Surgical Compliance and Survival Outcomes For Patients With Osteosarcoma: A Population-Based Database Study

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Abstract

Purpose

We aimed to determine the effect of surgical compliance on prognosis in patients with osteosarcoma and the risk factors leading to surgical noncompliance.

Methods

We analyzed the date collected 3412 osteosarcoma patients from the Surveillance Epidemiology and End Results (SEER) databases between 1973 and 2015. 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 3412 eligible osteosarcoma patients, the poor surgical compliance of patients with osteosarcoma is associated with the earlier time of diagnosis, advanced age, lower economic income, poor grade, distant stage, accepting radiotherapy and refusing chemotherapy. There were significant differences in the effects of diagnostic time, age, grade, radiotherapy, chemotherapy, tumor stage and economic income on surgical compliance (All $P < 0.05$). Patients' compliance was an independent prognostic factor for OS and CSS of osteosarcoma patients.

Conclusions

Osteosarcoma patients with good surgical compliance have favorable survival. This can help clinicians effectively realize patients' views on surgery and guide patients to learn the signification of surgery.

Introduction

Osteosarcoma is the most common primary malignant bone tumor in orthopedics, originating from mesenchymal cells[1]. Currently, the global annual incidence of osteosarcoma is approximately 1 to 3 per 1,000,000 population[2], and there are approximately 400 new cases in United States every year[3]. The median age of onset of osteosarcoma was 20 years, with 75% of patients aged 15-25 years. Osteosarcoma affects more men than women[4]. Osteosarcoma is characterized by the proliferation of tumor cells that directly form immature bone or bone-like tissue[5]. The most common site of osteosarcoma was long bone, usually distal femur or proximal tibia, followed by proximal humerus, and less often the skull, jaw, or pelvis[6]. Similar to other solid tumors, osteosarcoma has a high degree of malignancy, poor prognosis, high mortality, and it is prone to distant metastasis, especially lung metastasis in a short time[7].

Surgical treatment is one of the preferred methods for the treatment of osteosarcoma. In 1879, Gross advocated early amputation for sarcoma by studying 165 cases of sarcoma of the long bone. Most were probably osteosarcoma. This became the "standard" treatment for osteosarcoma[8]. Until the 1970s, amputation was the gold standard treatment for osteosarcoma. At the time of diagnosis, 80% of the patients have already developed micro-metastatic lesions, and the average time from surgical treatment to lung metastasis is 8 months. The 5-year overall survival rate is low, and most patients die within 1 year after diagnosis[9]. In recent years, with the development of imaging technology, the maturity of surgical technology, the development and progress of bone reconstruction technology, the most important is the emergence of neoadjuvant chemotherapy, which improves the safety of limb salvage surgery. Limb salvage surgery is generally used in combination with chemotherapy, which has obvious therapeutic effect on tumor and plays a very important role in clinical practice, and it has gradually replaced amputation as the preferred and mainstream surgery for osteosarcoma of the limb. Between 80-90 out of 100 patients received limb salvage surgery, and the disease-free survival probability was also increased from about 20% to >60%[10,11].

Many studies have analyzed the outcome and survival rate of osteosarcoma patients as well as the factors affecting prognosis. Rougraff et al[12] have reported there is no difference in survival between limb salvage patients and amputees, although local recurrence rates were higher in limb salvage patients. Bielack SS et al[13] analyzed 1702 patients with osteosarcoma and defined that tumor location, size, and metastasis were independent prognostic factors. Miller BJ et al[14] examine that advanced age, an axial tumor location, increasing tumor size, and residence in less affluent counties were potential risk factors predictive of metastatic disease at presentation by analyzing the epidemiology and tumor characteristics of a large number of patients with osteosarcoma. Kager L et al[15] made it clear that the completeness of surgical resection affect the prognosis of patients with osteosarcoma. If feasible, complete surgical resection is still the key to cure[16]. It is important to note that a certain number of patients with osteosarcoma who are recommended for surgery have no surgical operation. In addition to the high degree of malignancy of osteosarcoma itself, inadequate treatment in osteosarcoma is considered as the important reasons for poor prognosis. Faisham WI et al[17] reported that the patients who did not complete treatment had significantly poorer survival. Surgery noncompliance is a serious undertreatment. However, no attention has been given to the effect of surgical compliance on the prognosis of patients with osteosarcoma. Based on this hypothesis, our aim is to clarify that surgical compliance can predict the prognosis of osteosarcoma, and to identify the covariates leading to surgical noncompliance in this retrospective analysis. This is helpful to establish effective intervention measures, so as to ensure the surgical compliance of osteosarcoma and ultimately improve the surgical effect.

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). Exclusion criteria were as follows(1) age at diagnosis younger than 18 years (n=2587); (2) unknown marital status at diagnosis (n=118); (3) unknown race (n=11); (4) unknown survival months (n=20). We were primarily interested in surgical compliance, and we did not enroll patients who were unsure whether to undergo surgery (n=77). Overall our analysis included 3412 patients with osteosarcoma who were followed up from the date of diagnosis to death or at the end of follow-up.

Statistical analysis

We extracted basic information of all the selected patients from the database, including the time of diagnosis, gender, race, age, marital status and economic income, as well as information related to their diseases, such as radiotherapy, chemotherapy, tumor stage, pathological grading and surgery status. The time span of SEER database diagnosis was 42 years, and patients were divided into four groups according to the chronological order of diagnosis. These patients were divided into three subgroups according to different treatment regimens and patients' compliance. We referred to patients undergoing surgery as the surgical compliance group; patients who were recommended to have surgery but not surgery were classified as noncompliant groups; patients who were not recommended for surgery belonged to the non-surgical group.

Statistical analysis was performed using Statistical Program for Social Sciences (SPSS) software version 24. Chi-square analysis was performed to evaluate the patients’ demographics and clinical characteristics and its correlation to the presence of patients’ compliance. Kaplan-Meier curve was used to estimate the survival in different groups, 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 measure, which estimates the probability of osteosarcoma survival in our study. The patients were censored who are still alive at the date of last follow-up or those who die from other reasons other than osteosarcoma. 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. Multivariate Logistic regression was used to explore potential variables related to patients' surgical compliance. According to the minimum P-values and maximum χ^2 test statistical value of log-rank tests, X-tile software was conducted to find the optimal hierarchical age at diagnosis and economic income stratification boundaries. P-values of less than 0.05 were considered statistically significant.

Results

Identification of cutoff values for age and economic income

To identify the optimal age and income stratification for osteosarcoma patients, we constructed X-tile plots to explore the cutoff value on the prediction of OS predictive. The age of diagnosis was divided into three levels: <45 years，46-71 years，>71 years (**Figure 1A**). In a similar manner, the economic income is also identified the following optimal cutoffs: Q1:11350-25030$, Q2:25040-45610$, Q3:45620-56270$ (**Figure 1B**).

Baseline characteristics of patients

Using the Chi-square test, we examined the demographic and clinicopathological characteristics of patients with osteosarcoma. Baseline characteristics of patients were summarized in **Table 1**. After applying exclusion criteria, a total of 3,412 patients were enrolled in our cohort. Among them, 2608 patients received surgical treatment and 267 cases were recommended to surgery but not surgery. In addition,537 patients were not recommended for surgery.

In terms of time, the patient's compliance with surgery improved significantly with the passage of time. From 10.5% in 1973-1983 up to 40.7% in 2006-2015. Patients younger than 46 years had a higher percentage of compliance to surgery, while old patients more than 71 years had the lowest. There was no significant difference in the proportion of male and female between the groups. For race, the rate of surgical noncompliance was higher in whites. As to the patient's marital status, among patients who are willing to undergo surgery, married patients account for a higher proportion (46.0%), and widowed patients showed worse surgical compliance (4.6%). We found that patients who did not receive radiotherapy had better surgical compliance than those who received radiotherapy. This situation is exactly the opposite in chemotherapy. Pathological grade was not suitable for further analysis because a large percentage of patients in the nonconformity group that do not have valid information (69.7%). However, in SEER tumor staging, the proportion of patients with localized osteosarcoma who received surgery was significantly higher than that of patients with distal osteosarcoma. We also found that there was no significant difference between the groups in the affected areas, regardless of rural or urban areas. For the impact of economic income, low-income people are even more likely to refuse surgery.

Survival analysis

Comparison of the survival outcome between different groups

The patients were stratified based on the surgical status showed in **Figure 2A**. Comparing with the surgical compliance group, patients with surgical noncompliance have worse OS (HR= 2.79, 95% CI: 2.29-3.39, P < 0.001), and we could see the consistent result in CSS (HR= 2.91, 95% CI: 2.28-3.71, P < 0.001) (**Figure 2B**). In the same way, non-surgical surgical group demonstrated relatively worse outcome compared with surgical compliance group, no matter in OS or CSS (OS HR=3.35, 95%CI: 2.85-3.93, P < 0.001; CSS HR=3.41, 95%CI: 2.80-4.15, P < 0.001) (**Figure 2A & Figure 2B**). The survival curve of noncompliance group and non-surgical group were almost coincident.

Cox regression analysis for the prognostic factors

Cox regression was used to analyze prognostic factors for OS and CSS (**Table □ & Table □**). Univariate analysis showed that time of diagnosis, age, gender, marital status, pathological grading, histological type, radiotherapy, chemotherapy, surgical compliance, disease area and economic income were significant risk factors for OS and CSS. Compared with patients diagnosed in 1973-1983, patients in the last decade had a better OS (HR= 0.76, 95%CI: 0.66-0.87, P < 0.001) and CSS (HR= 0.69, 95%CI: 0.58-0.82, P < 0.001). Older age (age >71 years) was significantly associated with a worse OS (HR=6.01, ,95%CI: 5.32-6.80, P < 0.001) and CSS (HR=4.68, ,95%CI: 4.02-5.45, P < 0.001). Gender was associated with significant differences in OS (male vs female HR= 1.15, 95%CI: 1.05-1.26, P = 0.003) and CSS (male vs female HR= 1.21, 95%CI: 1.08-1.35, P = 0.003). With regard to both OS and CSS, race showed no significant effect on survival (**Table□ & Table □**). For marital status, there are significant differences in both OS and CSS. Poor marital status has a higher risk in OS (widowed vs married HR= 2.54, 95%CI: 2.18-2.95, P < 0.001) and CSS (widowed vs married HR= 2.31, 95%CI: 1.90-2.82, P < 0.001). We found that high pathological grade portend a worse prognosis for both OS and CSS (P < 0.001). In terms of Patients' compliance, Univariate analysis indicated that surgical noncompliance had a worse outcome than surgical compliance in OS (HR= 2.83, 95%CI: 2.46-3.26, P < 0.001) and CSS (HR= 2.96, 95%CI: 2.49-3.52, P < 0.001). No matter for OS or CSS, poor compliance had a higher risk. Patients who did not receive radiotherapy had better result than patients who received radiotherapy in OS (HR= 0.40, 95%CI: 0.40-0.49, P < 0.001) and CSS (HR=0.40, 95%CI: 0.38-0.50, P < 0.001). We found that Patients undergoing chemotherapy were significantly associated with a worse OS (HR= 1.20, 95%CI: 1.09-1.31, P < 0.001), but showing no significant difference in CSS (P = 0.157). For SEER historic stage, compared with patients with localized tumor, patients with distant had worse OS (HR= 1.20, 95%CI: 1.09-1.31, P < 0.001)but there was no significant difference in CSS (P = 0.247).We also found that patients living in rural areas have a higher risk of survival than patients living in urban in OS (HR= 1.31, 95%CI: 0.96-1.79, P = 0.093) and CSS (HR= 1.86, 95%CI: 1.59-2.18, P = 0.020).In addition, high-income patients have better outcome compared with low-income patients in OS (Q3 VS Q1,HR= 0.66, 95%CI: 0.54-0.80, P < 0.001) and CSS (Q3 VS Q1,HR= 0.65, 95%CI: 0.51-0.82, P < 0.001).

Objective to explore which variables have significant influence on the prognosis of patients with osteosarcoma. Based on the results of Univariate analysis, we selected variables with a P value of less than 0.1 and combined with clinical treatment methods to further conduct multivariate analysis. Then we further used multivariate analysis to confirm surgical compliance were independent prognostic factors for OS and CSS. Compared with patients with good surgical compliance, the risk increased when the patients were with poor compliance in the OS (HR= 1.62, 95%CI: 1.38-1.91, P < 0.001) and CSS (HR= 1.69, 95%CI: 1.38-2.07, P < 0.001). Moreover, multivariate analysis showed no statistically significant difference among marital status and chemotherapy.

Factors for poor surgical compliance

We used multivariate logistic regression model to identify the influencing factors of surgical compliance. When other factors were adjusted, several variables were proved to be significantly correlated with poor surgical compliance **Figure 3**. We found that the influencing factors have the following aspects: time of diagnosis, age, grade, radiation, chemotherapy, SEER historic stage and economic income. Patients who were 71 years or older (OR, 3.44; 95% CI,2.24-5.29; P < 0.001), at distant stage (OR, 4.07; 95% CI,2.67-6.22; P < 0.001), at unstaged stage (OR, 6.28; 95% CI,4.29-10.87; P < 0.001), no-chemotherapy (OR, 1.53; 95% CI,1.10-2.13; P = 0.012), histological grade II (OR, 3.69; 95% CI,1.17-11.61; P = 0.026) and histological grade unknown (OR, 4.43; 95% CI,1.55-12.63; P = 0.005) were less likely to undergo surgery. Additionally, Patients who were diagnosed at last decade, 2006-2015 (OR, 0.12; 95% CI,0.07-0.20; P < 0.001), no-radiation (OR, 0.61; 95% CI,0.43-0.87; P = 0.007) and higher economic status (Q2 vs Q1: OR, 0.57; 95% CI,0.37-0.89; P = 0.012) were more willing to accept surgical therapy.

Trends in survival stratified by the age at diagnosis

In order to better demonstrate that surgical compliance as a single factor had a significant impact on the survival of patients with osteosarcoma. Logistic regression indicated that age was a significant factor of poor surgical compliance. Patients were stratified by the time of diagnosis to investigate the trends in survival. From the results of OS shown in the figure4A we found that regardless of the age stage, patients in surgical compliance group had more favorable survival than the other two groups. Although the survival of the noncompliant group and non-surgical group were poor, the former was superior to the latter. As the age increases, the survival was getting worse in all groups. Similarly, in the figure4B that the outcome of CSS had the same characteristics.

Discussion

Osteosarcoma is a malignant tumor with poor prognosis. It is of great significance to conduct prognostic studies. Further study in this area enable clinicians to provide patients and their families with a more informed information. It can also determine the choice of treatment from the early stages of the disease. In addition, the identification of key prognostic factors provides a clearer goal for cancer anti-research[19].

Therefore, we thought that the surgical compliance of osteosarcoma was worthy of clinical research and application.

To our knowledge, there is almost no population-based study of osteosarcoma in surgical compliance. In our study, we aimed to investigate the effect of surgical compliance on survival among osteosarcoma. According to our criteria, a total of 3,412 patients were included, of which 2,608 (76.4%) patients had surgery, 267 (7.8%) patients had surgical noncompliance, and 537 (15.7%) patients had non-surgical treatment. We suspected that the prognosis of surgical noncompliance group was significantly worse than that of surgical compliance group. The outcomes of study were in line with our conjecture. Kamal AF et al[20] reported the similar result that patients with osteosarcoma undergoing surgery had better survival than non-surgical patients. Patients who were not recommended for surgery had generally poor basic conditions, serious complications, or advanced age. As we have expected, their prognosis was relatively poor compared to other two groups for OS and CSS. However, it is worth noting that although the prognosis of patients with poor surgical compliance was higher than that of non-surgical patients, the survival curves of the two were basically coincident for OS and CSS in our study. For the time being, we have no way of knowing the reason for this feature.

Survival analysis confirmed that Patients' surgical compliance has a significant impact on patient prognosis. This requires further research to determine relevant demographic and clinicopathological factors. We used logistic regression to find out that the diagnosis time affected the patients' surgical compliance. In the last decade of the study, patient compliance was significantly higher than in 1970s, which was similar to changes in adherence in other cancer patients. Liu GH et al[21] analyzed the surgical compliance of patients with gastric cancer, indicating that the patient's surgical compliance gradually improved over time. We speculate that this is due to the advancement of social health care, and patients' awareness of the disease has increased significantly compared with the past. The improvement of medical level also plays an important role in improving the patient's surgical compliance. Allison DC et al[22] reported that the treatment of osteosarcoma has developed rapidly in modern medicine.

In the analysis of age, we used X-tile software to determine the optimal age cut points for patients with osteosarcoma were 46 and 71 years old. Studies shown that clear differences in the surgical options at different ages, which was a negative risk factor for surgical compliance. Especially when the patient is over 71 years old, the chance of not undergoing surgery was more than three times. Many studies have shown that the age of diagnosis is related to the prognosis of patients with osteosarcoma. Jawad MU et al[23] points out that the survival of older patients was significantly lower compared to younger. Harting MT et al[24] indicated that patients in the fifth decade and older fare worse than younger patients for patients with osteosarcoma in OS. In our study, we also analyzed the prognostic factors of patients with osteosarcoma, and the conclusion reached were consistent with theirs. An inaccurate assessment of the surgical risks and benefits of elderly osteosarcoma patients, which resulted in poor surgical compliance was ascribed to the conclusion. In general, elderly osteosarcoma patients with multiple complications were often in advanced stages of osteosarcoma. This required us to have better cancer management for older patients, which was a vital prerequisite for surgical treatment of elderly patients with osteosarcoma[25]. It can help clinicians build confidence and improve patients' surgical compliance.

Our study shown that economic income was a factor that influenced patients' choices about whether they were willing to undergo surgery. Friedrich P et al[26] found that economic income was inversely proportional to abandonment of treatment by a state-centered analysis of osteosarcoma patients in middle-income countries, which was consistent with our findings. Miller BJ et al[14] used socioeconomic status (SES) to reflect the patient's economic situation, combined with the geographical location of the patients, rural or urban, and reported that SES is associated with metastasis of osteosarcoma patients, indirectly, which reflected the economic factors affecting the prognosis of patients. However, our study did not find significant differences in the areas of life for surgical compliance. For economic income, we believed that a lower income may reflect a less access to health care. It may also reflect that the patient was generally unwilling or unable to seek treatment in time, leading to delays in treatment. Our survival analysis also proves that this hypothesis that patients with poor economics have lower survival than those with economically developed.

In addition to demographic characteristics, logistic regression analysis showed that the characteristics of the tumor itself were also related to the patient's surgical compliance. Patients with high-grade osteosarcoma are more reluctant to undergo surgery than those with low-grade. Similar results were on the SEER historic stage. Distant patients had poor surgical compliance compared with localized patients. Zheng W et al[27] determined that tumor grade and histology were independent prognostic indicators for patients with osteosarcoma. Wang Z et al[28] cleared that localized stage and low grade were favorable factors for prolonging survival. Our findings were consistent with the outcomes of their studies. We believe that patients with localized stage and low grade have led to good surgical compliance because the patients had properly evaluated their prognosis at this stage, and they had a better understanding of osteosarcoma.

Moreover, there were therapies other than surgery in the treatment of patients, such as radiotherapy and chemotherapy. This situation also affected whether patients chose surgery treatment. At present, chemotherapy combined with surgery is the standard for the treatment of osteosarcoma[29]. Meyers PA et al[30] shown that chemotherapy can improve the survival of patients with osteosarcoma in OS. In the analysis of the relationship between chemotherapy and survival in patients with osteosarcoma, Ferrari S et al[31] found that histological response was statistically significant only in univariate. In our research, we also found that chemotherapy was not an independent prognostic factor for the survival of patients with osteosarcoma. Chemotherapy was statistically significant only in univariate. The results of our study showed that patients who did not receive chemotherapy were more reluctant to undergo surgery. We believe that such patients lack awareness of the treatment of osteosarcoma. It has been reported that biophysical therapy can play an auxiliary role in chemotherapy. Morri M et al[32] demonstrated that beginning to strengthen physical therapy for patients with bone tumors in chemotherapy is a viable treatment option and rehabilitation should be promoted based on the level of satisfaction reported by the patient during chemotherapy. Carina V[33] found that the biophysical therapies may be another therapeutic effect besides OS surgery, radiotherapy and chemotherapy. Therefore, we considered that the basic physical therapy can improve the patient's understanding of osteosarcoma treatment, which improve the patient's surgical compliance. Of course, this needs further research and confirmation.

Huang X et al.'s research indicated that radiotherapy does not improve the survival of patients with osteosarcoma[34]. However, the results of our study were contrary to their findings. our study cleared that patients who did not receive radiotherapy had favorable survival than patients who received radiotherapy in OS and CSS. In terms of surgical compliance, patients who did not receive radiotherapy had better surgical compliance. This still should be related to the insufficient understanding of standard osteosarcoma treatment options. Although radiotherapy was not a routine treatment for osteosarcoma, patients receiving radiotherapy believed that radiotherapy was effective and was easy to accept[35]. Thus, they refuse surgery treatment.

We also used COX regression to analyze factors that influence the prognosis of osteosarcoma. Gender was found to be of significant importance in our population, as opposed to reported in other studies conducted in the United States[36]. We also found that race and marital status did not significantly differ in the survival of patients with osteosarcoma. Similar conclusions are also reflected in surgical compliance.

These results suggest that differences in treatment adherence may be a key factor influencing the prognosis of patients with osteosarcoma. There are many treatments for osteosarcoma, including neoadjuvant chemotherapy, arthrodesis resection, bone grafting, resection and reconstruction, prosthesis reconstruction, Ilizarov extension technique, rotational angioplasty, etc[20,37]. However, any treatment was based on good compliance. Poor surgical compliance may mean poor compliance with other treatment options, which ultimately leaded to adverse outcomes.

There have several limitations in the study. First, the choice of samples has regional limitations, all the populations from the United States and lack certain global directivity. Second, we did not consider the social factors such as the family's family situation, education level, and tumor characteristics such as tumor location, size and metastasis status. They also may have an impact on the choice of surgical compliance. It needs further confirmations. Third, for particularity of osteosarcoma, there are amputation and limb salvage procedures in the surgical treatment. Patients who are recommended to undergo surgery may refused treatment because of different surgical procedures. We have not confirmed this due to the lack of relevant data. Last, this study is a retrospective population study, lacking certain persuasive power.

Conclusions

In our research, the SEER database was used to assess the impact of surgical compliance on the survival of patients with osteosarcoma. Osteosarcoma Patients with good surgical compliance have favorable survival. The poor surgical compliance of patients with osteosarcoma is associated with the earlier time of diagnosis, advanced age, poor grade, accepting radiotherapy, refusing chemotherapy, differentiation stage of tumor and lower economic income. This can help clinicians effectively realize patients' views on surgery and guide patients to learn the signification of surgery.

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 collected and assembled data. CT and DW 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 . Baseline demographics and characteristics for patients with osteosarcoma.

Characteristic	All patients	Surgical compliance group	Surgical noncompliance group	P Value
	N. (%)	N. (%)	N. (%)	
Total	3412	2608(76.4)	267(7.8)	
Year of diagnosis				<0.001
1973-1983	378(11.1)	274(10.5)	104(39.0)	
1984-1994	479(14.0)	353(13.5)	63(23.6)	
1995-2005	1174(34.4)	919(35.2)	78(29.2)	
2006-2015	1381(40.5)	1062(40.7)	22(8.2)	
Age at diagnosis (y)[a]				<0.001
<46	1966(57.6)	1668(64.0)	94(35.2)	
46-71	1003(29.4)	732(28.1)	92(34.5)	
>71	443(13.0)	208(8.0)	81(30.3)	
Sex				0.206
Female	1528(44.8)	1170(44.9)	109(40.8)	
Male	1884(55.2)	1438(55.1)	158(59.2)	
Race				<0.001
White	2663(78.0)	2019(77.4)	234(87.6)	
Black	471(13.8)	361(13.8)	25(9.4)	
Others	278(8.1)	228(8.7)	8(3.0)	
Marital status				<0.001
Married	1572(46.1)	1200(46.0)	130(48.7)	
Never married	1397(40.9)	1141(43.8)	72(27.0)	
Divorced/Separated	215(6.3)	146(5.6)	19(7.1)	
Widowed	228(6.7)	121(4.6)	46(17.2)	
Rural-Urban				0.289
Urban	528(15.5)	389(14.9)	51(19.1)	
Country	2779(81.4)	2138(82.0)	210(78.7)	
Rural	64(1.9)	49(1.9)	4(1.5)	

Unknown	41(1.2)	32(1.2)	2(0.7)	
Median household income[a]				0.040
Q1	389(11.4)	273(10.5)	41(15.4)	
Q2	2663(78.0)	2053(78.7)	195(73.0)	
Q3	360(10.6)	282(10.8)	31(11.6)	
Grade				<0.001
Grade I	189(5.5)	174(6.7)	4(1.5)	
Grade II	253(7.4)	222(8.5)	16(6.0)	
Grade III	640(18.8)	516(19.8)	28(10.5)	
Grade IV	1141(33.4)	942(36.1)	33(12.4)	
Unknown	1189(34.8)	754(28.9)	186(69.7)	
SEER historic stage				<0.001
Localized	1079(31.6)	941(36.1)	48(18.0)	
Distant	698(20.5)	347(13.3)	90(33.7)	
Regional	1375(40.3)	1210(46.4)	61(22.8)	
Unstaged	260(7.6)	110(4.2)	68(25.5)	
Radiotherapy				<0.001
Yes	547(16.0)	322(12.3)	75(28.1)	
No/Unknown	2865(84.0)	2286(87.7)	192(71.9)	
Chemotherapy				<0.001
Yes	2112(61.9)	1719(65.9)	106(39.7)	
No/Unknown	1300(38.1)	889(34.1)	161(60.3)	

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

Percentages may not total 100 because of rounding.

Table . 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)	P value
Year of diagnosis				
1973-1983	Reference		Reference	0.006
1984-1994	0.83(0.71-0.97)	0.019	0.93(0.79-1.09)	0.350
1995-2005	0.72(0.63-0.83)	<0.001	0.80(0.69-0.94)	0.005
2006-2015	0.76(0.66-0.87)	<0.001	0.77(0.65-0.91)	0.002
Age at diagnosis (y)[b]				
<46	Reference		Reference	
46-71	2.42(2.20-2.68)	<0.001	2.19(1.98-2.43)	<0.001
>71	6.01(5.32-6.80)	<0.001	4.47(3.93-5.10)	<0.001
Sex				
Female	Reference		Reference	
Male	1.15(1.05-1.26)	0.003	1.12(1.02-1.23)	0.013
Race				
White	Reference	0.160	—	
Black	0.98(0.86-1.11)	0.733		
Others	0.85(0.71-1.00)	0.056		
Marital status				
Married	Reference		—	
Never married	0.64(0.58-0.71)	<0.001		
Divorced/Separated	1.20(1.00-1,42)	0.046		
Widowed	2.54(2.18-2.95)	<0.001		
Rural-Urban				
Urban	Reference	0.019	Reference	0.022
Country	0.89(0.78-1.00)	0.047	1.15(0.98-1.36)	0.081
Rural	1.31(0.96-1.79)	0.093	1.60(1.16-2.20)	0.004
Unknown	0.88(0.61-1.29)	0.522	1.13(0.76-1.68)	0.535
Median household income[b]				

Q1	Reference		Reference	
Q2	0.79（0.69-0.91）	<0.001	0.83(0.69-1.00)	0.053
Q3	0.66（0.54-0.80）	<0.001	0.64(0.50-0.81)	<0.001
Grade				
Grade I	Reference		Reference	
Grade II	1.58（1.08-2.33）	0.020	1.35(.92-1.99)	<0.001
Grade III	3.96（2.84-5.50）	<0.001	2.87(2.06-4.00)	0.125
Grade IV	4.02（2.91-5.56）	<0.001	3.00(2.16-4.15)	<0.001
Unknown	4.84（3.51-6.68）	<0.001	2.95(2.13-4.08)	<0.001
SEER historic stage				
Localized	Reference		Reference	
Distant	5.53（4.87-6.28）	<0.001	3.77(3.30-4.32)	<0.001
Regional	1.58（1.40-1.78）	<0.001	1.44(1.27-1.62)	<0.001
Unstaged	2.65（2.23-3.14）	<0.001	1.44(1.20-1.73)	<0.001
Patients’ compliance				
Surgical compliance	Reference		Reference	
Surgical noncompliance	2.83（2.46-3.26）	<0.001	1.62(1.38-1.91)	<0.001
Non-surgical	3.47（3.11-3.88）	<0.001	1.98(1.74-2.25)	<0.001
Radiotherapy				
Yes	Reference		Reference	
No/Unknown	0.44（0.40-0.49）	<0.001	0.77(0.69-0.86)	<0.001
Chemotherapy				
Yes	Reference		—	
No/Unknown	1.20（1.09-1.31）	<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 [illegible]. Univariate and multivariate analysis of Cancer-specific survival (CSS) rates.

Characteristic	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95% CI[a])	P value	Hazard Ratio (95% CI)	P value
Year of diagnosis				
1973-1983	Reference		Reference	
1984-1994	0.78(0.64-0.95)	<0.001	0.82(0.67-1.01)	0.061
1995-2005	0.65(0.55-0.77)	0.015	0.66(0.54-0.80)	<0.001
2006-2015	0.69(0.58-0.82)	<0.001	0.64(0.53-0.79)	<0.001
Age at diagnosis (y)[b]				
<46	Reference		Reference	
46-71	1.89(1.67-2.14)	<0.001	1.74(1.52-1.98)	<0.001
>71	4.68(4.02-5.45)	<0.001	3.69(3.10-4.39)	<0.001
Sex				
Female	Reference		Reference	
Male	1.21(1.08-1.35)	<0.001	1.14(1.02-1.28)	0.025
Race				
White	Reference	0.439	—	
Black	0.91(0.77-1.07)	0.253		
Others	0.93(0.76-1.14)	0.476		
Marital status				
Married	Reference		—	
Never married	0.71(0.63-0.80)	<0.001		
Divorced/Separated	1.09(0.87-1.37)	0.458		
Widowed	2.31(1.90-2.82)	<0.001		
Rural-Urban				
Urban	Reference		Reference	0.004
Country	0.91(0.79-1.06)	<0.001	1.19(0.97-1.45)	0.100
Rural	1.54(1.07-2.22)	<0.001	2.00(1.38-2.90)	<0.001
Unknown	1.08(0.69-1.70)	<0.001	1.32(0.82-2.12)	0.255
Median household income[b]				

Q1	Reference	0.002	Reference	0.005
Q2	0.81(0.69-0.96)	0.015	0.84(0.66-1.06)	0.137
Q3	0.65(0.51-0.82)	<0.001	0.64(0.47-0.86)	0.003
Grade				
Grade I	Reference		Reference	
Grade II	1.69(0.98-2.92)	0.058	1.34(0.78-2.31)	0.293
Grade III	5.18(3.25-8.26)	<0.001	3.23(2.01-5.19)	<0.001
Grade IV	5.39(3.41-8.53)	<0.001	3.45(2.16-5.50)	<0.001
Unknown	6.23(3.94-9.85)	<0.001	3.22(2.02-5.13)	<0.001
SEER historic stage				
Localized	Reference	0.016	Reference	
Distant	7.30(6.20-8.59)	0.247	4.85(4.07-5.77)	<0.001
Regional	1.86(1.59-2.18)	0.020	1.65(1.41-1.94)	<0.001
Unstaged	2.75(2.19-3.46)	0.726	1.54(1.21-1.96)	0.001
Patients' compliance				
Surgical compliance	Reference		Reference	
Surgical noncompliance	2.96(2.49-3.52)	<0.001	1.69(1.38-2.07)	<0.001
Non-surgical	3.51(3.06-4.03)	<0.001	2.04(1.75-2.39)	<0.001
Radiotherapy				
Yes	Reference		Reference	
No/Unknown	0.44(0.38-0.50)	<0.001	0.76(0.66-0.87)	<0.001
Chemotherapy				
Yes	Reference		Reference	
No/Unknown	0.92(0.82-1.03)	0.157	0.85(0.74-0.97)	0.016

[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

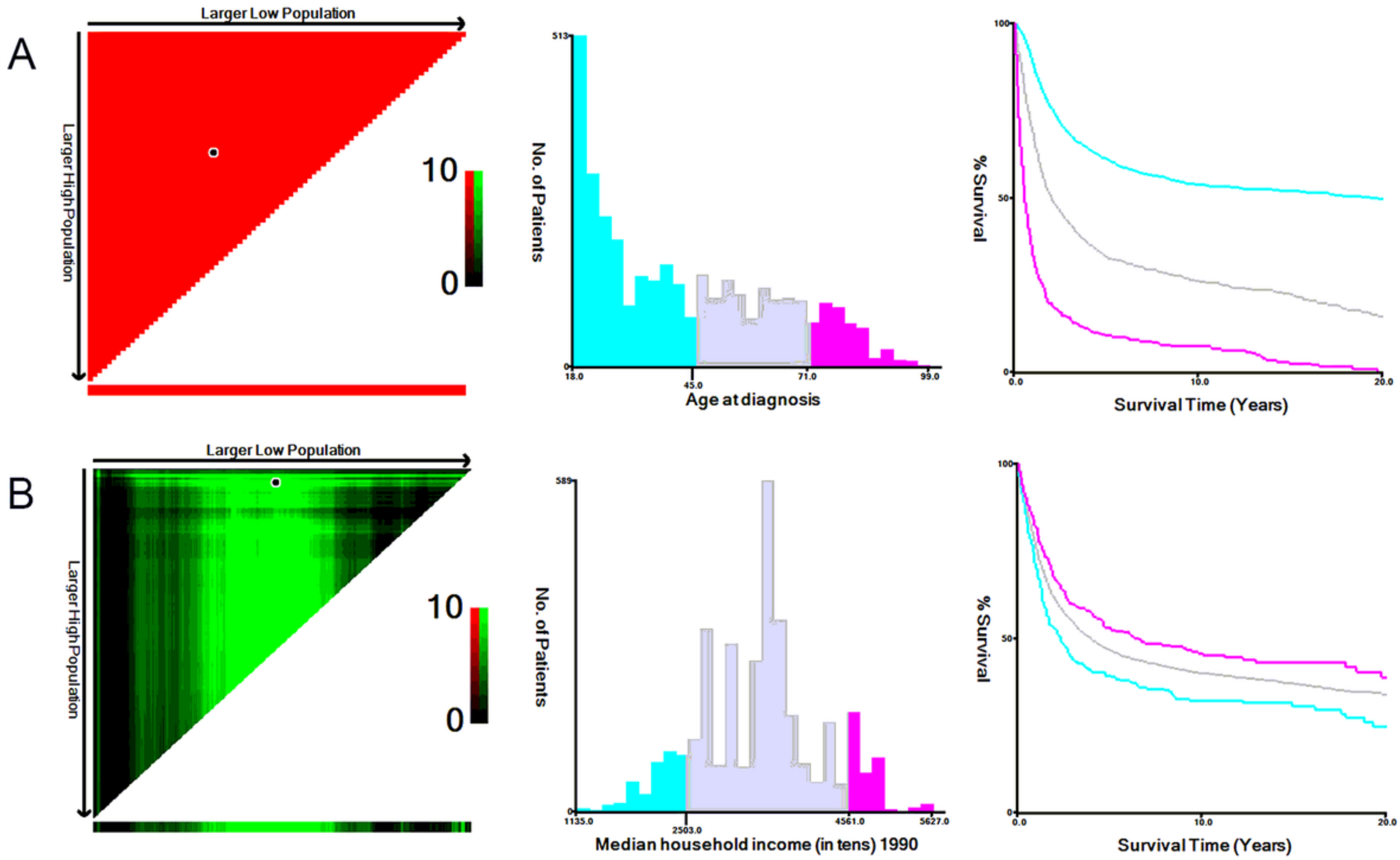

Figure 1

The X-tile analysis was used to identify the optimal cutoff values of age of diagnosis (A) and economic income (B).

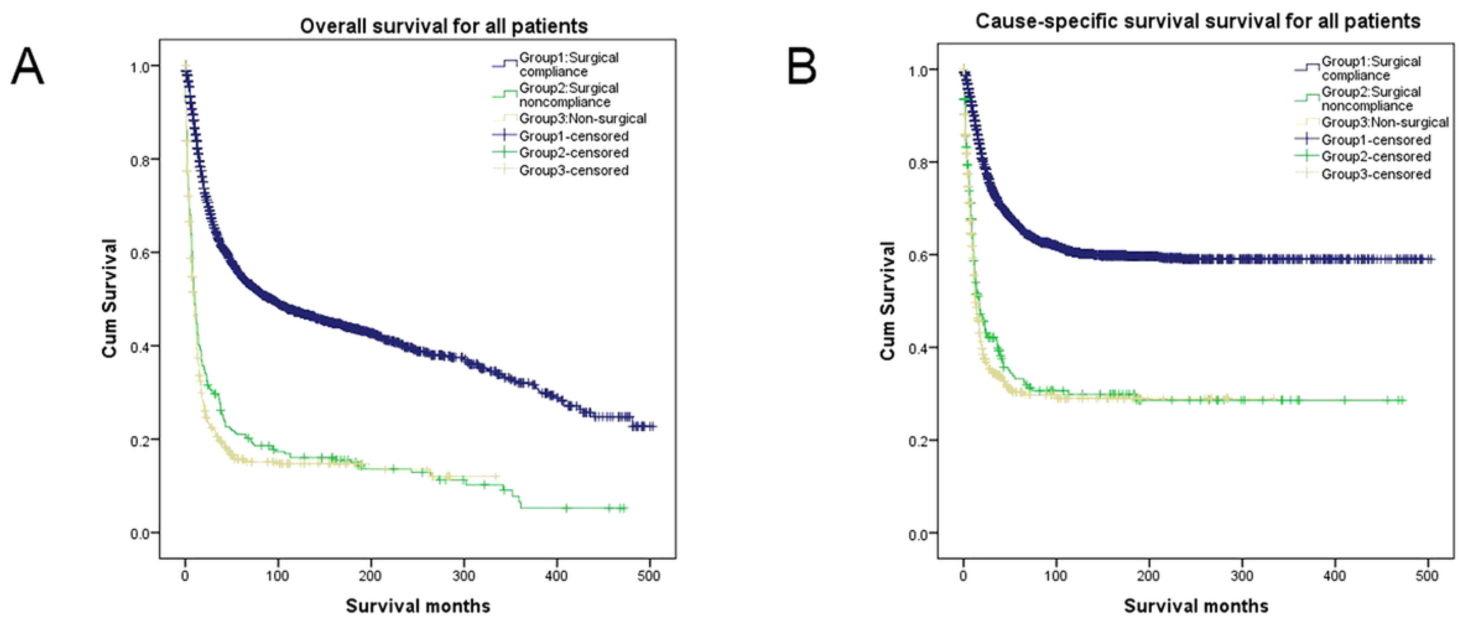

Figure 2

Kaplan-Meier estimates of the Overall survival (A) and Cancer-specific survival (B) for the total cohort among three groups (surgical compliance group; surgical noncompliance group; non-surgical group).

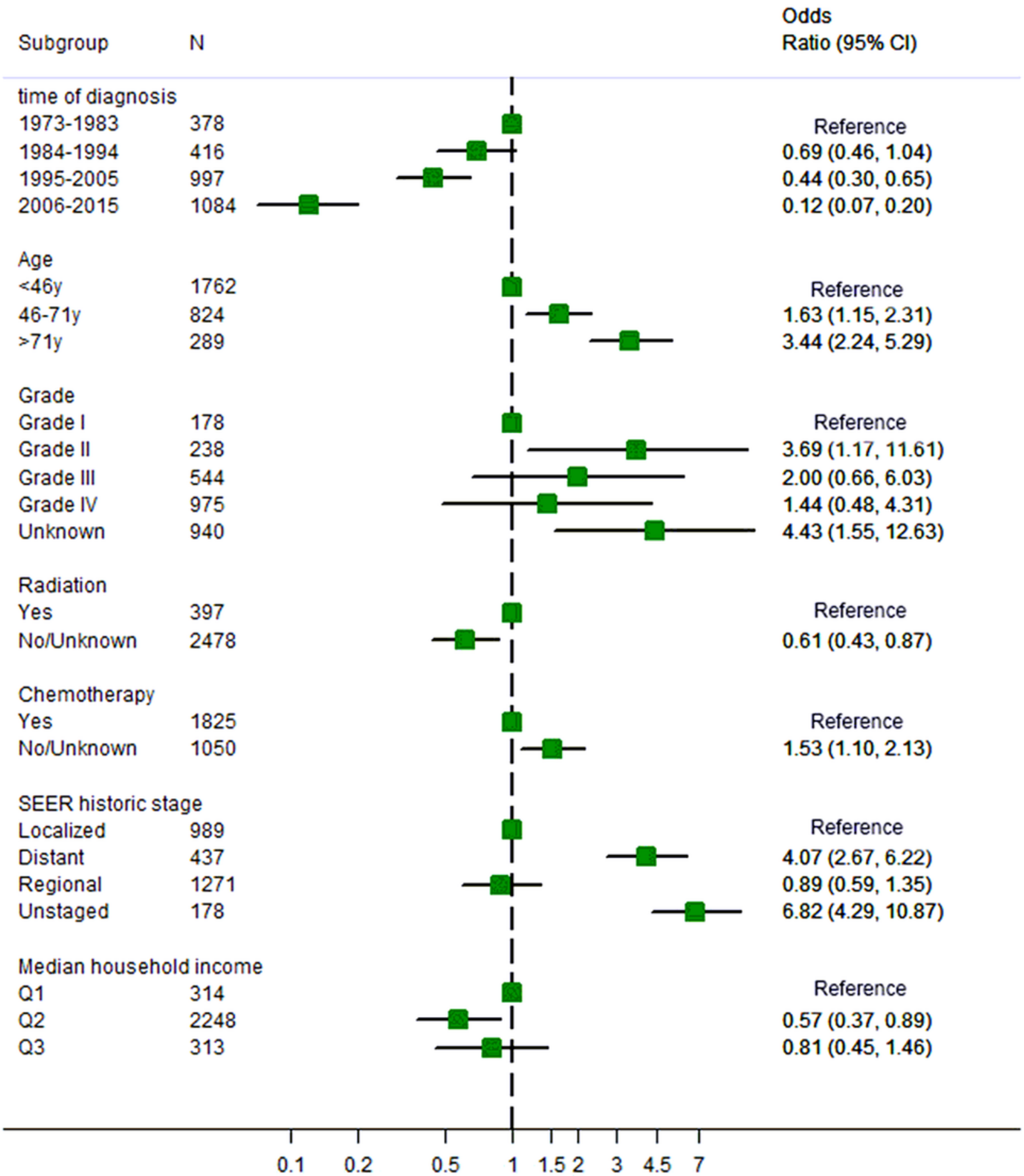

Figure 3

Forest plot of Multivariable Logistic analyses of surgical noncompliance adjusted by time of diagnosis, age, grade, radiation, chemotherapy, SEER historic stage and economic income. 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.

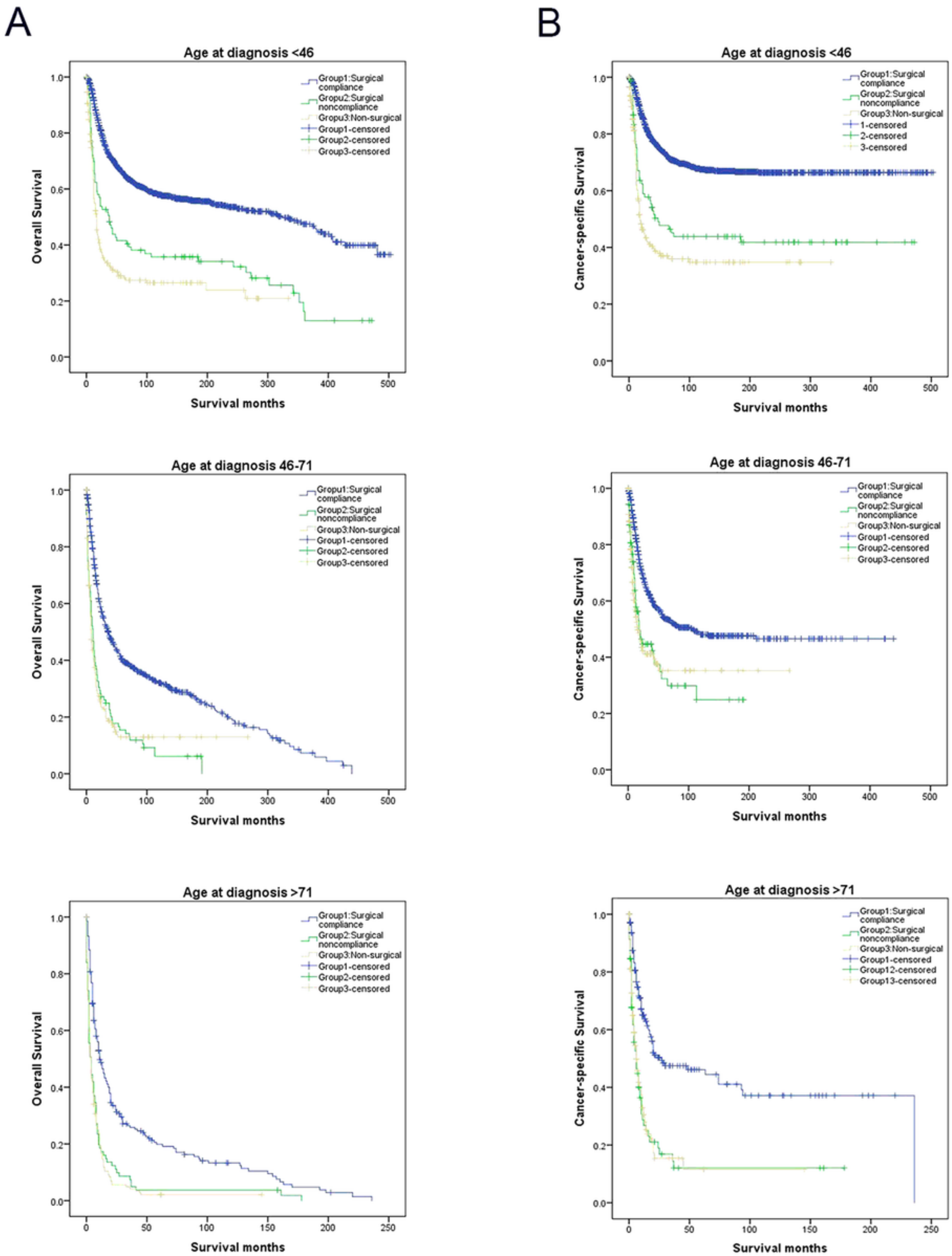

Figure 4

Kaplan-Meier estimates of the Overall survival (A) and Cancer-specific survival (B) for the patients diagnosed in different age among three groups (surgical compliance group; surgical noncompliance group; non-surgical group). The cut-off values of age and economic income were determined by X-tile program.