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Clinical outcomes of definitive chemoradiation followed by intracavitary pulsed-dose rate image-guided adaptive brachytherapy in locally advanced cervical cancer

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HIGHLIGHTS

- Image-guided brachytherapy in combination with concomitant chemoradiation provides high local control rates in locally advanced cervical cancer.
- Clear dose–effect correlations between dose to clinical target volumes and local control probability exist.
- Interstitial brachytherapy is mandatory to reach high doses in advanced staged diseases.

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ABSTRACT

Objective. To report the outcomes and late toxicities of patients with locally advanced cervical cancer treated with concomitant chemoradiation (CRT) followed by intracavitary image-guided adaptive brachytherapy (IGABT).

Methods. Data from consecutive patients with histologically proven stage IB-IVA cervical cancer treated with curative intent in a single institution were analyzed. After pelvic +/− para-aortic external-beam radiation therapy, they received pulsed-dose rate IGABT following GEC-ESTRO recommendations.

Results. Two hundred and twenty-five patients were enrolled. Sixty-five percent were stage ≥ IIB according to FIGO classification. Ninety-five percent received CRT. Mean D90 to HR and IR-CTV were 80.4 +/− 10.3 Gy and 67.7 +/− 6.1 Gy. After a median follow-up of 38.8 months, 3-year local control and overall survival rates were 86.4% and 76.1%, respectively. A trend for a detrimental effect of tumor stage on local control rates was observed with 3-year local control rates of 100% for stages IB1 and IIA, 90.5 for IB2, 85.8% for IIB, 50% for IIIA, 77.1 for IIIB, and 66.7% for IVA tumors ($p = 0.06$). Local control rates at 3 years were 95.6% in the group of patients with D90 of HR-CTV ≥ 85 Gy, 88.8% in those with D90 between 80 and 85 Gy, and 80% when D90 < 80 Gy ($p = 0.018$). Eighteen severe late gastrointestinal and urinary effects affecting 14 patients were reported corresponding with a crude incidence of 6.6%.

Conclusions. CRT followed by IGABT provides high local control rates with limited toxicity. Reaching high doses is mandatory to achieve local control and interstitial brachytherapy is necessary in advanced diseases.

1. Introduction

The standard treatment of locally advanced cervical cancer relies on a combination of external-beam radiotherapy (EBRT) and brachytherapy, which remains a predominant component of the treatment, as recently highlighted [1]. However, Gill et al. showed a decrease in the use of brachytherapy in the USA as a boost in locally advanced cervical cancer, in the benefit of modern EBRT techniques such as intensity modulated radiotherapy (IMRT) and stereotactic body radiation therapy (from 3.3% to 13.9% in the studied period, $p < 0.01$) [2]. Han et al. reported that this shift of techniques was parallel with a worsening of clinical outcomes, with a decrease of 4-year overall survival of 12% ($p < 0.001$) [3].

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In the field of brachytherapy, major technical advances have improved its efficiency during the last two decades, with the advent of image-guided adaptive brachytherapy (IGABT). This high-precision technique allows dose escalation to the target while evaluating accurately the dose delivered to surrounding organs at risk [4]. In 2005, the GEC-ESTRO (Groupe Européen de Curiethérapie-European Society for Radiation Oncology), aiming to harmonize reporting in brachytherapy, proposed recommendations featuring definitions of clinical target volumes, which gradually were imposed as a standard worldwide [5,6]. However, although most brachytherapy centers declare the use of 3D imaging to guide brachytherapy, most series are limited to a small amount of patients.

The aim was to report the outcomes and late morbidity of patients treated with concomitant chemoradiotherapy (CRT) followed by image-guided adaptive brachytherapy per GEC-ESTRO recommendations.

2. Materials and methods

2.1. Patient selection

Consecutive patients treated with image-guided adaptive brachytherapy were identified from the department database. Those with histologically proven locally advanced cervical cancer defined as IB1 N+, IB1-IVA according to the FIGO (International Federation of Gynecology and Obstetrics) classification were selected. Squamous cell, adenosquamous carcinomas, or adenocarcinomas were included, whereas clear cell and small cell carcinoma subtypes were excluded. Patients had to be treated with curative intent with a combination of EBRT followed by IGABT. Para-aortic extension was accepted, provided the highest border was below L1–L2, and covered by extended-field radiotherapy. Brachytherapy had to follow the GEC-ESTRO recommendations. Patients who received neo-adjuvant or adjuvant treatment (hysterectomy or chemotherapy) were not eligible. As well, the patients treated with Cesium concomitantly to the deployment of the technique (acquisition of a sufficient number of afterloaders) were excluded.

2.2. Patient work-up

FIGO stages were defined on clinical examination findings. All patients had an MRI at diagnosis for local extension. PET-CT was performed in the majority of patients for evaluation of regional and metastatic status. When not performed, especially in the first years of our experience, this evaluation was based on a CT and the MRI. No other imaging was mandatory.

From 2007, patients with negative para-aortic extension on PET-CT were offered laparoscopic para-aortic lymph node (PAN) staging to eliminate false negative PET-CT at this region [7]. This procedure was withdrawn in case of severe comorbidity or age >65–70 years. Radiotherapy fields were then adapted according to pathological findings of the staging.

2.3. External-beam radiation therapy (EBRT)

At first, all patients were treated with pelvic EBRT planned on a 3 mm slice thickness planning CT scan. Conventional fractionation was used in all patients (1.8–2 Gy per fraction, 5 times a week) for a total dose ranging from 44 to 50.4 Gy, with high energy photons (18–20 MV). The centro-pelvic clinical target volume (CTV) included the cervix, the whole uterus, the adnexa when visible on planning CT, the parametria, and at least the upper part of the vagina or more depending on its involvement. A systematic margin of at least 10 mm in all directions was added to generate the PTV (planning target volume). The nodal CTV contained bilateral external and internal iliac lymph node areas, ilio-obturator, presacral, and common iliac areas. Groins were included in case of distal vaginal invasion. Extension of the fields to the PAN depended on the findings of the PET-CT, MRI, and laparoscopic staging when performed. To generate a nodal PTV, a margin of 7 mm was added. Concomitant chemoradiation was systematically administrated, except in case of contraindication, severe comorbidity, or refusal. The standard regimen was cisplatin 40 mg/m^2 weekly, five times during EBRT delivery, with a sixth cycle administered during brachytherapy. In case of renal failure, AUC2 weekly carboplatin was used. After completion of brachytherapy, sequential nodal boosts were performed adapting the dose to the contribution of brachytherapy to this region. The aim was to reach a total nodal boost dose of 60 Gy. No parametrial boosts were performed.

2.4. Brachytherapy (IGABT)

Pulsed-dose rate image-guided brachytherapy systematically followed EBRT. A detailed description of the procedure is available in previous publications [8,9]. Implants were performed under general anesthesia. A personalized vaginal mould applicator was used in nearly all cases, which required a previous vaginal impression [10]. Then patients underwent an MRI in T2 sequence: axial, sagittal, and coronal slices were acquired [11]. Dummy sources were inserted in the catheters to facilitate the applicator reconstruction. In case of refusal or non-availability of MRI, a 3 mm thick CT scan was done with intra-venous iodine injection to enhance the cervix. The images were then transferred to Oncentra® (Nucletron, an Elekta company, Stockholm, Sweden) or Brachyvision® (Varian medical systems, Palo Alto, California, USA). Delineation consisted in contouring the high-risk and intermediate-risk clinical target volume (HR-CTV and IR-CTV) as defined by the GEC-ESTRO and organs at risk (OAR, bladder, rectum, and sigmoid) [5]. Planning aims were 85 Gy to 90% of the HR-CTV (D90), and 60 Gy to the D90 of the IR-CTV (doses in 2 Gy equivalents, EqD2, summing EBRT and BT and applying the linear quadratic model with an α/β ratio of 10 Gy and a half-time repair of 1.5 hours). Dose constraints were 75 Gy to the maximally 2 cm^3 exposed areas of the rectum and sigmoid colon (D2cm^3), and 85 Gy to the D2cm^3 of the bladder (EqD2, similar model with $\alpha/\beta = 3$ Gy). Beyond these thresholds, additional constraints were applied, based on our 2D experience: 15 Gy physical dose volume limited to 200–250 cm^3, and TRAK (total reference air kerma) ≤2–2.2 cGy/m^2. Dosimetry started with a standard loading pattern in regard to the delineated IR-CTV and a prescription of 15 Gy normalized to point A. Then optimization was performed manually to adapt the dwell times to the topography of the implant.

2.5. Follow-up

Patients were evaluated at 6–8 weeks with a pelvic MRI and a clinical examination. In case of complete remission, they were then followed every 3–4 months during 3 years, then every 6 months during the following 2 years and yearly thereafter. In case of doubt, MRI was repeated a few weeks later. MRI was repeated systematically at least once a year in all cases in follow-up. Biopsies were performed in case of relapse suspicion.

2.6. Definitions and statistical analyses

Survival was defined from the date of diagnosis (biopsy) to last follow-up or event occurrence. Local relapses were defined as any recurrence in the vagina, cervix, uterus, or parametria, regardless of its relationship to the target volume. Pelvic recurrence was defined as any local or nodal pelvic recurrence. Regional relapses were defined as any recurrence in the pelvis or in the PAN area. Other relapses were considered as metastatic failure, including carcinomatosis. Late toxicities consisted in any radiation-induced morbidity occurring or lasting 90 days after treatment initiation. They were defined and graded according to the common toxicity criteria for adverse events version 3 (CTC-AE 3.0).