Controversies in the management of clinical stage 1 testis cancer

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Summary of the Canadian Testis Cancer Workshop (Westin Toronto Airport Hotel, Toronto, ON, Canada, November 15–17, 2018)

Abstract

In November 2018, The Canadian Testis Cancer Workshop was convened. The two-day workshop involved urologists, medical and radiation oncologists, pathologists, radiologists, physician's assistants, residents and fellows, nurses, patients, and patient advocacy groups. One of the goals of the workshop was to discuss the challenging areas of testis cancer care where guidelines may not be specific. The objective was to distill, through discussion around cases, expert approach to working through these challenges. Herein, we present a summary of discussion from the workshop around controversies in the management of clinical stage 1 (CS1) disease. CS1 represents organ-confined, non-metastatic testis cancer that represents approximately 70–80% of men at presentation. Regardless of management, CS1 has an excellent prognosis. However, without adjuvant treatment, approximately 30% of CS1 non-seminomatous germ cell tumors (NSGCT) and 15% of CS1 seminoma relapse. The workshop reviewed that while surveillance has become the standard for most patients with CS1 disease, there remains debate in the management of patients at high risk of relapse. The controversy in the management of CS1 testis cancer surrounds the optimal balance between the morbidity of overtreatment and the identification of patients who may derive most benefit from adjuvant treatment. The challenge lies in a shared decision process, where discussion of options extends beyond the simple risk of relapse to include the long-term toxicities of adjuvant treatments and the favorable cancer-specific survival.

Introduction

Testis cancer is the most common malignancy in men aged 15–29 years. There are approximately 1100 new cases diagnosed in Canada per year and 70–80% are clinical stage 1 (CS1) at diagnosis.[1] CS1 represents organ-confined, marker-negative disease and has an excellent prognosis, with cancer-specific survival (CSS) of 99%, regardless of management choice.

Without adjuvant treatment, approximately 30% of CS1 non-seminomatous germ cell tumors (NSGCT) and approximately 15% of CS1 seminoma relapse.[2,3] While surveillance has become standard for the majority of patients with CS1 disease, there remains debate over management of patients with high-risk characteristics for relapse.[4,5]

Adjuvant therapies clearly reduce the risk of relapse. However, a shared decision-making process with patients should delve beyond relapse risk to include the potential long-term toxicities of adjuvant therapy and the equivalent CSS.[6,7] Patients have difficulties weighing complex information regarding multiple outcomes that are important to them and the lack of level 1 evidence to direct a patient towards their optimal treatment option leads to more discrepancies.

In November 2018, The Canadian Testis Cancer Workshop was convened in Toronto. 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 groups — all with an interest in testis cancer. One of the goals of the workshop was to discuss the challenging areas of testis cancer care where there is no universally accepted standard. The objective was to distill, through discussion around cases, expert approached to working through these challenges.

Herein, we present a summary of discussion from the workshop around controversies in the management of CS1.

Overview of management options for CS1

Treatment options for CS1 seminoma include active surveillance, para-aortic ± pelvis radiation or chemotherapy (typically carboplatin x 1 or 2 cycles). The European Association of Urology (EAU) guidelines advise offering surveillance "if the facilities are available and the patient is compliant."[2] Even more emphatically, the American Urological Association (AUA) and National Comprehensive Cancer Network (NCCN) guidelines offer surveillance as the "preferred option."[8,9]

For CS1 NSGCT, options include active surveillance, retroperitoneal lymph node dissection (RPLND), or chemotherapy (typically bleomycin, etoposide, and cisplatin x 1 or 2 cycles). The EAU guidelines are less direct here.[2] They suggest offering surveillance or a risk-adapted approach, with patients in the higher-risk group being offered chemotherapy or surveillance. Primary nerve-sparing RPLND is also an option for select patients. The AUA and NCCN guidelines recommend surveillance for CS1A patients, while RPLND or chemotherapy are alternatives for patients who decline surveillance. For CS1B patients, they suggest shared decision-making between surveillance, RPLND, and chemotherapy.[8,9]

The Canadian guidelines recommend surveillance as the management of choice for all risk groups, in both seminoma and NSGCT. This is in line with the Princess Margaret Cancer Centre non-risk-adapted approach, if the patient is willing and able to adhere to a surveillance program.[10,11]

The differing opinions regarding risk-adapted or non-risk-adapted treatment is the main controversial feature in the management of CS1.

Prognostic factors

Certain factors have been identified as predictors of relapse for CS1 disease and these form the basis for a risk-adapted approach.

For seminoma, primary tumor size and rete testis invasion were initially identified as being associated with relapse.[12] Later studies found tumor size as the most valuable prognostic factor.[13] In a Canadian-Danish surveillance cohort of seminoma patients, Chung et al demonstrated a continual increase in relapse risk with every centimeter increase in tumor size, ranging from 9% in a 1 cm tumor to 26% in an 8 cm tumor.[14] While a size cutoff of >4 cm as high-risk is consistently quoted, evidence supporting this specific cut-off is lacking. A recent systematic review by the European Testicular Cancer Guidelines Panel concluded that "the evidence on the prognostic value of size and rete testis invasion has significant limitations" and cautions against routine use in clinical practice.[15]

For NSGCT, there are more consistent prognostic features. The presence of lympho-vascular invasion (LVI) in the primary tumor and increasing predominance of the embryonal carcinoma component have been shown to associate with relapse risk (up to 50%).[16,17] The exact percentage of embryonal carcinoma that confers the increased risk remains unclear. Some argue the mere presence of embryonal carcinoma, others have used >50% component, while the Princess Margaret group suggest only pure (or 100%) embryonal carcinoma as a risk factor given the interrater variability in assigning percent tumor involvement.[11]

Because of disagreement over the embryonal component, LVI is the predominant factor behind risk-adapted guidelines. LVI upstages NSGCT from pT1 to pT2 and overall stage 1A to stage 1B. The largest series to date evaluating surveillance for CS1 NSGCT is a population-based cohort study from Denmark of 1226 patients.[18] They report that the presence of embryonal carcinoma (hazard ratio [HR] 3.85, 95% confidence interval [CI] 2.03–7.32), and LVI (HR 2.20, 95% CI 1.64–2.99) were significantly associated with relapse-free survival.

Adjuvant therapy with chemotherapy or radiotherapy

Professor Robert Huddart from the Royal Marsden in London discussed the advantages of adjuvant treatment and the settings in which he felt it appropriate.

The use of adjuvant treatment is mainly reserved for patients deemed at high risk of relapse and treated in centers that advocated a risk-adapted approach. Such an approach is popular in the U.K. The argument for adjuvant treatment focuses on the risks associated with non-compliance to surveillance, the intensive monitoring and cost of surveillance, the ongoing psychological stress, and the resultant intensive treatment if a relapse occurs. Ernst et al demonstrated a 22% non-compliance rate with clinic visits and a 36% non-compliance rate with imaging for patients undergoing surveillance for NSGCT across seven Canadian centers.[19] Not surprisingly, the compliance rates were highest at the centers with less frequent visits in their protocols. Furthermore, even at dedicated cancer centers, there was a 30% non-adherence rate to surveillance guidelines by physicians, which can result in inappropriate imaging, overtreatment, and related morbidity.[20]

Traditionally, radiotherapy had been the adjuvant treatment of choice for CS1 seminoma, with studies demonstrating a reduction in relapse risk from 15% to 4%.[21] However, radiotherapy is associated with long-term consequences, such as cardiovascular disease[22] and second malignancy,[23] and as a result, its use in CSI seminoma has declined rapidly.[24]

The use of carboplatin is popular in the U.K. Adjuvant chemotherapy with single-agent carboplatin for either one or two cycles has been shown to reduce the risk of relapse. The phase 3 British Medical Research Council (MRC) TE19 trial demonstrated that one cycle of carboplatin was non-inferior to radiotherapy (5.3% vs. 4% relapse) and without the long-term secondary malignancy risk.[25] In contrast, the SWENOTECA group, which may represent a more real-world

experience, reported less impressive absolute risk reductions associated with carboplatin.[26] In patients with no risk factors, the relapse risk in carboplatin-treated patients compared to surveillance patients was minimally different at 2.2% vs. 4%. Among patients with either one or both risk factors, the difference in relapse risk between carboplatin-treated patients (9.1–10.4%) and surveillance (15.5%) was larger but still much smaller than noted in the MRC TE19 trial. Aparicio et al reported the effective use of two courses of carboplatin in patients with seminoma and high-risk features (size >4 cm and rete testis invasion).[27] Chau et al echoed this with excellent results with the use of a single course of carboplatin, with five-year relapse-free rate of 95%.[28]

NSGCT is less radiosensitive, so the choice of adjuvant treatment lies between chemotherapy and RPLND. Cullen et al demonstrated the effectiveness of adjuvant BEP x2 in reducing the relapse rate of NSGCT from approximately 30% to <5%.[29] Since then, one cycle of BEP has been shown to be equally effective in reducing the relapse rate, while lowering the cumulative effect of chemotherapy toxicity.[16,30] The recently published "1:1:1 trial" of BEP x 1 showed similar outcomes to BEP x 2, with a two-year recurrence-free survival of 97% and a two-year overall survival of 99%.[31] Albers et al demonstrated the benefit of one cycle of BEP over a primary RPLND in reducing the number of relapses (2 vs. 13) for NSGCT.[32]

Adjuvant therapy with RPLND

Professor Peter Albers discussed the role for primary RPLND in CS1.

Currently there is no role for RPLND in CS1 seminoma, which is reflected in all the guidelines. There are two ongoing phase 2 trials evaluating primary RPLND in the setting of CSI seminoma relapse or CSIIA/B seminoma.[32,33] However, even if these trials show RPLND is safe and effective in the setting of known retroperitoneal disease, it may be hard to accept as adjuvant therapy in CSI seminoma, given the low risk of relapse and the lack of strong prognostic factors.

There is, however, a role for primary RPLND in CS1 NSGCT and it is offered by many centers. The benefit of a primary RPLND is the lack of long-term toxicity and accurate staging. Modern primary RPLND has been associated with relapse rates ranging from 0–20%, depending on pathological stage.[32,34] Long-term complications can include loss of ejaculation, ventral hernia, and bowel obstruction, although these are rare if performed in centers of excellence.

The advent of robotic RPLND has the potential to make this option more attractive. Robotic RPLND has been demonstrated to be feasible and safe in small series.[35] To date, 16 series of robotic RPLND have been published, with the majority reporting primary RPLND. The two largest series of primary robotic RPLND have shown 2–4-year recurrence rates similar to that of open RPLND, at 3–9%, when adjuvant chemotherapy is given to node-positive patients. Meanwhile, complication rates appear low, at 6.4% overall and 1.7% Clavien Dindo ≥3,[35,36] and similar to open series.[37] The Canadian Workshop felt we must exercise caution in adopting robotic RPLND until more is learned, and emphasized that if robotic RPLND is to be performed, it should be at expert centers with expert surgeons.

Whether open or robotic, the challenge remains in selecting the appropriate patients who would benefit from surgery. Complex surgery, such as RPLND, needs to be performed in cancer centers by high-volume surgeons, as this has been shown to be associated with less morbidity, blood loss, and length of stay, as well as fewer recurrences.[38,39]

Surveillance

Dr. Christian Kollmannsberger reviewed rationale and data supporting modern-era surveillance.

Surveillance has become the foremost approach for men with CS1 disease. Overall, surveillance avoids treatment beyond orchiectomy in 50–75% of patients. Based on data from the National Cancer Data Base, surveillance is the most commonly used management option for CS1 in the U.S.[40]

While many centers offer surveillance regardless of risk factors, a so-called, "non-risk-adapted" approach, debate still exists for whether surveillance is appropriate for patients with risk factors.

Seminoma

For seminoma, the argument for non-risk-adapted surveillance is most cogent. Robust prognostic markers do not exist and even in patients deemed high-risk (larger tumor size), the risk of relapse is only 20–25%. Kollmannsberger reported a large review of CS1 patients from Canada, U.S., and Europe on surveillance — 13% of CS1 seminomas relapsed.[3] Median time to relapse was 14 months, with most (92%) relapses occurring within three years. Most relapsed patients received cisplatin-based combination chemotherapy (61%), while 32% underwent radiation. After a median followup of 52 months, no patients died of disease and only one died of treatment-related complications.

Cummins et al assessed the treatment burden in patients who relapse on CS1 seminoma surveillance.[41] They noted a similar 13% relapse rate, with the majority (82%) being confined to the retroperitoneum. The disease-specific mortality was 1.3%. They explored morbidity of treating relapse and measured in "treatment units," where one unit represented one cycle of chemotherapy or one course of radiation. They observed an average of 0.46 treatment units per patient or 3.45 treatment units per relapsing patient. This can be compared to a hypothetical group of CSI seminomas treated with adjuvant radiotherapy or carboplatin, where each patient would have received one treatment unit with only

an approximate 4% relapse risk. Thus, overall, the morbidity of surveillance is less, however, for the individual relapsing patient, the morbidity of relapse therapy may be more than if an adjuvant treatment had been chosen upfront.

This morbidity equation is dependent on relapse therapy chosen and whether it is examined on an individual patient level as opposed to a population level. For example, Leung et al reviewed the Princess Margaret experience with CSI seminoma surveillance and, in contrast to other series, 78% of relapses were treated with radiation therapy and only 12% received chemotherapy.[20] In this case, the majority of relapsing patients would have had similar treatment burden to patients choosing adjuvant therapy upfront.

NSGCT

For NSGCT, the debate is more challenging for the CS1B patients, where relapse risk is 40–50%. However, arguments in favor of surveillance include: 1) half of patients avoid any treatment beyond orchiectomy; 2) the total burden of chemotherapy for the whole surveillance cohort (including those that relapse) is the same as a strategy where all receive adjuvant chemotherapy; 3) relapses after adjuvant BEP may harbor worse disease biology; 4) concerns about loss to followup are likely less prevalent or problematic than some studies suggest; and 5) concerns about morbidity associated with radiation exposure of surveillance imaging are unsubstantiated. These arguments have been reviewed elsewhere in more detail.[42]

In the same Kollmannsberger paper as noted earlier, 19% of CS1 NSGCT patients relapsed on surveillance.[40] For all relapsing patients, median time to relapse was six months (four months for LVI-positive vs. eight months for LVI-negative). Only 1% relapsed after three years. Five-year disease-specific survival was 99.4%. In this series capturing a multinational surveillance cohort, treatment for relapse consisted of cisplatin-based chemotherapy in 90% and primary RPLND in only 9% (most of which were from Princess Margaret).

Similar to seminoma, it could be argued that relapsing patients have a higher treatment burden than if they had chosen adjuvant therapy upfront. However, this burden also depends on how relapses are managed. Hamilton et al recently reported a 28% relapse rate following a non-riskadapted approach to CS1 NSGCT surveillance.[43] The majority (66%) relapsed within the retroperitoneum and in this series the use of RPLND as initial treatment for relapse was much higher at 38%, with 73% of these patients not requiring any chemotherapy after RPLND. In their modelling exercise, a theoretical cohort of 100 high-risk (i.e., CS1B) patients treated with surveillance and salvaged preferentially with RPLND when appropriate had similar treatment burden to a group treated with adjuvant BEP x 1.

What is currently happening in Canada?

Professor Christopher Booth from Queen's University presented a large, population-based database from the single-payer system in Ontario.

Leveridge et al recently reported the temporal trends in the management of testis cancer in Ontario.[44] Since 2000, there has been a substantial de-escalation of treatment, mainly due to the adoption of surveillance as opposed to radiation treatment of CS1 seminoma. In the last year of their followup, 84% of all newly diagnosed seminomas (all stages) were managed with surveillance, while 57% of NSGCTs were managed with surveillance. Over the same time period, the long-term survival outcomes have remained excellent: 10-year overall survival for all stages was 96% and the cancer-specific survival was 98%. The benefit of reporting population-based data is that it reflects real-world practice, outside of a clinical trial setting and incorporating all providers, as opposed to single- or multi-center of excellence studies. In this Ontario-based report, 72% of patients underwent their orchiectomy in a community hospital.

The Genitourinary Cancer Disease Site Group of the Cancer Care Ontario program produced two systematic reviews for the management of CS1 testis cancer; for both seminoma and NSGCT, surveillance is recommended for all patients.[45,46] Likewise, the previous 2010 Canadian Consensus guideline for the management of testicular cancer supports surveillance for all risk groups in patients willing to adhere to protocol.[9]

Future

The goal for the future is to maintain excellent oncological outcomes while minimizing potential morbidity of treatment. The challenge remains to identify the patients at higher risk of relapse and manage them with the least associated treatment-related morbidity. Prognostic serum biomarkers, such as miRNA371, which is expressed in >90% of GCT, may play a role in the choice of adjuvant therapy vs. surveillance.[47] To date, however, the ability of miRNA 371 post-orchiectomy in CS1 patients to predict future relapse remains totally unknown.[48]

Given there are standardized surveillance protocols in place, surveillance for CS1 lends itself favorably towards telemedicine or virtual clinic innovations. Virtual clinics may maintain high levels of adherence to followup schedules, as they minimize time away from work and daily activities for young patients; they also expand the reach of centers of excellence, allowing patients in more remote locations to still receive care by a high-volume provider. A randomized trial of virtual clinic surveillance vs. standard in-person care for CS1 patients is ongoing.[49] This should provide some level 1 evidence about the feasibility, safety, and satisfaction of virtual care for testis cancer CSI patients.

Finally, from a Canadian perspective, there has been a discussion regarding the role of regionalization of testis cancer. If this is to be adopted on a population basis, surveillance is a safe starting point for CS1 disease, and a standardized regional protocol could be developed to follow patients with CS1 locally.

Conclusions

Most patients with testis cancer present with CS1 disease and, regardless of treatment approach, their outcomes are excellent. The challenge lies in a shared decision process, where discussion and choice of management options extends beyond the simple risk of relapse but include the long-term toxicities of adjuvant treatments that may follow, given the favorable cancer-specific survival.

Competing interests: Dr. Chung has received honoraria from Sanofi and has participated in clinical trials supported by AbbVie. 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. 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. 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. The remaining authors report no competing personal or financial interests related to this work. The remaining authors report no competing personal or financial interests related to this work.

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