Radiotherapy and Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Post radiation hysterectomy in locally advanced cervical cancer: Outcomes and dosimetric impact

Renaud Mazeron [a,*], Sébastien Gouy [b], Cyrus Chargari [a], Eleonor Rivin del Campo [a], Isabelle Dumas [c], Augustin Mervoyer [d], Catherine Genestie [e], Enrica Bentivegna [b], Corinne Balleyguier [f], Patricia Pautier [g], Philippe Morice [b], Christine Haie-Meder [a]

[a] Department of Radiation Oncology; [b] Department of Surgery; [c] Department of Medical Physics, Gustave Roussy, University of Paris-Saclay, Villejuif; [d] Department of Radiotherapy, Institut de Cancérologie de l'Ouest, Saint-Herblain; [e] Department of Pathology; [f] Department of Radiology; and [g] Department of Medical Oncology, Gustave Roussy, University of Paris-Saclay, Villejuif, France

ARTICLE INFO

Article history:
Received 16 March 2016
Received in revised form 8 July 2016
Accepted 15 July 2016
Available online xxxx

Keywords:
Cervix cancer
Chemoradiation
Image-guided adaptive brachytherapy
Hysterectomy
Late morbidity

ABSTRACT

Purposes: Firstly, to evaluate the impact of completion hysterectomy after chemoradiation and image-guided adaptive brachytherapy (IGABT) in locally advanced cervical cancer. Secondly, to assess a potential differential dose–effect relationship for the rectum and bladder according to the realization of hysterectomy.

Material and methods: Two cohorts of patients were identified, differing by the realization of completion hysterectomy. Inclusions were limited to FIGO stage I–II, with no para-aortic involvement. All patients received a combination of pelvic chemoradiation followed by IGABT. Their outcomes and morbidity were reviewed. Log-rank tests were used to compare survivals. Probit analyses were performed to study dose–volume effect relationships.

Results: The two cohorts comprised 54 patients in the completion surgery group and 157 patients in the definitive radiotherapy group. They were well balanced, except for the mean follow-up, significantly longer in the post hysterectomy cohort and the use of PET-CT in the work-up, more frequent in the definitive radiotherapy cohort. Although less local relapses were reported in the hysterectomy group, the 5-year disease-free and overall survival did not differ between groups. The cumulative incidence of severe late morbidity was significantly increased in the hysterectomy cohort: 22.5% versus 6.5% at 5 years ($p = 0.016$). Dose–volume effects were observed for the bladder, with the D_{2cm3} corresponding with a 10% probability of late severe morbidity urinary events (ED_{10}) of 67.8 Gy and 91.9 Gy in the hysterectomy and definitive radiotherapy cohorts, respectively. A D_{90} CTV_{HR} of 85 Gy (planning aim) corresponded with a 93.3% rate of local control in the definitive radiotherapy cohort whereas it corresponded with a 77.3% chance to have a good histologic response (complete response or microscopic residual disease) in the hysterectomy group.

Conclusion: No benefit from completion hysterectomy in terms of overall or disease-free survival rates was observed, which was moreover responsible for an increase of the severe late morbidity. The realization of post-radiation hysterectomy resulted in a shift of the ED_{10} of 24.1 Gy.

The treatment of locally advanced cervical cancer relies on exclusive radiotherapy combining concomitant chemoradiation followed by brachytherapy [1]. Although considered as a standard worldwide, completion hysterectomy has been debated for decades [2]. Two randomized studies have been led to evaluate the role of adjuvant surgery. Both concluded the absence of benefit from hysterectomy in terms of overall survival. However, based on subgroup analyses, the first study suggested that patients with bulky tumors at diagnosis may benefit from it [3]. The second study, led in France, randomized completion hysterectomy in patients in complete remission and was unfortunately closed due to poor accrual, probably as a consequence of a reluctance to include patients, leaving room for doubt [4].

A recent national survey investigated the current practices in France. Completion hysterectomy was still performed in one third of academic centers in patients in complete remission with no

* Corresponding author at: Department of Radiation Oncology, Gustave Roussy, 114, rue Edouard Vaillant, 94805 Villejuif Cedex, France.
E-mail address: Renaud.mazeron@gustaveroussy.fr (R. Mazeron).

http://dx.doi.org/10.1016/j.radonc.2016.07.010
0167-8140/

para-aortic infiltration at diagnosis. In the adenocarcinoma subtypes, this rate was increased to 52% (data not published).

Gustave Roussy has a unique experience in that field. Concomitant chemoradiation was implemented in the late 1990s following the National Cancer Institute (NCI) alert and Image-guided brachytherapy in 2004 [5,6]. At that time, post radiation hysterectomy was still proposed in stage IB–IIB lesions as a standard. This procedure was later on withdrawn, after the completion of the UNICANCER GYNECO 2 study, and these tumors were treated with definitive radiotherapy [4].

The study aim was to compare the outcomes and morbidity of two cohorts of patients, one treated with systematic hysterectomy following radiotherapy and the other one with exclusive radiochemotherapy followed by image-guided adaptive brachytherapy. The secondary aim was to assess a potential differential dose effect relationship for the rectum and bladder according to the realization of hysterectomy.

Material and methods

Patient selection

Two cohorts were identified within patients from the radiotherapy department database. Data were collected for the purposes of the study, independently of the UNICANCER GYNECO 02 study, with no solicitation of its database. As completion hysterectomy was less likely proposed in FIGO (Fédération Internationale de Gynécologie Obstétrique) stage III–IV, inclusions were limited to stage IB–IIB lesions, treated with curative intent. For the same reasons, patients with evidence of para-aortic involvement were excluded. In the surgery group, hysterectomy had to be a component of the initial strategy, and not proposed as a salvage treatment. This cohort has been composed with patients who received EBRT and brachytherapy at Gustave Roussy between 2004 and 2008 (after GYNECO 2 completion). Some patients referred later on from other centers for brachytherapy with a strategy comprising post-radiation completion surgery were also included. Similarly, in the other cohort patients had to be treated with exclusive radiotherapy in intent. Squamous cell, adenosquamous, and adenocarcinomas were included, whereas small cell and clear cell carcinomas were excluded. In both groups, patients had to be treated with a combination of pelvic external beam radiotherapy followed by image-guided adaptive brachytherapy following the GEC-ESTRO (Groupe Européen de Curiethérapie – European Society for Radiation Oncology) recommendations [7,8].

Treatments

All patients began with pelvic conformal external beam radiotherapy (EBRT) delivering 45–50.4 in 25–28 fractions of 1.8 Gy over 5 weeks. Ballistic resulted in a four-field box. Details on techniques and volumes are available in a previous publication [9]. Chemotherapy was systematically administered, except in case of contra-indication or refusal, generally cisplatin 40 mg/m^2 weekly or carboplatin AUC 2 weekly in case of renal failure. Sequential nodal boosts were performed, after the completion of brachytherapy (BT). Their dose was adapted to the contribution of brachytherapy, with the aim of delivering a total dose of 60 Gy to all positive nodes. The decision of boosting was based on the node dimensions and shape on initial MRI/CT, or PET positivity when performed. For the patients receiving EBRT in other centers, dosimetric data on brachytherapy contribution were transmitted in order to perform the boosts.

EBRT was followed by pulsed-dose rate brachytherapy. A personalized vaginal mold was used in nearly all applications [10]. Patients underwent a pelvic MRI with acquisition of T2 axial, sagittal, and coronal images of the implant. Dummy sources were used to facilitate an accurate reconstruction of the applicator [11]. When the MRI was not available, refused, or contra-indicated, a pelvic CT was acquired with iodine contrast enhancement. The images were transferred to Plato®, Oncentra® (Nucletron, an Elekta Company, Stockholm, Sweden), or BrachyVision® (Varian Medical Systems, Palo-Alto, USA). The structures of interest were delineated following the GEC-ESTRO recommendations: CTV_{HR} (High risk clinical target volume), CTV_{IR} (intermediate risk-CTV), and outer contours of the rectum, bladder, and sigmoid colon [7]. The dwell positions in regard to the CTV_{IR} were activated and the dosimetry started from a standard prescription of 15 Gy, normalized to points A. Then, the dwell times and positions were adapted to reach the following planning aims:

- D_{90} (minimal dose received by 90% of the target) of the $CTV_{HR} \geqslant 85$ Gy, summing EBRT and BT, in 2 Gy equivalent (EqD2), using the linear quadratic model, an $\alpha/\beta = 10$ Gy, and a half-time repair of 1.5 h.
- D_{90} of the $CTV_{IR} \geqslant 60$ Gy in EqD2 using the same EqD2 parameters.
- Dose constraints of 75 Gy to the D_{2cm3} (minimal dose in the maximally exposed 2cm^3 of the organ) of the rectum and sigmoid (EqD2 with an α/β of 3 Gy), and 85 Gy for the bladder D_{2cm3}.

Para-aortic staging and radical hysterectomy

Hysterectomies were usually scheduled 8–12 weeks after the completion of brachytherapy, and were generally associated with para-aortic node (PAN) staging. In the group treated with exclusive radiotherapy, para-aortic laparoscopic staging was performed prior to treatment. As the positive predictive value of PET has been shown to be high, laparoscopic staging was withdrawn in patients with PAN uptake and extended-field radiotherapy was administered [12]. Those with PAN negative PET were offered a laparoscopic staging, and the decision of extending the fields was based on its results [13]. Patients with para-aortic extension or extended-field radiotherapy were not eligible in this study.

Definitions and statistics

Local relapses were defined as any failure in the cervix, parametria, uterus, vagina, regardless to EBRT or BT target volumes. After hysterectomy, local relapses comprised any relapse in the vaginal cuff, vagina, parametria. All times and survival were defined from the date of diagnosis (biopsy). After hysterectomy, microscopic residual disease was defined as $\leqslant$1 cm in width.

Late morbidity was defined as any event occurring or lasting over the threshold of 90 days from treatment initiation (first EBRT fraction), as defined by the RTOG (Radiation Therapy Oncology Group). Morbidity was graded using the CTC-AE (Common Toxicity Criteria for Adverse Events) version 3.0. Due to the retrospective nature of the study, morbidity reporting was limited to severe events (grade 3–4). Patients were censored for morbidity assessment at the date of relapse. For analyses, the highest graded event per patient was considered.

Means were compared using two-sided T-tests. Proportions were compared using X2 tests or Fischer's exact tests. Survival curves were generated using the Kaplan–Meier method and compared with the Log-rank test. Dose–effect relationships were assessed using the binary Probit model.

All statistics were performed using XLSTAT 2014 (Addinsoft SARL, Paris, France).

Please cite this article in press as: Mazeron R et al. Post radiation hysterectomy in locally advanced cervical cancer: Outcomes and dosimetric impact. Radiother Oncol (2016), http://dx.doi.org/10.1016/j.radonc.2016.07.010