The Evolving Management of Testicular Seminoma

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to describe the rationale and data supporting the various post-orchiectomy management strategies for clinical stage I seminoma and describe novel diagnostic and therapeutic options for the management of both localized and metastatic seminoma.

This AUA Update aligns with the American Board of Urology Module on Oncology, Urinary Diversion and Adrenal. Additional information on this topic can be found in the AUA Core Curriculum section on Oncology-Testis.

Richard Matulewicz, MD, MSCI, MS,1 Samuel Funt, MD,2 Darren R. Feldman, MD,2 and Joel Sheinfeld, MD1

1Department of Surgery, Urology Service, Memorial Sloan Kettering Cancer Center, New York, New York
2Department of Medicine, Genitourinary Medical Oncology Service, Memorial Sloan Kettering Cancer Center, New York, New York

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INTRODUCTION

Each year, about 10,000 cases of testicular cancer are diagnosed in the United States, approximately 60% of which are pure seminoma.1 Most patients with seminoma present with tumors localized to the testicle, but up to one-third of patients have advanced disease at diagnosis.2 Most patients with localized seminoma will be cured by orchiectomy alone. In advanced stages, the sensitivity of seminoma to both cisplatin-based chemotherapy and radiation also results in excellent survival. However, a greater understanding of the potential long-term side effects from chemotherapy and radiation has recently challenged traditional management paradigms. Clinicians now aim to reduce cardiovascular toxicities and/or second primary malignancies associated with these treatments by avoiding them, when possible.

Currently, clinical stage I (CSI) seminoma is usually managed with surveillance following orchiectomy, with the goal of reducing overtreatment.3 Recent advances in serum tumor biomarkers (STMs) may help clinicians select patients for adjuvant treatment and detect residual or relapsed disease sooner than traditional imaging and tumor markers. A better understanding of the molecular drivers of testicular cancer may help risk-stratify patients and guide second-line management in rare instances of relapse after first-line chemotherapy. Surgical treatment of low-volume retroperitoneal (RP) disease is being studied and, increasingly, adopted at high-volume centers. In this Update, we review studies that guide current treatment pathways and highlight recent research that may impact management of both localized and advanced testicular seminoma.

EVALUATION AND STAGING

When a testicular mass is discovered, evaluation should begin with a thorough history with attention to relevant signs and symptoms such as lymph node enlargement, breast growth or tenderness, and back pain. The clinician should complete a detailed assessment of the patient’s relevant medical history, including prior cryptorchidism or inguinal surgery, and of the patient’s personal or family history of testicular cancer. The physical exam should include a thorough genitourinary evaluation and lymph node examination. Scrotal ultrasonography should be used to further characterize the mass in the testicle and to identify any subclinical findings in the contralateral testis. For complete initial staging, STMs, including human chorionic gonadotropin (hCG), α-fetoprotein (AFP), and lactate dehydrogenase (LDH), should be drawn at diagnosis and after orchiectomy. Hormonal and fertility evaluations may be considered. Patients should always be counseled on and offered fertility preservation prior to treatment.

At initial diagnosis, patients should be evaluated for the presence of metastatic disease with either CT or MRI of the abdomen and pelvis. Contrast-enhanced CT of the abdomen and pelvis has varying sensitivity and specificity for pathologically confirmed disease based on node size thresholds.1 Relative changes in nodal size or appearance from prior imaging studies and the biological potential for metastatic disease should always be considered when making imaging-based treatment decisions. If a diagnosis of seminoma is established, the clinician should follow the “one above” principle, where CT should be ordered for each “level” above the most distant disease. For example, RP lymphadenopathy should prompt the clinician to consider CT of the chest. Otherwise, a chest x-ray is likely adequate for initial staging of patients with CSI seminoma.

Fluorodeoxyglucose (FDG)-positron emission tomography (PET) scans are not recommended for initial staging of seminoma due to cost, radiation exposure, and risk of false-positives. Currently, FDG-PET is indicated for patients with seminoma who have >3 cm residual masses following chemotherapy. When ordering FDG-PET following treatment, it is critical to wait a minimum of 6-8 weeks after completion of chemotherapy to reduce the risk of false-positive findings from the necrosis and/or the residual desmoplastic and inflammatory reaction caused by chemotherapy. Studies have reported a negative predictive value above 90% but only a 23%-69% positive predictive value for viable cancer with PET imaging.5,6 Brain imaging with MRI should be ordered for patients with excessively high hCG levels (usually >5,000, though rare with seminoma), extensive metastases in the lungs or other viscera, or neurological symptoms.

Diagnosis, staging, treatment, and surveillance of testicular cancer involve the use of STMs (traditionally AFP, hCG, and LDH). Elevated AFP excludes the diagnosis of seminoma. Elevated hCG is noted in 9%-32% of cases.7 LDH levels usually reflect disease burden. Small noncoding microRNAs (miRNAs) involved in the epigenetic regulation of gene translation are increasingly being evaluated as potential complementary biomarkers for testicular germ cell tumors. They are especially promising for seminomas given the low rate of elevation of conventional tumor markers.8,9 However, miRNAs are currently not used in clinical practice as their role, diagnostic accuracy, and kinetics remain undefined.

All patients should be assigned a TNM-S category. Those with advanced disease should be given an International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification, which is assigned prior to first-line chemotherapy and guides treatment, prognosis, and follow-up. Advanced seminoma is insufficiently characterized, but patients with >3 cm residual masses should be considered for curative chemotherapy.8,9 However, patients with >3 cm residual masses should be considered for curative chemotherapy.8,9 However, patients with >3 cm residual masses should be considered for curative chemotherapy.8,9 However, patients with >3 cm residual masses should be considered for curative chemotherapy.8,9 However, patients with >3 cm residual masses should be considered for curative chemotherapy.8,9 However, patients with >3 cm residual masses should be considered for curative chemotherapy.

ABBREVIATIONS: α-fetoprotein (AFP), 3 or 4 cycles of bleomycin, etoposide, and cisplatin (BEPx3 or BEPx4); clinical stage I (CSI), clinical stage II (CSII), clinical stage III (CSIII), European Association of Urology (EAU), 4 cycles of etoposide and cisplatin (EPx4), fluorodeoxyglucose (FDG), germ cell neoplasia in situ (GCNIS), human chorionic gonadotropin (hCG), high-dose chemotherapy (HDCT), International Germ Cell Cancer Collaborative Group (IGCCCG), International Prognostic Factors Study Group (IPFSG), lactate dehydrogenase (LDH), microRNA (miRNA), National Comprehensive Cancer Network (NCCN), nonseminomatous germ cell tumor (NSGCT), overall survival (OS), positron emission tomography (PET), progression-free survival (PFS), retroperitoneal (RP), retroperitoneal lymph node dissection (RPLND), serum tumor biomarker (STM)
designated “good risk” in 90% of patients. The remaining 10% are designated “intermediate risk” based only on the presence of nonpulmonary visceral metastases. Advanced seminoma is never designated “poor risk.” Levels of STMs do not change IGCCCG risk status, but the prognostic thresholds for good risk seminoma (>2.5 the upper limit of normal vs ≤2.5 the upper limit of normal) have recently been updated to reflect the potential benefit of substratification based on LDH levels.² Patients with IGCCCG good-risk seminoma and LDH >2.5× the upper limit of normal have outcomes that more closely approximate patients with intermediate-risk disease.

Any relapse after first-line treatment must be approached according to prior therapies received and extent of disease. These patients are reclassified according to International Prognostic Factors Study Group (IPFSG) classification.¹⁰ Comanagement and consultation with a medical oncologist who has extensive germ cell tumor experience are critical.

**TREATMENT**

**CSI seminoma.** Since most patients with early-stage seminoma are cured with orchiectomy alone, the National Comprehensive Cancer Network (NCCN), AUA, and European Association of Urology (EAU) all preferentially recommend surveillance following orchiectomy for patients with CSI seminoma. Accordingly, use of surveillance in the United States has increased from approximately 40% of patients in 2004 to almost 87% of patients in 2016 (see Figure).³ Among all patients with CSI seminoma managed with surveillance, approximately 15%-20% relapse (Table 1).¹¹,¹² When assessing who is at highest risk of relapse on surveillance, rete testis invasion and tumor size >4 cm have been proposed as independent risk factors.¹²,¹³ Pooled analyses report that patients with both risk factors have a 32% risk of relapse; those with neither factor have a 6% risk of relapse. However, with longer follow-up, the independent association of rete testis invasion with relapse was not significant, and when this strategy was used to guide treatment decision-making in 2 prospective nonrandomized risk-adapted adjuvant trials, there was a limited (~6%) absolute reduction in relapse between patients

![Figure. Treatment trends in localized seminoma, 2004-2016. Reprinted with permission from Frankel 2021;39(4):240.e1-e240.e8.³](image-url)

Table 1. Relapse Rates and Risk Factors for Relapse in Men With Clinical Stage I Seminoma Treated With Surveillance, Carboplatin, or Radiation

<table>
<thead>
<tr>
<th></th>
<th>Warde et al¹</th>
<th>Tandstad et al²</th>
<th>Aparicio et al³,⁴</th>
<th>Mortensen et al⁵</th>
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<tbody>
<tr>
<td></td>
<td>Surveillance</td>
<td>Surveillance</td>
<td>Carboplatin ×1 cycle</td>
<td>Surveillance</td>
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<tr>
<td>Risk factor</td>
<td>No.</td>
<td>% Rel</td>
<td>No.</td>
<td>% Rel</td>
</tr>
<tr>
<td>None</td>
<td>176</td>
<td>12.2</td>
<td>268</td>
<td>4.0</td>
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<td>&gt;4 cm</td>
<td>107</td>
<td>17.0</td>
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<td>19.1</td>
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<tr>
<td>RTI</td>
<td>75</td>
<td>14.4</td>
<td>54</td>
<td>13.6</td>
</tr>
<tr>
<td>Either</td>
<td>182</td>
<td>15.6</td>
<td>115</td>
<td>15.5</td>
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<tr>
<td>Both</td>
<td>95</td>
<td>31.5</td>
<td>12</td>
<td>16.7</td>
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Abbreviations: Rel, Relapsed; RT, radiotherapy; RTI, rete testis invasion.

Adapted with permission from van de Wetering 2018;36(9):837-840.⁵¹

ª≥6 cm.


managed with surveillance and those treated with adjuvant chemotherapy.11,14,15 The small difference in relapse seen in these studies and the near-universal cure provided by induction chemotherapy in those who relapse precludes adoption of these factors in clinical practice. Presently, these risk factors are not recommended to influence clinical decision-making regarding adjuvant treatment.

**Surveillance protocols.** Recommendations vary regarding the frequency, intensity, and approach to surveillance after orchiectomy for patients with CSI seminoma (Table 2). When pursuing surveillance, it is important to personally review the patient’s imaging and to involve experienced genitourinary radiologists. Controversy exists about the need for STMs and chest x-rays, and whether surveillance is needed after 5 years. Both the AUA and the NCCN recommend STMs “as indicated” or as “optional,” while the EAU guidelines suggest STMs twice in each of the first 3 years of surveillance and annually in years 4-5. These recommendations are based on the rarity of relapse detected by STMs in the absence of radiographically evident disease.16 Similarly, none of these guidelines includes chest x-rays as part of routine surveillance, though NCCN guidelines recommend them “as clinically indicated.” Retrospective studies have shown that virtually no relapses are detected by chest x-rays alone,17 limiting their utility in the absence of positive markers or concerning abdominopelvic imaging. Refined individualized strategies that limit unnecessary testing but effectively detect relapse continue to evolve.

Due to the frequency of staging and surveillance imaging with ionizing radiation, MRI has been proposed as an alternative to CT. TRISST (Trial of Imaging and Surveillance in Seminoma Testis) is a phase III, multicenter, factorially designed trial that aimed to assess noninferiority of MRI vs CT and de-escalation of scan frequency among patients with CSI seminoma being managed with surveillance.19 After randomizing over 660 patients, investigators determined that MRI was noninferior to CT scan and that a 3-scan schedule (at 6, 18, 36 months) was noninferior to a 7-scan schedule (at 6, 12, 18, 24, 36, 48, 60 months). Compliance was high (94% of scans attended, 79% within 4 weeks of planned date; 13% lost to follow-up) relative to real-world practice, where 20% of patients are lost to follow-up within 5 years of orchiectomy and compliance with frequent visits and imaging remains a challenge.20,21 These high-quality data may prompt changes in guideline recommendations.

Median time to relapse in patients managed with surveillance is about 1.4 years, and about 70% will relapse within the first 2 years.11 The majority of relapses are IGCCCG good risk and are detected by CT scans of the abdomen as the predominant site of relapse is the retroperitoneum.22 **Relapses beyond 5 years ("very late relapse") are rare, occurring in 0.5%-4.3% of patients, and are usually found secondary to symptoms such as back and abdominal pain.11,23,24** Approximately 50% of very late relapses have elevated STMs at re-presentation. It is unclear if continued long-term surveillance beyond 5 years in these studies would have detected disease recurrence prior to patients becoming symptomatic.

There are no standardized surveillance recommendations beyond 5 years. For patients with seminoma who experience late or very late relapse, long-term disease-specific survival following treatment remains excellent (>90% 10-year overall survival [OS]).23 We recommend continued follow-up beyond 5 years either with the treating urologist/oncologist or through a “survivorship care plan” in conjunction with the patient’s primary care physician.

**Adjuvant radiation or chemotherapy.** Adjuvant radiation in patients with CSI seminoma is associated with an approximately 4% risk of relapse, with lower rates of pelvic relapse seen in patients where “dogleg” fields were used.25,26 However, several studies have shown an increase in secondary solid malignancies in patients treated with radiation, particularly in

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Years 6+</th>
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<tbody>
<tr>
<td><strong>AUA</strong> H&amp;P and CT AP q4-6 mo</td>
<td>H&amp;P and CT AP q4-6 mo</td>
<td>H&amp;P and CT AP q6-12 mo</td>
<td>H&amp;P and CT AP q6-12 mo</td>
<td>H&amp;P and CT AP q6-12 mo</td>
<td>No specific recommendations</td>
</tr>
<tr>
<td>CXR and STMs as indicated</td>
<td>CXR and STMs as indicated</td>
<td>CXR and STMs as indicated</td>
<td>CXR and STMs as indicated</td>
<td>CXR and STMs as indicated</td>
<td>CXR and STMs as indicated</td>
</tr>
<tr>
<td><strong>EAU</strong> H&amp;P, CT AP, STMs 2 times</td>
<td>H&amp;P, CT AP, STMs 2 times</td>
<td>H&amp;P and STMs 2 times; CT AP once at 36 mo</td>
<td>H&amp;P and STMs once, no imaging</td>
<td>H&amp;P and STMs once, CT AP once at 60 mo</td>
<td>No specific recommendations</td>
</tr>
<tr>
<td><strong>NCCN</strong> H&amp;P q3-6 months; CT AP at 4-6 and 12 mo</td>
<td>H&amp;P and CT AP q6 mo</td>
<td>H&amp;P and CT AP q6-12 mo</td>
<td>H&amp;P annually; CT AP q12-24 mo</td>
<td>H&amp;P annually; CT AP q12-24 mo</td>
<td>CT not recommended beyond 5 y unless clinically indicated</td>
</tr>
</tbody>
</table>

Abbreviations: AP, abdomen/pelvis; AUA, American Urological Association; CSI, clinical stage I; CT, computerized tomography; CXR, chest x-ray; EAU, European Association of Urology; H&P, history and physical assessment; NCCN, National Comprehensive Cancer Network; STM, serum tumor biomarker.

*These recommendations are for CSI seminoma on active surveillance, or after adjuvant carboplatin or radiation.
subdiaphragmatic organs within the radiation field. Accordingly, adjuvant radiation therapy is no longer recommended as a preferred approach for CSI seminoma by NCCN, AUA, and EAU guidelines.

Chemotherapy remains an alternative to radiation for those unwilling or unable to undergo surveillance (Table 1). Several trials and reports of population-level treatment strategies have demonstrated that single-dose carboplatin reduces the risk of recurrence to approximately 5% in patients with CSI seminoma.\textsuperscript{1,2,5} Two doses of carboplatin have also been studied in a German registration trial, with reduction in relapse rate from 5% to 1.5% at 5 years.\textsuperscript{24} The majority (74%) of relapses occur in the retroperitoneum, which necessitates continued surveillance with axial imaging.\textsuperscript{25,26} Short-term treatment toxicities are mostly low grade and hematologic. It is still unclear whether similar long-term cardiovascular toxicities and/or risk of secondary cancers are seen among patients who receive adjuvant carboplatin compared with multi-cycle cisplatin-based chemotherapy.\textsuperscript{29}

Clinical stage II (CSI) and clinical stage III (CSIII) seminoma. Standard-of-care Treatment: Patients with regional lymph node involvement (CSI) can be treated with either radiation or IGCCCG risk-based multi-cycle cisplatin-based chemotherapy. The role of primary retroperitoneal lymph node dissection (RPLND) in treating these patients continues to expand; data supporting this approach are discussed in detail below. There are limited prospective randomized data to guide systemic treatment for CSI and CSIII seminoma, as most studies include patients with seminoma and nonseminomatous cancers, but 5-year progression-free survival (PFS) estimates approach 100% for patients with IIA disease and 87% for those with IIB disease treated with chemotherapy.\textsuperscript{15} Relapse rates in CSII disease treated with radiation are also stage dependent, with 4%-10% expected with IIA disease and 13%-26% expected with IIB disease. Generally, our preference is to treat patients who have CSI seminoma with nodules <3 cm with chemotherapy instead of radiotherapy, since patients who relapse after radiotherapy require chemotherapy, and having had both radiotherapy and chemotherapy triples the risk of second malignancies and cardiovascular disease compared to having had chemotherapy alone, where the risk is about 1.5-fold.\textsuperscript{27,29} Patients with CSIIb and bulky (>3 cm) RP nodal disease, patients with CSIIIC, and patients with CSIII should be treated with IGCCCG risk-based primary chemotherapy. For good-risk patients, 4 cycles of etoposide and cisplatin (EPx4) or 3 cycles of bleomycin, etoposide, and cisplatin (BEPx3) are first-line options.\textsuperscript{26,33} Individual factors should be considered when selecting between regimens: EPx4 avoids bleomycin toxicity (pneumonitis, Raynaud’s phenomenon) and is preferable in older patients, those with reduced kidney function, and those with lung disease, whereas BEPx4 is preferred for intermediate-risk patients.

In patients with advanced seminoma, management following chemotherapy is based on STMs and the size of residual masses on imaging. Among patients with normal STMs, masses <3 cm can be safely observed since there is only a 3% chance of viable disease in these lesions. The risk of viable seminoma increases to 27% in lesions >3 cm. Detection of residual disease in lymph nodes >3 cm can be improved through the use of PET imaging, which has an approximate- ly 95% negative predictive value.\textsuperscript{6} In patients with normal markers and >3 cm residual masses after chemotherapy, the recommendation is to wait 6 or more weeks post-treatment to pursue PET imaging to help decide on surgical consolidation. In patients with equivocal PET findings, PET can be repeated after several weeks. Percutaneous biopsy to guide treatment decisions can be considered in patients with equivocal PET scans or in those with unresectable residual masses. Post-chemotherapy, radical surgery is reserved for highly select cases in patients definitely determined to have viable cancer. Patients should be treated at high-volume centers with the goal of complete resection. There are significant risks of surgical morbidity and the need for adjunctive procedures due to the desmoplastic nature of post-chemotherapy seminoma and fibrosis. Among those treated with a complete surgical resection, if viable disease is found, 2 cycles of adjuvant therapy can be considered. Incomplete resection or progressive disease following surgery should prompt a complete course of salvage chemotherapy.

Treatment of relapse. Relapse after first-line chemotherapy is rare among patients with metastatic seminoma, but rates vary based on IGCCCG risk classification. A contemporary cohort of 2,451 patients was retrospectively pooled to reevaluate the original 1997 IGCCCG risk categories among patients treated with contemporary regimens. Among good- and intermediate-risk patients, 5-year PFS was 89% (95% CI 87-90) and 79% (95% CI 70-83), respectively.\textsuperscript{2} In a prospective study of 132 patients treated with a risk-adapted approach (EPx4 for good risk, VIPx4 for intermediate risk), 3-year PFS was 93% (range: 85%-97%) and 83% (range: 63%-93%), and 3-year OS was 99% and 87% for patients with good- and intermediate-risk seminoma, respectively.\textsuperscript{34}

To standardize nomenclature regarding relapse after first-line treatment, determine prognostic factors, and assess treatment effectiveness in this setting, the IPFSG pooled 1,594 patients from 38 centers worldwide for analysis.\textsuperscript{30} Patients with pure seminoma comprised 12.8% (n = 204) of this cohort. Factors predictive of 2-year PFS were assessed among patients with nonseminomatous germ cell tumor (NSGCT) and validated in patients with seminoma. Investigators found that histology type (seminoma vs NSGCT), primary site of disease (gonadal vs extragonadal), progression-free interval, initial response, AFP and hCG levels, and presence or absence of liver, bone, or brain metastases were independently associated with 2-year PFS. Post hoc analysis of patients with seminoma revealed 2-year DFS ranging from 75% in those designated “very low” risk to 25.9% among those at high risk.

Choice of salvage treatment regimen in these patients remains controversial. Among 80% (n = 1,594) of the initial IPFSG cohort who met criteria, effectiveness of high-dose chemotherapy (HDCT) with stem cell transplant was compared with conventional-dose chemotherapy.\textsuperscript{35} Improved PFS (HR 0.44, 95% CI 0.39-51) and OS (HR 0.63, 95% CI 0.56-0.75) were associated with HDCT when stratified on prognostic category. These findings differed from a prior flawed randomized study (IT-94)\textsuperscript{36} but corroborated the experience and approach at 2 high-volume institutions (Memorial Sloan Kettering Cancer Center and Indiana University). The TIGER Trial, a randomized phase III study, is assessing
the conventional-dose chemotherapy regimen of paclitaxel, ifosfamide, and cisplatin vs the HDCT regimen of paclitaxel plus ifosfamide followed by high-dose carboplatin plus etoposide with stem-cell support as initial salvage therapy and was expected to complete accrual in mid to late 2022.37

**Novel treatment strategies.** Increasing evidence of long-term toxicities associated with both chemotherapy and radiation has generated renewed interest in the role primary RPLND plays in metastatic seminoma localized to the retroperitoneum (Table 3). Two concurrent single-arm trials in the U.S. and Germany have explored progression-free and recurrence-free intervals after primary RPLND. The SEMS (Surgery in Metastatic Seminoma) trial is a prospective multicenter phase II study that aims to evaluate the efficacy of RPLND in treating early metastatic seminoma at 12 sites in the U.S. and Canada. Patients with isolated RP adenopathy (defined as 1 or 2 nodes 1-3 cm in size) were treated with open RPLND using a modified template. The primary outcome was 2-year recurrence-free survival. Preliminary results were reported at the 2021 American Society of Clinical Oncology Genitourinary Cancers Symposium for 55 patients (75% initial CSIIA-B vs 25% relapsed CSI). At a median follow-up of 24 months (range 8-52 months), 10 patients experienced recurrence. Recurrence was treated with standard chemotherapy regimens (BEPx3, EPx4) in 8 patients and repeat surgery in 2 patients. Within 1 year of surgery, 13% of patients experienced Clavien I-III complications. OS was 100%.38

PRIMETEST is a single-institution phase I/II study that enrolled 30 patients in Germany with either primary or relapsed (after single-dose carboplatin) RP node-positive (<5 cm) seminoma. This single-arm trial treated patients with either open or robotic unilateral template RPLND without planned adjuvant treatment.39 The most contemporary available data are from an interim analysis of the first 22 patients, presented at the American Society of Clinical Oncology symposium in 2019. Within 1 year of follow-up, 77% (n = 17) of patients were free from recurrence. Of the 5 patients who recurred, time to recurrence was approximately 5 months, and most (4 of 5) were “out of field.” SAkk 01/10 is a multicenter phase II single-arm study conducted by the German Testicular Cancer Study Group and the Swiss Group for Clinical Cancer Research that aims to de-escalate therapy for node-positive seminoma.40 The treatment regimen was single-dose carboplatin (AUC7) and node-directed radiation (30 Gy for IIA and 36 Gy for IIIB). The preliminary results of 116 patients were presented at the European Society for Medical Oncology congress in 2021. The cohort included 66% de novo CSII seminoma, and the rest experienced relapse with a median of 2 (range 1-8) lymph nodes in the retroperitoneum. The primary outcome, 3-year PFS, was 93.7% for all patients (95.2% in IIA, 92.6% in IIIB). Among the 7 patients who had a recurrence, all were outside the radiated regions and were treated successfully with standard chemotherapy. Significant (grade 3 or 4) thrombocytopenia and neutropenia occurred in 3.2% and 2.5% of patients, respectively. Long-term data are not yet available.

**FUTURE DIRECTIONS**

Role of miRNAs. miRNAs are small RNA molecules that play an important role in many biological and carcinogenic processes. Certain miRNAs are specifically expressed in embryonic stem cells and play a role in cell differentiation. This provided the basis for the initial exploration of their role in germ cell tumors. Several clusters have been discovered; to date miRNA-371-3, located on chromosome 19, has been the most widely studied. Compared to traditional STMs, miRNA371 appears to have superior sensitivity in patients with seminoma.8,41 This likely relates to the rarity of STM elevation in most patients with seminoma, while miRNA371 is expressed in 85% of patients with seminoma.8,42 Sensitivity also appears to increase with tumor size/burden, with R2= 0.69 indicating a moderately strong direct relationship. In patients

### Table 3. Attributes and results to date of PRIMETEST, SEMS, and SAKK 01/10 studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PRIMETEST (Albers et al49)</th>
<th>SEMS (Daneshmand et al80)</th>
<th>SAKK 01/10 (Papachristofilou et al29)</th>
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<td>Criteria</td>
<td>CSIIA or CSIIIB plus relapse after single-dose carboplatin</td>
<td>Isolated RP adenopathy (1 or 2 nodes) 1-3 cm in size</td>
<td>CSIIA or CSIIIB</td>
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<td>Enrollment goal</td>
<td>30 patients</td>
<td>55 patients</td>
<td>120 patients</td>
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<tr>
<td>Primary outcome</td>
<td>3-y progression-free survival</td>
<td>2-y recurrence-free survival</td>
<td>3-y progression-free survival</td>
</tr>
<tr>
<td>Secondary outcome(s)</td>
<td>Overall survival, quality-of-life, complication rates</td>
<td>Complications, treatment-free survival, adjuvant therapies, recurrence patterns</td>
<td>Time to progression, overall survival, patterns of progression, secondary malignancies</td>
</tr>
<tr>
<td>Preliminary/interim results</td>
<td>77% (17/22) patients free of recurrence at interim analysis Median time to recurrence 4.5 mo, 4/5 recurrences outside of template</td>
<td>Included: CSI n = 14, CSIIAB n = 41 2-y recurrence-free survival: 87%, median time to recurrence 8 mo</td>
<td>Included: CSIIA: 46, CSIIIB: 70; de novo: 76, relapsing: 40 3-y progression-free survival: 93.7% (95.2% for CSIIA, 92.6% for CSIIIB), median time to relapse 16.7 mo</td>
</tr>
</tbody>
</table>

Abbreviations: CSI, clinical stage I; CSIIA, clinical stage IIA; CSIIIB, clinical stage IIIB; RP, retroperitoneal; RPLND, retroperitoneal lymph node dissection; RT, radiotherapy.

*A trial includes only patients who have testicular seminoma and phase II disease and have completed accrual as of December 2021.*
Levels of miRNAs reflect the natural history of diagnosis and treatment in patients with CSI seminoma, as they are elevated before orchietomy, decrease following orchietomy, and rise at clinical relapse. Circulating miR-371a-3p has a half-life of less than 24 hours.43 Neither relative percent decline (from pre-orchietomy to post-orchietomy) nor absolute pre-orchietomy miRNA levels were associated with a higher risk of relapse, though studies to date to detect clinically significant differences have been underpowered.44 Modeling studies have demonstrated the potential for reduced costs and radiation exposure when using miRNA biomarkers instead of routine imaging. Since the kinetics of miRNAs are not yet well established, at present surveillance with imaging and classic STMs must continue to be used to prognosticate and/or detect relapse. The Southwest Oncology Group is currently enrolling patients into a prospective cohort study which aims to assess the role of miRNAs in predicting and determining relapse in patients undergoing active surveillance.

A small study demonstrated good discrimination for benign and viable seminoma in RPLND specimens among patients undergoing primary surgery for CSI or CSII disease, though only 4 patients included had pure seminoma in their orchietomy.45 In advanced seminoma, pre-treatment miRNA levels correlated strongly with S-stage but were not prognostic for PFS or OS.46 There may be utility in using miRNA to assess treatment response in advanced disease, as stepwise reductions in miRNA levels are seen after iterative cycles of chemotherapy. Similarly, increasing levels while on treatment may be an indicator of progression despite treatment.8 In a study of 4 patients with pure seminoma who relapsed after first-line chemotherapy, miRNA values were 10-fold higher at the time of relapse than during periods when disease was not evident.17

Role of molecular characterization. Alterations in the short arm of chromosome 12 have been established as a biological marker of germ cell tumors since the 1980s. However, classification of testicular germ cell tumors has historically been based on purely morphological features without consideration of cellular origin or molecular characteristics. This changed in 2016, when the World Health Organization adopted a new consensus term for a common cellular precursor entity, “germ cell neoplasia in situ (GCNIS),” and an updated classification system for testicular germ cell tumors based on whether tumors were derived from GCNIS precursor cells.48 The new system divides tumors into those that are non-GCNIS derived (type I and III) and those that progress from GCNIS (type II), a designation that aligns with molecular profiles, epidemiology, and outcomes.42,48,49 Most malignant germ cell tumors, including seminoma and those with mixed or nonseminoma components (embryonal, choriocarcinoma, yolk sac, and postpubertal type teratoma), are GCNIS related (type II). Type I tumors, prepubertal type teratoma and prepubertal yolk sac, and type III tumors (spermatocytic tumors) are derived from germ cells at a different stage of maturation and have unique pathogenesis.

In a cohort of 133 patients with mostly localized testicular germ cell tumors, unsupervised clustering analyses distinguished seminomas from NSGCT due to differences in protein, DNA methylation, mRNA, miRNA, and DNA copy number.42 Somatic mutational frequency also varied among histological subtypes with a median frequency of 0.5 mut/Mb. Three genes were found to be significantly somatically mutated in this analysis (KIT, 18%; KRAS, 14%, and NRAS, 4%), almost exclusively in seminoma and more so in patients with a history of cryptorchidism. Seminomas may be further differentiated by KIT-mutation status, as tumors lacking KIT mutations may be further differentiated into other NSGCT histological subtypes.

In addition to enabling granular classification, tumor sequencing may help elucidate how progression and treatment responsiveness vary among patients with advanced disease. There appears to be significant genomic heterogeneity between primary tumors and metastases, some of which may occur early and play a role in prognosis.10 Using the MSK-IMPACT sequencing platform, TP53 and MDM2 alterations were found to be associated with cisplatin-resistant tumors in a cohort of 180 patients, 30% of whom had pure seminoma. These alterations were associated with IGCCCG poor-risk classification, particularly those of NSGCT histology and mediastinal origin, but also predictive of adverse outcomes independent of the IGCCCG model. HDCT with stem cell transplant may overcome cisplatin resistance in a significant proportion of patients whose disease progresses, suggesting a growing role for genomic profiling of patients with advanced testicular cancer. The short-term clinical benefit of these findings for developmental therapeutics or targeted therapies remains to be seen, and several trials of targeted or immunological agents in advanced germ cell tumors are ongoing.

CONCLUSION

Current treatment paradigms for localized and advanced seminoma are effective in curing most patients. However, novel diagnostics and de-escalated treatment strategies may challenge these long-standing approaches in the near future.

DID YOU KNOW?

• Localized seminoma is the most common clinical situation encountered by physicians treating testicular cancer.
• The majority of patients with localized seminoma should be managed with close surveillance, as adjuvant treatments have not been shown to improve OS and may constitute overtreatment in many patients.
• Metastatic seminoma is highly curable with first-line chemotherapy regimens.
• Residual masses ≥3 cm following first-line chemotherapy should be evaluated with PET imaging at a minimum of 6–8 weeks after treatment. Post-chemotherapy surgery should be used for very select patients and should be performed at high-volume centers.
• Novel serum tumor markers like miRNA may improve the diagnostic paradigm for testicular cancer and result in more personalized risk-adapted treatment strategies.


1. What percentage of patients with clinical stage I seminoma will experience a relapse if managed with surveillance after orchiectomy?
   a. 0%-5%
   b. 15%-20%
   c. 50%-60%
   d. 100%

2. For patients with IGCCCG good-risk metastatic germ cell tumors, which of the following is not an accepted first-line treatment regimen?
   a. EPx4
   b. Single-agent carboplatin
   c. BEPx3
   d. VIPx2

3. The principal limitation of using currently available microRNA arrays in the management of testicular cancers is that these arrays
   a. Have low sensitivity for germ cell tumors
   b. Are produced by noncancerous tissue
   c. Have a very long half-life
   d. Cannot be used for detection of teratoma

4. The 2-year recurrence-free survival rate seen post-RPLND in the SEMS trial is approximately
   a. 87%
   b. 21%
   c. 64%
   d. 10%

5. A patient with pT2 seminoma who has a single 3 cm retroperitoneal lymph node in the landing zone and no other distant metastases is considered stage
   a. CSIIA
   b. CSIB
   c. CSIIB
   d. CSIII