Clinical dilemmas in local and regional testis cancer

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Based on discussions from the Canadian Testis Cancer Workshop (Westin Toronto Airport Hotel, Toronto, ON, Canada, Nov. 15–17, 2018)

Abstract

At the Canadian Testis Cancer Workshop, the multidisciplinary management of testis cancer care was discussed. The two-day workshop involved urologists, medical and radiation oncologists, pathologists, radiologists, physician's assistants, residents, fellows, nurses, patients, and patient advocacy group members.

This review summarizes the discussion regarding clinical dilemmas in local and regional testis cancer. We present cases that highlight the need for a coordinated approach to individualize care. Overarching themes include the importance of a multidisciplinary approach to testis cancer, willingness to involve a high-volume experienced center, and given that the oncological outcomes are excellent, a reminder that clinical decisions need to prioritize selecting a strategy with the least treatment-related morbidity when safe.

Introduction

Testis cancer is the most common solid organ malignancy in men aged 15–29 years. There are approximately 1100 new cases diagnosed in Canada per year. The net five-year survival from testis cancer in Canada is 96%.[1] Although 70–80% present as clinical stage 1 disease and the majority of these undergo surveillance, the remaining cases often present as clinical dilemmas in which there are a number of treatment options available.[2] These cases lead to lengthy discussions between uro-oncology, medical oncology, and radiation oncology, and often result in a challenging decision-making process for the patient.

In November 2018, The Canadian Testis Cancer Workshop was convened. This two-day meeting was comprised of urologists, medical and radiation oncologists, pathologists, radiologists, physician's assistants, residents and fellows, nurses, patients, and patient advocacy group members — all with an interest in testis cancer. One of the goals of the workshop was to discuss the challenging areas of testis cancer care — areas in which the guidelines are not necessarily clear or do not cover. The objective was to distill, through discussion around cases, expert approach to working through these challenges.

Herein, we present local/regional disease dilemmas; distant disease dilemmas are addressed in a separate manuscript.

Case 1

A 25-year-old man presented with a one-month history of a painless left testis mass.

- Medical history: Nil
- Social history: Accountant, single, no children
- Tumor markers: Alpha feto-protein (AFP) 1.7 ng/mL, human chorionic gondatropin (HCG) 1 IU/L, lactate dehydrogenase (LDH) 230 microkat/L (Normal)
- Left radical orchiectomy: 3.5 cm classic seminoma, lymphovascular invasion (LVI)-negative, tunica/epididymis-negative, rete testis-negative, spermatic cord margin-negative, pT1b
- Staging computed tomography (CT) thorax: Non-specific, 3 mm pulmonary nodule
- Staging CT abdomen/pelvis: 1.2 cm x 0.9 cm x 0.8 cm node in left para-aortic region (Figs. 1A, 1B)
- Postoperative tumor markers: AFP 2 ng/mL, HCG 1 IU/L, LDH 225 microkat/L (Normal)

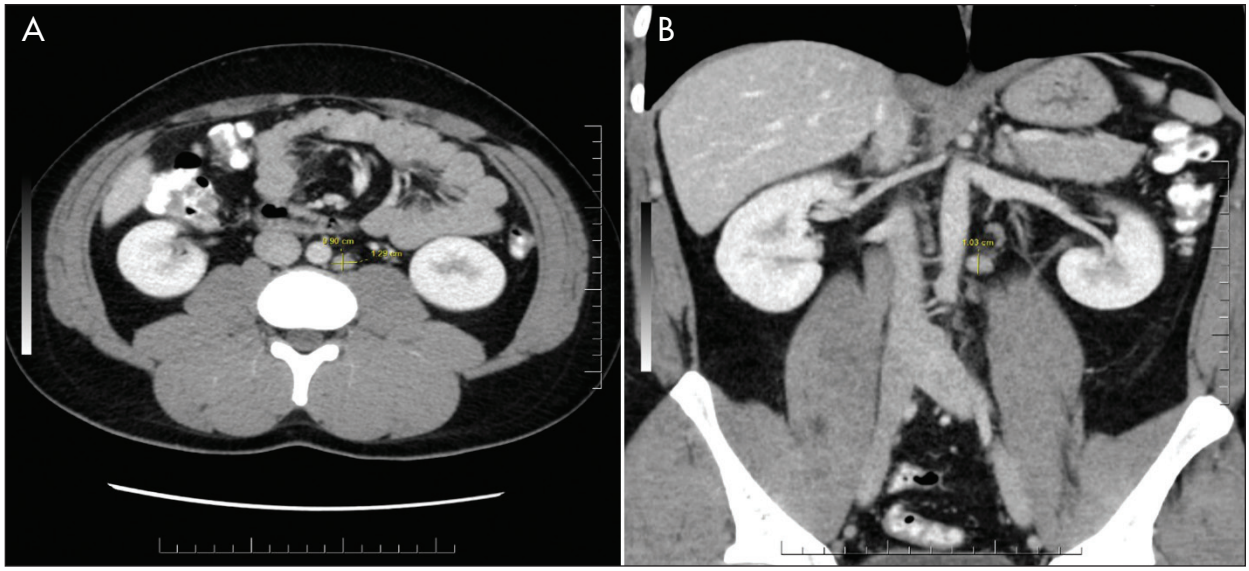

Fig. 1. Case 1: Stage 1/2A seminoma. Computed tomography demonstrating 1 cm node in left para-aortic region.

This patient has borderline findings placing him between a stage I and IIA presentation. He was referred for a multidisciplinary opinion from radiation oncology, medical oncology, and uro-oncology.

Given the borderline findings, he underwent an early repeat CT at three months to determine if the node in the retroperitoneum was true disease or false-positive. His CT at three months showed shrinkage of the left para-aortic node, such that it now measures 7 mm, thus rendering him stage I.

Options: Active surveillance, radiotherapy, chemotherapy, primary retroperitoneal lymph node dissection (RPLND)

Most of the meeting attendees favored a surveillance approach, however, primary RPLND in stage I seminoma is currently being evaluated in clinical trials.[3] It was felt that primary RPLND for stage I seminoma should not be considered standard of care at this point.

Issues raised

Issue #1: Re-imaging the borderline node

The challenge of surveillance in a case with borderline lymph nodes lies in the timing of the first scan and the risk of progressive disease. Most clinicians agree that an early re-staging CT scan is appropriate in borderline cases. There needs to be a balance between risk of recurrence, overtreatment, length of surveillance, and exposure to radiation with number of scans. In this case, if one had actively treated him based on his initial CT scan representing a stage II cancer, he would have been overtreated, with unnecessary morbidity. Regarding repeat imaging, options to reduce radiation dose include low-dose CT scans or magnetic resonance imaging (MRI). The Princess Margaret group compared the effectiveness of a low dose with standard dose CT protocol, which provided an acceptable quality of image in 99% and reduced the dose by 55% for stage 1 testis cancer surveillance.[4] This low-dose protocol is now the standard at the Princess Margaret Cancer Centre. In this case, a low-dose CT was used as followup imaging.

An issue that came up was whether a low-dose CT is optimal in such borderline cases and whether patients are better served with a repeat full-dose CT with intravenous contrast to aid in making the final staging decision. Most felt a standard-dose CT with intravenous contrast was preferable. Abdominal MRI is an alternative and is the imaging modality of choice in the Swedish and Norwegian Testicular Cancer Group (SWENOTECA) and can be used by experienced radiologists.[5,6] The acknowledged unknowns at present are the cost, resource availability, and access, as well as the true sensitivity and specificity in detecting retroperitoneal relapse in a timely way compared to the gold-standard CT scan. The TRial of Imaging and Schedule in Seminoma Testis (TRISST) is a trial from the U.K. comparing MRI and CT for surveillance in CS1 seminoma. The primary endpoint is to assess the proportion of patients relapsing with Stage 2C disease or greater. The study is no longer recruiting patients and had aimed for 660 patients. It is due to report this year.[7]

Issue #2: Pathology review

It is well-accepted that given the implications for management with significantly different morbidity profiles, all testis cancer cases should be reviewed by an expert genitourinary pathologist.[8-11] Harari et al demonstrated that a second-

opinion pathology report from an expert center resulted in a 31% discrepancy of histological subtype and the pathological stage was altered in 23% of cases.[12] A similar rate of discrepancy was found in Ontario, using population-level data. Our group observed that while only 10% of orchiectomy specimens underwent a second review, 40% of them had a meaningful change in parameters, although only a 5% change in histological subtype.[13] Similar central review of radiological imaging with standardized reporting would be welcomed.

Case 2

A 37-year-old man presented with a painless left testis mass and left flank/back pain.

- Medical history: Nil
- Social history: Married, two children (no desire for more)
- Left radical orchiectomy: Mixed germ cell tumor (90% embryonal, 10% choriocarcinoma), LVI-positive, rete testis-positive, spermatic cord-positive, pT3
- Staging CT thorax: Normal
- Staging CT abdomen/pelvis: 4.5 cm x 2.9 cm node in left para-aortic region (Fig. 2)
- Postoperative tumor markers: AFP 76 ng/mL, HCG 2713 IU/L, LDH 225 microkat/L
- Discussed at multidisciplinary rounds and was referred to medical oncology
- The patient received chemotherapy (bleomycin-etoposide-platinum [cisplatin] [BEP] x3).
- Post-chemotherapy markers normalized: AFP 2 ng/mL, HCG 3 IU/L, LDH 225 microkat/L
- CT abdomen/pelvis four weeks following completion of chemotherapy: Left para-aortic mass had shrunk from 4.5 cm to 1.2cm in short-axis dimension

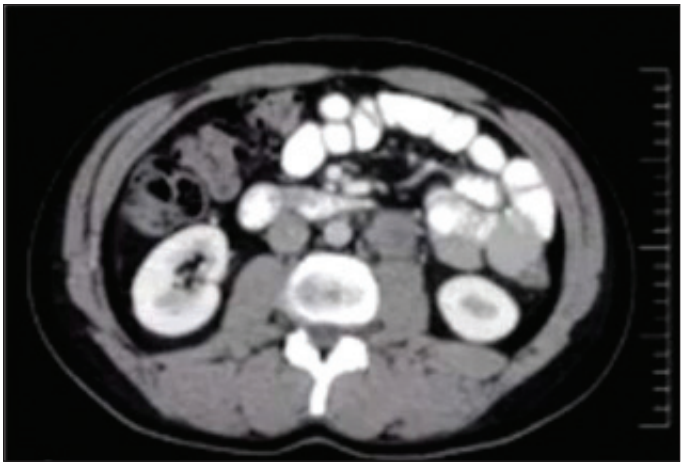

Fig. 2. Case 2: Stage 2B non-seminoma. Computed tomography demonstrating 4.5 cm left para-aortic lymph node.

Options: Surveillance, salvage chemotherapy, radiotherapy, post-chemotherapy RPLND

Most attendees at this stage favored a surveillance approach, with a short-interval repeat CT, while some advocated immediate post-chemotherapy RPLND (pcRPLND).

The patient underwent an initial period of surveillance. Repeat CT scan at three months showed the mass to now measure 9 mm with normal markers. He was maintained on surveillance and 10 years later, the mass remained 8 mm with normal markers.

Issues raised

Issue#1: Measurement of nodal masses

The measurement of nodal masses can be an area of confusion. The current European Association of Urology (EAU) guidelines specify that the node be measured "in greatest dimension," whereas some recommend decision-making based on maximum axial diameter or short-axis diameter.[10,14,15] Even this terminology is confusing. Lymph nodes are usually larger in the craniocaudal dimension (best visualized on a coronal view of the CT). The "long-axis" can be pictured as a line measuring the greatest length in the craniocaudal fashion. The "short-axis" is perpendicular to the long-axis. This would be the largest dimension measured in the axial view on the CT scan. For large masses, it is not of consequence, but for small or borderline masses, it can change management. Literature supporting surveillance of masses <1 cm was based on maximum short-axis dimension. Howard et al demonstrated that craniocaudal diameter was an independent predictor of relapse for non-seminomatous germ cell tumors (NSGCT).[15] Accuracy and standardisation of reporting are of paramount importance.

Issue#2: Repeat CT in good responders

Given the good response to chemotherapy in this case resulting in a node that is just over 1 cm in short-axis dimension, the group felt that an initial period of surveillance is reasonable. It was acknowledged that in many health systems with fixed operating room resource, such as Canada, there are challenges with surgical waiting lists and, thus, an initial period of surveillance often occurs anyway. Although a repeat CT in 'good responders' was favored by many as opposed to proceeding to post-chemotherapy RPLND, there is a lack of data to support this practice.

Issue #3: Surveillance of post-chemotherapy masses ≤1 cm

The initial dilemma in this case centered around the mass being just over 1cm as described. However, once repeat

imaging showed the mass to be ≤1 cm, there was uniform agreement on surveillance. However, such agreement is not true worldwide.

Two series from the *Journal of Clinical Oncology* in 2011 provide the most compelling data in support of surveillance of patients who achieve a complete response following chemotherapy (defined as normalization of markers and a residual mass ≤1 cm). They reported relapse-free rates of 94% at five years and 92% at 15 years, respectively.[16,17] At Princess Margaret, surveillance is the preferred option for patients with a complete response. Our data of 191 men demonstrates an 8.4% relapse on surveillance.[18]

The concern with a mass >1 cm is that at surgical resection these masses will harbor teratoma in up to 45% and viable cancer in 10%.[19] Post-chemotherapy RPLND is a morbid procedure associated with a complication rate of up to 40%, including significant morbidity such as chylous ascites, ejaculatory failure, vascular injuries, bowel obstruction, ventral hernia, and concomitant procedures such as nephrectomy, adrenalectomy, bowel and vascular resection.[20,21] Thus, there is merit in potentially avoiding post-chemotherapy RPLND if it can be done safely.

Issue #4: Extent of post-chemotherapy surgery

If patients are to undergo a post-chemotherapy RPLND for small masses, the extent of a surgical resection is continually debated. Cho et al summarized the Indiana experience with modified retroperitoneal template post-chemotherapy RPLND and observed a 7% relapse rate, but all relapses were outside of what a full bilateral RPLND would have covered. They argued in favor of modified template for select patients with small volume, unilateral disease.[22] Carver et al suggest that up to 32% of patients will relapse outside the boundaries of a modified unilateral template post-chemotherapy RPLND for NSGCT[23] and, as a result, they advocate for all patients to undergo a full bilateral template.

Debate remains regarding the definitions of the modified templates used in the Carver study and it is refuted that a modified template is safe in unilateral masses <5 cm.[24,25] It was the feeling of the group that most centers in North America perform bilateral post-chemotherapy RPLND and this remains the reference standard. There was complete agreement that post-chemotherapy RPLND must be performed by experienced surgeons at experienced sites.

Case 3

A 36-year-old man presented with a painless left testis mass.

- Medical history: Nil
- Preoperative tumor markers: AFP 1.2 ng/mL, HCG 1.1 IU/L, LDH 180 microkat/L (Normal)
- Left radical orchiectomy: 3.5 cm classic seminoma, LVI-negative, tunica/epididymis-negative, rete testis-negative, spermatic cord margin-negative, pT1b
- Staging CT thorax: Normal
- Staging CT abdomen/pelvis: 3.7 cm node in left para-aortic region (Figs. 3A, 3B)
- Postoperative tumor markers: AFP 1.1 ng/mL, HCG 1.2 IU/L, LDH 175 microkat/L (Normal)
- This patient has stage 2B disease

Options: Chemotherapy (BEP x3), radiotherapy, primary RPLND

The patient received radiotherapy (25 Gy in a dog-leg pattern to the retroperitoneal and pelvic nodes) and remains disease-free four years later.

Issues raised

Issue #1: Shared and multidisciplinary decision-making in the stage IIB seminoma

The dilemma in this patient is which treatment option is optimal. There needs to be a shared decision-making process with a well-informed patient. Most of the decision focuses on the risk of relapse and the treatment-related morbidity, given the long-term outcome is excellent with both approaches.[26]

The Princess Margaret approach to stage 2 seminoma has been to favor radiation treatment. Chung et al demonstrated an 89–91% relapse-free rate with radiation treatment alone for the overall cohort.[27,28] However, in observing that enlarging tumor size and number of nodes were associated with a higher risk of relapse, the risk of relapse for the IIB subgroup is 10.3%,[28] and this is what should be quoted to this particular patient. Patterson et al improved the relapse-free rate to 96% with the addition of a single cycle of carboplatin, which is used in the U.K.[29] The use of neoadjuvant chemotherapy may also reduce the extent of the radiotherapy field.[30] However, the addition of chemotherapy either before

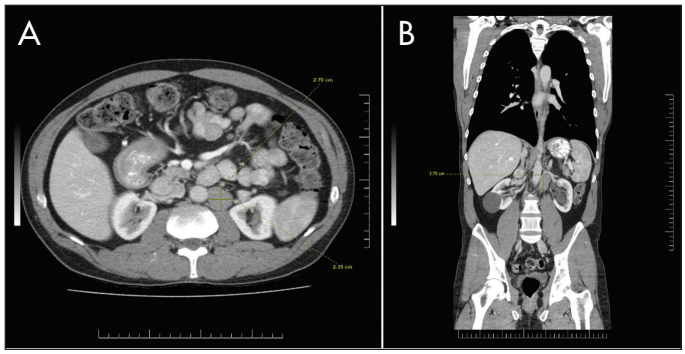

Fig. 3. Case 3: Stage 2 B seminoma. Computed tomography demonstrating 3.7 cm node in left para-aortic region.

or after radiation therapy is not standard of care and is not reflected in any guidelines to date.

Standard chemotherapy in this case would be bleomycin, etoposide, and cisplatin for three cycles. Relapse rate after chemotherapy for IIB seminoma is 8%.[31] The toxicity related to chemotherapy needs to be weighed against that of radiotherapy and the long-term consequences of second malignancy risk.[32] There is a concern regarding the increased secondary malignancy risk following treatment; this risk pertains equally to both chemotherapy and radiotherapy.[33,34] The PLATINUM study group has highlighted several of the key long-term toxicities of chemotherapy, with over 40% reporting >1 adverse health outcome.[35]

If this patient were to have had stage IIC disease, there was agreement that chemotherapy remains the standard of care.[36]

Issue #2: Primary RPLND for seminoma

The alternate strategy discussed was a primary RPLND. There are two ongoing phase 2 trials for primary RPLND in patients with clinical stage 2A/B seminoma assessing progression-free survival without adjuvant treatment: the German PRIMETEST trial and the U.S.-based SEMS trial.[3,37] The group felt a primary RPLND could be offered within a trial setting. Interim results from the PRIMETEST trial were presented at GU-ASCO in 2019 and observed 11 patients who underwent RPLND. Three of these patients (22%) received one cycle of carboplatin prior to RPLND. With a mean followup of 18 months, they had a 36% recurrence rate.[37] Acknowledging this recurrence rate, the group felt that while primary RPLND could be offered within a trial setting, that we best await final results from PRIMETEST and SEMS before considering this as a standard of care recommendation. If RPLND is to be chosen, internationally, debate persists regarding whether RPLND should be robotic or open. The early reports of primary robotic RPLND are encouraging. It appears a safe and feasible procedure and the reported ejaculation rates with a nerve-sparing approach exceed 90%.[38,39] Debate also remains regarding the extent of RPLND; a full bilateral template reduces the risk of recurrence, however, is associated with greater morbidity and operative time.[21,24,40,41] A patient-centered approach is important in cases where the individual has more than one viable option available to them.

Case 4

A 37-year-old man presented with a painless right testis mass.

- Medical history: Nil
- Social history: Not currently employed; otherwise unremarkable
- Preoperative tumor markers: AFP 1.4 ng/mL, HCG 1IU/L, LDH 165 microkat/L (Normal)
- Right radical orchiectomy: 2 cm classic seminoma, LVI-negative, tunica/epididymis-negative, rete testis-negative, spermatic cord margin-negative, pT1a
- Staging CT thorax: Normal
- Staging CT abdomen/pelvis: 1.8 cm node in inter aortocaval region (Fig. 4)
- Postoperative tumor markers: AFP 1.1 ng/mL, HCG 1 IU/L, LDH 180 microkat/L (Normal)
- This patient has stage 2A disease

Options: Chemotherapy (BEP x3), radiotherapy, primary RPLND, surveillance

This patient was unfortunately incarcerated and refused appointments; he only re-presented three months later with a CT showing a stable 1.8 cm node in inter aortocaval region.

Treatment options remained the same as before, but the group was in favor of active surveillance, given the complete stability of the node over three months. The drawback of this approach is that an abdominal CT scan using conventional size criterion for lymph node enlargement will miss a significant percentage (false-positive rates of 22–44%) of patients with retroperitoneal metastases.[42]

The challenge here also pertains to patient compliance. Ernst et al demonstrated patient compliance varies on surveillance protocols, with 78% being compliant with clinic visits and 64% with CT scans across seven different Canadian centers.[43] Paffenholz et al recently demonstrated that non-guideline direct care results in worse relapse-free survival rates.[44] In a patient in which compliance to surveillance may be an issue, consideration and discussion need to be given to upfront treatment. Despite this, this patient ultimately underwent a period of surveillance (given his non-compliance with appointments). As his disease remained stable on imaging, he

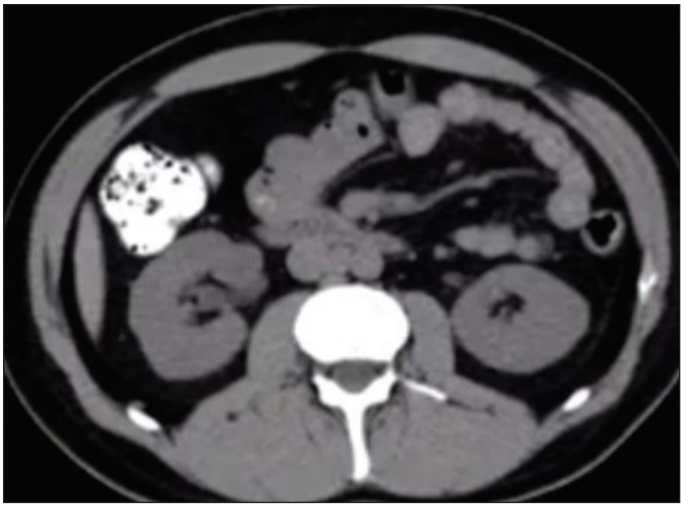

Fig. 4. Case 4: Stage 2A seminoma. Computed tomography demonstrating 1.8 cm inter-aortocaval node.

continued on surveillance as opposed to adjuvant treatment and remained disease-free at end of followup.

We do not advocate a surveillance approach to stage 2 disease, however, this patient enforced a surveillance protocol due to his non-compliance. We recommend repeat imaging in advance of intervention to get an up-to-date overview of the disease state.

Conclusions

This selection of clinical cases provides an insight into the complexity of the management of local and regional testis cancer. Overarching themes include the importance of a multidisciplinary approach to testis cancer, willingness to involve a high-volume experienced center, and given that the oncological outcomes are excellent, a reminder that clinical decisions need to prioritize selecting a strategy with the least treatment-related morbidity when safe. Testis cancer patients are usually young, fit men, and their needs to be an individualized patient-centered approach to their care to fit with their long-term life goals and expectations.

Competing interests: Dr. Rendon has been an advisory board and speakers' bureau member for, and has received honoraria from AbbVie, Amgen, Astellas, AstraZeneca, Bayer, Ferring, Jansen, and Sanofi. Dr. Wood has been an advisory board member (with no compensation) for Astellas, Pfizer, and Novartis; and has participated in clinical trials supported by Aragon, AstraZeneca, BMS, Exelixis, Merck, Pfizer, and Roche. Dr. Kollmannsberger has been an advisory board member for Astellas, BMS, Novartis, Pfizer, and Sanofi; has received honoraria from BMS, Novartis, and Pfizer; and has participated in clinical trials supported by Astellas, AstraZeneca, BMS, Janssen, Merck, Novartis, Pfizer, and Sanofi. Dr. Jewett has been an advisory board member for Pfizer and Theralase Tech; has received honoraria from Olympus, Pfizer, and Theralase Tech; and holds investments in Theralase Tech. Dr. Chung has received honoraria from Sanofi and has participated in clinical trials supported by AbbVie. The remaining authors report no competing personal or financial interests related to this work.

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