Clinical characteristics of testicular non-seminomatous germ cell tumor from West China: a 10-year experience

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To the Editor: Testicular tumor represents 1% of male neoplasms and 5% of urogenital tumors. Non-seminomatous germ cell tumor (NSGCT) accounts for nearly 40% of all testicular cancers. The survival of patients with NSGCT has been improved because of advanced multimodal therapies (orchiectomy, and if necessary, subsequent chemotherapy).[1] However, to the best of our knowledge, survival of NSGCT patients has not been studied in a large Chinese cohort yet. Therefore, this study assessed the clinical characteristics, treatments, and outcomes of patients with NSGCT.

Information on patients with NSGCT was obtained from January 2008 to June 2018 through the database of West China Hospital of Sichuan University (WCH cohort). The Ethics Committee on Biomedical Research of our center approved this study. The study was conducted in accordance with the *Declaration of Helsinki*. Written informed consent was obtained from each participant according to international and institutional guidelines. Data on a surveillance, epidemiology, and end results (SEER) cohort were obtained from the SEER database (2006–2016) using the SEER*Stat software provided by the National Cancer Institute. The inclusion criteria included NSGCT diagnosis. The WCH and SEER cohorts included 201 and 11,208 patients, respectively. All available data such as age, primary symptoms, laterality, tumor size, imaging examinations (ultrasound, X-ray, and computed tomography), tumor markers (serum lactate dehydrogenase [LDH], serum beta-human chorionic gonadotropin [β-HCG], and serum alpha-fetoprotein [AFP]), pathological classification and subtypes, staging, initial treatment, relapse time, and outcomes were recorded. The median follow-up time for the WCH cohort was 63 months. Our primary study parameter was the cancer-specific survival (CSS) of these patients. Kaplan-Meier method was used to estimate CSS. The Cox proportional hazards model was used to compare the survival durations for groups of patients differing in terms of varied parameters.

The median age of the WCH cohort was 17 (0–64) years; all patients underwent surgery (orchiectomy and testis sparing surgeries; Supplementary Table 1, http://links.lww.com/CM9/A964). The clinical stage (CS) was categorized as follows: CSIA in 32 (15.9%), CSIB in 3 (1.5%), CSIS in 115 (57.2%), CSIIAin 12 (6.0%), CSIIB in 3 (1.5%), CSIIIA in 6 (3.0%), CSIIIB in 21 (10.4%), and CSIIIC in 9 (4.5%) patients. The median age of the SEER cohort was 28 (0–91) years. The proportions of patients at CSs I, II, and III were 61.04% (5813), 15.14% (1442), and 23.82% (2269), respectively [Supplementary Table 2, http://links.lww.com/CM9/A964]. Comparison of the baseline characteristics of the patients at different CSs [Supplementary Tables 1 and 2, http://links.lww.com/CM9/A964] revealed that the age at diagnosis was significantly lower in patients at CSI than that in patients at CSII and CSIII ($P < 0.001$). Proportion of patients with an elevated level of tumor marker in the serum, a tumor size of ≥4 cm, and lymphovascular invasion (LVI) was higher in the CSII and CSIII categories than those in the CSI category ($P < 0.05$). Similar results were observed in the SEER cohort [Supplementary Table 2, http://links.lww.com/CM9/A964]. The proportion of patients with bilateral tumor, persistently elevated tumor markers after surgery, and pathological subtype distribution was significantly different across the CS categories.

In the WCH cohort, 181 patients underwent orchiectomy as the primary treatment. Of them, 37 (20.4%) underwent retroperitoneal lymph node dissection, 20 underwent testis sparing surgery, 73 (36.3%) received adjuvant chemotherapy after orchiectomy, one (T2N0M0 CSIB) received radiotherapy, and eight (4.0%) received both

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chemotherapy and radiotherapy as post-surgery therapies. Chemotherapy was administered to 37, 12, and 24 patients at CSI, CSII, and CSIII, respectively. Seven patients at CSI (CSIA: three, CSIB: one, and CSIS: three) and one at CSIIIC received a combination of both chemotherapy and radiotherapy as adjuvant therapies [Supplementary Table 1, http://links.lww.com/CM9/A964]. No difference was noted in the median survival duration between patients at CSI who received and did not receive chemotherapy after surgery (45.00 [7.00–122.00] *vs.* 47.00 [3.00–120.00] months). Although there was a difference in the median survival duration between patients at CSII who received and did not receive chemotherapy (52.50 [16.00–110.00] *vs.* 17.50 [10.00–116.00] months), it was not significant ($P > 0.05$). Among the 11,208 patients of the SEER cohort, 10,790 (96.28%) underwent orchiectomy and 11 (0.10%) underwent testis sparing surgery.

Four patients of the WCH cohort relapsed during observation, and three of them died. Four patients died because of advanced malignancies. Two of the patients at CSI (yolk sac tumor) relapsed, and one died 3 months after orchiectomy. No recurrence was noted in patients at CSII. Of 29 patients at CSIII, two relapsed after treatment and three died of advanced disease. The 3- and 10-year CSS rates were 95.6% and 88.7%, respectively. Patients at CSI and CSII showed significantly better prognosis than those at CSIII [$P < 0.05$; Supplementary Figure 1, http://links.lww.com/CM9/A964 and Supplementary Table 3, http://links.lww.com/CM9/A964]. In the SEER cohort, a significantly lower CSS rate was noted in patients at CSIII. The 3- and 10-year CSS rates in this cohort were 93.91% and 92.67%, respectively [Supplementary Figure 2, http://links.lww.com/CM9/A964]. Survival analysis revealed that patients with embryoma had better long-term survival than those with subtypes (mixed tumors, teratoma, yolk sac tumor, and choriocarcinoma) in the SEER cohort [Supplementary Figure 3, http://links.lww.com/CM9/A964 and Supplementary Table 3, http://links.lww.com/CM9/A964].

Maximum tumor diameter ≥4 cm correlated with a higher risk of cancer specific mortality (hazard ratio: 12.87, 95% confidence interval: 1.50–110.24, $P = 0.0197$) according to the Cox proportional hazard model based on WCH cohort. Age, LVI, and elevated serum tumor marker level did not significantly correlate with disease prognosis [Table 1] in the WCH cohort. Despite tumor size and

Table 1: Associations of clinical and pathological factors of non-seminomatous germ cell tumor with cancer-specific mortality risk.

	SEER cohort		WCH cohort	
Factors	**HR/β (95% CI)**	***P* value**	**HR/β (95% CI)**	***P* value**
Age (years)	1.04 (1.03, 1.05)	<0.0001	1.03 (0.99, 1.08)	0.1301
AFP pre-surgery				
Normal	1.0		1.0	
<1000 ng/ml	1.04 (0.71, 1.53)	0.8416	1.41 (0.20, 10.15)	0.7307
1000–10,000 ng/ml	2.72 (1.81, 4.08)	<0.0001	3.83 (0.64, 22.99)	0.1418
>10,000 ng/ml	6.54 (4.26, 10.05)	<0.0001		
HCG				
Normal	1.0		1.0	
<5000 IU/ml	1.51 (1.04, 2.20)	0.0313	3.73 (0.72, 19.46)	0.1179
5000–50,000 IU/ml	4.80 (3.10, 7.44)	<0.0001		
>50,000 IU/ml	8.48 (5.43, 13.24)	<0.0001		
LDH				
Normal	1.0		1.0	
<1.5 Normal	3.91 (2.29, 6.69)	<0.0001	0.28 (0.03, 2.66)	0.2653
1.5–10 Normal	8.06 (4.75, 13.66)	<0.0001	2.28 (0.45, 11.60)	0.3223
>10 Normal	11.04 (6.17, 19.76)	<0.0001		
Persistence of elevated serum tumor markers				
None	1.0			
Elevated	4.54 (1.31, 15.71)	0.0169		
Tumor size				
<4 cm	1.0		1.0	
≥4 cm	1.99 (1.63, 2.43)	<0.0001	12.87 (1.50, 110.24)	0.0197
LVI				
No	1.0		1.0	
Yes	1.72 (1.33, 2.24)	<0.0001	8.37 (0.97, 71.99)	0.0528
Pathological type				
Embryoma	1.0		1.0	
Yolk sac tumor	2.62 (1.73, 3.98)	<0.0001	Inf. (0.00, Inf)	0.9983
Teratoma	1.51 (1.02, 2.25)	0.0391	6,544, 954.53 (0.00, Inf)	0.9985
Mixed tumor	1.29 (0.99, 1.68)	0.0580	Inf. (0.00, Inf)	0.9984
Choriocarcinoma	5.62 (4.13, 7.66)	<0.0001		

AFP: Serum alpha-fetoprotein; CI: Confidence interval; HCG: Human chorionic gonadotropin; HR: Hazard ratio; LDH: Serum lactate dehydrogenase; LVI: Lymphovascular invasion; SEER: Surveillance, epidemiology, and end results; WCH: West China Hospital of Sichuan University.

metastatic disease, more factors were associated with disease prognosis in the SEER cohort. Elevated serum tumor marker levels, LVI, and pathological subtype distribution were all associated with a higher risk of poor prognosis [Table 1].

The demographics of the study cohorts showed a relatively poor prognosis in patients with NSGCT metastasis. A similar result was reported by Daugaard *et al*,[2] Ondru-sova *et al*,[3] and Necchi *et al*[4] in their long-term follow-up studies (>20 years); all these three studies relatively good prognosis in patients at CSI. Based on the outcomes of the WCH cohort, chemotherapy failed to improve the survival of patients at CSI; however, it may help in tumor control in patients at CSII. Although our result did not show statistical significance (possibly because of the relatively small sample size of our cohort), the difference was obvious between the median survival duration of patients at CSII who received or did not receive chemotherapy. These findings were consistent with the recommendation of guidelines mentioning that active surveillance is a satisfactory regimen for patients at CSI and that appropriate chemotherapy (platinum-based) should be administered to patients with metastatic tumors (CSII and CSIII).[1] Notably, patients in the WCH cohort who had a pathological diagnosis of embryoma showed longer median survival duration (58 [14–110] months) than those with yolk sac tumor (41 [3–110] months), teratoma (44 [8–117] months), and mixed tumors (48 [0–122] months). Although this result did not show the statistical significance and was not significant in the Cox proportional hazard model analysis for this cohort, a similar effect showed statistical significance in the SEER cohort. Other factors such as a maximum tumor diameter of ≥4 cm; elevated LDH, HCG, and AFP levels; bilateral neoplasms; and persistently elevated serum tumor marker levels were also associated with poor prognosis of patients with NSGCT.

Chemotherapy is recommended for advanced disease (CSII and CSIII). A maximum tumor diameter of ≥4 cm can be considered as an important prognosis-related factor for NSGCT. Elevated serum tumor marker levels, lymph-vascular invasion, pathological subtypes other than embryoma, and increasing age were also correlated with the prognosis of NSGCT patients.

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Conflicts of interest

None.

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