Clinical implications of the American Joint Committee on Cancer (AJCC) 8th edition update in seminoma pT1 subclassification

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Abstract

Background Seminoma accounts for 30-50% of Testicular Germ-Cell Tumors (TGCT) - the most common solid malignancy in men aged 15-35 years. The American Joint Committee on Cancer (AJCC) 8th edition (2018) created the subclassifications pT1a (tumor size < 3 cm) and pT1b (≥ 3 cm), despite not universally recognized. The authors propose to further understand its potential impact in clinical practice, by reviewing current evidence and reviewing clinical cases at their institutions.

Methods: All consecutive cases of seminoma stage I pT1 treated at two institutions between January 2005 and December 2016 were included. Clinical data were retrieved, and variables were analyzed using SPSS. Review of relevant literature on the topic.

Results: Seminoma pT1 was identified in 58 patients. By using newly AJCC criteria, 29 (50.0%) would have been staged as pT1a and 29 (50.0%) pT1b. Median follow- up time 5.8 years. Three recurrences were recorded (2 in pT1a and 1 in pT1b, all under surveillance protocol); no deaths occurred. *Rete testis* invasion (RTI) and extensive necrosis (EN) were associated with pT1b (P<0.0001 and P=0.023, respectively), therefore pT1b was associated with RTI and EN, known adverse biological features, but the clinical impact could not to be assessed with the present methodology.

Discussion: In our population, the retrospective analysis of the newly created AJCC criteria showed no significant difference in recurrence or death, although pT1b was associated to adverse biological markers. Our results also confirm an excellent prognosis, regardless of subcategorization, thus a larger population and a longer follow-up time are needed to understand the impact of the recently updated criteria. We would recommend using the latest AJCC staging system, although the individual risk of relapse, long-term toxicities and patient preferences should be taken into account when considering surveillance or active treatment options.

Background

Testicular germ-cell tumors (TGCT) are the most common solid malignancy in men aged 15-35 years old[1] and are classically divided in seminoma or non- seminoma. Seminoma histology accounts for 30-50% of the cases. TGCT are staged using the TNM system, whose criteria are used worldwide, according to mostly overlapping *American Joint Committee on Cancer* (AJCC) and *Union for International Cancer Control* (UICC) manuals[2, 3]. Seminoma category pT1 is a tumor pathologically limited to the testis with no lymphovascular invasion (LVI)[2, 3]. Since the latest updated edition (8^{th}, 2017/18)[2], there has been divergence regarding seminoma's pT1 category: AJCC created the subclassification of T1a (tumor < 3 cm) and T1b (tumor ≥ 3 cm)—Figure 1 a) and b), respectively, while UICC remained unchanged from the 7^{th} edition[3] (i.e. no subclassification). Of note, the subclassification does not change the stage grouping[2].

TGCT have remarkably high cure rates, even at recurrence. Therefore, much focus has been placed in adjuvant treatment options, specifically considering long-term toxicities management and

consequentially patient selection is crucial. The adjuvant stage-specific treatment options in stage I seminoma include surveillance, chemotherapy (CT) and radiotherapy (RT). In the clinical practice a risk-adapted approach can be considered using historically adverse prognostic factors for stage I seminoma[4]: tumor size > 4 cm and *rete testis* invasion (RTI)—Figure 2 a) and b), respectively. These factors, albeit retrospectively identified, have been considered recurrence predictors[5]. So far, they have not been validated prospectively, except that in the absence of both of them, it constituted an indication of low recurrence rate (6%)[6] and therefore the evidence for its routine use in clinical practice is limited (in patients undergoing surveillance)[7]. Additionally, other factors should be considered for treatment decision, such as, patient preference or compliance with recommended follow-up protocols. An emphasis on tumor size has been of importance for a considerable time, since, for example, TGCT are not graded (thus no clinical impact from its evaluation) and tumor markers will not be elevated in most cases (alpha-fetoprotein is never elevated in pure seminoma and human chorionic gonadotrophin may be elevated in up to 30% of cases)[4].

Objectives

We propose to retrospectively evaluate the impact of the AJCC 8th recent subclassification in stage I seminoma. Therefore, we aimed to understand its potential use for prognosis and clinical decision, namely adjuvant treatment decision and follow-up protocol, by applying the current criteria in our population and making considerations on how these changes could impact the clinical practice.

Methods

All consecutive cases of TGCT treated at two institutions (oncological center and a general hospital, located in Porto and Lisbon, respectively) were included, between January 2005 and December 2016, limited to seminoma Stage I. Clinical data were retrieved and re-reviewed according to most recent staging systems.

Pathology was also all re-reviewed by TGCT-dedicated Pathologists and updated according to the most recent 2016 World Health Organization (WHO) classification. The pathological criteria have been applied according with previously published[8], in summary, size was given to the dominant tumor nodule in case of multifocality, as recommended in staging systems. Extensive necrosis was defined as “easily spotted on low power magnification, including geographic necrosis and contiguous areas of necrosis, including infarct-type necrosis”, as opposed to focal necrosis (“only spotted at high power magnification, often of isolated cells/cell nests”). *Rete testis* invasion was documented when true stromal invasion was depicted, as indicated in ISUP recommendations[9]. Pagetoid extension was reported separately, but not counted as true *rete testis* invasion, as recommended.

The variables were analyzed using SPSS v.25. Potential statistical associations between categorical variables were evaluated using Chi-square test, using the two-sided Fisher’s significance level $p<0.05$. Distribution of continuous variables among groups was assessed by the non-parametric Mann-Whitney U test.

The study was approved by the local Ethics board.

Results

The population variables are characterized in Table 1. A total of 58 patients undergoing orchiectomy and diagnosed with pT1 seminoma were included, of which 29 patients would have been classified as pT1a (50.0%) vs 29 patients that would have been pT1b (50.0%), for the specified time frame (~11 years). The median follow-up time was 69 months, or approximately 5.8 years.

The median age at diagnosis was similar between groups (33 years in pT1a vs 32 years in pT1b, P=0.641).

Table 1

Studied clinical and pathological variables in seminoma Stage I cases. Additionally, cases are presented as aggregate and per center (Center 1 = Portuguese Institute of Oncology of Porto; Center 2 = Centro Hospitalar de Lisboa Ocidental).

	pT1 (N=58)		
	pT1a (center 1) (center 2)	pT1b (center 1) (center 2)	*P value*
N (%)	29 (50%) (21)(8)	29 (50%) (19)(10)	-
Median Age at Diagnosis, years (min – max)	33 (17-52) (33)(33)	32 (21-66) (31)(36)	0.641
Median tumor size (cm) Min – max size (cm) Tumor > 4 cm	1.7 (1.7)(1.8) 0.7 – 2.8 -	4.5 (4.3)(4.95) 3.0 – 12.0 16 (55.2%) (9)(7)	-
Rete testis invasion (RTI)	2 (6.9%) (2)(0)	12 (41.4%) (9)(3/4*)	< 0.0001
Median Mitosis/10 HPF	10 (10)(*)	18 (18)(*)	0.098
Extensive Necrosis (EN)	12 (41.4%) (9)(3/5*)	22 (75.9%) (17)(5/9*)	0.023
Anaplastic features	12 (41.4%) (10)(2/5*)	14 (48.3%) (12)(2/9*)	0.793
Adjuvant Treatment Surveillance Active treatment • *CT* • *RT*	 11 (44.0%) 14 (56.0%) *2 (8.0%)* *12 (48.0%)*	 6 (27.3%) 16 (72.7%) *3 (13.6%)* *13 (59.1%)*	-
Testicular contra-lateral metachronous tumor	1 (5.3%)	0	-
Distant Recurrence	2 (0)(2)	1 (0)(1)	-
Cancer-specific death	0	0	-

Abbreviations: CT: Chemotherapy; EN: Extensive Necrosis; RT: Radiotherapy; RTI: *Rete testis* invasion; HPF: High-Power Field. Note: sizes are presented in cm as is AJCC. *data missing.

In pT1a patients the median tumor size was 1.7 cm (0.7 - 2.8 cm) vs 4.5 cm (3.0-12.0 cm) in pT1b patients. In the latter subcategory, 16 cases (55.2%) were > 4 cm (classically a 'higher risk' feature in seminoma). Therefore 13 patients (44.8%) had their risk status 'upscaled', i.e. have a tumor size inferior to 4 cm, a classical 'lower risk' feature, but are now considered in the 'higher risk' pT1b category.

Four pathological features were evaluated: *rete testis* invasion, median number of mitosis/10 high power fields (HPF), evidence of extensive necrosis (EN) and anaplastic features (Table 1). RTI and EN were significantly associated with pT1b tumors (P<0.0001 and P=0.023, respectively).

In pT1a patients, active treatment was delivered in 14 patients (48.3%) vs 16 patients (55.1%) in pT1b, being RT the predominant option in both subcategories. The adjuvant chemotherapy used was 1 cycle of Carboplatin AUC 7; no data regarding RT dose or duration.

In one pT1a patient, a contra-lateral metachronous tumor was detected during follow-up (orchiectomy followed by surveillance protocol).

During follow-up, 3 cases of distant recurrence (retroperitoneal) were identified: 2 cases in pT1a (6.9%), neither with RTI, and 1 case in pT1b (3.4%), with both RTI and tumor size > 4 cm. All patients underwent BEP (cisplatin, etoposide and bleomycin) chemotherapy regimen, and currently have no evidence of disease.

The 5-year overall survival was 100% for both groups. No deaths were recorded during the follow-up period.

Discussion

Impact for prognosis and clinical decision

A focus on seminoma stage I is relevant since it is the most common single stage or histology of TGCT—it may account for up to 80% of seminomas and 40% of all testicular cancers[10]. Thus, having two staging criteria may have implications in clinical practice or clinical trial design: should we embrace the changes (AJCC) or ignore them (UICC)? Should adjuvant treatment be decided according to staging subcategory (i.e. higher risk could mean more aggressive treatment)? Should follow-up protocols take the new subcategories into consideration and have more intensive schedules in higher risk patients, even though, ultimately, survival would be similar? These clinically meaningful questions remain unanswered, creating additional anxiety on patients, their family and the physicians.

A fundamental notion is that the overall prognosis in stage I seminoma is exceptionally good[4]—confirmed in our retrospective analysis, with few recurrences recorded and a 5-year overall survival rate of

100%, regardless of subcategorization, with a median follow-up time ~6 years. The occurrence of few events may be a limitation (i.e. low rate recurrence or death), indicating high curability rate even after recurrence. This remarkable prognosis, plus low incidence, characteristically lead to accrual failure in TGCT clinical trials[11]. Retrospective data has emerged suggesting the 3 cm cut-off was significantly associated with metastatic status at presentation, but only if LVI or spermatic cord invasion (SCI) were present[12], which are known independent high-risk features. This conclusion is not applicable to pT1 stage, since LVI is, per definition, at least pT2, and SCI is pT3[2, 3]. The three recurrences identified (3 out of 17 surveillance patients, 17.6%), are within the overall estimation of 15-20% risk of recurrence for stage I seminoma without adjuvant treatment[13].

Another clinical concern is adjuvant treatment selection. Already in daily routine, again, is the presence of RTI and tumor size > 4 cm that can be taken into account in order to establish an individual recurrence risk and help choose treatment over surveillance[4]. Interestingly, size ≥ 3 cm, the current AJCC pT1b subcategory, in the univariate analysis, was significantly associated with RTI (P<0.0001) and EN (P=0.023). This may indicate that increasing size is related to adverse pathological features, a coherent finding, and yet its clinical relevance is unknown at this time and should be a focus of future research. Additionally, two recurrences were identified in the pT1a group (vs 1 in pT1b), with neither case showing RTI, which underscores the need to have better biomarkers to predict recurrence (in seemingly classical low risk patients).

Some considerations are justified regarding patients with a tumor size ≥ 3 cm but ≤ 4 cm, which were almost half of the pT1b group (44.8%, Table 1). Following the 8th edition AJCC criteria, they would be considered at higher risk of recurrence (vs pT1a) and yet below the classically considered higher risk size of 4 cm. Observing the combinations of no RTI/RTI and tumor size ≤ 4 cm and > 4 cm (Table 2) one can realize that even within the pT1b category, different risk groups can be identified. This is in accordance with a nomogram that suggested risks of recurrence depending on how many risk factors were present: none, 12%, presence of either one, 16% and in the presence of both, a 32% risk of recurrence[14]. RTI is explicitly considered by AJCC as a pathological feature that does not change staging (based on large contemporary cohorts data)[2]. Thus, the clinical significance of RTI remains controversial[7]. Combining our experience, in particular and as mentioned before, the observed significant association between RTI and increased tumor size (P<0.0001, Table 1), with large retrospective data whose importance is recognized in international guidelines[4, 13], RTI may still have a role in clinical practice. Actually, RTI could be, in the future, included for staging purposes as an adverse feature within the pT1b subclassification, such as a suffix pT1b(0) for no RTI (lower risk) vs pT1b(1) for RTI (higher risk)—like the precedent in melanoma M1 disease staging with (0) indicating normal lactate dehydrogenase (LDH) and (1) indicating elevated LDH[2]. This change could enable the evaluation of its significance prospectively, essentially like the decision to create pT1a vs pT1b subclassifications based on a size cut-off.

Table 2

Distribution within the pT1b group (tumor size ≥ 3 cm) of classically defined high risk features in stage I seminoma (RTI and tumor size > 4 cm – Figure 2 a) and b), respectively), that are not formally part of the

staging criteria, but are frequently used to guide clinical decision regarding surveillance vs adjuvant treatment.

pT1b (tumor size ≥ 3 cm)			
Variables	Tumor size ≤ 4 cm	Tumor size > 4 cm	Total
No RTI	**4 (18.2%)** (lower risk category)	6 (27.3%)	10
RTI	7 (31.8%)	**5 (22.7%)**† (higher risk category)	12
Total	11	11	22*

Abbreviations: RTI: *Rete testis* invasion. † the patient that recurred in the pT1b group had RTI plus tumor size > 4 cm, thus within the higher risk category. * Data missing in 7 patients.

Analysis of potential bias

This is an exploratory retrospective analysis of current criteria applied to a population that was treated regardless of them, therefore the interpretation of results is considerably limited, although it may offer glimpses into future directions, namely clinical or basic research aims of focus and unmet needs.

The follow-up time may be insufficient to detect enough events (recurrence or death) in a small population, which is a limitation in stage I seminoma studies, as previously detailed[15]. Nevertheless, the study that suggested the 3 cm cut-off (and now the basis for seminomas' pT1a vs pT1b cut-off in AJCC's) used the 3-year recurrence risk endpoint[16], thus considering that our population has over 5 years of follow-up we believed it would be appropriate to proceed with the analysis. We focused on stage I seminoma in order to obtain a more homogenous population, risking a smaller sample.

Our population was treated from 2005 onwards, and at that time one of the popular adjuvant treatment options was RT, that could explain the relevant percentage of treated patients with this technique (43.1% of the population, vs 8.6% chemotherapy and 29.3% surveillance), and might also help to explain the few recurrences, although, retrospectively, some patients may have been over- treated according to current trends of thinking[17]. The patients that recurred (2 in pT1a group and 1 in pT1b group, all undergoing surveillance protocol) were effectively treated, and their current status is no evidence of disease.

Additionally, some pathological data were missing due to suboptimal evaluation conditions of the material under analysis. Despite much focus is rightly placed on late toxicities, we were not able to gather meaningful clinical data regarding these issues.

Conclusion

Incorporating 'classical' risk factors for recurrence with the new pT1 subgrouping by newly created AJCC criteria may create new challenges in clinical practice. In our population, a two-center retrospective analysis, showed no difference in recurrence or death, although pT1b was significantly associated with adverse pathological findings, such as RTI and EN. This was an exercise to understand our population regarding recent changes to staging, that are not common to all systems in use. Our main goals were to

review this pressing topic, share and discuss our daily practice concerns and propose ways of addressing this issue. A larger population and a longer prospective follow-up time are needed to understand the impact of the updated criteria, namely when considering clinical trial design, disease prognosis, adjuvant treatment options and tailored follow-up protocols for the individual patient. Until then, we would recommend using the AJCC staging system, although the individual risk of relapse, long-term toxicities and patient preferences should be taken into account when considering surveillance or active treatment options.

Abbreviations

AJCC: American Joint Committee on Cancer

CT: chemotherapy

EN: extensive necrosis

HPF: high power fields

LDH: lactate dehydrogenase

LVI: lymphovascular invasion

RT: radiotherapy

RTI: *rete testis* invasion

SCI: spermatic cord invasion

SPSS: Statistical Package for the Social Sciences

TGCT: testicular germ-cell tumors

UICC: Union for International Cancer Control

WHO: World Health Organization

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee (CES-IPO-12-018) of the Portuguese Oncology Institute of Porto, Portugal.

Consent for publication

Not applicable,

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable written request.

Competing interests

All authors report no conflict of interest

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Authors' contributions

MFS: Protocol/project concept and development, Data collection or management, Data analysis, Manuscript writing/editing

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All authors read and approved the final manuscript

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016: Cancer Statistics, 2016. CA: A Cancer Journal for Clinicians. 2016;66:7–30.
2. Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th Edition. New York: Springer International Publishing; 2017.
3. Brierlwy JD, Gospodarowicz M, Wittekind C (editors). UICC TNM Classification of Malignant Tumours. 8th edition. New York: Wiley Blackwell; 2016.
4. Albers P. (Chair). EAU Guidelines on Testicular Cancer. 2017. https://uroweb.org/wp-content/uploads/11-Testicular-Cancer_2017_web.pdf. Accessed 3 Sep 2018.
5. Shelley MD, Burgon K, Mason MD. Treatment of testicular germ-cell cancer: a cochrane evidence-based systematic review. Cancer Treat Rev. 2002;28:237–53.
6. Aparicio J, Germà JR, del Muro XG, Maroto P, Arranz JA, Sáenz A, et al. Risk-Adapted Management for Patients With Clinical Stage I Seminoma: The Second Spanish Germ Cell Cancer Cooperative Group Study. Journal of Clinical Oncology. 2005;23:8717–23.
7. Boormans JL, Mayor de Castro J, Marconi L, Yuan Y, Laguna Pes MP, Bokemeyer C, et al. Testicular Tumour Size and Rete Testis Invasion as Prognostic Factors for the Risk of Relapse of Clinical Stage I Seminoma Testis Patients Under Surveillance: a Systematic Review by the Testicular Cancer Guidelines Panel. European Urology. 2018;73:394–405.
8. Lobo J, Costa AL, Vilela-Salgueiro B, Rodrigues Â, Guimarães R, Cantante M, et al. Testicular germ cell tumors: revisiting a series in light of the new WHO classification and AJCC staging systems, focusing on challenges for pathologists. Human Pathology. 2018;82:113–24.
9. Verrill C, Yilmaz A, Srigley JR, Amin MB, Compérat E, Egevad L, et al. Reporting and Staging of Testicular Germ Cell Tumors: The International Society of Urological Pathology (ISUP) Testicular Cancer Consultation Conference Recommendations. The American Journal of Surgical Pathology. 2017;41:e22–32.
10. Cooper DE, L'Esperance JO, Christman MS, Auge BK. Testis Cancer: A 20-Year Epidemiological Review of the Experience at a Regional Military Medical Facility. The Journal of Urology. 2008;180:577–82.
11. Williams MV, Mazhar D. Poor trial accrual hinders germ cell tumor therapy advances. Nat Rev Urol. 2012;9:243–5.
12. Farooq A, Jorda M, Whittington E, Kryvenko ON, Braunhut BL, Pavan N, et al. Rete Testis Invasion Is Consistent With Pathologic Stage T1 in Germ Cell Tumors. American Journal of Clinical Pathology. 2019;151:479–85.
13. Honecker F, Aparicio J, Berney D, Beyer J, Bokemeyer C, Cathomas R, et al. ESMO Consensus Conference on testicular germ cell cancer: diagnosis, treatment and follow-up. Annals of Oncology. 2018;29:1658–86.
14. Warde P, Specht L, Horwich A, Oliver T, Panzarella T, Gospodarowicz M, et al. Prognostic Factors for Relapse in Stage I Seminoma Managed by Surveillance: A Pooled Analysis. Journal of Clinical

Oncology. 2002;20:4448–52.
15. Delahunt B, Egevad L, Samaratunga H, Varma M, Verrill C, Cheville J, et al. UICC drops the ball in the 8th edition TNM staging of urological cancers. Histopathology. 2017;71:5–11.
16. Chung P, Daugaard G, Tyldesley S, Atenafu EG, Panzarella T, Kollmannsberger C, et al. Evaluation of a prognostic model for risk of relapse in stage I seminoma surveillance. Cancer Medicine. 2015;4:155–60.
17. van de Wetering RAW, Sleijfer S, Feldman DR, Funt SA, Bosl GJ, de Wit R. Controversies in the Management of Clinical Stage I Seminoma: Carboplatin a Decade in—Time to Start Backing Out. Journal of Clinical Oncology. 2018;36:837–40.

Figures

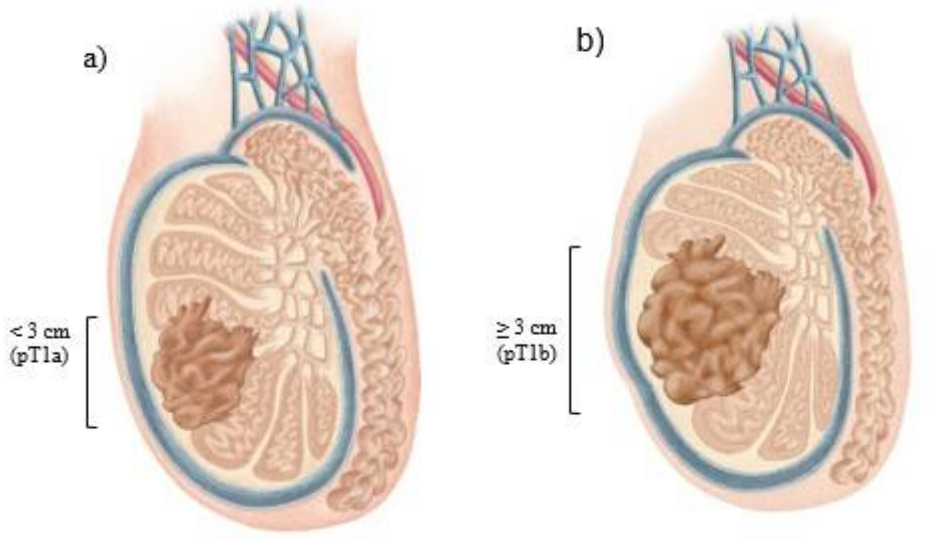

Figure 1

Newly implemented AJCC 8th edition exclusively for pT1 stage seminoma a) tumor size < 3 cm (pT1a) and b) tumor size ≥ 3 cm (pT1b).

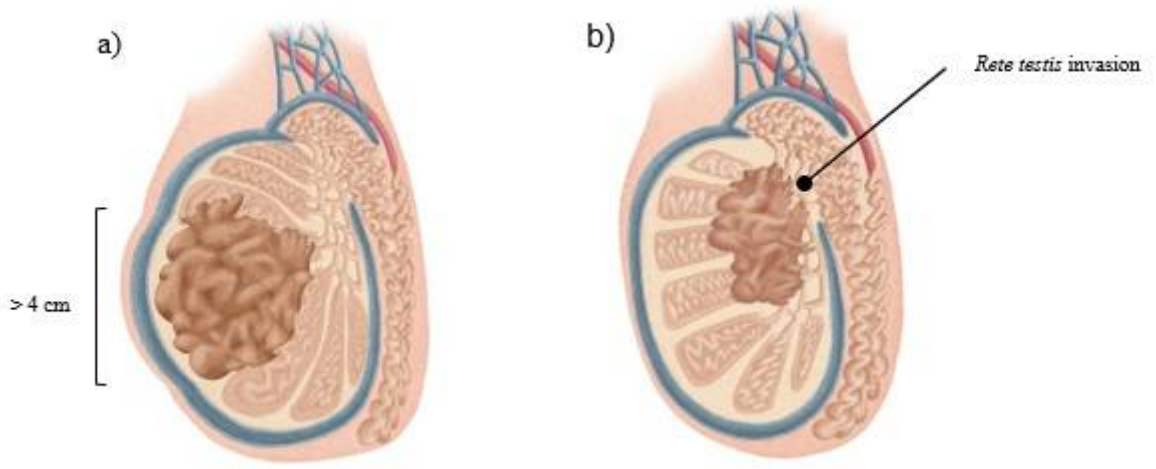

Figure 2

Classically described risk factors for seminoma: a) tumor size > 4 cm and b) rete testis invasion (RTI).