



Prognosis of stage III cervical cancer: a two-way outcome study

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Background: Cervical cancer is the second most common female malignancy worldwide, and the prognosis of patients with the locally advanced stage is poor, with a high risk of recurrent. This study aimed to explore the effect factors that influence the overall survival (OS), progression-free survival (PFS), and quality of life in patients with stage III cervical cancer.

Methods: A two-way follow-up method was utilized to collect information from patients with stage III cervical cancer. Survival analyses were performed by the Kaplan-Meier method and Cox regression model. Multiple linear regression was used to analyze the factors related to quality of life.

Results: Four hundred and sixty subjects were enrolled in this study. The median follow-up time was 28 months (range, 1–51 months). The 3-year OS and PFS rates were 69.0% and 55.0%, respectively. Primiparous age above 30 years, age at diagnosis below 40 years, lymph node metastasis, non-squamous cell carcinoma, and larger tumors were risk factors of OS and PFS, while the protective factors were weight loss, good mental status, and standardized treatment. The quality of life was better in patients with the following characteristics: younger age at diagnosis, active review according to medical orders, and earlier return to society.

Conclusions: Primiparous age above 30 years was a poor prognostic factor for OS, PFS, and quality of life. The common factors relevant to prognosis were confirmed to be significant.

Keywords: Stage III cervical cancer; prognosis; risk factors; survival analysis; quality of life

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Introduction

With an estimated 570,000 new cases and 311,000 deaths in 2018, cervical cancer is the second most common female malignancy worldwide; 1 in 75 women develop cervical cancer during a lifetime (1). In China, cervical cancer is

the second leading cause of cancer death among women, and there were over 102,000 new cases and 30,000 deaths in 2014 (2), making it a major public health problem. Approximately two-thirds of patients in developing countries have locally advanced stage disease at diagnosis,

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and the prognosis of these patients is poor, with a high risk of metastasis or relapse (3,4). Although the 5-year survival rate of stage III cervical cancer has increased by 30–35% in recent years (5), its prognosis is still unsatisfactory.

Although randomized controlled trials (RCTs) are regarded as the best study design for producing evidence of an intervention, ethical limitations and the generalization of their findings restrict the application of this design, and it is difficult to interpret the complex and diverse clinical scenarios associated with their findings (6,7). In contrast, with the increase in the digitization, availability, and accessibility of clinical information, outcome studies based on electronic medical records and other resources have been widely performed (8,9). Such studies on the prognosis of cervical cancer have mainly focused on treatment effectiveness or death by analyzing the influence of various clinicopathological factors (10,11). In this study, we used the two-way outcome study method to comprehensively analyze information from patients with stage III cervical cancer to determine the effect factors that influence overall survival (OS), progression-free survival (PFS), and quality of life, thus providing evidence for the improvement of the prognosis of these patients.

Methods

Patients

Patients with cervical cancer who were treated at Harbin Medical University Cancer Hospital from 1 January 2013 to 31 December 2015 were enrolled. The inclusion criteria were: International Federation of Gynecology and Obstetrics (FIGO) stage III cervical cancer; no other malignant tumors at diagnosis; and initial treatment at this hospital. The study was approved by the ethics committee at Harbin Medical University in Harbin, China.

Data collection

Case information collected during the first treatment were extracted from the Health Records Management System (Microsoft SQL Server 2012) using the Visual C# language and were associated by unique variable identification (ID). The required data were converted from text format and were entered into a database established using Epi Info 3.5.1; the required data included data of demographic characteristics, clinical stage, histological morphology, auxiliary examination, and treatment. Weight change

and mental status were based on the patients' complaint and doctor's assessment at the time of admission. Tumor diameter and lymph node status were assessed by magnetic resonance imaging and computed tomography at baseline.

Treatment

External beam radiotherapy (EBRT) was performed with a dose of 1.8 Gy per fraction five times per week for a total dose of 45–51 Gy; the dose was increased to 63.5 Gy in areas that were lymph-node-positive. Intra-cavity brachytherapy (ICBT) was delivered to point A (a reference location 2 cm lateral and 2 cm superior to the cervical os) once weekly during EBRT, and the total dose was 30 Gy. Chemotherapy was administered according to the following regimens: weekly platinum drugs or plus paclitaxel every 3 weeks. If the functions of the liver, kidney, and heart were too poor to tolerate chemotherapy or if the patients had other considerations, radiotherapy alone was performed.

Follow-up

From treatment completion until June 2017, the patient follow-up included hospital review and a questionnaire-based telephone survey. Hospital review was scheduled every 3 months for the first year and every 6 months from the second to the fifth years. Routine and gynecologic examinations were performed at each appointment to track disease progression. Suspected cases of recurrence were confirmed by biopsy or MRI. The questionnaire-based telephone survey was conducted by pre-trained investigators each year. The administered questionnaire was based on the Functional Assessment of Cancer Therapy-Cervix and other related scales, and it comprised five dimensions including the patient's survival status, disease progression, physical status, social/family status, and mental status. The summary score ranged from 0 to 100, where a higher score indicated a better quality of life. Family care, work load, and number of reviews 1 year after treatment were considered as independent variables.

Outcomes measures

The primary outcome measure was OS. Secondary outcomes included PFS and patient-reported quality of life. OS was defined as the time from diagnosis to cervical cancer-related death, and PFS was defined as the time from diagnosis to recurrence (including local relapse and distant

Table 1 Characteristics of the patients

Variable	Subgroup	N	%
Age at diagnosis (years)	≤40	32	7.0
	41–50	135	29.3
	51–60	174	37.8
	61–70	92	20.0
	>70	27	5.9
Medical insurance	Urban	250	54.3
	Rural	153	33.3
	Private expense	35	7.6
	Others	22	4.8
Pregnancy (times)	0	23	5.0
	1–2	196	42.6
	3–4	172	37.4
	5	69	15.0
Primiparous age (years)	<20	61	13.3
	20–24	214	46.5
	25–29	139	30.2
	≥30	46	10.0
Menopausal status	Yes	276	60.0
	No	184	40.0
Abortion (times)	0	188	40.9
	1–2	230	50.0
	>2	42	9.1
Hypertension	Yes	60	13.0
	No	400	87.0
Heart disease	Yes	38	8.3
	No	422	91.7
Family history	Yes	40	8.7
	No	420	91.3
Histology	SCC	429	93.3
	Adenocarcinoma	19	4.1
	Others	12	2.6
Tumor diameter (cm)	<4	182	39.6
	≥4	278	60.4
LNM	Positive	192	41.7
	Negative	268	58.3
CCRT	Yes	341	74.1
	No	92	20.0
	Incomplete	27	5.9

LNM, lymph nodal metastasis; SCC, squamous cell carcinomas; CCRT, concurrent chemotherapy radiotherapy.

metastasis) or all-cause death. Local relapse meant that the recurrent tumor was located in the pelvic cavity, and distant metastasis was defined as a recurrent tumor that was located in tissues or organs outside the pelvic cavity.

Statistical analysis

Data sorting, cleaning, and all statistical analyses were performed using SPSS 17.0. Uni- and multi-variate analyses of OS and PFS were performed using the Kaplan-Meier method and Cox proportional hazards regression model, respectively. Analysis of variance, linear correlation, and multiple linear regression was used for uni- and multi-variate analyses of quality of life. P values <0.05 were considered statistically significant.

Results

Patient characteristics

The patients' characteristics are summarized in *Table 1*. A total of 460 subjects were enrolled in this study, and 32 patients (7.0%) were younger than 40 years. Among them, the major histological subtype was squamous cell carcinoma (SCC; 93.3%); 60.4% of the patients presented with bulky tumors (≥4 cm), and 41.7% were lymph-node-positive. In total, 341 patients (74.1%) underwent concurrent chemoradiotherapy (CCRT), 92 patients (20%) received treatments other than CCRT, and 27 patients (5.9%) did not complete standardized treatment.

Follow-up

The median follow-up time was 28 months (range, 1–51 months). At the end of the follow-up, survival status and disease progression were assessed in the 460 patients: 119 patients died of cervical cancer-related causes (75 of these patients showed recurrence); of the 341 survivors, the number of patients with recurrence was 54, and 65 patients were lost to follow-up during the telephone interview; thus, the quality of life was unknown.

Survival analysis

The 3-year OS and PFS rates were 69.0% and 55.0%, respectively (*Figure 1*). As assessed by the Kaplan-Meier method, age at diagnosis (P=0.011), primiparous age (P=0.001), weight change (P<0.001), mental status (P=0.004)

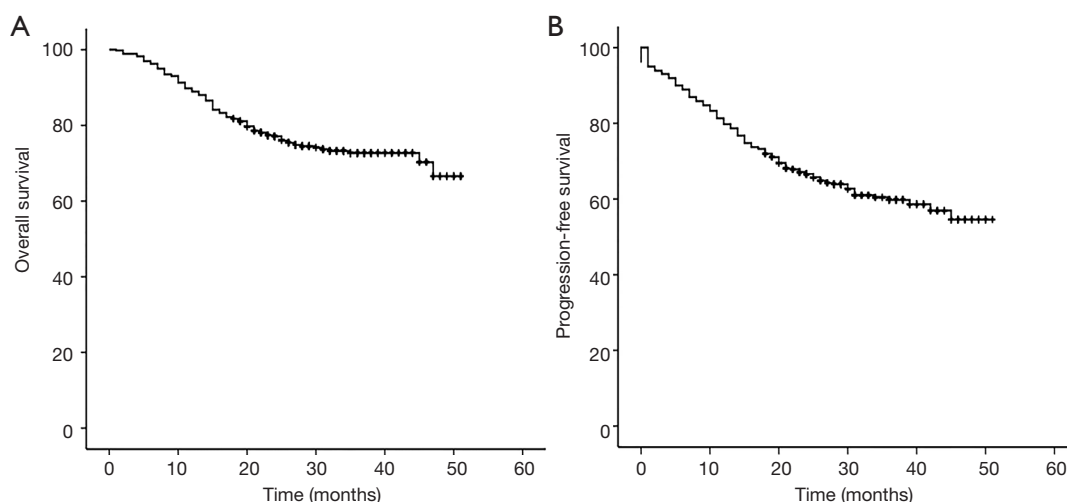


Figure 1 Survival curves of patients with stage III cervical cancer. (A) OS curve. (B) PFS curve. OS, overall survival; PFS, progression-free survival.

at admission, tumor diameter ($P=0.030$), lymph node metastasis (LNM; $P<0.001$), and CCRT use ($P<0.001$) were identified as significant factors for OS (Table 2 and Figure 2). Similar correlation results were obtained for PFS, but PFS was also significantly affected by histology ($P=0.032$) (Table 2 and Figure 3). Among the above factors, LNM, weight change, and CCRT use were included in the Cox proportional hazards regression model in Table 3. Only weight change was associated with OS.

Quality of life

The scores of overall quality of life, disease status, physical status, social/family status, and mental status for the 276 survivors were 85.4 ± 10.0 , 31.1 ± 3.0 , 32.8 ± 4.6 , 12.0 ± 2.3 , and 8.5 ± 2.8 , respectively; all modules were significantly related. The factors related to overall quality of life were age at diagnosis, disease progression, family care, work load, and number of reviews 1 year after treatment. Among these factors, family care and disease progression exerted an influence on all dimensions (Table 4). Next, multivariate linear regression analysis was performed using overall quality of life as a dependent variable, and the factors in Table 5 were included as independent variables. Disease progression, age at diagnosis, primiparous age, and work load 1 year after treatment were independent determinants of overall quality of life and explained 28.9% of the variation (Table 5).

Discussion

Recently, the OS of stage III cervical cancer has increased by 30–35% (5). A previous study reported that the 3-year OS and PFS rates were 61.3% and 54.8% for stage III disease (12). In the present study, the 3-year OS and PFS rates were 69.0% and 55.0%, respectively. The observation that the OS rate was higher than that in previous studies may be attributable to the fact that some patients were followed-up for less than 3 years.

LNM, non-SCC, and larger tumors were previously reported as poor prognostic factors for cervical cancer (13–15). This study had similar results, but only histology had a significant effect on PFS. This result may be explained by the small number of patients with non-SCC. CCRT is established as the standard treatment for patients with locally advanced cervical cancer as it improves OS and PFS rates (16–18). However, we found that although CCRT could improve OS and PFS rates, there was no significant difference in outcomes between patients with and without CCRT (Table 3). The reason may be that there was an intersection in the survival curve between two groups (Figures 2H, 3H). The OS and PFS rates of the two groups were similar within 12 months, with the CCRT group having slightly lower values, possibly because the incidence of adverse reactions increased during CCRT. However, similar to that in the abovementioned previous studies, the OS and PFS after 1 year were significantly higher in the CCRT group than in the no-CCRT group.

Table 2 Univariate analysis of OS and PFS

Variables	Subgroups	Number	OS			PFS		
			Case	χ^2	P value	Case	χ^2	P value
Age at diagnosis (years)	≤40	32	14	6.538	0.011	19	8.887	0.003
	>40	428	105			154		
Primiparous age (years)	<30	414	98	11.609	0.001	148	7.629	0.006
	≥30	46	21			25		
Histology	SCC	429	107	2.893	0.089	156	4.577	0.032
	Others	31	12			17		
Tumor diameter (cm)	<4	182	37	4.736	0.030	56	6.164	0.013
	≥4	278	80			115		
LNM	Positive	192	69	17.524	<0.001	98	27.077	<0.001
	Negative	268	50			75		
Weight	Not change	34	19	29.287	<0.001	21	14.439	<0.001
	Lose weight	426	100			152		
Mental status	Good	161	30	8.103	0.004	47	8.471	0.004
	General	273	80			114		
	Poor	26	9			12		
CCRT	Yes	341	69	52.519	<0.001	107	43.478	<0.001
	No	92	33			47		
	Incomplete	27	17			19		

LNM, lymph nodal metastasis; CCRT, concurrent chemotherapy radiotherapy; OS, overall survival; PFS, progression-free survival.

Body mass index (BMI) itself was not identified as a prognostic factor for OS and PFS in this study. This was inconsistent with the results reported by a previous study (19). However, we found that weight loss was a protective factor. At admission, patients who complained of weight loss had higher BMI than those without weight loss; thus, when they lost weight, the BMI tended to be normal, which might prevent the occurrence of adverse outcomes to some extent. The mental state of the patients at admission was also a prognostic factor. The worse the mental state of the patients at admission, the worse was their prognosis. One reason for this phenomenon might be the fact that poor mental state might exacerbate the patient's physical burden, thus increasing the risk of adverse outcomes.

The median age of the enrolled patients was 54 years. In total, 67.1% patients were aged between 40 and 60 years, and this age group was consistent with the age of high cervical cancer incidence. Whether age at diagnosis is a prognostic risk factor of cervical cancer is controversial,

and most studies have indicated that the prognosis of young patients with locally advanced disease is worse than that of older patients (20,21). In this study, patients younger than 40 years were more susceptible to disease progression, and their median OS and PFS were 35 and 23 months, respectively, which were lower than those of older patients.

In this study, primiparous age above 30 years was a prognostic risk factor in patients with stage III cervical cancer. Previous reviews have strongly suggested that marital history, such as younger age at marriage and childbirth, multiple pregnancies, and multiple births, were risk factors for cervical cancer incidence (22,23). However, the impact of these factors on prognosis has been seldom reported. We found that patients with primiparous age above 30 years were characterized by older age at marriage and the last childbirth, fewer pregnancies and births, and younger age at diagnosis compared with other patients. The increased risk of incidence and poor prognosis may thus be explained by increased burden of the uterus and other body

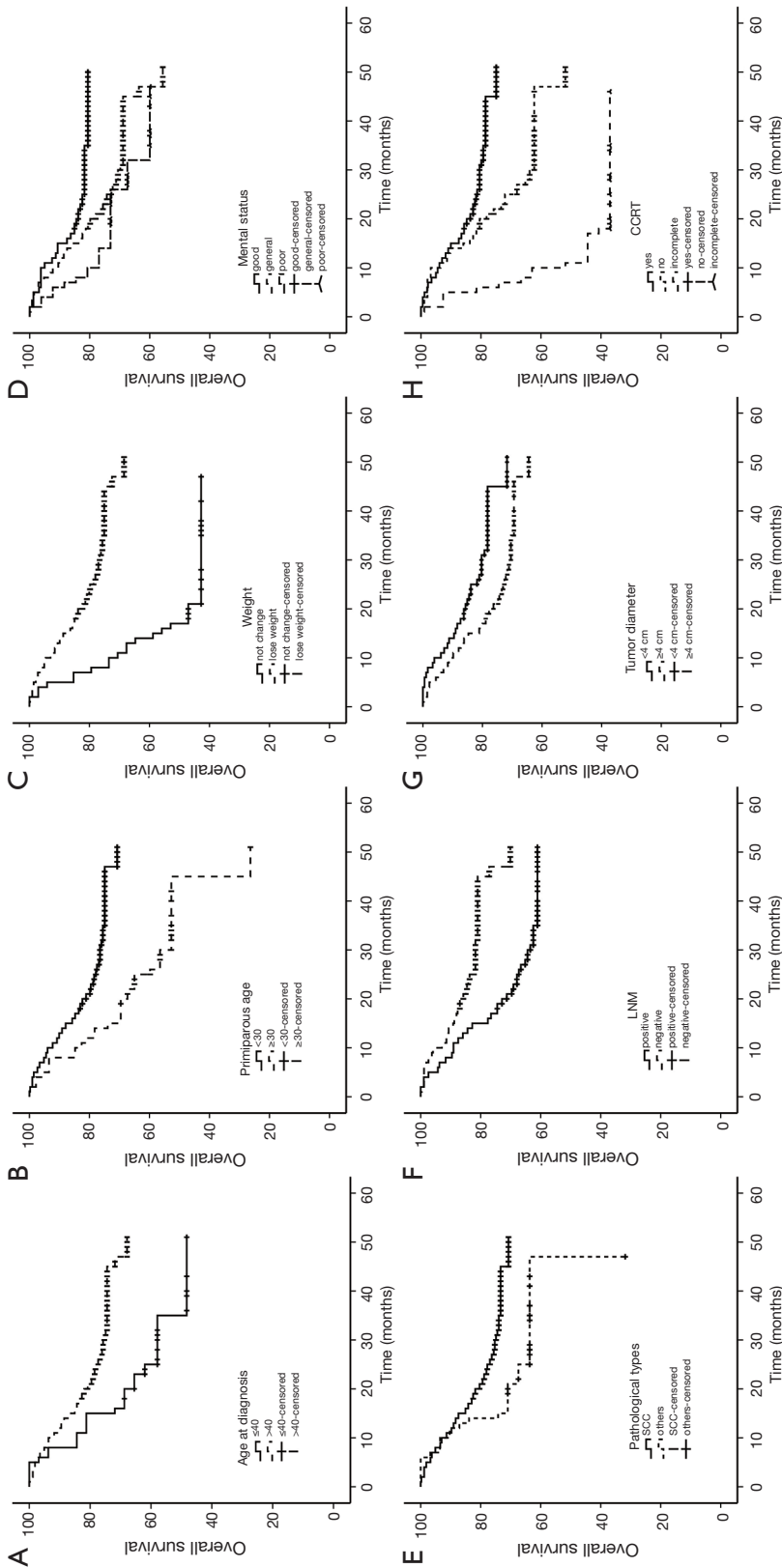


Figure 2 OS curves of patients with stage III cervical cancer. Factors from (A) to (H) were age at diagnosis, primiparous age, weight change, mental status, pathological types, LNM, tumor diameter, and CCRT, respectively. OS, overall survival; LNM, lymph nodal metastasis; CCRT, concurrent chemotherapy radiotherapy.

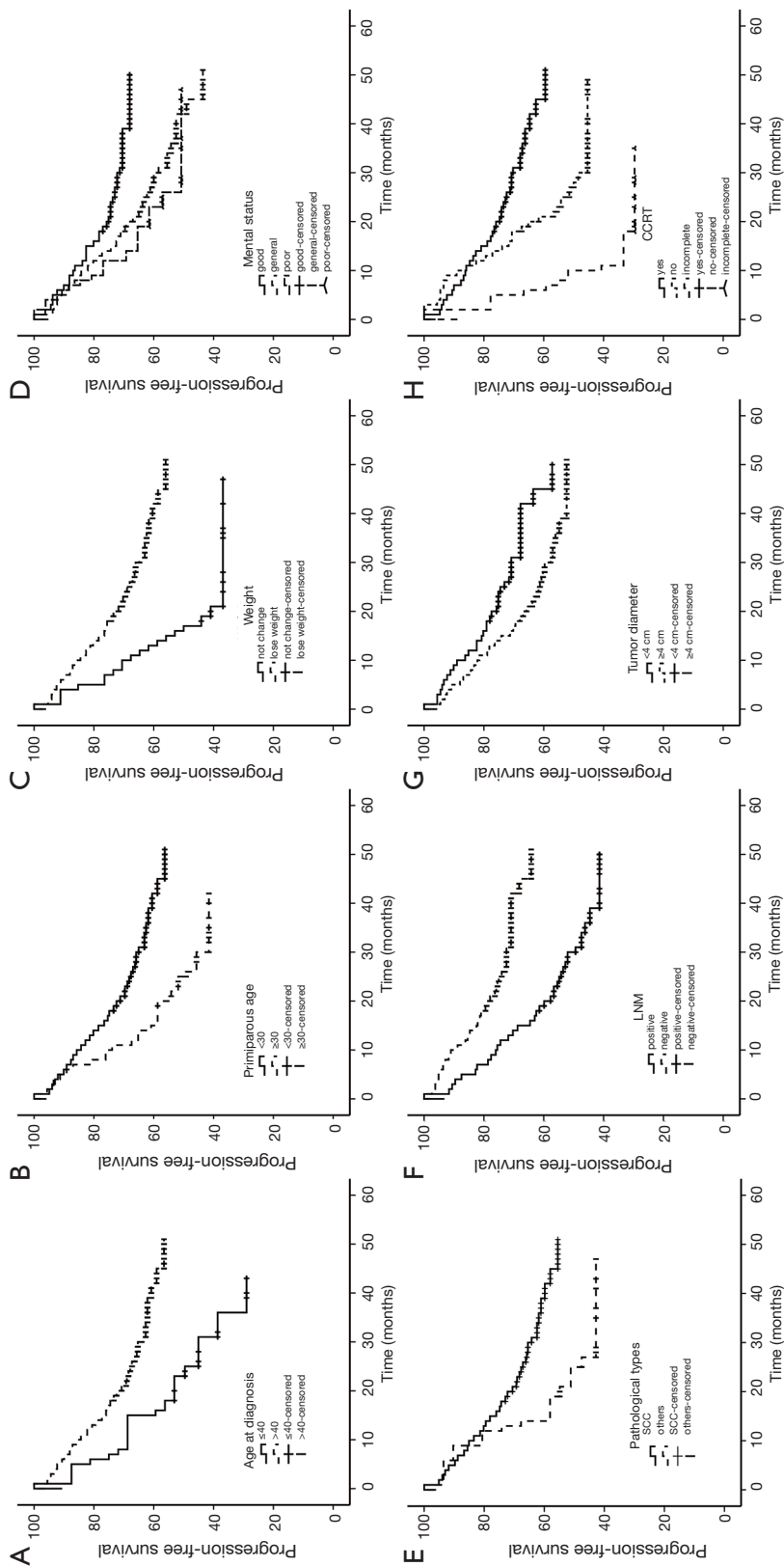


Figure 3 PFS curves of patients with stage III cervical cancer. Factors from (A) to (H) were age at diagnosis, primiparous age, weight change, mental status, pathological types, LNM, tumor diameter, and CCRT, respectively. PFS, progression-free survival; LNM, lymph nodal metastasis; CCRT, concurrent chemotherapy radiotherapy.

Table 3 Multivariate analysis of OS and PFS

Variables	OS			PFS		
	P value	HR	95% CI	P value	HR	95% CI
LNМ	<0.001	0.354	0.234–0.534	<0.001	0.402	0.286–0.564
Weight	0.003	0.422	0.238–0.750	0.172	0.690	0.405–1.175
CCRT	<0.001			<0.001		
No	0.173	1.389	0.866–2.228	0.083	1.415	0.955–2.095
Incomplete	<0.001	8.348	4.534–15.370	<0.001	5.309	2.996–9.408

LNМ, lymph nodal metastasis; CCRT, concurrent chemotherapy radiotherapy; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

Table 4 Univariate analysis of quality of life

Variables	Overall conditions		Disease condition		Physiological state		Social/family state		Mental state	
	r/F ^a	P value	r/F	P value	r/F	P value	r/F	P value	r/F	P value
Continuous (r)										
Age at diagnosis	-0.136	0.024	-0.060	0.323	-0.175	0.004	-0.246	<0.001	0.059	0.327
Menarche age	-0.098	0.104	-0.012	0.845	-0.155	0.010	-0.104	0.083	-0.001	0.981
Marry age	-0.104	0.084	-0.032	0.592	-0.080	0.186	-0.069	0.251	-0.152	0.011
Primiparous age	-0.099	0.109	-0.006	0.918	-0.069	0.260	-0.101	0.100	-0.150	0.014
Age at last delivery	-0.112	0.068	-0.028	0.652	-0.150	0.014	-0.129	0.035	-0.042	0.499
Categorical (F)										
LNМ	3.142	0.077	6.081	0.014	2.017	0.157	0.283	0.595	0.796	0.373
Medical insurance	2.149	0.094	1.661	0.176	2.183	0.090	0.097	0.961	3.183	0.024
Review times	3.453	0.017	4.991	0.002	2.507	0.059	3.223	0.023	1.022	0.383
Distant metastasis	30.644	<0.001	161.107	<0.001	8.65	0.004	6.826	0.009	2.326	0.128
Relapse	53.858	<0.001	219.143	<0.001	14.511	<0.001	14.167	<0.001	8.984	0.003
Family care	4.26	0.018	6.025	0.004	3.361	0.041	6.546	0.003	6.366	0.003
Work volume	6.996	<0.001	3.877	0.010	6.173	<0.001	7.742	<0.001	1.86	0.137

^a, r/F: r = correlation coefficient; F = F value of analysis of variance. LNМ, lymph nodal metastasis.

functions with increased primiparous age and the increased levels of sex hormones and decreased immunity during pregnancy (24,25). We speculate that these factors may be among the explanations for the recurrence of cervical cancer. Future in-depth studies are needed to clarify this issue.

The focus of the cancer control strategy proposed by World Health Organization in 2005 is not only the reduction of cancer cases but also the improvement of the quality of life of patients and their families (26). To some

extent, quality of life is more important than OS and PFS, especially for patients with advanced cancer. In this study, the quality of life score was higher than those in previous studies (27,28). This is likely because patients might intentionally avoid adverse options when self-reporting. Age at diagnosis, number of reviews, family care, and work load were associated with quality of life in univariate analysis (Table 4). The risk of chronic disease in patients increases with age, which might lead to a reduction in their quality of life. Frequent review, according to medical

Table 5 Multivariate linear regression analysis of quality of life

Variables	Regression coefficient	Standard regression coefficient	T value	P value
Constant term	109.883		17.388	<0.001
Relapse	-13.190	-0.357	6.331	<0.001
Distant metastasis	-7.622	-0.219	3.902	<0.001
Age at diagnosis	-0.198	-0.168	-3.010	0.003
Primiparous age	-0.477	-0.142	-2.499	0.013
Work volume				
>50%	-1.384	-0.061	-1.072	0.285
≤50%	-3.336	-0.124	-2.205	0.028
None	-7.016	-0.173	-3.078	0.002

Model parameters: F=8.024, P<0.001, R²=0.289.

orders, is useful in detecting the patients' conditions in a timely manner, thus effectively preventing the occurrence of adverse outcomes. Good care from family members and returning to work within 1 year after treatment can improve a patient's sense of social identity. Multivariate analysis (Table 5) showed that the quality of life decreased with increased primiparous age, which may be explained by reasons similar to those discussed for the survival analysis. In this study, there was no correlation between clinicopathologic factors and quality of life, possibly because of the low survival rate of patients with high-risk factors. Considering the patients' privacy and resistance, we did not analyze the association of quality of life with economic conditions and family burdens, considered to be influencing factors in previous studies (29,30). However, the relationship between medical insurance and the quality of life was analyzed, showing that this factor was only related to the mental state of patients.

Importance of the study

This was an outcome study aiming to achieve bidirectional translation between practice and theory. Regarding the translation from practice to theory, most data sources of outcome studies are electronic medical records and insurance databases, which were established at an earlier date in developed countries. In China, the digitization of electronic medical records began comparatively late and developed slowly. Moreover, the database systems vary, not only at individual hospitals but also between different

hospitals. These factors have resulted in low availability of, accessibility to, and utilization of real-world data. However, in this study, we overcame these difficulties to merge medical record files in different formats. All databases in the Health Records Management System were integrated and converted to the required data format, thus ensuring comprehensiveness and consistency, while telephone follow-ups were conducted to ensure the accuracy of data.

As for translating from theory to practice, we found that primiparous age above 30 years, age at diagnosis below 40 years, LNM, non-SCC, and larger tumors were risk factors of OS and PFS, while the protective factors were weight loss, good mental status, and standardized treatment. The quality of life was better in patients with the following characteristics: younger age at diagnosis, active review according to medical orders, and earlier return to society. Patients with these high-risk factors should undergo enhanced intervention and be actively followed-up to prolong survival and improve their quality of life.

Strengths and limitations

This study was an outcome study exploring not only OS but also the PFS and quality of life of patients with stage III cervical cancer. Despite being observational in nature, the two-way outcome study design, including a retrospective investigation and prospective follow-up, overcame some of the limitations of RCTs. The limitations of this study are the general limitations of an observational study and its single-center design, although the sample size was not small.

Conclusions

Primiparous age above 30 years was a poor prognostic factor of OS, PFS, and quality of life. Common factors such as age at diagnosis below 40 years, LNM, non-SCC, and larger tumors were confirmed to be poor prognostic factors of OS and PFS, while the protective factors were weight loss, good mental status, and standardized treatment. The quality of life was better in patients with a younger age at diagnosis, active review according to medical orders, and earlier return to society.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2020.02.70>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the ethics committee at Harbin Medical University in Harbin, China. All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

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