial needles to increase the degree of freedom for the optimization. According to the gynaecological (GYN) GEC-ESTRO guidelines [1,2] and the upcoming ICRU GEC-ESTRO report 89 [3] the $D_{0.1cm3}$ and D_{2cm3} of the major organs at risk (OAR), i.e. bladder, rectum, sigmoid and bowel were suggested to be reported at time of BT. Recommendations for reporting of dose given to the vagina are included in the upcoming ICRU report and previous ABS recommendations [3,4]. The vagina has an ambivalent role in the treatment of cervical cancer, being as well a target organ (upper vagina) as an organ at risk (lower parts of the vagina). Although the upper vagina is treated to a significant dose since it is in close

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proximity of the cervix and thus at risk (CTV), there is no oncological rationale for treating the lower parts of the vagina in case of no or minimal (<2 cm) involvement of the upper vagina.

Vaginal morbidity after radiotherapy has not been investigated extensively so far. Although the reported incidence of severe (grade $\geqslant 3$) vaginal morbidity is low [5–7], mild to moderate vaginal morbidity is frequently reported by patients and has a negative impact on sexual functioning, self-image and consequently quality of life [8–10]. Recently, a prospective analysis about the acute and late vaginal morbidity in cervical cancer patients treated with the current treatment strategies described above was published [11]. This paper showed that 89% of the patients had grade $\geqslant 1$ vaginal morbidity, and 29% grade $\geqslant 2$ within the first two years, with vaginal stenosis and dryness as most frequently observed symptoms. Grade $\geqslant 3$ vaginal morbidity was seen in only 3.6% of the patients.

Although it is to be expected that vaginal morbidity is a result of radiation dose to a specific part of the vagina, only limited data about dose–effect relationships in the vagina are known from literature [12,13]. Recently, a large study from EMBRACE was published describing a dose–effect relationship between the dose to the ICRU-rectum (ICRU-R) point and $\geqslant$grade 2 vaginal stenosis [14]. A few small studies have investigated the relationship between vaginal morbidity and volume (DVH) parameters [15–18]. However, results from these studies are inconclusive; some found a dose–effect relationship, while others did not. Several reasons may explain these different findings, e.g. difficulties in delineation and reconstruction of the vaginal wall in current planning systems, uncertainties in reporting the dose at the vaginal top due to steep dose gradients nearby the vaginal sources, and the often assumed 'radio-resistance' of the upper vagina [12,13]. Ideally, a 3D vaginal surface map should be available for every patient. However, this tool is not present in the currently available treatment planning systems.

Recently, a novel vaginal dose reporting method was proposed to evaluate the total (EBRT and BT) dose in Gy (EQD2) given to the upper, mid and lower parts of the vagina [19] which is included in the upcoming ICRU report [3]. This study was conducted in a single centre using a tandem-ring applicator and HDR. The recent study was designed to evaluate, if the new vaginal reporting method is applicable in a multicentre setting, wherein different applicators, dose rates and protocols were used.

Material and methods

The EMBRACE study is an int**E**rnational prospective observational study on **M**RI-guided **BR**achytherapy in locally **A**dvanced **CE**rvical cancer. From 2008 to 2015 1412 patients were included in this study. Inclusion criteria were a biopsy-proven (squamous, adenosquamous or adenocarcinoma) locally advanced cervical cancer (FIGO stage IB–IVA) and patients had to be treated with definitive radiochemotherapy including image guided brachytherapy. The study was approved by the Ethics Committees of all participating centres.

In a subset of patients of the EMBRACE study, MRI based brachytherapy (BT) plans (images, dose and plans) were submitted for QA purposes and detailed dosimetric evaluations. Patients from centres of which full BT information was available for at least 10 patients at the 1st of August 2013, were included in this study. To diminish the centre effect, a maximum of 30 patients per centre were included.

All patients were treated with a combination of external beam radiotherapy (EBRT) and MRI-guided brachytherapy (BT), either intracavitary (IC) or IC with interstitial needles (IC/IS). Clinical data were extracted from the EMBRACE database. The EBRT total dose varied between 45 and 50.4 Gy in fractions of 1.67 to 2 Gy and was prescribed to the primary CTV, including the upper most part of the vagina, and the pelvic lymph nodes (elective CTV). Patients were treated with a tandem-ring or tandem-ovoid applicator, according to centre's practice. HDR as well as PDR schedules were applied. For detailed information about the centre's most often used BT prescription doses, see Supplement I.

According to a recently described vaginal dose reporting method [19] (Supplement II), the dose at the Posterior–Inferior Border of Symphysis (PIBS) vaginal point and two points at a distance of 2 cm in cranial and caudal direction along the vaginal axis, were determined at time of EBRT and the first BT application. The PIBS vaginal dose point was defined 2 cm posterior from the inferior border of the pubic bone in the sagittal axis for EBRT and for BT at the point of this line where it crosses the applicator tandem. The PIBS+2 point was regarded as an indicator of the anatomical mid of the vagina. The PIBS−2 point was regarded as an indicator of the vaginal introitus, representing the lower part of the vagina. EBRT doses at PIBS and PIBS±2 cm were collected by the centres. In addition, as recommended by the ABS guidelines [4], doses at the applicator surface left/right and anterior/posterior as well as at 5 mm depth were determined at time of the first BT application, representing the dose at the upper vagina. For every patient, to get a relative reproducible estimation of the (irradiated) length of the vagina, the vaginal reference length (VRL) at time of BT was determined, defined by the distance from the centre of the vaginal sources to the PIBS point [19].

The lower part of the vagina was not always part of the transversal or sagittal MR scan, and thus the doses could not be determined directly. In those cases the PIBS−2 cm was estimated by extrapolation.

All physical doses were converted to EQD2 using the linear quadratic model with α/β of 3 Gy, and half time of repair of 1.5 h. For calculation of the total dose in the vaginal top, full EBRT dose in EQD2 was used (45 to 50.4 Gy in fractions of 1.67 to 2 Gy depending on the centre's protocol). For the PIBS points the total physical dose was extracted from the EBRT planning system and calculated in EQD2. The dose to the ICRU-rectum (ICRU-R) point was extracted from the EMBRACE database.

Descriptive data are reported with mean and standard deviation or median and (interquartile-) range, depending on data distribution. Dose correlations were evaluated with a non-parametric correlation test because of skewed distribution and displayed in scatter dot plots. The Spearman's rank correlation coefficient *rho* indicates the direction and strength of the relation, following the common rules of 0.3 weak, 0.5 moderate and 0.7 strong relation.

The SPSS statistical software system, version 22 (Armonk, NY: IBM Corp.) was used for calculations.

Results

One-hundred fifty-three patients from seven different centres were included in this study. Centres from different countries in Europe ($n = 5$) and from India ($n = 2$) were included. Patients and treatment characteristics are shown in Table 1. Approximately half of the patients had vaginal involvement at time of diagnosis, most frequently in the upper third. At time of the first BT application, 35 (23%) patients still had vaginal involvement.

Five centres used a tandem-ring applicator; two centres used a tandem-ovoid applicator. Four centres used only HDR, two only PDR and one used both PDR and HDR brachytherapy during the study period. Four out of seven centres used interstitial needles at the first BT application for in total one-third (34%) of the patients. The median number of needles used per patient was 4.0 (range 1–13).

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