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Original article

Preoperative image-guided brachytherapy in early stage cervical cancers

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ABSTRACT

Objective: To examine the clinical results of a preoperative image-guided pulse-dose-rate brachytherapy (PDR-BT) in early stage cervical cancer.
Materials/methods: We examined the outcome of consecutive patients with early stage cervical cancer undergoing preoperative image-guided PDR-BT between 2004 and 2013 because of risk factors (lympho-vascular embols and/or tumour > 2 cm). The objective was to deliver 60 Gy to 100% of the intermediate risk clinical target volume. Brachytherapy was followed, 6–8 weeks later, by a radical hysterectomy/bi-lateral salpingo-oophorectomy plus pelvic +/− para-aortic lymph node dissection. Patients with positive lymph nodes had postoperative chemoradiation.
Results: 77 patients met the above criteria of preoperative PDR-BT. On hysterectomy specimen, 54 (70.1%) presented a complete histological response. Four (5.2%) had a tumour residuum ⩾ 1 cm. Median follow-up was 46.8 months. 5-Year disease-free survival (DFS) rate was 84.4%. Only one local recurrence was observed. The presence of lymph nodal metastases, a tumour size > 3 cm and a brachytherapy/surgery time interval ⩾ 9 weeks correlated with a poorer DFS. Six postoperative complications were encountered (7.8%). Total reference air kerma correlated with late vaginal toxicity ($p = 0.02$).
Conclusions: A preoperative image-guided PDR-BT was safe and effective. Predictive factors for survival and toxicity were evidenced.
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For locally advanced cervical cancer (LACC), the optimal treatment is well defined, based on concomitant chemoradiation followed by a brachytherapy boost [1]. The implementation of image-guided adaptive brachytherapy (IGABT) in LACC, following guidelines of the Gynaecological Brachytherapy Group of the European Society of Therapeutic Radiology and Oncology (GEC-ESTRO), has been associated with a significant decrease in local relapses and severe toxicities [2–7].

For early stage cancers, the optimal treatment remains unclear and various treatment modalities have been proposed, with comparable oncologic outcomes [8–26]. For stage IB1–IIA1 according to the International Federation of Gynaecology and Obstetrics (FIGO) classification, upfront radical hysterectomy is usually the preferred treatment, combined with pelvic lymph node dissection (LND). A second option is a definitive EBRT, followed by brachytherapy, mainly in case of surgical contra-indication. The third option, which is used in France for selected cases of IB1–IIA1 cervical cancers, is a multimodal treatment combining a preoperative brachytherapy and a surgery, which is performed 6 to 8 weeks later. This strategy has been associated with high local control rates and satisfactory toxicity profiles [8–26].

No study has demonstrated the benefit of image-guided brachytherapy in early stage cancer, but it is now possible to accurately document the doses delivered to relevant clinical target volumes and organs at risk (OAR) and to optimize dose distribution. Based on the rationale that the therapeutic index could be potentially improved by applying the concepts of IGABT to early stage cancers, our retrospective experience of preoperative brachytherapy as part of a multimodal strategy is reported, with special emphasis on dose/volume parameters and on clinical prognostic factors. To our best knowledge, this is the first study examining the potential of image-guided pulse-dose rate (PDR) brachytherapy in early stage cervical cancers.

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Materials and methods

Patients and tumours

The clinical records of consecutive patients treated between March 2005 and May 2013 for a histologically confirmed early stage cervical cancer and undergoing uterovaginal PDR brachytherapy followed by surgery were examined. All patients underwent a primary locoregional staging based on clinical examination and pelvic/abdominal magnetic resonance imaging (MRI). Patients with IB1–II1A cervical cancers were candidates for brachytherapy if they presented with a tumour $\geqslant 2$ cm in the greatest dimension and/or in case of lymphovascular invasion (LVI) on biopsy samples or conization and if there was no lymph node involvement on MRI. Treatments were decided after a multidisciplinary discussion.

Treatments

The brachytherapy procedure consisted of intracavitary uterovaginal implantation, as previously described [18]. A vaginal mould and a semi-flexible tandem catheter were inserted under general anaesthesia after a careful clinical examination confirming the early stage of the disease. The brachytherapy was based on a 3D computerized assisted treatment planning through the PDR Selectron® seed projector (Nucletron, an Elekta Company, Stockholm, Sweden) or Varian afterloader (Varian Medical System, Palo Alto, CA). Delineation of volumes was performed on a T2-weighted MRI or on a computerized tomography scan. The intermediate-risk clinical target volume (IR-CTV) was systematically delineated according to the GEC-ESTRO guidelines [1]. The IR-CTV corresponded to the whole cervix plus vaginal tumour extension if any, with a safety margin of 15 mm cranio-caudally including the upper third of the vagina, 10 mm laterally to the parametria and 5 mm in antero-posterior axis. High-risk clinical target volumes (HR-CTV), defined as the whole cervix plus any macroscopic tumour, were retrospectively delineated to evaluate DVH parameters. OAR (bladder, sigmoid and rectum) were systematically delineated.

One single endocavitary application *per* patient was delivered. The planning aim was to deliver at least 60 Gy to 90% of the IR-CTV. Physical doses were converted into biological effective doses normalized to a radiobiologically weighted dose equivalent of 2 Gy/fraction ($\alpha/\beta = 10$ Gy for tumour and 3 Gy for late reactions, half-time of 1.5 h for both). Dose constraints to the D2 cm^3 rectum, bladder and sigmoid colon were respectively 70, 75, and 70 $Gy_{\alpha/\beta=3}$. The irradiation was delivered through continuous hourly pulses. If the limit of 0.6 Gy per hour to the organs at risk was exceeded, the dose rate was decreased and the total number of pulses was consequently increased. Dwell time optimization was done by manually adding or removing stopping positions and adjusting the dwell times. The dose and target coverage were adapted according to the dose–volume constraints for the OARs. For each OAR, the radiation doses delivered to 1 and 2 cm^3 were assessed (D1 cm^3, D2 cm^3, respectively).

Six to eight weeks after brachytherapy, patients underwent a modified radical hysterectomy associated with bilateral salpingo-oophorectomy and bilateral pelvic LND. In case of histological pelvic nodal metastases evidenced on frozen section analysis during surgery, a para-aortic LND was also performed. Patients with positive nodes underwent postoperative EBRT (45 Gy in 25 fractions of 1.8 Gy) delivered through a conformal technique (using antero/posterior–postero-anterior fields) with a median shielding of the pelvis by a midline block individualized according to the brachytherapy isodoses or with an intensity modulated technique. Weekly cisplatin 40 mg/m^2 was delivered concomitantly with EBRT.

Follow-up and statistical analysis

Follow-up was scheduled at six weeks after surgery, then every three months during two years, then every six months during three years. Complications were scored according to the Common Terminology Criteria for Adverse Events version 4. Failures were defined as recurrence after complete remission with a follow-up of more than three months. Only first sites of relapse were considered and classified into: centropelvic, pelvic nodal, para-aortic nodal or metastatic.

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 Student's t test if needed. The log-rank test for qualitative factor, Cox model for quantitative factor and PROBIT model for DVH parameters were used for analyzing survival rates. 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).

Results

Patients and tumours

77 patients were identified. Tumour was classified as Stage IB1 in 74 patients (96.1%) and IIA1 in three patients (3.9%). The median largest tumour diameter was 2.4 cm (range: 0–3.9 cm), as assessed by clinical examination and/or by initial MRI. All patients had disease confined to the central pelvis after primary staging. Twenty-five (32.5%) had undergone a conization prior to brachytherapy. Histology showed squamous cell carcinoma in 57 patients (74.0%) and adenocarcinoma in 20 (36.0%). LVI was found in 16 patients (20.8%) (Table 1).

Dose–volume histogram parameters

The delineation was performed on MRI in 56 patients (72.7%) and on CT in 21 patients (37.3%). The median number of pulses was 113 (60–150). Median dose per pulse was 0.5 Gy (0.35–0.6 Gy). The median volume of the HR-CTV was 17.4 cm^3 (1.3–74 cm^3). The median dose delivered to 98% of the HR-CTV (D98 HR-CTV) was 76.9 $Gy_{\alpha/\beta=10}$ (21.0–175.1 $Gy_{\alpha/\beta=10}$). The median dose delivered to 90% of the HR-CTV (D90 HR-CTV) was 95 $Gy_{\alpha/\beta=10}$ (43.1–180.6 $Gy_{\alpha/\beta=10}$). The median volume of the IR-CTV was 60.4 cm^3 (22.3–154 cm^3). The median D90 IR-CTV was 64.9 $Gy_{\alpha/\beta=10}$ (36.4–101.0 $Gy_{\alpha/\beta=10}$).

Table 1
Patients and tumour characteristics.

Characteristics	*n* (%)	Mean (min–max)
Age (years)	–	46.7 (18.7–77.6)
Tumour stage (FIGO):		–
IB1	74/77 (96.1%)	
IIA1	3/77 (3.9%)	
Tumour differentiation:		–
Well	38/77 (49.4%)	
Moderately	15/77 (19.5%)	
Poor	17/77 (22.1%)	
Not reported	7/77 (9.0%)	
Histological type:		–
SCC	57/77 (74.0%)	
Adenocarcinoma	20/77 (26.0%)	
Largest tumour diameter (cm)	–	2.4 (0–3.9)
Lymphovascular space invasion	16/77 (20.8%)	–

FIGO: International Federation of Gynaecology and Obstetrics; SCC: squamous cell carcinoma.

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