Treatment of Osteosarcoma from the Spine: A Population-Based Database Study

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Research

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Abstract

Purpose

The treatment of osteosarcoma of the spine remains controversial. Our aim is to explore the treatment of patients with spinal osteosarcoma.

Methods

We analyzed the data collected 727 spinal osteosarcoma patients from the Surveillance Epidemiology and End Results (SEER) databases between 1973 and 2015. X-tile software was performed to find the optimal cut-off values of age and economic income. Univariate and Multivariate Cox analyses were used to identify the independent prognostic factors. Logistic regression model was conducted to clear the factors associated to surgical compliance; Kaplan-Meier estimator method was adopted to analyze the Overall survival (OS) and Cancer-specific survival (CSS).

Results

Among 727 eligible spinal osteosarcoma patients, 370 (50.9%) patients received surgical treatment, 357 (49.1%) cases without surgery. There were significant differences in the effects of age at diagnosis, SEER historic stage and tumor grade on surgical treatment (All $P < 0.05$). Surgery was an independent prognostic factor for OS and CSS of spinal osteosarcoma patients. Spinal osteosarcoma patients undergone surgery group showed favorable survival than the other group.

Conclusions

Surgery can provide survival benefits for patients with osteosarcoma of the spine. Spinal osteosarcoma patients with undergone surgery have favorable survival and surgery can become a suitable treatment for patients.

Introduction

Osteosarcoma is the most common primary malignant bone tumor(1). The characterized of osteosarcoma is the proliferation of tumor cells that directly form immature bone or bone-like tissue(2). Currently, the global annual incidence of osteosarcoma is approximately 1 to 3 per 1,000,000 population(3, 4). Osteosarcomas tend to occur in adolescents and has been the second leading cause of cancer-related deaths in pediatric age group (5). Osteosarcoma affects more men than women(6). The most common site of osteosarcoma is the metaphysis of long bones and less often the skull, jaw, or pelvis(7). Osteosarcoma that occurs in the spine has a poor prognosis compared to the high incidence of osteosarcoma of the limbs, accounting for only 3% of all primary osteosarcomas(8). Since osteosarcoma has high malignant degree, poor prognosis, high mortality and easy to occur distant metastasis, which has a deep impact on society(9).

Surgical treatment is one of the first choices for the treatment of osteosarcoma. Amputation has been the gold standard for treating osteosarcoma(10). However, the overall 5-year survival rate is low, and most patients die within 1 year after diagnosis(11). In recent years, with the advent of neoadjuvant chemotherapy, the safety of limb salvage surgery has been improved. Limb salvage surgery is generally used in combination with chemotherapy, which has obvious curative effects on tumors, and plays a very important role in clinical practice. It has gradually replaced amputation as the first choice and mainstream surgery for limb osteosarcoma. 80 to 90 of the 100 patients underwent limb salvage surgery, and the disease-free survival probability also increased from about 20–60%(12, 13). However, whole tumor resection is not easy to use for the treatment of spinal osteosarcoma, and spinal osteosarcoma has strong local invasiveness and high local recurrence rate. Moreover, spinal osteosarcoma may spread through early blood-borne metastases, and the effect of surgical resection on prolonging survival is unclear(14).

In previous case series, factors such as age at diagnosis, tumor size and location, pathology, presence and location of metastases, surgical strategy, surgical margins and histological responses, and acceptance of chemotherapy were reported to affect overall survival (15–17). The effect of surgical treatment of spinal osteosarcoma on overall survival is currently unclear, due to the small proportion of patients with spinal osteosarcoma. The treatment of spinal osteosarcoma still confuses many surgeons, even experienced surgeons. In our study, we used data from the SEER cancer registry to explore treatment options for patients with spinal osteosarcoma to improve the prognosis of osteosarcoma.

Patients And Methods

Data source and patients

The data presented in this paper were retrieved from the Surveillance Epidemiology and End Results (SEER) database, funded by the National Cancer Institute. The current SEER database includes 18 population-based cancer registries acquired between 1973 and 2015, which represent patient demographics and cancer characteristics for about 28 percent of the U.S. population(18). SEER data can be published for cancer-based epidemiological studies and survival analysis. All case data was retrieved using the SEER*Stat application (version 8.3.5).

Study population

Retrospective case lists were obtained from the SEER database from 1973 to 2015. We collected data by limiting the histological types of osteosarcoma with ICD-O-3 morphology codes (n=6225,9180-9187/9192-9194/9200). Histological types were based on the WHO classification of salivary tumors and were limited to osteosarcoma, nos (9180), chondroblastic osteosarcoma (9181), fibroblastic osteosarcoma (9182), telangiectatic osteosarcoma (9183), osteosarcoma in Paget's disease of bone (9184), small cell osteosarcoma (9185), central osteosarcoma (9186), intraosseous well differentiated osteosarcoma (9187), parosteal osteosarcoma (9192), periosteal osteosarcoma (9193), high grade surface osteosarcoma (9194), intracortical osteosarcoma (9195). Site-specific codes were first used to

identify all primary tumors that originated in the osseous spine: C41.2 (vertebral column) and C41.4 (pelvic bones, sacrum, coccyx, and associated joints). Exclusion criteria were as follows (1) unknown marital status at diagnosis (n=16); (2) unknown diagnostic confirmation (n=5). Finally, as shown in **Figure 1**, we left 727 eligible patients diagnosed with osteosarcoma of the spine.

Statistical analysis

Basic information of all selected patients, including diagnosis time, gender, race, age, marital status, and disease-related information, such as radiotherapy, chemotherapy, tumor staging, pathological grade, and treatment methods, can be extracted from the database. According to the chronological order of diagnosis, the patients in the SEER database with a diagnosis span of 42 years were divided into 4 groups. Patients were divided into two groups according to different treatment schemes. We refer to patients undergoing surgery as the surgical treatment group, and those who have not undergone surgery are the non-surgical treatment group.

Statistical analysis was performed using Statistical Program for Social Sciences (SPSS) software version 24. Chi-square analysis was used to evaluate the demographic and clinical characteristics of patients and their correlation with treatment. Kaplan-Meier curve was used to estimate the survival time of each group, and the difference between the curves was analyzed by log-rank test. The Overall survival (OS) time is from the date of diagnosis to death from any reason or the date on which data were censored. Cancer-specific survival (CSS) is a net survival indicator that estimates the likelihood of osteosarcoma survival of the spine in our study. Univariate and multivariate Cox proportional regression models were performed to estimate the hazard ratios (HR) and 95% confidence intervals (CI) to analyze independent prognostic factors. X-tile software was conducted to find the optimal hierarchical age at diagnosis. P-values of less than 0.05 were considered statistically significant.

Results

Identification of cutoff values for age

To determine the optimal age stratification for patients with osteosarcoma of the spine, we constructed an X-tile plot to explore the predicted cutoff values. The age of diagnosis was divided into 3 levels: <48 years, 49-62 years, and > 62 years (**Figure 2**).

Baseline characteristics of patients

Using chi-square test, we studied the demographic and clinicopathological characteristics of patients with osteosarcoma of the spine. The baseline characteristics of the patients are reviewed in **Table I**. After applying exclusion criteria, a total of 727 patients were included in our cohort from 1973 to 2015. Among them, 370 cases were treated by surgery and 357 cases were not treated.

Chi-square test showed that different treatment patterns was related to age at diagnosis ($p<0.001$), marital status ($p<0.001$), SEER historic stage ($p<0.001$), tumor grade ($p<0.001$) radiotherapy ($p<0.001$)

and chemotherapy ($p < 0.001$). Patients younger than 48 years of age choose surgical treatment, while patients older than 62 years old prefer non-surgical treatment. In terms of marital status, married patients accounted for a relatively high proportion (48.0%) of the patients who chose surgery, and divorced or separated patients had poor surgical compliance (4.0%). In SEER tumor staging, patients with regional osteosarcoma of the spine were more likely to receive surgical treatment than patients with distant. As to the chemotherapy, the proportion of patients who received chemotherapy chose surgery treatment was significantly higher than that of patients with no chemotherapy. However, this situation is exactly the opposite in radiotherapy.

Survival analysis

Comparison of the survival outcome between different treatment groups

By analyzing the Kaplan-Meier curve with a log-rank test, we found that age at diagnosis ($p < 0.001$), Year of diagnosis ($p = 0.008$) marital status ($p = 0.002$), SEER historic stage ($p < 0.001$), tumor grade ($p < 0.001$), surgery ($p < 0.001$), radiotherapy ($p < 0.001$) and chemotherapy ($p < 0.001$) were associated with OS (**Table II**). However, marital status and chemotherapy treatment were not associated with CSS (**Table II**). The OS median survival time of patients undergoing surgery was 27 months and that of patients without surgery was 8 months (**Table II** and **Figure 3a**). For CSS median survival time, patients undergoing surgery was 44 months and patients without surgery was 11 months (**Table II** and **Figure 3b**). In both OS and CSS, surgically treated patients had significantly longer survival time than non-surgically treated patients (**Figure 3**).

Cox regression analysis for the prognostic factors

Cox regression was used to analyze prognostic factors for OS and CSS (**Table III** and **Table IV**). Univariate analysis showed that age, marital status, SEER historic stage, surgery and radiotherapy were significant influence factors for OS and CSS. However, chemotherapy had no effect on CSS. Compared with patients received surgery, patients without surgery had a worse OS ($HR = 2.69$, 95%CI: 2.27-3.19, $P < 0.001$) and CSS ($HR = 2.53$, 95%CI: 2.06-3.10, $P < 0.001$). In terms of radiotherapy, patients who have not received chemotherapy was significantly associated with a better OS ($HR = 0.67$, 95%CI: 0.56-0.79, $P < 0.001$) and CSS ($HR = 0.62$, 95%CI: 0.50-0.77, $P < 0.001$). For chemotherapy, without chemotherapy had a higher risk in OS ($HR = 1.39$, 95%CI: 1.18-1.65, $P < 0.001$).

Objective to explore which variables have significant influence on the prognosis of patients with osteosarcoma of the spine. We further used multivariate analysis to confirm that surgery was an independent prognostic factor for OS and CSS. Compared to patients with surgery treatment, the risk was increased when the patients without surgery in the OS ($HR = 1.66$, 95%CI: 1.36-2.02, $P < 0.001$) and CSS ($HR = 1.56$, 95%CI: 1.24-1.97, $P < 0.001$). Moreover, for age and SEER historic stage, multivariate analysis also showed statistically significant difference in both OS and CSS.

Factors willing to undergo surgery

We used multivariate logistic regression model to determine the factors that influence whether to undergo surgery. When adjusting for other factors, some variables were proved to be significantly correlated with rejection of surgery (**Figure 4**). We found that the influencing factors have the following aspects: age, grade, and SEER historic stage. Patients who were 62 years or older (OR, 3.86; 95% CI, 2.63-5.56; $P < 0.001$), at regional stage (OR, 6.05; 95% CI, 3.71-9.87; $P < 0.001$) and at unstaged stage (OR, 4.62; 95% CI, 2.45-8.72; $P < 0.001$). Additionally, Patients who were at histological grade $\geq$ (OR, 0.79; 95% CI, 0.14-4.62; $P = 0.797$) were more willing to accept surgical therapy.

Trends in survival stratified by the age at diagnosis and SEER historic stage

In order to better demonstrate that surgery as a single factor had a significant impact on the survival of patients with osteosarcoma of the spine. Patients were stratified by the age at diagnosis and SEER historic stage to investigate the trends in survival. For OS and CSS, we found that regardless of the age stage, patients in surgery group had more favorable survival than the other group (**Figure 5**). Similarly, the outcome in SEER historic stage had the same characteristics (**Figure 6**).

Discussion

Osteosarcoma of the spine is a rare malignant tumor with the potential for local invasive destruction and systemic metastasis, and is considered to have a poor prognosis(19, 20). Osteosarcoma mainly occurs in adolescents or young adults, which seriously damages social productivity(21). Surgery is one of the effective treatments for osteosarcoma(22), but osteosarcoma of the spine is excluded in a considerable proportion of cases due to its aggressiveness and the special anatomical structure adjacent to the spinal cord and nerve roots(23). Currently, there are few studies on the optimal treatment for osteosarcoma of the spine. Whether surgical treatment is appropriate for osteosarcoma of the spine remains controversial. Therefore, it is of great significance to conduct the studies.

Surgery is considered to be an effective way to treat some malignant tumors, which is derived from some characteristics of the tumor itself. Many literatures have confirmed the rationality of this treatment. Khan reports that primary tumors could lead to metastatic spread, and surgery could reduce the burden on the tumor, thereby reducing the possibility of metastatic spread(24). Cook AD et al believed that reducing tumor load may reduce the occurrence of serious complications such as hypoproteinemia and cachexia, thus reducing the risk of cancer death(25). In addition, Surgical removal of the tumor results in a reduction in volume, which can improve the effect of later chemotherapy and reduce the risk of local recurrence(26). These theories confirm the mechanism by which surgery can improve tumor patient survival.

Similarly, we considered that surgery can improve the survival time of patients with osteosarcoma of the spine. The outcomes of study were in line with our conjecture. According to our criteria, a total of 727 patients were included, of which 370 (50.9%) patients had surgery and 357 (49.1%) patients had non-surgical treatment. Survival analysis confirmed that surgical treatment has a significant impact on patient prognosis. In our study, survival of patients undergoing surgery is significantly higher than that of

patients not undergoing surgery. Many clinical studies support aggressive surgical treatment of patients with osteosarcoma of the spine. Surgical patients have a better prognosis, which is consistent with our findings. Ozaki et al evaluated 22 patients with osteosarcoma of the spine and found that the survival of the 5 patients who underwent surgical resection was significantly different from the 17 patients without resection(27). Debraj Mukherjee et al studied 158 patients with osteosarcoma of the spine and found that patients with surgical resection had a better survival advantage(28).

Although studies have shown that age increase is independently related to poor survival(29), in our study it was confirmed that regardless of age, the survival time of surgically treated patients is always higher than that of non-surgical resection. In the same way, even if the stage of osteosarcoma of the spine affects the patient's prognosis(30), our research shows that the effect of surgery on patient survival is beneficial and is an important factor affecting the prognosis. Combining multiple demographic and clinicopathological factors, surgery is still an independent factor. The findings of Pan Y et al also support our point(31). Surgical treatment has a positive impact on the prognosis of patients with osteosarcoma of the spine.

We used logistic regression analysis to find out the effect of age, grade, and SEER historic stage on patients' choice of surgery. Our study found that patients with lower age groups, lower tumor grades, and localized tumor distribution were more likely to undergo surgery. In addition, multiple groups of studies found that age tumor grade and distribution were independent factors affecting prognosis(31, 32). The patients with lower age group, lower tumor grade, and localized tumor distribution have better prognosis. We believe this is due to the fact that these patients received surgical treatment, which resulted in longer survival.

This study has several limitations. First, this study is retrospective and has obvious limitations. Second, the SEER database lacks specific information about the operation, such as the surgical method and the extent of surgical resection. Moreover, because the database cannot accurately provide specific treatment methods, the effects of radiation and chemotherapy on tumors cannot be considered comprehensively. Despite this, the study is based on a fairly large demographic and is still very convincing.

Conclusions

In our research, the SEER database was used to assess the impact of surgery on survival in patients with osteosarcoma of the spine. Surgery can provide survival benefits for patients with osteosarcoma of the spine. Spinal osteosarcoma patients with undergone surgery have favorable survival and surgery can become a suitable treatment for patients.

Declarations

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Availability of data and materials:

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

Authors' contributions:

CT and HZ were involved in the study conception and design. CT and RW collected and assembled data. CT, and HX were involved in data analysis and interpretation. CT wrote the manuscript.

Ethics approval and consent to participate:

This article does not contain any studies with human participants performed by any of the authors. All the data used in our research comes from the publicly available SEER database, which is granted access to the research data (SEER-Stat username: tyang).

Patient consent for publication:

Our study was based on public data from the SEER database. Informed consent was waived because no personally identifiable information was used and there was no interaction with human subjects.

Competing interest:

The authors of this manuscript have no conflict of interest.

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Tables

Table 8.
Baseline demographics and characteristics for patients with osteosarcoma of the spine.

Characteristic	All patients	Surgical group	Non-surgical group	P Value
	N. (%)	N. (%)	N. (%)	
Total	727	370(50.9)	357(49.1)	
Age at diagnosis (y) ^a				< 0.001
< 48	359(0.49)	228(0.62)	131(0.37)	
49–62	127(0.17)	68(0.18)	59(0.17)	
> 62	241(0.33)	74(0.20)	167(0.47)	
Year of diagnosis				0.102
1973–1983	94(0.13)	37(0.10)	57(0.16)	
1984–1994	107(0.15)	56(0.15)	51(0.14)	
1995–2005	230(0.32)	125(0.34)	105(0.29)	
2006–2016	296(0.41)	152(0.41)	144(0.40)	
Sex				0.158
Female	335(0.46)	161(0.44)	174(0.49)	
Male	392(0.54)	209(0.56)	183(0.51)	
Race				0.477
White	596(0.82)	304(0.82)	292(0.82)	
Black	84(0.12)	39(0.11)	45(0.13)	
Other	47(0.06)	27(0.07)	20(0.06)	
Marital status				< 0.001
Married	357(0.49)	178(0.48)	179(0.50)	
Single	269(0.37)	159(0.43)	110(0.31)	
Divorced/Separated	45(0.06)	14(0.04)	31(0.09)	
Widowed	56(0.08)	19(0.05)	37(0.10)	
SEER historic stage				< 0.001

^a The cutoff values of age and economic income were determined by X-tile program.

Percentages may not total 100 because of rounding.

Characteristic	All patients	Surgical group	Non-surgical group	P Value
	N. (%)	N. (%)	N. (%)	
Localized	137(0.19)	95(0.26)	42(0.12)	
Regional	274(0.38)	183(0.49)	91(0.25)	
Distant	238(0.33)	67(0.18)	171(0.48)	
Unstaged	78(0.11)	25(0.07)	53(0.15)	
Grade				< 0.001
I	11(0.02)	8(0.02)	3(0.01)	
II	34(0.05)	29(0.08)	5(0.01)	
III	139(0.19)	75(0.20)	64(0.18)	
IV	215(0.30)	122(0.33)	93(0.26)	
Unknown	328(0.45)	136(0.37)	192(0.54)	
Radiotherapy				< 0.001
Yes	216(0.30)	88(0.24)	128(0.36)	
No	511(0.70)	282(0.76)	229(0.64)	
Chemotherapy				< 0.001
Yes	453(0.62)	258(0.70)	195(0.55)	
No	274(0.38)	112(0.30)	162(0.45)	
^a The cutoff values of age and economic income were determined by X-tile program.				
Percentages may not total 100 because of rounding.				

Table 8.

Kaplan–Meier analysis overall survival and cancer-specific survival for astrocytoma patients.

Characteristic	OS MST (months)	Kaplan-Meier		CSS MST (months)	Kaplan-Meier	
		Log Rank χ^2 test	P value		Log Rank χ^2 test	P value
Age at diagnosis (y) ^a		183.745	< 0.001		89.265	< 0.001
< 48	26.000			35.000		
49–62	14.000			24.000		
> 62	6.000			10.000		
Year of diagnosis		11.759	0.008		9.870	0.02
1973–1983	8.000			13.000		
1984–1994	11.000			18.000		
1995–2005	14.000			24.000		
2006–2016	16.000			22.000		
Sex		2.301	0.129		0.977	0.323
Female	14.000			20.000		
Male	14.000			20.000		
Race		0.208	0.901		1.354	0.508
White	14.000			21.000		
Black	15.000			17.000		
Other	11.000			11.000		
Marital status		65.764	0.002		35.441	0.065
Married	11.000			17.000		
Single	26.000			35.000		
Divorced/Separated	10.000			16.000		
Widowed	5.000			8.000		

^aThe cutoff values of age and economic income were determined by X-tile program.

Percentages may not total 100 because of rounding.

Characteristic	OS MST (months)	Kaplan-Meier		CSS MST (months)	Kaplan-Meier	
		Log Rank χ^2 test	P value		Log Rank χ^2 test	P value
SEER historic stage		139.147	< 0.001		110.560	< 0.001
Localized	31.000			103.000		
Regional	19.000			29.000		
Distant	7.000			11.000		
Unstaged	15.000			27.000		
Grade		27.434	< 0.001		14.103	0.007
I	55.000			-		
II	15.000			-		
III	15.000			20.000		
IV	11.000			18.000		
Unknown	14.000			18.000		
Surgery		143.815	< 0.001		86.471	< 0.001
Yes	27.000			44.000		
No/ Unknown	8.000			11.000		
Radiotherapy		21.532	< 0.001		20.608	< 0.001
Yes	10.000			14.000		
No	16.000			26.000		
Chemotherapy		15.462	< 0.001		1.338	0.247
Yes	17.000			23.000		
No	7.000			16.000		
^a The cutoff values of age and economic income were determined by X-tile program.						
Percentages may not total 100 because of rounding.						

Table 8.
Univariate and multivariate analysis of overall survival (OS) rates.

Characteristic	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95% CI ^a)	P value	Hazard Ratio (95% CI ^a)	P value
Age at diagnosis (y) ^b				
< 48	Reference		Reference	
49–62	1.68(1.34–2.12)	< 0.001	1.80(1.43–2.27)	< 0.001
> 62	3.39(2.81–4.09)	< 0.001	3.02(2.48–3.69)	< 0.001
Year of diagnosis				
1973–1983	Reference		Reference	
1984–1994	0.78(0.58–1.04)	0.088	0.81(0.61–1.09)	0.174
1995–2005	0.73(0.57–0.94)	0.016	0.78(0.60–1.02)	0.074
2006–2016	0.65(0.50–0.84)	0.001	0.63(0.48–0.83)	0.001
Sex				
Female	Reference		—	—
male	1.13(0.96–1.34)	0.137		
Race				
White	Reference		—	—
Black	0.99(0.76–1.29)	0.952		
Others	1.07(0.78–1.48)	0.663		
Marital status				
Married	Reference		—	—
Never married	0.57(0.47–0.69)	< 0.001		
^a Confidence interval.				
^b The cutoff values of age and economic income were determined by X-tile program.				
After univariate analysis, we selected variables with P < 0.1 for further multivariate analysis. At the same time, we will also consider the impact of clinical practice.				

Characteristic	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95% CI ^a)	P value	Hazard Ratio (95% CI ^a)	P value
Divorced/Separated	1.16(0.82–1.63)	0.403		
Widowed	1.65(1.22–2.23)	0.001		
SEER historic stage				
Localized	Reference		Reference	
Distant	1.44(1.12–1.85)	0.005	1.44(1.11–1.87)	0.006
Regional	3.52(2.72–4.56)	< 0.001	3.04(2.30–4.01)	< 0.001
Unstaged	1.70(1.23–2.36)	0.001	1.33(0.94–1.87)	0.104
Grade				
I	Reference		Reference	
II	1.43(0.48–4.26)	0.516	1.60(0.53–4.80)	0.401
III	3.23(1.19–8.78)	0.022	2.47(0.90–6.75)	0.078
IV	3.56(1.32–9.60)	0.012	2.89(1.06–7.84)	0.037
Unknown	3.95(1.47–10.59)	0.006	2.62(0.97–7.10)	0.058
Surgery				
Surgery	Reference		Reference	
No/ Unknown	2.69 (2.27–3.19)	< 0.001	1.66(1.36–2.02)	< 0.001
Radiotherapy				
Yes	Reference		—	—
No/Unknown	0.67(0.56–0.79)	< 0.001		
Chemotherapy				

^aConfidence interval.

^bThe cutoff values of age and economic income were determined by X-tile program.

After univariate analysis, we selected variables with $P < 0.1$ for further multivariate analysis. At the same time, we will also consider the impact of clinical practice.

Characteristic	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95% CI ^a)	P value	Hazard Ratio (95% CI ^a)	P value
Yes	Reference		—	—
No/Unknown	1.39(1.18–1.65)	< 0.001		
^a Confidence interval.				
^b The cutoff values of age and economic income were determined by X-tile program.				
After univariate analysis, we selected variables with $P < 0.1$ for further multivariate analysis. At the same time, we will also consider the impact of clinical practice.				

Table 8.
Univariate and multivariate analysis of overall survival (CSS) rates.

Characteristic	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95% CI ^a)	P value	Hazard Ratio (95% CI ^a)	P value
Age at diagnosis(y) ^b				
< 48	Reference		Reference	
49–62	1.36(1.02–1.80)	0.034	1.46(1.10–1.95)	0.009
> 62	2.81(2.24–3.52)	< 0.001	2.58(2.03–3.28)	< 0.001
Year of diagnosis				
1973–1983	Reference		Reference	
1984–1994	0.73(0.52–1.04)	0.085	0.74(0.52–1.06)	0.105
1995–2005	0.66(0.49–0.90)	0.008	0.67(0.49–0.91)	0.011
2006–2016	0.64(0.47–0.86)	0.003	0.60(0.44–0.81)	0.001
Sex				
Female	Reference		—	—
Male	1.10(0.90–1.35)	0.330		
Race				
White	Reference		—	—
Black	1.03(0.75–1.40)	0.874		
Others	1.24(0.86–1.79)	0.252		
Marital status				
Married	Reference		—	—
Never married	0.62(0.49–0.77)	< 0.001		
Divorced/Separated	1.02(0.66–1.58)	0.940		
Widowed	1.65(1.14–2.39)	0.008		

^aConfidence interval.

^bThe cutoff values of age and economic income were determined by X-tile program.

After univariate analysis, we selected variables with P < 0.1 for further multivariate analysis. At the same time, we will also consider the impact of clinical practice.

Characteristic	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95% CI ^a)	P value	Hazard Ratio (95% CI ^a)	P value
SEER historic stage				
Localized	Reference		Reference	
Distant	1.50(1.10–2.06)	0.011	1.57(1.15–2.16)	0.005
Regional	3.83(2.80–5.26)	< 0.001	3.51(2.51–4.92)	< 0.001
Unstaged	1.61(1.07–2.44)	0.024	1.31(0.86–2.02)	0.213
Grade				
I	Reference		—	—
II	1.50(0.43–5.25)	0.530		
III	3.06(0.97–9.73)	0.057		
IV	3.40(1.08–10.71)	0.036		
Unknown	3.40(1.09–10.65)	0.036		
Surgery				
Surgery	Reference		Reference	
No/ Unknown	2.53(2.06–3.10)	< 0.001	1.56(1.24–1.97)	< 0.001
Radiotherapy				
Yes	Reference		—	—
No/Unknown	0.62(0.50–0.77)	< 0.001		
Chemotherapy				
Yes	Reference		—	—
No/Unknown	1.13(0.92–1.40)	0.254		
^a Confidence interval.				
^b The cutoff values of age and economic income were determined by X-tile program.				
After univariate analysis, we selected variables with P < 0.1 for further multivariate analysis. At the same time, we will also consider the impact of clinical practice.				

Figures

Figure 1

Schematic flow diagram of inclusion and exclusion criteria for our study cohort.

Figure 2

The X-tile analysis was used to identify the optimal cutoff values of age of diagnosis.

Figure 3

Kaplan-Meier estimates of the Overall survival (a) and Cancer-specific survival (b) for the total cohort among two groups (surgery group; non-surgical group).

Figure 4

Forest plot of Multivariable Logistic analyses of surgical noncompliance adjusted by age, grade and SEER historic stage. The green squares on the transverse lines represent the Odds ratio (OR), and the transverse lines represent 95% CI. The cut-off values of age and economic income were determined by X-tile program.

Figure 5

Kaplan-Meier estimates of the Overall survival and Cancer-specific survival for the patients diagnosed in different age among two groups (surgery group; non-surgical group). The cut-off values of age and economic income were determined by X-tile program. In the left column, a, c, e is the Overall survival of patients diagnosed at different ages in the two groups (surgical group; non-surgical group). In the right

column, b, d, f is the Cancer-specific survival of patients diagnosed at different ages in the two groups (surgical group; non-surgical group).

Figure 6

Kaplan-Meier estimates of the Overall survival and Cancer-specific survival for the patients diagnosed in different SEER historic stage among two groups (surgery group; non-surgical group). The cut-off values of age and economic income were determined by X-tile program. In the left column, a, c, e, j is the Overall

survival of patients diagnosed at different SEER historic stage in the two groups (surgical group; non-surgical group). In the right column, b, d, f, h is the Cancer-specific survival of patients diagnosed at different SEER historic stage in the two groups (surgical group; non-surgical group).