Discrepancy in pathology reports upon second review of radical orchiectomy specimens for testicular germ cell tumors

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Abstract

Introduction: We sought to evaluate the discrepancies between primary pathology report and second pathology review of radical orchiectomy (RO) specimens.
Methods: A retrospective review was performed of RO specimens from the Ontario Cancer Registry. All cases required both a primary pathology report and a second pathology review from another institution. Histopathological variables assessed included histological subtype and components of mixed germ cell tumor (GCT), pathological tumor (pT) stage, lymphovascular invasion (LVI), spermatic cord invasion, and surgical margin.
Results: Between 1994 and 2015, 5048 ROs were performed with 2719 (53.9%) seminoma and 2029 (40.2%) non-seminoma. Of these, 519 (10.3%) received a second pathology review. There was concordance between primary pathology report and second pathology review in 326 (62.8%) cases. The most common discrepancies involved a change in pT stage (n=148, 28.5%), with upstaging in 83 (16%) and downstaging in 65 (12.5%) cases relative to the original pT stage. The second most common discrepancy regarded the reporting of LVI (n=121, 23.3%), with 62 (11.9%) reporting presence of LVI when the primary pathology report did not. Other discrepancies included a change in the histological subtype in 28 (5.4%) cases and spermatic cord margin status in five (9.6%) cases.
Conclusions: Only 10% of orchiectomy specimens underwent a second pathology review, with nearly 40% of reviews leading to a meaningful change in parameters. Such variation could lead to incorrect tumor staging, estimate of relapse risk, and inappropriate treatment decisions. Expert pathology review of RO specimens should be considered, as it has significant implications for decision-making.

Introduction

Testis cancer is the most common solid organ malignancy in men aged 15–44.[1] Most men present with clinical stage one (CS1) disease, with cancer confined to the testis and no evidence of metastatic disease. In such cases, radical orchiectomy (RO) alone is the mainstay of treatment with ongoing clinical and radiological surveillance;[2] and five-year survival is 99%.[1] Given the excellent overall survival rate, surveillance is the predominant management strategy for CS1 disease, with a concerted awareness to minimize the morbidity of any treatment.[3] As surveillance protocol may be individualized based on risk of relapse,[4] an accurate initial pathological diagnosis is of paramount importance.

The Canadian guidelines for the management of testis cancer recommend that all histological specimens be assessed by a pathologist experienced in testis cancer.[5] They also advise the histopathological report should document the following points: localization and size of the tumor, multiplicity, tumor extension (rete testis, tunica albuginea, tunica vaginalis, epididymis, spermatic cord, scrotum), pT category according to the Union for International Cancer Control (UICC) classification, histological type, the presence or absence of tubular intra-epithelial neoplasia, as well as the presence or absence of vascular invasion of blood or lymphatic vessels. The American Urological Association (AUA) guideline states, "An expert review of pathologic specimens should be considered in clinical scenarios where treatment decisions will be impacted."[6] It could be argued that this is true for all cases. Although the European Association of Urology (EAU) guideline does not specify a dedicated testis cancer pathologist, it suggests mandatory pathological requirements from the histopathological report.[7]

Standardized techniques have been established on the handling and processing of RO specimens by both urologists and pathologists.[8] Despite this, numerous studies have highlighted the discrepancies in reporting after a central pathology review.[9-12]

There have been many calls for regionalization of testis cancer due to the rarity of the disease and the nuances within its management. The first step in the diagnosis of testis cancer is predominantly a RO; Nayan et al demonstrated that the institution where the RO is performed did not affect oncological outcomes.[13] Given the importance of the pathological diagnosis, the initiation of regionalization could be a central pathological review.

The aim of this study was to evaluate the discrepancies between primary pathology report and second pathology review of RO specimens in Ontario.

Methods

A retrospective review was performed of RO specimens from the Ontario Cancer Registry using the diagnostic codes "malignant neoplasm of testis" and "malignant neoplasm of undescended testis." Cancer Care Ontario collected all pathology reports. All cases required both a primary pathology report from the institution where the RO was performed and a second pathology review from another institution. Cases were excluded if both reports were not available. Histopathological specimens were not reviewed.

Variations in reporting were recorded. Histopathological variables assessed for comparison included histological subtype and components of mixed germ cell tumor (GCT), pathologic tumor (pT) stage, lymphovascular invasion (LVI), spermatic cord invasion (involved or uninvolved), and surgical resection margin (positive or negative).

Categorical variables were summarized with counts and percentages. Statistical analysis was performed using χ^2 test and Fisher exact test. Results were considered significant if $p < 0.05$. Statistical analyses were performed using version 9.4 of the SAS system for Windows (2002-2012 SAS Institute, Inc., Cary, NC, U.S.). The study was approved by the institutional review board (CAPCR # 14-7509).

Results

Between 1994 and 2015, 5048 ROs were performed in Ontario, 2719 (53.9%) seminoma and 2029 (40.2%) non-seminoma. Of these, 519 (10.3%) received a second pathology review. The vast majority (411, 79.2%) of second pathology reviews occurred at two institutions. However, second pathology reviews occurred at 21 different institutions, with a median of two (range 1–319) reviews per institution.

There was concordance between the primary pathology report and second pathology review in 326 (62.8%) cases. The most common discrepancy involved a change in pT stage (n=148, 28.5%), with the second pathology review leading to upstaging in 83 (16%) cases and downstaging in 65 (12.5%) cases. The details in pT stage change are listed in Table 1.

The second most common discrepancy regarded the reporting of LVI (n=121, 23.3%). LVI was reported as present in the primary pathology report and absent in the second pathology review in 58 (11.2%) cases. Conversely, LVI was reported as absent in the primary pathology report and present in the second pathology review in 37 (7.1%) cases. LVI was not commented on in 26 (5%) primary pathology reports but was reported as present in 25 (4.8%) and absent in one (0.2%) upon second pathology review.

There was a change in the histological subtype in 28 (5.4%) cases. The changes were between types of GCT in 23 (4.4%) cases: seminoma to non-seminoma (NSGCT) in 13 (2.5%) cases, NSGCT to seminoma in eight (1.5%) cases, Leydig cell tumor to a seminoma in one (0.2%) case, and NSGCT to a Leydig cell tumor in one (0.2%) case. There was a change from a GCT (seminoma) to lymphoma in three (0.6%) cases. Two (0.4%) cases were described as no tumor seen in the primary pathology report but on second pathology review revealed a seminoma in one (0.2%) and a NSGCT in the other (0.2%) (Table 2). Within mixed GCT, there was a change in the components in 146 (28.1%) cases. Embryonal carcinoma was reported present and changed to absent in 13 (2.5%) cases, while it was reported absent and changed to present in 31 (6%) cases. Choriocarcinoma was reported present and changed to absent in 19 (3.7%) cases, while it was reported absent and changed to present in 14 (2.7%) cases. Yolk sac tumor was reported present and changed to absent in 10 (1.9%) cases, while it was reported absent and changed to present in 60 (11.6%) cases.

There was a change in spermatic cord involvement in 20 (3.9%) cases. The spermatic cord was initially reported as involved and changed to uninvolved in eight (1.5%) cases, while it was reported as uninvolved and changed to involved in 12 (2.3%) cases. Spermatic cord margin status was changed in 5 (1%) cases. The surgical margin was ini-

Table 1. Change in pathological tumor (pT) stage following second pathology review

Primary review	Secondary review	n (%)
Upstage		83 (16)
pTx	pT1	23 (4.4)
pTx	pT2	2 (0.4)
pTx	pT3	1 (0.2)
pT1	pT2	49 (9.4)
pT1	pT3	1 (0.2)
pT2	pT3	7 (1.3)
Downstage		65 (12.5)
pT1	pTx	1 (0.2)
pT2	pTx	2 (0.4)
pT2	pT1	53 (10.2)
pT3	pT1	1 (0.2)
pT3	pT2	7 (1.3)
pT4	pT3	1 (0.2)

Table 2. Change in histological subtype on second pathology review

Primary review	Second review	n (%)
GCT to GCT		
Seminoma	NSGCT	13 (2.5)
NSGCT	Seminoma	8 (1.5)
Leydig cell tumor	Seminoma	1 (0.2)
NSGCT	Leydig cell tumor	1 (0.2)
GCT to other malignancy		
Seminoma	Lymphoma	3 (0.6)
No tumor to GCT		
No tumor	Seminoma	1 (0.2)
No tumor	NSGCT	1 (0.2)

GCT: germ cell tumor; NSGCT: non-seminomatous germ cell tumor.

Table 3. Discordance rates between primary pathology report and second pathology review comparing the site of second review

	Two most common institutions n=411	Other 19 institutions n=108	p
Overall discordant rate	136 (33.1%)	69 (63.9%)	0.0001
Histological subtype	16 (3.9%)	12 (11.1%)	0.007
LVI involvement	97 (23.6%)	31 (29.5%)	0.315
Pathologic pT stage	110 (26.8%)	38 (35.2%)	0.09
Surgical margin involvement	14 (3.4%)	9 (8.3%)	0.036

LVI: lymphovascular invasion.

tially reported negative and changed to positive on second pathology review in two (0.4%) cases. Conversely, the surgical margin was initially reported positive and changed to negative on second pathology review in three (0.6%) cases.

We compared the discordance rates of the primary pathology report and second pathology review based on the two most common second review institutions collectively (n=411, 79.2%) and the other 19 second review institutions collectively (n=108, 20.8%) (Table 3). Overall, the discordance rate was significantly lower among pathology reviewed at the two highest-volume centers (33.1% vs. 63.9%, p=0.0001). Driving this difference was discordance in histological subtypes (3.9% vs. 11.1%, p=0.007) and surgical margin involvement (3.4% vs. 8.3%, p=0.036) between the two most common second review institutions and the others. There was no difference noted in discordance rates of reporting of LVI (23.6% vs. 29.5%, p=0.315) and pathological stage (26.8% vs. 35.2%, p=0.09).

Discussion

Despite guidelines encouraging second pathology review,[5-7] in Ontario, this only occurred in 10% of cases. Our study highlights that variations in pathology reporting of RO specimens is not uncommon. We observed discordance between primary pathology reports and second pathology review in almost 40% of cases and these discrepancies pertained to clinically meaningful parameters, including pathological stage in 28%, LVI in 23%, surgical margin status in 9.6%, and histological subtype in 5.4%. Such discrepancies could lead to inappropriate treatment decisions. There were significantly different discordance rates between the two most common second review institutions, which performed almost 80% of the reviews, and the other 19 institution, with almost a two-fold increase in the number of discordant reviews at the less established review institutions.

Central pathology review has clinical consequences and alters management in many cancers. Recently, de Boer et al reported that central pathology review as part of a high-risk endometrial cancer trial resulted in changes to histological type and grade in 43% of women, an almost identical discrepancy rate to our study, leading to ineligibility for the PORTEC-3 trial in 8%.[14] Soga et al demonstrated a 41% discordant rate in prostate biopsy reports for the classification of intermediate-risk disease, which has significant management implications given low-risk disease is usually managed with active surveillance whereas radical treatment is offered for intermediate-risk disease.[15] Rare tumors, such as pediatric bone and soft tissue tumors, are often challenging cases for general pathologists. A review of over 1600 such cases reported a diagnosis was suggested in less than half (42%), and of these, there were discrepancies in 29%.[16] The main reasons for referral for a second pathology review included a self-perceived lack of experience with pediatric mesenchymal tumors, a second opinion requested by the clinician or patient, and a perceived or real need for ancillary studies not available at the referring institution. Given the remarkably different discordant rates at second pathology review between the two most common second review institutions and the others in our series, this highlights the need for a formal pathway of second review directed towards high-volume centers.

In testis cancer, certain factors have been identified as predictors of relapse and, hence, the reporting of these factors is important. There is debate that in the presence of these high-risk factors, patients should be offered adjuvant treatment in a risk-stratified approach. Tumor size was deemed to be the most valuable prognostic factor in a systematic review of CS1 seminoma relapse; rete testis invasion plays a more minor role.[17] For NSGCT, LVI and >50% embryonal component have been shown to be predictors of relapse. The risk of relapse with evidence of LVI approaches 30–50%.[18] The presence of these risk factors has significant implications for the management of CS1 testis cancer. Although surveillance has been largely adopted for CS1 disease, the guidelines still stratify CS1 NSGCT into stage 1A and stage 1B (based upon the presence or absence of LVI). For stage 1A, NSGCT surveillance is uniformly the preferred option; however, for stage 1B, the AUA, EAU, and National

Comprehensive Cancer Network (NCCN) guidelines discuss a risk-adapted approach as an option on a shared decision basis.[6,7,19] Avulova et al performed a decision analysis of high-risk (LVI) NSGCT and found surveillance to be superior to chemotherapy or primary retroperitoneal lymph node dissection when integrating all possible chance occurrences and survival-related morbidities.[20] Although non-risk-adapted surveillance is the mainstay for CS1 disease in Canada, adjuvant treatment with chemotherapy is being used routinely in some jurisdictions for CS1 disease with high-risk features.[21,22] The high-risk feature of LVI was altered in 23% following second review in our study.

A major error in pathological interpretation is histological subtype (i.e., seminoma vs. NSGCT), which we observed in 4.4% of cases. Surveillance schedules are adjusted based on GCT subtype, with seminomas surveilled with less intensity but followed for longer (nine years vs. five years) than NSGCT. Thus, patients with inaccurate histological subtyping may be surveilled with inappropriate intensity. Worse yet, treatment decisions at relapse are based on understanding of primary pathology. For example, a presumed seminoma relapse is treated with retroperitoneal radiation most commonly at Princess Margaret. This would be largely ineffectual and a non-guideline-concordant treatment if, in fact, the primary had been a NSGCT.

The status of the spermatic cord margin and spermatic cord invasion was altered in 1% and 4% in our cohort, respectively. Invasion of the spermatic cord is associated with more advanced disease and higher rates of relapse,[23] with some institutions advocating hemiscrotectomy or adjuvant radiation.

Previous studies have highlighted the disparities in reporting of primary testis cancer.[9-12] Harari et al compared the final diagnosis between outside institutions and a central review by expert genitourinary pathologists at Indiana University, a centre well-known for testis cancer.[11] Of 221 cases reviewed, 31% demonstrated some discrepancy with histological subtype (all NSGCT), 22% in LVI reporting, and 9% regarding spermatic cord invasion. The pathological stage was altered in 10.4%, with 40% of these being upstaged. Sharma et al noted disparities in 21% of RO specimens resulting in a clinically significant change in 6.8%, defined as change in subtype from seminoma to NSGCT (or vice versa) or a change in LVI status.[10] The most common discrepancy appears to be differences in reporting LVI. Similar to our findings, Sesterhenn et al found a discordance rate of 36% for LVI, which correlated with relapse rates as a high-risk feature.[24]

The current Canadian and American guidelines for testis cancer both refer to a pathology review by a dedicated or expert uro-pathologist given the implications for further treatment.[5,6] While we advocate pathology review at high-volume centers for all orchiectomy specimens, it is important to note that practicing non-risk-adapted active surveillance for CS1 seminoma and NSGCT renders the primary pathology report accuracy less important. We have practiced this way at Princess Margaret since 1980, and this has been echoed by others.[3,25] Non-risk-adapted surveillance is controversial,[26] and while endorsed by Canadian guidelines, the American and European guidelines acknowledge that adjuvant treatment may be chosen for higher-risk CSI seminoma and NSGCT. One advantage to a non-risk-adapted approach is that the presence of LVI, the amount of embryonal carcinoma, and the presence of rete testis invasion is inconsequential to the decision to apply adjuvant therapy.

Interobserver variability is well-recognized within many facets of diagnostic reporting, both in pathology and radiology. Standardized specimen handling, processing, and reporting techniques have been developed to try to minimize variability.[8,27] Improvements in immunohistochemical staining techniques have increased the diagnostic accuracy, particularly between histological subtypes.[27] Future studies will focus on the use of micro-RNA as a biomarker, which will help in the diagnosis of testis cancer, differentiating subtypes, and also in predicting relapse.[28]

Recommending RO pathology review is part of a larger discussion of regionalization of care for testis cancer, a prevalent topic at the recent Canadian Testis Cancer Workshop. Cancer Care Ontario (CCO) understands the importance of regionalizing care of rare cancers and has been successful in regionalizing certain cancers to date. The management of sarcoma is one such example.[29] Quality sarcoma care mandates pathology review at the host center by pathologists with a specialty or special interest in sarcoma working at centers with access to molecular diagnostics, site-specific imaging, advanced limb salvage and abdominal surgery, high-precision radiotherapy, and the delivery of complex chemotherapy regimens. Most aspects of subsequent care are also mandated to occur at designated host sites.

The National Health Service (NHS) in the U.K. is a similar publicly funded, single-payer health service to Canada. In 2002, the National Institution for Clinical Excellence (NICE) released a manual, "Improving outcomes in urological cancers."[30] Similar to regionalization, they recommended the development of networks to provide and co-ordinate a wide range of services for patients with urological cancers within a defined geographical area. The NICE guideline stipulates the initial diagnosis and management (RO) can be provided locally and then referral to the testis cancer network within 24 hours after surgery unless there is evidence of de novo metastatic disease.

This retrospective review of a population database has a number of limitations. First, these databases may not capture all second review cases; however, it is likely that any further cases would mirror these findings. Second, given that approximately 10% of cases received a second review, our main concern is that the other 90% of cases may have some

degree of error within their primary pathology report, which may have impacted treatment decisions. Third, the Canadian guideline recommends a review of all specimens by a pathologist experienced in testis cancer; although the majority of second reviews occurred at two high-volume centers with a dedicated genitourinary pathologist, we do not have details of the experience level of the primary or secondary reporting pathologist in many of these institutions. Finally, this study was based on a review of pathology reporting; none of the specimens were reviewed as a quality assessment.

Conclusions

Despite international guidelines encouraging pathology review in testicular cancer, in Ontario, only 10% of specimens are reviewed. We observed that in up to 40% of cases, discrepancies are noted in meaningful pathological parameters and such discrepancies could lead to inaccurate categorization of subtype (e.g., seminoma vs. NSGCT), staging, relapse risk estimate, and inappropriate treatment decisions. Given the relative rarity of testicular GCTs, pathology review of orchiectomy specimens at an experienced center should be considered because of the significant implications for decision-making.

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