European Review for Medical and Pharmacological Sciences 2024; 28: 1095-1102

Survival assessment of nephron-sparing surgery or radical nephrectomy in children with unilateral Wilms tumor receiving adjuvant chemotherapy: a retrospective cross-sectional study

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Abstract. – OBJECTIVE: Surgical treatment of unilateral Wilms tumor (WT) in children is controversial. In this study, we aimed to evaluate the survival and prognosis of radical nephrectomy (RN) and nephron-sparing surgery (NSS) in children with unilateral WT receiving adjuvant chemotherapy.

PATIENTS AND METHODS: Data on pediatric patients with WT were collected from the Surveillance, Epidemiology, and End Results (SEER) database from 2000 to 2019. Multivariate logistic regression was used to analyze factors influencing the choice of surgical strategy. Cox proportional hazard models were used to assess factors associated with overall survival.

RESULTS: We included 1,825 patients with unilateral WT (<14 years) who received adjuvant chemotherapy and surgery. Between 2000 and 2019, the percentage of patients treated with NSS increased from 4% in 2000 to 8% in 2019. There was no significant difference in 10-year overall survival between the two surgical strategies [NSS vs. RN, 93.26% (95% CI, 86.88%-100%) *vs.* 92.17% (95% CI, 90.75%-93.61%), *p*=0.98]. Patients with unilateral WTs ≤4 cm were more likely to be treated with NSS. There was no survival benefit for patients treated with RN compared with that for those treated with NSS (HR, 0.74; 95% CI, 0.29-1.86; *p*=0.5).

CONCLUSIONS: The use of NSS in children with unilateral WT has increased over the last two decades. Tumor size is an important influencing factor for the surgical application of NSS. Patients who underwent NSS had an equivalent OS compared with the overall group of patients with unilateral tumors who received RN.

Key Words:
Wilms tumor, Nephron-sparing surgery, Radical nephrectomy, Pediatric.

Introduction

Wilms tumor (WT) is the most common renal tumor in children, accounting for approximately 95% of all pediatric renal malignancies[1]. With developments brought about by the collaboration between large international groups, the overall survival (OS) of children with WT has increased to >90%[2]. Therefore, the current focus is on how to better protect renal function in children and improve long-term outcomes for patients with WT[3]. Radical nephrectomy (RN) is still recommended by the Children's Oncology Group (COG) and the International Society of Pediatric Oncology (SIOP) for children with unilateral WT. However, some studies[3,4] have shown that damage to the renal function of patients is substantial, and problems such as renal and cardiovascular system dysfunction may occur during long-term follow-up. Therefore, more and more clinicians are attempting to identify new surgical alternatives.

Nephron-sparing surgery (NSS) is widely used for the treatment of adult renal cancer[5-7]. The basic goal is to completely remove the renal tumor while preserving the renal parenchyma as much as possible to maintain long-term normal renal function and prevent the development of distant renal failure. The use of NSS in adults with early-stage renal cancer can reduce the incidence of long-term deterioration of renal function[8]. While RN is considered the global standard of care for unilateral Wilms tumors in patients without known genetic predisposition, there has been a growing interest and use of nephron-sparing approaches in anatomically favorable unilateral WT following neoadjuvant chemotherapy[9]. Data on NSS in terms of maintaining long-term renal function, cardiovascular function, and overall health provide insights into the potential applicability of NSS in children with WT. Therefore, more and more patients with unilateral WT undergo NSS, and

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promising results have been achieved[10,11]. With few isolated institutional case series available, the existing literature lacks comprehensive data regarding the utilization of NSS for WT and its corresponding specific outcomes[12], which may be one of the main reasons why NSS is not widely used.

This study involved screening and analyzing numerous clinical cases from the Surveillance, Epidemiology, and End Results (SEER) database. Considering that all patients included in the SEER database are based in the US, it is reasonable to assume that most, if not all, of these patients, were treated following the COG protocols, which typically do not involve the use of neoadjuvant chemotherapy. Although the SEER database does not contain detailed information on staging, changes in renal function, safety margin status, and recurrence, it does provide valuable hypothesis-generating data that were analyzed using Kaplan-Meier statistics and Cox proportional hazard regression.

Patients and Methods

Study Population

The SEER database (http://seer.cancer.gov) was searched to identify patients diagnosed with WT (ICD-O-3:8960) as the first primary malignancy between 2000 and 2019. The exclusion criteria were as follows: 1) bilateral or unknown; 2) age >14 years; 3) unknown follow-up time and survival status; and 4) no chemotherapy. The SEER database covers more than 30% of the population of 18 states in the United States. It contains detailed and reliable clinical data and relatively complete follow-up information.

Variable Selection

Information on multiple variables regarding selected study participants was extracted. Demographics included age at diagnosis (≤1 year, 2-4 years, and 5-14 years), sex (male and female), ethnicity (white, black, and other), and disease-specific factors such as the type of surgery (NSS and RN), year of diagnosis (2000-2005, 2006-2010, 2011-2015, and 2016-2019), radiotherapy (yes and no/unknown), laterality (left and right), size (≤4 cm, >4 cm, and unknown), regional lymph nodes confirmed by pathology (negative, positive, and unknown), stage (local, regional, distant, and unknown), follow-up time, and vital status (alive and dead).

Statistical Analysis

Patient clinical characteristics were compared using the χ^2 appropriate test or Fisher's exact test. A trend test was used to assess changes in the use of different surgical strategies over time. The Kaplan-Meier method and log-rank test were used for survival analysis. Multivariate logistic regression was used to analyze the factors influencing different surgical strategies. Cox proportional hazard models were used to assess the factors associated with OS. The test was two-sided, and $p<0.05$ was considered statistically significant. All data analyses were performed using R (http://www.R-project.org) or SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 1,825 patients with unilateral WT who received adjuvant chemotherapy and surgery were included in our study: 83 patients (4.5%) received NSS, and 1,742 patients (95.5%) received RN. The proportion of male and female patients was equal. About half the patients (48.9%) were treated at 2-4 years of age, and 23.1% and 28.0% of patients were treated within 1 year and after 5 years of age, respectively. A total of 350 (19.2%) patients had distant metastases (Table I).

We examined pediatric patients under 14 years of age with unilateral WT who received surgical therapy from 2000 to 2019. There was a significant increase of 4.0% in the use of NSS over time, from 4 (4.0%) of 93 patients in 2000 to 6 (8.0%) of 76 patients in 2019 (test for trend, $p=0.003$). In particular, the proportion of NSS has been increasing since 2010, possibly due to the advancement in surgical techniques and the greater benefit of NSS in children (Figure 1).

Survival analysis showed that the 5-year survival rate for children with WT receiving NSS was 95.7% [95% confidence interval (CI), 0.909-1] and the 10-year survival rate was 93.3% (95% CI, 0.869-1), while those who received RN had a 5-year survival rate of 93.8% (95% CI, 0.926-0.951) and a 10-year survival rate of 92.2% (95% CI, 0.907-0.936), with no significant difference between the two surgical strategies ($p=0.98$) (Figure 2A). The 5-year survival rate was 95.7% (95% CI, 0.936-0.978) for patients treated when they were under 1 year, 93.8% (95% CI, 0.922-0.955) for those treated when they were 2-4 years old, and 92.6% (95% CI, 0.901-0.951) for those treated when they were older than 5 years ($p=0.081$) (Fig-

Table I. Characteristics of pediatric patients with Wilms tumor who underwent NSS or RN.

	All (n = 1,825)	NSS (n = 83)	RN (n = 1,742)	p
Age, years				0.035
0-1	422 (23.12)	21 (25.30)	401 (23.02)	
2-4	893 (48.93)	49 (59.04)	844 (48.45)	
5-14	510 (27.95)	13 (15.66)	497 (28.53)	
Sex				0.175
Female	978 (53.59)	51 (61.45)	927 (53.21)	
Male	847 (46.41)	32 (38.55)	815 (46.79)	
Ethnicity				0.736
Black	316 (17.32)	17 (20.48)	299 (17.16)	
Other	111 (6.08)	5 (6.02)	106 (6.08)	
White	1,398 (76.60)	61 (73.49)	1,337 (76.75)	
Year				0.313
2000-2005	514 (28.16)	18 (21.69)	496 (28.47)	
2006-2010	483 (26.47)	21 (25.30)	462 (26.52)	
2011-2015	491 (26.90)	23 (27.71)	468 (26.87)	
2016-2019	337 (18.47)	21 (25.30)	316 (18.14)	
Size, cm				< 0.001
≤ 4	102 (5.59)	23 (27.71)	79 (4.54)	
> 4	1,335 (73.15)	43 (51.81)	1,292 (74.17)	
Unknown	388 (21.26)	17 (20.48)	371 (21.30)	
Regional nodes				< 0.001
Negative	1,244 (68.16)	40 (48.19)	1204 (69.12)	
Positive	308 (16.88)	7 (8.43)	301 (17.28)	
Unknown	273 (14.96)	36 (43.37)	237 (13.61)	
Radiation				0.001
Yes	922 (50.52)	26 (31.33)	896 (51.44)	
None/Unknown	903 (49.48)	57 (68.67)	846 (48.56)	
Stage				< 0.001
Localized	607 (33.26)	46 (55.42)	561 (32.20)	
Regional	519 (28.44)	17 (20.48)	502 (28.82)	
Distant	350 (19.18)	10 (12.05)	340 (19.52)	
Unknown	349 (19.12)	10 (12.05)	339 (19.46)	
Laterality				0.399
Left	929 (50.90)	38 (45.78)	891 (51.15)	
Right	896 (49.10)	45 (54.22)	851 (48.85)	

ure 2B). Among different ethnicities, white people had the highest 5-year survival rate compared with those who were black or of other ethnicities [black *vs.* white *vs.* other, 92.8% (95% CI, 0.897-0.959) *vs.* 94.4% (95% CI, 0.931-0.957) *vs.* 91.0% (95% CI, 0.856-0.968), p=0.007] (Figure 2C). The 5-year survival rate was significantly lower in patients with regional node positivity than that in those with regional node negativity [positive *vs.* negative, 86.6% (95% CI, 0.826-0.908) *vs.* 96.0% (95% CI, 0.948-0.972), p<0.0001] (Figure 2D). The 5-year survival rate of patients with distant metastases was significantly lower than that of patients without distant metastases [distant *vs.* regional *vs.* localized: 85.7% (95% CI, 0.818-0.898) *vs.* 94.7% (95% CI, 0.926-0.968) *vs.* 97.9% (95% CI, 0.967-0.992), p<0.0001] (Figure 2E). In addition, we found that the 5-year survival rate of patients who received radiotherapy was significantly lower than that of patients who did not receive radiotherapy [yes *vs.* no/unknown, 91.4% (95% CI, 0.895-0.934) *vs.* 96.4% (95% CI, 0.951-0.977), p=0.00019] (Figure 2F).

Multivariate logistic regression was performed to assess the factors influencing surgical strategy. The results showed that tumors ≤4 cm in size were more likely to be treated with NSS [odds ratio (OR), 0.1427, 95% CI, 0.078-0.2648, p<0.001]. However, we did not find that other clinical features, such as regional lymph node positivity or tumor stage, were associated with NSS, although previous reports in the literature have indicated that these features may influence the decision to perform surgery (Table II).

The Cox proportional hazards model showed that surgical strategy was not an independent prognostic factor for OS, and patients with unilateral WT who received RN had no survival benefit

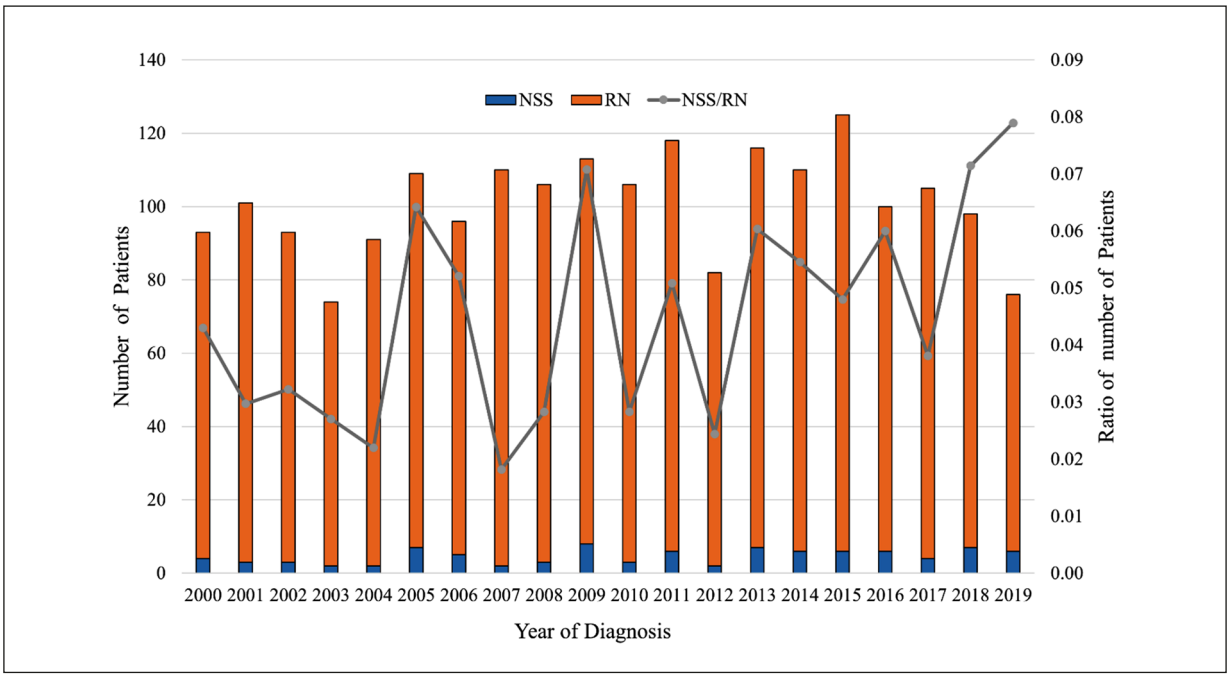

Figure 1. Receipt of NSS and RN for children with WT from 2000 to 2019. NSS, nephron-sparing surgery; RN, radical nephrectomy; WT, Wilms tumor.

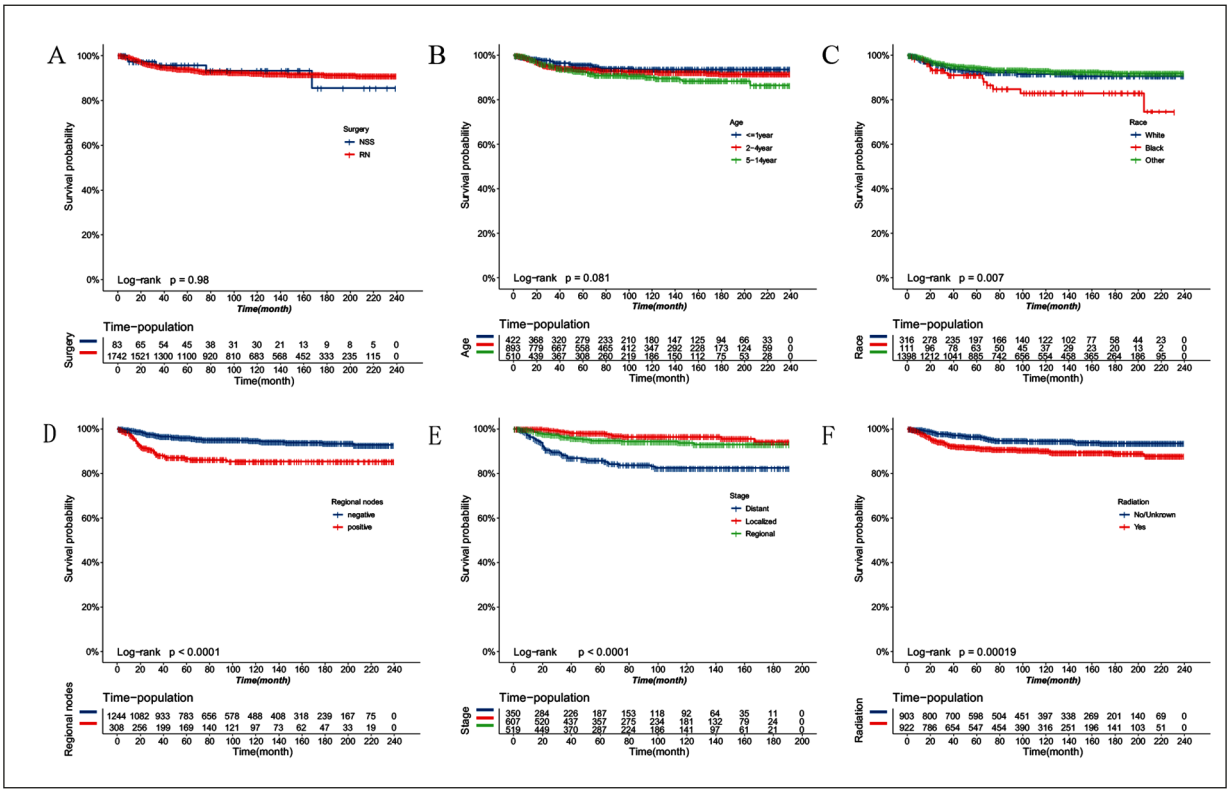

Figure 2. Kaplan-Meier analysis of children with WT. Survival according to surgical management strategy (**A**), survival by age (**B**), survival by race (**C**), survival by the regional nodes (**D**), survival by the stage (**E**), and survival by radiation (**F**). WT, Wilms tumor.

Table II. Multivariable logistic regression analysis of NSS.

Characteristic	OR (95% CI)	p
Age, years		
≤ 1	1 (Reference)	
2-4	0.7847 (0.4324-1.3820)	0.4112
5-14	1.8829 (0.8796-4.1695)	0.1083
Sex		
Female	1 (Reference)	
Male	1.3680 (0.8460-2.2433)	0.2062
Race		
White	1 (Reference)	
Black	0.8234 (0.4644-1.5321)	0.5211
Other	1.0483 (0.4152-3.2777)	0.9274
Year		
2000-2005	1 (Reference)	
2006-2010	1.0609 (0.4504-2.3946)	0.889
2011-2015	0.6942 (0.2995-1.5378)	0.3795
2016-2019	0.4914 (0.2093-1.1067)	0.0928
Size, cm		
> 4	1 (Reference)	
≤ 4	0.1427 (0.0783-0.2648)	< 0.0001
Unknown	0.1851 (0.0790-0.4844)	0.0002
Regional nodes		
Negative	1 (Reference)	
Positive	0.6925 (0.2852-1.8666)	0.4371
Unknown	0.1933 (0.1155-0.3235)	< 0.0001
Radiation		
None/Unknown	1 (Reference)	
Yes	1.5616 (0.8562-2.9079)	0.1519
Stage		
Localized	1 (Reference)	
Regional	1.6819 (0.8671-3.3988)	0.134
Distant	2.1505 (0.9527-5.2212)	0.076
Unknown	7.5285 (2.1465-25.4857)	0.0013
Laterality		
Left	1 (Reference)	
Right	0.8881 (0.5493-1.4309)	0.6261

If the OR is less than one, NSS is more likely. NSS, nephron-sparing surgery; OR, odds ratio; CI, confidence interval.

compared with those who underwent NSS [hazard ratio (HR), 0.74, 95% CI, 0.29-1.87, p=0.5]. Regional node positivity was associated with a higher risk of death than regional node negativity (HR, 1.96, 95% CI, 1.23-3.12, p=0.004). In addition, patients with distant metastases had a higher risk of death than patients with localized tumors (HR, 3.80, 95% CI, 2.01-7.18, p<0.001]. Interestingly, we observed a lower risk of death (p<0.05) among patients who underwent surgery after 2005 (Table III).

Discussion

Long-term survival and a good quality of life are particularly important in pediatric patients with WT. Studies[13] have shown that end-stage renal disease has become the second leading cause of long-term death in children with WT. Therefore, preserving as many nephrons as possible and reducing the incidence of long-term renal insufficiency or end-stage renal disease can improve the long-term survival of children. Previously, RN was the gold standard for the treatment of unilateral WT. This is because of its ability to avoid positive margins, residual tumors, and recurrence[14-16]. However, patients with RN have deteriorated renal function after long-term follow-up[17]. To avoid these adverse effects, surgery

Table III. Cox proportional hazards regression analysis of overall survival.

Characteristic	HR (95% CI)	p
Age, years		
≤ 1	1 (Reference)	
2-4	1.03 (0.61-1.73)	> 0.9
5-14	1.3 (0.75-2.26)	0.3
Sex		
Female	1 (Reference)	
Male	1.29 (0.90-1.85)	0.2
Ethnicity		
White	1 (Reference)	
Black	1.22 (0.76-1.94)	0.4
Other	2.44 (1.40-4.25)	0.002
Year		
2000-2005	1 (Reference)	
2006-2010	0.54 (0.33-0.89)	0.016
2011-2015	0.38 (0.21-0.67)	< 0.001
2016-2019	0.43 (0.19-0.97)	0.041
Size, cm		
> 4	1 (Reference)	
≤ 4	0.56 (0.20-1.56)	0.3
Unknown	1.09 (0.42-2.81)	0.9
Regional nodes		
Negative	1 (Reference)	
Positive	1.96 (1.23-3.12)	0.004
Unknown	1.54 (0.95-2.49)	0.079
Radiation		
None/Unknown	1 (Reference)	
Yes	1.12 (0.70-1.79)	0.6
Stage		
Localized	1 (Reference)	
Regional	1.35 (0.69-2.64)	0.4
Distant	3.8 (2.01-7.18)	< 0.001
Unknown	0.98 (0.32-2.96)	> 0.9
Laterality		
Left	1 (Reference)	
Right	0.84 (0.59-1.21)	0.4
Surgery		
NSS	1 (Reference)	
RN	0.74 (0.29-1.87)	0.5

HR, hazard ratio; NSS, nephron-sparing surgery; RN, radical nephrectomy; CI, confidence interval.

using NSS as an alternative treatment for unilateral WT has attracted considerable attention[18].

Our study demonstrates an overall trend of increasing use of NSS in children with unilateral WT over the last two decades. The use of NSS in children might have attracted the attention of pediatricians owing to the successful application of NSS technology in adult renal cancer[19]. Interestingly, in recent years, NSS may be relatively more frequent in some patients possibly due to increased patient screening and monitoring. Therefore, we need further research to determine the sustainability of this trend and the factors affecting patients' selection of NSS, including the child's condition, tumor characteristics, and case connections.

As the application of NSS in unilateral WT is not yet mature, the indication for surgery remains controversial. Our study demonstrated a lower risk of NSS in patients with unilateral WT ≤4 cm, which is consistent with previous results[20,21]. Tricard et al[20] systematically evaluated 4,288 children with unilateral nephroblastoma who underwent RN (3,994 cases) and NSS (294 cases) in 14 publications and concluded that small tumors ≤4 cm were an indication for NSS. In a study[22] on adult renal cancer, patients with renal tumors >4 cm had higher complication rates and prolonged hospital stays after receiving NSS than patients with renal tumors with a diameter ≤4 cm. WTs are not biopsied prior to surgery, and tumors greater than 4 cm are more likely to be WTs (especially among those aged 5-9 years old). As a result, tumors greater than 4 cm may have undergone RN because there was a higher suspicion they were WTs prior to surgery. However, although the current surgical indications for NSS in children with unilateral WT are not uniform, we cannot blindly retain the nephrons, as this may lead to residual tumors in the residual renal tissue, increasing the probability of tumor recurrence.

Other studies[23,24] have shown that regional lymph node positivity and distant metastasis can influence the decision to perform surgery. We found no effect of lymph node positivity on the two surgical strategies. However, the multiple logistic regression analysis showed an association between the surgical strategy and unknown lymph node status. This may be due to inadequate sampling of regional lymph nodes in both groups of patients. As shown in Table I, 43% of NSS patients had an unknown nodal status *vs.* only 13% of RN patients. However, current guidelines from SIOP and COG recommend thorough sampling of lymph nodes. Adequate sampling of lymph nodes can help prevent recurrence and ensure long-term survival in patients with WT. Importantly, the involvement of lymph nodes remains an independent prognostic risk factor, as determined by subsequent Cox model analysis. Therefore, standardized lymph node sampling is crucial regardless of the surgical strategies.

As reported in other studies[15,25], our results demonstrate no difference in survival among pediatric patients with unilateral WT who received NSS and those who received RN. It appears that patients who received NSS potentially gained a survival advantage over those who received RN, although the difference was not statistically significant. The potential benefit of NSS may be due to better renal function and reduced incidence of cardiovascular diseases[8,26]. However, it is worth noting that patients in the RN group had larger tumors and a higher proportion of patients receiving radiation therapy, indicating a potentially poorer prognosis in the RN group. This potential bias should be taken into consideration.

Limitations

There are some limitations to our study which need to be considered when interpreting our results. Our data were obtained from the SEER database, which may have excluded certain confounding factors such as renal function changes, safety margin state, and presence or absence of diffuse anaplasia that could potentially impact our conclusion. Researchers should address this limitation by conducting multicenter, double-blind, randomized controlled trials to support this evidence in the future.

Conclusions

The use of NSS in children with unilateral WT has increased over the last two decades. Tumor size is an important influencing factor for surgical application of NSS. Patients who underwent NSS had an equivalent OS compared with the overall group of patients with unilateral tumors who received RN.

Conflict of Interest

The authors declare that they have no conflict of interests.

Informed Consent

Not applicable.

Ethics Approval
This study used previously collected deidentified data available in the SEER database, and thus, the study did not require approval.

Authors' Contribution
Conceptualization, WXW, ZPP, and DQ; formal analysis: WXW, ZPP; writing-review and editing: WXW, DQ; All authors have read and agreed to the published version of the manuscript.

Funding
This research received no external funding.

Data Availability
Patients data were collected from the Surveillance, Epidemiology, and End Results (SEER) database. The data produced by this study are made available by authors upon reasonable request..

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