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Title: Pathologic Risk Factors for Metastatic Disease in Post-pubertal Patients with Clinical Stage I Testicular Stromal Tumors

Authors: Kyle O. Rove, MD[a], Paul D. Maroni, MD[a], Carrye R. Cost, MD[b], Diane L. Fairclough, DrPH, MSPH[c], Gianluca Giannarini, MD[d], Anne K. Harris, MPH[e], Kris Ann P. Schultz, MD[e], Nicholas G. Cost, MD[a]

[a] Department of Surgery, Division of Urology, University of Colorado, Aurora, CO

[b] Department of Pediatrics, Division of Pediatric Oncology, University of Colorado, Aurora, CO

[c] Department of Biostatistics and Informatics, University of Colorado, Aurora, CO

[d] Academic Medical Centre Hospital "Santa Maria della Misericordia", Urology Unit, Udine, Italy

[e] Department of Cancer and Blood Disorders, Children's Hospitals and Clinics of Minnesota, Minneapolis, Minnesota

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Corresponding Author:

Nicholas G. Cost, M.D.

Department of Surgery, Division of Urology

University of Colorado School of Medicine

13123 East 16th Ave., B 463

Aurora, CO 80045

Mobile: (214) 883-3199, Office: (720) 777-5084, Fax: (720) 777-7370

Email: nicholas.cost@ucdenver.edu

Abstract

Objective: To systematically review the existing literature in order to analyze the impact of previously identified pathologic risk factors on harboring occult metastatic disease (OMD) in patients with Clinical Stage I TSTs.

Methods: A literature search using PubMed was conducted using the terms: "testicular stromal tumors," "testicular Leydig cell tumors," "testicular Sertoli tumors," "testicular interstitial tumors," "testicular granulosa tumor," and "testicular sex cord tumors." For analysis we included only studies with data on available recurrence, survival, and time-to-event. We hypothesized patients with ≥2 risk factors would experience lower 5yr OMD-Free Survival (OMDFS) than those with <2 risk factors.

Results: 292 patients from 47 publications were included with a median age at diagnosis of 35yrs (range 12−76). 5yr OMD-Free survival (OMDFS) and overall survival in patients with Stage I TSTs were 91.2% and 93.2%, respectively. When comparing those who harbored OMD to those who did not, we observed an increased risk of OMD for each additional risk factor ($p<0.001$). 5yr OMDFS was 98.1% for those with <2 risk factors vs. 44.9% for those with ≥2 risk factors ($p<0.001$).

Conclusions: The existing literature on pathologic risk factors for OMD in this population is insufficient to make broad clinical recommendations. However, these factors appear to risk-stratify patients and may be useful for future research investigating adjuvant therapy in higher-risk patients. This review indicates that such a stratification system has a rational basis.

Introduction

Testicular stromal tumors (TSTs) are rare, arising from non-germinal cell lines of the male testis. They represent 3-5% of all primary testicular masses, and across all age groups, about 10% demonstrate malignant behavior.[1,2] Puberty and its requisite changes in the hormonal milieu have been traditionally felt to alter the natural history of TSTs, portending an increased risk of malignant behavior.[3] While germ cell tumors in adolescents appear to behave like their adult counterparts and have been advocated to be treated in a similar manner, only small case reports and case series have elucidated current clinical knowledge of management and known outcomes of adolescents and adults who present with TSTs.[4] As a result, there has been varied guidance on how best to treat and follow individual patients, particularly those who present with localized, clinical stage I disease (TMN stage pT1-4 N0 M0), about 10% of whom will go on to develop recurrent disease after orchiectomy.[2,5,6]

Previous studies have demonstrated that certain histologic findings found in radical orchiectomy specimens may portend a malignant phenotype, including large tumor size (> 5 cm), increased number of mitoses per high-powered field, positive margins, rete testis invasion, lymphovascular invasion (LVI), cellular atypia, and necrosis.[7-10] These features were initially elucidated in series of Leydig cell tumors and then Sertoli cell tumors, but have since been used for all sub-types of TSTs.[2] The presence or absence of these pathologic criteria can aid the clinician in determining malignant potential, but the presence of any particular feature has not been noted to predict metastatic behavior.[11] Young et al first suggested a cutoff of two or more pathologic risk factors to determine malignant potential of TSTs, which might allow for earlier intervention to alter the natural course of the disease.[9]

Patients that recur after complete excision of the primary tumor likely had occult microscopic metastases that were not detectable at initial staging with cross-sectional imaging (as opposed to *de novo* lesions). Additionally, as TSTs do not typically respond well to conventional chemotherapy regimens nor radiotherapy. Surgery (most typically in the form of a retroperitoneal lymph node dissection, RPLND) remains one of the few interventions that offers curative potential to patients with recurrence.[6] To date, the best approach and management of patients with TSTs has remained controversial given the lack of data, experience and unknown natural history.

We sought to systematically review the existing literature to analyze the impact of known pathologic risk factors on the presence of occult metastatic disease (OMD) in post-pubertal patients (≥ 13 years old or documented pubertal status) with clinical stage I TSTs. In doing so,

we aimed to clarify questions regarding risk of malignant and metastatic potential of this disease process and determine what factors most contribute to risk of harboring OMD. We hypothesized that patients with ≥ 2 pathologic risk factors would experience a lower 5-year OMD-Free Survival (OMDFS) than those with 0 or 1 risk factors. Similarly, we hypothesized that older age (> 50 years old) would result in lower 5-year OMDFS as compared to younger patients (≤ 50 years old).

Material and Methods

Study identification

A systematic literature search of the PubMed database was conducted on December 1, 2014 to identify human studies using the terms: "testicular stromal tumors," "testicular Leydig cell tumors," "testicular Sertoli tumors," or "testicular interstitial tumors." The methodology used to identify and select studies for patient inclusion in the quantitative synthesis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12] Duplicate studies were identified and removed.

Studies were included if they contained post-pubertal patients greater than or equal to 13 years old (or documented pubertal status) with clinical stage I TSTs. Clinical stage I disease is defined as disease clinically confined to the testis, completely removed at orchiectomy with negative staging imaging that at minimum includes cross sectional imaging of the retroperitoneum, the most common site of metastasis.[1,13,14] TSTs are classified into several subtypes, including Leydig cell tumors, Sertoli cell tumors, large cell calcifying Sertoli cell tumors, sclerosing Sertoli cell

tumors, Sertoli-Leydig tumors, interstitial cell tumors, granulosa cell tumor, mixed stromal tumors, unclassified stromal tumors, and testicular interstitial cell tumors.

Study exclusion criteria were those published prior to 1980, non-English language articles, individual patients within series less than 13 years old, individual patients with ≥ clinical stage II disease at time of diagnosis, and articles with inadequate data on initial clinical stage, data on presence of pathologic risk factors, or post-orchiectomy follow up. The pathologic risk factors were: largest tumor > 5 cm, ≥ 3 mitoses per high-powered field, positive margins, rete testis invasion, lymphovascular invasion, cellular atypia, and necrosis. If length of follow up was not specifically assigned in the published series to an individual patient, then median or mean length of follow up for the series was assigned to that patient. In patients with bilateral disease, the largest tumor size was recorded. If pathologic risk factors were present, each was recorded regardless of laterality.

Unique articles returned in the literature search were screened, and those that did not meet inclusion criteria were excluded. Of the full-text articles that remained, references were further analyzed to locate any studies not returned in the original search, and these were also screened. Finally, full-text articles were assessed for eligibility based on the stated inclusion and exclusion criteria, leaving studies with patients for final quantitative analysis (Supplementary Table 1 and Supplementary Figure 1).

For analysis, we included only those patients with data available on recurrence, survival, and time-to-event. In reviewing patients in published studies, the main outcome of interest was

presence of occult metastatic disease, defined as (1) any new metastasis detected during surveillance after orchiectomy for apparent clinical stage I disease, or (2) positive lymph nodes found at primary RPLND in patients with apparent clinical stage I disease.

Statistical Analysis

Descriptive analyses of the patients from the identified studies are reported in median values (range). For time-dependent analyses, log-rank analysis was used, and patients were censored at the mention of the last time they were disease free or still surviving. Univariate and multivariate logistic regressions for survival analysis using a Cox Proportional Hazards Model were performed to determine effects of covariates on the development of OMD. Log-rank analysis was performed to compare 5-year OMDFS with regards to number of pathologic risk factors, age by decile (13-20, 21-30, 31-40, 41-50, 51-60, and > 60 years) and age by dichotomy (≤ 50 and > 50 years). We further examined the time intervals between orchiectomy and identification of those with OMD. Comparisons of categorical variables were performed using the Fisher's exact test or Chi-squared test, whereas comparisons of continuous variables were performed using the Mann–Whitney U test. In all analyses, two-sided p values < 0.05 or a 95% confidence interval (CI) not crossing 1.0 were considered significant.

Results

Of the 4,827 studies located during the literature search, 47 studies met screening and eligibility criteria for inclusion. Supplementary Figure 1 shows the PRISMA schematic for how these studies were identified for inclusion and patient extraction. Included studies are listed within Supplementary Table 1. Within these 47 studies, 292 patients with clinical stage I TSTs with

available data were abstracted for this quantitative analysis. Demographics are listed in Table 1A. Median patient age was 37 years old (range 12–76) with a median tumor size of 1.5 cm (range 0.5–13 cm). Median follow up across all patients was 47 months (range 1–249 months). Primary tumor management was clearly stated in the reports on 204 (69.9%) patients, of these 148 (72.5%) underwent radical orchiectomy and 56 (27.5%) were managed with partial orchiectomy (testis sparing surgery). Primary RPLND was performed in 25 patients (8.6%) with positive lymph nodes in 2 patients (0.7% of all patients or 8.0% of patients who underwent RPLND). Overall, 27 (9.2%) patients were noted to have OMD. As for the anatomic site of disease, 81.5% of patients with OMD had disease in the retroperitoneum, followed by lungs (14.8%). Overall survival was 91.5% across all patients and 44.1% in those with OMD.

Tables 1B and 1C provide a breakdown of tumor histology, pathologic risk factors, and numbers of risk factors present. The most common histology was Leydig cell tumor, in 169 (69.8%) patients, followed by Sertoli cell tumor, in 51 (21.1%) patients. In terms of the number of pathologic risk factors, 216 (74%) patients had zero risk factors, and 253 (86.6%) had zero or 1 risk factor. The most common pathologic risk factor was ≥ 3 mitoses per HPF (34 of 242 patients or 14%).

Comparison of patients with and without OMD is presented in Table 2. Age and tumor size were significantly different between the two groups ($p < 0.001$). Patients with OMD were older (median 52 years old) and had larger tumors (median 5.4 cm) than patients without OMD (37 years old, 1.5 cm). The tumor sub-types were significantly different between the two groups as

well (p = 0.008). Similarly, the breakdown of pathologic risk factors present and number of risk factors per patient was significantly different between the two groups (p < 0.001).

When examining 5-year OMDFS by age, histology, and risk factors, there were significant differences noted, as shown in Table 3. We examined 5-year OMDFS for different age-cut offs. When comparing OMDFS in patients less than 50 years age (94.5%, 95% CI 90.8–98.2%) to those greater than 50 years old (79.5%, 95% CI 65.8–93.2%), differences were significant (p < 0.001). Univariate and multivariate analyses were also performed. On univariate logistic regression analysis of covariate predictors of 5-year OMDFS, age, classic Sertoli cell and undifferentiated histologies, and all seven pathologic risk factors were statistically significant. However, on multivariate analysis, age and histology fell out in this multivariate model as predictors of 5-year OMDFS and only presence of LVI (HR 8.563, 95% CI 1.788–41.013, p = 0.007) and tumor size > 5 cm (HR 10.951, 95% CI 2.786–43.047, p = 0.001) predicted lower 5-year OMDFS. Further on the importance of these two risk factors specifically, in the 37 patients with only one risk factor, 3 (8.1%) harbored OMD and of these two had LVI and one had a tumor >5cm.

As for our primary study objective, comparing the 5-year OMDFS in patients with 0–1 pathologic risk factor to those with 2 or more, we observed a significant difference (98.3% vs. 48.1%, p < 0.001). A Kaplan-Meier curve demonstrating this difference is shown in Figure 1A. Figure 1B demonstrates the increasing risk of OMD with each additional pathologic risk factor. The latency between radical orchiectomy and detection of OMD was also determined for all study patients. Supplementary Figure 2 shows that while the majority of patients with OMD are

identified within the first 5 years, detection of OMD has been reported as late as 17 years after initial diagnosis.

Comment

TSTs are rare entities compared to germ cell tumors, and the vast majority (>90%) of post-pubertal patients with clinical stage I disease do well and are cured with orchiectomy alone. However, OMD present at the time of diagnosis and undetectable on cross-sectional staging imaging can be pernicious and later harm the patient. This analysis shows that patients who are found to have OMD tend to be older with larger-diameter primary tumors with a greater proportion of classic Sertoli cell and undifferentiated tumor histology. Furthermore, patients with OMD were more likely to have 2 or more pathologic risk factors present in the orchiectomy specimen.

In TSTs, the association of pathologic risk factors and patients with poor clinical outcomes was first noted by Kim et al.[7] In previous pathologic reports, the presence of mitoses alone was used to denote malignant behavior. We would argue, as others have, that utilizing the entire clinical picture including an array of pathologic risk factors from the orchiectomy specimen can help personalize decisions about disease management.[14] The use of these risk factors to stratify patients with and without malignant TSTs (presumably patients harboring OMD at time of orchiectomy) was previously proposed by Young et al.[9] From our quantitative analysis of patients in the literature, this stratification scheme appears to hold up well.

Puberty and its changes in various hormone levels have been felt to be responsible for the change in clinical behavior of TST, namely that TST in pre-pubertal patients are virtually never malignant while up to 10% of those in adults can be. A separate analysis from our group throws this assumption into question. We found that no patients aged 13 to 21 years-old with clinical stage I TSTs and median follow up of 45.6 months developed OMD. Even the presence of pathologic risk factors was rare in this age group.[15] While the patho-physiologic mechanisms in the development of TST may well still be dependent on a post-pubertal hormonal milieu, patients under 21 years-old appear to be at decreased risk of malignant behavior.

Regardless of age at diagnosis, latent detection up to 17 years out has been reported (see Figure 3 for histogram of time to detection of OMD), highlighting the difficulty in recommending a standardized follow up regimen and duration of follow up that maximizes safety and minimizes cost and potential morbidity of repeated ionizing cross-sectional imaging. Judicious use of non-ionizing MRI over CT imaging would allow for low-impact evaluation for retroperitoneal metastasis. Chest imaging (either in the form of chest radiograph or chest CT) might also be advised periodically given that 14.8% of OMD recurrences were noted in the lungs. Due to the low risk of OMD observed in patients with few or no risk factors, strong consideration should be given to a lower impact follow-up regimen that balances the risk of recurrence and assumed benefits of early detection with risks and costs of imaging. Previous reports varied greatly in their recommendations for patient follow up (some of which pertain to higher initial stages of disease).[5,11,16]

While a systematic review provides a robust picture of post-pubertal patients with TSTs, our study is not without limitations. Publication bias and the centering of reports at tertiary care institutions may omit certain cases. Follow up regimens were not standardized nor explicitly stated in many instances. With longer follow up, the outcomes may well be different. This review does not attempt to answer whether primary RPLND selectively applied in this clinical stage I population would alter the natural course of the disease, while noting that such aggressive surgery (metastectomy) likely remains the only current form of therapy that offers the possibility of durable cure in the setting of metastatic disease.

Conclusions

Approximately 10% of patients with clinical stage I TSTs develop OMD. Identifying those at risk of OMD is but a first step toward altering the natural history of this disease by allowing for design of surveillance mechanisms and possible earlier interventions, strong recommendations for which are beyond the scope of this paper. However, risk-stratification using age and pathologic risk factors may be useful for future research investigating adjuvant therapy (i.e., RPLND) for patients with apparent clinical stage I TSTs. Prospective study of these patients is needed, and entry into a tumor registry such as the International Ovarian and Testicular Stromal Tumor Registry (www.otstregistry.org) is key to learning more about these rare entities.

Key of Definitions for Abbreviations

CT - computed tomography

LVI - lymphovascular invasion

MRI - magnetic resonance imaging

OMD - occult metastatic disease

OMDFS - occult metastatic disease free survival

RPLND - retroperitoneal lymph node dissection

TST - testis stromal tumor

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Figure Legends:

Supplementary Figure 1. Schematic of systematic review of literature using Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) to identify, screen, determine eligibility and ultimately include in final quantitative synthesis.

Supplementary Figure 2. Histogram of time to detection of occult metastatic disease (OMD) demonstrating that while most patients with OMD have disease detected early after orchiectomy, detection has been documented as late as 17 years out.

Figure 1. a) Kaplan-Meier curve demonstrating worse occult metastatic free survival (OMDFS) in patients with 2 or more pathologic risk factors as opposed to those with only 0 to 1 risk factor. Difference in 5-year OMDFS between the curves significant to p-value < 0.001 by log-rank comparison. b) Kaplan-Meier curve demonstrating worse occult metastatic free survival (OMDFS) in patients with increasing numbers of risk factors. Difference in 5-year OMDFS between the curves significant to p-value < 0.001 by log-rank comparison.

Tables 1A, 1B, 1C. A) Demographic, clinical, and outcome variables for 292 patients included in this analysis from 47 separate publications identified. B) Breakdown of tumor histology (when available) and patients with pathologic risk factors (a single patient can have more than one risk factor). C) Number of patients with various numbers of risk factors, and cumulative number of patients with n or more risk factors. OMD = occult metastatic disease

A. Demographic and clinical variables		
Number of patients	292 (% of Total N)	
Median age (range)	37 years	(Range = 12–76)
Median tumor size, largest diameter	1.5 cm	(Range = 0.5–13)
Primary RPLND	25	8.6%
Positive lymph nodes at RPLND	2	8.0%
Patients with OMD	27	9.2%
Location of first site of metastasis		
Retroperitoneum	22	81.5%
Lungs	4	14.8%
Inguinal lymph nodes	1	3.7%
Death	19/292	8.5%
Death from disease	15/292	5.1%
Overall survival in patients with OMD	12/27	44.4%
Median Follow Up	47 mo	(Range = 1–249 mo)

B. Tumor histology (when listed)	**N**	**% of Total**
Leydig cell tumor	169	69.8%
Sertoli cell tumors	51	21.1%
Classic SCT	20	8.3%
Large cell calcifying	14	5.8%
Sclerosing	17	7.0%
Granulosa cell tumor	14	5.8%
Mixed	3	1.2%
Undifferentiated	5	2.1%
Pathologic risk factors		
≥ 3 Mitoses per HPF	34/242	14.0%
Positive margins	7/230	3.0%
Rete testis invasion	8/230	3.5%
LVI	13/242	5.4%
Cellular atypia	32/242	13.2%
Necrosis	13/242	5.4%
Largest tumor diameter > 5 cm	21/240	8.8%

C. Patients with # of risk factors			**Patients with *n* or more risk factors**		
	N	% of Total		N	% of Total
Zero risk factors	216	74.0%	Zero risk factors	216	74.0%
1 risk factor	37	12.7%	1 or more risk factor	76	26.0%
2 risk factors	15	5.1%	2 or more risk factors	39	13.4%
3 risk factors	14	4.8%	3 or more risk factors	25	8.6%
4 risk factors	5	1.7%	4 or more risk factors	10	3.4%
5 risk factors	3	1.0%	5 or more risk factors	5	1.7%
6 risk factors	2	0.7%			
			0–1 risk factors	253	86.6%
			2 or more risk factors	39	13.4%

Table 2. Comparison of patient characteristics, histologies, and pathologic risk factors of those with and without occult metastatic disease (OMD). RFs = risk factors.
Note: * Mann-Whitney-U test, ‡ Log-rank test

	Patients without OMD	**Patients with OMD**	**Patients with # of pathologic RFs who have OMD**	**P-value**
Number of patients	265 (90.7%)	27 (9.3%)		
Median age (range)	37 years (12–76)	52 years (29–70)	—	**< 0.001 ***
Median tumor size, largest diameter (range)	1.5 cm (0.5–13.0)	5.4 cm (2.0–12.0)	—	**< 0.001 ***
Median follow up (range)	47 months (1–249)	49 months (2–264)	—	0.402 *
Tumor histology (Denominator for % is all patients with listed histology)				
Leydig cell tumor	160 (91.4%)	15 (8.6%)	—	**0.008 ‡**
Sertoli cell tumors	46 (86.8%)	7 (13.2%)		
Classic SCT	17 (77.3%)	5 (22.7%)		
Large cell calcifying	12 (85.7%)	2 (14.3%)		
Sclerosing	17 (100.0%)	0 (0.0%)		
Granulosa cell tumor	13 (86.7%)	2 (13.3%)		
Mixed	3 (100%)	0 (0.0%)		
Undifferentiated	6 (66.7%)	3 (33.3%)		
Pathologic risk factors				
≥ 3 mitoses per HPF	18/219 (8.2%)	16/23 (69.6%)	—	**< 0.001 ‡**
Positive margins	2/210 (1.0%)	5/20 (25.0%)	—	**< 0.001 ‡**
Rete testis invasion	4/210 (1.9%)	4/20 (20.0%)	—	**< 0.001 ‡**
LVI	3/219 (1.4%)	10/23 (43.5%)	—	**< 0.001 ‡**
Cellular atypia	21/219 (9.6%)	11/23 (47.8%)	—	**< 0.001 ‡**
Necrosis	4/219 (1.8%)	9/23 (39.1%)	—	**< 0.001 ‡**
Tumor diameter >5 cm	9/219 (4.1%)	12/21 (57.1%)	—	**< 0.001 ‡**
Patients with *n* risk factors				
	Patients without OMD	**Patients with OMD**	**Patients with # of pathologic RFs who have OMD**	**P-value**
Number of patients	265 (N/265)	27 (N/27)		

Zero risk factors	214 (80.8%)	2 (7.4%)	2/216 (0.9%)	
1 risk factor	34 (12.8%)	3 (11.1%)	3/37 (8.1%)	
2 risk factors	8 (3.0%)	7 (25.9%)	7/15 (46.7%)	
3 risk factors	6 (2.3%)	8 (29.6%)	8/14 (57.1%)	**< 0.001 ‡**
4 risk factors	3 (1.1%)	2 (7.4%)	2/5 (40.0%)	
5 risk factors	0 (0.0%)	3 (11.1%)	3/3 (100.0%)	
6 risk factors	0 (0.0%)	2 (7.4%)	2/2 (100.0%)	
Patients with *n* or more risk factors				
	Patients without OMD	**Patients with OMD**	**Patients with # of pathologic RFs who have OMD**	**P-value**
Number of patients	265 (N/265)	27 (N/27)		
1 or more risk factor	51 (19.2%)	25 (92.6%)	25/76 (32.9%)	
2 or more risk factors	17 (6.4%)	22 (81.5%)	22/39 (56.4%)	
3 or more risk factors	10 (3.8%)	15 (55.6%)	15/25 (60.0%)	**< 0.001 ‡**
4 or more risk factors	3 (1.1%)	7 (25.9%)	7/10 (70.0%)	
5 or more risk factors	0 (0.0%)	5 (18.5%)	5/5 (100.0%)	

Table 3. 5-year occult metastatic disease free survival (OMDFS) for studied covariates. Univariate and multivariate hazard ratios are shown for tested age ranges, tumor histologies and pathologic risk factors. Only the presence of LVI and tumor size > 5 cm in greatest dimension were significant predictors of lower 5-year OMDFS. CI = confidence interval, NS = non-significant.
Note: ‡ Log-rank test

	5-year OMDFS (95% CI)	P-value	Univariate HR (95% CI, P-value)	Multivariate HR (95% CI, P-value)
< 40 vs. ≥ 40 years age	97.3% (93.9–100.0%) vs. 84.3% (76.5–92.1%)	**< 0.001 ‡**	**6.897 (2.326–20.447, p < 0.001)**	NS
< 50 vs. ≥ 50 years age	94.5% (90.8–98.2%) vs. 79.5% (65.8–93.2%)	**< 0.001 ‡**	**5.762 (2.523–13.162, p < 0.001)**	NS
Tumor Histology				
Leydig cell tumor	92.1% (87.4–96.8%)	**0.008 ‡**	1 (reference)	NS
Sertoli cell tumors				
Classic SCT	79.3% (60.7–97.9%)		**3.035 (1.073–8.588, p = 0.036)**	NS
Large cell calcifying	92.3% (77.8–100.0%)		NS	—
Sclerosing	100.0%		NS	—
Granulosa cell tumor	90.0% (71.4–100.0%)		NS	—
Mixed	100.0%		NS	—
Undifferentiated	71.1% (35.8–100.0%)		**6.762 (1.885–24.254, p = 0.003)**	NS
Pathologic risk factors				
≥ 3 mitoses per HPF	46.6% (26.0–67.2%)	**< 0.001 ‡**	**20.374 (8.338–49.781, p < 0.001)**	NS
Positive margins	42.9% (6.2–79.6%)	**< 0.001 ‡**	**15.555 (5.425–44.958, p < 0.001)**	NS
Rete testis invasion	Not Reached	**< 0.001 ‡**	**19.457 (5.924–63.907, p < 0.001)**	NS
LVI	21.1% (0–46.4%)	**< 0.001 ‡**	**23.541 (10.075–55.004, p < 0.001)**	**8.563 (1.788–41.013, p = 0.007)**
Cellular atypia	58.9% (36.6–81.2%)	**< 0.001 ‡**	**9.131 (3.945–21.134, p < 0.001)**	NS
Necrosis	49.2% (19.0–79.4%)	**< 0.001 ‡**	**17.234 (7.218–41.149, p < 0.001)**	NS
Largest tumor size > 5 cm	68.9% (41.1–89.7%)	**< 0.001 ‡**	**17.898 (7.262–44.107, p < 0.001)**	**10.951 (2.786–43.047, p = 0.001)**

Patients with *n* risk factors				
Zero risk factors	98.5% (96.5–100.0%)	—	—	—
1 risk factor	96.3% (89.2–100.0%)	—	—	—
2 risk factors	69.6% (44.7–94.5%)	—	—	—
3 risk factors	41.6% (8.3–81.5%)	—	—	—
4 risk factors	40.0% (0–98.2%)	—	—	—
5 risk factors	0.0%	—	—	—
6 risk factors	0.0%	—	—	—
Patients with *n* or more risk factors				
0 or 1 risk factors	98.3% (95% CI 96.3%–100.0%)	**< 0.001** ‡	—	—
2 or more risk factors	48.1% (95% CI 29.9–66.3%)		—	—