Original Article

# A novel T1a/b classification for testicular cancer: not only seminoma

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**Background:** The 8th edition of the American Joint Committee on Cancer (AJCC) manual divides T1 stage testicular cancer into T1a and T1b, but it is only applicable to seminoma. The purpose of this observational study is to discuss further the possibility of extending this classification system to any T1 testicular cancer.

**Methods:** Testicular cancer patients from 2000 to 2018 in the Surveillance, Epidemiology, and End Results (SEER) database were included in this analysis. After patient selection, univariate and multivariate Cox regression were used to evaluate the impact of tumor size on survival in patients with T1 testicular cancer. A time-dependent receiver operation curve (ROC) was used to determine the best tumor size cut-off value for further T1 subgroup classification. Restricted cubic splines (RCS) analysis was used to compare different tumor sizes with the best tumor size cut-off value. Propensity score matching (PSM) analysis was conducted to generate baseline balanced data to validate findings.

**Results:** A total of 6,630 patients were included in this study. In the Cox regression model, we found that T1b staged tumor (>34 mm) was an independent risk factor of overall survival [OS, adjusted hazard ratio (HR): 1.57, 95% confidence interval (CI): 1.12–2.21] and cancer-specific survival (CSS, adjusted HR: 5.027, 95% CI: 1.95–12.93). Further PSM analysis consolidated our results.

**Conclusions:** For any T1 testicular cancer, a tumor size of 34 mm could be used as the demarcation point to assess the prognosis. Adopting personalized treatments and follow-up plans may help improve the OS and CSS rate for testicular cancer patients.

**Keywords:** Testicular cancer; Surveillance, Epidemiology, and End Results database (SEER database); T1 stage; classification; propensity score matching (PSM)

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## Introduction

Testis cancer is one of the most common malignant tumors in young adult men, and the incidence has been on the rise globally in the past two decades (1). Malignant tumors derived from germ cells are the most dominant source of testicular cancer, accounting for more than 90%. Testicular cancers derived from non-germ cells are sporadic (2). Seminoma is the largest category among the germ cell-derived testicular cancers, accounting for more than 50% of all germ cell-derived testicular cancers (3,4). Therefore, in many pieces of literature for testicular cancer, seminoma is the focus of the report. In the 7th edition of the American Joint Committee on Cancer (AJCC) Testicular Cancer Staging Guidelines, all pathological types of testicular cancer T staging are divided into stages T1 to T4 according to tumor size, and stage T1 is defined as the tumor confined

to the testis and epididymis without vascular/lymphatic invasion (5). In the recently published AJCC 8th edition of the testicular cancer staging guidelines, the T1 stage is further divided into two sub-groups, T1a and T1b. However, this subgroup classification scheme is emphasized only for seminoma (6). The grading of non-seminoma has not been clearly defined and there are no prognostic indicators available.

According to previous literature reports, tumor size is a significant predictor of survival or prognosis (7-9). Although there is still no separate study indicating that tumor size has a vital role in distinguishing T1 stage testicular cancer, the 8th edition of AJCC proposed the T1 sub-group stage for seminoma, suggesting that in other non-spermatogonia-derived testicular cancers, there may still be the possibility of T1 subgroup classification.

Therefore, the purpose of this study is to combine the massive cohort of testicular cancer cases in the Surveillance, Epidemiology, and End Results (SEER) database to explore whether there may be a subgroup plan applicable to all T1 stage testicular cancer patients. This will expand the scope of application of the 8th edition of the AJCC guidelines on the T1 sub-group of testicular cancer and provide evidence for the refinement of the diagnosis and treatment plan for testicular cancer. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-544/rc).

**Highlight box**

**Key findings**

- The size of testicular cancer, whether it is seminoma or non-seminoma, is an important factor affecting its overall survival (OS) and cancer-specific survival (CSS); 34 mm can serve as the dividing line for any testicular cancer stage T1a and T1b.

**What is known and what is new?**

- Previous classifications were limited to seminoma, but this study extends the classification system to include any T1 testicular cancer.
- This manuscript adds evidence supporting the use of tumor size (>34 mm) as a demarcation point for prognosis assessment in T1 testicular cancer.

**What is the implication, and what should change now?**

- Physicians should consider tumor size when determining personalized treatment plans and follow-up strategies for T1 testicular cancer patients.
- Implementing personalized treatments and follow-up plans based on tumor size may lead to improved OS and CSS rates in testicular cancer patients.

## Methods

### *Study population*

Histologically confirmed testicular cancer patients [primary site labeled as C62.9-Testis, not otherwise specified (NOS)] from 2000 to 2018 with complete follow-up information in the SEER database were included in this analysis. The detailed selection criteria were as follows: (I) site and morphology. Primary site labeled = C62.9-Testis, NOS; (II) diagnostic confirmation = positive histology; (III) follow-up = complete dates were available; (IV) reporting source = not autopsy only, not death certificate. The exclusion criteria were as follows: (I) patients with any other cancer before or after testis cancer diagnosis; (II) patients with any identified positive N stage or M stage before surgery; (III) patients with any unclear T-stage information; (IV) patients with unclear follow-up information; (V) patients who did not receive surgery; (VI) patients with unclear tumor size or age information (such as 85+ years old).

Overall survival (OS) and testis cancer-specific survival (CSS) were two main outcome events in this study, and the SEER follow-up project offered related information. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

### *Statistical analysis*

Since this study was not a comparative study, the baseline characteristics of the included patients would be presented in a descriptive table. Univariate and multivariate Cox regression analysis would determine the effect of tumor size on the outcome events. The time-dependent receiver operation curve (ROC) was used to calculate the optimal cut-off value of determining tumor size. After determining the tumor size threshold, restricted cubic splines (RCS) analysis was utilized to calculate and plot the crude and adjusted hazard ratio (HR) diagram of the tumor size. To avoid any possible biases caused by sample selection, a balanced baseline cohort was generated by using propensity score matching (PSM) analysis. After PSM, further Kaplan-Meier (KM) analysis was applied to compare the impact of tumor size threshold found in this study on survival prognosis for T1 stage testis cancer. All statistical analyses above were achieved through R v.4.0.3 (www.r-project.

 

**Table 1** Baseline characteristics of included patients

| Variables | Testicular cancer* (n=6,630) |
|---|---|
| Age (years), mean ± SD | 35.18±11.0 |
| Size (mm), median [IQR] | 35 [22, 53] |
| Race, n (%) | |
| White | 5,886 (88.8) |
| Black | 200 (3.0) |
| Asian or Pacific Islander | 311 (4.7) |
| American Indian/Alaska Native | 41 (0.6) |
| Unknown | 192 (2.9) |
| Laterality, n (%) | |
| Left | 3,078 (46.4) |
| Right | 3,543 (53.4) |
| Unknown/both | 9 (0.1) |
| Grade, n (%) | |
| Well-differentiated: grade I | 48 (0.7) |
| Moderately differentiated: grade II | 17 (0.3) |
| Poorly differentiated: grade III | 34 (0.5) |
| Undifferentiated: grade IV | 33 (0.5) |
| Unknown | 6,498 (98.0) |
| Pathological type (seminoma), n (%) | 4,309 (65.0) |
| Chemotherapy history**, n (%) | 917 (13.8) |
| Radiation therapy history**, n (%) | 1,405 (21.2) |

*, only T1N0M0 patients included; **, adjuvant therapeutic measures after orchiectomy. SD, standard deviation; IQR, interquartile range.

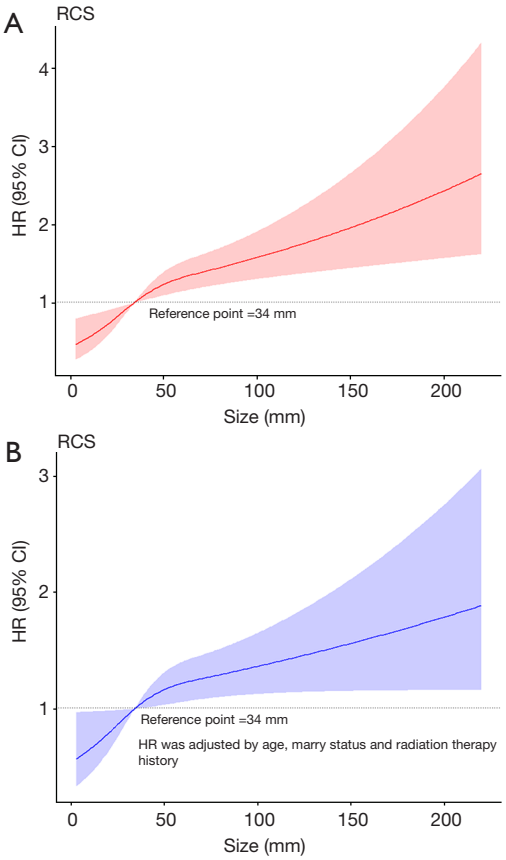


**Figure 1** Restricted cubic spline plotted for different tumor size; reference point was set as 34 mm. (A) Crude HR calculated by Cox regression. (B) Adjusted HR calculated by multivariable Cox regression. HR was adjusted by age, and radiation therapy history. HR, hazard ratio; CI, confidence interval; RCS, restricted cubic splines.

org), rms, survival, caret, broom, survminer, Matching, and tableone were the main R packages used in this study. All the reported P values were two-sided, and significance was indicated as P<0.05.

## Results

After the patient selection according to the inclusion and exclusion criterion, there were 6,630 patients included in this analysis. Detailed baseline characteristics are displayed in *Table 1*. It should be noted that the pathological grade of most cases was unknown, so this variable was not included in the subsequent Cox regression analysis. We determined that the tumor size had a significant predictive effect on all pathological types of T1 stage testicular cancer, the time-dependent ROC was drawn. The optimal tumor size threshold was found to be 34 mm (Figure S1, Table S1). After determining the optimal tumor size threshold for all pathological types of testicular cancer, the RCS curve was drawn with a 34 mm tumor as the reference point. When 34 mm was used as the tumor threshold, it could provide a good ability to distinguish survival risk. In this analysis, RCS was plotted based on both crude and adjusted HR (*Figure 1*). After the PSM, there were 5,968 patients finally included in the baseline-balanced analysis (Table S2), in the follow-up KM analysis, it was found that when T1a and T1b were defined as 34 mm (T1a: tumor size ≤34 mm, T1b: tumor size >34 mm), stage T1a testicular cancer could provide better OS and CSS (*Figure 2*). After the variable

 

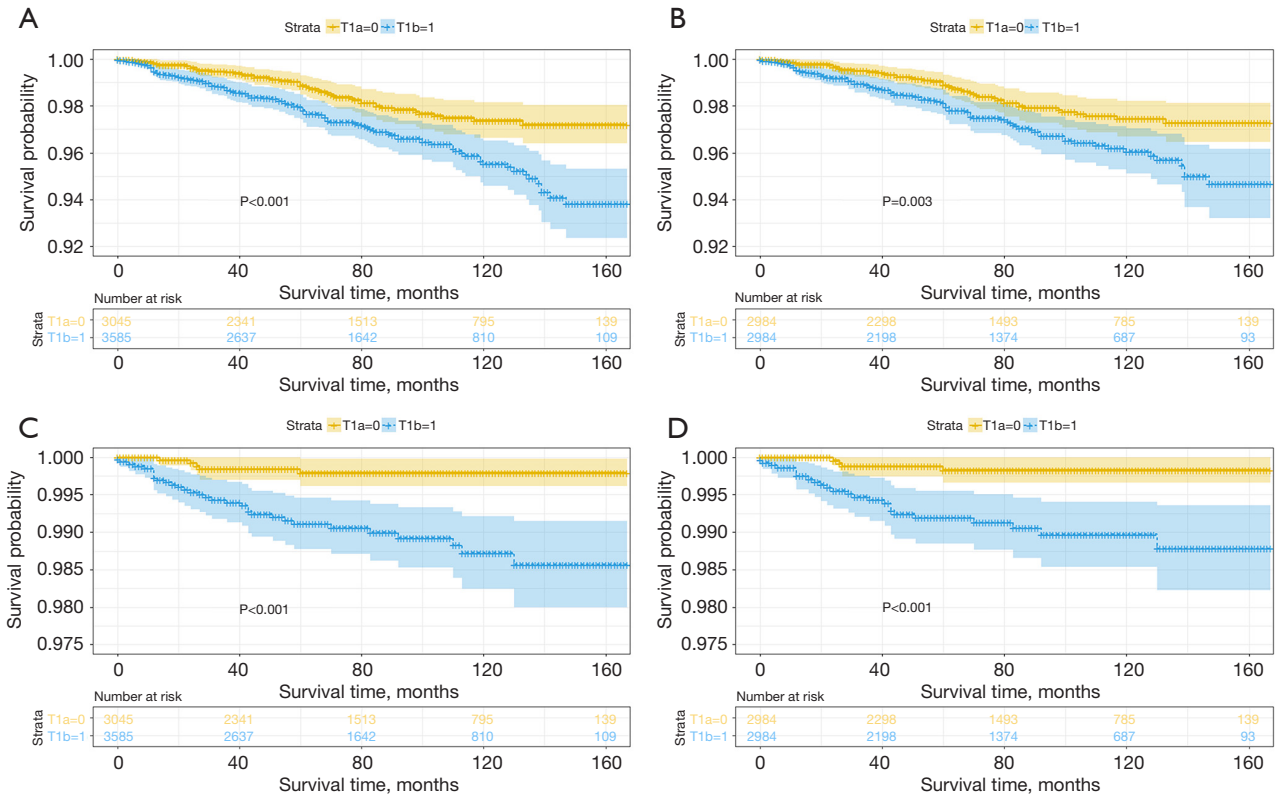


**Figure 2** Kaplan-Meier analysis between newly defined T1a and T1b in testicular cancer cohort. (A) Overall survival comparison between T1a and T1b patients in full overall testicular cancer cohort (n=6,630). T1a: tumor size ≤34 mm, T1b: tumor size >34 mm. (B) Overall survival comparison between T1a and T1b patients in PSM cohort (n=5,968). (C) Cancer-specific survival comparison between T1a and T1b patients in full overall testicular cancer cohort (n=6,630). (D) Cancer-specific survival comparison between T1a and T1b patients in PSM cohort (n=5,968). PSM, propensity score matching.

selection conducted by univariable Cox regression, in the multivariable Cox regression, T1b staged tumors (diameter larger than 34 mm) (HR: 1.57, 95% CI: 1.12–2.21, P=0.009) were identified independent risk factor for OS (*Table 2*, OS part). The important role of tumor size for T1 testicular cancer was also found in the Cox analysis for CSS (*Table 2*, CSS part. T1b staged tumor, HR: 5.027, 95% CI: 1.95–12.93, P<0.001).

Other characteristics such as age (per year-old, HR: 1.07, 95% CI: 1.06–1.08, P<0.001), in marriage status (compared with not in marriage, HR: 0.34, 95% CI: 0.24–0.49, P<0.001), radiation therapy history (HR: 0.54, 95% CI: 0.37–0.79, P=0.002) were also found to be relative risks of OS (*Table 2*, OS part).

All the analysis mentioned above were based on the total cohort (including patients with seminoma and patients with non nonseminomatous testicular cancer). In order to further verify the new T1 grading standard, we also re-analyzed in the cohort of patients with nonseminomatous testicular cancer. There were 2,321 patients with nonseminomatous testicular cancer included in the subgroup analysis. PSM was also used to avoid baseline bias (Table S3) and we found that novel T1a/b classification could bring OS and CSS benefits in full nonseminomatous testicular cancer cohort and PSM matched nonseminomatous testicular cancer cohort (*Figure 3*).

## Discussion

Testicular cancer accounts for 1% of adult tumors and 5% of urinary system tumors. There are 3 to 10 new cases per 100,000 men in Western society each year (10). At diagnosis, 1–2% of cases are bilateral, and the primary histology is germ cell tumor (GCT) (90–95% of cases) (10). GCT

 

**Table 2** Univariable and multivariable Cox regression

| Characteristics | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P | Adjusted HR | 95% CI | P |
| Overall survival | | | | | | |
| Age (per year-old) | 1.06 | 1.05–1.07 | <0.001 | 1.07 | 1.06–1.08 | <0.001 |
| Newly introduced T1 stage | | | | | | |
| T1a (≤34 mm) | Ref. | | | Ref. | | |
| T1b (>34 mm) | 1.86 | 1.32–2.60 | <0.001 | 1.57 | 1.12–2.21 | 0.009 |
| Laterality | | | | | | |
| Left | Ref. | | | | | |
| Right | 1.22 | 0.88–1.68 | 0.23 | | | |
| Unknown/both* | – | – | – | | | |
| Grade | | | | | | |
| Well-differentiated: grade I | Ref. | | | | | |
| Moderately differentiated: grade II | 3.40 | 0.21–54.43 | 0.39 | | | |
| Poorly differentiated: grade III | 1.54 | 0.10–24.67 | 0.76 | | | |
| Undifferentiated: grade IV | 2.38 | 0.22–26.24 | 0.48 | | | |
| Unknown | 1.21 | 0.17–8.61 | 0.85 | | | |
| Pathological type (seminoma *vs.* other) | 0.83 | 0.60–1.15 | 0.26 | | | |
| Chemotherapy (yes *vs.* no/unknown) | 1.43 | 0.94–2.19 | 0.09 | | | |
| Radiation therapy (yes *vs.* no/unknown) | 0.66 | 0.45–0.97 | 0.03 | 0.54 | 0.37–0.79 | 0.002 |
| Cancer-specific survival | | | | | | |
| Age (per year-old) | 1.02 | 0.99–1.05 | 0.20 | | | |
| Newly introduced T1 stage | | | | | | |
| T1a (≤34 mm) | Ref. | | | Ref. | | |
| T1b (>34 mm) | 5.65 | 2.20–14.51 | <0.001 | 5.027 | 1.95–12.93 | <0.001 |
| Laterality | | | | | | |
| Left | Ref. | | | | | |
| Right | 1.41 | 0.72–2.74 | 0.31 | | | |
| Unknown/both* | – | – | – | | | |
| Pathological type (seminoma *vs.* other) | 0.16 | 0.08–0.34 | <0.001 | 0.16 | 0.07–0.40 | <0.001 |
| Chemotherapy (yes *vs.* no/unknown) | 4.06 | 2.09–7.90 | <0.001 | 2.84 | 1.43–5.65 | 0.003 |
| Radiation therapy (yes *vs.* no/unknown) | 0.32 | 0.11–0.91 | 0.03 | 0.72 | 0.20–2.59 | 0.61 |

*, insufficient sample size. HR, hazard ratio; CI, confidence interval.

 

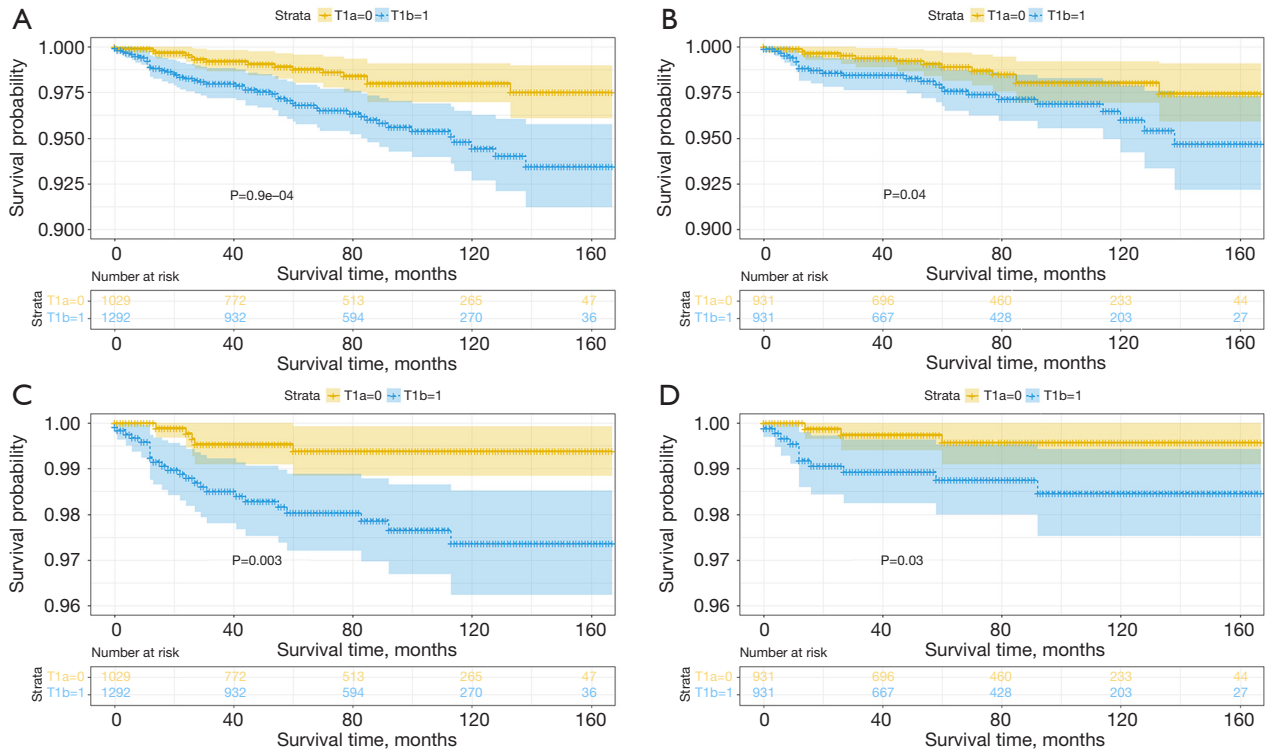


**Figure 3** Kaplan-Meier analysis between newly defined T1a and T1b in nonseminomatous testicular cancer cohort. (A) Overall survival comparison between T1a and T1b patients in full nonseminomatous testicular cancer cohort (n=2,321). T1a: tumor size ≤34 mm, T1b: tumor size >34 mm. (B) Overall survival comparison between T1a and T1b patients in PSM cohort (n=1,862). (C) Cancer-specific survival comparison between T1a and T1b patients in full nonseminomatous testicular cancer cohort (n=2,321). (D) Cancer-specific survival comparison between T1a and T1b patients in PSM cohort (n=1,862). PSM, propensity score matching.

has two basic categories based on its developmental and epigenetic characteristics. Most malignant post-adolescent GCT (or type II GCT) originate from germ cell neoplasm in situ (GCNIS). They are clinically and histologically divided into seminoma and non-seminoma, the latter including somatic and extraembryonic components of embryonal carcinoma, yolk sac, choriocarcinoma, and teratoma (11). When testicular tumors occur, the current main staging schemes include AJCC staging schemes and Union for International Cancer Control (UICC) staging schemes. The main difference between the two schemes is that for T1 stage testicular cancer, the AJCC system believes that when the pathological diagnosis of testicular cancer is determined to be seminoma, it can be divided into T1a and T1b with 30 mm as the boundary. AJCC 8$^{th}$ edition also considers the hilar soft tissue invasion case to be included in the T2 stage, and the discontinuous invasion of the spermatic cord should be considered the M1 stage (6,12). At present, there is still no published literature on the comparison of the survival and prognosis of these two classification systems for patients with testicular cancer. In terms of treatment, since testicular cancer is highly sensitive to cisplatin-based chemotherapy, the reported cure rate of testicular cancer is relatively high (13). As for surgical treatment, orchiectomy is the first choice for testicular tumors. However, approximately 15% of clinical stage I seminoma patients have subclinical metastatic disease, usually retroperitoneum, and will recur after a single orchiectomy, therefore, postoperative adjuvant chemotherapy and adjuvant radiotherapy are usually recommended (14-16).

In the staging and grading of testicular cancer, whether it is according to the AJCC or UICC grading system, the determination of the staging system does not mention about the impact of the T1 subgroup. Although in the 8$^{th}$ edition of the AJCC, the T1 staging is divided into T1a and T1b for seminoma, the staging level of T1b seminoma is not separately improved in subsequent grading (such as clinical

 

stage I or stage II). In this study, the impact of T1 subtypes (the T1 stage was divided into T1a and T1b) on all types of testicular tumors was discussed, but the impact of the new T1 classification scheme on clinical staging was not further proposed due to the lack of available data.

In this study, we found that tumor size was a significant prognostic factor for testicular cancer of any cell origin. Based on the time-dependent ROC, we found that 34 mm was the best subgroup cut-off value for any T1 stage testicular cancer. Further RCS analysis and PSM analysis consolidate this cut-off value. Therefore, we suggest that after sufficient external verification, the T1 staging of any testicular cancer can be divided into two types, T1a and T1b, with a 34 mm boundary. Despite the discrepancy with the 30-mm cutoff specified by the AJCC, this cutoff was extended to the entire T1-staged testicular cancer based on the fact that the sample population in this study was limited to the SEER database and the inclusion of the non-seminoma tumor category, and our study demonstrated the significant impact of this cutoff on CSS and OS (17). It is also hoped that more clinical studies can confirm the clinical significance of this size grading on this basis. The proposal of a new classification scheme for T1 testicular cancer subtypes may be helpful for the screening and evaluation of relatively high-risk patients and the further optimization of follow-up schemes.

Recurrence is a clinical risk that needs to be looked at in patients with testicular cancer. Indicators other than size were also analysed in this study. radiation therapy history was a relative risk factor for OS, whereas chemotherapy history was a protective factor for CSS. This may be due to the fact that the clinical risk assessment was higher in those who received chemotherapy with radiotherapy than in those who did not. Bidirectionality appeared due to interference with the results of Cox regression analyses.

There were several limitations in this study. The diagnosis period of testicular cancer covered a number of years. During this time period, advances in diagnosis and treatment methods might reduce the stability of our results. This study was based on the SEER database. The pathological data did not provide detailed information, such as vascular invasion and rete testis infiltration, which might bring a selection bias to the included cases. Hence, we only conducted subgroup analysis based on seminoma and non-seminoma testicular cancer. The database did not also provide clinical stage information at time of orchiectomy and subsequent adjuvant therapy after orchiectomy. OS and CSS are affected by too many additional variables, including stage of recurrence, prognostic classification, chemotherapy received, and quality of treatment. Inclusion of graded evidence of recurrence would have enhanced the quality of evidence in the article even more. Finally, because this study focuses on the urologist's perspective, there was no focus on the different practice models of pathologists, and their diagnostic formulation would also introduce and amplify selection bias. However, considering the retrospective design and the data collection scheme of SEER database, further prospective studies are needed to validate our results.

## Conclusions

For any T1 testicular cancer, the tumor size of 34 mm could be used as the demarcation point to assess the prognosis. Adopting personalized treatments and follow-up plans may help improve the OS and CSS rate for testicular cancer patients. Further prospective designed trials are still needed to consolidate the results of this study.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-544/rc

*Peer Review File:* Available at https://tau.amegroups.com/article/view/10.21037/tau-23-544/prf

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-544/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).



 

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