VALUE OF SUPRAREGIONAL MULTIDISCIPLINARY REVIEW FOR THE CONTEMPORARY MANAGEMENT OF TESTICULAR TUMOURS

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ABSTRACT

Purpose

Testicular cancers are an uncommon and highly curable group of tumours that are typically managed by specialist multidisciplinary teams (MDTs). While recent guidelines emphasise the importance of tumour prognostic factors in predicting recurrence and personalising therapy in early stage disease, the role of central pathology review in determining these is unclear.

Methods

We compared referring histopathology reports with those obtained following expert central review for all cases reviewed by the UK Thames Valley Cancer Network testicular tumour MDT between August 2004 and September 2012. Where these differed, we recorded the impact of the alteration on estimates of patient prognosis and predicted clinical management according to international (ESMO) and local guidelines.

Results

Histopathology reports were altered following central review in 129 of 465 (27.7%) cases referred to the testicular tumour MDT during the study period, resulting in changes to estimation of prognosis in 42 patients (9.0% total), with predicted impact on management according to ESMO guidelines in 30 (6.5%) cases. These proportions were broadly similar for both seminomas and non-seminomas, although the reasons for discrepancies differenced between the two (principally errors in categorisation of rete testis invasion in seminomas, and of lymphovascular invasion in non-seminomas). Changes to tumour type were uncommon (two cases).

Conclusion

Central MDT review results in frequent, clinically relevant alterations to testicular tumour histopathology reports for testicular tumours. Our study demonstrates the importance of specialist MDTs to inform patient-centred care and ensure best practice in the management of these uncommon cancers.

BACKGROUND:

Although testicular cancer is the commonest malignancy among young men in the UK, it is relatively infrequent overall with ~2000 cases annually (1,2). Most testicular tumours are germ cell tumours (GCTs) – divided into seminomas and non-seminomatous GCTs (NSGCTs) – for which diagnosis is usually relatively straightforward. However, there are a number of histological pitfalls in diagnosis and staging. For example, other testicular tumour types (such as sex cord stromal tumours) may resemble GCTs causing risk of misdiagnosis, and determining the presence of lymphovascular invasion (LVI) may be challenging as it may be confused with smearing artefact. Consequently, the European Society of Medical Oncology (ESMO) guidelines recommend that the care of all men with testicular tumours is co-ordinated by a specialist multidisciplinary team (MDT) (3), and that expert central pathology review is performed in all cases. While it is generally believed that MDTs have improved diagnosis and staging, and helped facilitate timely and evidence-based treatment for cancer patients, definitive evidence of benefit is limited, particularly for uncommon tumours such as those of the testis (4). Given the substantial financial and staff investments required to support MDT working (an estimated £50 million and more than one million person hours in the UK each year (4)), it is important to evaluate their impact on patient care. Previous studies have suggested that specialist pathology review alters histological diagnosis and staging in 4-6% of testicular tumours, although its impact on the estimation of prognosis was not examined (5,6). Since the publication of these reports, increasing awareness of the toxicities of chemotherapy and radiotherapy has led to a shift towards surveillance for early-stage GCTs, reflected in recent international guidelines (7, 8). However, the presence of pathological features that indicate increased risk of relapse (tumour size >40mm and/or, less conclusively, rete testis invasion (RTI) in seminomas, and lymphovascular invasion (LVI) and/or a majority embryonal component in NSGCTs (9-12)) may still prompt patients and clinicians to opt for adjuvant treatment (13). An accurate histopathological report is therefore essential to provide patients and clinicians with the necessary information to make individualised management plans – the importance of which has

recently been emphasised in the literature (7, 13)

Since 2004, all incident testicular tumours across the UK Thames Valley Cancer Network (TVCN) (c.2.5 million population) have been reviewed at a centralised MDT meeting that includes histopathologists expert in testicular tumour pathology. Anecdotally, we noted that the amendment of histopathology reports following this review frequently appeared to alter the assessment of prognosis with potential implications for patient care. We therefore formally examined this in all testicular tumours reviewed during an eight-year period.

PATIENTS AND METHODS:

Identification of cases and discrepancies in histopathological reports

Cases were identified from a prospective database of all testicular tumours reviewed by the TVCN MDT between August 2004 and September 2012. For all external referrals, the original histopathology report from the referring hospital and the final histopathology report following central review were compared. Discrepancies were classified according to the UK Royal College of Pathologist (RCPath) guidelines (Supplementary Table 1) (14).

Effect of specialist pathology review on estimation of prognosis and patient management

Central review was performed by a single histopathologist expert in testicular tumour pathology (CV, IR or GT). In cases of diagnostic uncertainty, slides were reviewed by a second specialist histopathologist and disagreements resolved by discussion. The impact of central pathology review on the estimation of patient prognosis was evaluated by review of the frequency of alteration of known prognostic factors in early-stage GCTs (size >40mm and stromal RTI in seminoma, and LVI and >50% embryonal carcinoma component in NSGCT (9-12)). The implications of these

alterations for patient management were assessed according to the current (2013) European Society of Medical Oncology (ESMO) testicular tumour clinical practice guidelines and the local TVCN clinical practice guidelines in place at the time of MDT discussion (Supplementary data).

Statistical analysis

Interobserver variability between referring and specialist central pathologists was determined by the kappa statistic. Values of 0.4-0.6, 0.6-0.8 and >0.8 were taken to reflect moderate, substantial or excellent concordance. (15)

Ethical approval

Not required for this service evaluation audit, which was performed in accordance with the Caldicott principles.

RESULTS:

Of 670 patients reviewed at the supraregional testicular tumour MDT between August 2004 and September 2012, 465 were referrals from external hospitals. The histopathology report was revised following central review in 129 (27.7%) of these, of which 42 (9.0% of all referrals) involved alteration to tumour prognostic factors (Table 1), and 30 (6.5% of all referrals) were predicted to impact on management according to current ESMO guidelines (Figure 1). All discrepancies were type B3 (a diagnosis where interobserver variability is known to be large) (Supplementary Table 1).

Seminomas

The referring and final pathology reports were discordant in 66 of 254 (26%) classical seminomas during the study period, with several cases harbouring more than one discrepancy (Figure 1). The most frequent discordances were in the categorisation of RTI (stromal or pagetoid – 33 cases

[13.0% of all referrals], interobserver agreement=86.3%, kappa=0.72) and LVI (27 cases [10.6% of all referrals], interobserver agreement=89.2%, kappa=0.69), resulting in a change to tumour staging in 37 patients (14.6% of all cases, interobserver agreement=85.6%, kappa 0.63) (Table 1, Fig. 1). Tumour prognostic factors (principally stromal RTI status) were altered in 29 cases (11.4% of all seminoma referrals, 43.9% of all discrepancies), including 23 (9.1% of all referrals, 34.8% of all discrepancies) patients with stage I disease. According to ESMO guidelines, twenty of these (7.9% of all seminoma referrals) would have been reclassified from low risk to high risk and three from high risk to low risk (3), with consequent change in management from a clear recommendation for surveillance (low risk) to consideration of adjuvant treatment (high risk) or vice versa. However, as local guidelines required the presence of both risk factors to support a preference for adjuvant treatment, pathology review was predicted to impact on patient management in five cases (2.0% of all referred seminomas).

Non-Seminomatous Germ Cell Tumours (NSGCT)

Histopathology reports were revised in 57 of 180 (31.7%) NSGCTs during the study period. 13 of these (7.2% of all NSGCT referrals, 22.8% of all discrepancies) involved changes in tumour prognostic factors, including alteration of LVI status in nine cases (5% of all NSGCT referrals; interobserver agreement=94.9%, kappa=0.89), and in changes in the estimated proportion of tumour embryonal component to above or below 50% in four cases (2.2% of all NSGCT referrals). Of the tumours in which LVI was revised, five (2.8% of all NSGCTs) occurred in patients with stage I disease, resulting in reclassification from high-risk to low-risk disease, and a change in recommended management from consideration of adjuvant treatment to a clear recommendation for surveillance according to current ESMO guidelines. As local guidelines regarded both LVI and the presence of ≥50% tumour embryonal carcinoma (not considered in the EMSO guidelines) as risk factors, central pathology review was predicted to impact upon management according to these in two additional cases (i.e. a total of 7 cases; 3.9% of all NSGCTs). In both of these, an alteration in the proportion of embryonal tumour would have led to a recommendation for adjuvant

chemotherapy.

Rare histological subtypes

Discordances between initial and final histopathology reports were noted in 6/55 (10.9%) non-germ cell testicular tumours reviewed by the MDT during the study period, two of which were predicted to alter management. One of these was a spermatocytic seminoma originally classified as a seminoma of size <40mm without evidence of RTI, and the other was a Sertoli cell tumour originally classified as a NSGCT with <50% embryonal component and lacking LVI. In both cases, the favourable prognosis of these cancers meant that neither adjuvant treatment nor intensive GCT follow-up was required.

CONCLUSIONS:

In this large study, we have shown that central review of testicular tumours by specialist pathologists results in alteration of histopathology reports in almost a third of cases, with change in estimation of prognosis in just under one in ten cases. The proportion of alterations likely to change management according to local and international guidelines was more modest, but it remained clinically important in the context of this patient cohort where the aim of treatment is to preserve chance of cure while avoiding unnecessary toxicities. Our results are concordant with those from earlier studies, which suggested that 4% to 6% of testicular tumour histopathology reports are altered following specialist review, and that roughly two-thirds of these changes impact upon patient management (5,6). However, the focus of these analyses was largely on discrepancies of tumour type (e.g. seminoma to NSGCT), rather than those affecting important prognostic factors such as RTI and LVI. While the trend towards surveillance for early-stage GCTs has led to uncertainty regarding the relevance of specialist histopathology review in contemporary clinical practice (7,8), our study demonstrates that it provides patients and clinicians with essential clinical details upon which to base individual treatment choices (3, 13).

Management options for stage I seminomas include surveillance, adjuvant radiotherapy or adjuvant chemotherapy, with clinician and patient choice informed by the presence or absence of RTI and or tumour size of ≥40mm (3,10,11). While the significance of these risk factors has been questioned by recent prospective studies, these lacked important clinical details in an appreciable fraction of cases (17). Consequently, current practice is variable (18) and a recent multicentre study showed that approximately one quarter of patients with stage I seminomas received adjuvant chemotherapy (13). In NSGCTs, LVI and/or tumour comprising >50% embryonal carcinoma are recognised as risk factors for relapse and distant metastasis (9, 20). Current ESMO guidelines recommend adjuvant chemotherapy (two cycles of bleomycin, etoposide and cisplatin (BEP)) if LVI is reported, and a discussion regarding adjuvant chemotherapy versus surveillance on an individual basis for men whose tumours lack LVI (7,8,18). Thus, the impact of pathology review on patient management may vary between centres according to differing clinical management algorithms.

In addition to its impact on diagnosis of GCTs, our results also highlight the importance of correct histological subtyping of rarer testicular tumours. Spermatocytic seminoma is an uncommon tumour that is often misdiagnosed as seminoma – an important distinction as it has an excellent prognosis and does not require treatment beyond orchidectomy (22). Similarly, Sertoli cell tumours, also misdiagnosed by referring pathologists in our analysis, are also very uncommon. An incorrect tissue diagnosis of these subtypes may have significant implications for patient care.

Our study has limitations. Comprehensive data on treatment and outcome were not available for all cases, meaning that evaluation of the impact on patient management was made according to ESMO and local guidelines at the time of patient diagnosis rather than on actual events. Furthermore, the identification of cases from a central database means that, in theory some cases from peripheral

hospitals may have not been referred, though previous service evaluation has suggested this is unlikely.

Although the last decade has witnessed a trend towards surveillance for both seminomas and NSGCTs, a detailed and accurate histopathological report is a prerequisite for informed decision making for both clinicians and patients. We have shown that specialised histopathology review serves a vital role in providing this, and that in doing so it represents an essential component of the contemporary multidisciplinary management of testicular tumours.

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CONFLICTS OF INTEREST

None

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Table 1: Frequency of discordance in tumour risk factors between referring and central histopathology reports

Tumour type / prognostic feature		No. of patients at referral (%)	No. of patients post-MDT (%)	% interobserver agreement (kappa)
Seminoma	**n=254**			
RTI	Present	98 (38.6)	123 (48.4)	86.3 (0.72)
	Absent	144 (56.7)	119 (46.6)	
	Unknown	12 (4.7)	12 (4.7)	
Size*	<40mm	139 (54.7)	139 (54.7)	NA
	≥40mm	92 (36.2)	92 (36.2)	
	Unknown	23 (9)	23 (9)	
NSGCT	**n=180**			
LVI†	Present	95 (52.8)	92 (51.1)	94.9 (0.90)
	Absent	83 (46.1)	86 (47.8)	
	Unknown	3 (1.7)	3 (1.7)	
Proportion of embryonal component	<50%	50 (27.8)	48 (26.7)	98.5 (0.97)
	>50%	82 (45.6)	84 (46.7)	
	Unknown	48 (26.7)	48 (26.7)	

*Tumour size was determined at referring hospital prior to tissue processing and was not re-measured on central review

† includes one patient with two tumours with differing LVI status

LVI – lymphovascular invasion; RTI – Rete testis invasion; NA – not applicable

Figure 1. Clinical relevance of central histopathology review in testicular tumours

The frequency and clinical impact of revisions to histopathology reports following specialist central review according to tumour histology (seminoma and non-seminomatous germ cell tumour – NSGCT). Discrepancies were regarded as of potential impact on clinical management if they involved alteration to recognised tumour prognostic factors in patients with stage I disease.

* indicates the total number of cases with any discrepancy and reflects the presence of >1 discrepancy in several cases. † changes to tumour subtype of prognostic importance all involved revision of the proportion of embryonal carcinoma to greater, or less than 50%.