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Original Article

A retrospective analysis of prognostic factors in patients with cervical non-squamous cell carcinoma treated with concurrent chemoradiotherapy

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Abstract: Objective: To investigate the prognostic factors for cervical non-squamous cell carcinoma (NSCC) patients who were treated with concurrent chemoradiotherapy (CCRT). Methods: We retrospectively analyzed the clinical records of 111 cervical NSCC patients who were treated with CCRT at Peking Union Medical College Hospital between January 2005 and December 2014. Survival data were analyzed by Kaplan-Meier method. Univariate analysis of prognostic factors for overall survival was performed by Wilcoxon (Gehan) test. Prognostic factors for overall survival and progression free survival (PFS) were further analyzed by multivariate Cox regression model. Results: Of the 111 patients, 83 (74.8%) had adenocarcinoma, 16 (14.4%) had adenosquamous carcinoma, and 12 (10.8%) had other special types. According to FIGO staging system, 9 (8.1%) had stage I, 8 (7.2%) had stage IIA. 75 (67.6%) had stage IIB, and 19 (17.1%) had stage III/IV. Fifty-five patients had tumor diameter < 4 cm. Forty-three patients (38.8%) had positive pre-treatment CA125. Fifty-five patients (49.5%) had pelvic lymph node enlargement. The 5-year overall survival rate was 66.0%. Univariant and multivariant analysis identified FIGO stage, local tumor size, histological grade, lymph node enlargement as prognostic factors for overall survival. FIGO stage and tumor size were independently assocaited with the progrssion-free survival of these patients. Conclusion: FIGO stage, local tumor size, histological grade, lymph node enlargement are prognostic factors for cervical NSCC. Patients with higher FIGO stage and/or tumor diameter ≥ 4 cm have poor posnosis and early tumor progression following CCRT. New treatment strategies should be considered for these patients.

Keywords: Cervical non-squamous cell carcinoma, concurrent chemoradiotherapy, prognosis, cervical adenocareinoma, overall survival

Introduction

Cervical cancer is one of the most common cancers and the fourth leading cause of cancer death in women worldwide [1, 2]. Each year, more than 20,000 women die of cervical cancer in China [3]. Cervical cancer is classified into two major histological types: squamous cell carcinoma (SCC) and non-SCC (NSCC), such as adenocarcinoma, adenosquamous carcinoma, clear cell carcinoma, papillary adenocarcinoma, serous adenocarcinoma, and neuroendocrine small cell carcinoma. While SCC accounts for approximately 75% of all cervical cancer, adenocarcinoma and adenosquamous carcinoma account for around 20% and 3%, respectively [4]. Although NSCC comprises a minor proportion of cervical cancers, it substantially differs from SCC in histological origin, risk factors, metastasis rates and recurrence sites. Studies have suggested that patients with early and advanced stage adenocarcinoma have poorer prognosis compared with SCC [5].

Despite the improvement of cervical cancer treatment, the prognosis remains unsatisfactory [6]. Several prognostic factors for cervical cancer have been identified, including age, tumor histology, FIGO stage, tumor size, as well

as pelvic and para-aortic lymph node metastasis [7-9]. Nevertheless, most of the previous studies were conducted in patient populations that were mainly composed of SCC patients, but included very few NSCC patients. To our best knowledge, no studies on prognosis have been performed until now with cervical NSCC patients as a major group. Therefore, additional research efforts are needed to identify the prognostic factors in NSCC patients in order to accurately predict the treatment outcome.

Concurrent chemoradiotherapy (CCRT) is a treatment modality that is generally composed of concurrent radiotherapy and cisplatin-based chemotherapy. Several clinical trials have suggested a significantly improved survival rate for patients treated by CCRT when compared with those who receive radiotherapy alone [10-13]. CCRT has now become a standard management for locally advanced cervical cancer [14-16]. The present study reviewed the medical records of 111 cervical NSCC patients who recieved CCRT in a single cancer center in Bejing between January 2005 and December 2014. The objective of this study was to determine the most valuable prognostic factors for overall survival (OS) in order to accurately predict the treatment outcome in cervical NSCC. Moreover, this study could also be beneficial for individualized treatment planning in patients with cervical NSCC.

Material and methods

Patients

This retrospective study included a total of 123 patients with primary cervical NSCC who were treated in the Department of Radiotherapy at the Beking Union Medical College Hospital between January 2005 and December 2014. Patients were selected based on the following inclusion criteria: newly diagnosed patients with pathologically confirmed FIGO staging I-IV cervical NSCC who had completed all radiotherapy sessions. Exclusion criteria were as follows: pathologically confirmed cervical SCC patients; NSCC patients with prior cancer surgery or radiotherapy and/or failed to complete all radiotherapy sessions. Complete medical chart of each patient was reviewed to record the age, symptom, pathological type, clinical stage, tumor size, treatment method, treatment time, tumor regression and survival. Twelve cases (9.76%) were lost to follow-up, resulting in a total of 111 cases in subsequent analyses. This study was approved by the Ethics Committee at the Beking Union Medical College Hospital. All patients (families in case that the patient already died) signed the informed consent form for sharing the clinical records.

Treatment method

None of the patients had any other immune-related diseases, prior history of cancer, medication of steroids and immunosuppressants, surgery or radiotherapy. All patients were required to sign the informed consent before receiving any treatment. All patients received conformal intensity-modulated radiotherapy (IMRT). IMRT was delivered to a total dose of 45 to 50.4 Gy in 25 to 28 fractions in 8 weeks. In 9 cases, Pelvic and paraaortic field IMRT was delivered to a total dose of 50.4 Gy in 8 weeks. High-dose rate intracavity brachytherapy was delivered to a total dose of 30 to 36 Gy in 5 to 6 fractions in 8 weeks to the point A with a mHDRV2 192-iridium afterloading system (Elekta Inc., Beijing, China) according to the ICRU 38.

Patients were given one of the following three standard chemotherapys: cisplatin chemotherapy at a planned weekly dose of 30 mg/m^2 with a one-week interval for 5-6 courses, FP (5- fluorouracil + cisplatin): cisplatin chemotherapy and a weekly dose of 50 mg/m^2 with a 3-week interval for 3 courses or TC protocol (paclitaxel + carboplatin): a weekly dose of 135 mg/m^2 paclitaxel and carboplatin AUC5 with a 3-week interval for 3 courses Chemotherapy was started concomitantly with IMRT.

Follow-up study

Patients were followed up through either outpatient visit or telephone interview until December 2015. The follow-up time ranged between 3 to 109 months with a median time of 24 months. A total of 12 cases (9.76%) were lost to follow-up. As a result, 111 cases were included in subsequent analyses. The survival time (months) of each patient was recorded staring from the date of diagnosis.

Statistical analyses

Count data were expressed as percentages and analyzed by SPSSI9.0 (IBM SPSS, Chicago,

Table 1. Summary of the seven categorical variables used in the multivariate Cox regression analyses

Factor	Categorical variable	Definition
Age (year)	X1	< 50 = 1, ≥ 50 = 2
FIGO Stage	X2	I = 1, IIA = 2, IIB =3, III, IV = 4
Histological type	X3	Adenocarcinoma = 1, Adenosquamous carcinoma = 2, Other types = 3
Histological grade	X4	Well differentiated = 1, Moderately differentiated = 2, Poorly differentiated = 3, Undifferentiated = 4, Undetermined = 5
Tumor diameter	X5	< 4 cm = 1, ≥ 4 cm = 2
Pretreatment serum CA125 level	X6	Negative (≤ 35 U/mL) = 1, Positive (> 35 U/mL) = 2, N/A = 3
PLN enlargement	X7	No = 1, Yes = 2

Table 2. Summary of clinical features of patients

Characteristic	Value
Age (year)*	52 (27-76)
FIGO Stage	
I, n (%)	9 (8.1)
IIA, n (%)	8 (7.2)
IIB, n (%)	75 (67.6)
III, n (%)	18 (16.2)
IV, n (%)	1 (0.9)
Histological type	
Adenocarcinoma, n (%)	83 (74.8)
Adenosquamous carcinoma, n (%)	16 (14.4)
Clear cell carcinoma, n (%)	6 (5.4)
Papillary adenocarcinoma, n (%)	2 (1.8)
Serous adenocarcinoma, n (%)	1 (0.9)
Neuroendocrine small cell carcinoma, n (%)	1 (0.9)
Other, n (%)	2 (1.8)
Histological grade	
Well differentiated, n (%)	21 (18.9)
Moderately differentiated, n (%)	33 (29.7)
Poorly differentiated, n (%)	19 (17.1)
Undifferentiated, n (%)	7 (6.4)
Undetermined, n (%)	31 (27.9)
Tumor diameter	
< 4 cm, n (%)	55 (49.5)
≥ 4 cm, n (%)	56 (50.5)
Pretreatment serum CA125 level	
Negative (≤ 35 U/mL), n (%)	40 (36.0)
Positive (> 35 U/mL), n (%)	43 (38.8)
N/A, n (%)	28 (25.2)
PLN enlargement	
Yes, n (%)	55 (49.5)
No, n (%)	56 (50.5)

*, Value is presented as median (range). PLN: pelvic lymph node.

IL, USA). Survival rates were estimated by the Kaplan-Meier method and compared by the log-rank test. Univariate analysis of prognostic factors for overall survival was performed by Wilcoxon (Gehan) test. Multivariate Cox regression analysis was used to select prognostic factors for overall survival and progression free survival (PFS). Seven variables were used for the analyses (**Table 1**). Hazard ratios (HRs) and 95% confidence intervals (CIs) were determined using Cox proportional hazards models. $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics of patients

Table 2 summarizes the clinical characteristics of the 111 patients in this study. The median age of patients was 52 years (range, 27 to 76 years). According to the FIGO ovarian cancer staging system, 9 (8.1%) patients were in I, 8 (7.2%) were in IIA, 75 (67.6%) were in IIB, 18 (16.2%) were in III, and 1 (0.9%) was in IV. Eighty-three (74.8%) had adenocarcinoma, 16 (14.4%) had adenosquamous carcinoma, 12 (10.8%) had other histological types including clear cell carcinoma, papillary adenocarcinoma, serous adenocarcinoma, Neuroendocrine small cell carcinoma, etc. Among the 111 patients, 56 (50.5%) had tumor ≥ 4 cm, and the others had tumor < 4 cm. Forty-three patients (38.8%) had positive serum CA125 (> 35 U/mL), 40 (36%) were negative (≤ 35 U/mL), and the remaining did not undergo CA125 test. Pelvic lymph node enlargement was detected in 55 patients (49.5%).

Treatment outcome

The 1-, 2-, 3- and 5-year overall progression free survival (PFS) rates of the patients were 79.2%, 73%, 65.9%, and 65.9%, respectively

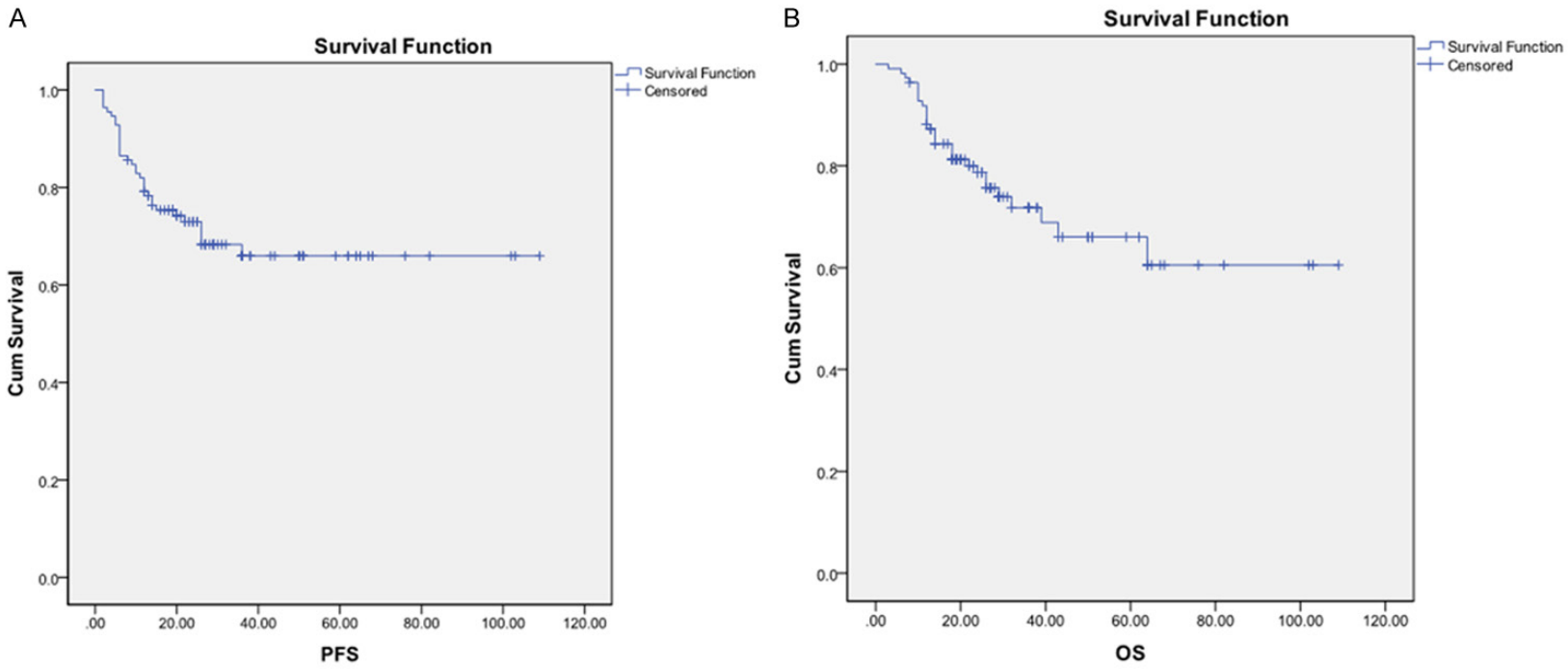
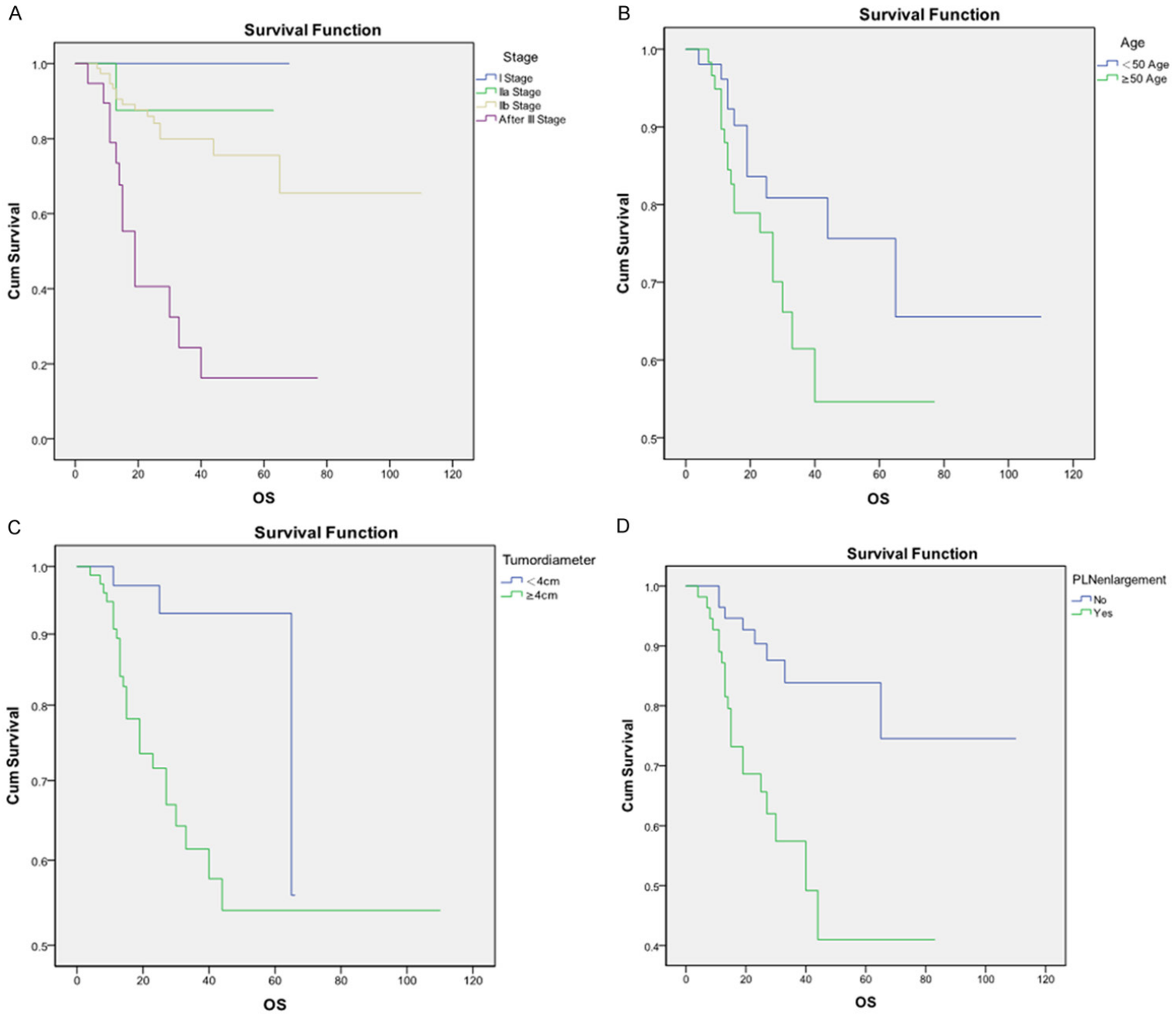


Figure 1. A. Kaplan-Meier plot for progression free survival (PFS) in 111 patients with cervical non-squamous cell carcinoma treated with concurrent chemoradiotherapy. B. Another Kaplan-Meier analysis of overall survival (OS) rate in these patients.


A
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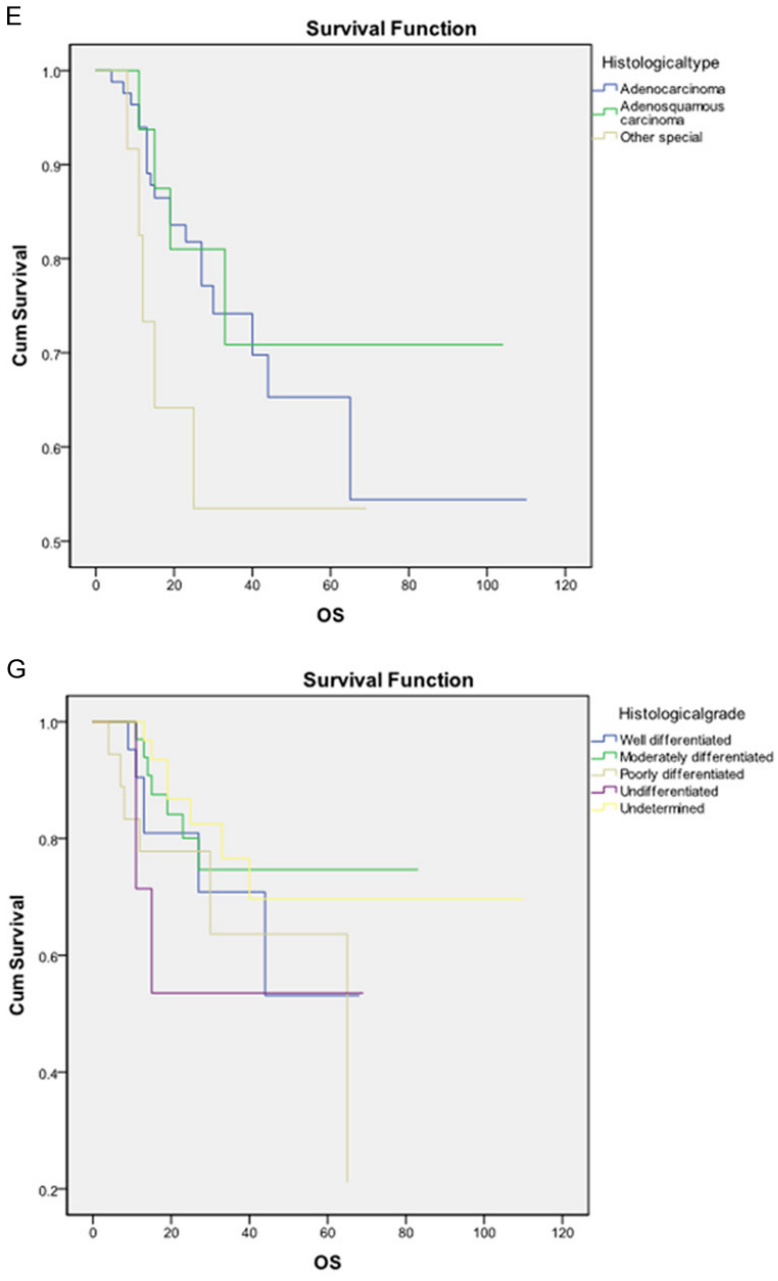

Figure 2. Kaplan-Meier analysis comparing the overall survival rates among different subgroups of the 111 patients with cervical non-squamous cell carcinoma treated with concurrent chemoradiotherapy. Patients were divided into subgroups based on (A) FIGO Stage, (B) age (year), (C) tumor diameter, (D) pelvic lymph node (PLN) enlargement, (E) histological type, (F) pretreatment serum CA125 level, and (G) histological grade.

Table 3. Wilcoxon (Gehan) analyses of prognostic factors for overall survival rates in cervical non-squamous cell carcinoma

	Wilcoxon (Gehan) statistics	df	*P* value
Tumor diameter (≥ 4 cm)	8.891	1	0.003
FIGO Stage	19.708	3	0.000
CA125 level	13.993	2	0.001
Age	1.897	1	0.168
PLN enlargement	10.845	1	0.001
Histological grade	4.705	4	0.319
Histological type	3.106	2	0.212

Table 4. Multi-variant Cox proportional hazard model analyses of prognostic factors for overall survival rates in cervical non-squamous cell carcinoma

Variant	HR	95.0% CI for HR	*P*
Tumor diameter (≥ 4 cm)	4.239	1.220-14.727	0.023
Histological type	2.306	1.174-4.527	0.015
Histological grade	0.702	0.497-0.992	0.045
CA125	1.191	0.688-2.060	0.533
Swollen pelvic lymph nodes	3.887	1.449-10.430	0.007
Age	2.195	0.943-5.106	0.068
FIGO stage	3.607	1.643-7.916	0.001

as shown by the Kaplan-Meier PFS curve (**Figure 1A**). The 1-, 2- and 5-year overall survival rates were 88.2%, 78.7%, and 66.0%; respectively (**Figure 1B**). As of the last follow-up visit, 73 patients remained disease free, 33 had recurrence (n = 28, 25.23%) or metastasis (n = 5, 4.5%), and the remaining 5 died of cancer-related causes despite that the recurrence or metastasis was not clearly identified. Among the patients who died, 2 had recurrence, 11 had lung metastasis, 4 had liver metastasis, 2 had bone metastasis, 8 had pelvic, retroperitoneal, mediastinal, or cervical lymph node metastasis. In addition, one patient died of renal failure, and another patient died of intestinal obstruction. A total of 20 patients died within 24 months since the date of diagnosis.

Prognostic factors for cervical NSCC

The patients were then classified into the following 4 subgroups based on the FIGO stage: I, IIA, IIB, and III or higher. As shown in the Kaplan-Meier OS curves (**Figure 2A**), the overall survival rates in stage I and IIA were 100% and 87.5%, respectively. The 1-, 2- and 5-year survival rates in stage IIb were 89.2%, 84.2% and 75.9%, respectively. The 1-, 2- and 5-year survival rates in stage III or higher were73.7%, 41.7% and 16.7%, respectively. As shown in **Figure 2B-D**, the overall survival rate in age group (< median), tumor diameter (< 4 cm), and pelvic lymph node enlargement (no) was higher compared with age group (≥ median), tumor diameter (≥ 4 cm), and pelvic lymph node enlargement (yes), respectively. The overall survival rate in adenocarcinoma and adenosquamous carcinoma was higher than that in other special types (**Figure 2E**). As shown in **Figure 2F**, the overall survival rate in pretreatment serum CA125 level (≤ 35 U/mL and N/A) was higher than compared with CA125 (> 35 U/mL).

Further Wilcoxon (Gehan) analyses revealed that patients with tumor diameter ≥ 4 cm, higher FIGO stage, swollen pelvic lymph nodes, increased CA125 level, and poor/no differentiation had significantly poorer prognosis and lower 5-year survival rate ($P < 0.05$, **Table 3**). Age and histological type were irrelevant to the prognosis of cervical NSCC. Moreover, subsequent multivariant Cox proportional hazard model analysis showed that FIGO stage, tumor diameter, histological type, histological grade, swollen pelvic lymph nodes were independent prognostic factors for cervical NSCC ($P < 0.05$, **Table 4**). Patients with higher FIGO stage, larger tumor size (≥ 4 cm), swollen pelvic lymph nodes, special histological type, and poor/no differentiation had markedly poorer prognosis.

Factors associated with PFS in cervical NSCC

Cox multivariant analyses showed that FIGO stage and tumor size were independent factors associated with PFS in non-squamous cervical cancer (**Table 5**). Following CCRT, tumor progression occurred earlier in patients with higher FIGO stage and/or tumor diameter ≥ 4 cm when compared with other patient groups.

Discussion

To date, several studies have been performed on the prognostic factors in cervical adenocarcinoma. Stehman et al. have suggested the prognostic value of tumor size, histological grade, myometrial invasion, lymph node metas-

Table 5. Multivariant Cox analyses of factors associated with PFS in cervical non-squamous cell carcinoma

Variant	HR	95.0% CI for HR	P
Tumor diameter (≥ 4 cm)	3.604	1.228-10.581	0.02
Histological type	1.511	0.819-2.787	0.187
Histological grade	0.825	0.609-1.119	0.217
CA125	1.069	0.643-1.779	0.796
Swollen pelvic lymph nodes	2.196	0.946-5.100	0.067
Age	1.173	0.554-2.487	0.677
FIGO stage	3.196	1.580-6.465	0.001

tasis in cervical adenocarcinoma [17]. In this study, univariant and multivariant analysis identified FIGO stage, local tumor size, histological grade, lymph node enlargement as independent factors affecting the prognosis of cervical NSCC. These findings were consistent with previous studies, suggesting that early diagnosis and treatment is essential for the prognosis of cervical cancer. Furthermore, our multivariate analyses also showed that FIGO stage and tumor diameter were independent risk factors for PFS in cervical NSCC. In our study, 23 out of 33 patients with higher FIGO stage and/or tumor diameter ≥ 4 cm had tumor progression within 1 year since the date of diagnosis even after receiving CCRT. These results suggested that new treatment strategies should be considered for locally advanced cervical NSCC with tumors ≥ 4 cm.

Currently, there is not any tumor marker with high specificity for the prognosis of cervical NSCC. Zhou et al. have suggested the value of serum CAI25 and CAI99 level in the assessment of clinical staging, treatment and prognosis of cervical adenocarcinoma [18]. He et al. have also reported an association between pre-treatment serum CAI25 level and the prognosis of cervical cancer [19]. In this study, univariate analyses showed that the 5-year survival rate in patients with positive CAI25 level (> 35 U/mL) was significantly lower compared with patients with normal CAI25 level. Nevertheless, subsequent multivariant analyses revealed that CAI25 level was not related to the survival rate of these patients. Therefore, the value of combined detection of CA125, CA199 and CEA in the diagnosis of cervical NSCC needs further investigation.

Studies have suggested the high lymph node metastasis rate and poor prognosis of cervical adenocarcinoma [20]. Consistently, in the current study, patients with treatment failure mostly had metastasis to the lung, liver or lymph nodes. Some scholars believe that cervical adenocarcinoma patients receiving chemoradiotherapy or adjuvant chemotherapy may achieve longer DFS [21]. In this study, a 50-year-old stage IIA patient with a 7 × 8 cm cauliflower-like moderately differentiated adenocarcinoma was treated by concurrent chemoradiotherapy. Pelvic wall, iliac and cervical lymph node metastasis was detected at 5 month after treatment, and the patient died at 12 month since the diagnosis. The treatment failure might be because no sequential chemotherapy was performed to prevent lymph node metastasis. Recent clinical trials have proposed that sequential chemotherapy after standard CCRT might provide a therapeutic benefit [22, 23]. Therefore, it remains a question whether sequential chemotherapy may improve the treatment outcome.

Previous studies have reported a 5-year overall survival rate of 25% to 68% in cervical adenocarcinoma [24]. The 5-year survival rates of FIGO stage I, II, III and IV patients were 60%-90%, 37%-90%, 8%-38%, and 0-14%, respectively [9]. The overall 5-year survival rate of the cervical NSCC patients in our study was 66.0%. None of the stage I patients died as of the last follow-up visit (64 months). The 5-year survival rates of stage IIA, IIB and III/IV patients were 87.5%, 75.9% and 16.7%, respectively, which was slightly higher than those in the literature [9]. Although younger patients have been suggested to have higher survival rate and better prognosis, our results showed that age was irrelevant to the prognosis or PFS in cervical NSCC.

In summary, univariant and multivariant analysis identified FIGO stage, local tumor size, histological grade, lymph node enlargement as prognostic factors for cervical NSCC. FIGO stage and tumor size were independently assocaited with the progrssion-free survival of these patients. Patients with higher FIGO stage and/or tumor diameter ≥ 4 cm have poor posnosis and early tumor progression following CCRT. Therefore, new treatment strategies should be considered for these patients.

Disclosure of conflict of interest

None.

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