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Original contribution

Pathological risk factors for metastatic disease at presentation in testicular seminomas with focus on the recent pT changes in AJCC TNM eighth edition☆,☆☆

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Summary Management of clinical stage (CS) 1 testicular seminoma is controversial. Treatment choice is based on a number of pathological risk factors. However, they have been inconsistently associated with risk of metastatic disease. The eighth edition of the American Joint Committee on Cancer Tumor-Node-Metastasis staging system has separated pT1a and pT1b tumors according to a 3-cm size cutoff and upstaged invasion of hilar soft tissue and epididymis as pT2. We investigated pathological predictors of metastatic disease at presentation in 332 testicular seminomas. Age, tumor size, invasion of vessels, hilar soft tissue, rete testis, epididymis, spermatic cord, tunica vaginalis and tumor at spermatic cord margin were assessed and correlated with CS at presentation. A total of 290 (87%) tumors were CS 1; 42 (13%) were CS 2/3. Median patient age of CS 1 was 36 years (20-81); that of CS 2/3 was 36 years (26-63). Mean tumor size of CS 1 was 38 mm (5-95 mm); that of CS 2/3 was 54 mm (8-95 mm). On univariate analysis, lymphovascular invasion ($P = .044$), epididymal invasion ($P = .009$) and tumor size ($P = .0001$) were associated with higher CS. On multivariate analysis, tumor size ($P = .0001$) and epididymis invasion ($P = .023$) remained significant. Optimal tumor size cutoff was 4.25 cm. We conclude that tumor size and epididymal invasion are the strongest predictors of metastatic disease at presentation. The results validate changes in American Joint Committee on Cancer Tumor-Node-Metastasis staging eighth edition but suggest a tumor size of 4 cm as better cutoff value.

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1. Introduction

Testicular germ cell cancer is the most common cancer in young men aged 15-44 years [1], with pure seminoma diagnosed in 60% of the cases [2]. Approximately 80% of the patients are diagnosed with clinical stage (CS) 1 disease at presentation without clinical, radiological or serologic evidence of metastatic disease [3]. Although the majority are cured with orchidectomy alone [4], there is a 15%-20% relapse rate within 5 years of follow-up because of subclinical/occult metastatic disease at presentation [5]. The identification of pathological factors involved in metastatic disease is paramount to identify patients at higher risk of subclinical metastases at presentation and, therefore, subsequent relapse [6]. Although there have been many attempts to identify risk factors in previous studies, tumor size has been the only consistent predictor of metastatic disease with other variables reported by others, such as rete testis invasion, lymphovascular invasion (LVI) and epididymis invasion [5-17]. The lack of defined criteria is likely due to low relapse and death rate after adjuvant therapy, which makes studies difficult to power the rarity of the tumors. This can cause a risk of misdiagnosis of stage and type in nonspecialist centers [18-21], increased by the fact that some centers receive a small volume of cases compared to others [22]. All of these factors contribute to create variability in pathological interpretation of germ cell tumors (GCTs), affecting the final diagnosis and consequently the clinical decision. This variability has been highlighted by the result of a survey developed by the European Network of Uro-Pathology sent to genitourinary experts and members. One of most evident disagreement was the staging of epididymal and hilar soft tissue invasion without LVI, split fairly evenly between pT1, pT2 and pT3 [22].

The eighth edition of the American Joint Committee on Cancer Tumor-Node-Metastasis (AJCC 8 TNM) staging system has taken into account these concerns and the changes recommended by pathologists during a consultation meeting of expert urological pathologists in 2015 [22-24]. These include the staging of both hilar soft tissue and epididymal invasions as pT2. This was for practical anatomical reasons and previous lack of concordance, as actual evidence of worse behavior was lacking. Also, for seminoma only, the importance of tumor size was recognized by substaging pT1 according the tumor size cutoff of 3 cm: pT1a (<3 cm) and pT1b (≥3 cm), with reliance on the study by Chung et al [10,25]. No changes have been made for rete testis invasion which is still considered pT1.

The Union for International Cancer Control (UICC) has not amended the eighth edition and it has been kept the same as the previous version. UICC TNM staging eighth edition acknowledges the changes in the AJCC TNM staging eighth edition but has agreed not to include them.

Thus, we wished to identify pathological predictors of higher CS in seminomas with reference to the AJCC TNM staging eighth edition classifications to attempt to examine the validity of these changes.

2. Materials and methods

Barts Health NHS Trust Database was searched from January 2007 to December 2017. The Systematized Nomenclature of Medicine Clinical Terms and various text search terms were used for data retrieval and to search for the anatomical sites, surgical procedures and final histological diagnosis. In total, 551 pathological reports were found for pure seminoma and of them, 332 were included in our final study cohort because of complete information available. The diagnosis of testicular neoplasms was entirely subspecialized with review by 2 expert pathologists (D. B. and L. B.). The following microscopic pathological features were recorded without knowledge of the CS: LVI, invasion of hilar soft tissue, rete testis, epididymis, spermatic cord and spermatic cord margin, tunica vaginalis and maximum tumor size diameter, recorded macroscopically. Direct rete testis invasion versus pagetoid involvement was specifically recorded. Multifocality was also noted. Clinical data, including age and clinical stages at presentation, were obtained from medical records. Patients were deemed to have CS 1 disease if their postoperative tumor markers were normal and there was no evidence of metastases on a computed tomographic scan of chest abdomen and pelvis. Patients with metastatic disease (CS 2 or 3) went on to receive chemotherapy.

2.1. Ethics

Ethical approval was obtained by Local Ethics Committee (REC no: 09/H0704/4 + 5) for the use of anonymized data from Barts Health NHS Trust.

2.2. Statistical analysis

Medians were calculated for continuous variables (age and tumor size) for a skewed distribution and were compared between CS 1 and CS 2/3 using Mann-Whitney. Binary categorical variables (LVI, invasion of hilar soft tissue, rete testis, epididymis, spermatic cord, spermatic cord margins, tunica vaginalis) were collected for CS 1 and CS 2/3; frequencies and proportions were assessed. Univariate and multivariate analyses were performed to compare CS 1 versus CS 2/3 in relation to the pathological variables. Univariate analysis was performed using Fisher exact test of independence. Logistic regression was performed in a forward stepwise model. Odds ratio and its 95% confidence interval (CI) were calculated for each pathological variable. The power of final significant variables in predicting higher clinical stage, in the logistic regression, was tested using receiver operating curve (ROC). The optimal tumor size cutoff was calculated using an ROC curve. $P < .05$ was set to be statistically significant for all tests. All statistical analyses were completed using SPSS version 24 software (SPSS Inc, IBM Corp, Armonk, NY).

Table 1 Comparison of clinical and histological variables between CS 1 and CS 2/3 seminoma patients

	CS 1 (290)	CS 2/3 (42)	Total, N = 332	*P*
Age, median	36 y	36 y	332	.328
Tumor size, median	33.5 mm	57.5 mm	332	.0001
LVI				
No	251 (87%)	31 (74%)	282 (85%)	.044
Yes	39 (13%)	11 (26%)	50 (15%)	
Hilar soft tissue invasion				
No	255 (88%)	36 (86%)	291 (88%)	.622
Yes	35 (12%)	6 (14%)	41 (12%)	
Rete testis invasion				
No	155 (53%)	17 (40%)	172 (52%)	.138
Yes	135 (47%)	25 (60%)	160 (48%)	
Epididymis invasion				
No	280 (97%)	36 (86%)	316 (95%)	.009
Yes	10 (3%)	6 (14%)	16 (5%)	
Direct spermatic cord invasion				
No	284 (98%)	39 (93%)	323 (97%)	.092
Yes	6 (2%)	3 (7%)	9 (3%)	
Tunica vaginalis				
No	284 (98%)	39 (93%)	323 (97%)	.092
Yes	6 (2%)	3 (13%)	9 (3%)	

3. Results

Of the 332 seminoma cases, 290 (87%) were CS 1 and 42 (13%) were CS 2/3 at presentation (Table 1). The mean patient age was 38.5 years old (20-81), median (interquartile range [IQR]) 36 (25-36). Mean age for CS 1 was 38 years (13–59), median (IQR) 36 (31-44); mean age for the CS 2/3 was 40, median (IQR) 36 (32-47). Comparison of the median age for the CS 1 and CS 2/3 showed that a higher clinical stage was not affected by age ($P = .328$).

Overall, mean tumor size was 40.4 mm (5-112). Mean tumor size for CS 1 cases was 38mm (5-95), median (IQR) 33.5 (22-50); mean tumor size for CS 2/3 was 54 (8-95) mm, median (IQR) 57.5 (35-73). Higher clinical stage had a significantly larger tumor size ($P < .001$). Multifocality was present in 40 cases: 32 were CS 1 and 8 were CS 2/3. In CS 1, LVI was identified in 39/290 (13%), rete testis invasion in 135/290 (46%), hilar soft tissue invasion in 35/290 (12%), epididymis invasion in 10/290 (3%), direct spermatic cord invasion in 6/290 (2%), tunica vaginalis invasion in 6/290 (2%).

In CS 2/3, LVI was identified in 11/42 (26%), hilar soft tissue invasion in 6/42 (14%), rete testis invasion in 25/42 (59%), epididymis invasion in 6/42 (14%), direct spermatic cord invasion in 3/42 (7%), tunica vaginalis in 3/42 (7%).

Tumor at spermatic cord margin was not observed in any of the included 332 cases.

Histopathological features were compared between CS1 and CS2/3 cases (Table 1).

On univariate analysis, LVI, epididymis invasion and tumor size were the only variables significantly more common in patients with metastatic disease at presentation (Table 2), whereas age, rete testis with pagetoid involvement, rete testis invasion, invasion of hilar soft tissue, spermatic cord and tunica vaginalis were not significantly different between CS 1 and CS 2/3. On multivariate analysis, only epididymal invasion and tumor size were significant independent predictors of higher clinical stage (Table 3). A logistic regression model

Table 2 Univariate model showing association between pathological variables and clinical stage

Variables	Odds ratio (95% CI)	*P*	AUC
Age	1.018 (0.989-1.048)	2.18	
LVI	2.284 (1.061-4.913)	.044	
Hilar soft tissue invasion	1.214 (0.477-3.089)	.689	
Rete testis invasion	1.688 (0.874-3.260)	.115	
Epididymis invasion	4.667 (1.601-13.605)	.009	
Direct spermatic cord invasion	3.641 (0.875-15.150)	.102	
Tunica vaginalis invasion	3.641 (0.875-15.150)	.102	
Tumor size (mm)	1.028 (1.014-1.042)	.0001	0.708

Table 3 Multivariate logistic regression model showing potential predictors of clinical stage

Variables	Odds ratio (95% CI)	*P*
Epididymis invasion	3.588 (1.194-10.784)	.023
Tumor size (mm)	1.027 (1.013-1.041)	.0001

was created using the 2 significant variables and the stability of the model is represented by the ROC curve with an area under the curve (AUC) of 0.708. The ROC curve was also used to determine the optimal cutoff point that predicts metastatic disease. In our cohort, this cutoff was 4.25 cm (Figure).

4. Discussion

In this study, we have shown that tumor size and epididymal invasion were strong predictors of metastatic disease at presentation in patients with pure testicular seminomas. Our findings partly support the changes introduced by the AJCC TNM staging eighth edition, including the upstaging of epididymis invasion as pT2 and the inclusion of tumor size in the classification. We found the optimal cutoff value of 4.25 cm to predict higher clinical stage, which aligns with many of the previous studies but not with the AJCC TNM eighth edition cutoff value of 3 cm [5,6,9,11,14,16,26].

Tumor size is a well-established predictor of metastatic disease in testicular seminomas. Several studies have shown the association of increased tumor size with higher clinical stage or relapse in CS 1 undergoing surveillance. However, advocating adjuvant treatment in CS 1 patients based on tumor size

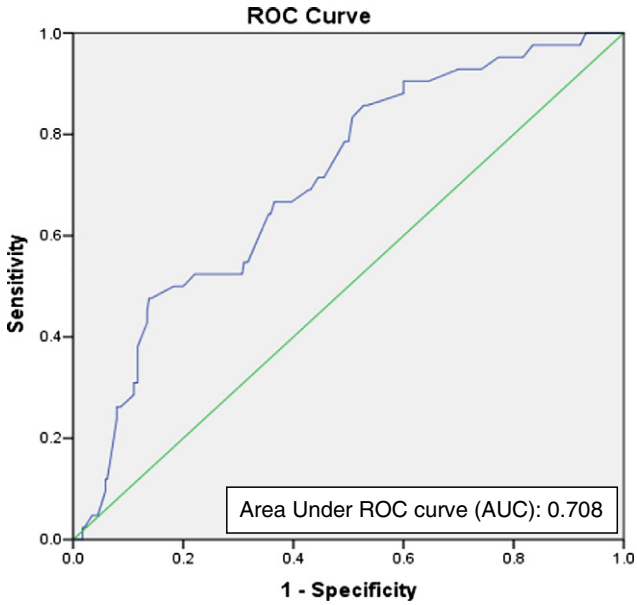

Figure ROC curve for tumor size cutoff of 4.25 cm, with AUC 0.708.

only is problematic as recently shown by Mortensen et al [27]. They compared the outcomes for 473 CS 1 seminoma patients at 'high risk' of disease recurrence, presenting with a tumor size ≥6 cm. Of 219 patients undergoing surveillance, the relapse rate was 32% versus 3% in patients treated with adjuvant radiotherapy, indicating that even in patients with large tumors, adjuvant treatment led to overtreatment in two thirds of the patients. Another issue relating to tumor size is the lack of a clinically applicable and prognostic relevant cutoff value. The European Society of Medical Oncology recommends clinicians to consider the presence of a "large" tumor before deciding the treatment in patients with seminoma [28]. In 2 recent systematic reviews, Zengerling et al [8] and Boormans et al [7], respectively, have attempted to evaluate the best tumor size cutoff in CS 1 seminomas. Both reviews failed in the accomplishment of this task because of the lack of consistent results of previous studies, due to the fact that tumor size cutoff ranged between 3 and 7 cm and because the variable has been considered as continuous in some studies and as dichotomized in others.

We contend that analysis as a continuous variable is needed for tumor size in all studies. A tumor size cutoff of 4 cm is frequently used as guide to identify high-risk patients and then to treat them accordingly. It is included in the European Association of Urology guidelines, together with rete testis invasion [29]. The choice of this value is supported by previous studies. In a pooled analysis of 638 CS 1 patients under surveillance, Warde et al [30] identified tumor size as risk factor for relapse. Age at diagnosis, tumor size, histologic subtype, invasion of rete testis and vessels were analyzed. Tumor size >4 cm and rete testis invasion were the only variables to be predictive of relapse. Dieckmann et al [11] reviewed the standard treatment used in Germany for CS 1 seminoma with the consideration of possible risk factors that can affect the treatment choice. A total of 725 patients with CS 1 seminoma were prospectively enrolled from different institutions, undergoing, respectively surveillance, radiotherapy and carboplatin. Age, duration of follow-up, rete testis invasion and tumor size (greater or less than 4 cm) were included. They showed that tumor size >4 cm was the only predictor associated with relapse in the entire cohort, independently from the treatment. The AJCC TNM staging eighth edition has instead proposed a tumor size cutoff of 3 cm to separate pT1a and pT1b tumors in seminoma only. This conservative cutoff point of 3 cm is based on the study by Chung et al [10]. They evaluated the risk of relapse in a cohort of 684 CS 1 seminoma cases managed by surveillance. The criteria included were age, vessels, rete testis invasion and tumor size. The cutoff point used was the median tumor size of 3 cm. On univariate analysis, only tumor size was associated with risk of relapse, and specifically, on multivariate analysis, they found that the risk of relapse increases when the tumor size is ≥3 cm, whereas LVI and rete testis invasion did not show any difference. When the risk of relapse was considered in relation to tumor size only, they found that the 3-year relapse risk increased from 9% for 1-cm primary tumor to 26% for 8-cm tumor. However, the data were collected from a

number of centers and no central pathological review was conducted.

Because of the extremely low risk of metastatic disease between tumor size 3 and 4 cm observed in this study, the cutoff value of 3 cm is not supported by our study. We align and add support to the recent study by Trevino et al [6] that the use of 4 cm as cutoff is more appropriate to identify patients at increased risk of metastases and should be considered as pT2 in future staging systems.

In our study, LVI was univariately significant, but it was not confirmed on multivariate analysis. Its role is not clear in seminoma. The identification of true LVI from artifact is often challenging in seminoma, where artifactual spread is often seen. Similar results were found by Soper et al [14]. The ambiguous role has been showed also in other studies [15,31], and only in few was LVI a significant factor of relapse or metastatic disease [6] [12].

Similar to the study by Trevino et al [6], in our cohort, invasion of rete testis in CS 2/3 was not significantly different from CS 1 (60% versus 47%). There are discordant opinions in regard to the consideration of rete testis invasion as risk factor of metastatic disease. It is included in the European Association of Urology guidelines based on the pooled data analysis from 4 different studies by Warde et al [30]. Valdevenito et al [17] have also found that rete testis invasion and tumor size (>6 cm) correlate with the presence of clinical metastases. However, the new AJCC TNM staging eighth edition has kept it as pT1. There is not enough evidence to support an upstaging due to the lack of data showing distinction between pagetoid and stromal rete testis invasion. More studies should be conducted to address the issue.

Invasion of hilar soft tissue and epididymis have been upstaged as pT2 in the AJCC TNM eighth edition. In our cohort, epididymis invasion (3% in CS 1 versus 14% in CS 2/3) and hilar soft tissue invasion (12% CS 1 versus 14% CS 2/3) were found to be significant in univariate analysis, although hilar soft tissue invasion was not significant in multivariate analysis. There is little other evidence showing that higher CS or risk of relapse is associated with epididymal and/or hilar soft tissue invasion. Mortensen et al [5] evaluated the effects of surveillance in CS 1 seminoma in a nationwide cohort and possible pathological risk factors involved in relapse. The study showed tumor size as the most important factor involved in relapse; epididymis and vascular invasions were both significant but only when the other factor was excluded. Trevino et al [6] found that, on univariate analysis tumor size, LVI, spermatic cord invasion, hilar soft tissue and epididymal invasion were related to higher CS, but on multivariate analysis, tumor size and LVI were the only 2 strongest variables involved.

Table 4 Summary of results from previous studies in CS 1 seminoma showing pathological variables involved in the prediction of higher clinical stage and risk of relapse.

Author, year	No patients CS 1	Type of study	Pathological risk factors	No treated by surveillance, relapse rate (%)	No treated by adjuvant treatments, relapse rate (%)
Aparicio et al, 2011 [9]	227	Multicenter study	Tumor size ≥4 cm; rete testis invasion	153, 15/153 (6%)	74, 1/74 (0.4%)
Chung et al, 2015 [10]	685	Multicenter study	Age, LVI and rete testis invasion, tumor size < and ≥ 3 cm	685, 88/685 (13%)	0
Dieckmann et al, 2016 [11]	725	Multicenter study	Age, tumor size, rete testis invasion	256, 21/256 (8%)	469, 20/469 (8%)
Horwich et al, 1992 [12]	103	Single institution	LVI	103, 17/103 (16.5%)	0
Kamba et al, 2010 [13]	425	Multicenter study	Rete testis invasion	186, 19/186 (10%)	239, 11/239 (5%)
Mortensen et al, 2014 [5]	1954	Multicenter study	Tumor size, LVI, and rete testis invasion	1954, 369/1954 (19%)	0
Nayan et al, 2017 [34]	775	Single institution	Tumor size (<3 cm and ≥ 3 cm)	135, 135/775 (17%)	0
Soper et al, 2014 [14]	502	Single institution	Tumor size, LVI, and rete testis invasion on univariate analysis only	94, 11/94 (12%)	408, 9/408 (2%)
Tandstad et al, 2011 [15]	1192	Multicenter study	No factors identified in relapse in surveillance	512, 65/512 (13%)	680, 11/680 (2%)
Tandstad et al, 2016 [16]	1118	Multicenter study	Tumor size ≥4 cm, rete testis invasion	422, 29/422 (6.5%)	690, 40/690 (6%)
Tyldesley et al, 2006 [26]	458	Multicenter study	Tumor size ≥4 cm, rete testis invasion	93, 16/93 (17%)	not available
Warde et al, 2002 [30]	638	Multicenter study	Tumor size >4 cm and rete testis invasion	121, 121/638 (19%)	0
Yoshida et al, 2009 [35]	64	Single institution	pT classification	64, 7/64 (11%)	0

Direct spermatic cord and tunica vaginalis invasion in our results were not significant. There is a lack of research in regard to these 2 variables. The role of direct spermatic cord invasion is not clear. It may be due to contamination in seminoma [32]; moreover, it is a rare event, making power in the studies almost impossible, although it has been found univariately significant by Trevino et al [6].

A list of previous studies reporting predictor factors of higher clinical stage and relapse in CS 1 is summarized in Table 4.

Decision making for adjuvant therapy in CS 1 testicular seminoma remains difficult. Definitive agreement on any high-risk factors would significantly aid clinicians and patients in the discussions on the risks and benefits of adjuvant treatment which is of lower morbidity risk than a treatment given after relapse.

The UICC TNM eighth edition is now discordant with the recent AJCC TNM classification [25]: epididymal invasion is still considered pT1, the staging of soft tissue invasion is left unclear and it does not include a size cutoff for seminoma. The UICC TNM staging eighth edition has not taken into account the role of tumor size and the difficulties in staging criteria for testicular cancer, as suggested by the International Society of Urological Pathology in 2015 [33] and by the results of the survey developed by European Network of Uro-Pathology [22].

It has to be emphasized that most of the results in the literature refer to retrospective data, not reviewed according to the AJCC TNM staging eighth edition. These limitations do apply to our study and its use of pathological surrogates for outcomes and nonstandardized treatments. Its strengths include its size as a large single-center cohort, a complete dataset, and use of expert uropathologists in the reports.

In conclusion, our results suggest that size-based stratification and epididymal invasion are important risk factors, supporting the AJCC rather than the UICC TNM staging eighth edition classifications. Further studies should anyway be conducted to validate these finding and to assign the risks in CS 1 seminoma.

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References

[1] Trabert B, Chen J, Devesa SS, Bray F, McGlynn KA. International patterns and trends in testicular cancer incidence, overall and by histologic subtype, 1973-2007. Andrology 2015;3(1):4-12.

[2] Kanyilmaz G, Saricanbaz I, Bora H, Karahacioglu E, Erkal EY. Adjuvant radiotherapy for stage I seminoma: a single-institutional experience. J Cancer Res Ther 2019;15(Supplement):S87-90.

[3] Nichols CR, Roth B, Albers P, et al. Active surveillance is the preferred approach to clinical stage I testicular cancer. J Clin Oncol 2013;31(28):3490-3.

[4] Boujelbene N, Cosinschi A, Boujelbene N, et al. Pure seminoma: a review and update. Radiat Oncol 2011;6(90).

[5] Mortensen MS, Lauritsen J, Gundgaard MG, et al. A nationwide cohort study of stage I seminoma patients followed on a surveillance program. Eur Urol 2014;66(6):1172-8.

[6] Trevino KE, Esmaeili-Shandiz A, Saeed O, Xu H, Ulbright TM, Idrees MT. Pathological risk factors for higher clinical stage in testicular seminomas. Histopathology 2018;73(5):741-7.

[7] Boormans JL, Mayor de Castro J, Marconi L, et al. Testicular tumor 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. Eur Urol 2017;73:394-405.

[8] Zengerling F, Kunath F, Jensen K, Ruf C, Schmidt S, Spek A. Prognostic factors for tumor recurrence in patients with clinical stage I seminoma undergoing surveillance—a systematic review. Urol Oncol 2018;36(10):448-58.

[9] Aparicio J, Maroto P, del Muro XG, et al. Risk-adapted treatment in clinical stage I testicular seminoma: the third Spanish Germ Cell Cancer Group study. J Clin Oncol 2011;29(35):4677-81.

[10] Chung P, Daugaard G, Tyldesley S, et al. Evaluation of a prognostic model for risk of relapse in stage I seminoma surveillance. Cancer Med 2015;4(1):155-60.

[11] Dieckmann KP, Dralle-Filiz I, Matthies C, et al. Testicular seminoma clinical stage 1: treatment outcome on a routine care level. J Cancer Res Clin Oncol 2016;142(7):1599-607.

[12] Horwich A, Alsanjari N, A'Hern R, Nicholls J, Dearnaley DP, Fisher C. Surveillance following orchidectomy for stage I testicular seminoma. Br J Cancer 1992;65(5):775-8.

[13] Kamba T, Kamoto T, Okubo K, et al. Outcome of different post-orchiectomy management for stage I seminoma: Japanese multi-institutional study including 425 patients. Int J Urol 2010;17(12):980-7.

[14] Soper MS, Hastings JR, Cosmatos HA, Slezak JM, Wang R, Lodin K. Observation versus adjuvant radiation or chemotherapy in the management of stage I seminoma: clinical outcomes and prognostic factors for relapse in a large US cohort. Am J Clin Oncol 2014;37(4):356-9.

[15] Tandstad T, Smaaland R, Solberg A, et al. Management of seminomatous testicular cancer: a binational prospective population-based study from the Swedish norwegian testicular cancer study group. J Clin Oncol 2011;29(6):719-25.

[16] Tandstad T, Stahl O, Dahl O, et al. Treatment of stage I seminoma, with one course of adjuvant carboplatin or surveillance, risk-adapted recommendations implementing patient autonomy: a report from the Swedish and Norwegian Testicular Cancer Group (SWENOTECA). Ann Oncol 2016;27(7):1299-304.

[17] Valdevenito JP, Gallegos I, Fernandez C, Acevedo C, Palma R. Correlation between primary tumor pathologic features and presence of clinical metastasis at diagnosis of testicular seminoma. Urology 2007;70(4):777-80.

[18] Lee AH, Mead GM, Theaker JM. The value of central histopathological review of testicular tumors before treatment. BJU Int 1999;84(1):75-8.

[19] Delaney RJ, Sayers CD, Walker MA, Mead GM, Theaker JM. The continued value of central histopathological review of testicular tumors. Histopathology 2005;47(2):166-9.

[20] Ulbright TM. The most common, clinically significant misdiagnoses in testicular tumor pathology, and how to avoid them. Adv Anat Pathol 2008;15(1):18-27.

[21] Purshouse K, Watson RA, Church DN, et al. Value of supraregional multidisciplinary review for the contemporary management of testicular tumors. Clin Genitourin Cancer 2017;15(1):152-6.

[22] Berney DM, Algaba F, Amin M, et al. Handling and reporting of orchidectomy specimens with testicular cancer: areas of consensus and variation among 25 experts and 225 European pathologists. Histopathology 2015;67(3):313-24.

[23] Idrees MT, Ulbright TM, Oliva E, et al. The World Health Organization 2016 classification of testicular non-germ cell tumors: a review and update from the International Society of Urological Pathology Testis Consultation Panel. Histopathology 2017;70(4):513-21.
[24] Verrill C, Perry-Keene J, Srigley JR, et al. Intraoperative consultation and macroscopic handling: the International Society of Urological Pathology (ISUP) testicular cancer consultation conference recommendations. Am J Surg Pathol 2018;42(6):e33-43.
[25] Delahunt B, Egevad L, Samaratunga H, et al. UICC drops the ball in the 8th edition TNM staging of urological cancers. Histopathology 2017;71 (1):5-11.
[26] Tyldesley S, Voduc D, McKenzie M, Duncan G, Liu M, Wu D. Surveillance of stage I testicular seminoma: British Columbia Cancer Agency Experience 1992 to 2002. Urology 2006;67(3):594-8.
[27] Mortensen MS, Bandak M, Kier MG, et al. Surveillance versus adjuvant radiotherapy for patients with high-risk stage I seminoma. Cancer 2017; 123(7):1212-8.
[28] Honecker F, Aparicio J, Berney D, et al. ESMO Consensus Conference on testicular germ cell cancer: diagnosis, treatment and follow-up. Ann Oncol 2018;29(8):1658-86.
[29] Albers P, Albrecht W. Algaba F, et al. Guidelines on testicular cancer: 2015 update. Eur Urol 2015;68(6):1054-68.
[30] Warde P, Specht L, Horwich A, et al. Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. J Clin Oncol 2002;20(22):4448-52.
[31] Aparicio J, Maroto P, Garcia del Muro X, et al. Prognostic factors for relapse in stage I seminoma: a new nomogram derived from three consecutive, risk-adapted studies from the Spanish Germ Cell Cancer Group (SGCCG). Ann Oncol 2014;25(11):2173-8.
[32] Nazeer T, Ro JY, Kee KH, Ayala AG. Spermatic cord contamination in testicular cancer. Mod Pathol 1996;9(7):762-6.
[33] Clare Verrill JP-K, Srigley John R, Zhou Ming, Humphrey Peter A. Antonio Lopez-Beltran, Lars Egevad, Thomas M. Ulbright, Satish K. Tickoo, Jonathan I. Epstein, Eva Compérat, Daniel M. Berney and the Members of the ISUP Testicular Tumor Panel. Reporting and staging of testicular germ cell tumors the International Society of Urological Pathology (ISUP) testicular cancer consultation conference recommendations. Am J Surg Pathol 2017;41(6).
[34] Nayan M, Jewett MA, Hosni A, et al. Conditional risk of relapse in surveillance for clinical stage I testicular cancer. Eur Urol 2017;71(1): 120-7.
[35] Yoshida T, Kakimoto K, Takezawa K, et al. Surveillance following orchiectomy for stage I testicular seminoma: long-term outcome. Int J Urol 2009;16(9):756-9.