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Predictors of distant metastasis or local recurrent after radiotherapy in patients with cervical cancer

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Abstract

Objective To evaluate risk factors for survival, recurrence and metastasis in patients with FIGO stage IA-IVA cervical cancer who underwent radical radiotherapy (RT) or concurrent chemoradiotherapy (CCRT).

Methods We performed a retrospective analysis of 1288 cervical cancer patients. Kaplan–Meier curves, Cox regression models, and log-rank tests were used for statistical analysis.

Results The 5-year overall survival rate for patients with stage I-II and stage III-IVA are 81.1% and 70.4%. In multivariable analysis, pathological type, 2009 FIGO stage, pre-treatment SCC-Ag level, pre-brachytherapy tumor size, and CCRT are independent influencing factors for patient OS. Patients with non-squamous cell carcinoma are more likely to occur distant metastasis compared to those with squamous cell carcinoma. No significant correlation was observed between histological types among patients with local recurrence. In patients with squamous cell carcinoma, multivariable analysis showed that SCC value > 11.75 at diagnosis was an independent predictor of distant metastasis and local recurrence ($P = 0.001$ and $P = 0.038$, respectively). Lymph node metastasis was an independent risk factor for distant metastasis. Age, treatment time of RT, CCRT, and pre-treatment Hb classification showed no significant correlation with cervical cancer distant metastasis and local recurrence.

Conclusions Non-squamous cell carcinoma patients may have a worse prognosis than squamous cell carcinoma patients. In patients with squamous cell carcinoma, SCC value at diagnosis, and lymph node metastasis are independent influencing factors for distant metastasis, while SCC value at diagnosis is an independent influencing factor for local recurrence.

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Background

Cancer is a major public health issue in the world [1]. In recent years, the incidence and mortality of cervical cancer in China have shown an upward trend, with 2018 and 2022 recording 106,000 and 150,700 new cases, and 48,000 and 55,700 deaths, respectively [2, 3]. Most cancer treatments aim to reduce cancer cells by killing them or preventing them from migrating [4].

The primary treatments for cervical cancer include surgery and radiotherapy, but 25–61% of cases recur after initial treatment [5]. About one-third of women treated for cervical cancer will have recurrence during follow-up, with most recurrences occurring in the first two to three years after treatment [6]. The 5-year survival rate for patients with recurrent or metastatic cervical cancer is only 17% [7]. Additionally, the survivors deal with a wide array of morbidities caused by the disease itself, as well as treatment-related toxicities [8]. Cancer is a complex and multifaceted disease that requires comprehensive research in order to improve early detection and treatment methods, improvements in understanding of the complexity of cancer biology have been instrumental in advancing cancer treatments [9, 10]. Therefore, preventing and reducing the metastasis and recurrence in patients with cervical cancer poses a significant challenge in clinical practice [11, 12].

Given the limited research on the risk factors for recurrence or metastasis in patients who have undergone radical radiotherapy or concurrent chemoradiotherapy (CCRT). This study evaluated risk factors for survival, recurrence and metastasis, specifically. The findings aim to provide valuable insights for the prevention and treatment of cervical cancer recurrence.

Methods

Study population

Clinical records of 1,556 locally advanced cervical cancer patients who underwent RT or CCRT from August 2011 to December 2017 at Zhejiang Cancer Hospital were retrieved from the electronic medical record system. Excluding 197 cases of lost follow-up, the details of 1,288 primary treatment patients were analyzed.

Pathologic characteristics and adjuvant therapy

Patients data were collected, including histotype, tumour size, grade of differentiation, imaging diagnosis of lymph nodemetastasis (LNM), FIGO stage (2009), serum levels of squamous cell carcinoma antigen (SCC-Ag) and Hb classification at initial diagnosis. The diagnosis criteria for pelvic or para-aortic lymph node metastasis were CT or MRI imaging with a short axis diameter ≥ 1 cm, or PET-CT diagnosis. Recurrence-free survival (RFS) was calculated as the number of months from the date of initial diagnosis to either the date of recurrence or the date of censoring. Overall survival (OS) was calculated as the number of months from the date of initial diagnosis to either the date of death or censoring. Cut-off levels for cancer antigens recommended by detection kit manufacturers were 1.5 ng/ ml for SCC-Ag. The clinical cut-off value applied for SCC-Ag in this study was 11.75 ng/ml. RT or CCRT was administered to all patients. Treatment consisted of pelvic (with or without paraaortic and/or inguinal) EBRT with 45–50 Gy at 1.8–2 Gy per fraction, and brachytherapy. We applied concurrent chemotherapy with cisplatin 40 mg/m2 for 4–5 cycles, or paclitaxel (135 mg/m^2) with cisplatin (60 mg/m^2) every 3 weeks for 1–2 cycles weekly to the patients without comorbidity and who were aged of 75 years or younger.

Statistical analysis

GraphPad Prism 9.5 was used for graph creation, and SPSS 26.0 software was employed for statistical analysis. Survival analysis was conducted after excluding missing follow-up data, using the Kaplan-Meier method to calculate survival curves. Log-rank tests determined significance for single-factor analysis, and Cox proportional hazards regression models were used for multivariate analysis, with $P < 0.05$ indicating statistical significance.

Results

The clinicopathological features of the 1,288 eligible patients are summarised in Table 1. The median age of the patients was 57 years (25–90 years). Pathological types included 1,249 cases of squamous cell carcinoma (97%) and 39 cases of non-squamous cell carcinoma (3%). There are 316 patients with cervical recurrence or metastasis and 249 detailed cases, among which include 56 local recurrences (LR), 157 distant metastases (DM), and 36 cases presenting both LR and DM. The cut-off date for follow-up was December 2022 or the date of patients' death, with a median follow-up time of 76 months. Treatment modalities included RT alone in 31.7% of patients, and CCRT in 68.3%.

The 5-year overall survival rate for patients with stage I-IVA cervical cancer after treatment is 75.9%. For stage I-II and stage III-IVA, the 5-year overall survival rates are 81.1% and 70.4%, respectively (5-year overall survival rates for stage I, IIA, IIB, IIIA, IIIB, and IVA are 82.6%, 85.3%, 80.6%, 64.0%, 71.2%, and 77.8%, respectively). Among the 972 patients without recurrence or metastasis, the 5-year overall survival (OS) rate is 92.9%, while for the 316 patients with recurrence or metastasis, it is 23.7%. As shown in Table 2, univariate analysis revealed that pathological type, 2009 FIGO stage, squamous cell carcinoma Ag (SCC-Ag) level at diagnosis, pre-brachytherapy cervical tumor size, LNM, and CCRT were risk factors affecting patient OS. In multivariable analysis, pathological type, 2009 FIGO stage, SCC-Ag level at

Table 1 Patient, disease, and treatment characteristics

Characteristic	Frequency (%)
Age (years)	
≤ 60	742(59.6)
>60	504(40.4)
Tumour size (pre-treatment)	
≤ 4 cm	656(52.6)
>4 cm	590(47.4)
FIGO Stage (2009)	
I-II	640(51.4)
III-IVA	606(48.6)
Pretreatment SCC level	
≤ 11.75 ng/ml	765(61.4)
>11.75 ng/ml	481(38.6)
Pretreatment Hb classification	
0–2 degrees	1028(82.5)
3–4 degrees	218 (17.5)
Tumour size (pre-brachytherapy)	
≤ 2 cm	660(53.0)
>2 cm	586(47.0)
LNM	
No	530(42.5)
Yes	711(57.1)
Treatment of RT, (days)	
≤ 60	890(71.4)
>60	356(28.6)
CCRT	
No	399(32.0)
Yes	847(68.0)

diagnosis, pre-brachytherapy tumor size, and CCRT are independent influencing factors for patients' OS.

Survival analysis of patients with recurrence or metastasis

As shown in Table 3, both univariate and multivariable analysis showed that non-squamous cell carcinoma patients were more prone to distant metastasis than squamous cell carcinoma patients, with no significant correlation observed in local recurrence patients. Among patients with squamous cell carcinoma, univariate analysis revealed higher risks of distant metastasis and local recurrence in patients with 2009 FIGO stage, SCC value > 11.75 at diagnosis, LNM, and pre-treatment tumor size > 4 cm. Patients with pre-brachytherapy tumor diameter > 2 cm are more prone to local recurrence, and there is no correlation in distant metastasis. Multivariable analysis showed that patients with SCC value > 11.75 at diagnosis had a 66% significantly increased risk of distant metastasis, compared to those with SCC ≤ 11.75 (HR = 1.66, 95% CI = 1.223–2.270, $P<0.001$). When SCC value was > 11.75 at diagnosis compared to SCC ≤ 11.75, and the risk of local recurrence increased by 57.8% (HR = 1.578, 95%CI = 1.026–2.427) (Fig. 1). Lymph node metastasis was significantly correlated with distant metastasis (HR = 1.433, 95% CI = 1.037–1.980) and was an independent influencing factor for distant metastasis in patients (Fig. 2). Age, treatment time of RT, CCRT, and Pre-treatment Hb classification showed no significant correlation with cervical cancer distant metastasis and recurrence.

Discussion

After standard treatment for cervical cancer, some patients still face the risk of recurrence [13]. Approximately one-third of women treated for cervical cancer experience recurrence during follow-up, with most relapses occurring within the first two to three years after treatment [14–16]. Clinical manifestations of cervical cancer patients with recurrent or metastatic lack specificity, and diagnosis often relies on laboratory and imaging examinations, leading to delayed treatment and poor prognosis. Therefore, analyzing risk factors for patients with recurrent or metastatic cervical cancer can help identify recurrent patients early. Literature [17, 18] reported indicate that survival-related factors after RT for cervical cancer include chemotherapy, pathological type, lymph node metastasis, cervical tumor size, etc. In

Table 2 Clinicopathological features associated with overall survival

Characteristic	Overall survival univariate analysis	Multivariate analysis
	P-value	*P*-value HR(95% CI)
Histology (SCC vs. non-SCC)	0.6	
Cervical squamous cell carcinoma		
Age(≤60years VS.>60years)	0.254	
Tumour size (pre-treatment)(≤4 cm VS.>4 cm)	0.448	
FIGO Stage(I-II VS.III-IVA)	0.018	0.138 1.391(0.899 ~ 2.152)
Pretreatment SCC level (≤ 11.75ng/ml VS.11.75ng/ml)	0.003	0.038 1.578(1.026 ~ 2.427)
Hb(0–2 degrees VS.3–4 degrees)	0.165	
Tumour size (pre-brachytherapy)(≤2 cm VS.>2 cm)	0.013	0.050 1.531(1.000 ~ 2.343)
LNM (No VS.Yes)	0.037	0.234 1.315(0.837 ~ 2.066)
Treatment time of RT(≤60days VS.>60days)	0.135	
CCRT(No VS.Yes)	0.473	

Table 3 Patient and treatment characteristics associated with distant metastasis

Characteristic	Univariate analysis	Multivariate analysis
	P-value	*P*-value HR(95% CI)
Histology (SCC vs. non-SCC)		
DM	0.009	<0.001 3.498(1.866 ~ 6.556)
LR	0.6	
Cervical squamous cell carcinoma		
Age(≤60years VS.>60years)		
DM	0.706	
LR		
Tumour size (pre-treatment)(≤4 cm VS.>4 cm)		
DM	0.275	
LR	0.254	
FIGO Stage(I-II VS.III-IVA)		
DM	0.001	0.051 1.359(0.999 ~ 1.848)
LR	0.018	0.138 1.391(0.899 ~ 2.152)
Pretreatment SCC level (≤ 11.75ng/ml VS.11.75ng/ml)		
DM	<0.001	0.001 1.666(1.223 ~ 2.270)
LR	0.003	0.038 1.578(1.026 ~ 2.427)
Pretreatment Hb classification(0–2 degrees VS.3–4 degrees)		
DM	0.188	
LR	0.165	
Tumour size (pre-brachytherapy)(≤2 cm VS.>2 cm)		
DM	0.090	
LR	0.013	
LNM(NO VS.Yes)		
DM	0.001	0.029 1.433(1.037 ~ 1.980)
LR	0.037	0.234 1.315(0.837 ~ 2.066)
Treatment of RT(≤60days VS.>60days)		
DM	0.461	
LR	0.037	0.234 1.315(0.837 ~ 2.066)
CCRT(No VS.Yes)		
DM	0.631	
LR	0.473	

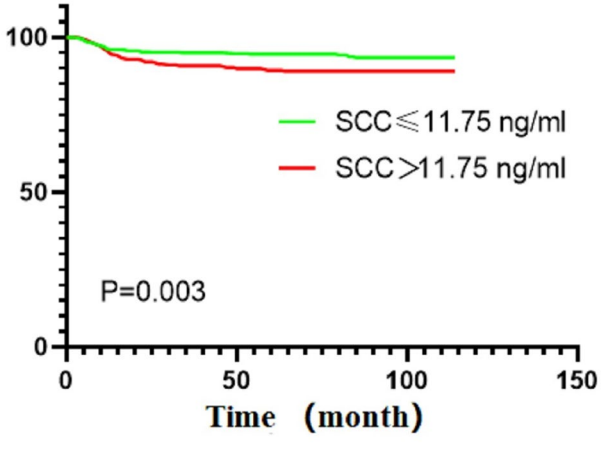

Fig. 1 Kaplan -Meier curves of overall survival for patients with local recurrence

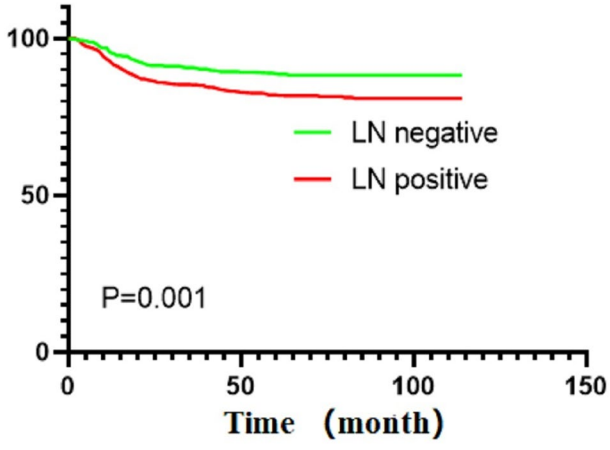

Fig. 2 Kaplan -Meier curves of overall survival for patients with distant metastasis

our study, a single-center sample was followed up for a long period of time and clinical and pathological factors available for analysis were analyzed. Pathological type, 2009 FIGO stage, SCC value at diagnosis, pre-brachytherapy cervical tumor size, lymph node metastasis, and CCRT significantly affect patient overall survival (OS) and disease-free survival (RFS). In our study, 879 patients (68.2%) received concurrent CCRT, and the 5-year OS rate in the CCRT group increased by 7.4% compared to the RT alone group. This result is consistent with previous reports [19, 20]. Patients' recurrence or metastasis is significantly associated with pathological type, 2009 FIGO stage, SCC value at diagnosis, pre-brachytherapy cervical tumor size, and lymph node metastasis. Pathological type, SCC value at diagnosis, and lymph node metastasis are independent influencing factors for DM in patients, while SCC value at diagnosis is an independent influencing factor for LR.

In 2012, Korean scholars [21] established a DM risk model for late-stage cervical cancer, with four parameters significantly correlated with distant recurrence (positive pelvic and para-aortic lymph nodes in PET-CT, non-squamous cell histology, and pre-treatment serum SCC antigen levels). Subsequently, in 2021, their team further validated the model, showing good predictive efficacy for low and intermediate recurrence risk groups but some deviation for the high recurrence risk group. They suggested that there might be unaccounted parameters [22]. Our study showed that OS and PFS were significantly lower in patients with non-squamous cell carcinoma than in patients with squamous cell carcinoma. Research by Hu et al. [23]. from Peking Union Medical College Hospital, comparing 744 cases of cervical squamous cell carcinoma and 71 cases of adenocarcinoma patients receiving radical radiotherapy, found a 3-year overall survival rate of 85.2% and 75.4%, respectively ($P = 0.005$). Non-squamous cell carcinoma is identified as an important prognostic risk factor. Our study revealed that patients with non-squamous cell carcinoma have a higher risk of distant metastasis, but there was no significant difference in local recurrence. Consistent with most studies, adenocarcinoma has a poorer prognosis and is more prone to DM [24, 25] compared to squamous cell carcinoma. A study [26] found that patients with adenocarcinoma or adenosquamous carcinoma have a higher risk of LR and require higher doses to achieve the same effect. Dose-response analysis demonstrated that a minimal dose of 90% to 85 Gy to the high-risk clinical target volume resulted in 95% local control 3 years post-intervention for squamous cell carcinoma, compared to 86% for adeno/adenosquamous carcinoma histology. Overall, this suggests that patients with non-squamous cell carcinoma have a higher risk of recurrence and a poorer prognosis. This indicates that non-squamous cell carcinoma patients may require more aggressive systemic treatment, possibly even combined with immunotherapy, which needs to be confirmed by further clinical trials or studies.

The follow-up monitoring of patients can detect disease recurrence at an early stage and improve survival rates. Tumor marker analysis is widely used for early detection of recurrent diseases [27, 28]. SCC-Ag levels are closely associated with the recurrence and mortality rates after radiotherapy in patients with cervical squamous cell carcinoma and are an effective indicator for assessing disease progression [29–31]. Literature reports indicate that 70–86% of recurrent cervical cancer patients show an increase in SCC-Ag levels during follow-up [32, 33]. Our study showed that patients with SCC value at diagnosiss ≤ 11.75 ng/ml and > 11.75 ng/ml had recurrent or metastatic probabilities of 20.1% and 31.9%, respectively. Multivariate analysis revealed that SCC > 11.75 at diagnosis is an independent prognostic factor for local recurrence and distant metastasis in cervical cancer. Jeong et al. [34] found that SCC levels were not only elevated at diagnosis in about 59% of recurrent cases, but also related to the severity of cervical cancer [35, 36]. In addition, the study reported 22 patients with elevated SCC-Ag levels at diagnosis but without recurrence. Our study showed 146 cases of hematogenous metastasis, mainly to the lungs, liver, and bones, consistent with Park KJ's findings [15]. Therefore, especially for patients with no increase in SCC during recurrence, the high-risk group identified in this study with SCC > 11.75 at diagnosis should be cautious during follow-up and focus on imaging examinations.

The 2018 FIGO staging system primarily introduced changes, including the addition of stage IIIC associated with imaging or pathological lymph node involvement. It emphasizes the importance of metastatic lymph nodes as a prognostic indicator for cervical cancer. Relevant studies have shown that the size of metastatic lymph nodes is an indicator of poor prognosis in patients with cervical cancer [37, 38]. Song et al. found that for patients with no lymph node metastasis, metastatic lymph node sizes < 1.5 cm, and metastatic lymph nodes ≥ 1.5 cm, the 5-year disease-free survival rates were 80%, 67%, and 50%, respectively. In our study, 726 patients (56.3%) had a short diameter of pelvic or para-aortic lymph nodes ≥ 1 cm. The 5-year recurrent or metastatic probability was 28.2% in the lymph node-positive group, while it was 19.9% in the lymph node-negative group. Multivariate analysis in this study showed that lymph node metastasis at the time of diagnosis in initial cervical squamous cell carcinoma was more likely to lead to distant metastasis, with no apparent correlation with local relapse in the radiation field. A study [15] indicated that lymph node metastasis was related to the type of recurrence, with patients without lymph node involvement at initial diagnosis more likely to have LR, while patients with lymph

node involvement were more likely to recur in the lymph nodes, in distant, or multiple locations. This suggests that patients with lymph node metastasis are more likely to spread to distant locations through vascular channels, whereas lymph nodes within the radiation field are more sensitive to radiotherapy, resulting in better local control. Therefore, this supports the inclusion of lymph node metastasis in stage IIIC in the 2018 FIGO staging system.

In terms of the distribution of recurrent diseases, we found 109 patients with local recurrences in the radiation field, and among them, 65 patients (cervix, vagina, parametrium) had central recurrences, mainly in the cervix and vagina, consistent with the report of Schieda et al. In univariate analysis, a pre-brachytherapy tumor size > 2 cm was significantly correlated with local recurrence in cervical squamous cell carcinoma. In multi-factor analysis, it was marginally significant. A recent study [26] showed that a CTVHR > 45 cm3 had a significant impact on LR. Increasing the volume of CTVHR reduced the absolute effect of a specific dose and decreased the probability of local tumor control. Sun et al. [39] discussed the relationship between tumor volume reduction rate and prognosis in 217 patients with late-stage cervical cancer, finding that the tumor volume reduction rate was a powerful prognostic parameter.

This study has limitations, being retrospective and single-center, and the model has not been validated in other regions or populations. In addition, recent studies have shown that non-HPV-related cervical cancer has a worse prognosis than HPV-related cervical cancer. Previous studies have included factors such as abortion times, smoking, age of first sexual activity, and HPV infection in the analysis of risk factors, while the factors included in this study are relatively limited. Given the complexity of cancer development, there may be common mechanisms shared across different cancer types, hence, pan-cancer analysis of genes of interest, especially those genes that might play common roles in multiple cancer types, can contribute to clinical cancer diagnosis, prognosis, and therapies.

Conclusion

In conclusion, this study preliminarily explored the risk factors for recurrent or metastatic in patients with locally advanced cervical cancer after RT. Pathological type, 2009 FIGO stage, SCC value at diagnosis, pre-brachytherapy cervical tumor size, lymph node metastasis, and CCRT had a significantly influence on patient prognosis. Recurrence was significantly correlated with pathological type, 2009 FIGO staging, SCC value at diagnosis, pre-brachytherapy cervical tumor size, and lymph node metastasis. Among them, pathological type, SCC value at diagnosis, and lymph node metastasis were independent influencing factors for DM in patients, while pre-treatment SCC was an independent influence on LR. In the future, it is expected to further establish recurrence-related factors in multicenter and large-sample studies, to establish an ideal recurrence prediction model, and to actively screen people at high risk of recurrence to improve their survival rates.

Abbreviations

RT	radiotherapy
CCRT	concurrent chemoradiotherapy
LNM	lymph nodemetastasis
DSI	depth of stromal invasion
OS	overall survival
SCC-Ag	squamous cell carcinoma antigen
LR	local recurrences
DM	distant metastases

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None.

Author contributions

HML and XJZ conceived and designed the study. CFW and XJL collected patient data. XJZ and CFW analyzed and interpreted the patient data. CFW was a major contributor in writing the manuscript. XJZ and QX revised the manuscript. XJZ and HML reviewed the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The present study was approved by the Ethic Committee of Zhejiang Cancer Hospital, and all participants gave written informed consent.

Consent for publication

Informed consent was obtained from all individual participants included in the study.

Competing interests

The authors declare no competing interests.

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