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MRI-guided brachytherapy in locally advanced cervical cancer: Small bowel $D_{0.1cm^3}$ and D_{2cm^3} are not predictive of late morbidity

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ABSTRACT

PURPOSE: To establish dose−volume effect correlations for late small bowel (SB) toxicities in patients treated for locally advanced cervical cancer with concomitant chemoradiation followed by pulsed-dose rate MRI-guided adaptive brachytherapy.

METHODS AND MATERIALS: Patients treated with curative intent and followed prospectively were included. The SB loops closed to CTV were delineated, but no specific dose constraint was applied. The dosimetric data, converted in 2-Gy equivalent, were confronted with the occurrence of late morbidity assessed using the CTC-AE 3.0. Dose−effect relationships were assessed using mean-dose comparisons, log-rank tests on event-free periods, and probit analyses.

RESULTS: A total of 115 patients with a median followup of 35.5 months were included. Highest grade per patient was: Grades 0 for 17, 1 for 75, 2 for 20, and 3 for 3. The mean D_{2cm^3} and $D_{0.1cm^3}$ were, respectively, 68.7 ± 13.6 Gy and 85.8 ± 33.1 Gy and did not differ according to event severity ($p = 0.47$ and $p = 0.52$), even when comparing Grades 0−1 vs. 2−4 events (68.0 ± 12.4 vs. 71.4 ± 17.7 Gy; $p = 0.38$ and 83.7 ± 26.4 vs. 94.5 ± 51.9 Gy; $p = 0.33$). Log-rank tests were performed after splitting the cohort according to four D_{2cm^3} levels: >80 Gy, 70−79 Gy, 60−70 Gy, and <60 Gy. No difference was observed for Grades 1−4, Grades 2−4, or Grades 3−4 ($p = 0.21$−0.52). Probit analyses showed no correlation between the dosimetric parameters and probability of Grades 1−4, 2−4, or 3−4 events ($p = 0.19$−0.48).

CONCLUSION: No significant dose−volume effect relationships were demonstrated between the D_{2cm^3} and $D_{0.1cm^3}$ and the probability of late SB morbidity. These parameters should not limit the pulsed-dose rate brachytherapy optimization process.

Keywords: Image-guided adaptive brachytherapy; Cervical cancer; Dose−volume parameters; Morbidity; Normal tissue complication probability; Small bowel

Introduction

Image-guided brachytherapy (BT) offers the ability to optimize dosimetry with dose escalation to the targets, while accurately controlling the dose delivered to the organs at risk (OARs) with dose−volume histograms (DVH). Volumetric assessment became the standard to report the doses because the Groupe Européen de Curiethérapie−European Society for Radiation Oncology and American Brachytherapy Society recommended to report doses delivered to OAR in small volumes (0.1 and 2 cm^3) (1, 2). For the bladder and rectum, recent studies showed clear dose−volume relationships between these parameters and the probability of occurrence of late morbidity (3, 4). Further studies are required to evaluate the impact of other clinical factors such as comorbidities on these relationships. Nevertheless, it is therefore possible to balance the risk of late radiation-induced morbidity with the benefit of achieving local control (5, 6).

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However, some of the most common radiation-induced late toxicities in cervical cancer patients concern the small bowel (SB). For decades, BT has been based on 2D orthogonal X-rays, and while the doses delivered to the bladder and rectum were reported using the International Commission for Radiation Units and measurements points, no specific dosimetric parameter was available for the SB. With the guidance of MRI or CT, it is therefore possible to delineate the loops closed to CTV and generate DVHs with external beam radiotherapy (EBRT) (7). Moreover, EBRT techniques have improved substantially with intensity-modulated radiotherapy, image-guided radiotherapy, and adaptive radiotherapy leading to a better avoidance of the SB. However, the risk of intestinal radiation injury remains an important dose-limiting factor in radiation therapy for pelvic tumors. Acute radiation enteropathy is common during the course of radiation therapy, while late SB morbidity develops after a latency period of variable length, usually installed for months or years and deeply impacting quality of life (8). Kavanagh *et al.* proposed benchmarks in a review of literature dedicated to quantitative analyses of normal tissues effects in the clinic that help to optimize EBRT dosimetries. To limit the acute toxicities, the absolute volume of SB receiving more than 15 Gy should be kept below 120 cm^3, whereas delineating the SB loops or alternatively, if the entire volume of peritoneal space is defined, the volume receiving more than 45 Gy should be ideally be kept <195 cm^3. However, the authors underlined the lack of data regarding the risk of late morbidity (9).

With BT, no dose−volume effects could be established between the modern volumetric dosimetric parameters and the occurrence of late SB events. The aim was to evaluate the ability of BT DVH parameters ($D_{0.1cm^3}$ and D_{2cm^3}, minimal dose calculates in the maximally exposed 0.1 or 2 cm^3 of the organ) to predict late SB morbidity.

Methods and materials

Patients

From 2009, patients with locally advanced cervical disease defined as Fédération Internationale de Gynécologie Obstétrique Stage IB1 with infiltrated nodes to Fédération Internationale de Gynécologie Obstétrique Stage IVA and treated in curative intent and with a combination of EBRT and BT, both performed at our institute, were followed prospectively. According to the local ethical committee, patients gave their written consent for the use of their data. For the purpose of this study, we selected the patients who had completed their treatment at least 1 year before analysis (15 September 2014), with a minimum followup of 3 months according to the definition of late morbidity applied.

Their initial workup comprised a pelvic MRI and a PET-CT. Those with positive para-aortic nodes (PANs) extension below the level of L1−L2 were treated with extended-field radiotherapy, whereas those with no significant uptake outside the pelvis underwent a laparoscopic PAN staging, except in case of contraindication (age $>$ 70 years, major comorbidity, or important left hydronephrosis) to determine the extent of radiation fields (10).

The radiation procedure has been reported in detail elsewhere (11). Briefly, all patients started with pelvic ± para-aortic EBRT, with concomitant chemotherapy when not contraindicated, with a normal fractionation (45 Gy, in 25 fractions over 5 weeks). A systematic margin of at least 10 mm in all directions was applied to the centropelvic clinical target volume (CTV) to generate the planning target volume, up to 12 mm in the anteroposterior direction. This margin was 7 mm for the nodal planning target volume. A four-field box with high-energy photons was used in all patients. No midpelvis block or parametrial boost was used. A few days after the completion of EBRT, patients were hospitalized for a pulsed-dose rate (PDR) MRI-guided BT (12). Nodal boosts were performed sequentially after BT taking into account its contribution to the treatment of nodes. Anteroposterior fields were used, avoiding the centropelvic region.

BT procedure

The implantation technique description is available in a previous publication (11). Before the insertion of the applicator, a bladder catheter was placed and left open during the image acquisition and treatment delivery to ensure the reproducibility of the bladder emptiness. After the implantation, a pelvic MRI was acquired, with T2 sagittal, axial, and coronal sequences, which were transferred to Oncentra (Nucletron, an Elekta Company, Stockholm, Sweden) or BrachyVision (Varian Medical Systems, Palo Alto) platforms for planning. The applicator was localized and the volumes of interest: high-risk CTV (CTV_{HR}) and intermediate-risk CTV (CTV_{IR}), and rectum, bladder, sigmoid colon, and SB were delineated according to the Groupe Européen de Curiethérapie−European Society for Radiation Oncology recommendations (13). For SB, the loops closed to CTV were delineated, excluding the colon (Fig. 1).

The planning started with an activation of the dwell positions in regard to the CTV_{IR}, and a standard dose of 15 Gy prescribed and normalized to Point A. The optimization process aimed to reach the following planning aims: D_{90} (dose received by 90% of the volume) to the $CTV_{HR} \geq 85$ Gy, D_{90} $CTV_{IR} \geq 60$ Gy, D_{2cm^3} of the bladder $\leq$ 85 Gy, D_{2cm^3} of the rectum, and sigmoid $\leq$ 75 Gy (all doses in 2-Gy equivalents, applying the linear quadratic model with a α/β ratio of 10 Gy for CTVs and 3 Gy for OARs, adding EBRT and BT contributions, considering that small volumes studied in BT, 0.1 and 2 cm^3, received 100% of the