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Review

Cervical cancer with paraaortic involvement: do patients truly benefit from tailored chemoradiation therapy? A retrospective study on 8 French centers

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ABSTRACT

We retrospectively studied the therapeutic significance of extended-field radiotherapy combined with concurrent platinum-based chemotherapy for the management of cervical carcinoma with paraaortic spread. Treatment response and survival outcomes were evaluated. One hundred and fifteen women were retrospectively studied. Radiological staging was conducted in 101 (87.8%) patients and paraaortic lymphadenectomy in 78 (67.8%). Patterns of treatment comprised chemoradiation therapy (100%), intracavitary brachytherapy (81.7%), completion surgery (60%) and neoadjuvant chemotherapy (4.3%). Four-year overall and disease-free survivals were 32.7% and 28.8%, respectively. Progression and relapse mostly involved the locoregional area and distant organs, rather than the paraaortic area. Advanced FIGO stage at baseline was the most significant prognostic factor (HR = 3.02, $p = 0.01$). Despite systematic extended-field chemoradiation therapy, paraaortic involvement in cervical cancer is associated with poor survival outcomes. The patterns of progression and recurrence suggest the existence of occult metastatic disease at presentation. Additional systemic treatment might thus be beneficial.

Contents

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Introduction

Despite the tremendous progress in prevention due to effective screening and vaccination, cervical cancer is the second most common malignancy among women worldwide and 40% of patients are diagnosed at advanced stages (FIGO stages IB2, IIA >4 cm and IIB-IVA) [1]. The mainstay of treatment for locally advanced cervical cancer (LACC) involves a combination of external beam radiotherapy and concurrent cisplatin-based chemotherapy, followed by intracavitary brachytherapy [2–5]. Completion surgery may be proposed, depending on the amount of residual disease after chemoradiation (CRT) [6–8].

Lymph node status defines the extent of radiation fields [9]. Extended-field radiotherapy (EFR) is therefore performed in patients with paraaortic (PA) spread. However, specific research addressing its impact on survival is lacking, as PA involvement was an exclusion criterion in the studies assessing CRT [10–12]. To date, benefit from tailored CRT has only been demonstrated in patients presenting with PA micro-metastasis, when associated with prior lymph node dissection [13,14]. EFR also leads to increased morbidity [15]. The role of EFR with or without concurrent chemotherapy is thus still undefined. Therefore, should it be considered as the standard treatment when PA involvement is present?

In this observational study, we aimed to evaluate the outcomes in women who received optimal CRT for cervical cancer metastatic to the PA area.

Materials and methods

This retrospective study evaluated 115 patients with cervical cancer with PA involvement and treated in 8 French gynecological oncology units from August 1999 to August 2012. All women received standard treatment. The study was approved by the local institutional review board.

Disease characteristics

All patients presented with biopsy-confirmed cervical cancer. Disease was retrospectively classified according to the 2009 FIGO staging system. Histological type, tumor volume and lymph node status were retrospectively collected. The diagnosis of PA spread was based on imaging assessment of the PA area and/or pathological examination of harvested PA lymph nodes when staging lymphadenectomy was performed.

Imaging modalities comprised PET, CT and/or MRI. Because of the long inclusion period (1999–2012), 9 patients treated before the introduction of PET guidelines were evaluated by MRI or CT according to the established criteria for lymph node detection. The nodes were over one centimeter in size on the CT scan and MRI. On PET images, nodes in the para-aortic area were considered suggestive of abnormality if, during the visual interpretation, they exhibited FDG uptake above background uptake. Lymphadenectomy was performed when PET was negative in 8 centers. Surgical lymph node staging was not carried out systematically as this procedure is recommended but not mandatory when PET is positive.

Tumor progression was defined as an increase in tumor volume or spread during first-line treatment. A relapse was defined as tumor recurrence after initial response to first-line treatment. Tumor progression and relapse were categorized according to their anatomical locations: locoregional (cervix or pelvic lymph node (PN+)), paraaortic or distant metastasis.

Patterns of treatment

All patients studied received CRT. EFR delivered 45 Gy to the pelvis and PA area over 5 weeks at 1.8 Gy per fraction, using a four-field arrangement. Concurrent cisplatin chemotherapy (40 mg/m^2) was given weekly on days 1, 8, 15, 22 and 29. Clinical and imaging examinations evaluated the response to treatment 6 weeks after completion of CRT. Imaging assessment was performed by MRI, PET and/or CT.

Intracavitary brachytherapy consisted of 15 Gy (patients with completion surgery) or 22 Gy (patients without completion surgery). It was performed in patients with neither tumor progression nor local contraindications (vaginismus, genital tract malformations, uterine perforation).

Partial response to treatment systematically led to completion surgery. In patients achieving complete response, surgery was not performed routinely. Completion surgery was performed in 6 centers despite a complete response. Two centers did not perform surgery in complete response cases since 2011.

Some patients underwent neoadjuvant platinum-based chemotherapy. Courses were given at 3-week intervals.

Follow-up

After completion of initial treatment, patients received regular follow-up every 4 months for the first 2 years, then every 6 months thereafter. A clinical examination was performed at each follow-up visit. A systematic radiographic examination (TEP or IRM) was conducted annually the first 2 years, in 8 centers.

Statistical analysis

Two survival outcomes were reported: overall survival (OS) and disease-free survival (DFS). In both survival outcomes, the starting point was the date of diagnosis. The events of interest for the calculation of DFS and OS were death of any cause, relapse and progression. Patients who were lost to follow-up or alive without the event of interest at the time of analysis were censored at the date of last contact.

We estimated the OS and DFS functions using the Kaplan–Meier method. For multivariate analyses, we applied Cox proportional hazards models, including the prognostic factors identified by Stehman et al. [16]. We also included in the multivariate survival models those variables which were associated with survival in bivariate analysis ($p \leq 0.05$). All statistical tests were 2-sided and differences were considered statistically significant when $p \leq 0.05$. All analyses were performed using Stata Statistical Software® release 11.2 (Stata Corporation, College Station, TX).

Results

Demographics (Table 1)

One hundred and fifteen patients matched our inclusion criteria. Mean age at the start of treatment was 52.4 ± 12.4 years