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Outcome of early stage cervical cancer patients treated according to a radiosurgical approach: Clinical results and prognostic factors

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HIGHLIGHTS

- Optimal treatment for early invasive cervical cancer still remains unclear.
- Brachytherapy (BT) seems a safe preoperative option.
- 70% of patients had complete histological response after BT.
- Pelvic node, tumor size and residue are associated with poorest outcome.
- The interval between BT and surgery should be <9 weeks.

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ABSTRACT

Objective. To report clinical results of a multimodal strategy based on preoperative brachytherapy followed with surgery in early stage cervical cancer.

Materials/Methods. The outcome of consecutive patients receiving brachytherapy in our Institution for an early stage IB1-IIA1 invasive cervical cancer with risk factors (lymphovascular embols and/or tumor >2 cm) between 2000 and 2013 was analyzed. The treatment consisted of preoperative low dose or pulse dose-rate utero-vaginal brachytherapy followed, 6–8 weeks later, by a radical hysterectomy/bilateral salpingo-oophorectomy plus pelvic ± para-aortic lymph node dissection. A postoperative chemoradiation was delivered in patients with histological evidence of lymph nodes metastases.

Results. 182 patients were identified. Histological examination of hysterectomy specimen showed the presence of a tumor residuum in 55 patients (30.2%). One patient (0.5%) had residual tumor cells in the parametria. With a median follow-up of 5.3 years, 14 patients (7.7%) presented tumor relapse, including three (1.6%) local relapses. Five-year disease-free survival (DFS) rate was 93.6% (95%CI: 91.6–95.6%). In log-rank analysis, presence of pelvic nodal metastases at time of lymphadenectomy ($p = 0.001$) and tumor size ≥3 cm ($p = 0.003$) correlated with a poorer DFS. Presence of a tumor residuum on hysterectomy specimen correlated with a higher risk of pelvic or para-aortic failure ($p = 0.035$). A time interval > 10 weeks between brachytherapy and surgery correlated with a higher risk of failure outside the pelvis ($p = 0.003$). Significant postoperative complications were reported in 16 patients (8.8%). All delayed toxicities were mild to moderate.

Conclusions. A preoperative brachytherapy is a safe and effective option in early stage cervical cancer.
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1. Introduction

There is no definitive consensus on the optimal treatment of early stage cervical cancers, IB1-IIA1 according to the International

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Federation of Gynaecology and Obstetrics (FIGO) classification. Three therapeutic options have been proposed, yielding to comparable oncologic outcomes [1–5]. To date, the most frequently used therapeutic approach worldwide consists of an upfront radical hysterectomy combined with pelvic lymph node dissection (LND). A second option, usually kept for patients who are unfit for surgery because of co-morbidities, consists of a definitive external beam radiotherapy (EBRT), followed by brachytherapy. Finally, the third option, frequently used in France, is a multimodal radiosurgical treatment combining a preoperative uterovaginal brachytherapy followed with surgery, which is performed 6 to 8 weeks later. The rationale of this debated option is to optimize the local control and to potentially decrease the need for postoperative EBRT because of adverse histological findings on hysterectomy specimen. Although no randomized trial has demonstrated the benefit of a preoperative brachytherapy in patients with an early stage cervical cancer, retrospective reports have examined the clinical outcome of patients treated according to this radiosurgical modality and shown high local control rates and a satisfactory toxicity profile [6–14].

Our retrospective experience of preoperative brachytherapy as part of a multimodal strategy is reported. Patterns of relapse, long-term sequelae and clinical prognostic factors are examined.

2. Materials and Methods

2.1. Patients and tumours

The clinical records of consecutive patients receiving a preoperative uterovaginal brachytherapy in our Institute between December 2000 and December 2013 for a histologically confirmed early stage invasive cervical cancer were reviewed. To be considered as with early stage cancer, patients should had disease confined to the pelvis, with no parametrial extension, a tumor ≤4 cm in greatest dimension, and no evidence of pelvic nodal metastasis after a primary staging consisting of a clinical examination and a pelvic/abdominal magnetic resonance imaging (MRI) that was systematically done to refine primary tumor staging. Only patients with high-risk factors (lymphovascular embols and/or tumor >2 cm) were eligible for this preoperative uterovaginal brachytherapy, as per standard in our Institute.

2.2. Treatments

The brachytherapy procedure has been reported before [1,13]. Briefly, a vaginal mold applicator with two vaginal catheters and a semi-flexible intra-uterine tandem catheter were inserted under general anesthesia [15]. The treatment planning aimed at delivering 60 Gy to the cervix, the proximal part of the parametria and the upper third of vagina. Depending on the treatment period, treatment planning was done from radiographs or from 3D acquisition, and patients were treated with low-dose rate (LDR) brachytherapy using Cesium sources or with pulse dose rate (PDR) brachytherapy.

For radiograph-based treatment planning, the maximum width of the applicator in the upper third of the vagina was measured from radiographs and the dose of 60 Gy was prescribed to the isodose that encompassed this volume with a 0.5 cm margin deep to the vaginal wall in all three planes, without exceeding I.C.R.U (International Commission on Radiation Units) 38 points dose constraints [1,16]. For 3D treatment planning, volumes were delineated on a T2–weighted MRI or on a computed tomography (CT) scan. The aim was to deliver at least 60 Gy to 90% of the intermediate risk clinical target volume (IR-CTV), defined according to the Brachytherapy Group of the European Society of Therapeutic Radiology and Oncology (GEC-ESTRO) guidelines, without exceeding dose constraints to the most irradiated D2cm^3 of rectum, bladder and sigmoid colon [17,18].

The length of each source and the period for which each was inserted (for LDR treatments) or the position and dwell time (for PDR treatments) were determined on an individual basis, taking into account clinical examination, and computerized dosimetry acquired from radiographs of the application or from 3D imaging. For PDR treatments, continuous hourly pulses were delivered, 24 h per day. In all cases, a dose rate of 0.6 Gy per hour to ICRU points or to the most irradiated D2cm^3 of organs at risk was not exceeded.

Six to eight weeks after brachytherapy, patients underwent modified radical hysterectomy, bilateral salpingo-oophorectomy and bilateral pelvic LND. A para-aortic LND was also performed if histological analysis showed pelvic nodal metastases. Surgery type depended on surgeons' judgment and institution. Patients undergoing surgery in our Institution were treated with class B hysterectomy according to Querleu classification (modified radical hysterectomy, ureters dissected in the paracervical region only) [19].

A postoperative EBRT with high energy (Megavoltage) photons was delivered in case of histological evidence of lymph node metastasis, delivering 45 Gy in 25 fractions of 1.8 Gy through a conformal technique using antero/posterior – postero/anterior fields, treating pelvic lymph nodes ± the para-aortic area, depending on histological findings. A midline shielding block individualized according to the brachytherapy isodoses was used. Weekly cisplatin 40 mg/m^2 was delivered concomitantly for all patients requiring postoperative EBRT.

2.3. Follow-up and statistical analysis

Assessment of tumor control and toxicity began six weeks after surgery and was done every three months during two years and then every six months during three years. Complications were retrospectively scored using the Common Terminology Criteria for Adverse Events version 4 and failures defined as recurrence after complete remission with a follow-up of more than three months. Analysis of patterns of relapse considered only first sites of relapse.

Disease-free survival (DFS) and overall survival (OS) times were estimated using Kaplan-Meier method and calculated from the time of surgery. Proportions and means were compared by chi-squared test, Mann-Whitney and the Student's *t*-test if needed. The log-rank test for qualitative factor and Cox model for quantitative. A p value <0.05 was considered as statistically significant. Statistical analyses were carried out using Statistical Package for the Social Sciences (version 21; SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patients and tumours

182 patients were identified, 176 with Stage IB1 tumours (96.7%) and six with Stage IIA1 tumours (3.3%). A total of 74 patients (40.7%) had undergone a cervical conization prior to brachytherapy procedure, as part of the diagnostic procedure.

At time of brachytherapy, median largest tumor diameter was 2.3 cm (range: 0–4 cm), as assessed by clinical examination and/or by MRI. Histology was squamous cell carcinoma in 128 patients (70.3%) and adenocarcinoma in the 54 (29.7%) remaining patients. Thirty patients (16.5%) had LVI on biopsy sample or cone biopsy tissue (Table 1).

3.2. Characteristics of brachytherapy and surgery

Brachytherapy was performed with LDR in 98 patients (53.8%) and with PDR in 84 patients (46.2%). A total of 111 patients (61%) had an image-guided treatment planning, based on MRI (n = 77) or on CT scan (n = 34). The 71 remaining patients (39%) had their treatment planning based on radiographs. Median time interval between brachytherapy and surgical procedure was 58 days (ranging from 32 days to 13 months). One patient had a protracted time interval of 13 months, because she initially refused surgery after receiving brachytherapy procedure and was lost to follow-up. She finally presented, approximately one year later, with a demand for hysterectomy. A laparoscopic surgical

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