Prognostic role of primary tumor size in Wilms tumor

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Abstract. Wilms tumor (WT) is the most common childhood malignant kidney tumor. The aim of the present study was to determine the impact of primary tumor size on the survival of patients with WT. The data of 1,523 patients diagnosed with WT between 2000 and 2017 were retrieved from the Surveillance, Epidemiology, and End Results database. Receiver operating characteristic curves were plotted to determine the optimal cut-off value of primary tumor size. Overall survival (OS) and cancer-specific survival (CSS) were analyzed using the Kaplan-Meier method and the Cox proportional hazards regression model. The optimal cut-off value for primary tumor size was found to be 11.15 cm. No significant difference in the distribution of tumor size was detected between male and female patients. However, lymph node metastasis and distant metastasis were significantly more frequent in patients whose tumor was ≥11.15 cm in size compared with those with smaller tumors. In addition, patients with larger tumors exhibited significantly worse OS and CSS rates compared with those with smaller tumors. Furthermore, primary tumor size was identified as an independent prognostic factor for OS and CSS in the multivariate analyses. In summary, the present study indicates that primary tumor size is an independent prognostic factor for patients with WT, and tumors ≥11.15 cm are associated with worse OS and CSS.

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Introduction

Wilms tumor (WT), also known as nephroblastoma, is the most common pediatric malignancy of the kidney (1), and originates from poorly differentiated mesenchymal kidney stem cells (2). It accounts for >90% of pediatric renal tumors and 7% of all childhood cancers (3). In addition, most patients are diagnosed at <5 years of age (4).

The current treatment strategies for WT include surgery, chemotherapy and radiotherapy. Surgical procedures include upfront nephrectomy as recommended by the Children's Oncology Group and nephrectomy following chemotherapy according to the International Society of Pediatric Oncology guidelines (5). The selection of chemotherapy drugs and radiotherapy depends on the risk stratification of the patient (5). In the last several decades, the overall survival (OS) of patients with WT has steadily improved in high-income countries and is ~90%, compared with <50% in low-income countries (6).

Several prognostic factors have been identified for WT, such as the tumor volume after preoperative chemotherapy (7). However, few studies have reported on the prognostic significance of primary tumor size. Therefore, the aim of the present study was to evaluate the association of primary tumor size with the clinicopathological characteristics and survival of patients with WT.

Materials and methods

Study population. The data of 2,443 patients with WT diagnosed between January 2000 and December 2017, inclusively, were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database. The cases were filtered according to the following exclusion criteria: i) Incomplete information on primary tumor size and ii) lack of surgery. Based on these criteria, 1,523 eligible cases were selected for inclusion in the present retrospective study.

Study variables. The covariates for each patient included demographic characteristics, namely age, ethnicity and sex, and clinicopathological characteristics, namely primary tumor size, lymph node status, distant metastasis, the retention or removal of regional lymph nodes and the type of surgery. The main endpoints were OS and cancer-specific survival (CSS). OS was calculated from the date of WT diagnosis to the date of death from any cause or the date of censoring. CSS was calculated from the date of WT diagnosis to the date of death due to this malignancy or

Table I. Association of primary tumor size with demographic and clinicopathological characteristics in patients with Wilms tumor.

Variables	All patients, n (%)	Tumor size <11.15 cm, n (%)	Tumor size ≥11.15 cm, n (%)	P-value
No. of patients	1,523 (100.0)	838 (55.0)	685 (45.0)	
Age, years				<0.001
<5	1,090 (71.6)	642 (76.6)	448 (65.4)	
≥5	433 (28.4)	196 (23.4)	237 (34.6)	
Ethnicity				0.048
White	1,149 (75.4)	645 (77.0)	504 (73.6)	
Black	270 (17.7)	131 (15.6)	139 (20.3)	
Other	104 (6.8)	62 (7.4)	42 (6.1)	
Sex				0.718
Female	826 (54.2)	451 (53.8)	375 (54.7)	
Male	697 (45.8)	387 (46.2)	310 (45.3)	
Lymph node status				<0.001
Negative	1,012 (66.4)	571 (68.1)	441 (64.4)	
Positive	245 (16.1)	101 (12.1)	144 (21.0)	
Unknown	266 (17.5)	166 (19.8)	100 (14.6)	
Distant metastasis				<0.001
No	1,185 (77.8)	698 (83.3)	487 (71.1)	
Yes	318 (20.9)	126 (15.0)	192 (28.0)	
Unknown	20 (1.3)	14 (1.7)	6 (0.9)	
Regional lymph node removal				0.018
No	269 (17.7)	169 (20.2)	100 (14.6)	
Yes	1,244 (81.7)	664 (79.2)	580 (84.7)	
Unknown	10 (0.6)	5 (0.6)	5 (0.7)	
Surgery				<0.001
Non-radical	332 (21.8)	211 (25.2)	121 (17.7)	
Radical	1,191 (78.2)	627 (74.8)	564 (82.3)	

the date of censoring (8). All patients were followed up until the date of death or until December 31, 2017. The cause of death for each patient was obtained from the death certificate.

Statistical analysis. The data were extracted from the SEER database using SEER*Stat Software version 8.4.0 (Information Management Services, Inc.). The optimal cut-off point of primary tumor size was determined by receiver operating characteristic (ROC) curve analysis. Chi-square test was used to compare demographic and clinicopathological variables. The Kaplan-Meier method was used to identify the factors that had a significant association with OS and CSS, and to calculate survival probabilities in different groups, and the log-rank test was used to compare survival rates. The significant indicators identified by the Kaplan-Meier analyses were included in a Cox proportional hazards regression model for multivariate analysis. Statistical significance was determined by calculating the hazard ratio (HR) and 95% confidence intervals (95% CI). Forest plots were drawn using Excel 2019 (Microsoft Corporation). Two-sided P<0.05 was considered to indicate a statistically significant result. All statistical analyses were conducted using SPSS 22.0 (IBM Corp.).

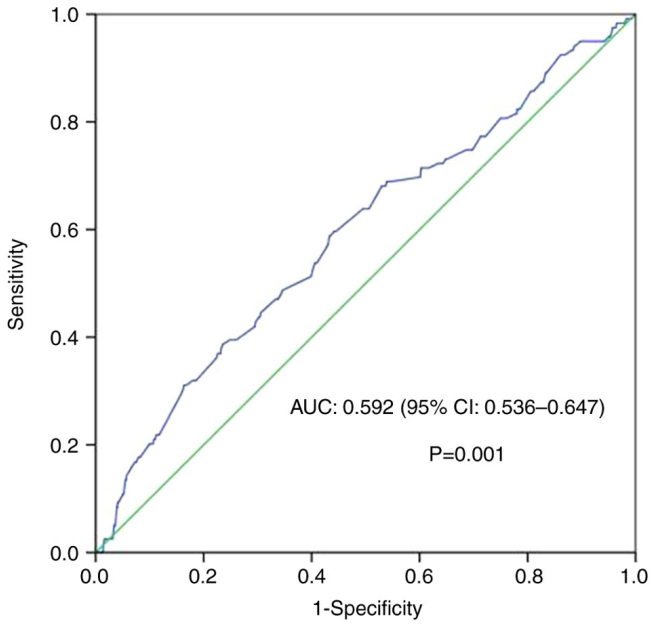

Figure 1. Receiver operating characteristic curve for primary tumor size. AUC, area under the curve; 95% CI, 95% confidence interval.

Table II. Kaplan-Meier predictions of the overall survival and cancer-specific survival of patients with Wilms tumor.

	5-Year overall survival		5-Year cancer-specific survival	
Variables	Probability, % (SEM)	P-value	Probability, % (SEM)	P-value
Age, years		0.002		0.001
<5	94.0 (0.8)		95.0 (0.7)	
≥5	88.6 (1.6)		89.3 (1.6)	
Ethnicity		0.422		0.931
White	92.7 (0.8)		93.1 (0.8)	
Black	91.3 (1.8)		93.2 (1.7)	
Other	92.2 (2.8)		94.7 (2.6)	
Sex		0.345		0.448
Female	92.9 (0.9)		93.6 (0.9)	
Male	91.9 (1.1)		93.1 (1.0)	
Lymph node status		<0.001		<0.001
Negative	95.2 (0.7)		96.1 (0.7)	
Positive	84.6 (2.4)		85.3 (2.4)	
Unknown	89.4 (2.0)		90.5 (1.9)	
Distant metastasis		<0.001		<0.001
No	95.3 (0.7)		96.1 (0.6)	
Yes	82.6 (2.2)		83.5 (2.2)	
Unknown	83.3 (8.9)		88.0 (8.1)	
Regional lymph node removal		0.017		0.052
No	89.1 (2.0)		90.2 (1.9)	
Yes	93.3 (0.8)		94.1 (0.7)	
Unknown	87.5 (11.7)		87.5 (11.7)	
Surgery		0.181		0.084
Non-radical	94.0 (1.4)		94.9 (1.3)	
Radical	92.0 (0.8)		92.9 (0.8)	
Tumor size		0.001		<0.001
<11.15 cm	94.4 (0.9)		95.3 (0.8)	
≥11.15 cm	90.2 (1.2)		91.1 (1.1)	

SEM, standard error of the mean.

Results

Cut-off point identification of primary tumor size. The area under the curve for primary tumor size in the ROC curve analysis was 0.592 (95% CI 0.536-0.647), and the optimal cut-off value was 11.15 cm (sensitivity, 59.7%; specificity, 55.8%; P=0.001; Fig. 1). A total of 1,523 eligible patients with WT were included in the study, of which 838 (55%) patients had a tumor size of <11.15 cm and 685 (45%) patients had a tumor size of ≥11.15 cm. The median follow-up period was 74 months (range 0-167 months). During the time period of the study, 119 (7.8%) patients died, and the cause of death was associated with WT for 102 patients.

Demographic and clinicopathological characteristics. The associations of primary tumor size with demographic and clinicopathological characteristics are summarized in Table I. The analysis revealed a significant association of age and ethnicity with primary tumor size, and indicated that children <5 years old (P<0.001) and of white ethnicity (P=0.048) were more susceptible to WT. However, no significant difference was found in the prevalence of WT between male and female patients (P=0.718). Moreover, lymph node metastasis (P<0.001) and distant metastasis (P<0.001) were more frequent in patients with WT and a tumor size of ≥11.15 cm than in those with tumors <11.15 cm. In addition, regional lymph node removal (P=0.018) and radical surgery (P<0.001) were more frequently performed in patients with larger tumors.

Kaplan-Meier analyses predicting OS and CSS. As shown in Table II, patients with a tumor size ≥11.5 cm had significantly worse OS and CSS than those with tumor size <11.15 cm (P=0.001 and P<0.001, respectively). Moreover, significant associations with OS and CSS were also found for age (P=0.002 and P=0.001, respectively), lymph node status (P<0.001 for both) and distant metastasis (P<0.001 for both). In

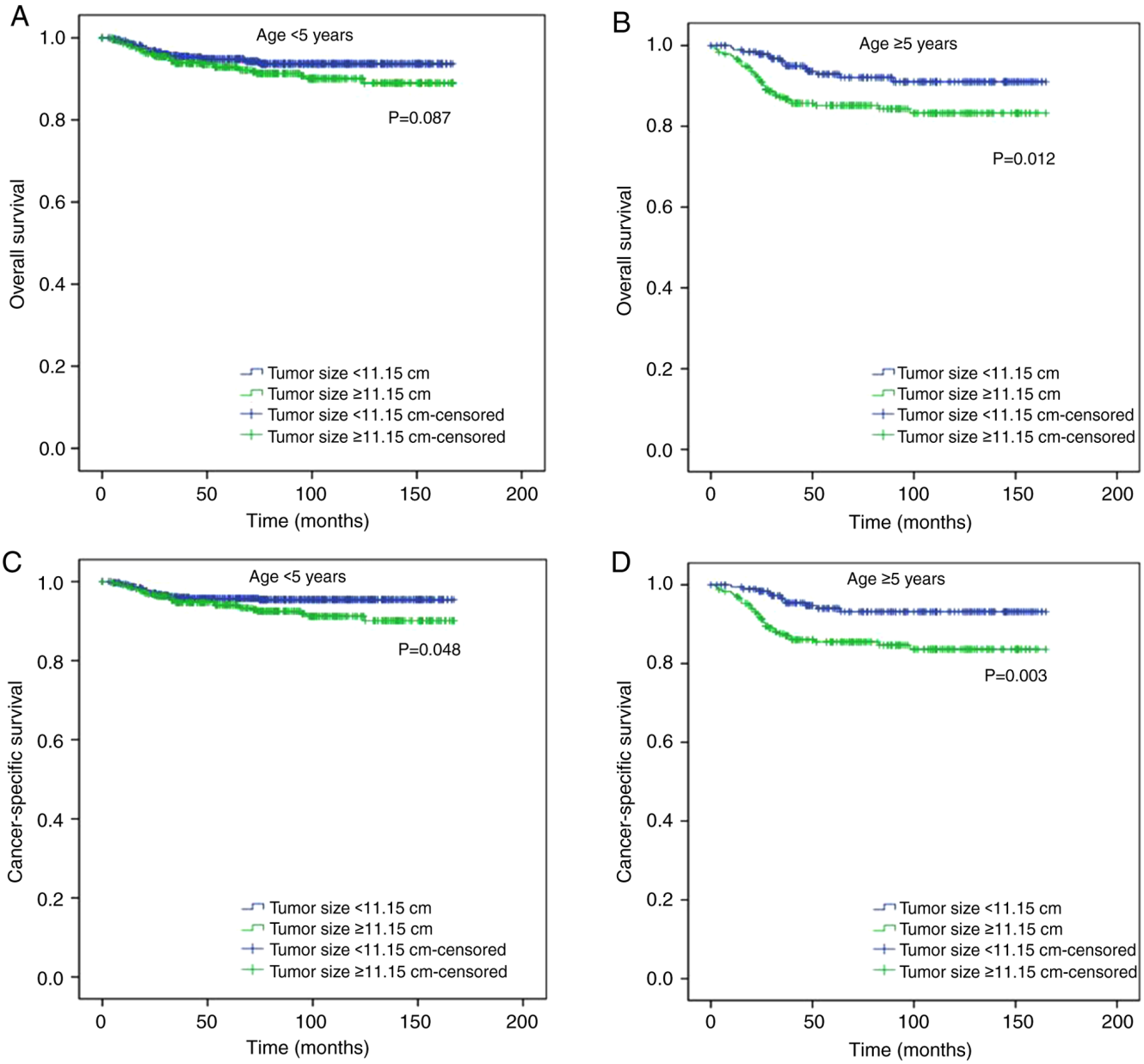

Figure 2. Kaplan-Meier analyses according to patient age stratified by primary tumor size. Overall survival of patients aged (A) <5 years and (B) ≥5 years. Cancer-specific survival of patients aged (C) <5 years and (D) ≥5 years.

addition, regional lymph node removal was also significantly associated with OS (P=0.017). These factors were included in a Cox proportional hazards regression model for multivariate analysis.

Stratified Kaplan-Meier analyses predicting OS and CSS. The stratified Kaplan-Meier analyses revealed that tumor size ≥11.15 cm was significantly associated with worse OS and CSS in the following subgroups: age ≥5 years (P=0.012 and P=0.003, respectively; Fig. 2B and D), white ethnicity (P=0.005 and P=0.001, respectively; Fig. 3A and D), male (P<0.001 for both; Fig. 4B and D), no regional lymph node removal (P=0.003 and P<0.001, respectively; Fig. 5A and C), regional lymph node removal (P=0.027 and P=0.016, respectively; Fig. 5B and D) and radical surgery (P=0.001 and P<0.001; Fig. 6B and D). The results also indicated that tumor size ≥11.15 cm was significantly associated with worse CSS in patients <5 years of age (P=0.048; Fig. 2C), of other ethnicities (P=0.023; Fig. 3F), and with no distant metastasis (P=0.017; Fig. 7C). In addition, tumor size ≥11.15 cm was significantly associated with worse OS in patients with lymph node metastasis (P=0.031; Fig. 8B). Moreover, the removal of regional lymph nodes significantly improved OS (P=0.001; Fig. 9B) and CSS (P<0.001; Fig. 9D) compared with the retention of regional lymph nodes in patients with tumors ≥11.15 cm in size. By contrast, regional lymph node removal had no impact on the OS (P=0.292; Fig. 9A) and CSS (P=0.840; Fig. 9C) of patients with a tumor size of <11.15 cm.

Multivariate analyses of the predictors of OS and CSS. As shown in Figs. 10 and 11, primary tumor size was an independent prognostic factor for OS (HR 1.478, P=0.044) and CSS

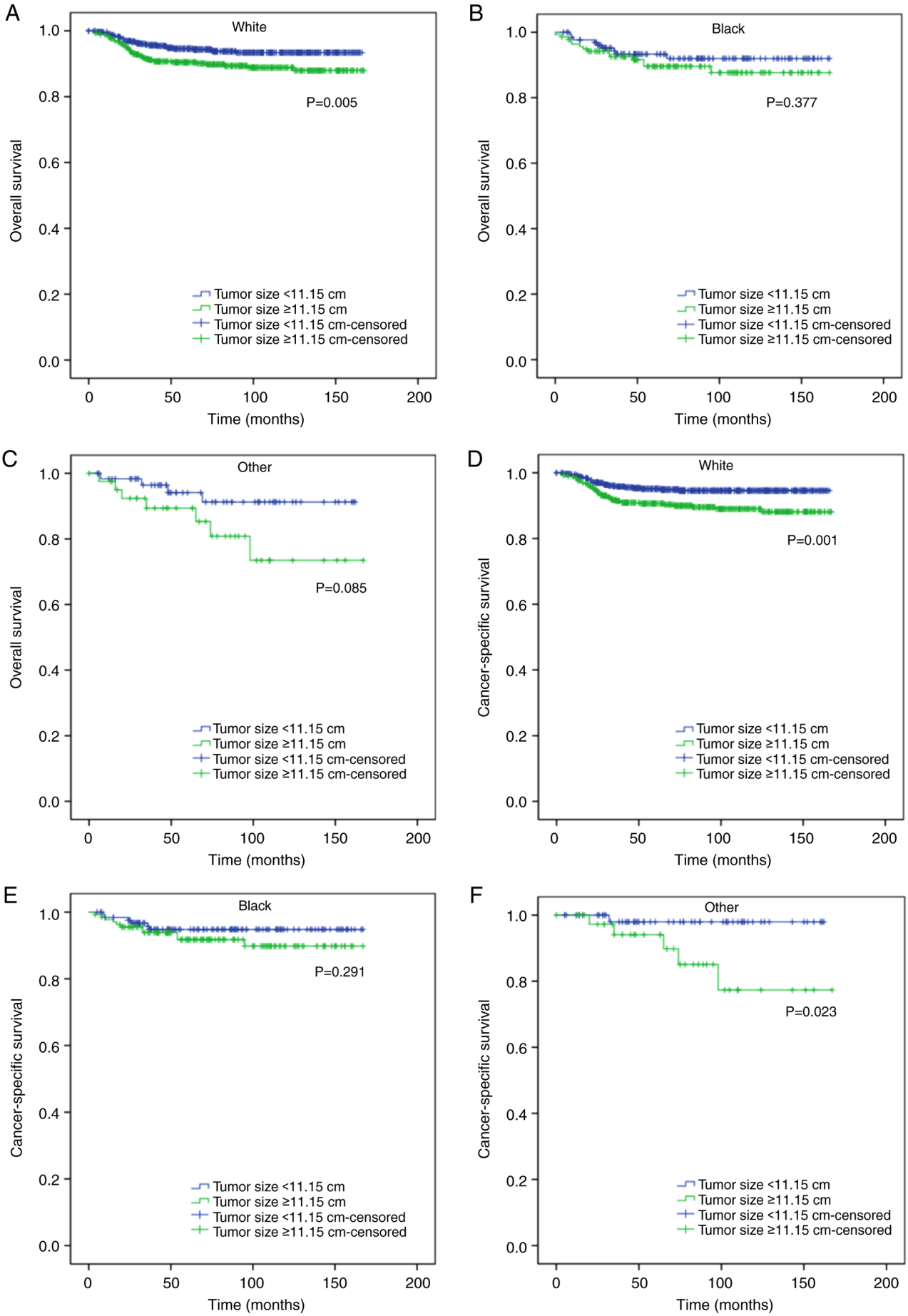

Figure 3. Kaplan-Meier analyses of patient ethnicities stratified by primary tumor size. Overall survival of patients with (A) white, (B) black and (C) other ethnicities. Cancer-specific survival of patients with (D) white, (E) black and (F) other ethnicities.

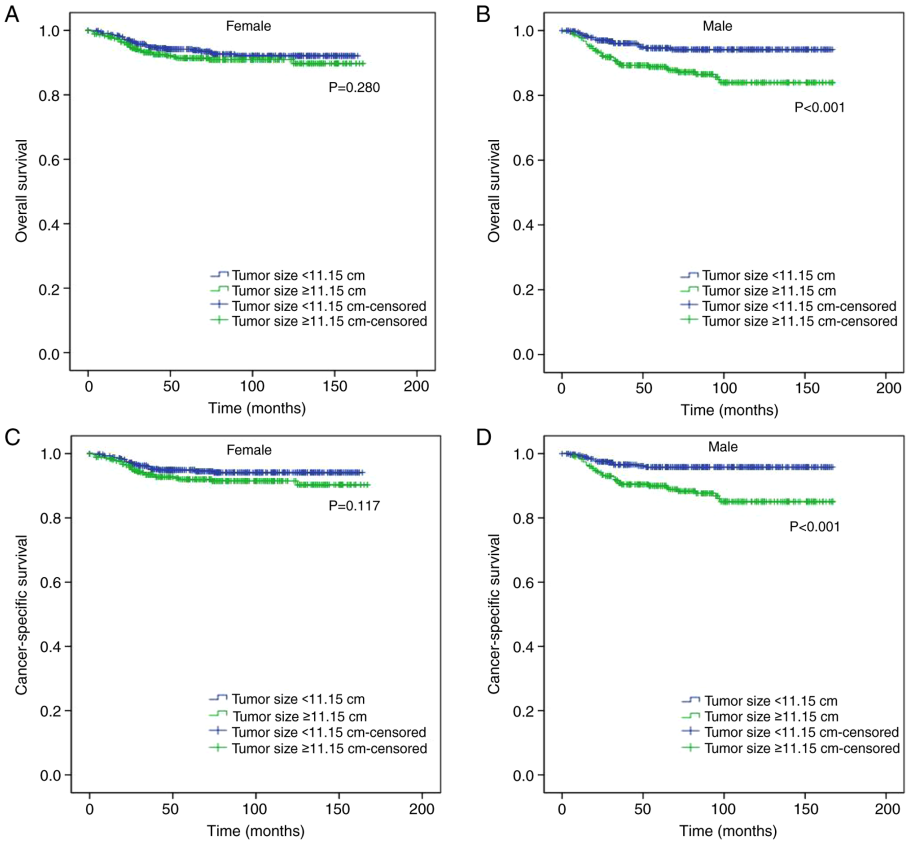

Figure 4. Kaplan-Meier analyses of patient sex stratified by primary tumor size. Overall survival of (A) female and (B) male patients. Cancer-specific survival of (C) female and (D) male patients.

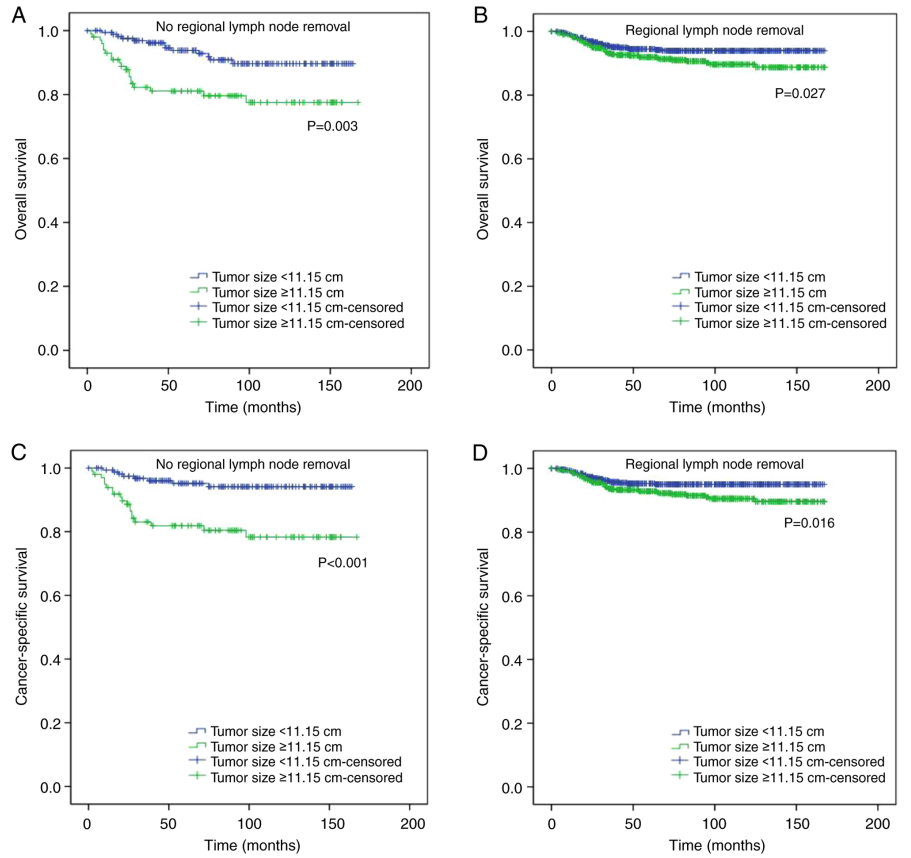

Figure 5. Kaplan-Meier analyses of patients with or without regional lymph node removal stratified by primary tumor size. Overall survival of patients (A) without and (B) with regional lymph node removal. Cancer-specific survival of patients (C) without and (D) with regional lymph node removal.

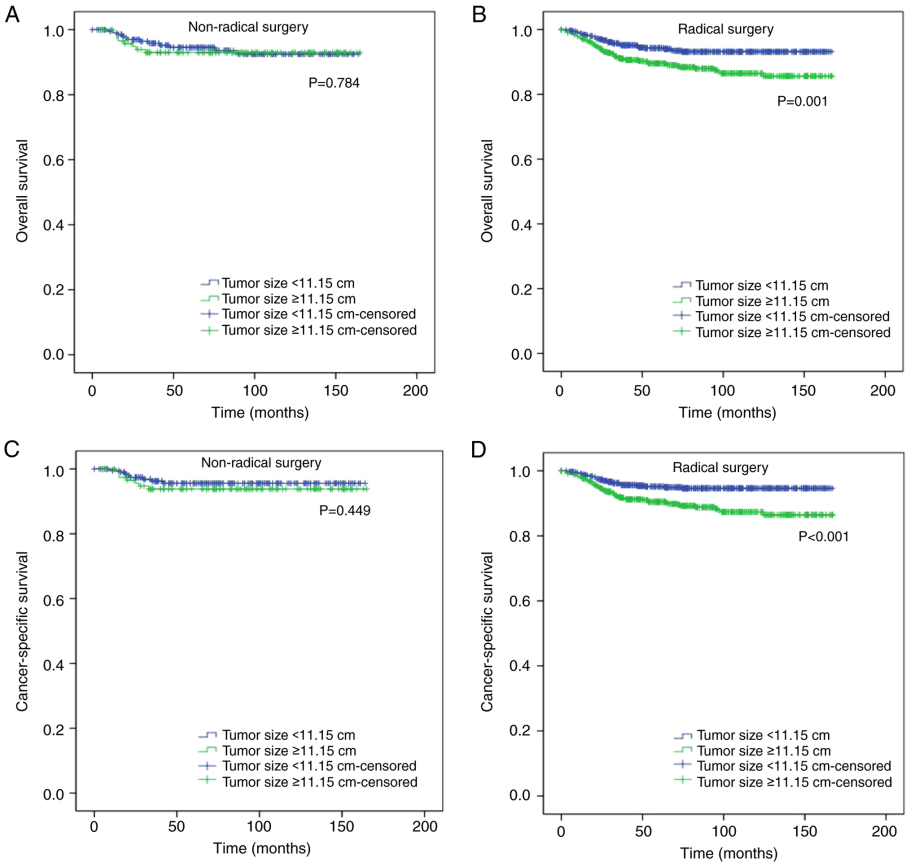

Figure 6. Kaplan-Meier analyses of patients who underwent non-radical or radical surgery stratified by primary tumor size. Overall survival of patients in the (A) non-radical and (B) radical surgery groups, Cancer-specific survival of patients in the (C) non-radical and (D) radical surgery groups.

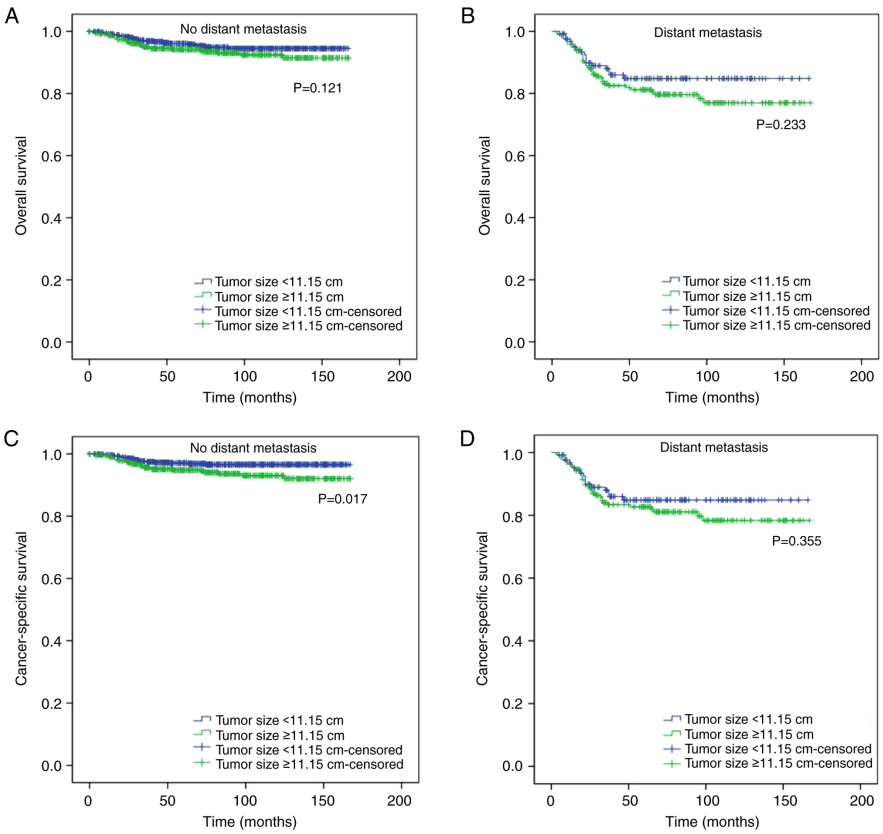

Figure 7. Kaplan-Meier analyses of patients with and without distant metastases in patients stratified by primary tumor size. Overall survival of patients with (A) without and (B) with distant metastasis. Cancer-specific survival of patients (C) without and (D) with distant metastasis.

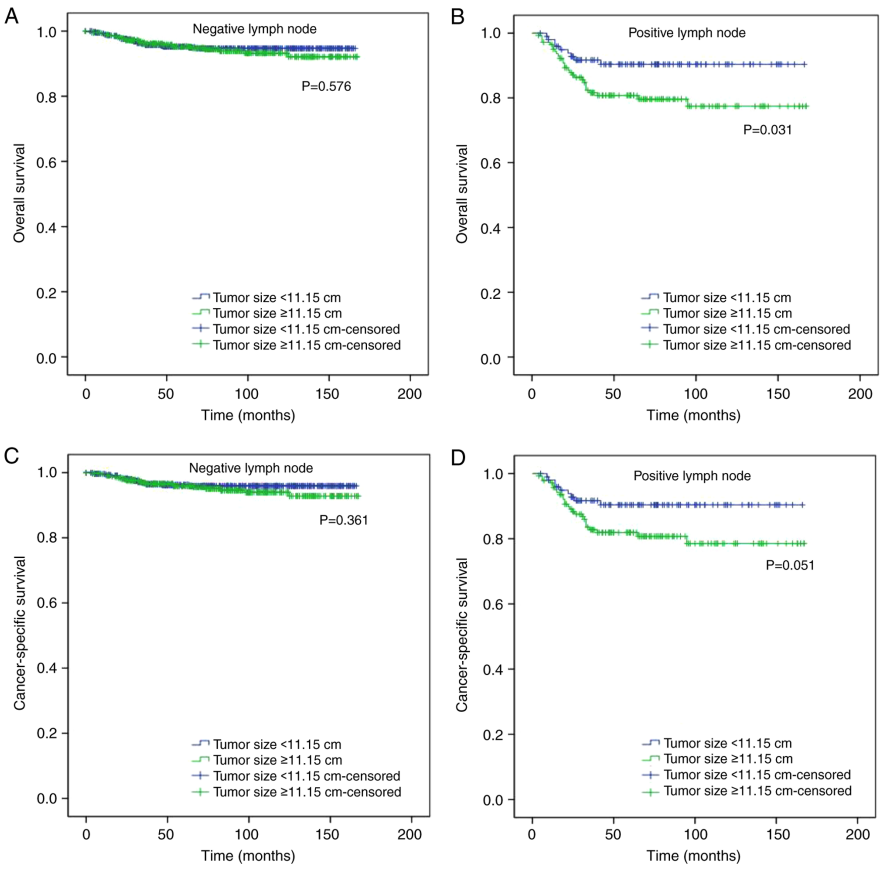

Figure 8. Kaplan-Meier analyses according to lymph node metastasis status in patients stratified by primary tumor size. Overall survival of patients with (A) negative and (B) positive lymph nodes. Cancer-specific survival of patients with metastasis (C) negative and (D) positive lymph nodes.

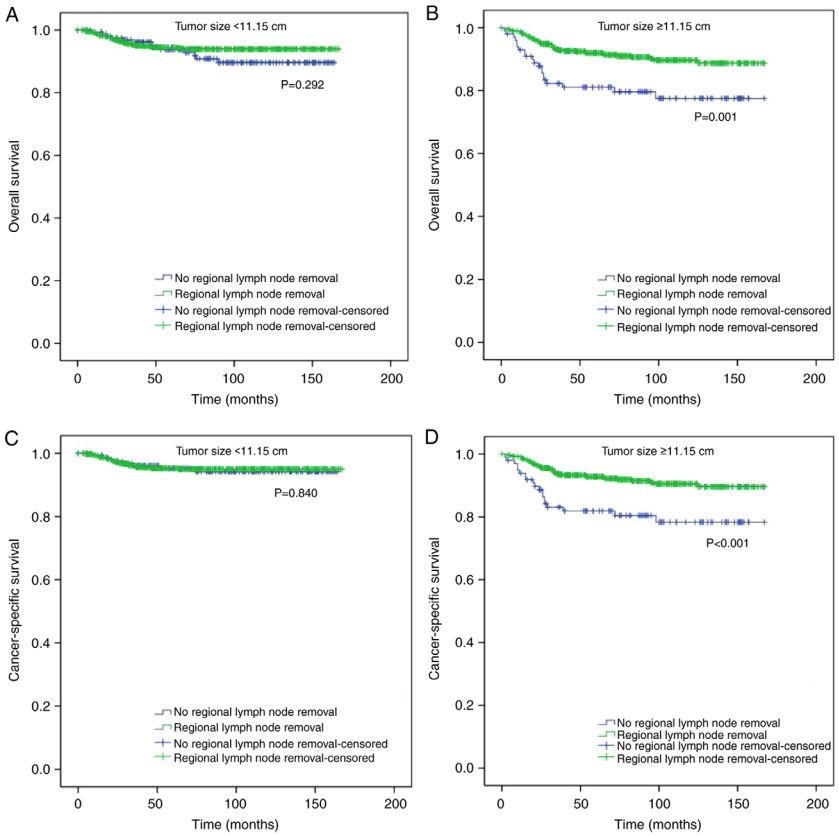

Figure 9. Kaplan-Meier analyses according to tumor size in patients stratified by regional lymph node removal. Overall survival of patients with a tumor size of (A) <11.15 cm and (B) ≥11.15 cm. Cancer-specific survival of patients with a tumor size of (C) <11.15 cm and (D) ≥11.15 cm.

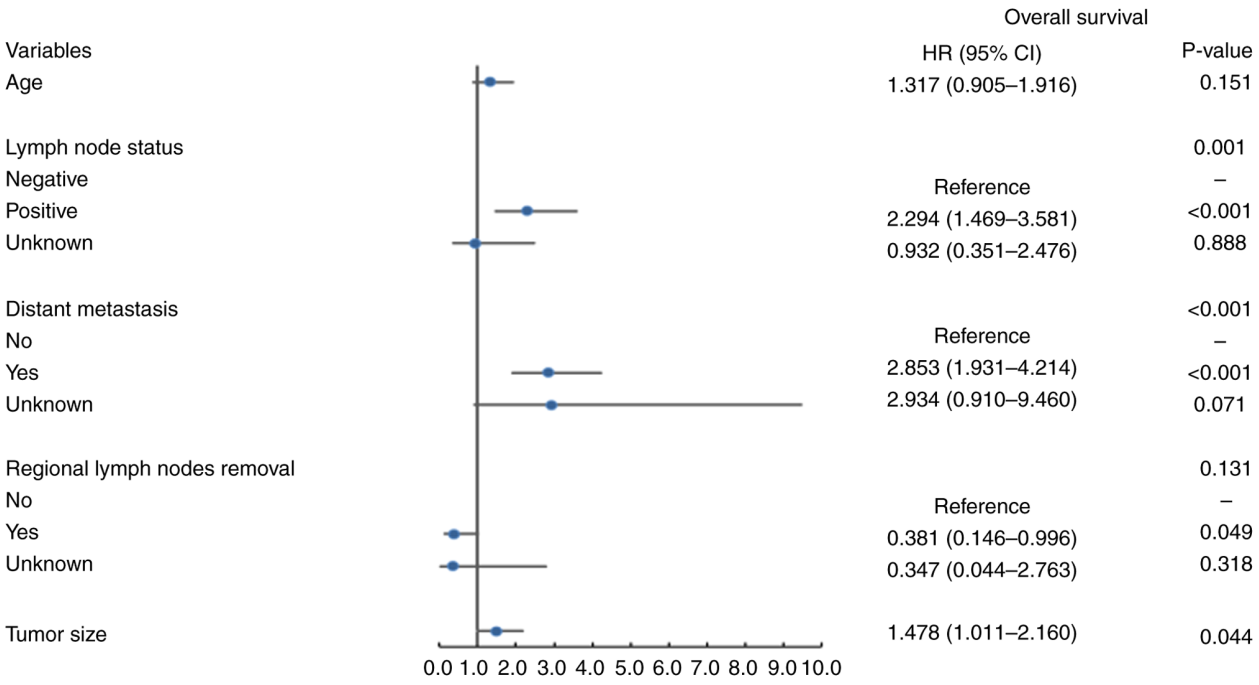

Figure 10. Multivariate Cox regression analyses of the predictors of overall survival.

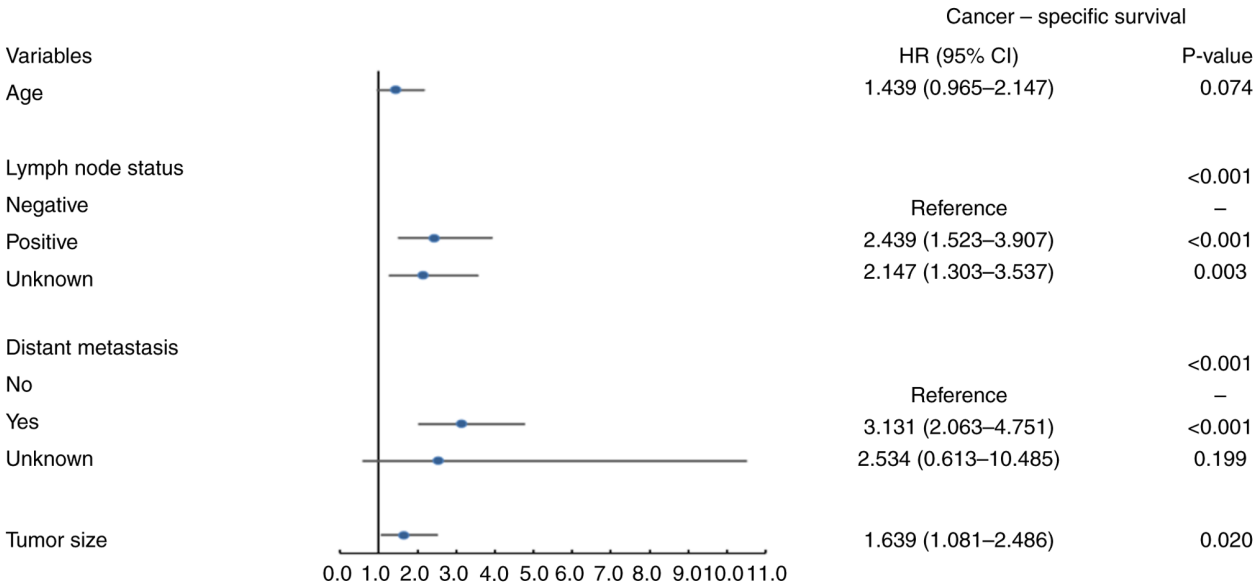

Figure 11. Multivariate Cox regression analyses of the predictors of cancer-specific survival.

(HR 1.639, P=0.020). Moreover, lymph node status (P=0.001 and P<0.001, respectively) and distant metastasis (P<0.001 for both) were also independent predictors for OS and CSS. However, age (HR 1.317, P=0.151 and HR 1.439, P=0.074, respectively) was not significantly associated with OS or CSS, and regional lymph node removal (P=0.131) was not identified as an independent prognostic factor for OS.

Discussion

Despite advances in treatment strategies and the favorable prognosis of most patients with WT, the mortality rate is still 10% (9). Poor outcomes have been reported for advanced, bilateral and recurrent WT (10). Therefore, it is critical to identify novel prognostic factors for WT to guide the development of individualized treatment strategies. The present retrospective study demonstrated that patients with large WT (tumor size ≥11.15 cm) had worse OS and CSS than those with smaller tumors, and primary tumor size was an independent prognostic factor for OS and CSS.

Consistent with a previous study (4), the present study found that WT was more prevalent in children <5 years old. In addition, patients of white ethnicity were more susceptible to WT compared with other racial groups. However, previous studies have shown that the incidence of WT varies widely among different ethnic groups, with black and East Asian

populations having the highest and lowest incidence rates respectively (11,12). Moreover, no significant difference in the incidence of WT was observed in the present study in terms of sex. By contrast, Cunningham *et al* (13) reported that WT was slightly more prevalent among female patients, with the exception of those in Eastern Asia These discrepancies can be explained by differences in the study populations.

In the present study, patients with WT larger tumors had significantly worse OS and CSS compared with those with smaller tumors, and were also more likely to develop lymph node metastasis. Previous studies have shown that lymph node involvement portends a poor prognosis in WT (14-16). Since the patients with WT and positive lymph nodes had significantly lower 5-year OS and 5-year CSS rates compared with those without lymph node involvement in the Kaplan-Meier analyses, we hypothesize that lymph node metastasis is a key cause of the poor prognosis of patients with large tumors. Indeed, the results of the stratified Kaplan-Meier analyses showed that larger tumors were associated with significantly worse OS among patients with lymph node metastasis, whereas tumor size did not affect the prognosis of patients without lymph node involvement. These results further support this hypothesis.

The present study found that the removal of regional lymph nodes significantly improved OS and CSS in the patients with large tumors, while regional lymph node removal had no effect on the survival of patients with smaller tumors. Thus, it is recommended that regional lymphadenectomy should be considered for patients with WT whose tumor is ≥11.15 cm in size to prolong survival. Consistent with these findings, Zhuge *et al* (17) also reported that patients who had not undergone lymph node biopsy had a significantly lower 5-year OS, and the removal of lymph nodes increased the 5-year OS of the patients.

The patients with WT in the present study who had larger tumors were more likely to develop distant metastasis, and distant metastasis was associated with significantly lower 5-year OS and 5-year CSS rates when compared with those for patients without distant metastasis. A previous study also reported a dismal prognosis for patients with WT and distant metastasis (1). Moreover, Iaboni *et al* (18) found that the 5-year OS rate of patients with WT and bone metastases was only 14.3% Thus, distant metastasis is a risk factor in patients with WT who have large tumors.

Reinhard *et al* (19) previously reported that a reduction in tumor volume after preoperative chemotherapy was an effective factor for the stratification of WT patients for postoperative treatment. In addition, Provenzi *et al* (4) found that the tumor volume after preoperative chemotherapy could independently predict poor prognosis in patients with WT. However, the prognostic significance of the primary tumor size of WT has not been thoroughly studied in previous studies. The present study has demonstrated for the first time, to the best of our knowledge, that primary tumor size is an independent prognostic factor for WT, along with lymph node status and distant metastasis.

Although the type of surgery was not found to be significantly associated with the OS and CSS in the Kaplan-Meier analyses, the curves of the stratified Kaplan-Meier analyses indicated that tumor size <11.15 cm was associated with improved OS and CSS in patients with WT who had undergone radical surgery. By contrast, tumor size was shown to have no impact on the OS and CSS of patients who underwent non-radical surgery. Therefore, radical surgery may provide survival benefits for WT patients with a tumor <11.15 cm in size.

In a previous study, Bahoush and Saeedi (20) showed that sex is not an independent predictor of OS in patients with WT, which is consistent with the findings of the present study. Nevertheless, male patients with smaller tumors had significantly improved OS and CSS rates compared with those with larger tumors, whereas no significant difference was observed between the two tumor-size groups in female patients. Differences in sex hormone levels may be an important reason for this result. Similarly, a previous study showed that orchiectomy or estradiol treatment significantly reduced tumor weight in male WT model rats, while testosterone treatment significantly increased tumor weight in female rats (21). Based on these findings, it is recommended that the primary tumor size of male patients with WT should be taken into consideration, in order to provide more effective individualized treatment.

There are several limitations to this retrospective study. Firstly, the SEER database does not include data on adjuvant chemotherapy or comorbidities that may significantly affect survival. In addition, the SEER database does not provide information on whether the patients had undergone pre-operative chemotherapy. Furthermore, all patients included in the study were from the United States. Nevertheless, the present study has shown for the first time that primary tumor size is an independent prognostic factor for WT, which has potential clinical applications.

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Availability of data and materials

Publicly datasets were used in the study and can be found in the SEER database (https://seer.cancer.gov/).

Author's contributions

KL, HXY and CBF conceived and designed the study. KL and KZ collected and analyzed the data. KL, HXY and CBF wrote the manuscript. All authors read and approved the final version of the manuscript. KL and CBF confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Institutional review board approval and informed consent from patients are not required for the study of data from the SEER database, as it is a de-identified public-use database.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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