Taiwanese Journal of Obstetrics & Gynecology 53 (2014) 330–336

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Outcome of patients with bulky IB (≥ 6 cm) cervical squamous cell carcinoma with and without cisplatin-based neoadjuvant chemotherapy

Peng-Hui Wang [a, b, c, d, *, h], Yen-Hou Chang [a, h], Ying-Hui Yang [a, d], Wen-Hsun Chang [a, d], Shu-Yun Huang [a, d], Chiung-Ru Lai [e], Chi-Mou Juang [a], Yi-Jen Chen [a], Huann-Cheng Horng [a], Kuo-Chang Wen [a], Heung-Tat Ng [a, f], Chiou-Chung Yuan [g], Kuan-Chong Chao [a], Ming-Shyen Yen [a, *]

[a] Division of Gynecology, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan
[b] Immunology Center, Taipei Veterans General Hospital, Taipei, Taiwan
[c] Department of Medical Research, China Medical University Hospital, Taichung, Taiwan
[d] Department of Nursing, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan
[e] Department of Pathology, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan
[f] Foundation of Gynecologic Cancer, Taipei, Taiwan
[g] Department of Obstetrics and Gynecology, Taipei Medical University-Shuang Ho Hospital, New Taipei City, Taiwan

ARTICLE INFO

Article history:
Accepted 22 May 2014

Keywords:
bulky cervical squamous cell carcinoma
cervical cancer
neoadjuvant chemotherapy
radical hysterectomy

ABSTRACT

Objective: To study the surgical morbidity and outcomes of patients with markedly bulky cervical squamous cell carcinoma (≥ 6 cm Cx-SCC) who underwent radical hysterectomy (RH) with and without neoadjuvant chemotherapy (NACT).
Materials and methods: This retrospective study enrolled patients with International Federation of Gynecology and Obstetrics (FIGO) IB markedly bulky Cx-SCC who were treated with either three courses of weekly single agent cisplatin NACT (50 mg/m2) and subsequent radical hysterectomy (NACT-RH) or direct radical hysterectomy (RH) between 1996 and 2001. A total of 60 patients fulfilled the criteria, including 35 and 25 patients with NsACT-RH and RH, respectively.
Results: There was no statistically significant difference in basic characteristics between the two groups, except the smaller pathological tumor size, less blood loss, and lower immediate complication rate in the NACT-RH group. Median survival was 143.8 months in the NACT-RH group and 129.8 months in the RH group, respectively, without a statistically significant difference. Multivariate analysis showed that large pathological tumor size [hazard ratio (HR) 10.66, 95% confidence interval (CI) 2.93–38.80], the presence of para-aortic lymph node metastases and an immediate complication (HR 8.33 and 4.55, 95% CI 1.66–41.75 and 1.35–15.27, respectively) contributed to a worse outcome.
Conclusion: Weekly single agent cisplatin NACT indeed reduced the pathological tumor size and immediate complication rate during the RH, supporting the feasibility of subsequent RH in the management of patients with bulky Cx-SCC.

Introduction

Cervical (Cx) cancer is still a serious health problem, second only to breast cancer as the most common female malignancy in both incidence and mortality worldwide [1]. In recent years, both overall survival (OS) and disease-free survival rates have been significantly improved as a result of advances in the technologies of surgery, chemotherapy (CT), and radiotherapy (RT) [2]. However, patients

* Corresponding authors. Division of Gynecology, Department of Obstetrics and Gynecology, National Yang-Ming University School of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan.
E-mail addresses: phwang@vghtpe.gov.tw, phwang@ym.edu.tw (P.-H. Wang), msyen@vghtpe.gov.tw (M.-S. Yen).
[h] Both of these authors contributed equally to this work.

http://dx.doi.org/10.1016/j.tjog.2014.05.001

with early-stage bulky Cx cancer are difficult to manage, because of the high recurrence rate and worse prognosis, compared to those with smaller tumors at the same stage [3]. In this situation, the role of surgery [radical hysterectomy and pelvic lymph node dissection (RH and PLND)] is controversial [2], compared with the role of concurrent chemoradiotherapy (CCRT). CCRT is now considered the treatment of choice for patients who are not candidates for initial surgical therapy [4–7]. In clinical practice, Cx cancer is classified according to the clinical International Federation of Gynecology and Obstetrics (FIGO) staging system [1], and this is mainly based on clinical examination, which makes the selection of those that will benefit from surgical intervention much more difficult. Therefore, modification of the treatment strategy, including the use of neoadjuvant chemotherapy (NACT), RT (external beam RT or brachytherapy) and CCRT, is much more frequent either before or after surgery.

To perform successful surgery, the induction of tumor shrinkage might be of most importance. This not only facilitates radical excision but also makes reconstruction easier. Although many strategies can be used to bring about tumor shrinkage, chemotherapy may be effective. NACT is well accepted in the management of various types of tumor, such as breast cancer [8]. However, the application of NACT for Cx cancer is debated, although it is often used in Asia, Italy, and South America [2]. The theoretical rationale for the use of NACT in Cx cancer includes the aforementioned induction of tumor shrinkage to facilitate radical excision, and a possible sterilization of lymph nodes and parametrial tissues, thereby reducing the risk factors of adjuvant therapy after surgery [1]. NACT regimens for Cx cancer vary, ranging from single-agent to many forms of multiagent regimens. In addition, the therapeutic interval also varies, ranging from every week to every 2, 3, or 4 weeks [9–15]. The clinical effects of NACT are not always consistent with the theoretical benefits, and that is why there is a great deal of conflicting data in the literature [9–15]. The available reports on the effect of NACT on Cx cancer are mainly with regard to FIGO IB and IIA bulky tumors, sometimes up to stage IVA [9–16]. The heterogeneity of the study population, including the differences in stage and cell types, and comorbidity with other medical or surgical illnesses make it difficult to reach a conclusion [9–16]. In addition, there is no study addressing markedly bulky Cx squamous cell carcinoma (Cx-SCC) ($\geq$ 6 cm). Therefore, we conducted this retrospective study to investigate the effect of NACT on the management of early-stage bulky Cx-SCC before surgery.

Materials and methods

The population of this study was derived from the Cancer Registry in the Department of Obstetrics and Gynecology of Taipei Veterans General Hospital. All patients with markedly bulky $\geq$ 6 cm Cx-SCC undergoing RH and PLND between 1996 and 2001 were evaluated. The study aimed to compare the difference between weekly cisplatin-based NACT-RH and RH as an initial therapy for patients with $\geq$ 6 cm Cx-SCC. To make this study even more uniform and consistent, eligibility criteria were as follows: histologically verified uterine Cx-SCC; locally advanced stage FIGO IB disease without parametrial invasion or distant metastases; initial magnetic resonance image- or computed tomography-measurable tumor diameter $\geqq$ 6 cm in size; age younger than 65 years with a life expectancy $\geq$ 1 year; World Health Organization performance status of 0-2, treatment with type III RH and pelvic and para-aortic lymphadenectomy, no prior treatment with RT or CT, but three courses of weekly cisplatin 50 mg/m^2 were permitted; absence of prior malignant diseases or surgical illness, but cesarean section was permitted; and adequate renal, pulmonary, hepatic, bone marrow, and cardiac function.

Basic characteristics of the patients, including surgical parameters and complications, were recorded. Immediate complication included visceral organ injury, prolonged hospitalization because of instability or significant delay ($\geq$ 7 days) of immediate postoperative adjuvant therapy (such as CT, RT, or CCRT); difficulty in urination and constipation were excluded. Late complication included any therapy-related sequelae, such as long-term ureter or urethra catheter use ($\geq$ 12 months), radiation colitis, and cystitis. We used the following parameters to define the radiation colitis or radiation cystitis. The diagnosis of radiation colitis and/or cystitis was made when those patients who had at least one attack of anal bleeding and gross hematuria that required medical care for relief and the diagnosis of radiation colitis and/or cystitis had excluded other radiation-unrelated or tumor-related possibility at first, such as infection, acute gastroenteritis, hemorrhoid, or tumor recurrence.

Periodic follow-ups of patients, including postoperative adjuvant therapy, such as CT, RT, or CCRT in accordance with the patients' risk analysis [17–22], physical examination, vaginal cytology, and imaging or intravesical ureterography, continued until the patients died or for more than 5 years after surgery. To determine an appropriate decision point for the continuous data, such as age, tumor size, blood loss, and number of lymph nodes, the receiver operating characteristic was used [23].

Survival was determined on the basis of treatment and patient outcomes. Estimates of the proportion of OS were calculated by the Kaplan-Meier procedure, and differences in survival were evaluated via the log-rank test. Covariance analysis and the hierarchic Chi-square test were used to control for potential confounding factors in the comparison of clinicopathologic characteristics and risk factors. The log-rank test, hazard ratio (HR), and 95% confidence interval (CI) of mortality from cancer were calculated via the Cox proportional hazards model with univariate and multivariate analysis of OS. Statistical significance was determined by an unpaired two-tailed Student t test using a pooled estimator of variance, and was defined as $p < 0.05$. SPSS version 20 (SPSS, Chicago, IL, USA) was used for statistical analysis.

Results

A total of 60 patients fulfilled the aforementioned criteria and were enrolled into the analysis. Thirty-five patients received three cycles of weekly intravenous cisplatin 50 mg/m^2-based NACT, followed by RH and PLND and para-aortic lymph node sampling (NACT-RH group) on Day 18 after the first course of NACT. The remaining patients ($n = 25$) underwent RH and PLND and para-aortic lymph node sampling (RH group). Follow-up ranged from 11 months to 205 months (median 138 months).

There was no statistically significant difference in age, initial image tumor size, number of removed lymph nodes, cell grade, and presence of deep stromal invasion, vaginal invasion, parametrial invasion, lymphovascular invasion, and pelvic or para-aortic lymph node invasion between the two groups (Table 1). The percentage of patients in both groups who were treated with postoperative adjuvant therapy was also similar. The mortality rate seemed to be lower in the NACT-RH group (37.1% in the NACT-RH group and 48.0% in the RH group), although without a statistically significant difference. Pathological tumor size, estimated blood loss during operation, and immediate postoperative complications were significantly different between the two groups. In the NACT-RH group, the pathological tumor size was significantly smaller (4.5 $\pm$ 1.4 cm vs. 5.7 $\pm$ 0.8 cm, $p < 0.001$). In addition, a lesser amount of estimated blood loss during the RH procedure was also noted in the NACT-RH group (558 $\pm$ 1328 mL vs. 930 $\pm$ 356 ml, $p < 0.001$). The immediate postoperative complication rate overall