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Site of extranodal metastasis impacts survival in patients with testicular germ cell tumors

Hiten D. Patel, MD, MPH[*,1], **Nirmish Singla, MD**[*,2], **Rashed A. Ghandour, MD**[2], **Yuval Freifeld, MD**[2], **Joseph G. Cheaib, MD, MPH**[1], **Solomon L. Woldu, MD**[2], **Phillip M. Pierorazio, MD**[**,1], **Aditya Bagrodia, MD**[**,2]

[1]The James Buchanan Brady Urological Institute and Department of Urology, Johns Hopkins University School of Medicine, Baltimore, MD

[2]Department of Urology, University of Texas Southwestern, Dallas, TX

Abstract

Background: We systematically evaluated the impact of the location and burden of extranodal testicular germ cell tumor (TGCT) metastases on survival using a large, nationally representative population-based cancer registry.

Methods: Men with stage III TGCT captured by the Surveillance, Epidemiology, and End Results registry from 2010–2015 with distant extranodal metastases were identified. Clinicopathologic information were collected, and patients were subdivided based on specific organ site(s) of metastatic involvement (lung, liver, bone, and/or brain). Kaplan-Meier analysis and multivariable Cox regression were used to evaluate cancer-specific survival (CSS), and model performance was assessed using Harrell's C-statistic.

Results: 969 patients with stage III TGCT were included, with predominantly nonseminomatous histology (84%). Most patients (91%) had pulmonary metastases, while 20%, 10%, and 10% had liver, bone, and brain metastases, respectively. Over a median follow-up of 21 months, 19% of men died of TGCT. When grouped by primary site of metastasis, patients with more than one extrapulmonary metastasis exhibited the worst CSS (HR 4.27 (95% CI 2.60–7.00), vs. isolated pulmonary involvement, $p<0.01$). Among patients with isolated extrapulmonary involvement, those with brain metastases had the poorest survival (HR 3.24 (95% CI 1.98–5.28), $p<0.01$), followed by liver (HR 2.29 (95% CI 1.56–3.35), $p<0.01$) and bone (HR 1.97 (95% CI 1.11–3.50), $p=0.02$). Multivariable Harrell's C-statistic was 0.71.

Address for correspondence: Aditya Bagrodia, MD, Department of Urology, University of Texas Southwestern Medical Center, 2001 Inwood Rd, WCBE3, 4th floor, Dallas, TX 75390-9110, Phone: (214) 645-8765, Aditya.bagrodia@utsouthwestern.edu, Phillip M. Pierorazio, MD, The James Buchanan Brady Urological Institute and Department of Urology, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Marburg 144, Baltimore, MD 21287, Phone: (410) 502-5984, philpierorazio@jhmi.edu.

*Co-First Authors

**Co-corresponding authors

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Conflicts of interest: none

Conclusions: Site of metastatic involvement impacts survival outcomes in patients with TGCT, which may reflect both the aggressive biology and challenging treatment of these tumors. Further incorporation of organotropism into current prognostic models for metastatic TGCT warrants attention.

Precis:

Site of metastatic involvement impacts survival outcomes in patients with testicular cancer, which may reflect both the aggressive biology and challenging treatment of these tumors. Further incorporation of organotropism into current prognostic models for metastatic testicular cancer warrants attention.

Keywords

testicular cancer; metastasis; organotropism; outcomes; epidemiology

INTRODUCTION

Testicular germ cell tumors (TGCT) are the most common malignancy in young men, and approximately 9,560 new cases are expected to be diagnosed in the U.S. in 2019.[1] Given the multimodal strategies available to manage these tumors, patients with TGCT tend to exhibit favorable clinical outcomes, with >80% 5-year overall survival and fewer than 500 cancer-specific deaths annually in the U.S.[1,2] Poor outcomes in TGCT are driven primarily by extranodal metastatic involvement (clinical stage III disease), and even among patients with metastatic disease, predictors of survival are multifactorial.[3]

The current staging system for testis cancer attempts to differentiate among sites of metastatic involvement by categorizing non-pulmonary metastatic disease (M1b, stage IIIC) into a higher stage compared to pulmonary or non-regional lymph node involvement (M1a, predominantly stage IIIA-B).[4] This classification is based on earlier studies suggesting relatively worse outcomes in patients that have non-pulmonary metastatic sites involved, and accordingly, patients with M1b disease are categorized into a worse risk stratification according to the International Germ-Cell Cancer Cooperative Group (IGCCCG).[2] Aside from the lung, the most common extranodal sites of TGCT involvement include the liver, bone, and brain; involvement of these sites—particularly the bone and brain—has been associated with worse outcomes.[5–9] However, the relative impact of involved organ sites on survival among patients with M1b disease has not been systematically assessed.

Herein, we systematically evaluate the impact of the location and burden of extranodal TGCT metastases on survival using a large, nationally representative, population-based cancer registry. Elucidating the specific impact of organotropism on survival outcomes may help refine current prognostic models for metastatic TGCT and provide insight into the heterogeneous behavior of these tumors.

METHODS

Patient Population, Variables, and Outcomes

A cohort of men with stage III TGCT from 2010–2015 captured by the Surveillance, Epidemiology, and End Results (SEER) Program were identified. Men with sites of known distant extranodal metastasis (lung, bone, liver, or brain) were included (M1a or M1b). Extragonadal GCT, patients under 16 years of age, and those without distant metastasis were excluded. Demographic and clinical data included age, race, year of diagnosis, histology (seminoma or nonseminoma (NSGCT)), laterality, and staging (AJCC, 7th Edition) classified as IIIA, IIIB, IIIC, or III not otherwise specified (NOS). The independent variable of interest was site of distant metastasis. The primary outcome of interest was cancer-specific survival (CSS; death due to testicular cancer).

Statistical Analysis

Baseline characteristics were tabulated for included patients. Univariable and multivariable Cox proportional hazards regression models were constructed to evaluate the impact of each variable on CSS. The relative impact of metastasis to the lung, liver, bone, and brain was assessed. Patients were further categorized into five groups of interest by their primary site of metastasis including the following: lung metastasis only, bone metastasis (with or without lung metastasis), liver metastasis (with or without lung metastasis), brain (with or without lung metastasis), and multiple non-pulmonary sites of metastasis. Model performance was assessed by computing Harrell's C-statistic. Kaplan-Meier curves were created to visualize the five groups of interest, and survival probabilities were tabulated at 2 years and 3 years for CSS. Statistical analyses were performed using STATA v.15.0 (STATA Corp, College Station, TX, 2017) with two-sided alpha set to 0.05.

RESULTS

Cohort

A total of 969 patients diagnosed with stage III TGCT with distant metastasis were included. The median age was 29 years (IQR 23–38). The majority of patients were white (55.2%) or Hispanic (34.9%), and the predominant histology was NSGCT (84.2%) (Table 1). In this cohort with high metastatic burden, most patients had distant metastasis to the lung (90.5%), while approximately 20% of patients had metastasis to the liver and 10% each had bone and brain metastases.

Impact of Individual Metastatic Sites on CSS

Over a median follow-up of 21 months (IQR 8–43), 185 (19.1%) men were confirmed to have died due to testicular cancer, while 225 (23.2%) died of any cause. In total, 23 (2.4%) were confirmed as deaths due to non-testis cancer causes while 17 (1.8%) were not definitively confirmed as deaths either related or unrelated to testis cancer (Supplemental Table 1). Increasing age was a statistically significant predictor for worse CSS, while histology, year of diagnosis, and lymphovascular invasion were not associated with CSS (Table 2). Stage IIIC disease was strongly associated with CSS on multivariable analysis (HR 5.17 (95% CI 2.83–9.42), $p<0.01$). On assessment of individual sites of metastasis,

metastasis to the brain appeared to have the greatest association with poor CSS among included sites (HR 2.49 (95% CI 1.69–3.66), p<0.01) followed by liver and bone. Harrell's C-statistic for multivariable models ranged between 0.71 and 0.73.

Comparison of CSS by Primary Site of Metastasis

When grouped by primary site of metastasis, patients with primary brain metastasis were confirmed to have the worst prognosis (HR 3.24 (95% CI 1.98–5.28), p<0.01), while patients with liver and bone metastasis appeared to have similar CSS (Table 3). Harrell's C-statistic was 0.71 for the multivariable model. Brain metastasis was associated with presence of choriocarcinoma as the primary histology (41.1% of patients with brain metastasis vs. 11.1% without brain metastasis, p<0.01). On a sensitivity analysis of histology, both brain metastasis (HR 2.98 (95%CI 1.79–4.95), p<0.01) and presence of choriocarcinoma (HR 1.86 (95% CI 1.09–3.19, p=0.02) remained statistically significant predictors of CSS in a multivariable model (Supplemental Table 2).

Kaplan-Meier curves estimated 3-year CSS of 83.5% for lung only, 71.3% for bone, 64.5% for liver, 56.6% for brain, and 43.7% for multiple non-pulmonary sites (log-rank p<0.0001; Figure 1). The latter group included 52 patients with 2 non-pulmonary sites and 5 patients with all 3 non-pulmonary sites.

DISCUSSION

The distribution of metastatic involvement has been shown to carry prognostic value in several malignancies.[10–17] The tendency of a tumor to metastasize to a particular organ site may reflect an interplay between the underlying biology of the tumor cells and a permissive host organ microenvironment.[18–21] In the setting of TGCT, involvement of extranodal non-pulmonary sites is traditionally associated with poor outcomes.[2] Here, we have systematically evaluated a large, nationally representative, population-based cancer registry to evaluate the impact of the specific location and extent of metastases on survival in patients with TGCT using multivariable regression modeling. We found that among stage III patients with only one non-pulmonary site involved, those harboring brain metastases exhibited the worst survival, followed by those with liver or bone involvement, which appeared to have a more similar impact on CSS. Consistent with current staging schema,[4] patients with isolated pulmonary involvement tended to exhibit the best survival outcomes. Furthermore, patients with involvement of more than one non-pulmonary site had worse outcomes than those with only one non-pulmonary metastasis, including the brain.

While metastasizing tumor clones from testicular cancer tend to follow a predictable pattern of lymphatic drainage to the retroperitoneum,[22] hematogenous routes enabling spread beyond the retroperitoneum, or even occasionally skipping the retroperitoneum altogether,[23] facilitate colonization of solid organ sites. For reasons that are not understood, when the lung is the only organ involved, outcomes appear to be superior to cases involving either isolated or concomitant metastasis to other organ sites. The tropic pattern of spread may conceivably reflect the aggressiveness of the tumor biology, though importantly, the lack of a clear consensus on the optimal management strategy for extranodal metastases and the

frequently resistant nature of these tumor clones to conventional therapies may contribute to the decreased survival observed.[5–9,24,25]

In a recent analysis of 1,594 patients with GCT who experienced treatment failure with cisplatin-based frontline chemotherapy, the International Prognostic Factors Study Group attempted to construct a prognostic model to guide salvage strategies.[5] Notably, 50%, 17%, 7%, and 13% of their cohort exhibited lung, liver, bone, and brain metastases, respectively. On combining liver, bone, and brain metastases into a composite variable (LBB), they identified LBB as an independently poor prognostic feature on multivariable analysis for patients with NSGCT and found it to be the only significant predictor in their seminoma cohort. However, the influence of each involved organ site on outcome was not independently assessed.

Studies evaluating unique cohorts of GCT patients exhibiting brain metastases have reported on the attempted use of multimodal therapies that include, often, some combination of chemotherapy, radiotherapy, and surgery,[6,24] yet the benefit of utilizing a multimodal approach was more evident among patients with brain metastases at relapse rather than at initial diagnosis.[6] As in our cohort, brain metastases usually coexist with pulmonary metastases,[6,24] and the presence of multiple brain metastases and concomitant involvement of liver or bone metastases were found to be independent adverse prognostic features.[6] While we did not have data on the number of brain metastases present in our SEER cohort, we similarly noted that a higher burden of non-pulmonary metastases conferred worse outcomes. Attesting to the poor outcomes of patients with brain metastases, Feldman et al. reported that over 50% of patients with brain metastases experience disease progression and death within one year of identifying intracranial involvement.[6] They note that these poor outcomes are likely driven, in large part, by chemoresistance, given that mortality in these patients is frequently due to systemic progression rather than uncontrolled brain metastases.

The optimal management of bone and liver metastases from TGCT also remains challenging without a clear consensus.[7–9,25] The role for surgery in managing hepatic metastases has been debated,[9,25] and the advantage of multimodal treatment for bone metastases has not been clearly demonstrated.[7] In fact, Oing et al. reported that the outcomes of NSGCT patients with bone metastases were even worse than expected for a typical IGCCCG poor risk cohort.[7] Furthermore, they noted that while the presence of concomitant liver or brain metastases was significant for poor progression-free survival on univariable analysis, significance was lost on multivariable analysis, and seminomatous histology was found to be the strongest independent predictor for favorable outcomes, which was not reflected in our analysis. Their cohort was notably limited by a small sample size and included patients with primary mediastinal and retroperitoneal GCT in addition to TGCT.

Limitations inherent to the use of the SEER registry, including its retrospective nature, selection bias, and missing data for certain variables of interest, such as serum tumor markers and the number and size of metastatic lesions, must be considered in the context of our findings. Patients with stage III disease driven by elevated serum tumor markers only (cM0S2–3) were also not included for analysis. While a prior study noted TNM staging errors for GCT in SEER, this was largely driven by the S and N categories, which are

avoided in the present analysis;[26] the present cohort includes only M1a and M1b patients with identified sites of distant metastasis and excludes node-only disease. More recent studies have also relied on extent of disease variables to recreate TNM staging for early-stage GCT.[27,28] Most cases of extrapulmonary metastases were confounded by concomitant pulmonary involvement in the majority of patients. Involvement of other organ sites beyond the lung, liver, bone, and brain were also not captured in SEER, though for TGCT, these are typically the most common sites involved. Treatment strategies for patients with metastatic TGCT, including chemotherapy agents which are not captured by SEER, vary considerably among practitioners and would conceivably influence outcomes in our cohort; however, this heterogeneity reflects the challenges and lack of guidelines in managing these patients. Nonetheless, our study is strengthened by its large population-based cohort, representative of national practice patterns across multiple centers.

CONCLUSION

We have systematically evaluated the impact of the location and extent of extranodal metastases on survival in patients with TGCT using a large, nationally representative, population-based cancer registry. Patients with more than one extrapulmonary site involved exhibit the worst outcomes, and among patients with isolated extrapulmonary involvement, those with brain metastases tend to have the poorest survival. These outcomes may reflect both the aggressive biology of these tumors and the challenging nature of treating these patients. Further incorporation of organotropism into current prognostic models for metastatic TGCT warrants attention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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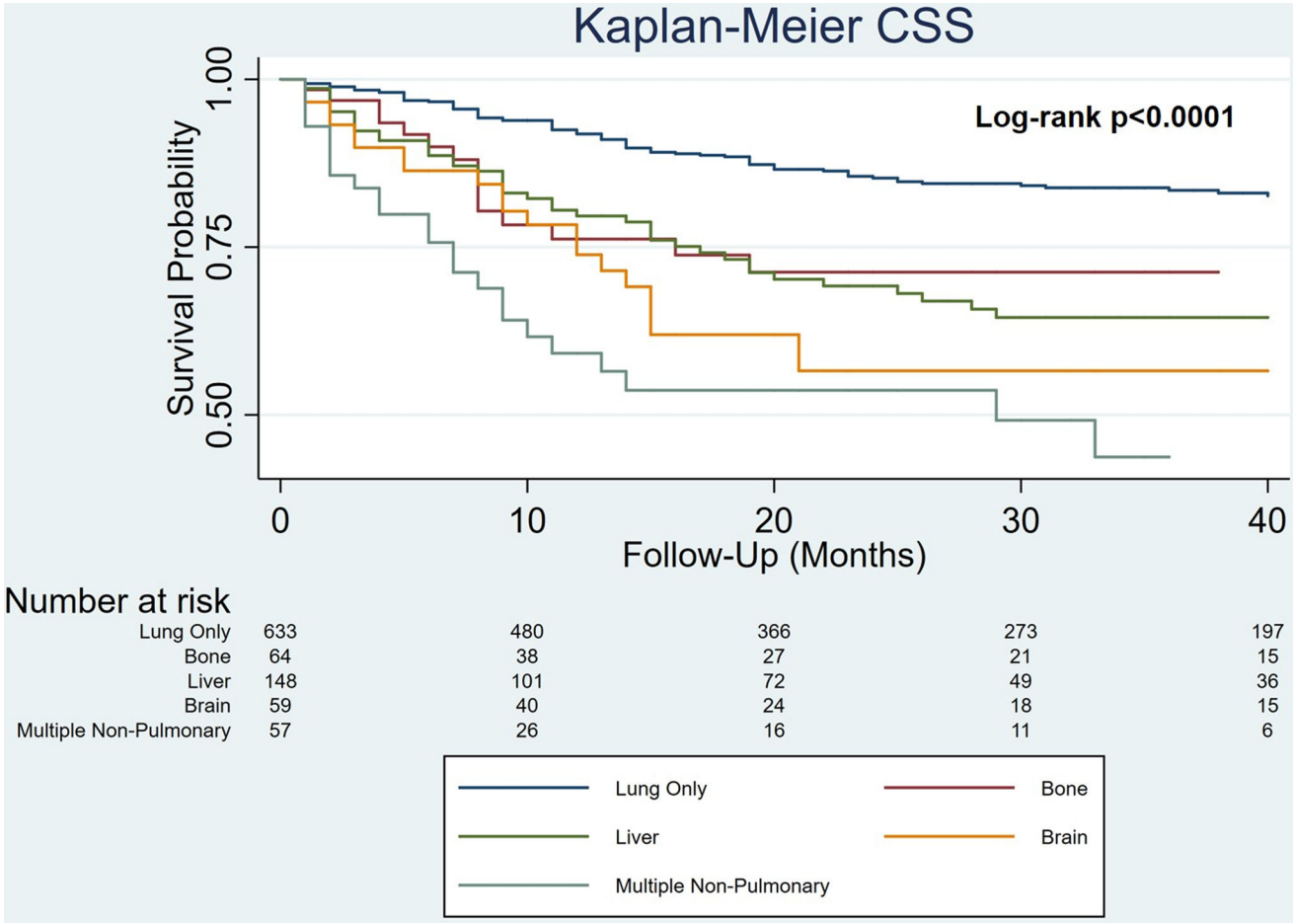

Figure 1.

Kaplan-Meier survival curves of cancer-specific survival stratified by site of distant metastases for men with stage III primary testicular germ cell tumors (log-rank p<0.0001). Surveillance, Epidemiology, and End Results Program 2010–2015.

Table 1.

Demographics and sites of distant metastases for included patients with stage III primary testicular germ cell tumors. Surveillance, Epidemiology, and End Results Program 2010–2015.

		Overall	
		Value	(% or IQR)
N		969	-
Age, years (median)		29	23–38
Race	**White**	535	55.2%
	Black	38	3.9%
	Hispanic	338	34.9%
	Asian	39	4.0%
	Native[1]	18	1.9%
	Unknown	1	0.1%
Year of Diagnosis	**2010**	146	15.1%
	2011	167	17.2%
	2012	152	15.7%
	2013	192	19.8%
	2014	164	16.9%
	2015	148	15.3%
Laterality	**Right**	480	49.5%
	Left	433	44.7%
	Unknown	56	5.8%
Histology	**Seminoma**	153	15.8%
	NSGCT	816	84.2%
Metastasis	**Lung**	877	90.5%
	Liver	203	20.9%
	Bone	94	9.7%
	Brain	95	9.8%
Stage	**III NOS**	232	23.9%
	IIIA	196	20.2%
	IIIB	94	9.7%
	IIIC	447	46.1%

[1] Native American or Alaskan

NOS = not otherwise specified; SD = standard deviation

Table 2.

Survival analysis evaluating impact of stage and metastatic sites on cancer-specific survival among included stage III primary testicular germ cell tumor patients. Model 1 Harrell's C 0.723. Model 2 Harrell's C 0.714. Surveillance, Epidemiology, and End Results Program 2010–2015.

		HR	95% CI		p-value	HR	95% CI		p-value	HR	95% CI		p-value
			Low	High			Low	High			Low	High	
		Univariable				Multivariable Model 1[1]				Multivariable Model 2[1]			
Age		1.03	1.02	1.04	<0.01	1.03	1.01	1.04	<0.01	1.03	1.01	1.04	<0.01
Histology	**NSGCT**	REF	-	-	-	REF	-	-	-	REF	-	-	-
	Seminoma	0.92	0.61	1.38	0.68	0.59	0.13	0.38	0.92	0.73	0.47	1.14	0.16
Metastasis[2]	**Lung**	0.85	0.53	1.35	0.49	-	-	-	-	1.38	0.83	2.30	0.21
	Liver	2.29	1.69	3.10	<0.01	-	-	-	-	2.04	1.46	2.84	<0.01
	Bone	1.94	1.29	2.92	<0.01	-	-	-	-	1.62	1.04	2.53	0.03
	Brain	2.79	1.95	4.01	<0.01	-	-	-	-	2.49	1.69	3.66	<0.01
Stage	**IIIA**	REF	-	-	-	REF	-	-	-	-	-	-	-
	IIIB	2.74	1.28	5.86	0.01	3.10	1.44	6.66	<0.01	-	-	-	-
	IIIC	5.63	3.12	10.17	<0.01	5.17	2.83	9.42	<0.01	-	-	-	-
	III NOS	1.82	0.92	3.60	0.08	1.64	0.82	3.27	0.16	-	-	-	-

[1] Multivariable Cox-proportional hazards models also adjusted for race, diagnosis year, laterality, and presence of lymphovascular invasion.

HR = hazard ratio, 95% CI = 95% confidence interval

[2] Reference group for each organ site corresponds to the lack of involvement of the corresponding organ

Table 3.

Survival analysis comparing groups by primary site of distant metastasis for cancer-specific survival among included stage III primary testicular germ cell tumor patients. Harrell's C 0.713. Surveillance, Epidemiology, and End Results Program 2010–2015.

		HR	95% CI		p-value	HR	95% CI		p-value
			Low	High			Low	High	
		Univariable				Multivariable[1]			
Age		1.03	1.02	1.04	<0.01	1.03	1.01	1.04	<0.01
Histology	**NSGCT**	REF	-	-	-	REF	-	-	-
	Seminoma	0.92	0.61	1.38	0.68	0.65	0.42	1.02	0.06
Metastasis	**Lung Only**	REF	-	-	-	REF	-	-	-
	Liver (+/− Lung)	2.40	1.65	3.48	0.01	2.29	1.56	3.35	<0.01
	Bone (+/− Lung)	2.10	1.21	3.64	<0.01	1.97	1.11	3.50	0.02
	Brain (+/− Lung)	3.21	1.99	5.18	<0.01	3.24	1.98	5.28	<0.01
	Multiple Nonpulmonary Sites	4.94	3.13	7.79	<0.01	4.27	2.60	7.00	<0.01

[1]Multivariable Cox-proportional hazards models also adjusted for race, diagnosis year, laterality, and presence of lymphovascular invasion.

HR = hazard ratio, 95% CI = 95% confidence interval