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Pathologic Risk Factors for Higher Clinical Stage in Testicular Seminomas

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Abstract

Introduction:
Testicular seminomas require accurate staging for effective management. 20% are metastatic at presentation while 80% are clinical stage I, requiring only orchiectomy and surveillance. Tumor size, rete testis invasion, hilar soft tissue invasion, and lymphovascular invasion have been shown to incur a higher risk of metastasis and recurrence in clinical stage I seminomas, with little congruence between studies.

Materials and Methods:
We reviewed 211 cases of testicular seminomas and recorded patient age, tumor size, lymphovascular invasion and rete testis, hilar soft tissue, epididymis, spermatic cord, tunica albuginea, and tunica vaginalis involvement. A univariate and multivariate analysis was performed comparing clinical stage I to advanced clinical stage patients (stages II and III) in reference to these factors.

Results:
We found that tumor size (p=0.02), vascular invasion (p=0.02), and invasion of rete testis stroma (p=0.01), epididymis (p=0.02), spermatic cord (p=0.047), and hilar soft tissue (p=0.04) were predictors of higher clinical stage at the univariate level. However, multivariate analysis showed that only tumor size and vascular invasion remained significant (p=0.008 and 0.032, respectively). A tumor size of 4 cm was the size cutoff found to be significant.

Discussion:
Tumor size and vascular invasion are the strongest predictors of higher clinical stage in testicular seminomas. Our univariate data suggests that rete testis and hilar soft tissue invasion relate to higher clinical stage. However, neither of these factors were found to be independent risk factors at multivariate analysis. Therefore, this study supports tumor upstaging based only upon size and vascular invasion.

Key Words: Germ cell tumor; seminoma; rete testis; lymphovascular space invasion; testis

Introduction

Testicular germ cell tumors are the most common solid organ malignancy in males 20-35 years old, with pure testicular seminomas representing up to 60%.[1] Seminomas are highly treatable, with 80% of patients presenting at low stage disease (clinical stage I) and managed with orchiectomy and imaging surveillance.[2] However, many large studies have now shown that the relapse rate of clinical stage I seminoma treated by orchiectomy and surveillance alone is between 15 and 20%.

Most of these cases recur within 12-18 months and many are theorized to have occult metastases at the time of presentation.[3] Therefore, identifying risk factors for metastatic disease (or advanced clinical stage) is important to understand which patients are at a higher risk of subclinical metastases at presentation and, therefore, recurrence.

Previous studies have attempted to develop models for risk of recurrence in clinical stage I seminomas. The results of these studies have been inconsistent, with tumor size as the only consistent predictor of increased recurrence but with difference in size cutoffs. Other purported predictors including lymphovascular invasion, rete testis invasion, and hilar soft tissue invasion have had variable support.[4-9] Kollmannsberger et al. demonstrated that advanced disease was seen with both early and late relapse patients, and did not see a correlation between current IGCCC risk stratification criteria and likelihood of relapse as all of their relapsed seminoma cases were good risk disease. Thus, further characterization of risk factors for recurrence, such as degree of locally advanced disease at the time of diagnosis, is needed.[10] Therefore, we wished to undertake a comprehensive analysis of possible prognostic factors in seminomas and their relationship to metastasis at the time of presentation, particularly in light of recent changes to the pathologic staging of testicular germ cell tumors in the American Joint Committee on Cancer staging manual (8th edition).[11]

Methods

We retrospectively collected 211 consecutive in-house cases (2000-2016) of pure testicular seminomas and reviewed the microscopic slides, pathology reports, and clinical histories. The final cohort consisted of 170 cases, as clinical stage was not available in 41 cases. The microscopic slides were reviewed by three pathologists prior to the collection of clinical stage data. Patient age, tumor size, lymphovascular invasion (LVI) and rete testis, hilar soft tissue, epididymis, spermatic cord, tunica albuginea, and tunica vaginalis involvement were recorded. Direct rete testis and epididymal invasion versus pagetoid spread was specifically recorded. Rete testis tumor invasion was defined as

tumor cells in the stroma on both sides of a tubular channel or clear destruction of the testicular hilum (figure 1), and hilar soft tissue invasion was defined as tumor extension into the soft tissue beyond the rete testis at the same plane of section as the testis parenchyma (figure 2). Spermatic cord invasion was defined as tumor grossly extending beyond the hilum, with the base defined as the section just superior to the head of the epididymis. Lymphovascular invasion was defined as cohesive cells, adherent to the wall of the blood vessel, preferably located in a peritumoral or tunica albuginea location. Associated fibrin material further supports the presence of lymphovascular invasion. Tunica albuginea invasion was defined as invasion into the fibrous layer immediately surrounding the testicular parenchyma. Tunica vaginalis invasion was defined as invasion into or through the mesothelial layer surrounding the tunica albuginea. These definitions were composed by a combination of recent suggestions in the AJCC 8th edition guidelines for testis staging, Verrill et al.'s recommendations in the recent International Society of Urological Pathology (ISUP) guidelines on reporting and staging of testicular germ cell tumors, and the combined experience of multiple specialist genitourinary pathologists at our institution in situations where the two previously mentioned sources are not entirely clear.[11,12]

Clinical stage was assessed from medical records at the time of presentation. Abdominal and pelvis CT and chest X-ray were available for all 170 patients included in the cohort. Additional evidence of metastasis and serum tumor markers were additionally noted when determining the clinical stage. Cases were then sub-classified as either clinical stage I (including IA, IB, and IS stages) or advanced clinical stage (stage II and above).

Binary categorical variables (lymphovascular, rete testis, hilar soft tissue, epididymis, spermatic cord, tunica albuginea, and tunica vaginalis invasion) were collected and frequency and proportions were recorded for clinical stage I and advanced clinical stage groups. Continuous variables (age and tumor size) were kept in whole years for age and rounded to the nearest 1 mm for tumor size. Means were calculated for both age and tumor size in the clinical stage I and advanced clinical stage groups. On gross report and slide review, only tumor size, vascular invasion,

spermatic cord invasion, and tunica vaginalis invasion could be evaluated on every case included. A number of cases did not have adequate sampling of the testicular hilum and epididymis due to the year range that was included in the cohort. Therefore, each incomplete category had frequencies counted and proportions were calculated based on the number of cases that were evaluable for that particular variable. Additionally, frequencies were calculated for the number of cases less than and greater than 2cm, 3cm, and 4cm in both the clinical stage I and advanced clinical stage groups.

A univariate and multivariate analysis was performed comparing clinical stage I to higher clinical stage patients (stage II and III) in reference to these factors. Univariate analysis was performed using Fisher's exact test for binary variables and the two sample t-test for continuous variables. Additionally, chi square testing was used to evaluate tumor size data with the various cutoffs recorded (2 cm, 3 cm, and 4 cm). Logistical regression was performed for multivariate analysis with forward stepwise selection of variables. The odds ratio was calculated for all statistically significant variables at the multivariate level. The final logistical regression model was used to form a receiver operating curve to evaluate the performance of the statistically significant variables at predicting higher clinical stage. A p-value of <0.05 was set as statistically significant for all tests. All statistics were performed using Excel and SAS programs (Microsoft Office 2016, SAS Institute 2013).

Results

Clinical findings

Of the 170 cases included in the cohort, 138 (81%) were clinical stage I and 32 (19%) were advanced clinical stage (stages II and III). The mean patient age was 37 years (range 19-68 years). (Table 1)

Pathologic findings

Of the 170 cases, the mean tumor size was 4.2 cm (range of 0.4-11.5 cm). Lymphovascular invasion was demonstrated in 25 cases (15%), spermatic cord invasion in 5 (3%), and tunica vaginalis involvement in 4 (2%). Rete testis invasion was identified in 90/155 (58%) cases whereas pagetoid spread was seen in 28/145 (19%). Invasion of hilar soft tissue occurred in 34/158 (22%), epididymis in 9/162 cases (6%) (with pagetoid spread in 1/160 [<1%]), and tunica albuginea in 48/148 (32%). (Figure 1A-D) None of the cases had revised diagnoses (all remained pure seminoma) or revised clinical staging on re-review of the pathologic and clinical data. As pathologic staging was irrelevant to the analysis of each binary and continuous variable individually, this data was unaffected by the AJCC 8th edition update to testicular cancer staging. All cases were unilateral, with 211 separately represented patients.

The clinical and pathologic findings in clinical stage I cases versus those of advanced clinical stage are shown in Table 1. On univariate analysis, tumor size, vascular invasion, spermatic cord invasion, and epididymal invasion were significantly more common in cases of advanced clinical stage than in stage I disease (Table 1). Additionally, on univariate analysis, age, rete testis invasion, rete testis pagetoid spread, hilar soft tissue invasion, epididymal pagetoid spread, tunica vaginalis involvement, and tunica albuginea involvement were not significantly different between cases of clinical stage I and advanced clinical stage.

On multivariate analysis, only tumor size and vascular invasion were significant independent predictors of higher clinical stage (Table 2). A logistical regression model was created using these two variables and is represented in a receiver operating curve with an area under the curve of 0.7 (figure 2).

Additionally, the various cutoffs trialed for tumor size showed significantly higher risk of metastatic disease only with use of the 4 cm cutoff (Table 3). There was no statistical difference in the rate of advanced clinical stage when using both 2 cm and 3 cm cutoffs.

Discussion

This study identified tumor size and vascular invasion as strong predictors of advanced clinical stage and thus metastases at presentation in pure testicular seminomas. Additionally, we found the most appropriate cutoff point for upstaging based on tumor size to be <4 cm versus >/=4 cm based on the increased likelihood of metastases in tumors >/=4 cm. This was not true of the smaller cutoff values, 2 cm and 3 cm respectively. These findings differ from those previously described in nonseminomatous germ cell tumors in the lack of support for hilar soft tissue, epididymal invasion, and rete testis invasion as prognostic risk factors, as well as the recently revised American Joint Committee on Cancer staging of germ cell tumors, which includes hilar soft tissue and epididymal invasion and a size cut off of 3 cm.[11,13]

Previous studies on risk factors for recurrence in pure seminomas have identified tumor size, vascular invasion, rete testis invasion, and increased age as predictors of recurrence or metastasis at presentation. However, many studies have found different and conflicting factors as significant, with validation in different institutions proving to be difficult. The largest of these studies demonstrated tumor size and rete testis invasion to be significant risk factors for recurrence in clinical stage I seminomas.[9] However, this study utilized pooled data from 4 different centers and historical data from pre-existing pathology reports without re-review of historic slides, unlike our study. Furthermore, external validation of this study by Chung et al.[4] identified only tumor size to be an independent risk factor at multivariate analysis, which was additionally supported by Vogt et al. who found rete testis involvement not to be a significant risk factor in a combined seminoma and nonseminoma cohort.[4,7] The significance of tumor size was reconfirmed in a follow up study by Nayan et al. which described significant differences in relapse rates of seminomas based on tumor size.[14]

Other studies have found lymphovascular invasion and age to be significant risk factors, but these findings have not been confirmed in other institutions.[5,8] As Lymphovascular invasion is a well-supported prognostic factor in nonseminomatous germ cell tumors, the recent ISUP publication on

reporting and staging testicular germ cell tumors specifically calls for further studies to provide high level evidence of lymphovascular invasion in pure seminomas.[10 12]Thus, our study helps to fill this need by providing clear evidence of multivariate significance of lymphovascular invasion in pure seminomas specifically.

Unlike the recent study on nonseminomatous germ cell tumors by Yilmaz et al[10], our study did not find hilar soft tissue invasion and rete testis invasion to be independent predictors of advanced clinical stage in pure seminomas. However, our study did concur with Yilmaz et al that vascular invasion is an independent risk factor. This lack of congruence between support for these risk factors (in particular hilar soft tissue and rete testis invasion) in seminomas and nonseminomas could be due to the aggressive nature of nonseminomas in comparison to pure seminomas, and this fact is not adequately addressed by the current AJCC staging system which cites evidence for upstaging based on hilar soft tissue and epididymal invasion based on studies done on only nonseminomas.[11]

Although our results did not support other histologic and clinical criteria as independent risk factors for metastases outside of tumor size and vascular invasion, there were limits to our study. As testicular germ cell tumors are fairly uncommon tumors, the number of cases available to study was low and impact the power of the study. In particular, the number of cases with advanced clinical stage (N=32) in cases of pure seminoma were limited. In comparison to studies of non-seminomas in which presentation at a higher clinical stage is more likely, a large cohort of advanced clinical stage patients is unavailable. Similarly, our ability to analyze the impact of factors associated with local growth (advanced pathologic T-stage) was limited by few cases showing aggressive local invasion because of the relatively indolent tendencies of many seminomas. Hence, we found only 5 cases with spermatic cord invasion, 1 with epididymal pagetoid spread, 9 with epididymal invasion, and 4 with tunica vaginalis invasion. The remaining criteria evaluated had a larger number of positive cases (N>/=25).

Additionally, our multivariate analysis was impacted by missing data. Of the criteria studied, only vascular invasion, tumor size, age, and spermatic cord invasion were available in all cases, while a number of the other cases were missing one or more of the studied criteria (Table 1). This led to cases being eliminated from consideration in the logistical regression. Likewise, a number of the criteria examined demonstrated a great deal of overlap; rete testis and hilar soft tissue for example, which made proving independence difficult. Thus, hilar invasion may be more easily proven significant by grouping all hilar invasion (rete testis, hilar soft tissue, and epididymis invasion) into one category in future studies. While this would not allow for elucidation of each factor individually, it would allow for clarification of the impact of hilar invasion in pure seminomas, which other studies have also struggled to validate.[4]

Our study was additionally limited by the use of advanced clinical stage at presentation as a proxy for increased risk of relapse. The use of advanced clinical stage at diagnosis as an alternative to direct recurrence data as a prognostic indicator was performed in a cohort of nonseminomas by Yilmaz et al previously, and this paper is regarded as strong evidence in the recent AJCC 8th edition update.[11,13] Advanced stage disease was additionally chosen over relapse data directly due to the confounded nature of current relapse data due to differences in treatment among those with clinical stage I disease over the time period tested. While there is much support to the use of surveillance in all of these patients, the clinical scenario including the degree of locally advanced disease, the likelihood of patient compliance, and patient anxiety, all influence the decision of whether to use adjuvant chemotherapy or radiation at the time of orchiectomy.[15] Additionally, our institution is a tertiary care center that provides orchiectomy and care planning for a large surrounding area. Thus, a number of patients chose to undergo surveillance closer to home once their original care plan is in place, making this data unavailable to us currently.

Lastly, this project was limited by data collection from a single institution. Collaboration was attempted with outside institutions, but we found the completeness of outside data sets (i.e. not differentiating rete testis invasion from pagetoid spread or lack of hilar soft tissue invasion data) to be a recurring problem. Additionally, grossing protocols differed between institutions, and we found sampling of both hilar regions and spermatic cord to be drastically different over time and in different locations. By adhering to a single institution, we were able to adequately review the slides from all cases included and access clinical data necessary to confirm the clinical stage.

The results of this study underscore the importance of tumor size and lymphovascular invasion in the risk stratification of pure testicular seminomas. While tumor size has recently been added to the AJCC staging system for testicular germ cell tumors, the cutoff provided is 3 cm, which is not supported by our current study. Additionally, tumor size is only used to subclassify pathologic staging of pT1 into pT1a and pT1b. Without other evidence of advanced disease, these cases will both be considered clinical stage IA, and therefore, at very low risk for recurrence. We have identified tumor size >/= to 4 cm as a risk factor for metastases, and, as such, given equal weight as lymphovascular invasion in pathologic staging. Consequently, our study supports adding tumor size of >/= 4 cm to future staging systems as pT2 in cases of pure seminomas, and we call for continued study to further validate this at other institutions or in larger data sets. Other large cohort studies have also demonstrated the importance of tumor size in seminomas, leaving this factor as the lone histologic criteria that has been well supported by outside studies in seminomas in particular.[4,7,9] In addition to this outside support, the AJCC system notes that there is minimal support for a specific size cutoff in the current literature.[11] While Chung et al. and Nayan et al. both showed significant increase in relapse using a cutoff of 3 cm, both Warde et al.'s study and Groll, Warde, and Jewett's comprehensive review support the use of a 4 cm tumor size cutoff and our study adds support to this value.[4,9,14,15]

In conclusion, vascular invasion and tumor size >/= 4 cm are strong independent predictors of metastases in cases of pure testicular seminomas with a fair predictive model using these two criteria alone (AUC=0.7, figure 3). Extratesticular extension in the hilum was not found to be a significant risk factor for metastases as has been shown for nonseminomatous germ cell tumors, likely due to the low rate of cases that present at this advanced stage in comparison to nonseminomatous germ cell tumors and the great deal of overlap between hilar soft tissue and rete testis invasion, making independence difficult to support by multivariate analysis.

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Figure Legend:

Figure 1. Invasion of rete testis by seminoma, 1A; Gross morphology of seminoma extending into hilar structures, 1B; Stromal invasion of rete testis by seminoma (arrows showing rete testis tubules), 1C; Rete testis pagetoid extension of seminoma (arrows indicating seminoma cells) , 1D; Invasion of hilar soft tissue by seminoma.

Figure 2. ROC curve for the prediction of advanced clinical stage based on logistic regression model

Tables:

Table 1. Comparison of clinical and histologic variables between clinical stage I and advanced clinical stage patients.

Table 2. Multivariate logistical regression of risk factors for metastatic disease.

Table 3. Analysis of various tumor size cutoff values and the relationship to metastatic disease.

Table 1. Comparison of clinical and histologic variables between clinical stage I and advanced clinical stage patients.

Variables	Total (N = 170)	Clinical Stage I (N = 138)	Clinical Stage II or III (N = 32)	P Value
Age, mean (sd)	37.4 (9.5)	36.7 (9.1)	39.9 (10.8)	0.087
Tumor size, mean (sd)	4.2 (2.3)	3.9 (2.1)	5.4 (2.7)	0.006
Vascular invasion				0.01
No	145 (85.3%)	123 (89.1%)	22 (68.8%)	
Yes	25 (14.7%)	15 (10.9%)	10 (31.3%)	
Rete testis invasion				0.11
Unknown	15	15		
No	65 (41.9%)	56 (45.5%)	9 (28.1%)	
Yes	90 (58.1%)	67 (54.5%)	23 (71.9%)	
Rete pagetoid spread				0.068
Unknown	25	22	3	
No	117 (80.7%)	90 (77.6%)	27 (93.1%)	
Yes	28 (19.3%)	26 (22.4%)	2 (6.9%)	
Tunica vaginalis invasion				0.16
No	166 (97.6%)	136 (98.6%)	30 (93.8%)	
Yes	4 (2.4%)	2 (1.4%)	2 (6.3%)	
Tunica albuginea invasion				0.51
Unknown	22	19	3	
No	100 (67.6%)	82 (68.9%)	18 (62.1%)	
Yes	48 (32.4%)	37 (31.1%)	11 (37.9%)	
Hilar soft tissue invasion				0.05
Unknown	12	11	1	
No	124 (78.5%)	104 (81.9%)	20 (64.5%)	
Yes	34 (21.5%)	23 (18.1%)	11 (35.5%)	
Epididymal invasion				0.012
Unknown	8	6	2	

No	153 (94.4%)	128 (97.0%)	25 (83.3%)	
Yes	9 (5.6%)	4 (3.0%)	5 (16.7%)	
Epididymal pagetoid extension				1
Unknown	10	7	3	
No	159 (99.4%)	130 (99.2%)	29 (100%)	
Yes	1 (0.6%)	1 (0.8%)	0 (0%)	
Spermatic cord invasion				0.047
No	165 (97.1%)	136 (98.6%)	29 (90.6%)	
Yes	5 (2.9%)	2 (1.4%)	3 (9.4%)	

Table 2. Multivariate logistical regression of risk factors for metastatic disease.

	Odds Ratio (95% Confidence interval)	P- Value
Tumor size	1.27 (1.06 - 1.5)	0.008
Vascular invasion	2.83 (1.09 - 7.32)	0.032

Table 3. Analysis of various tumor size cutoff values and the relationship to metastatic disease.

Tumor size	Clinical stage I (N=138)	Clinical stage II and III (N=32)	p-value	Odds ratio	Confidence Interval (95%)
<2 cm	22	5	0.965	1.02	0.36-2.95
>/= 2 cm	116	27			
<3 cm	49	8	0.257	1.65	0.73-3.73
>/= 3 cm	89	24			
<4 cm	80	9	0.002	3.52	1.63-7.61
>/= 4 cm	58	23