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Original Article

The Role of Elective Para-aortic Lymph Node Irradiation in Patients with Locally Advanced Cervical Cancer☆

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Abstract

Aims: Pelvic lymph node positivity in cervical cancer is known to be an adverse prognostic factor and is associated with an elevated risk of clinically occult para-aortic lymph node metastases. The purpose of this study was to examine the benefit of elective para-aortic lymph node radiotherapy (PART) in patients with no clinical or radiographic evidence of para-aortic lymph node metastases receiving concurrent cisplatin chemotherapy.

Materials and methods: Patients treated with radiotherapy and concurrent cisplatin for cervical cancer from 1999 to 2009 were identified in two prospective databases. All patients received external beam pelvic radiotherapy (PRT) to a median dose of 50 Gy concurrently with weekly cisplatin 40 mg/m^2. This was followed by pulse dose rate intracavitary brachytherapy to a median dose of 40 Gy. Patients at high risk of occult para-aortic metastases also received PART to a median dose of 40 Gy.

Results: There were 228 patients suitable for analysis; the median follow-up was 4.6 years. The addition of PART to PRT was not associated with a significant difference in disease-free survival (hazard ratio 1.1, confidence interval 0.7–1.8, $P = 0.75$) or overall survival (hazard ratio 1.6, confidence interval 0.9–2.7, $P = 0.11$) on multivariate analysis. There was no significant difference in the rate of para-aortic relapse with PART versus PRT (hazard ratio 2.01, confidence interval 0.79–5.12, $P = 0.14$). The 3 year grade 3–4 late toxicities were 11% for the PART group versus 8% for PRT (hazard ratio 1.39, confidence interval 0.58–3.37, $P = 0.47$).

Conclusions: These results suggest that cervical cancer patients treated with radiotherapy and concurrent cisplatin do not benefit from elective PART.

Key words: Cervical cancer; chemoradiotherapy; para-aortic lymph nodes; radiotherapy

Introduction

Cervical cancer accounts for the third highest cancer incidence and mortality in women worldwide [1]. Many patients present with locally advanced disease that involves adjacent tissues or regional lymph nodes and are best treated with radiotherapy. Lymph node positivity affects about 47% of patients and is an important predictor of overall survival [2]. Nodal spread usually occurs in a contiguous manner, from the primary tumour to pelvic lymph nodes, then para-aortic, mediastinal and supraclavicular lymph nodes [3].

In patients treated primarily with radiotherapy, the extent of disease at diagnosis is assessed clinically using a physical examination and imaging. Computed tomography, magnetic resonance imaging (MRI) and positron emission tomography (PET) play important roles in identifying lymph node metastases, but all have limited sensitivity for the detection of small-bulk metastases in lymph nodes of normal size [4]. In surgical series, clinically occult para-aortic lymph node involvement has been reported in up

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to 29% of patients [5] and is more common in those with large tumour size, advanced stage, lymphovascular space invasion or pelvic lymph node metastases [6].

Elective irradiation of clinically and radiologically negative para-aortic lymph nodes (PART) at high risk of harbouring occult metastases is a treatment that can be used in conjunction with pelvic radiotherapy (PRT) to reduce the risk of para-aortic recurrence and improve patient survival [7]. However, most of the evidence to support its use was derived from patients treated with radiotherapy alone before the widespread uptake of radiotherapy and concurrent cisplatin chemotherapy. Randomised trials of radiotherapy and concurrent cisplatin versus radiotherapy alone showed improved overall survival and a reduction in distant metastases [8]. This prompted us to question the efficacy of PART for occult metastases in patients receiving radiotherapy and concurrent cisplatin, especially given higher rates of acute haematological and gastrointestinal toxicity [9].

The primary aim of this study was to examine the effect of elective PART on disease-free survival (DFS) for clinically occult metastases on para-aortic recurrence and patient survival. A secondary objective was to compare the late toxicities associated with PART with those associated with PRT alone.

Materials and Methods

Patient Characteristics

After institutional research ethics board approval was obtained, the records of 335 patients who received radiotherapy and concurrent cisplatin for primary cervical cancer between 1999 and 2009 were retrieved. Outcome information was derived from two prospective clinical databases: (i) the Gynecologic Cancer Anthology of Outcomes, established in 2006, which includes a process for recording tumour control, patient survival and side-effects at point-of-care as described previously for head and neck cancer [10] and (ii) a clinical research database of patients who participated in previous studies of cervical cancer hypoxia [11], established in 1994. Tumour control and patient survival were evaluated prospectively using the Gynecologic Cancer Anthology of Outcomes and the prospective hypoxia research database. Late toxicity as per CTCAE v 3.0 was obtained from the Anthology of Outcomes, supplemented by retrospective examination of the medical records of patients treated before the Anthology was implemented in 2006.

Seventy-nine patients were excluded due to distant metastatic disease at diagnosis, rare histologies (sarcoma or small cell carcinoma) or participation in clinical trials of the biological agents sorafenib or celecoxib. Another 23 patients were excluded because of para-aortic lymph node enlargement (>1 cm in short axis dimension of computed tomography) at diagnosis and five because para-aortic status was not assessed before treatment. Two hundred and twenty-eight patients were therefore suitable for analysis of recurrence and survival. Of these, 73 were treated with PART and 155 received PRT alone.

Our treatment policy during this period specified adjuvant PART for patients with enlarged pelvic lymph nodes (short axis diameter >1 cm) or equivocal pelvic nodes (short axis diameter 0.8–1 cm) in the setting of a hypoxic primary tumour. We previously reported that hypoxic cervical tumours are more likely to have lymph node metastases at diagnosis [12]. However, the final decision to use PART was at the discretion of the responsible oncologist, balancing the risk of occult para-aortic metastases against the potential for increased acute and late toxicity.

Patients underwent history and physical examination, tumour biopsy, computed tomography scan of the abdomen and pelvis and a chest X-ray or computed tomography scan of the chest. In recent years, patients also had MRI of the pelvis. Surgical staging was not carried out. The median follow-up time was 4.6 years.

Treatment Technique

Patients receiving PRT alone were treated using a four-field technique to a dose of 45–50 Gy in daily 1.8–2.0 Gy fractions. Patients were computed tomography planned with a three-dimensional conformal radiotherapy technique. The superior field border was typically at the L5/S1 junction. Patients receiving PART were usually treated with parallel-opposed fields to T12/L1, with both the pelvis and para-aortics encompassed in a single AP/PA field. In 19 of the 73 patients, a 'mini' para-aortic (mPART) field was used that encompassed the common iliac and low para-aortic lymph nodes to the level of L3/L4. This was used in some patients with positive pelvic nodes or lower common iliac nodes with the objective of sparing toxicity compared with full PART. The median para-aortic dose was 40 Gy (range 40–50 Gy) in 1.8–2 Gy daily fractions. All patients received cisplatin administered concurrently with external beam radiotherapy at a dose of 40 mg/m^2.

Brachytherapy was delivered immediately after external beam radiotherapy using an intrauterine tandem and iridium-192 (source activity 15–37 GBq) pulsed dose rate technique to a median dose of 40 Gy. Treatment was delivered continuously over about 60 h with an interval between pulses of 1 h. Most of these patients were treated using conventional two-dimensional brachytherapy with the dose prescribed to Point A. In total, 33 patients in 2008 were treated with three-dimensional MRI-guided brachytherapy as part of prospective clinical study [13]. For these patients, target and organ-at-risk delineation and planning dose constraints conformed to the Groupe Européen de Curiethérapie and the European SocieTy for Radiotherapy & Oncology (GEC-ESTRO) GEC-ESTRO guidelines [14].

Ten patients received an external beam boost to the primary tumour (typically 25 Gy in 14 daily fractions) because of comorbidities that precluded brachytherapy. These patients were equally distributed between the PART and PRT groups. Of the 256 patients, 229 (89.5%) finished their treatment course within 8 weeks (56 days).

After treatment, patients were followed with history and a physical examination every 3–6 months for the first 5 years, then annually thereafter. MRI of the pelvis was