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Prognostic value of primary tumor surgery in seminoma patients with distant metastasis at diagnosis: a population-based study

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The aims of this study were to determine the prognostic value of primary tumor surgery and identify optimal candidates for such surgery among patients with seminoma and distant metastasis at diagnosis. We identified 521 patients with seminoma and distant metastasis at diagnosis between 2004 and 2014 from the Surveillance, Epidemiology, and End Results database. Among these patients, 434 had undergone surgery, whereas 87 had not. The prognostic value of primary tumor surgery was assessed by Kaplan–Meier methods, log-rank analyses, and multivariate Cox’s proportional hazards model. Survival curves and forest plots were also plotted. Survival analysis indicated that patients who underwent surgery had a better 5-year overall survival and cancer-specific survival than those who did not. Multivariate analyses demonstrated that primary tumor surgery is an independent prognostic factor for overall survival and cancer-specific survival, along with age at diagnosis, M stage, and marital status. In addition, primary tumor surgery still had considerable prognostic value in the subgroup of patients with lymph node metastasis. Further, forest plots demonstrated that patients with M1a stage, N1 or N2–3 stage, and a younger age at diagnosis (<60 years) may benefit from primary tumor surgery. In conclusion, our findings indicate that primary tumor surgery is correlated with improved survival in patients with seminoma and distant metastasis. Furthermore, primary tumor surgery is an independent prognostic indicator for patients with seminoma and distant metastasis.

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Keywords: distant metastasis; primary tumor surgery; prognosis; seminoma

INTRODUCTION

Seminoma, a rare malignant cancer that is a major subtype of germ cell testicular tumors, has had an increasing morbidity in recent years.¹ It is estimated that 5.7 of 100 000 men are diagnosed as having germ cell testicular tumors in the USA annually, of which nearly 50% have seminoma.² Although only a few patients with seminoma have distant metastasis at diagnosis, this has become a great challenge in management.³

According to the 2018 edition of European Association of Urology (EAU) guidelines on testicular cancer, chemotherapy is recommended for patients with seminoma and distant metastasis at initial presentation.⁴ For patients with residual masses (RM) after first-line chemotherapy, retroperitoneal lymph node dissection (RPLND), fluorodeoxyglucose-positron emission tomography (FDG-PET) scan, and salvage treatment should also be considered according to the size and histology of RM.^{5–7} However, the findings of several studies have indicated that the above treatments may increase long-term morbidities. The risk of secondary malignancies may triple in patients who have received chemotherapy.⁷ Therefore, better therapeutic

approaches are needed to improve the prognosis of patients with seminoma and distant metastasis.

Primary tumor surgery (PTS) has become an option for some patients with metastatic cancers. Findings of some studies have indicated that PTS has a favorable influence on the prognosis of metastatic breast cancer, bladder cancer, and colorectal cancer.^{8–10} Hu and Daneshmand¹¹ proposed that RPLND surgery be recommended as the primary treatment for patients with seminoma and distant metastasis. However, the benefit of PTS in such patients is still unclear and more studies are required to explore its prognostic impact.

In this study, we used population-based data from the Surveillance, Epidemiology, and End Results (SEER) database to explore the prognostic value of PTS and identify optimal candidates for this procedure among patients with seminoma and distant metastases at diagnosis.

PATIENTS AND METHODS

Patients

Eligible patients were identified and relevant data were extracted from the SEER database (<https://seer.cancer.gov/>). The permission to access

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the research data was obtained by reference number 12198-Nov2018, and the last accessed date was January 25, 2019. The inclusion criteria were as follows: (1) patients with seminoma and distant metastasis at diagnosis (ICD-O-3 codes for histological subtype 9061, 9062, and 9063; defined by M1 in the variable "Derived AJCC M" in the SEER database); (2) seminoma – the first or only malignancy; (3) diagnosed between 2004 and 2014; and (4) complete information on treatment, age at diagnosis, and follow-up available.

Covariates and follow-up information

Baseline factors included relevant patient characteristics (age at diagnosis, marital status, and race), tumor characteristics (laterality, T stage, N stage, and M stage), and treatment modality (surgical resection of primary tumor and chemotherapy). In this study, PTS denotes total removal of the primary tumor with or without adjacent sites. Local destructive therapies, such as electrocautery and cryosurgery, were excluded from the definition of PTS. The factor of chemotherapy was simply categorized as having or not having received chemotherapy because of a lack of specific information in the SEER database.

The follow-up information assessed included survival in months, overall survival (OS) status, and cancer-specific survival (CSS) status. The major end points were all-cause (overall) death and cancer-specific death. The duration of OS and CSS was calculated as the time from initial diagnosis to the date of all-cause and cancer specific death, respectively.

Statistical analyses

Clinicopathological variables of two subgroups (PTS and no-PTS) were collected for analysis. Continuous variables were compared by Student's *t*-test and categorical variables by Pearson's Chi-square test or Fisher's exact test. Survival differences were calculated using the log-rank test and Kaplan–Meier methods. Multivariate analyses were carried out using Cox's proportional hazards model to assess the independent effect of clinicopathological factors on OS and CSS. In addition, survival curves and forest plots were also plotted.

All statistical tests and Kaplan–Meier survival curves were performed by SPSS (version 21.0, IBM, Armonk, NY, USA). Forest plots were constructed by R (version 3.5.1, <http://www.r-project.org/>). All statistical tests were two sided and statistical significance was set at $P < 0.05$.

Ethics statement

The study was approved by the Research Ethics Committee of Shanghai Cancer Center, Fudan University (Shanghai, China), according to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013). It was also approved by the Institutional Review Board of Shanghai Cancer Center, Fudan University. All the included patients were identified from the public SEER database. Thus, informed consent from the patients was not needed.

RESULTS

Patient baseline characteristics

Our study cohort included 521 patients with seminoma and distant metastasis between 2004 and 2014 identified from the SEER database. Among these patients, 434 (83.3%) had undergone PTS, whereas 87 (16.7%) had not undergone any surgery to the primary tumor. The baseline characteristics of all patients with metastatic seminoma are summarized in **Table 1**. The overall median age at diagnosis was 40 (range 17–81) years, with most patients ($n = 490$, 94.0%) being under 60 years old. Overall, 298 patients were unmarried (57.2%) and 465 (89.3%) were White, thus comprising the majority of the

total cohort. As for tumor characteristics, the distribution of tumor laterality (left side, $n = 230$, 44.1%; and right side, $n = 239$, 45.9%) was roughly even. More than half of the patients had T1–2 ($n = 316$, 60.7%), N+ ($n = 316$, 60.7%), and M1a stage ($n = 336$, 64.5%). Moreover, the majority of patients had received chemotherapy ($n = 453$, 86.9%). Patient characteristics in no-PTS and PTS subgroups are also presented in **Table 1**.

Prognostic factors for OS and CSS in the overall cohort

We used multivariate Cox analysis to evaluate the prognostic significance of all the studied factors for OS and CSS in the overall cohort; the results are shown in **Table 2**. Multivariate analysis revealed that age at diagnosis ($P < 0.001$), marital status ($P = 0.002$), M stage ($P = 0.001$), and surgery to primary tumor ($P = 0.048$) were independent prognostic factors for OS. In addition, we identified age at diagnosis ($P < 0.001$), marital status ($P = 0.008$), M stage ($P = 0.003$), and surgery to primary tumor ($P = 0.020$) as independent prognostic indicators for CSS. However, T stage and N stage had no statistically significant impact on OS or CSS (all $P > 0.05$). Our analysis indicated that younger age at diagnosis (under 60 years), being married, M1a stage, and PTS associated with better CSS and OS, indicating that PTS is an independent prognostic factor for both of these end points.

Prognostic significance of PTS in seminoma patients with distant metastasis

We then analyzed whether PTS is associated with improved survival outcomes of patients with metastatic seminoma. Overall, patients who had undergone PTS showed better survival outcomes than those who had not undergone it. The Kaplan–Meier curves and log-rank test showed statistically significant differences in OS ($P < 0.001$) and CSS ($P < 0.001$) between the PTS and no-PTS groups (**Figure 1**). We then conducted subgroup analyses to evaluate the therapeutic role of PTS. For patients with N1 metastatic seminoma, Kaplan–Meier curves showed statistically significant differences in OS ($P < 0.001$; **Figure 2a**) between patients who had and had not undergone PTS. PTS was also associated with a statistically significant survival advantage ($P = 0.017$; **Figure 2b**) in patients with N2–3 stage disease. However, PTS did not have a statistically significant favorable ($P = 0.201$; **Figure 2c**) impact on patients with Nx stage. Similar results were also found for CSS in patients with different N stages (N1: $P < 0.001$; N2–3: $P = 0.007$; and Nx: $P = 0.105$; **Figure 2d–2f**).

We also performed multivariate Cox's proportional hazard analyses to assess the prognostic value of PTS. The hazard ratios (HRs) and 95% confidence intervals (95% CIs) for PTS versus no-PTS of each subgroup are shown in forest plots (**Figure 3**). Compared with no-PTS, PTS independently predicted statistically significantly favorable OS and CSS in the subgroups of patients who had M1a stage (OS: $P < 0.001$, CSS: $P < 0.001$), N1 stage (OS: $P < 0.001$, CSS: $P < 0.001$), N2–3 stage (OS: $P = 0.026$, CSS: $P = 0.014$), and a younger age at diagnosis (OS: $P < 0.001$, CSS: $P < 0.001$). In contrast, PTS was not a significant risk factor in the subgroups of N0 stage (OS: $P = 0.923$, CSS: $P = 0.849$) and patients older than 60 years at diagnosis (OS: $P = 0.061$, CSS: $P = 0.258$), indicating that PTS is not indicated for patients with metastatic seminoma at N0 stage or aged more than 60 years.

DISCUSSION

The optimal strategy for managing patients with seminoma and distant metastasis has been developing over the last few decades. Currently, the choice of treatment modality for metastatic seminoma mainly depends on the tumor histology, prognostic group (defined by the

Table 1: Baseline characteristics of seminoma patients with distant metastasis at diagnosis

Characteristics	Total (n=521)	No-PTS (n=87)	PTS (n=434)	P
Age at diagnosis (year), median (range)	40 (17–81)	43 (22–81)	39 (17–75)	0.002
<60, n (%)	490 (94.0)	77 (88.5)	413 (95.2)	
≤60, n (%)	31 (6.0)	10 (11.5)	21 (4.8)	
Marital status, n (%)				0.407
Married	223 (42.8)	41 (47.1)	182 (41.9)	
Unmarried	298 (57.2)	46 (52.9)	252 (58.1)	
Race, n (%)				0.962
White	465 (89.3)	78 (89.7)	387 (89.2)	
Black	27 (5.2)	4 (4.6)	23 (5.3)	
Others	29 (5.6)	5 (5.7)	24 (5.5)	
Laterality, n (%)				<0.001
Left	230 (44.1)	22 (25.3)	208 (47.9)	
Right	239 (45.9)	16 (18.4)	223 (51.4)	
Bilateral	52 (10.0)	49 (56.3)	3 (0.7)	
T stage, n (%)				<0.001
T1	208 (39.9)	0 (0)	208 (47.9)	
T2	108 (20.7)	0 (0)	108 (24.9)	
T3	60 (11.5)	0 (0)	60 (13.8)	
T4	27 (5.2)	3 (3.4)	24 (5.5)	
Tx	118 (22.6)	84 (96.6)	34 (7.8)	
N stage, n (%)				<0.001
N0	149 (28.6)	20 (23)	129 (29.7)	
N1	145 (27.8)	29 (33.3)	116 (26.7)	
N2–3	171 (32.8)	14 (16.1)	157 (36.2)	
Nx	56 (10.7)	24 (27.6)	32 (7.4)	
M stage, n (%)				0.002
M1a	336 (64.5)	43 (49.4)	293 (67.5)	
M1b	185 (35.5)	44 (50.6)	141 (32.5)	
Chemotherapy, n (%)				0.056
No	68 (13.1)	17 (19.5)	51 (11.8)	
Yes	453 (86.9)	70 (80.5)	383 (88.2)	
Radiotherapy, n (%)				0.454
No	490 (94.0)	84 (96.6)	406 (93.5)	
Yes	31 (6.0)	3 (3.4)	28 (6.5)	
5-year OS (%)	0.815	0.653	0.847	<0.001
5-year CSS (%)	0.856	0.689	0.889	<0.001

OS: overall survival; CSS: cancer-specific survival; TNM: tumor-node-metastasis; PTS: primary tumor surgery

International Germ Cell Cancer Collaborative Group), and serum marker values (such as alpha-fetoprotein [AFP], human chorionic gonadotropin [HCG], and lactate dehydrogenase [LDH]) during the first cycle of chemotherapy. The standard treatment for patients with Stage IIA/B metastatic seminoma is radiotherapy. Chemotherapy, usually three-course BEP (cisplatin, etoposide, and bleomycin) or four-course EP (etoposide and cisplatin), is an alternative as standard treatment. Chemotherapy such as BEP, EP, or VIP (etoposide, cisplatin, and ifosfamide) is considered as first-line treatment for patients with Stage IIC and Stage III metastatic seminoma, according to the patient's prognostic group. Excision of local tumor is only recommended when concentrations of serum markers (AFP, HCG, and LDH) remain high after the administration of chemotherapy.⁷

Although patients with metastatic seminoma are generally reportedly treated with systemic chemotherapy and radiotherapy, there is some evidence that systemic radiotherapy and chemotherapy cause long-term morbidities in some patients.^{12,13} The relapse rate after first-line radiotherapy has been reported as 9%–24%.^{14,15} Up to 66%–80% of patients with metastatic seminoma have residual masses after

chemotherapy.¹⁶ The risk of secondary malignancies is approximately two-fold higher in patients who have had either chemotherapy or radiation therapy than in those who have not. The risk of cardiovascular disease over 20 years in survivors of testicular cancer is also up to 2.6-fold compared to patients who have not received chemotherapy or radiation therapy.¹⁷ Lung injury, metabolic syndrome, renal toxicity, and decreased fertility are also common adverse effects during and after treatment.¹¹ Given that many survivors of metastatic seminoma will live for decades, treatment-related morbidity and mortality may more adversely influence their lives than the disease itself. Therefore, treatment options with fewer and less severe long-term complications should be considered.

PTS, a commonly used treatment for solid tumors, has been confirmed to be effective in various metastatic cancers. Warschkow *et al.*⁸ suggested that PTS has a favorable impact in patients with metastatic breast cancer. Tarantino *et al.*¹⁰ also found that palliative PTS is associated with improved overall and cancer-specific survival in patients with Stage IV colorectal cancer. The application of PTS in the management of patients with other types of metastatic

Table 2: Multivariate Cox analyses of prognostic factors for overall and cancer-specific survival in the overall cohort

Variables	OS			CSS		
	HR	95% CI	P	HR	95% CI	P
Age at diagnosis	1.042	1.024–1.061	<0.001	1.039	1.018–1.061	<0.001
Marital status			0.002			0.008
Married	Reference			Reference		
Unmarried	2.040	1.311–3.175	0.002	2.017	1.203–3.382	0.008
T stage			0.600			0.922
T1	Reference			Reference		
T2	1.296	0.703–2.391	0.407	1.019	0.476–2.182	0.962
T3	1.520	0.769–3.004	0.228	1.249	0.550–2.834	0.595
T4	1.538	0.603–3.922	0.368	1.132	0.352–3.636	0.836
Tx	0.898	0.344–2.343	0.826	0.728	0.233–2.279	0.586
N stage			0.125			0.300
N0	Reference			Reference		
N1	1.740	1.022–2.960	0.041	1.704	0.913–3.180	0.094
N2–3	0.999	0.547–1.826	0.998	1.174	0.588–2.344	0.650
Nx	1.162	0.581–2.324	0.672	0.987	0.426–2.283	0.975
M stage			0.001			0.003
M1a	Reference			Reference		
M1b	2.081	1.356–3.195	0.001	2.141	1.297–3.535	0.003
Surgery to primary tumor			0.048			0.020
No	Reference			Reference		
Yes	0.388	0.152–0.991	0.048	0.266	0.087–0.810	0.020
Chemotherapy			0.051			0.510
No	Reference			Reference		
Yes	0.585	0.342–1.002	0.051	0.791	0.394–1.588	0.510

HR: hazard ratio; CI: confidence interval; TNM: tumor-node-metastasis; OS: overall survival; CSS: cancer-specific survival

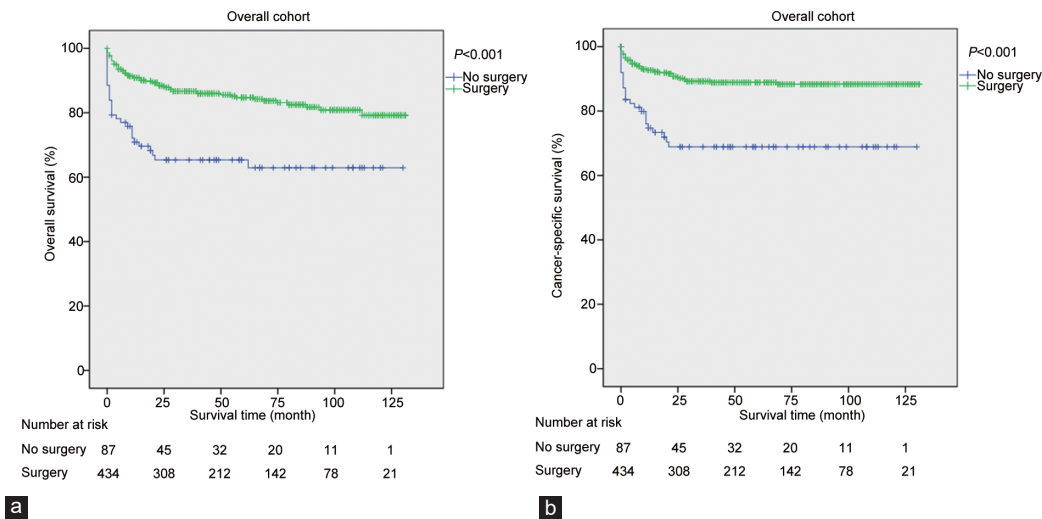


Figure 1: Kaplan–Meier curves of (a) overall and (b) cancer-specific survival according to whether or not PTS was performed in the overall cohort (*n* = 521). PTS: primary tumor surgery.

tumor implies that this option warrants exploration in patients with metastatic seminoma. However, because it is rare, current research has mainly focused on chemotherapy for patients with metastatic seminoma.^{14,18} Little research has investigated the therapeutic value of PTS in metastatic seminoma. As far as we know, this is the first study to have investigated the prognostic influence of PTS on patients with metastatic seminoma at initial presentation. In our study of a large cohort of patients with metastatic seminoma obtained from the SEER database, we divided patients into different subgroups according to

their clinical features and evaluated the prognostic influences of PTS in those subgroups. Our aim was to provide new insights into the prediction of the prognosis of metastatic seminoma and to help stratify patients into prognostic categories.

In our research, we studied the prognostic value of PTS in patients with seminoma and distant metastasis at diagnosis; this has rarely been previously reported. Interestingly, similar to previous findings concerning other types of cancer, we found that PTS is an independent prognostic indicator in patients with metastatic

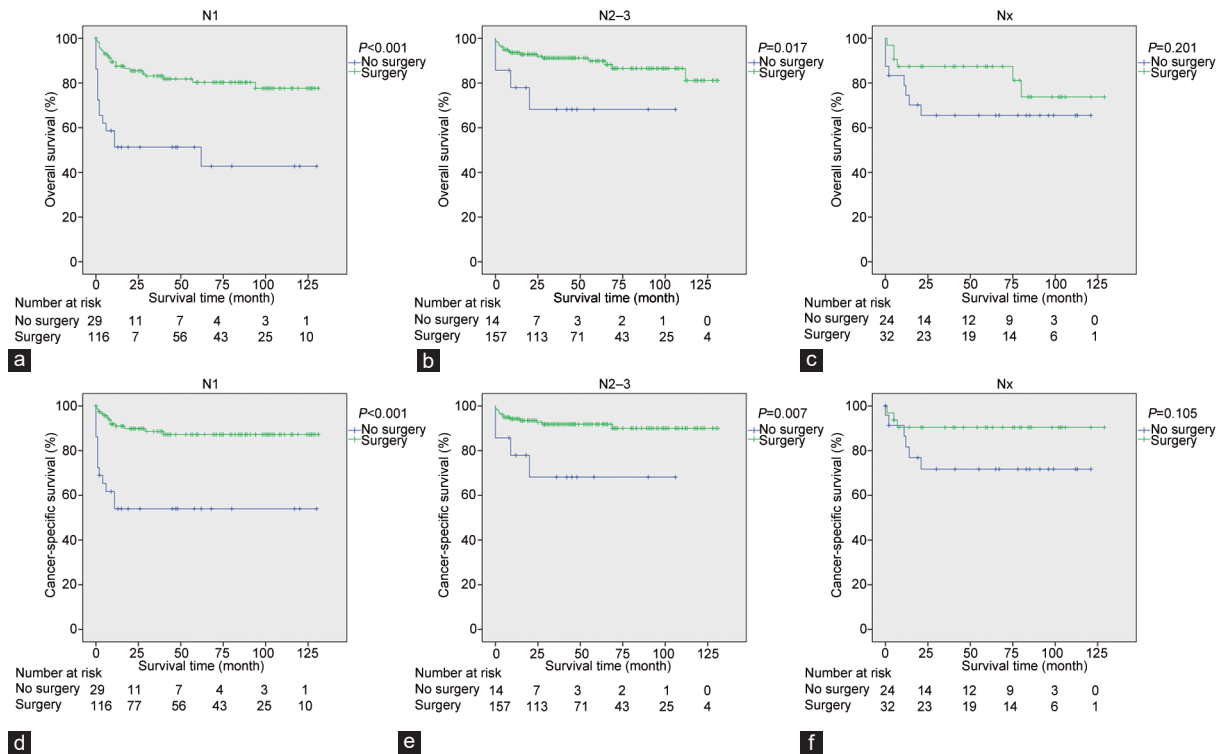


Figure 2: Kaplan-Meier curves of overall survival according to whether or not PTS was performed in patients with (a) N1, (b) N2-3 and (c) Nx stage. Kaplan-Meier curves of cancer-specific survival according to whether or not PTS was performed in patients with (d) N1, (e) N2-3 and (f) Nx stage.

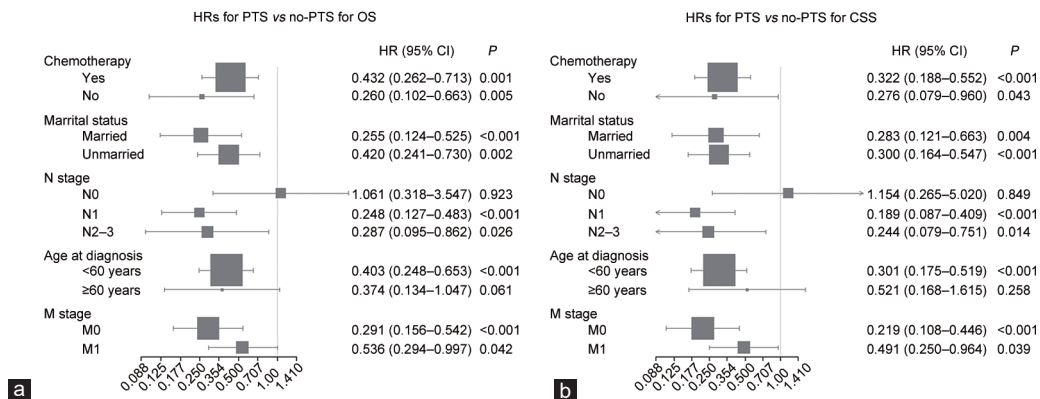


Figure 3: Forest plots summarizing the HRs and 95% CIs of (a) overall and (b) cancer-specific survival for PTS versus no-PTS subgroup analyses. PTS: primary tumor surgery; OS: overall survival; CSS: cancer-specific survival; TNM: tumor-node-metastasis; HR: hazard ratio; CI: confidence interval.

seminoma. Furthermore, we found that PTS is a statistically significant prognostic factor for OS and CSS in subgroups of patients who have received chemotherapy, have N1 or N2-3 stage disease, and are younger at diagnosis (<60 years). These findings demonstrate that PTS may be a valid therapeutic option for patients with metastatic seminoma and the above clinical features. However, PTS did not have a significant prognostic value in the subgroup of patients with N0 stage disease. This phenomenon can possibly be explained by the hypothesis that patients with N0 stage disease tend to have a favorable survival outcome after undergoing chemotherapy. Surgical resection can therefore have little additional beneficial impact on their prognosis, while possibly resulting in local complications and even increasing the risk of death due to surgical complications.

Although the prognostic value of PTS has been confirmed in metastatic seminoma and many other types of cancer, there is no accepted theory to explain the relationship between PTS and improved prognosis. Infection and anemia are common complications of primary cancer and are considered an important reason for disease progression and even death.¹⁷ It is, therefore, reasonable to assume that excision of primary tumor may reduce the corresponding risk. Moreover, Cook *et al.*¹⁹ have demonstrated that resection of primary tumors may decrease the risk of weight loss and nutritional depletion, and thus reduce local obstruction or postchemotherapy physiologic and immune compromise. Some researchers have inferred that the primary tumor may act as a “seed source” for the development of new metastases; thus, its removal would diminish the chances of

disease progression.²⁰ In addition, the presence of primary tumors may suppress the immune system and PTS may therefore eliminate immune suppression effect.²¹ More well-designed studies are needed in future to investigate these hypotheses.

Inevitably, our study has several limitations. First, selection biases are inevitable because it was a retrospective study and the SEER database lacks information on factors such as performance status and comorbidities. It is reasonable to assume that healthier patients with better performance status may be more likely to undergo PTS. However, other similar SEER-based studies have also reported this disadvantage, concluding that the significant prognostic effect of PTS in highly selected groups could not possibly be attributed solely to this unadjusted confounding factor.^{8,10,22–24} Second, we did not include several known prognostic factors, such as histological type and degree of differentiation, in the analysis, because of the low incidence of each subtype and relatively less rigorous pathological diagnosis during clinical management. Third, many patients in the no-PTS group were merely recorded as Tx stage, preventing us from analyzing the prognostic value of specific T stage. Therefore, more population-based and multi-institutional analyses are required to confirm our findings.

CONCLUSION

To the best of our knowledge, our study is the first to determine that PTS is correlated with improved survival in patients with seminoma and distant metastasis, and that PTS is an independent prognostic indicator in patients with metastatic seminoma. Furthermore, patients who have M1a, N1, or N2–3 stage disease and are younger at diagnosis are optimal candidates for PTS.

AUTHOR CONTRIBUTIONS

SMJ and JMW analyzed the data and drafted the manuscript. JLW helped analyze the data. BHW, HLG, CY, and PHX helped interpret the data. FNW, WJG, and YW prepared all figures. SMJ, JMW, and JLW edited all tables. YJS and DWY designed the study. All authors have read and approved the final manuscript and agreed with the order of presentation of the authors.

COMPETING INTERESTS

All authors declare no competing interests.

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