Rete Testis Invasion Is Consistent With Pathologic Stage T1 in Germ Cell Tumors

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Key Words: Testis; Seminoma; Nonseminomatous germ cell tumor; Rete; Pathologic stage; Epididymis

Am J Clin Pathol 2018;XX:1-7

DOI: 10.1093/AJCP/AQY168

ABSTRACT

Objectives: *Rete testis invasion by germ cell tumors is frequently concomitant with lymphovascular or spermatic cord invasion (LVI/SCI); independent implications for staging are uncertain.*

Methods: *In total, 171 seminomas and 178 nonseminomatous germ cell tumors (NSGCTs; 46 had 1%-60% seminoma component) came from five institutions. Metastatic status at presentation, as a proxy for severity, was available for all; relapse data were unavailable for 152. Rete direct invasion (ReteD) and rete pagetoid spread (ReteP) were assessed.*

Results: *ReteP and ReteD were more frequent in seminoma than NSGCT. In seminoma, tumor size bifurcated at 3 cm or more or less than 3 cm predicted metastatic status. Tumors with ReteP or ReteD did not differ in size from those without invasions but were less than with LVI/SCI; metastatic status or relapse did not show differences. In NSGCT, ReteP/ReteD did not correlate with size, metastatic status, or relapse.*

Conclusions: *Findings support retaining American Joint Committee for Cancer pathologic T1 stage designation for rete testis invasion and pT1a/pT1b substaging of seminoma.*

The testicular hilum is the predominant pathway for extratesticular extension of germ cell tumors,[1] and since 2011, the College of American Pathologists and International Society for Urologic Pathology (ISUP) have recommended routinely sampling it for histology.[2,3] Hilar fat invasion predicts advanced clinical stage at diagnosis, and 91% of cases in which hilar fat is invaded also have rete testis invasion, suggesting rete testis invasion as a precursor.[4] However, the independent effects of rete testis, hilar adipose tissue, epididymis, and tunica vaginalis invasion with regard to germ cell tumor staging are largely uncertain, because these four structures are often invaded in conjunction with each other and with lymphovascular invasion.

In 2015, ISUP held a consensus conference on reporting and staging of testicular specimens[5] and addressed whether the invasion of these four structures was most compatible with pathologic stage 1 or stage 2. A survey completed by participants in advance of the conference disclosed a relative lack of consensus about staging. The European Network of Uropathology surveyed its members, who were almost evenly split as to whether hilar adipose tissue invasion constituted pathologic stage T1, T2, or T3.[6]

Rete testis invasion may be pagetoid **Image 1** or direct **Image 2**; the former has been proposed to be infiltration of germ cell neoplasia in situ rather than invasive tumor. Many outcome studies did not distinguish

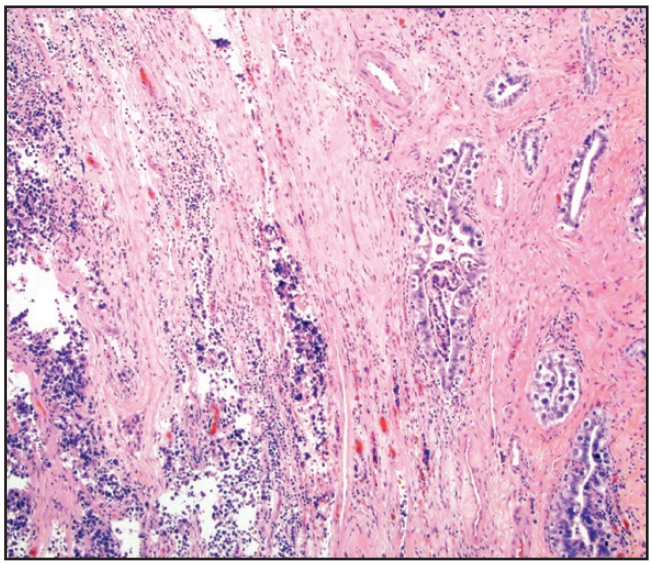

Image 1 Pagetoid spread of seminoma (left) into the rete testis (right) (H&E, ×200).

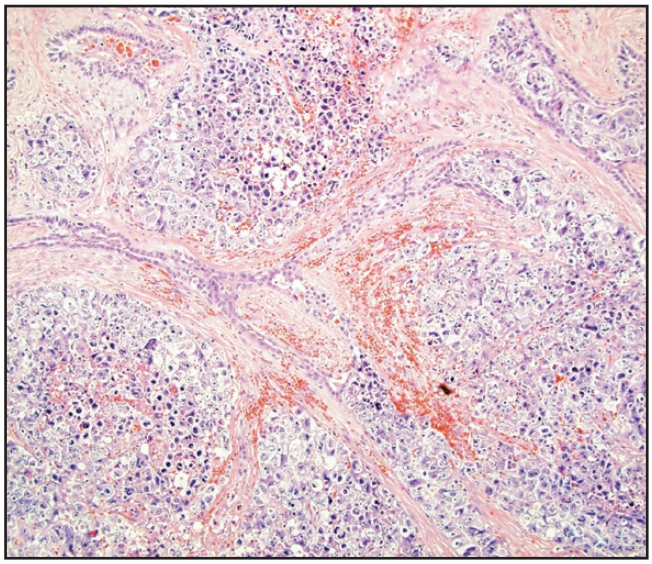

Image 2 Direct invasion of embryonal carcinoma into the rete testis (H&E, ×200).

between pagetoid spread and direct invasion.[7-13] However, particularly for seminoma, rete testis invasion seems to be a predictor of relapse[5,7,8] and metastasis.[9] Two cohort analyses of 425 and 744 patients with seminoma, respectively, supported this.[9,10] However, three other studies of 685 patients with seminoma,[11] 1,954 patients with seminoma,[12] and 136 patients with seminoma and nonseminomatous germ cell tumor (NSGCT)[13] suggested that rete testis invasion did not independently predict relapse when tumor size was taken into account. For NSGCT, data are scant and are confounded by studies that did not specify tumor types. Although the ISUP consensus was to keep rete testis invasion consistent with pathologic stage T1,[5] comparative data to support this decision were lacking. Thus, the following study is the first to address the staging question by directly comparing cases with invasion of rete testis (and other structures) alone against those with pathologic stages 2 to 3 according to established criteria, on one hand, and to cases without invasion of any histologic structure, on the other hand. It is also the first to make these determinations for both NSGCT and seminoma.

Materials and Methods

Patients and Data Collection

In total, 349 orchiectomy cases accessioned from 2000 to 2012 from five contributing medical centers were reviewed: Medical College of Wisconsin/Froedtert Hospital, Christie Hospital (Manchester, United Kingdom), Charles University Hospital (Plzeň, Czechia), University of Colorado, and the University of Miami Miller School of Medicine. These cases included 171 seminomas and 178 NSGCTs (of which 46 had a 1%-60% seminoma component). All glass slides for cases included in the study were reviewed by the contributing pathologists who are authors of this article. The following gross and microscopic parameters were recorded: tumor size, rete testis invasion (direct or pagetoid), epididymis invasion, hilar fat invasion, spermatic cord invasion, tunica vaginalis invasion, lymphovascular invasion (LVI), and spermatic cord invasion (SCI). Tumor histology was noted as seminoma or mixed germ cell tumor, including percentages of embryonal carcinoma, yolk sac tumor, teratoma, and choriocarcinoma. Pathologic staging was performed using the eighth edition of the American Joint Committee for Cancer (AJCC/TNM) staging system.

Because all follow-up was based on surveillance, and most patients were treated—especially those with higher stage tumors—a data set of recurrence alone is a flawed indicator of natural tumor history. Metastatic status at presentation (ie, clinical stages 2 and 3 before treatment) becomes a useful proxy for tumor natural history, especially for NSGCT.[4] Thus, the data collected from electronic medical records included whether the tumor was metastatic at diagnosis, postoperative relapse/metastasis of tumor, pre- and postoperative chemotherapy and/or radiotherapy, hormonal therapy, surgery, date and duration of last follow-up after diagnosis, and vital status of patient.

DOI: 10.1093/ajcp/aqy168

Statistical Analysis

All analysis was performed by statisticians (J.L. and A.S.) using SAS version 9.4 (SAS Institute). The Kruskal-Wallis test and Wilcoxon test were used to assess between-group differences in continuous measures such as size (<3 cm or ≥3 cm) and follow-up duration. A three-way comparison was made of no invasion vs invasion of a given structure vs LVI/SCI; for those that were significant, three two-way comparisons were made between the three groups. Associations between categorical measures (eg, metastatic at diagnosis) were assessed by exact χ^2 test or Fisher exact test.

Poisson regression was used to estimate the risk of recurrence per patient year of follow-up. Logistic regression analysis was performed to compare each type of structure invaded by tumor with a no-invasion group, on one hand, and an LVI/SCI group, on the other, as far as risk factors for metastatic status at diagnosis or recurrence. Tumor size, bifurcated at 3 cm or more vs less than 3 cm, was assessed by logistic regression analysis for metastatic status at diagnosis and by Poisson regression for risk of recurrence per patient year of follow-up. The log-rank procedure was used to compare vital status according to invasion findings. Statistical significance for all results was set at $P < .05$.

Results

Clinicopathologic Characteristics of Study Patients

Metastatic status at diagnosis was twice as frequent in NSGCT as seminoma, at 28% vs 14%, respectively Table 1. LVI and SCI were more than twice as frequent in NSGCT (50%) as seminoma (21%). However, invasion of structures other than LVI and SCI was more common in seminoma than NSGCT, occurring in 35% and 10% of cases, respectively. This difference was driven by rete direct and pagetoid spread being more frequent in seminoma, the latter significantly so, whereas hilar, epididymis, and tunica vaginalis invasion did not differ in frequency. Further analyses thus focused mostly on the rete testis.

Rete Testis Invasion in Pure Seminoma

Seventy-six (44%) cases had no invasion of any type Table 2. For 28 cases with rete pagetoid spread, median tumor size was 3.5 cm, intermediate between the 2.5 cm for cases with no invasion and 4.75 cm for those with LVI or SCI. Two-way comparisons for tumor size showed that the cases with pagetoid spread differed from the LVI or SCI group ($P = .047$) but not from the no-invasion group ($P = .09$). For 15 cases with rete direct invasion, median tumor size was 3.0 cm, significantly less than the LVI or SCI group ($P = .001$) but similar to the no-invasion group ($P = .49$).

Metastatic status at diagnosis did not differ according to structures invaded for either pagetoid spread or direct invasion of the rete. Recurrence (data missing in 83 cases) did not differ by three-way comparison between pagetoid spread and other invasion status groups ($P = .16$). Recurrence did not differ according to direct invasion ($P = 1.0$). A difference in vital status between the three groups was not detected ($P = .53$).

Table 1
Comparative Findings in Seminoma and Nonseminomatous Germ Cell Tumor (NSGCT)[a]

Characteristic	Seminoma	NSGCT	*P* Value (95% CI)
No. of patients	171	178	
Mean follow-up (range), y[b]	3.83 (0.08-17)	4.84 (0.08-21)	<.001[c]
Metastatic at diagnosis	13 (14)	37 (28)	.013[d]
Staging group			
1. No structure invaded	76 (44)	71 (40)	<.001[d]
2. Invasion of rete, hilar fat, epididymis, or tunica vaginalis without lymphovascular or cord invasion	59 (35)	18 (10)	<.001[d]
3. Lymphovascular or cord invasion	36 (21)	89 (50)	<.001[d]
Rete pagetoid spread	37 (22)	15 (8)	<.001[d]
Invasion			
Rete direct	24 (14)	14 (8)	.064[d]
Hilar	13 (8)	8 (5)	.22[d]
Epididymis	8 (5)	12 (7)	.41[d]
Tunica vaginalis	4 (2)	6 (3)	.75[d]
Lymphovascular	34 (20)	83 (47)	<.001[d]
Spermatic cord	4 (2)	12 (7)	.049[d]

[a]Values are presented as number (%) unless otherwise indicated.
[b]Thirty-six patients with seminoma and 16 patients with NSGCT had no follow-up.
[c]Wilcoxon rank-sum test.
[d]χ^2 test.

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Rete Testis Invasion in NSGCT

Of the 178 NSGCTs, 71 (40%) cases had no invasion of any type Table 3. For four cases with pagetoid spread, two-way tumor size comparisons with no invasion and with the LVI or SCI group were not significant. Median tumor size for 15 cases with rete direct invasion only was similar to the no-invasion group (P = .20) but different from the LVI or SCI group (P = .041).

Cases with pagetoid spread did not differ from the no-invasion group or the LVI or SCI group with regard to metastatic status at presentation or recurrence (recurrence data missing in 69 cases). Likewise, no differences in

Table 2
Rete Testis Invasion in Pure Seminoma

Characteristic	Tumor Size, Median, cm	Metastatic at Diagnosis, No. (%)[a]	Recurrence, No. (%)[b]
Pagetoid spread (n = 140)[c]			
No invasion, n = 76	2.5	2 (7)	2 (7)
Rete pagetoid spread only, n = 28	3.5	2 (7)	1 (4)
LVI or SCI, n = 36	4.75	5 (26)	4 (33)
P (three-way comparison)	.001[d]	.073	.16
P for no invasion vs rete pagetoid	.09[e]		
P for rete pagetoid vs LVI or SCI	.047[e]		
P for no invasion vs LVI or SCI	.0002[e]		
Direct invasion (n = 127)[f]			
No invasion, n = 76	2.5	2 (7)	2 (7)
Rete direct spread only, n = 15	3.0	0 (0)	1 (7)
LVI or SCI, n = 36	4.75	5 (26)	4 (33)
P (three-way comparison)	<.001[d]	.08	.21
P for no invasion vs rete direct	.49[e]		
P for rete direct vs LVI or SCI	.001[e]		
P for no invasion vs LVI or SCI	.0002[e]		

LVI, lymphovascular invasion; SCI, spermatic cord invasion.
[a]Fisher exact test (whole column).
[b]Poisson regression per patient year.
[c]Numbers exclude missing data from 46, 0, and 17 cases in the three compared groups.
[d]Kruskal-Wallis test.
[e]Wilcoxon rank-sum test.
[f]Numbers exclude missing data from 46, 10, and 17 cases in the three compared groups for metastatic and 49, 10, and 24 for recurrence.

Table 3
Rete Testis Invasion in Nonseminomatous Tumor

Characteristic	Tumor Size, Median, cm	Metastatic at Diagnosis, No. (%)[a]	Recurrence, No. (%)[b]
Pagetoid spread (n = 164)[c]			
No invasion, n = 71	2.8	6 (12)	10 (24)
Rete pagetoid spread only, n = 4	4.3	1 (25)	0 (0)
LVI or cord, n = 89	3.5	27 (39)	14 (28)
P (three-way comparison)[d]	.087[d]	.006	.772
P for no invasion vs rete pagetoid[e]	.13[e]	.43, .63 after size[f]	
P for rete pagetoid vs LVI or SCI[e]	.26[e]	1.0, .61[f]	
P for no invasion vs LVI or SCI[e]	.02[e]	.0009, .02[f]	
Direct invasion (n = 166)[g]			
No invasion, n = 71	2.8	6 (12)	10 (24)
Rete direct invasion only, n = 15	2.0	1 (7)	1 (7)
LVI or SCI, n = 89	3.5	27 (39)	14 (28)
P (three-way comparison)[d]	.05[d]	.007	.769
P for no invasion vs rete direct[e]	.20[e]	.43, .20 after size[f]	
P for rete direct vs LVI or SCI[e]	.04[e]	.56, .60[f]	
P for no invasion vs LVI or SCI[e]	.02[e]	.0006, .02[f]	

LVI, lymphovascular invasion; SCI, spermatic cord invasion.
[a]Fisher exact test (whole column).
[b]Poisson regression per patient year.
[c]Numbers exclude missing data from 20, 0, and 20 cases in the three compared groups for metastatic and 29, 0, and 38 for recurrence.
[d]Kruskal-Wallis test.
[e]Wilcoxon rank-sum test.
[f]Second P value is after adjusting for size less than 3 cm or 3 cm or more.
[g]Numbers exclude missing data from 20, 2, and 20 cases for metastatic and 29, 2, and 38 for recurrence.

DOI: 10.1093/ajcp/aqy168

these comparisons were observed for cases with rete direct invasion only. The only significant difference was between the no-invasion and the LVI/SCI group (P = .0009), and this significance held after multifactorial analysis, including size 3 cm or more or less than 3 cm (P = .02). A difference in vital status between the three groups was not detected (P = .25).

Epididymis and Other Invasion

One case of seminoma had epididymis invasion but in conjunction with rete testis invasion Table 4. Four cases of NSGCT had epididymis invasion only. One (33%) case was metastatic at diagnosis, and one (33%) case had recurrence. Three-way comparison between the groups—no invasion, epididymis invasion only, and LVI or SCI—was significant for being metastatic at diagnosis (P = .002) but not for recurrence (P = .92). Hilar fat invasion was observed in 13 seminomas and eight NSGCTs; tunica vaginalis invasion was observed in four seminomas and six NSGCTs. No NSGCT had hilar fat or tunica vaginalis invasion without LVI or SCI. Only one seminoma had hilar fat invasion, and one had tunica vaginalis invasion, without LVI or SCI.

Tumor Size

Because of the relationship between rete testis involvement and tumor size, particularly for seminoma, analysis was performed for the ability of tumor size to predict metastatic status at diagnosis or recurrence. For seminoma, size (≥3 cm vs <3 cm) significantly predicted metastasis at diagnosis (P = .03) Table 5. However, recurrence was not significantly different (P = .09) based on this size cutoff. When cases with LVI or SCI were excluded, however, the correlation of size with metastatic status at diagnosis lost its significance (P = .08).

Among NSGCTs, overall, the 3-cm size cutoff did not show a significant difference for metastasis (P = .13) or recurrence (P = 1.0).

Discussion

This study demonstrates no evidence that rete testis involvement, particularly the more important direct invasion, should justify a pathologic T2 stage for either seminoma or NSGCT. Rete pagetoid and direct involvement alone differed from stage T2 or higher—lymphovascular and spermatic cord invasion—with respect to seminoma recurrence. Neither type of involvement predicted metastatic status at presentation or recurrence for NSGCT. Hilar fat, epididymis, and tunica vaginalis invasion were also studied, but the number of cases with follow-up from these categories was insufficient for meaningful conclusions. Our finding of seminoma size (≥3 cm or <3 cm) correlating with metastatic status at presentation supports the current subdivision of pathologic T1a and T1b stages for seminoma, in line with prior findings.[10,11] However, significance faded when cases with LVI or SCI were excluded. Notably for NSGCT, size lacked any

Table 4
Epididymis Invasion in Nonseminomatous Tumor (n = 164)[a]

Characteristic	Metastatic at Diagnosis, No. (%)	Recurrence, No. (%)	Vital Status: Died, No. (%)
No invasion, n = 71	6 (12)	10 (24)	3 (5)
Epididymis invasion only, n = 4	1 (33)	1 (33)	1 (25)
LVI or SCI, n = 89	27 (39)	14 (28)	4 (5)
P (three-way comparison)	.007[b]	.939[c]	.417[b]

LVI, lymphovascular invasion; SCI, spermatic cord invasion.
[a]Numbers exclude missing data from 20, 1, and 20 in the three compared groups for metastatic and 29, 1, and 38 for recurrence.
[b]Log-rank test.
[c]Poisson regression per patient year.

Table 5
Tumor Size (≥3 cm vs <3 cm) Prediction of Metastatic Status at Diagnosis or Recurrence

	Seminoma Overall		Seminoma Excluding LVI and SCI		Nonseminomatous Tumor Overall, *P* Value	Nonseminomatous Tumor Excluding LVI and SCI, *P* Value
Characteristic	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)		
Metastatic at diagnosis[a]	.0282	6.6 (1.2-∞)	.0839	4.6 (0.8-∞)	.1325	.4316
Recurrence[b]	.0887	4.1 (0.8-∞)	.2233		1.0000	.8520

CI, confidence interval; LVI, lymphovascular invasion; OR, odds ratio; SCI, spermatic cord invasion.
[a]By logistic regression analysis.
[b]By Poisson regression per patient year of follow-up.

DOI: 10.1093/ajcp/aqy168

significant relationship, as noted before,[14] probably since NSGCT outcome is very dependent on the percentage of embryonal carcinoma.

Our findings support, in retrospect, the current approach of the ISUP[5] and AJCC[15] to classify rete testis involvement as pathologic stage pT1 for seminoma and NSGCT. In seminoma, lymphovascular invasion has long been recognized to have prognostic significance.[5] Rete testis invasion has been shown to have prognostic significance for stage 1 seminoma since 1997[5]; it correlates with metastasis at presentation for all seminomas,[8] and it is considered a predictor of relapse.[7] A meta-analysis revealed that rete testis invasion conferred a 1.7 times risk of recurrence.[8]

In 120 NSGCTs, Rodriguez et al[14] found that invasion of rete testis, epididymis, or spermatic cord was associated with metastasis, but 45% of the study group had missing data, making this result less compelling. Another study, despite not dividing type of invasion into direct or pagetoid or separating seminoma from NSGCT, found that rete testis invasion did not independently predict outcome, although it did correlate with serum markers.[13] Yilmaz et al[4] in 2013 performed a correlative study of vascular, rete testis (direct), hilar fat, spermatic cord, and epididymis invasion with NSGCT stage at presentation. One-third of their cases (n = 54) had metastasis—clinical stages 2 and 3— while 94 were clinical stage 1. By multivariate analysis, only the invasion of vessels, rete testis directly, or hilar fat significantly correlated with stage at presentation (*P* values of .011, .007, and .017, respectively). Pagetoid spread into the rete, at 17%, was less frequent than direct invasion at 52%, and direct invasion depended on stage, being present in 40% of stage 1 cases and 74% of stage 2 to 3 cases. We found a higher rate of pagetoid spread than direct invasion in seminoma, 22% vs 14%, and our frequencies in NSGCT are lower than with Yilmaz et al[4] because they represent only cases without other invasions.

ISUP consensus and the eighth edition of AJCC staging make no recommendation that rete testis invasion alone should raise the pathologic stage above pT1.[14] This decision may have been partly due to the frequent coexistence of rete testis invasion with lymphovascular invasion, making it difficult to assess the importance of rete testis invasion as an isolated finding, and studies designed to address this issue were lacking. When Yilmaz et al[4] divided rete invasion into direct stromal invasion and the less common pagetoid spread of neoplastic germ cells into the rete epithelium, only direct invasion was significantly correlated with presentation stage (*P* = .001, univariate analysis), but this was not compared with LVI/SCI to assess its relative impact on staging. The newness of this finding may explain why the distinction between pagetoid and direct involvement was made by just 63% of surveyed European Network of Uropathology (ENUP) members, whereas 96% of experts made this distinction.[6] The ISUP, a few years later, recommended not only grossly sampling the rete, epididymis, and hilar soft tissue but also distinguishing pagetoid invasion of the rete from direct stromal invasion.[16] Pooled analysis of four surveillance studies of pure seminoma showed that specific direct rete testis invasion independently predicted recurrence at 5 years by multivariate analysis by a factor of 1.7 (95% confidence interval, 1.1-2.6).[17] Our study was the first to compare rete testis invasion with LVI/SCI, but for seminoma only one of 15 cases with direct rete invasion had recurrence, a result in line with retaining pathologic stage T1 for isolated rete testis invasion, as done in current ISUP and AJCC practice.

Our study, unlike some predecessor studies, included separate analyses of both seminoma and NSGCT; moreover, it incorporated long-term relapse (occurring in 28% and 17% of surveillance patients with NSGCT and seminoma, respectively[8]), and because most patients receive therapy, we included stage at presentation as a proxy for outcome. The lack of response to chemotherapy in NSGCT is a negative prognostic factor[18]; however, the small number of deaths precluded rete testis invasion as a predictor of vital status.

As for hilar soft tissue invasion and epididymis invasion, Yilmaz et al[4] found that hilar fat was invaded in 28% of NSGCTs and epididymis was invaded in 8%. Epididymis invasion did not significantly correlate with metastasis at presentation in their study (and likewise in our study, the small number of cases without lymphovascular invasion precluded statistical significance), but it is designated stage pT2 by the ISUP and in the eighth edition of AJCC staging.[14] The ENUP members also could not agree on whether invasion of tunica vaginalis without lymphovascular invasion was stage pT1.[6] Sixty-seven percent of members interpreted it as stage pT1 and 33% as stage pT2. The AJCC staging accepts it as stage pT2.

Limitations of this study include missing follow-up in a certain percentage of cases, thus reducing the impact of relapse assessment. Epididymis, hilar fat, and tunica vaginalis invasion, isolated from LVI/SCI, were too infrequent to assess their independent value. We performed several hypothesis tests; thus, for certain questions that were addressed, false-positive findings may have occurred. Finally, we did not analyze NSGCT outcome according to the percentage of embryonal carcinoma vs other tumor types or by treatment choice.

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DOI: 10.1093/ajcp/aqy168

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DOI: 10.1093/ajcp/aqy168