Available online at www.sciencedirect.com

ScienceDirect

EJSO 39 (2013) 1428–1434

EJSO the Journal of Cancer Surgery

www.ejso.com

Evaluation and impact of residual disease in locally advanced cervical cancer after concurrent chemoradiation therapy: Results of a multicenter study

D. Hequet [a,j,*], E. Marchand [a,j], V. Place [b,j], V. Fourchotte [c], A. De La Rochefordière [d], S. Dridi [e], C. Coutant [e], F. Lecuru [f], A-S. Bats [f], M. Koskas [g], J-J. Bretel [h], A. Bricou [i], Y. Delpech [a,j,k], E. Barranger [a,j,k]

[a] *Department of Obstetrics and Gynecology, Lariboisière Hospital, AP-HP, 2 rue Ambroise Paré, 75010 Paris, France*
[b] *Department of Radiology, Lariboisière Hospital, AP-HP, 2 rue Ambroise Paré, 75010 Paris, France*
[c] *Department of Surgery, Institut Curie Paris, 27 rue d'Ulm, 75005 Paris, France*
[d] *Department of Radiotherapy, Institut Curie Paris, 27 rue d'Ulm, 75005 Paris, France*
[e] *Department of Surgery, Centre Georges François Leclerc, 1 rue Professeur Marion, 21000 Dijon Cedex, France*
[f] *Department of Gynecology, Hôpital Européen Georges Pompidou, AP-HP, 20, rue Leblanc, 75015 Paris, France*
[g] *Department of Obstetrics and Gynecology, Bichat Hospital, AP-HP, 46 Rue Henri Huchard, 75018 Paris, France*
[h] *Department of Radiotherapy, Bichat Hospital, AP-HP, 46 Rue Henri Huchard, 75018 Paris, France*
[i] *Department of Obstetrics and Gynecology, Jean Verdier Hospital, AP-HP, Avenue du 14 Juillet, 93140 Bondy, France*
[j] *University Paris-Diderot, Sorbonne Paris Cité, 10 Avenue de Verdun 75010 Paris, France*

Accepted 7 October 2013
Available online 23 October 2013

Abstract

Background: The aim of this study was to evaluate the diagnosis and impact of residual disease (RD) after concurrent chemoradiation therapy (CRT) in locally advanced cervical cancer (FIGO IB2-IVA).
Methods: This retrospective multicenter study included 159 patients who were treated with completion surgery after CRT between 2006 and 2012. Magnetic resonance imaging (MRI) was performed 4–6 weeks after CRT and compared to pathological evidence of residual disease. Kaplan–Meier survival curves were plotted and univariate/multivariate analyses were performed to assess the association between RD and the outcome.
Results: Residual disease was present in 45.3% of the patients and detected by MRI in 57.1%. The MRI had a 29.2% false positive rate and an 11.1% false negative rate. The overall survival (OS) rates at 3 and 5 years were 78.6% (CI 95% [71%–86.9%]) and 76.5% (CI 95% [68.2%–85.7%]), respectively. The disease free survival (DFS) rates at 3 and 5 years were 73.4% (CI 95% [65.6%–82%]) and 71.1% (CI 95% [62.7%–80.1%]), respectively. RD greater than 10 mm decreased DFS (HR = 4.84, $p = 0.03$), whereas RD between 1 and 10 mm (HR = 0.31, $p = 0.58$) and less than 1 mm (HR = 0.37, $p = 0.54$) had no impact on DFS. The OS was not changed by RD.
Discussion: The MRI accuracy value is not sufficient to select patients who might benefit from completion surgery. Residual disease over 10 mm decreased DFS but did not impact OS.

Keywords: Advanced cervical cancer; Completion surgery; Residual disease

Introduction

The gold standard treatment for patients with locally advanced cervical cancer is concurrent chemoradiation therapy (CRT).[1–7] The efficacy of completion surgery (simple or radical hysterectomy) after CRT is still debated.[8,9] Retrospective studies reported complication rates as high as 25% when completion hysterectomy was performed after CRT.[8–11] Moreover, the benefit of completion surgery

* Corresponding author. Department of Obstetrics and Gynecology, Lariboisière Hospital, AP-HP, 2 rue Ambroise Paré, 75010 Paris, France. Tel.: +33 1 49 95 62 78, +33 6 73 19 45 59; fax: +33 1 45 59 62 15.
E-mail address: delphine.hequet@gmail.com (D. Hequet).
[k] Yann Delpech and Emmanuel Barranger contributed equally to this article, and both should be considered senior author.

0748-7983/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejso.2013.10.006

to overall or disease free survival has never been demonstrated. In addition, completion surgery after CRT in locally advanced cervical cancer is not performed in most countries, which is likely why there is little knowledge regarding its usefulness. Nonetheless, it has been reported that residual disease is a prognostic factor for disease free survival (DFS) and overall survival (OS).[11–15] However, there are few studies evaluating residual cervical tumor after CRT; furthermore, in most studies, residual disease is diagnosed only by clinical examination.[10,13,14,16,17]

The aim of this study was to evaluate the diagnosis and impact of residual disease after concurrent chemoradiation therapy (CRT) in locally advanced cervical cancer (FIGO IB2-IVA).

Patients and methods

Patients

This retrospective multicenter French study included 159 patients with locally advanced cervical cancer who were treated by completion surgery after CRT between June 2006 and June 2012. This study was performed in four university teaching hospitals (Lariboisière hospital, Hôpital Européen Georges Pompidou, Bichat Hospital, Jean Verdier Hospital) and two cancer treatment and research centers (Institut Curie, Centre Georges François Leclerc).

The following were the inclusion criteria: age over 18 years, biopsy-proven carcinoma of the cervix, stage IB2-IVA cancer according to the FIGO classification,[18] treatment using concurrent chemoradiation, and hysterectomy (simple or radical) after CRT. A pre-therapy magnetic resonance imaging (MRI) and/or CT scan confirmed that the tumors were confined to the pelvic cavity. Depending on the time period and place of inclusion, lymph node involvement could be radiologically evaluated [by MRI and/or a computed tomography (CT) scan and/or position emission tomography/computed tomography (PET/CT)) or by surgical evaluation (para-aortic lymphadenectomy and/or pelvic lymphadenectomy)] before CRT or during hysterectomy.

The following were the exclusion criteria: age less than 18 years, non-biopsy proven carcinoma, rare histological types of cervical carcinoma (other than squamous cell carcinoma or adenocarcinoma), a tumor stage less than FIGO IB2, extra-pelvic disease on conventional imaging (abdominal MRI or CT scan), external radiotherapy treatment without chemotherapy, and absence of completion hysterectomy after CRT.

Consecutive patients that fit the inclusion criteria were considered for the study. Individual medical charts were reviewed.

Concurrent chemoradiation therapy and brachytherapy

Patients were treated with external radiation therapy at a mean dose of 45 Gy (31–50 Gy) to the pelvic cavity, delivered in five fractions of 1.8–2 Gy. The pelvic field extended from the upper margin of L5 to the lowest level of disease with a 2–3 cm margin, and also extended laterally to 1.5–2 cm beyond the lateral margins of the bony pelvic wall. During external radiation therapy, concurrent chemotherapy was performed with 40 mg/m^2 of cisplatin per week or 20 mg/m^2 of cisplatin and 400–600 mg/m^2 of 5FU per day every 3 weeks for 5 days with a mean of 5 cures. An external radiation boost (10–15 Gy) was administered to patients with parametrial spread and/or node involvement based on initial imaging and/or surgical pre-therapeutic lymphadenectomy. Depending on the center and the time period of therapy, uterovaginal brachytherapy was performed at a dose of 15 Gy (13–30 Gy). Applicator insertion was made under general anesthesia and imaging realized at the same time.

Residual disease evaluation after CRT

Residual disease was assessed with a clinical examination and a pelvic MRI 4–6 weeks after CRT was completed (or brachytherapy if administered).

MRI images were acquired with a 1.5 T magnet using a phased-array pelvic coil. Each exam included sagittal and axial T2-weighted turbo spin-echo (TSE) sequences of the pelvis (axial T2-weighted images were usually obtained perpendicularly to the endocervical canal). T1-weighted images with fat suppression were acquired before and after the injection of gadolinium. Diffusion weighted MRI sequences may additionally be performed. In some cases, vaginal distension with sterile water-based gel was performed before the MRI examination.

At each center, the MRI studies were interpreted by a radiologist with experience in gynecological imaging. Tumor response was evaluated by comparing post-treatment MRI images with pre-treatment data, if available.

Residual disease in the cervix was evaluated based on tumor size, integrity of the stromal ring, parametrial involvement and vaginal infiltration. Lymph nodes were also evaluated.

Completion surgery

Completion surgery was performed in all patients between 8 and 10 weeks after the completion of CRT (or brachytherapy if administered). Completion surgery included a simple or radical (extended to parameters) hysterectomy; the type of surgery performed was determined based on parametrial residual disease at clinical examination, pre-surgical MRI and intra-operative observations. If not performed prior to CRT, nodal dissection could be added to the procedure and consisted of pelvic and/or para-aortic lymphadenectomy.

Statistical analysis

The primary endpoints evaluated in this study were the overall and disease free survival. The secondary endpoints