Review Article

Contemporary management of early stage testicular seminoma

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Abstract: Therapy for early stage testicular seminoma has changed radically over the past several decades. Given high cure rates and clinical trials supporting less active therapy in most cases, close observation after radical orchiectomy is now considered standard of care for clinical stage (CS) IA/IB seminoma, with either radiation therapy (RT) or chemotherapy salvage options possible. For CS IIA/IIB seminoma characterized by non-bulky retroperitoneal lymph node involvement (≤5 cm in greatest dimension), RT or combination chemotherapy are the standard of care. Given high comparable survival rates, preventing treatment-related toxicity and second malignancy, and limiting quality of life deficits associated with intense treatment has gained much greater importance. Clinical trials are currently testing the feasibility of retroperitoneal lymph node dissection (RPLND) for low volume CS IIA/IIB metastatic testicular seminoma to this end. Likewise, one cycle of chemotherapy is being evaluated as an adjuvant approach to reduce recurrence rates in CS I disease with unfavorable risk factors. Moreover, recent genomic and molecular studies have recently identified novel signatures and a potential biomarker for testicular seminoma. In this review, we first summarize the evolution of early stage seminoma management and discuss the effectiveness and drawbacks of contemporary treatment strategies. We further outline future perspectives and potential challenges in management of early stage testicular seminoma.

Keywords: Testicular cancer; seminoma; surveillance; radiotherapy; chemotherapy

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Introduction

Testicular germ cell tumor (TGCT) is the most commonly occurring malignancy among men between the ages of 15 and 44 years; and slightly more than half of all TGCT (52%) are testicular seminomas (1,2). Seminoma is characterized by sheets of large cells with abundant cytoplasm and round, hyperchromatic nuclei with prominent nucleoli. Histologically unique from testicular non-seminomatous germ cell tumors (NSGCT), seminoma is also highly curable and radiosensitive.

For testicular seminoma, all treatment regimens are determined according to information obtained after radical orchiectomy. This procedure provides a complete specimen for appropriate histologic diagnosis and pathologic staging. In the most recent 8th edition of the American Joint Committee for Cancer (AJCC) staging system, T-stage is determined by tumor invasion and N-stage by size and location of nodes (3-5). Positive lymph nodes contribute to clinical stage (CS) II disease, and distant metastasis to CS III. While human chorionic gonadotropin (hCG) may be slightly above normal, serum markers should not be markedly elevated in seminoma; any elevation of alpha-fetoprotein (AFP) raises concern for a NSGCT (6). In

the current staging system, lactate dehydrogenase (LDH) elevation is seldom seen in the absence of hCG or AFP elevation, and is related to disease burden. Moreover, tumor size above a 3-cm cut point is associated with higher risk of relapse (HR 1.87) (7). The 3-year relapse risk has been reported as approximately 9% for 1 cm primary tumors and up to 26% for 8 cm tumors in a prognostic model for relapse risk in patients with CS I seminoma (7). Thus, in the recent 8th edition of the AJCC staging system (5), the pT1 category for pure seminoma was split into two categories (pT1a and pT1b) based on the 3-cm cut point due to the prognostic significance of tumor size (8).

By definition, early stage seminoma includes CS IA/IB and stage CS IIA/IIB disease, which is characterized by non-bulky retroperitoneal lymph node involvement (≤5 cm in greatest dimension). The cancer-specific survival (CSS) rate for CS I seminoma is 99% regardless of use of adjuvant treatment (9). Likewise, the 5-year overall survival (OS) for CS IIA and IIB seminoma is quite high; 93% and 92% with adjuvant chemotherapy compared to 99% and 95% with adjuvant radiation therapy (RT), respectively (10). However, short term and long term adjuvant treatment-related toxicity in patients with low volume metastatic seminoma, such as infertility, major cardiac events and second malignancy have generated concern (11,12). Thus, over the past several decades, the standard approach to managing seminoma has become quite minimalistic, driven by a coherent desire to decrease toxicity for CS I seminoma patients with a high likelihood of cure. The aim of this review is to present the evolution and current status of clinical management, unique challenges and future perspectives in patients diagnosed with CS IA/IB and CS IIA/IIB seminoma.

Evolution of the management of early stage testicular seminoma

The management of early stage seminoma has evolved significantly. In earlier years, the addition of retroperitoneal lymph node dissection (RPLND) to orchiectomy and RT was not found to improve survival for patients with seminoma (13). To decrease the morbidity of therapy, retroperitoneal surgical component of this multimodal management strategy was discontinued and RT was widely utilized in the 1960's (13,14). Data from the US Patterns of Care studies defined target volumes and doses so that radiation was more uniformly available and standardized than other therapies during this period (14). Into the 1990's, the RT field of choice was a "dog-leg" or "hockey stick" field that covered the bilateral retroperitoneal nodes and the ipsilateral pelvis. In the 1990's, two medical research council studies further refined RT practice for CS I seminoma. The two studies evaluated the extent of radiation (retroperitoneal only *vs.* dog-leg), and the radiation dose (20 *vs.* 30 Gy) in CS I seminoma, and demonstrated similar efficacy with 5-year disease-free survival (DFS) rates of approximately 95% for the different protocols (15,16).

About this time, retrospective data were published detailing a large number of second primary malignancies and cardiovascular toxicities in patients treated with RT for seminoma (17-20). These data were concerning and led to two divergent approaches aimed to reduce RT use in this population. Some clinicians opted for careful observation post-operatively, and some investigated a brief chemotherapy course instead. In the first arena, Duchesne and colleagues reported that the 3-year actuarial risk of relapse was 15.8% for the patients on surveillance following orchiectomy and all patients who experienced relapse were eventually free of disease with subsequent treatments (21). The authors concluded that close surveillance was a safe alternative to adjuvant RT although the need for "intensive use of resources" during prolonged observation was underscored as a major drawback. Between 1982 and 1992, Oliver and colleagues conducted a prospective trial of 1–2 doses of carboplatin following radical orchiectomy in CS I testicular seminoma and only a single relapse was noted among 78 patients receiving single agent chemotherapy (22).

In the 2000s, tumor size >4 cm and rete testis invasion were described as predictive features for relapse in CS I seminoma and the pendulum of public opinion began to shift towards the use of adjuvant chemotherapy on a risk-based approach (23). However, the significance of these clinicopathological factors were rendered less important in subsequent reports. Cancer specific survival was excellent regardless of adjuvant treatment and the relapse rates (9% to 15%) were comparable following adjuvant carboplatin or surveillance in CS I seminoma (24,25). Thus, surveillance has gained favor compared to adjuvant treatments of RT and chemotherapy over the last decade.

The current standard of care for CS I seminoma

The most recent edition of the National Comprehensive Cancer Network (NCCN) testicular cancer guideline (26) currently includes all three options for management

of CS I seminoma: surveillance (preferred option), 1–2 cycles of carboplatin, or RT. The European Association of Urology (EAU) guidelines (27) recommends surveillance for management of compliant patients and opposes any type of adjuvant treatments for patients at low-risk of occult metastatic disease (tumors <4 cm and no rete testis invasion). One cycle of carboplatin is recommended as the appropriate dose if adjuvant chemotherapy is planned whereas adjuvant RT is clearly opposed for any kind of CS I seminoma.

Noninferiority of single dose of carboplatin to RT was confirmed for treatment of CS I seminoma in a multi-institutional randomized clinical trial (MRC TE19/EORTC 30982) that included a total of 1,477 patients, either treated by carboplatin [573] or RT [904] (28). Updated results with a median follow-up of 6.5 years from the same trial reported only one death and the 5-year DFS as 96.1% for single dose carboplatin and 96.0% for RT (29). Of note, a significant reduction in the likelihood of contralateral TGCTs was also noted in favor of carboplatin chemotherapy (2 *vs.* 15 patients).

In two consecutive prospective Spanish cohorts that consisted of 314 and 227 patients who were treated from 1999 to 2003, and from 2004 to 2008, significance of risk factors for relapse were tested. These factors were defined as tumor size larger than 4 cm, and rete testis involvement at orchiectomy specimen (30,31). In the first study, all patients having at least one of two factors received two courses of adjuvant single-agent carboplatin (with 21-day interval). The 5-year OS was 100% and actuarial 5-year DFS were similar, 93.4% and 96.2% for patients on surveillance and for patients treated with adjuvant chemotherapy, respectively. In the second study, only patients having both of the two local risk factors were offered the same chemotherapy regimen. Although the actuarial 3-year DFS appeared longer for adjuvant chemotherapy group (98.0% *vs.* 88.1%), referral bias, and significant variation in incidence of risk factors were major drawbacks in these studies. Moreover, some proposed alternative risk factors such as tumor size, vascular invasion, age, and hCG level at orchiectomy were not associated with relapse in CS I seminoma, thus the benefit of a risk-adapted management approach was not confirmed (32). The 5-year OS and CSS rates were over 99% in any adjuvant treatment and surveillance groups, and approximately 13% (65 of 512) of the patients relapsed following surveillance, about 4% (7 of 188) after carboplatin, and less than 1% (4 of 481) after RT. Although these findings underline slightly higher DFS with adjuvant treatment; RT, chemotherapy and surveillance all provide the same CSS in CS I seminoma. Thus, there is currently no standard criteria for administration of adjuvant chemotherapy.

Treatment outcomes in routine clinical care settings are similar to those reported in clinical trial settings. In a recent prospective study that consisted of 725 patients with CS I seminoma from 130 institutions, where adjuvant treatment decisions were left to the discretion of treating physicians, CSS was 100%. After a median follow-up of 30 months, relapse rates only ranged between 1.5% (for two cycles of carboplatin) and 8.2% (for surveillance) (33). Of note, the relapse rate was significantly correlated with tumor size (0% for <2 cm, 3.4% for 2–4 cm, 6.8% >4 cm, (9.3% >5 cm), 5.0% for all tumors) in patients treated with one cycle of carboplatin, therefore the same authors recommended use of two cycles of carboplatin for large tumors.

Nevertheless, the slightly better DFS with adjuvant treatment in CS I seminoma is at the expense of serious treatment-related adverse events. Myelosuppression due to adjuvant carboplatin is common with leukopenia and thrombocytopenia rates of 30% (grade ≥3 in 3%) and 44% (grade ≥3 in 5%), respectively (34). Acute toxicity of paraaortic field radiation for CS I seminoma includes significant gastrointestinal toxicity such as nausea (46%), leukopenia (14%) and diarrhea (7%) as well as peptic ulcer (7%) (15). Moreover, these adjuvant treatments impair spermatogenesis. Depending on the pretreatment sperm counts, it takes about 13 to 24 months after RT to return to the first normal posttreatment sperm count ranges. Normalization of sperm counts, morphology and motility during carboplatin chemotherapy could last up to 4 years after carboplatin therapy (35).

The most significant the long-term risks of TGCT treatment, secondary malignant neoplasms, typically occur more than 10 years following treatment (36). A large multi-institutional study investigated rate and pattern of secondary malignant neoplasm among 5,848 survivors who were treated for testicular cancer between 1976 and 2007 (37). After a median follow-up of 14 years, the solid secondary malignancy risk was 1.52 times higher for patients with seminoma survivors compared to the general population. The patients treated for seminoma, of whom 73% were treated with RT, were found to have increased risks of small intestine, pancreas, and urinary bladder cancers. Of note, among all testicular cancer survivors, the hazard ratio (HR) of an infradiaphragmatic secondary malignancy was

increased by 8% per Gray of radiation dose administered. Similarly, higher platinum dosage (more than 400 mg/m^2) was associated with increased solid malignancy risk and the HR of a gastrointestinal malignancy was increased by 53% per 100 mg/m^2 of platinum-containing chemotherapy. Thus, the subsequent cancer development risk following adjuvant treatment should be considered strongly during patient counseling.

Intensive follow-up or CT imaging is not recommended beyond five years (26,27). Per NCCN guidelines, visits and radiological imaging are required about twice as often for the surveillance arm than for either of the treatment arms through three years; all revert to annual follow-up afterwards (26). Nevertheless, several patient factors must also be considered when recommending a course of surveillance after orchiectomy. Patient compliance is critically important since adherence with follow-up visits and imaging is mandatory. Likelihood of continuing insurance coverage is similarly important. If either of these is suspect, active treatment may become a better management approach. The other concern is the cumulative radiation exposure during follow-up and lifetime attributable risk of radiation-induced cancer as the follow-up of patients under surveillance is more intensive (38). Indeed, it was reported that diagnostic radiation exposure was not associated with an excess risk of second cancers in testicular cancer patients under follow-up protocols (39). Nevertheless, this study had a median of 11 years follow-up, and most radiation-induced cancers was expected to appear 15 to 45 years after exposure in this young patient population (40). Thus, needless utilization of radiological imaging must be avoided.

Recently, in order to reduce the frequency and burden of surveillance, an individualized follow-up protocol based on the conditional risk of relapse as opposed to static protocols was suggested (41). It was demonstrated that conditional risk of relapse decreased over time in patients managed with surveillance for CS I TGCT. At orchiectomy, the risk of relapse within five years was 12.2% and 20.3% in tumors < 3cm in size *vs.* ≥3 cm, respectively. After 24 months of follow-up without any relapse, the relapse risk within the next five years was only 3.9 to. 5.6%, and after 60 months of follow-up without any relapse, the relapse risk within the next five years was further decreased to 0 to 2.7%.

NCCN guidelines currently recommend a history and physical exam every 3–6 months in the first year, and every 6–12 months in years 2–3 and annually up to five years for patients under surveillance after orchiectomy (26). Axial imaging of the abdomen with or without the pelvis is also recommended at 3, 6 and 12 months, then every 6–12 months in years 2–3 and then every 12 to 24 months up to five years. For patients managed with adjuvant chemotherapy or RT, history and physical exam is required every 6–12 months in the first two years, and then annually up to five years. Axial imaging of the abdomen with or without the pelvis is required annually up to three years. Regardless of adjuvant treatment status, a chest X-ray is not required for follow-up of any patient with CS I seminoma unless clinically indicated. If the patient has related symptoms, chest CT might be considered. Annual measurement of serum hormone levels including total testosterone, luteinizing hormone and follicle-stimulating hormone has been recommended by some investigators, with serum tumor markers being eliminated based on known patterns of tumor recurrence (42).

Almost all (94%) of CS I patients on active surveillance that experience disease recurrence relapse in the retroperitoneum and are identified through routine CT scan assessment at a median of 1.4 years (32). Only approximately 10% of relapsing CS I seminoma patients are symptomatic at the time of recurrence (30). Induction chemotherapy is by far the most utilized salvage therapy for relapse (over 95%), and four cycles of EP (etoposide, and cisplatin) is the preferred regimen in more than 85% of relapsed cases (32). Although relapse rates following adjuvant carboplatin and RT are lower than patients on active surveillance, the patterns of relapse and the choices of therapeutic strategies are similar and dependent upon the extent of relapse and cancer stage (32).

The current standard of care for CS II seminoma

The long-standing treatment for low volume CS IIA and select CS IIB seminoma patients has been RT targeting the para-aortic and ipsilateral iliac lymph nodes with a total dose of 30 and 36 Gy, respectively. RT may be considered for both CS IIA and CS IIB patients but some centers preferentially use RT in patients with low volume metastatic disease, with no single lymph node mass >3 cm (43). Classen and colleagues evaluated 94 patients managed with RT for CS IIA/IIB disease and reported 95.3% and 88.9% actuarial DFS rates at six years for CS IIA and CS IIB, respectively. Early gastrointestinal toxicity was reported in 8–10% of patients but late toxicity was not observed in either of their groups (44). In a review of the Surveillance, Epidemiology, and End Results (SEER) database between

1988-2013, the rate of RT was 53.3% in 605 patients with CS IIA seminoma and 42.7% in 365 patients with CS IIB seminoma (45). The 15-year CSS were 98% and 96% for patients with CS IIA and CS IIB seminoma, respectively. A concerning factor within the same study was the two-fold associated risk of a secondary malignancy in patients undergoing RT for the treatment of seminoma with the most common secondary malignancies being gastrointestinal, respiratory, and hematologic in nature.

A full course of induction chemotherapy is also a common modality for the treatment of CS IIA/IIB seminoma and may be used as an alternative to RT (4,46). The most common combination of multi agent chemotherapy is three cycles of bleomycin, etoposide and cisplatin (BEP). If there is concern for bleomycin toxicity or the patient is bleomycin ineligible, four cycles of EP may be used. The Spanish Germ Cell Cancer Group demonstrated complete and partial response rates of 83% and 17% to cisplatin-based induction chemotherapy in 72 patients with CS IIA/IIB seminoma. Six CS IIB patients relapsed at a median follow up of 71.5 months resulting in one seminoma-related death. Progression-free and OS rates were 90% and 95%, respectively. However, 22% of patients experienced neutropenia and 15% experienced febrile neutropenia (46). Late chemotherapy-related side effects included ototoxicity, neuropathy, nephrotoxicity, pulmonary fibrosis, fertility disorders and secondary malignancy, with each side effect experienced by 3–7% of patients.

To date, no randomized control trials have compared induction chemotherapy and RT for low volume, stage IIA or stage IIB seminoma. However, population-based, retrospective data from the National Cancer Data Base (NCDB) has been studied. Glaser and associates reported on 2,437 patients with CS IIA-C seminoma (IIA =960, IIB =820, IIC =665) (10). RT and systemic chemotherapy were used in 78.1% and 21.9% of CS IIA patients, respectively. RT in CS IIA patients was associated with an improved 5-year OS of 99% compared to 93% for patients managed with chemotherapy (HR 0.28; 95% CI, 0.09–0.86; P=0.027). However, 5-year OS was not significantly different for CS IIB patients: 95.2% for RT and 92.4% for induction chemotherapy. Predictive factors for the use of induction chemotherapy for both CS IIA and CS IIB patients included pathological confirmation of clinically positive lymph nodes by biopsy, more recent year of diagnosis, and treatment at an academic center. Similarly, other investigators reviewed the NCDB and found that RT was utilized less frequently for patients with Medicaid insurance, more recent year of diagnosis and higher pathologic stage (47).

The follow-up schedule advocated by the NCCN for CS II patients is based on CS and whether patients received RT or chemotherapy (26). Patients with lower volume stage II tumor undergo history and physical exam every three months in the first year, and every six months during years 2–5. A chest X-ray is required every six months for two years. Axial imaging of the abdomen with or without the pelvis is required at three months, between months 6–12 during the first year and then yearly through year 3. Follow-up of bulky disease after chemotherapy is more intensive, includes the assessment of tumor markers, and is carefully outlined according to NCCN guidelines (26). FDG-PET imaging is advocated for post-chemotherapy residual masses measuring >3 cm to assist in determining the need for post-chemotherapy surgical resection.

Ongoing clinical trials for early stage seminoma

In contrast to most solid malignancies, the significantly younger age at initial diagnosis and excellent survival in early stage seminoma cause a unique challenge: long-term treatment related sequelae in men living at least 40 years more following cure (40). In order to avoid toxicities and secondary malignancies associated with adjuvant RT and chemotherapy, there are currently two ongoing clinical trials for low-volume metastatic seminoma (48). An interim analysis of phase I/II clinical trials (PRIMETEST study) recently demonstrated feasibility of primary RPLND for treatment of 22 patients with CS IIA/IIB testicular seminoma (49). Median operation time was 134 min and median blood loss was 70 mL. After a mean follow-up of 24 months (1–51 months), 17 (77%) patients were free of recurrence. Overall, the majority of the complications were minimal with the exception of a ureteral stricture requiring ileal ureter substitute after robotic assisted RPLND. All of the 5 patients were recurrence free after salvage chemotherapy (four) and radiotherapy (one), which justified the feasibility of this approach. At the time of this review, trial accrual continues for patients with CS IIA/IIB seminoma (nodes <5 cm in size) (NCT02797626) (50). Another multi-institutional single arm clinical trial (SEMS study) is currently enrolling patients with isolated retroperitoneal lymphadenopathy ≤3 cm in size and no more than 2 nodes (NCT02537548) (51). The primary end-point is 2-year DFS in patients with early metastatic testicular seminoma treated with first-line RPLND. Secondary aims include

the assessment of short-term complications, long-term sequelae, retrograde ejaculation and quality of life.

As carboplatin chemotherapy was shown to have modest efficacy with recurrence rates of approximately 10% in higher-risk CS I seminoma patients, an interest for more effective adjuvant treatment regimens has developed (25). Currently, a randomized phase III clinical trial (SWENOTECA-ABC Study) is comparing efficacy of one course of adjuvant BEP chemotherapy with one course of adjuvant carboplatin (NCT02341989) (52). The primary endpoint is disease recurrence in CS I seminoma patients with one or two risk factors (tumor size over 4 cm and/or stromal invasion of the rete testis by tumor cells). Secondary endpoints include the determination of chemotherapy regimen on health-related quality of life and toxicity.

Future perspectives

Apart from available management options, there is no targeted therapy option for patients with TGCT, owing to both its unique carcinogenesis (malignant transformation of primordial germ cells), and also the paucity of driver gene alterations in TGCT (53). Moreover, immunotherapy is expected to show limited efficacy in seminoma since it has low tumor mutational load (approximately 0.3 to 0.4 mutations per million base) (54,55) and a recent phase II trial of pembrolizumab failed to show efficacy in metastatic chemotherapy refractory NSGCT (56). Nevertheless, a recent study for molecular characterization of TGCT that consisted of 137 primary TGCT cases revealed distinctive molecular landscapes in testicular seminoma (54). *KIT* gene mutation, which was predominantly seen among 72 seminoma cases with a mutation frequency of 35%, was associated with unique characteristics such as history of cryptorchidism, extensive lymphocytic infiltration and lack of DNA methylation, defining a particular subset within testicular seminoma. Therefore, *KIT* gene mutation might still enable risk stratification and potential therapeutic targeting in seminomas in the future.

There is no sensitive tumor biomarker for seminoma and only a minority of CS I seminomas (10–20%) express hCG (6). However, miR-371a-3p, tested by reverse transcriptase real-time quantitative PCR, recently appeared as a promising serum biomarker for seminoma and it was to reflect disease state, with changing marker levels in accordance with treatment and disease recurrence (57). In a prospective multi-institutional study, approximately 85% of patients with seminoma were found to express miR-371a-3p although its expression was relatively lower in tumors less than 1 cm in size (59%) (58). Future multi-institutional prospective studies of this epigenetic biomarker are warranted in order to evaluate its potential role in detection of micro-metastatic disease in CS I/II seminoma and in identification of viable residual cancer in post-chemotherapy residual masses (58,59).

Lastly, from a public health perspective, new obstacles can arise in the management of seminoma. First, the proportions of seminoma cases occurring in men between the ages of 15–34 were expected to increase among all affected men (60). In the US a disproportional increase in incidence of seminoma was recently noted in Hispanics in contrast to an observed, stabilized, overall incidence rate (60). Between 2013 and 2026, testicular seminoma incidence rates were forecast to increase at a faster rate (by 2.58% annually) in Hispanics (60), who were shown to present younger at initial diagnosis (30 *vs.* 35 yr) and were affected unfavorably by health disparities (61). The frequency of non-guideline directed care such as inappropriate imaging, misdiagnosis and undertreatment was also found notably higher in Hispanics (62). Thus, the negative effects of health and racial disparities might possibly be more evident and common in the future.

Conclusions

Currently, the CSS rates in CS I and CS II testicular seminoma are over 99% and approximately 95%, respectively. Given the excellent survival rates, consideration of long-term sequela of adjuvant therapies has gained even more importance during clinical decision-making processes. Long-term risks, especially following adjuvant RT, appear to outweigh the benefits in the stage I setting. Therefore, surveillance has become the recommended management option for CS I seminoma, although long-term benefits of an active surveillance approach have yet to be fully elucidated. The results of ongoing clinical trials, primary RPLND for low volume metastatic seminoma and adjuvant one cycle BEP chemotherapy for high-risk CS I seminoma are eagerly expected. Together with these clinical trials, the future genomic studies enabling better risk stratification and bringing more insight into the carcinogenesis of

testicular seminoma may lead to future paradigm shifts in management of early stage seminoma.

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Footnote

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