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Total radiation dose and overall treatment time are predictive for tumor sterilization in cervical carcinoma treated with chemoradiation and pulsed-dose-rate brachytherapy

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ABSTRACT

BACKGROUND AND PURPOSE: Treatment of locally advanced cervical cancer involves multidisciplinary care using external beam radiotherapy, chemotherapy, brachytherapy, and surgery. We aimed to compare both tumor and treatment characteristics between patients with complete pathologic response (CR) and patients with residual disease (RD).

PATIENTS AND METHODS: This monocentric retrospective study included 40 consecutive patients, treated with external beam radiotherapy, pulsed-dose-rate brachytherapy, and completion surgery. Treatment planning was performed to obtain a cumulative D_{90} value for the intermediate-risk clinical target volume (CTV) ≥60 $Gy_{\alpha/\beta=10}$. Different clinical and dosimetric parameters were analyzed and compared between patients with RD and those with CR.

RESULTS: We observed 18 (45%) patients with CR and 22 (55%) patients with RD. In univariate analysis, patients with RD had a significantly longer overall treatment time than those with CR (59.5 vs. 53 days, $p = 0.0321$). The D_{90} value for the high-risk CTV (HR-CTV) was higher in the group with CR than in the group with RD (65.9 vs. 64.2 $Gy_{\alpha/\beta=10}$; $p = 0.0439$). In multivariate analysis, overall treatment time remained the only predictive factor for CR ($p = 0.033$), even if the difference for D_{90} HR-CTV kept a trend toward significance ($p = 0.057$).

CONCLUSIONS: This study showed that tumor sterilization is significantly correlated with overall treatment time and probably with cumulative dose delivered to the HR-CTV. These results emphasize the attention that must be given to treatment organization and dosimetry optimization.

Keywords: Cervical cancer; Brachytherapy; Pathologic response; Predictive factors

Introduction

Chemoradiation therapy followed by brachytherapy (BT) has become the standard of care for locally advanced cervical cancer (from Stage IB2 according to the Fédération Internationale de Gynécologie et d'Obstétrique [FIGO] classification), allowing 5-year survival rates of about 70% (1, 2). BT is a major component of treatment of cervical carcinoma (3) as its rapid dose falloff enables high doses to target volumes, while sparing critical organs (4, 5). Three-dimensional (3D) image-guided treatment planning has been a major advance for the BT of cervical cancer, allowing target volume and critical organ delineation. The Gynaecological Groupe Européen de Curiethérapie-European SocieTy of Radiation Oncology (GEC-ESTRO) working group published recommendations on BT treatment planning to harmonize practices (6, 7). Three target volumes were defined for delineation and dose prescription: the gross tumor volume (GTV), high-risk clinical target volume (HR-CTV), and intermediate-risk clinical target volume (IR-CTV) allowing comparisons between different teams. Another major progress was the development of afterloaders as it made optimization of dosimetric parameters possible by adjusting dwell positions and dwell times.

The role of completion hysterectomy is still debated, given that, so far, published studies failed to prove its benefits (8–13). However, analysis of the hysterectomy specimens has led to identify pathologic response as a prognostic

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factor for progression-free and overall survival. Patients with complete pathologic response (CR) have a significantly longer survival than those with residual disease (RD) (14–18).

Several reports (17, 19) have identified predictive factors for CR in cervical cancer, but, to our knowledge, there are no data about the impact of pulsed-dose-rate (PDR)-BT dosimetric parameters on tumor sterilization. Available information concern low-dose-rate (LDR) BT and report a correlation between total dose delivered to Point A and the rate of CR (20, 21).

The aim of our study was to correlate pathologic findings on the hysterectomy specimen with clinical data and dose–volume histogram (DVH) parameters at the time of BT. We assessed the impact of these different parameters on tumor sterilization.

Patients and methods

Patient and tumor characteristics

This retrospective study was conducted at the Institute Jean Godinot, between 2006 and 2013. Inclusion criteria were diagnosis of locally advanced cervical carcinoma according to the FIGO definition, confirmed by biopsy and histologic examination, treatment with concomitant chemotherapy and external beam radiotherapy (EBRT), PDR-BT, and completion surgery. A total of 40 patients with full clinical and technical charts were included in this study.

The initial staging was based on physical examination under general anesthesia and pelvic MRI. Cystoscopy and rectoscopy were performed when there was a doubt on the MRI concerning a potential involvement of the bladder or the rectum. FIGO classification was used to stage the disease, and the size of tumor was assessed using the biggest dimension measured on the MRI. Twenty patients (50%) underwent a positron-emission tomography/CT at diagnosis.

The mean age of these patients at diagnosis was 48.9 years. A total of 10 patients presented with nodal involvement at diagnosis: nine pelvic nodal involvement and 1 para-aortic and pelvic nodal involvement. All patients were treated with curative intent. Patient characteristics are summarized in Table 1.

Table 1
Patient and tumor characteristics

Characteristics	*N*
Age at diagnosis	
Median	46.7
IQR	40.6–58.3
Histology, *n* (%)	
Squamous cell carcinoma	34 (85)
Adenocarcinoma	4 (10)
Glassy cell carcinoma	1 (2.5)
Small cell carcinoma	1 (2.5)
Tumor size	
Median	50
IQR	42.3–60
FIGO stage, *n* (%)	
IB1	1 (2.5)
IB2	6 (15)
IIA1	5 (12.5)
IIA2	3 (7.5)
IIB	23 (57.5)
IIIA	1 (2.5)
IIIB	1 (2.5)
Lymph node involvement	
Yes	10 (25)
No	30 (75)

IQR = interquartile range; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique.

Treatment characteristics

All patients were treated with pelvic EBRT with or without para-aortic irradiation with a linear accelerator; treatment was based on CT-assisted 3D treatment planning. EBRT was in most cases delivered concurrently with chemotherapy (39 of 40 patients = 97.5%). EBRT was not always performed in our institution as patients were coming from the whole region to undergo BT, however, all treatment plans were available. For 92.5% of patients, treatment consisted of 3D conformal EBRT using four-field treatment, 3 patients (7.5%) were treated using TomoTherapy (Accuray, Inc., Sunnyvale, CA). The mean dose delivered was 45.6 Gy (range, 41.4–50), with fractions of 1.8–2.25 Gy. A simultaneous integrated boost was used for the 3 patients treated with TomoTherapy, delivering fractions of 1.8 Gy on nodal areas and 2.25 Gy on the uterus. Only 1 patient, for whom one para-aortic nodal involvement has been found, received a para-aortic irradiation.

Concomitant weekly intravenous chemotherapy was delivered during EBRT: cisplatin (87.5%), cisplatin–cetuximab (5%), cisplatin–etoposide (2.5%), or carboplatin (2.5%); 1 patient (2.5%) did not receive any chemotherapy because of poor physical condition. The median number of chemotherapy cycles was 5.

After EBRT, the BT was delivered at our institution for all patients. The PDR Microselectron by Nucletron, an Elekta company (Elekta AB, Stockholm, Sweden), was used to deliver the PDR boost, with iridium-192. One insertion was performed for each patient.

BT procedure

A few days before BT, all patients underwent MRI to evaluate tumor response after EBRT and guide the delineation of CTVs.

BT was performed under general anesthesia and began with clinical examination to assess clinical response. In our institution, Fletcher CT/MRI applicators made by Nucletron, an Elekta company, were used for the treatment, and the radiation oncologist had the choice between three different sizes of vaginal ovoid pair and three uterine applicators to fit the patient's anatomy the best. No patient received interstitial BT.