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Editorial

Expert Genitourinary Pathology Review of Orchiectomy Specimens Should Be Mandatory for Optimal Management. Recommendations from the European Association of Urology Guidelines Panel on Testicular Cancer

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Although orchiectomy is a relatively simple procedure for urologists, pathological examination to ensure accurate diagnosis and correct treatment is a challenge. The vast majority (>95%) of testicular neoplasms are testicular germ-cell tumors, and most patients presenting with stage I disease (~85% of seminomas and 60% of nonseminomas) have excellent prognosis. However, this success comes at the cost of overtreatment, which can lead to long-term toxicity from chemotherapy exposure in young men.

Accurate risk stratification is critical in selecting patients for active surveillance and discriminating those who are likely to benefit from intense follow-up or treatment. Importantly, most of the established risk factors for patients with seminoma [1] or nonseminoma [2] depend on careful histopathological assessment of the orchiectomy specimen. Although consensus data sets [3] and guidelines [4,5] offer a list of core items and risk factors to be included in the pathology report, assessment of testicular cancer specimens is challenging. Reasons for this include: (1) the overall lower prevalence of testicular tumors, meaning that most pathologists may not encounter them often enough to acquire the necessary experience in reporting; (2) the vast morphological heterogeneity of testicular neoplasms, with frequent mimics and diagnostic pitfalls; and (3) the possibility of encountering particularly rare phenotypes, including those in the sex cord-stromal tumor category, some of which have important implications for prognosis or genetic screening (eg, frequent association with Carney complex for large-cell calcifying Sertoli-cell tumors). In addition, careful macroscopic handling and extensive sampling of the orchiectomy specimen are required for proper interpretation of histology findings. Therefore, it has been recommended that testicular cancer cases should be reviewed by expert pathologists who see a minimum of 30 cases per year [6].

Several studies support the clinical benefit of centralized review of orchiectomy specimens by expert genitourinary pathologists [7–10]. In a study of 221 consecutive cases sent for consultation in a single center by Harari et al. [7], there were discrepancies in histological subtype (the most frequent was failure to recognize yolk sac tumor and teratoma components) in 31%, lymphovascular invasion in 22%, and spermatic cord invasion in 9% of the cases, resulting in modification of pT stage in 23% of cases. Similarly, a study by Purshouse et al. [10] revealed a pathology report discrepancy in 129/465 cases (27.7%) on centralized review in a single center, which resulted in a change in risk stratification for 9% of patients and a predicted impact on patient management in 30 cases (6.5%). The study highlights rete testis invasion in seminomas and lymphovascular invasion

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Table 1 Recommended core items to be reported in testis tumors (adapted from [3,4])

Item	Content	Remarks
Surgical procedure	– Partial orchiectomy – Radical orchiectomy – Other	
Tumor focality	– Unifocal – Multifocal – Cannot be assessed	If multifocal, specify the number of tumors
Maximum tumor diameter	– Dimension of the largest tumor	Specify at least the dimension of the largest tumor (preferably in 3 axes)
Histologic subtype	Histological subtype (and percentage of each component)	Use the most recent World Health Organization classification
Extent of invasion	– Rete testis invasion (stromal/interstitial) – Epididymis invasion – Hilar invasion – Tunica vaginalis invasion – Spermatic cord invasion – Scrotal invasion	Discriminate stromal/interstitial rete testis invasion from pagetoid-only extent
Lymphovascular invasion	– Not identified – Present	
Presence of germ cell neoplasia in situ	– Not identified – Present	Discriminate other intratubular lesions present
Margin status	– Involved – Not involved – Cannot be assessed	In partial orchiectomy, assess the distance of the tumor to the closest margin
Pathological stage	pT stage according to the 8th edition of the TNM classification	

in nonseminomas (two strong risk factors for relapse [1,2]) as the two major reasons for discrepancies. Nason et al. [9] reported that only 519/5048 (10.3%) radical orchiectomy procedures from the Ontario Cancer Registry underwent histopathology review between 1994 and 2015. In this study, there was discordance in the report for 37.2% of the cases, the most frequent of which was a change in pT stage (28.5%, including upstaging in 16% and downstaging in 12.5%), followed by a change in lymphovascular invasion status (23.3%).

Taken together, these data call for stronger recommendations on centralized histopathology review of testicular tumors by experienced genitourinary pathologists, which not infrequently results in changes that impact clinical management.

Illustrating this fact is the recent validation of lymphovascular invasion as an independent predictor of relapse in patients with seminoma [1], which did not achieve consensus in previous studies (possibly because of misinterpretations of smearing of tumor cells into vessels, a common pitfall for seminomas) but achieved statistical significance in a study in an unselected cohort that included centralized expert histopathology review.

In a 10-yr study by the Anglian Germ Cell Cancer Collaborative Group [8], the rate of central histopathology review increased with awareness of its value for clinical management. The study found changes in reports in 9.4% of cases. Of note, eight cases benefited from testing for 12p gains. Additional advantages of referral of testicular tumor cases to tertiary centers is the greater access to diagnostic tests that may not be available in lower-volume centers. These may include microRNA-371a-3p testing in liquid biopsies, as well as fluorescence in situ hybridization for 12p gains, which may be useful in specific settings for accurate classification, such as confirming the diagnosis of prepubertal-type teratoma or somatic malignant transformation in the metastatic setting. Moreover, active participation by pathologists with expertise in testicular tumors in multidisciplinary tumor board meetings may result in relevant input for challenging cases and rarer forms of the disease. The presence of an expert testicular pathologist at preoperative meetings for orchiectomy cases can also prevent unnecessary procedures, an example being occasional unnecessary orchiectomy procedures in men with congenital adrenal hyperplasia and testicular adrenal rest tumors [11].

Looking ahead, accurate histopathological assessment and centralized review of testicular tumors will become increasingly critical for establishment of clinical trials and should result in more robust findings. At the same time, centralized histopathological review is a fundamental part of translational research and can allow the establishment of robust biobanks and multi-institutional studies on biomarkers with a greater chance of achieving clinically meaningful results. From a practical perspective, the increasing adoption of digital pathology may offer an opportunity for establishing networks between different centers to facilitate the distribution of consult cases and expert review in a timely manner.

To conclude, available evidence supports the benefit of centralized review of orchiectomy specimens by expert genitourinary pathologists, which would ultimately contribute to better patient management and more personalized treatment plans. Therefore, the European Association of Urology guidelines panel for testicular cancer currently recommends that orchiectomy specimens should be centrally reviewed by genitourinary pathologists (pathologists who have received dedicated training in genitourinary pathology and who practice genitourinary pathology as their main or one of their main routine diagnostic areas) with experience in testicular pathology (seeing a minimum

of 30 cases per year). Pathology reports should follow the recommended data sets [3,4] (summarized in Table 1) and should always include the type of specimen, tumor focality, maximum tumor diameter, histological subtype, extent of invasion, lymphovascular invasion, presence of germ cell neoplasia in situ, margin status, and pathological stage as core items.

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