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CLINICAL ARTICLE

Surgical morbidity and oncologic results after concurrent chemoradiation therapy for advanced cervical cancer

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ABSTRACT

Objective: To evaluate the surgical morbidity and oncologic results after concurrent chemoradiotherapy (CCRT) followed by completion surgery for advanced cervical carcinoma. **Methods:** The present retrospective analysis included 192 patients with advanced cervical cancer (stage IIB–IVA) treated with CCRT followed by surgery and 186 control patients without completion surgery. Disease-free and overall survival rates were compared. **Results:** Of the patients who underwent surgery, 27 (14.1%) had pathologic evidence of residual disease; the local control rate with CCRT was 85.9%. After a median follow-up period of 190 months, 32 (16.7%) patients who underwent completion surgery had a recurrence compared with 59 (31.7%) of those who did not. The overall survival rate among patients who underwent extrafascial hysterectomy, extended hysterectomy, or no surgery was 72.2%, 60.1%, and 45.9% at 3 years, and 53.5%, 40.7%, and 32.2% at 5 years, respectively. **Conclusion:** Surgery after CCRT for advanced cervical cancer enabled evaluation of the pathologic response to therapy, improved local disease control in patients with a partial pathologic response, and enhanced survival. The most appropriate surgical approach was extrafascial hysterectomy with pelvic lymph node dissection.

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1. Introduction

Cervical cancer is the most common cancer-related cause of death among women in low-income countries [1]. Concurrent chemoradiation therapy (CCRT) is considered to be the standard treatment for cervical cancer classified as advanced according to the International Federation of Gynecology and Obstetrics (FIGO) staging system [2,3].

The role of additional surgery following CCRT for advanced cervical cancer is controversial [4], and only a few studies [5,6] are available that compare CCRT combined with surgery with CCRT alone. These studies vary in terms of disease stage, extent of surgery, and CCRT modalities (dose of radiation, presence of brachytherapy, type of chemotherapy) [7]. Completion surgery after CCRT has been reported to improve local disease control and overall survival, but concerns remain regarding a potential increase in treatment-related complications [8,9]. No large studies are available that have analyzed the surgical morbidity and oncologic outcome after completion hysterectomy.

The aim of the present study was to evaluate histologic factors associated with the prognosis of patients with and without completion surgery after CCRT, and to assess the morbidity associated with completion surgery.

2. Materials and methods

The present retrospective analysis included 192 patients with advanced cervical cancer (FIGO stages IIB–IVA [10]) who were treated with CCRT followed by surgery and 186 control patients treated without surgery at Shandong Cancer Hospital, Jinan, China, between July 1, 1992, and December 31, 2012. The study was approved by the Research Ethics Committee at the study hospital. All patients provided signed informed consent.

Concurrent chemoradiation therapy was performed in agreement with the recommendations of the International Commission on Radiation Units [11]. The patients were treated with pelvic external radiation therapy delivered at 45–50 Gy and uterovaginal brachytherapy irradiation at 45–55 Gy. Concurrent chemotherapy consisted of cisplatin at 40 mg/m² and 5-fluorouracil at 500 mg/m² per week, administered by continuous intravenous infusion over 24 hours on days 1–4 and 27–30.

At 10–12 weeks after CCRT completion, patients with a confirmed or suspected residual tumor in the cervix underwent uterine removal, and the parametrial and surgical margins were inked for further analysis. Patients in poor physical condition (American Society of Anesthesiologists categories III–IV) and those with progressive disease despite cervical carcinoma or with metastatic spread did not undergo surgery.

The modalities of completion surgery ranged from simple extrafascial hysterectomy to extended hysterectomy (Piver type II procedure [modified radical hysterectomy] or Piver type III procedure [classic radical hysterectomy]). To decrease the risk of postoperative morbidity

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associated with complete lymphadenectomy in a previously irradiated area, patients with residual lymphadenomegaly underwent selective lymphadenectomy.

Information on postoperative complications was extracted from the medical charts. All complications occurring up to 90 days following surgery were taken into account. Complications were classified as early and late, and graded according to Chassagne et al. [12]. As of December 31, 2012, the median follow-up duration was 190 months (range, 60–245 months).

Disease-free survival (DFS) was defined as the time from the date of surgery to the date of clinically proven recurrence or the date of the last follow-up examination. Overall survival (OS) was defined as the time from the date of surgery to the date of cancer-related death or the date of the last follow-up examination.

The Kaplan–Meier method was used to calculate DFS and OS and the survival curves were compared using the long-rank test. The odds ratios (OR) and hazard ratios (HR) for predictors of DFS and OS were estimated using JMP version 6.0 (SAS Institute, Cary, NC, USA) and XLSTAT version 7.5.2 (Addinsoft, New York, NY, USA).

The degree of significance represents the probability (P : chosen as $G < 0.05$) that the observed differences are the effect of chance. The 95% confidence interval for the OS was also given. Qualitative variables in the different patient groups were compared with the Fisher exact test, and quantitative variables were compared with the Mann–Whitney U test.

To investigate independent prognostic factors associated with survival, a multivariate analysis was performed using the Cox proportional hazards model, with survival and recurrence as the censored variables. The probabilities (P : chosen as $G < 0.05$) of the differences in the multivariate analysis were considered significant prognostic factors.

3. Results

In total, 378 patients fulfilled the inclusion criteria. The median age was 48 years (range, 20–75 years). The 2 study groups were similar in terms of tumor stage and subtype, with squamous cell carcinoma being the most common subtype (Table 1).

Of the 192 patients who underwent completion surgery, 99 (51.6%) had a simple extrafascial hysterectomy and 72 (37.5%) underwent a Piver II or III (subradical or radical hysterectomy) procedure; of these patients, 22 (11.5%) had a radical hysterectomy (Table 1). Sixty-six (34.3%) patients underwent pelvic lymph node resection and 36 (18.7%) patients had a complete lymphadenectomy.

Histologic evidence of residual tumor in the cervix was detected in 27 (14.1%) women. Positive margins were observed in 12 (6.3%) women, and the parametrial transfer rate was 11.9% ($n = 23$). Lymph node metastasis was diagnosed in 24/102 (23.5%) women. Of 38 patients with enlarged pelvic lymph nodes on initial imaging, 10 (5.2%) had involved nodes in the pelvic lymphadenectomy metastasis specimen. The only patient with stage IV disease in the present study had a single supraclavicular lymph node metastasis, which could be excised. Table 2 shows the association between nodal spread, surgical margin status, and size of the residual tumor.

Postoperative complications were seen in 38 (19.8%) patients (Table 3). The early complication rate among patients who had extended hysterectomy was 23.9% ($n = 46$), and the corresponding rate among patients who had a simple extrafascial hysterectomy was 13.2% ($n = 25$; $P < 0.05$). The respective late complication rates were 14.1% ($n = 27$) and 9.3% ($n = 18$; $P < 0.05$). The morbidity rate of completion surgery comprising extended hysterectomy with or without lymphadenectomy was 20.4%, and the overall rate of urinary or bowel tract complications was 19.8%. Risk factors for postoperative complications were radical hysterectomy (OR 2.4; reference: extrafascial hysterectomy; $P > 0.05$) and the presence of residual cervical tumor (OR 4.3 for a tumor size of more than 1 cm; OR 2.5 for a tumor size of less than or equal to 1 cm; reference: no residual tumor; $P > 0.01$).

Table 1
Surgical and pathologic characteristics of the participants.^a

Characteristic	Cases	Controls
Tumor histology	192	186
SCC	149 (77.6)	140 (75.2)
Adenocarcinoma	30 (15.6)	32 (17.2)
Mixed subtypes	13 (6.8)	15 (8.1)
Tumor stage		
IIB	90 (46.9)	84 (45.2)
III	101 (52.6)	100 (53.7)
IVA	1 (0.5)	2 (1.1)
Pelvic surgery		
Extrafascial hysterectomy	99 (51.6)	None
Extended hysterectomy	81 (42.2)	None
Piver type II	50 (26.0)	None
Piver type III	22 (11.5)	None
Piver type not determined	9 (4.7)	None
Other procedures		
Bowel resection	4 (2.1)	None
Appendectomy	5 (2.6)	None
Omentectomy	3 (1.6)	None
Lymphadenectomy		
None	90 (46.9)	None
Pelvic	60 (31.2)	None
Para-aortic	17 (8.9)	None
Pelvic and para-aortic	29 (15.1)	None
Histologically confirmed residual tumor in the cervix		
No residual tumor	165 (85.9)	None
<0.2 cm	7 (3.6)	None
0.2–1.0 cm	8 (4.2)	None
>1.0 cm	6 (3.1)	None
Residual tumor of undetermined size	2 (1.0)	None
Lymphovascular space involvement on hysterectomy specimen	4 (2.1)	None
Location of extracervical (residual) disease	36 (18.7)	None
Vagina	8 (4.2)	None
Parametrium	23 (12.0)	None
Peritoneal carcinosis	2 (1.0)	None
Ovarian metastasis	3 (1.6)	None
Status of surgical margins		
Free of disease	165 (85.9)	None
Positive margins	12 (6.3)	None
Presence of positive nodes ^b		
Pelvic nodes include para-aortic nodes	18 (9.3)	None
Pelvic nodes only	10 (5.2)	None
Para-aortic nodes only	8 (4.2)	None

Abbreviations: SCC, squamous cell carcinoma.

^a Values are given as number (percentage).

^b Confirmed by magnetic resonance imaging or histologic examination.

Three years after the end of treatment, 32 (16.7%) patients had a pathologically confirmed cancer recurrence as determined by cytology or vaginal stump biopsy. Patients with a residual tumor had a higher risk for death (HR 4.12) than patients without a residual tumor (HR 1.85; $P < 0.05$) for 3-year overall survival. Moreover, patients with positive pelvic nodes or positive para-aortic nodes had a higher risk for death (HR 4.57) than patients without nodal involvement (HR 1.90; $P < 0.05$). The presence of residual disease (HR 1.90 for residual tumors of 1 cm or less; HR 3.67 for residual tumors of more than 1 cm; $P < 0.05$) and lymph node involvement (HR 1.53 for positive pelvic nodes; HR 3.80 for positive para-aortic nodes; $P < 0.01$) were associated with higher risks for death.

After a median follow-up of 190 months, 32/192 (16.7%) patients with completion surgery had a recurrence compared with 59/186 (31.7%) of those without surgery ($P < 0.05$). Among patients with extended hysterectomy, the recurrence rate was 13.9% (10/72); among those with simple extrafascial hysterectomy, it was 17.2% (17/99; $P > 0.05$).

The DFS rates among patients who underwent extrafascial hysterectomy, extended hysterectomy, or no completion surgery were 83.2%, 71.7%, and 54.1%, respectively, at 3 years, and 66.4%, 50.7%, and 37.2% at 5 years ($P < 0.05$ for all comparisons). The respective OS rates among patients who underwent extrafascial hysterectomy, extended hysterectomy, or no completion surgery were 72.2%, 60.1%,

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