Clinical Characteristics of Testicular Nonseminomatous Germ Cell Tumor from West China: A 10-Year Experience of a Super regional Center

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Research article

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Abstract

Objectives: To evaluate the clinical characteristics and prognostic factors of Nonseminomatous Germ Cell Tumor (NSGCT). **Patients and methods:** Testicular cancer (TC) survey was conducted by Department of Urology, West China Hospital from 2008 to 2018. Details such as age, tumor size, tumor markers, histopathology, clinical stage, initial treatment, follow up, and clinical outcomes were provided by the database of our center. Tumor stage was classified according to the NCCN criteria(1). **Results:** Orchiectomy, chemotherapy and radio-therapy were the main treatments for these patients. Clinical stage I, stage II and stage III patients accounted for 74.6% (150), 7.5% (15) and 17.9% (36), respectively. After a median follow up time of 63 months, 4 patients relapsed during observation and 3 of them died. 4 patients died because of advanced malignancies. Among CSI patients, 2 relapsed and 1 died in 3 months after orchiectomy. No recurrence was found in CSII patients. 2 out of 29 stage III cases relapsed after treatment and 3 died of advanced cancer. The 3- and 10- year OS was 95.6% and 88.7%, respectively. For all the patients, the 3- and 10-year PFS was 94.9% and 88.8%. According to our data, we found that the metastasis and tumor size were risk factors for NSGCTs. **Conclusion:** The present report showed a good prognosis at non-metastatic stage(CSI). However, the prognosis of advanced disease(CSII and CSIII) is significantly worse than that of early stage. We also found that maximum tumor diameter of >5cm was a potential risk factor for NSGCT.

Background

Testicular tumor represents 1% of male neoplasms and 5% of urogenital tumors. The incidence of testicular cancer (TC) in China is lower than western countries, which is approximately 1 case per 100 000 person-years and showed a slight increase over the past decades. Non-seminomatous germ cell tumors(NSGCT) accounts for nearly 40% of all testicular cancers. Survival of TC including NSGCT has been improving due to advanced multimodal therapeutic options. The majority of NSGCT patients can be cured by orchiectomy and, if necessary, subsequent adjuvant chemotherapy or radiotherapy(2-4). Although accurate diagnosis and improved treatment contribute a lot to its good prognosis, there are still some controversies to the treatment of NSGCT for the diverse side effects of those adjuvant therapeutic regimens.

To study the clinical characteristics, treatment and outcome of NSGCT, we have carried out a study of TC adapted by our hospital from 2008 to 2018.

Methods

Information of NSGCT was provided by the database of our center. As this was a retrospective study, ethical approval was not conducted. The inclusion criteria were diagnosis of NSGCT by surgery or needle biopsy. The database included all available details such as age, primary symptoms, laterality, tumor size, imaging examinations(Ultrasound, X-Ray, Computer Tomography), tumor markers(serum lactate dehydrogenase (LDH), serum β -human chorionic gonadotropin (HCG), serum alpha fetoprotein (AFP)),

pathological classification, staging(TNM stage and S stage , clinical stage), initial treatment, time of relapse, and outcome were recorded. Then, according to the criteria of our institution: Normal serum LDH was <220 IU/L, β -HCG <3.81 mIU/ml and AFP <8ng/ml.

Overall survival (OS) was measured from the time of diagnosis to the time of death or the latest follow up. Progression-free survival (PFS) was measured from the time of diagnosis to the time of the disease progression, relapse, death or the latest follow up. Kaplan-Meier method was used to estimate PFS and OS. The Cox proportional hazards model was used to compare the survival times for groups of patients differing in terms of varied parameters.

Results

Baseline characteristics

Age ranged from 0 to 64 with the mean age of approximately 17 years. Primary symptoms of most patients were simply scrotal masses(187 93.5%), 24(11.9%) presented pain of testis, only 5(2.5%) patient presented respiratory symptoms for lung metastasis(Table 1). All of these patients were diagnosed pathologically. 8 patients were identified as embryonal carcinomas, 37 were yolk sac tumors, 68 were teratomas, and 88 were mixed tumors(Table 1). 200(99.5%) cases were located unilaterally in the body, merely 1(0.5%) occurred bilaterally. Of those unilateral cases, 89(44.5%) suffered mass of the left testis, with 111(55.5%) on the right (Table 1).

Overall, according to the NCCN staging system, we categorized clinical stage IA in 32 patients (15.9%), IB in 3 (1.5%), IS in 115(57.2%), IIA in 12(6.0%), IIB in 3(1.5%), IIIA in 6 (3.0%) , IIIB in 21 patient (10.4%) and CSIIIC in 9(4.5%)(Table 2). Retroperitoneal lymph node and lung were the most common metastatic site.

Tumor markers

Tumor markers were measured in all 201 patients before initial treatments. AFP was elevated in 117(58.2%) of them. 44(21.9%) showed an extremely elevated AFP value of >1210 ng/mL. β -HCG value was elevated in 56(27.9%) patients, and the demographic was extremely high(>1000mIU/ml) in 13 patients. LDH was elevated in 109 (54.2%) patients and 8(4.0%) elevated more than 5-fold the normal level. According to the information above, we measured the S stage of these patients, 17 (8.5%) patients were S0, 27 (13.4%) Sx, 87(43.3%) S1, 66 (32.8%) S2 and 4(2.0%) S4(Table 2).

Treatments

As the first-line treatment for seminoma, orchiectomy was performed in 181 patients, 37(20.4%) of these patients received retroperitoneal lymph node dissection and 20 patients received simply testicular tumor dissection. 73 patients (36.3%) received adjuvant chemotherapy after orchiectomy, 1 (T2N0M0 CSIB) received radiotherapy and 8 (4.0%) took both chemotherapy and radiotherapy as the post-surgery therapeutic option. Chemotherapy was performed in 37 CSI cases, 12 CSII and 24 CSIII patients,

respectively. 7CSI, 3CSIA, 1CSIB and 3 CSIS and 1CSIIIC patients got both chemotherapy and radiotherapy as adjuvant treatment.

Survival Data

After a median follow up time of 63 months, 4 patients relapsed during observation and 3 of them died. 4 patients died because of advanced malignancies. Among patients with stage I, 2 cases relapsed and 1 died in 3 months after orchiectomy. No recurrence was found in CSII patients. 2 out of 29 stage III cases relapsed after treatment and 3 died of advanced disease. The 3- and 10- year OS was 95.6% and 88.7%, respectively. For all the patients, the 3- and 10-year PFS was 94.9% and 88.8%. For all the patients, the 3- and 10- year OS and PFS rate was 95.6%, 88.7%, 94.9% and 88.8%, respectively.

Prognostic Factors

According to our statistics, for non-metastatic NSGCT(CSI), the 3- and 10- year PFS was 97.7% and 92%, and for metastatic patients(CSII and CSIII), the 3- and 10-year PFS was 85.3% and 77.5%, respectively(Figure 1). Thus showed a significant difference PFS($p=0.003$). No relapse or death was found in CSI patients with normal tumor marker, and the 10-year PFS of elevated tumor marker was 86.1%. However, there was no statistical difference between these 2 groups($p=0.226$). Comparing PFS between CSI patients who were performed RPLND or not, 2 patients who didn't receive RPLND were observed disease progression after orchiectomy and no progression was found in patients received RPLND. Thus showed a relatively better prognosis for RPLND patients than RPLND-free patients, however, no statistical difference was found between these two groups($p=0.492$). Similar result was found between metastatic patients who received RPLND or not($p=0.898$). No statistical difference was observed between patients who received chemo therapy or not. Taking tumor size into consideration, we found no recurrence or death was found in patients with the maximal tumor diameter of $<5\text{cm}$, however, for those $>5\text{cm}$, the 5-year PFS was 77.9% and showed a notable difference($p=0.003$)(Figure 2).

Discussion

The present study is the first large-scale population-based study of the characteristics and survival of NSGCT in China based on registry data of an experienced center. The most common symptoms of NSGCT is simply testicular mass discovered by multiple methods. And all of our testis samples collected through surgery were identified pathologically.

The first line therapy for NSGCT is orchiectomy. RPLND was not suggested in CSI patients according to the EAU guidelines on TC(2), similarly, RPLND did not contribute to the survival of CSI patients according to the information of our center. We managed to evaluate the difference on survival between CSI patients with normal tumor markers and elevated tumor markers, however, no differences was showed. Further more, no statistical difference was found between patients who was performed chemotherapy versus surveillance. A similar retrospective study was conducted by Ondrusova et al. ,in their study, the relapse rate for surveillance group was 16.7 times higher than that for adjuvant chemotherapy group, so they

suggested surveillance was recommended only in patients with low-risk CSI NSGCT. EAU and NCCN guidelines had both recommended surveillance to those CSIA patients and adjuvant therapy for CSI patients with primary tumor of pT2-T4(2, 4). For those advanced diseases(CSII and CSIII), no difference in survival was observed in patients who had received RPLND other than orchiectomy and orchiectomy only, there is also no statistical difference in PFS between those who had received chemotherapy and surveillance. However, it was reported by some previous researches and guidelines that RPLND should be performed on CSI patients with conditions against surveillance or chemotherapy, CSIIA patients with or without elevated tumor markers and CSIIB patients with normal tumor markers, chemotherapy should be conducted on all metastatic NSGCT patients(2, 4, 5). 21 out of 51(41.2%) metastatic patients was lost. Among those patients were followed, chemotherapy was conducted on 23 patients, only 1 patient (T2N0M1bS1 CSIIIC) had received both chemotherapy and radiotherapy. Unlike seminoma, radiotherapy was not suggested in any treatment regimens of NSGCT except for intracranial metastasis(2, 4).

However, it was reported recently that the incidence of secondary malignant neoplasms were obviously higher in patients who received chemotherapy than those not(6, 7). Other chemotherapy-related multi-system side effects like cardiovascular disease, leukemia, etc. were also reported by some researchers(8-11). Every sword has its two sides, advantages and disadvantages of chemotherapy should be evaluated comprehensively. Considering the high relapse rate of high risk CSI NSGCT(9) and relatively poor prognosis of advanced disease, utilization of chemotherapy is of heavy necessity.

According to the data of our institution, the 3- and 10- year OS was 95.6% and 88.7%, respectively. For all the patients, the 3- and 10-year PFS was 94.9% and 88.8%. For all the patients, the 3- and 10- year OS and PFS rate was 95.6%, 88.7%, 94.9% and 88.8%, respectively According to our statistics, for non-metastatic NSGCT(CSI), the 3- and 10- year PFS was 97.7% and 92%, and for metastatic patients(CSII and CSIII), the 3- and 10-year PFS was 85.3% and 77.5%, respectively(Log Rank $p=0.003$). The 3- and 10- year OS in metastatic patients were 88.4% and 80.4%, 97.7% and 90.7% in CSI patients(Breslow $p=0.016$). Thus showed a significant difference in survival of metastatic vs non-metastatic cases. These demographics demonstrated a relatively poor prognosis in metastatic NSGCT patients, adjuvant therapy was strongly needed for them. Similar result was reported by the Japanese Urological Association in a nation-wide investigation on testicular cancer by registering newly diagnosed testicular cancers in 2005 and 2008, the 3- year OS were 98.5%, 95.1% and 83.7% in CSI, CSII, CSIII NSGCT, respectively(12). However, long term follow up was not conducted in their study. Daugaard et al., Ondrusova et al. and Necchi et al. had carried out very long term follow up study(>20 years), all showed relatively good prognosis in CSI patients (13-15).

Several prognostic factors of NSGCT were reported by previous studies. Significant difference was found between the PFS of patients with maximum tumor diameter of >5cm and ≤5cm(95%CI 113.24-119.63 vs 82.43-113.77, $p<0.05$). And PFS between non-metastatic patients and metastatic diseases were different according to our information(95%CI 114.10-122.39 vs 82.40-115.62, $p<0.05$). And patients of normal tumor markers seemed to show better survival than those elevated, however, no statistical difference was observed between them. Serum LDH is reported to be correlated with tumor burden, growth rate, cellular

proliferation, and is commonly higher in patients with advanced disease(16). It was reported that elevated levels of HCG at the time of treatment completion would eventually relapse, while those with normal or lower levels often achieved cure(12, 14, 17, 18) . As for AFP, researchers had found that AFP is elevated in 10–20% CSI seminoma while those with metastatic disease have elevated AFP 40–60% of the time(19). Laterality was not an risk factor according to our data. Primary mediastinal NSGCT (PMNSGCT) and increasing age were reported by other studies as prognosis factors for NSGCT(14).

For the natural shortcomings of retrospective study, one potential drawback of this study is that not all clinical data was collected, such as tumor markers, weight, dose of chemotherapy and radiotherapy etc. However, this could not be avoided. Another limitation of this study is that it spanned over ten years so that 71 patients were unable to follow-up on account of missed telephone numbers or death and other unavoidable reasons.

Conclusions

The present report is the first large-scale study of the clinical characteristics and prognostic factors of NSGCT patients in China based on uni-institutional data. Chemotherapy is recommended for CSI patients of stage T2-4 and advanced disease(CSII and CSIII), however, considering of those severe adverse effects of chemotherapy, advantages and disadvantages should be evaluated comprehensively especially for CSI patients. Maximum tumor diameter of >5cm can be considered as a important risk factor for NSGCT. What's more, primary mediastinal NSGCT (PMNSGCT), elevation in logarithmic β -hCG and increasing age were also reported as prognostic factors for NSGCT.

Abbreviations

Nonseminomatous Germ Cell Tumor (NSGCT), Testicular cancer (TC), Clinical stage(CS), serum lactate dehydrogenase (LDH), serum β -human chorionic gonadotropin (HCG), serum alpha fetoprotein (AFP), Overall survival (OS) , Progression-free survival (PFS), Retroperitoneal lymph node dissection(RPLND).

Declarations

Ethics approval and consent to participate

The collection and processing of all data were conducted per the Declaration of Helsinki. After obtaining written informed consent, each patient was evaluated. This study adhered to the Declaration of Helsinki guidelines. Furthermore, as the study include no intervention upon patients, ethical approval was not needed after consulting the the Committee of the West China Hospital, Sichuan University.

Consent to publication

Not applicable.

Availability of data and materials

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Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Professor Liangren Liu, Qiang Wei and Mr. Zeyu Chen, Dehong Cao planned the study. Zeyu Chen, Xingyuan Wang and Bo Chen collected the data. Zeyu Chen and Xingyuan Wang carried out the literature review and prepared the draft of the paper. Data analysis was planned and implemented by Zeyu Chen and Yige Bao. Jianbing Guo, Shi Qiu and Zeyu Chen provided input and feedback on the content data analysis and on the paper drafts. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline Characters of NSGCT

Mean age $\pm$ SD(years)	17.72 $\pm$ 16.66
Laterality	n=201
Right	111(55.2%)
Left	89(44.3%)
Bilateral	1(0.5%)
Presenting symptoms	
Scrotal mass	187(93.0%)
Pain of testicular	24(11.9%)
Respiratory symptoms	5(2.5%)
Tumor classification	N=201
Embryonal carcinoma	8(4.0%)
Yolk sac tumor	37(18.4%)
Teratoma	68(33.8%)

Table 2. Tumor staging

T classification	
Tx	6(3.0%)
T1/Tis	170(84.5%)
T2	19(9.5%)
T3	4(2.0%)
T4	2(1.0%)
N classification	
N0	112(55.6%)
Nx	46(23.0%)
N1	21(10.4%)
N2	20(10.0%)
N3	2(1.0%)
M classification	
M0	178(88.5%)
Mx	1(0.5%)
M1a	15(7.5%)
M1b	7(3.5%)
S classification	
S0	17(8.5%)
Sx	27(13.4%)
S1	87(43.3%)
S2	66(32.8%)
S3	4(2.0%)
Clinical stage	
	n=201
I	150(74.6%)
IA	32(21.3%)
IB	3(2.0%)
IS	115(76.7%)
II	15(7.5%)
IIA	12(80.0%)
IIB	3(20.0%)
IIC	0
III	36(17.9%)
IIIA	6(17.0%)
IIIB	21(58.3%)
IIIC	9(25.0%)

Figures

Figure 1

Difference in PFS between metastatic patients and non-metastatic patients.

Figure 2

Difference in PFS between patients with maximum tumor diameter of <5cm and ≥5cm.