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Original Research Report

Preoperative chemoradiotherapy in locally advanced cervical cancer: Long-term outcome and complications

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Abstract

Objective. To demonstrate the efficacy and feasibility of preoperative chemoradiotherapy in a consecutive series of 100 locally advanced cervical cancer (LACC) patients.

Methods. Between October 1997 and December 2004, 100 LACC patients were consecutively staged and treated at the Catholic University of the Sacred Heart of Rome. Radiotherapy was administered to the whole pelvic region (1.8 Gy/day, totaling 39.6 Gy) in combination with cisplatin (20 mg/m^2) and 5-FU (1000 mg/m^2) (both on days 1–4 and 27–30). Radical surgery was performed 5–6 weeks after the end of the treatment.

Results. A clinical complete or partial response was observed in 96 patients (56 and 40, respectively). Radical surgery was performed in 95 patients and an overall complication rate of 12.6% was observed in the early postoperative time. At pathological examination, 43 of 95 patients (45.2%) undergoing radical surgery showed complete response to treatment, 28 patients (29.5%) only had a microscopic disease, 18 patients (19%) had a partial response and 6 (6.3%) had no change of disease. With a median follow-up time of 25 months, the 5-year disease-free survival was 76% and the 5-year overall survival was 78%.

Conclusions. These data confirm the possibility of achieving encouraging rates of local control and OS in LACC patients submitted to chemoradiation plus surgery, with a low rate of toxicity and complications.

Keywords: Locally advanced cervical cancer; Preoperative chemoradiation; Radical surgery; Complications

Introduction

In the last few years, 5 out of 6 recent clinical trials produced by the American Scientific Society have demonstrated an advantage in terms of disease-free (DFS) and overall survival (OS) for LACC patients treated with concomitant radiation and cisplatin-based chemotherapy [1–6] with respect to exclusive radiotherapy, so that it currently represents the gold standard in the treatment of these patients. On the other hand, different experiences from Europe and South America have shown comparable results using neoadjuvant chemotherapy followed by radical surgery in the same group of cases [7–9]. Finally, in spite of the enormous energies involved in all these studies, results are still unsatisfactory, with an OS rate for LACC patients corresponding to 53% [10].

In this context, the possibility to combine different strategies to maximize local control and eventually improve quality of life of these patients should be considered. Among different approaches to this issue (i.e. different drugs, schedule and doses), the use of a three-modality treatment, including radiotherapy, chemotherapy and surgery, has been previously investigated [11,12]. Despite the initial disappointing results related to the high rate of surgical complications, the theoretical potential advantages to perform surgery after neoadjuvant chemoradiation, such

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as the removal of potential chemoresistant foci, the assessment of the pathological response and the potential favorable psychological impact of "feeling free of disease" should not be underestimated.

We previously demonstrated that neoadjuvant chemoradiotherapy followed by surgery resulted in a high rate of complete response to treatment and an acceptable rate of DFS and OS. Moreover, a low percentage of intra- and postoperative complications were observed [13,14].

In the present study, we report the long-term follow-up and complications of preoperative chemoradiation in larger single-institutional series of LACC cases.

Patients and methods

This study includes 100 consecutive LACC patients accrued between October 1997 and December 2004 at the Division of Gynecologic Oncology of the Catholic University of Rome.

Inclusion criteria were the following: biopsy-proven squamous cell carcinoma of the cervix (stage IB2–IIIB); no evidence of disease outside the pelvis; age < 75 years; Eastern Cooperative Oncology Group performance status < 2; adequate bone-marrow function (WBC > 3000, platelets > 120,000/mm^3); adequate renal function (blood urea nitrogen < 25 mg/dl, creatinine < 1.5 mg/dl); normal liver function (bilirubin < 2 mg/dl) and no prior cancer other than basal cell carcinoma. All patients signed a written informed consent agreeing to be submitted to all the procedures described and for their data to be used prospectively. Pretreatment work up included a medical history, clinical examination, chest radiography, abdominopelvic MRI, cystoscopy and proctoscopy if there was a clinical suspicion of invasion, complete blood count and measurement of liver and renal function.

Neoadjuvant chemoradiotherapy was performed as previously described [13]. Briefly, external radiotherapy was administered to the whole pelvic region in 22 fractions (1.8 Gy/day, totaling 39.6 Gy) in combination with cisplatin (20 mg/m^2, 2-h intravenous infusion) and 5-FU (1000 mg/m^2, 24-h continuous intravenous infusion) (both on days 1–4 and 27–30). Four weeks after the end of concomitant chemoradiotherapy, patients were evaluated for objective response and debulking based on a second MRI and clinical examination. Clinical responders underwent radical hysterectomy according to Piver et al. [15] and pelvic ± lumboaortic lymphadenectomy, 5 to 6 weeks after the end of chemoradiation.

Toxicity assessment was performed according to the Radiation Therapy Oncology Group acute and late toxicity criteria [16]. Patients were assessed weekly for acute toxicity during treatment. Operative complications were defined as bowel, bladder, ureteral, vascular injuries and estimated blood loss exceeding 500 ml. Postoperative complications were defined as any adverse event occurring within 30 days from surgery, and considered severe if they resulted in unplanned admission or a secondary surgical procedure.

After surgery, patients underwent physical examination, complete blood count and blood chemistry every 3 months for the first 2 years and every 6 months thereafter. Chest radiography and abdominopelvic MRI were performed every 6 months for the first 3 years and every 12 months thereafter. Eighty-nine percent of patients were followed for at least 1 year. The median follow-up time was 25 months (range 4–110 months).

Objective tumor response was assessed according to the World Health Organization (WHO) score. Pathologic response was defined according to the TNM classification. In particular, complete response included cases with absence of any residual tumor after treatment at any site level, and microscopic partial response included cases with persistence of only microscopic foci at any site levels. Disease-free survival was calculated from the date of surgery to the date of relapse or the date of the last follow-up, and overall survival was calculated from the date of diagnosis to the date of death or the date of the last follow-up. Medians and life tables were computed using the product limit estimate by Kaplan–Meier methods [17] and the log-rank test was used to assess the statistical significance.

Results

Patient characteristics are shown in Table 1. Chemoradiotherapy-related toxicity was evaluated in all patients. Eleven patients required a brief interruption of treatment due to acute toxicity ($n = 7$) or a thrombotic event ($n = 4$). Five patients required a reduction in the chemotherapy dosage (50% of the prescribed dose) in the last week of radiotherapy due to hematological toxicity. Overall, 18 patients

Table 1
Clinico-pathological characteristics of the patients

Characteristics	
Number of patients	100
Mean age (range)	52 (25–75)
FIGO Stage	
IB2	3
IIB	73
IIIA	7
IIIB	17
Tumor volume (cm)	
<4	27
≥4	73
Node status (MRI)	
Negative	64
Positive	36
Grade	
G1–2	31
G3	44
n.a.	25