Research and Reports in Urology

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REVIEW

Testicular Cancer: Diagnosis, Treatment, and Biomarker Advances

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Abstract: Recent advances in testicular cancer have led to a paradigm shift toward more precise, patient-centered care. Current challenges include the identification of accurate biomarkers, the management of incidentally detected small testicular masses (STM), the refinement of surgical techniques through robotic and modified-template approaches to minimize morbidity, and the prevention of overtreatment while maintaining oncological safety. Advanced molecular biomarkers, such as microRNA-371a-3p, currently demonstrate >90% sensitivity for detecting viable germ cell tumors, surpassing classical markers, yet remain limited by their inability to detect teratomatous components. Circulating tumor DNA have also emerged as a promising biomarker for minimal residual disease detection and personalized follow-up. The management of STMs is of growing interest, driven by the rising use of high-resolution scrotal ultrasonography and the consequent improvement in lesion detection. As most incidental findings are benign, this has prompted reconsideration of traditional radical orchiectomy as the standard intervention. STMs require careful evaluation that integrates imaging characteristics, clinical context, and intraoperative frozen section analysis to enable more tailored management. Given the high survival rates of testicular cancer, the avoidance of overtreatment and associated morbidity remains critical. Accordingly, contemporary strategies emphasize active surveillance for low-risk tumors, selective use of adjuvant therapy, and the adoption of minimally invasive surgical techniques. These advances, supported by improved imaging and biomarker profiling, facilitate more accurate patient stratification, balancing curative intent with preservation of quality-of-life.

Keywords: testis cancer, biomarker, diagnosis, treatment

Introduction and Background

Epidemiology

Testicular cancer, predominantly testicular germ cell tumors (TGCT), represents the most common malignancy among males aged 14–44 years.[1,2] Although globally rare, incidence demonstrates significant regional and ethnic variation.[3] In 2022, 72,031 new cases were reported with a global age-standardized incidence rate of 1.7 per 100,000 person-years.[4] Highest rates occurred in Western Europe (ASR=9.3) followed by Northern Europe (ASR=7.5), and Australia/New Zealand (ASR=7.0).[5] Incidence rates continue steady worldwide increase, including historically low-incidence regions such as Asia and Eastern Europe.[1,2] These trends underscore the necessity for continued research to enhance understanding, detection, therapeutic approaches, and survivorship outcomes.

Risk Factors

Multiple factors contribute to testicular germ cell tumor development, with genetic susceptibility demonstrating particular significance. Single-nucleotide polymorphisms account for approximately 44% of heritability,[6] while family history confers 4–8-fold increased risk.[7] Prior testicular germ cell tumor elevates contralateral tumor likelihood up to 12-fold.[8] Cryptorchidism represents the most consistent risk factor, associated with 4-fold risk elevation.[9] Infertility demonstrates

https://doi.org/10.2147/RRU.S511445
Received: 31 October 2025
Accepted: 4 January 2026
Published: 14 January 2026

nearly doubled risk (RR 1.86, 95% CI 1.41–2.45; p<0.001).[10] Additional risk factors include small testicular volume (<12 mL) and testicular microlithiasis.[11] Non-Hispanic white men demonstrate highest incidence rates, with peak occurrence between ages 25–35 years and secondary rise after age 80 years.[12,13]

Classification

TGCTs are categorized into seminomas (55–60%) and nonseminomatous germ cell tumors (NSGCTs) (40–45%), the latter including teratoma, embryonal carcinoma, choriocarcinoma, yolk sac tumor, and other trophoblastic tumors.[14] Seminomas typically grow slowly and are radiosensitive, whereas NSGCTs present more aggressively and often require multimodal therapy. Consistent with these features, ~85% of seminomas are diagnosed at clinical stage (CS) I, compared to about 60% of nonseminomas.[11,14,15]

Clinical Presentation

Testicular cancer most often (~90%) presents as a painless testicular mass, usually detected incidentally. A smaller portion of patients (~10%) report testicular pain, which may result from rapid tumor growth leading to infarction, intratesticular hemorrhage or less commonly, torsion. Other local symptoms including swelling, heaviness, atrophy or discomfort are less common.[11,14,16]

In 10–20% of cases, initial symptoms reflect metastatic disease. Thus, retroperitoneal lymph node involvement may cause abdominal masses, flank pain, gastrointestinal symptoms, or back pain. Some patients may develop varicocele from impaired venous return. Pulmonary metastases (~5%) may present with chest pain, dyspnea, cough, or hemoptysis.[15] Less common manifestations include gynecomastia (~2%) from elevated β-hCG, lower limb swelling from inferior vena cava (IVC) compression secondary to retroperitoneal lymph node metastases, neurological symptoms from brain metastases, or infertility.[15]

Current Challenges and Emerging Directions in TGCT Management

Despite excellent survival outcomes for TGCTs, several challenges persist in the care of these patients.

Early detection with current serum tumor markers, including alpha-fetoprotein (AFP), human chorionic gonadotropin (β-hCG), and lactate dehydrogenase (LDH), is limited by low sensitivity and specificity. Recently, circulating microRNAs (eg miR-371a-3p) have shown superior diagnostic performance.[17] However, further validation is needed before their adoption into routine clinical practice.

Overtreatment remains a concern in CS I disease, where excellent outcomes may be achieved with less intensive approaches. While platinum-based chemotherapy and radiotherapy are highly effective, their long-term toxicities warrant careful consideration, given the young age and long-life expectancy of most patients. Moreover, improved risk stratification tools are needed to better predict relapse and guide decisions on adjuvant therapy versus surveillance.[18]

Long-term survivorship also requires more attention. Late effects of the disease and/or its treatment, including neurotoxicity, hypogonadism, and secondary cancers, affect quality of life in many survivors, underscoring the need for long-term follow-up strategies to minimize toxicity and support recovery.[19] Finally, there is growing interest in personalized treatment guided by molecular profiling. Genomic studies have identified recurrent alterations and subtype-specific features, but their clinical utility, cost-effectiveness, and real-world impact remain uncertain.[20]

Diagnosis

Initial testicular cancer evaluation requires a comprehensive medical history investigation, including ascertaining if there is any history of cryptorchidism, prior orchidopexy, inguinal hernia repair, and family history of testicular malignancy. Subsequently, patients undergo systematic diagnostic and staging procedures.[11,16]

Clinical Examination and Initial Imaging

Physical examination encompasses scrotal inspection and palpation, as testicular cancer typically manifests as a palpable testicular mass. Abdominal, chest and neck evaluation should screen for suspicious lymphadenopathy.

Ultrasound constitutes the first-line imaging modality. High-frequency transducers (>10 MHz) with B-mode and color-Doppler are used to assess testicular morphology and vascularization, and confirm presence, location, and volume of masses. Solid, hypoechoic, vascularized intratesticular lesions are highly suspicious to represent a malignancy. Bilateral examination remains essential for additional lesion detection and risk factor assessment.[11,16]

Staging

In patients with suspected metastatic disease, staging with computed tomography of the chest, abdomen, and pelvis is recommended prior to orchiectomy. Abdominopelvic imaging remains essential for the identification of retroperitoneal lymph node metastasis, typically following predictable drainage patterns.[11,16]

Further cerebral magnetic resonance imaging and bone scintigraphy are required in patients with skeletal or central nervous system symptoms, or in those with poor-prognosis disease per International Germ Cell Cancer Collaborative Group criteria. In addition, brain imaging should be considered in the presence of extensive pulmonary metastases, pure choriocarcinoma, or β-HCG levels exceeding 5000 IU/L.[11,16]

Positron emission tomography (PET), including PET/CT and PET/MRI, is not indicated for initial staging of GCTs due to poor sensitivity and specificity, and inability to reliably detect teratoma. The only role for PET is in seminoma when masses >3 cm persist 6 to 8 weeks post-chemotherapy, offering high sensitivity and negative predictive value (<90%) to confirm complete response by excluding viable tumor.[21–24] Routine PET scanning is not recommended for NSGCT after chemotherapy because PET cannot reliably distinguish teratoma from necrosis and its sensitivity (59–70%) and specificity (48–92%) insufficient for decision making.[11,14,16,21]

Tumor Markers

Serum tumor markers are essential for diagnosis, staging, prognosis and monitoring of treatment response or relapse in testicular cancer. The three classical markers are AFP, β-HCG and LDH.

AFP is commonly elevated in NSGCT and should never be elevated in cases with pure seminomas. As AFP is not perfectly sensitive nor specific, false positives and elevations may occur due to other conditions like liver dysfunction.[25] In pure seminoma, elevated AFP should prompt suspicion for an undetected NSGCT component. β-HCG produced, by syncytiotrophoblasts, can be elevated in NSGCT as well as in seminomas.[14] LDH correlates with tumor burden but lacks specificity, as it may be elevated in various benign and malignant conditions due to its release from apoptotic cells. Overall, these serum tumor markers demonstrate limited sensitivity and specificity, with marker elevation occurring in only 15% of pure seminomas and 50% of non-seminomatous germ cell tumors at presentation.[14]

Tumor markers levels should be measured prior to orchiectomy and reassessed within 1 to 3 weeks after surgery. These values should be monitored until they normalize, in line with the biological half-lives of AFP (< 7 days) and β-HCG (<3 days). Persistent elevation or rising levels of tumor markers after orchiectomy suggest the presence of metastatic disease.[11,16]

These markers remain essential although they may also be elevated in other malignancies such as liver, stomach, or pancreatic cancer, or in benign conditions such as marijuana use or viral hepatitis.[25,26] Novel immunohistochemical markers have been investigated for diagnostic use, while recent research has highlighted circulating microRNAs as promising emerging biomarkers in testicular cancer.

Biomarkers

Rationale for New Biomarkers in Testicular Cancer

Despite high cure rates, TGCT management lacks reliable biomarkers. The classic serum tumor markers (AFP, β-hCG, LDH) have significant limitations, with elevations in only ~50–60% of TGCTs at initial diagnosis.[27] This limited sensitivity and specificity necessitates frequent imaging, exposing patients to unnecessary radiation and potential psychological distress. Therefore, more accurate biomarkers are needed to enhance risk stratification and monitoring, particularly for early metastasis or relapse detection, CS I risk stratification, post-chemotherapy residual tumors assessment and chemoresistance identification.[28]

Conventional and Tissue Biomarkers (Histologic Markers)

Traditional serum markers (AFP, β-hCG, LDH) remain important but frequently underperform. Tissue biomarkers such as isochromosome 12p [i(12p)], placental-like alkaline phosphatase (PLAP), OCT3/4, and CD30 are valuable for confirming TGCT histology. Isochromosome 12p is notably prevalent in invasive TGCTs and serves as a hallmark diagnostic feature but is not routinely used as a circulating biomarker.[29] PLAP is one of the earliest identified immunohistochemical markers for TGCTs, demonstrating strong membranous staining in 95–100% of seminomas and up to 64% of nonseminomatous tumors. However, its limited specificity has reduced its diagnostic reliability.[30] Similarly, OCT3/4, a pluripotency-associated transcription factor, is consistently expressed in pre-invasive germ cell neoplasia in situ (GCNIS), seminomas, and embryonal carcinomas, although its specificity may be limited by occasional expression in non-germ cell tumors and normal adult stem cells.[31]

A key limitation of these tissue-based markers is their reliance on surgical or biopsy specimens. Since they cannot be measured in blood, they are not suitable for dynamic monitoring of disease status, relapse detection, or treatment response. This limits their clinical utility in surveillance and real-time decision-making.

MicroRNAs as Emerging Biomarkers

MicroRNAs (miRNAs) are the most promising new serum biomarkers for TGCTs. These small non-coding RNAs regulate gene expression and are abundant in most GCT histologies, except teratoma.[17,32] The best studied, miR-371a-3p, is nearly absent in normal adult tissues but highly expressed in malignant TGCTs (both seminomas and non-seminomas).[33]

Numerous studies confirm miR-371a-3p's superior diagnostic performance compared to traditional markers, with sensitivity and specificity exceeding 90% in many studies.[32,34] Its limitation is poor detection of pure teratomas or GCNIS.[32] While one study suggested combining miR-371a-3p with miR-375 may overcome the inability to detect teratoma, the study only had 100 patients with teratoma and has not been validated by others.[35]

Clinically, miR-371a-3p supports early relapse detection, risk stratification, and assessment of post-chemotherapy residual masses. Prospective studies demonstrate that serum miRNA levels correlate with tumor burden, providing an ability to detect microscopic metastases earlier than imaging and traditional markers, helping guide adjuvant therapy decisions.[17] In the first study dedicated to small testis masses, Chavarriaga et al, showed plasma miRNA 371a-3p could discriminate between benign and malignant small testis masses (AUC 0.93).[36]

International guidelines recognize miRNA biomarkers as emerging tools but recommend further prospective validation before routine clinical adoption.[37] Key steps towards standardization of testing (RNA isolation kits, PCR platforms, positivity thresholds) are required prior to broader clinical use and regulatory approval. If available, clinicians should interpret miRNA results in context with imaging and pathology and remain aware of its caveats (eg teratoma invisibility).

Circulating Tumor DNA: A Promising Novel Biomarker

Circulating tumor DNA (ctDNA) is another novel biomarker under investigation in TGCTs. It consists of tumor-derived DNA fragments in blood (cell-free DNA) released by tumor cells and detected with sensitive methods such as digital PCR for hotspot mutations and next-generation sequencing (NGS).[34]

Although ctDNA analysis is well-established in several malignancies (eg bladder), its application in TGCTs is still being defined. Early evidence shows detectability in advanced disease, correlating with tumor burden and predicting relapse even when traditional serum markers are negative.[38] For example, an initial study in TGCT reported ctDNA detection with ~88% sensitivity and ~97% specificity, and ctDNA levels correlated with tumor stage (including detection in some patients who had normal conventional serum markers).[39] Several groups have presented preliminary data which confirmed a high proportion of TGCT patients shed ctDNA. In one series of 35 patients, ctDNA was detectable pre-orchiectomy in 92% of men with CS I disease and 100% of those with CS II–III.[40] Another small series demonstrated that in patients with undetectable ctDNA after chemotherapy, there were no observed relapses.[41]

A notable limitation, shared with miRNA, is unreliable identification of teratoma. There have been no studies directly comparing novel biomarkers such as miRNAs and ctDNA. A systematic review and meta-analysis suggested that

miRNAs outperformed ctDNA due to slightly superior sensitivity with similar specificity.[42] Further research comparing and/or combining novel biomarkers is warranted.

Challenges include detecting low-volume disease, and standardizing panels for characteristic genetic alterations. Although promising, ctDNA testing in testicular cancer remains experimental, requiring further standardization and validation before clinical integration.

Circulating Tumor Cells

Circulating tumor cells (CTCs) are another emerging liquid biopsy approach in TGCTs. Shed from clonal populations within the primary tumor, they may contribute to metastasis.[43] In a prospective study by Nastaly et al, CTCs were detected in ~18% overall, rising to 41% in metastatic disease and 100% in chemo-refractory tumors.[44] While CTCs are associated with aggressive disease and poor prognosis, their clinical utility remains limited. Detection is technically challenging, with sensitivity often below 60%.[45] Moreover, CTC levels do not consistently reflect tumor burden, particularly in patients with minimal disease.[34] As a result, despite their biological relevance, CTCs are not currently applicable for routine clinical use in TGCT management.

The Small Testis Mass Dilemma

Small testicular masses are increasingly detected in 1–4% of scrotal ultrasounds.[46,47] Ultrasound demonstrates 98–100% sensitivity for tumor detection but cannot reliably differentiate benign from malignant lesions.[46–48] The presence of a small testicular mass warrants careful evaluation, as normal serum tumor markers do not exclude an underlying malignancy.[15] Incidentally discovered, non-palpable small testicular masses demonstrate benign pathology in up to 80% of cases.[47] Tumor size serves as one predictive parameter: benign likelihood approaches 100% for lesions <3mm and approximately 70% for <10mm.[49] Staudacher et al identified <13.5 mm threshold with 53% sensitivity and 85% specificity.[50] Tumor volume >2.8 cm^3 predicted malignancy with 83% sensitivity and 89% specificity.[51]

Concern regarding missed malignant germ cell tumors in small testicular masses was analyzed by Pratsinis et al in multicenter testicular cancer registry.[52] Among 849 orchiectomies, 25 involved small testicular masses (<10 mm). Five presented with metastases at diagnosis and two relapsed during follow-up.[52] These findings challenge assumptions that small size equates to low risk. However, this study included only orchiectomy patients, potentially overestimating risk. In surveillance series reflecting typical management, only 2 of 286 patients developed metastatic disease.[47]

Small testicular mass management presents a clinical dilemma between oncological safety and overtreatment prevention. Testis-sparing surgery provides histological diagnosis while preserving function. Intraoperative frozen section analysis demonstrates high sensitivity and specificity preventing unnecessary radical orchiectomy.[53,54] Current guidelines support considering testis-sparing surgery in cases of bilateral tumors, solitary testis tumors, or small suspicious lesions requiring testicular preservation.[11,16]

Chavarriaga et al proposed orchiectomy criteria including growth rate >1–3 mm annually, size doubling, abnormal tumor markers, metastases, and patient preference.[47] AS eligibility encompasses masses <2 cm, no undescended testis history, no personal or family testicular cancer history, absence of calcification, and negative markers.

Serum miR-371a-3p is a highly accurate biomarker (>90% sensitivity/specificity) for detecting viable non-teratomatous GCTs also in small testicular mass, outperforming conventional markers (AFP, β-hCG, LDH).[36] Recent studies have investigated microRNA roles in synaptic and memory regulation, suggesting future small testicular mass management may increasingly involve targeting microRNA pathways.[15,32,36]

Treatment

TGCT management is guided by CS at presentation, with therapeutic strategies ranging from AS to multimodal interventions including surgery, chemotherapy, and radiotherapy. The treatment strategy is determined by tumor histology, metastatic disease presence, patient comorbidities, and adherence to surveillance protocols. Stage-specific management approaches for CS I–III follow standardized algorithms. Regardless of disease stage, all patients require comprehensive fertility preservation counseling with sperm banking offered prior to treatment initiation, as therapeutic interventions may impair spermatogenesis. Treatment options and procedure are shown for each CS in Figures 1–5.

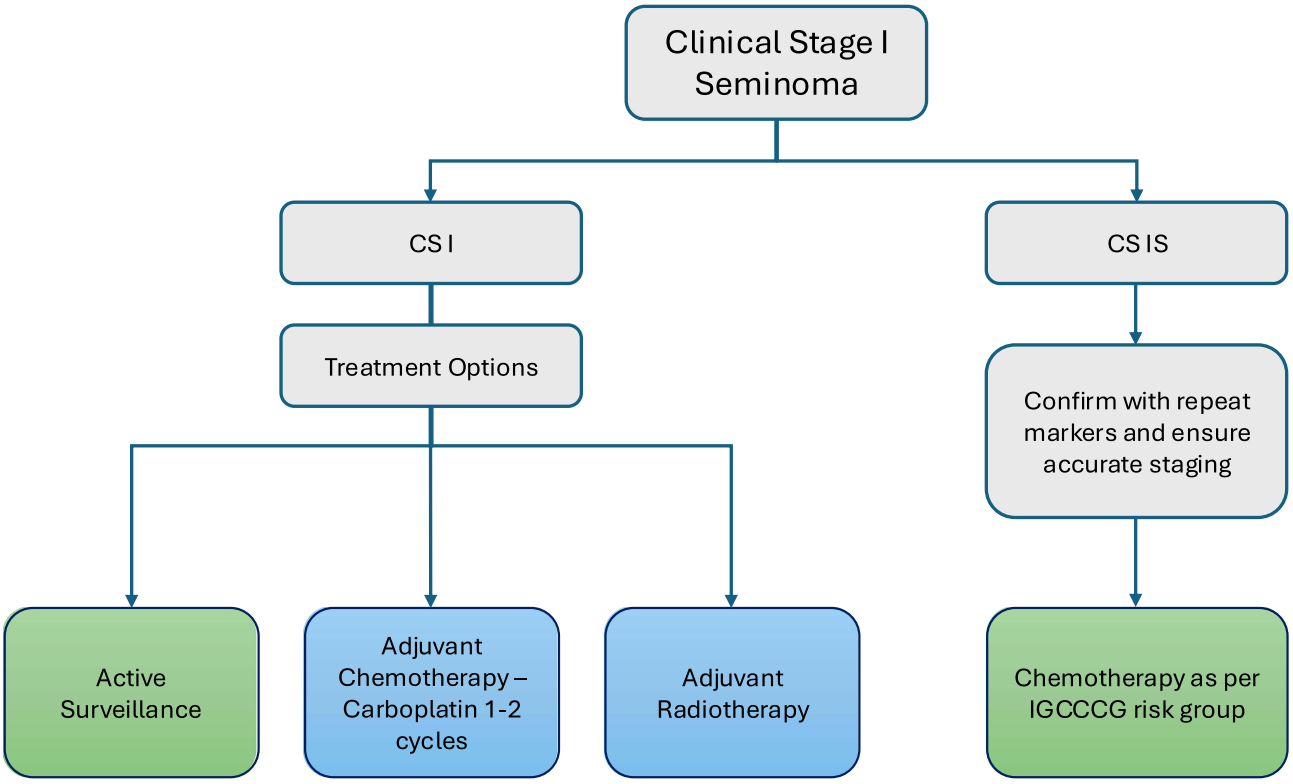

Figure 1 Treatment options and procedure for Clinical Stage I Seminoma.
Abbreviations: CS, clinical stage; green, preferred treatment option, blue alternative treatment option.

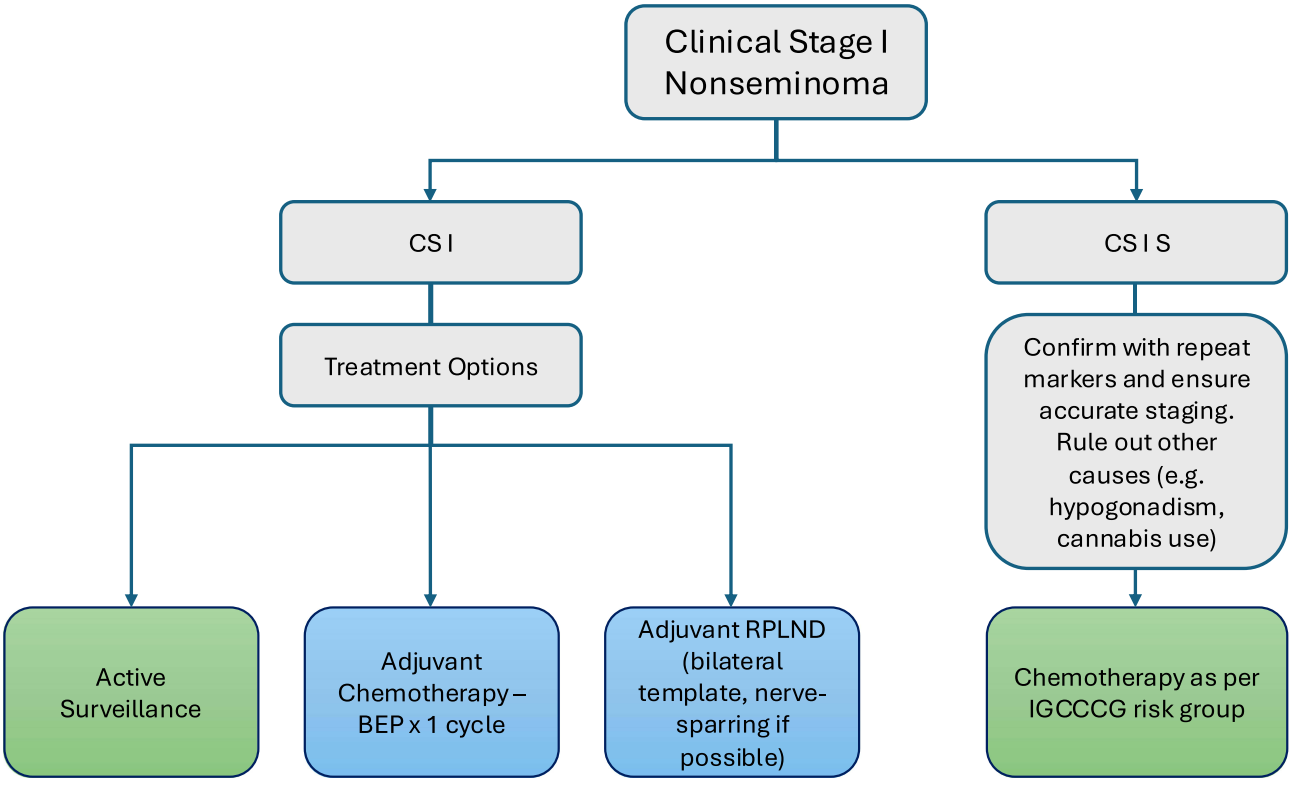

Figure 2 Treatment options and procedure for Clinical Stage I Nonseminoma.
Abbreviations: CS, clinical stage; RPLND, retroperitoneal lymph node dissection; IGCCG, International Germ-Cell Cancer Collaborative Group; BEP, Bleomycin; Etoposide and Cisplatin; green, preferred treatment option, blue alternative treatment option.

https://doi.org/10.2147/RRU.S511445

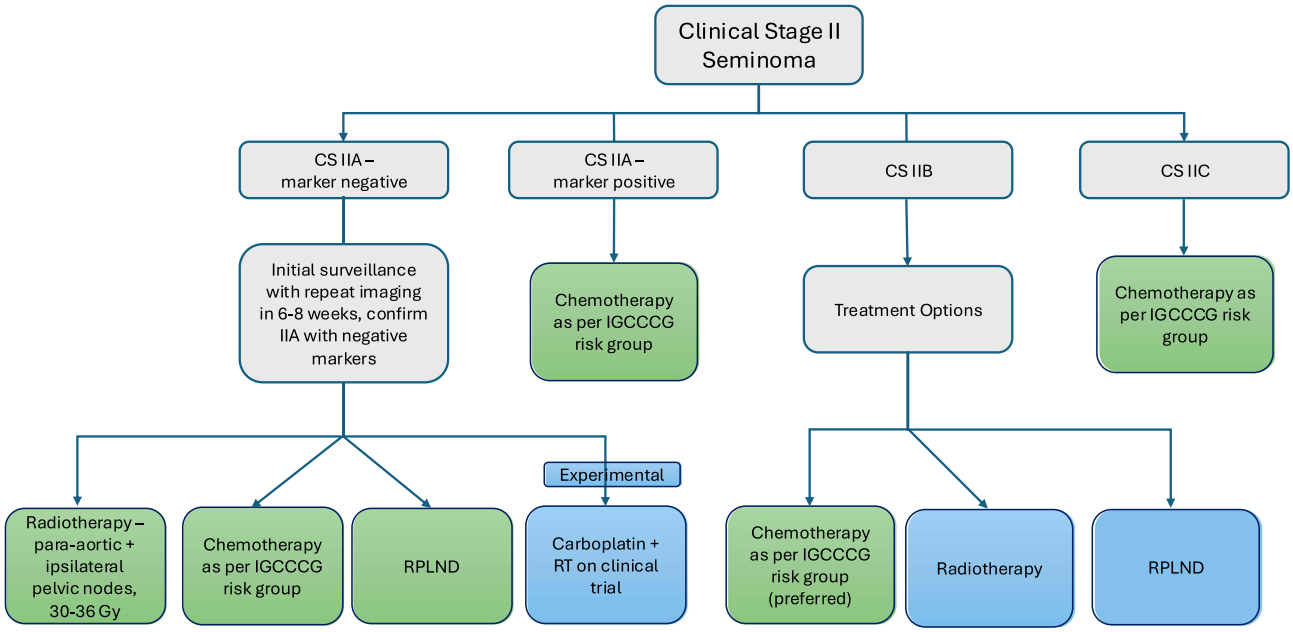

Figure 3 Treatment options and procedure for Clinical Stage II Seminoma.
Abbreviations: CS, clinical stage; RPLND, retroperitoneal lymph node dissection; IGCCG, International Germ-Cell Cancer Collaborative Group; Gy, Gray; green, preferred treatment option, blue alternative treatment option.

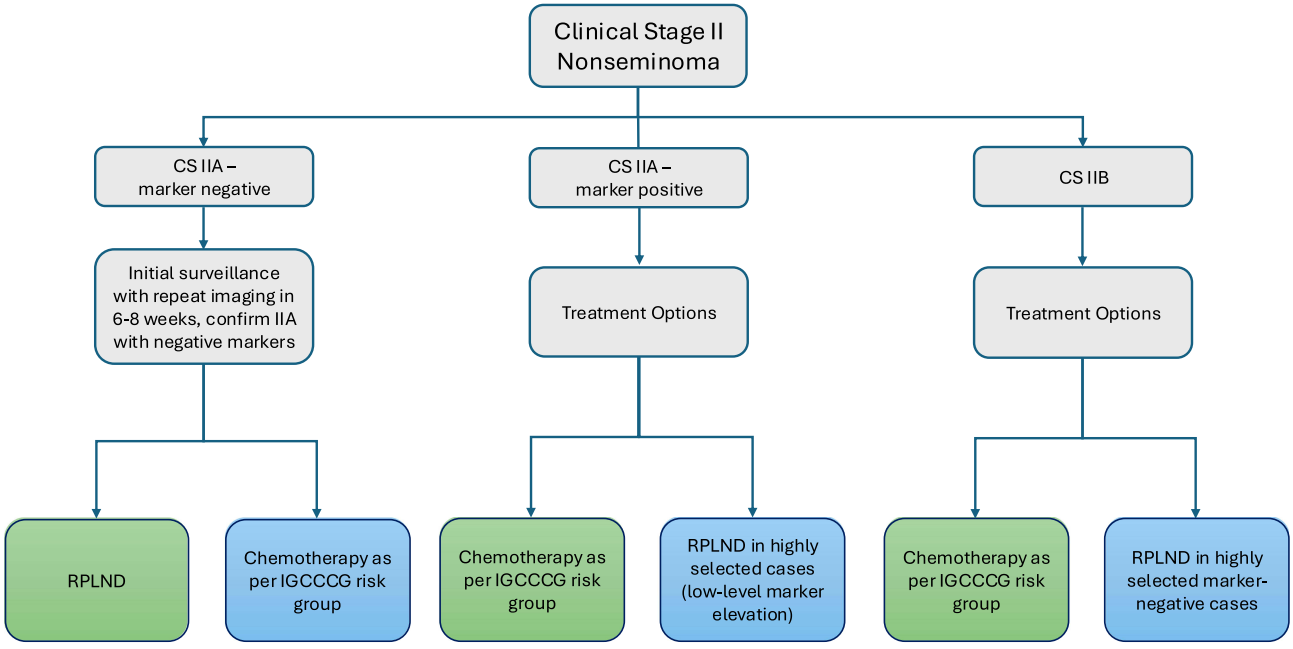

Figure 4 Treatment options and procedure for Clinical Stage II Nonseminoma.
Abbreviations: CS, clinical stage; RPLND, retroperitoneal lymph node dissection; IGCCG, International Germ-Cell Cancer Collaborative Group; green, preferred treatment option, blue alternative treatment option.

Orchiectomy

Radical inguinal orchiectomy represents the initial therapeutic procedure, providing histopathological diagnosis and definitive localized disease treatment. The approach encompasses complete testis and spermatic cord removal up to the internal inguinal ring via inguinal access.[16]

https://doi.org/10.2147/RRU.S511445

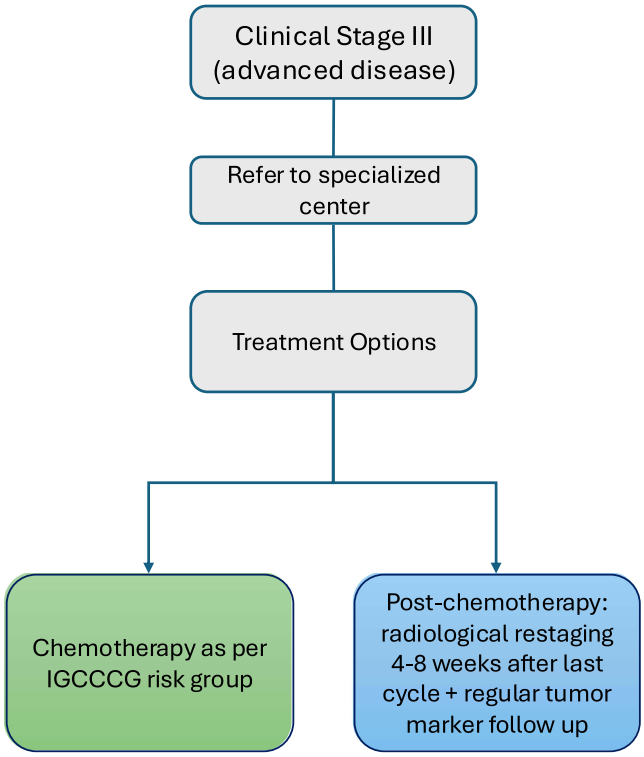

Figure 5 Treatment options and procedure for Clinical Stage III/Advanced Disease.
Abbreviation: IGCCG, International Germ-Cell Cancer Collaborative Group; green, preferred treatment option, blue alternative treatment option.

All patients require comprehensive testicular prosthesis counseling.[55] Preferentially, the prothesis is inserted concurrently with the orchiectomy as the tract and pocket are already developed.[56,57] Alternatively, a prosthesis can be placed as a separate procedure. Both approaches have low complication rates.[58]

In selected cases with significant metastatic disease at presentation and when the histology can be inferred from marker patterns (eg elevated AFP, or HCG >5000), or when a metastatic biopsy has confirmed histology, radical orchiectomy may be deferred to allow immediate primary chemotherapy.[59]

Active Surveillance

AS is the preferred management for CS I seminoma and NSGCT following orchiectomy, achieving nearly 100% cancer-specific survival through rigorous follow-up while avoiding overtreatment.[60–62] Surveillance protocols include scheduled cross-sectional imaging, tumor marker monitoring, and clinical assessments at standardized intervals for early relapse detection and timely salvage.[11,16] Relapse occurs between 12–20% of seminoma and 17–40% of NSGCT cases, respectively, mainly within the first two years and typically at retroperitoneal sites.[16,63]

In CS I seminoma, despite larger tumor size, rete testis invasion, and lymph vascular invasion being associated with increased relapse probability, AS remains the recommended strategy. Alternatively, single-cycle carboplatin may be used as adjuvant therapy in unsuitable patients.[11,64]

Retroperitoneal Lymph Node Dissection

Retroperitoneal lymph node dissection (RPLND) is a surgical approach used in selected patients CS II and rarely in CS I. RPLND constitutes the treatment of choice in patients with persistent retroperitoneal disease following chemotherapy or recurrence after initial surveillance.[11,16,65] Surgical access is typically achieved through a midline laparotomy and all lymphatic tissue from the renal hilum to the common iliac vessels is excised.

Primary Retroperitoneal Lymph Node Dissection

Primary RPLND provides staging information and therapeutic control for selected patients.

Primary Retroperitoneal Lymph Node Dissection in CS I

In CS I disease, primary RPLND is rarely indicated and is reserved for highly selected NSGCT patients with teratomatous elements in the histology or contraindications to chemotherapy or for those who have relapsed in the retroperitoneum after surveillance for CS I.[11]

Primary Retroperitoneal Lymph Node Dissection in CS II - Seminoma

RPLND constitutes a treatment alternative to chemotherapy and radiotherapy in CS II seminoma, mitigating long-term toxicities associated with conventional therapies.[11,15] Although chemotherapy and radiotherapy achieve 5-year progression-free survival rates of 87–95%, they are associated with risks of cardiovascular disease, metabolic syndrome, and secondary malignancy.[66,67] In contrast, primary RPLND has limited long-term morbidity, with ejaculatory dysfunction in approximately 7%, as the primary concern.[68]

Thus, the SEMS trial evaluated RPLND in low-volume CS II disease, reporting 2-year relapse-free survival of 81% with 100% cancer specific survival at two years.[69] Similarly, the PRIMETEST trial, enrolling CS IIA/IIB seminoma patients with retroperitoneal nodes <5 cm, reported 32-month progression-free survival of ~70% with 100% overall survival following successful salvage.[70] The CORTRIMS trial, similar in design to PRIMETEST and SEMS, documented ~10% recurrence rate at a median follow-up of 21 months.[71] These findings suggest primary RPLND as a safe and efficacious option with reduced long-term treatment burden in selected limited-volume CS II disease. However, primary RPLND remains investigational in this setting, and extended follow-up is required to clarify retroperitoneal and systemic relapse risks.

Primary Retroperitoneal Lymph Node Dissection in CS II - NSGCT

Primary RPLND constitutes a treatment option for patients with limited retroperitoneal disease (either de novo, or relapsed after CS I surveillance), and normal markers.[63] Relapse rates following primary RPLND are ~10–20% for pathological CS IIA and 20–35% for pathological CS IIB.[72,73] Hamilton et al reported a 27% relapse rate after primary RPLND for those with retroperitoneal relapse after CS I surveillance.[63] Though positive markers have generally been considered a contraindication to RPLND, a study from Princess Margaret Cancer Centreof 65 patients with elevated markers undergoing primary RPLND showed a relapse rate of 25% and a cancer-specific survival rate of 96%.[74]

Post-Chemotherapy Retroperitoneal Lymph Node Dissection

Post-chemotherapy RPLND remains essential in the management of patients with residual retroperitoneal metastases following chemotherapy for NSGCT, with approximately one-third of patients demonstrating residual retroperitoneal masses with teratoma or viable tumor following chemotherapy.[75] According to current guidelines, retroperitoneal residual mass management depends on primary histology. NSGCT masses <1 cm have a relapse risk <10% and should undergo observation, while masses >1 cm typically require resection via nerve-sparing RPLND. RPLND is recommended typically 6–8 weeks after completion of the chemotherapy.[11,16,75]

Post-chemotherapy RPLND is selectively used in SGCT based on mass size and imaging characteristics. Masses <3 cm should undergo observation as the risk of viable tumor is low, whereas masses >3 cm warrant FDG-PET/CT evaluation, with resection considered for persistent masses demonstrating significant FDG activity.[11,16]

Post-chemotherapy resection patients with necrosis or teratoma undergo observation, whereas viable germ cell tumor detection may warrant adjuvant therapy.

Subsequent relapses require management based on prior treatment and timing: early relapse (<2 years) following first-line therapy favors clinical trial enrollment, chemotherapy, and surgical resection when feasible; late relapse (>2 years) is primarily managed surgically when resectable, with chemotherapy or trial enrollment reserved for unresectable disease.[11,16]

Surgical Strategies and Technical Considerations in RPLND

Primary surgical objectives encompass definitive cure while preserving functional integrity and minimizing long-term morbidity in young patient populations.

Open RPLND remains the reference technique for complex surgical cases, providing superior exposure and tactile feedback. Robotic RPLND demonstrates increasing acceptance for selected low-volume cases in high-volume centres, achieving reduced hospitalization and decreased blood loss with comparable oncological outcomes.[76–78] However, robotic approaches correlate with prolonged operative times, elevated costs, and, in some series higher incidence of chylous ascites.[76,77]

Using nerve-sparing surgical techniques, antegrade ejaculation is preserved in 80–95% of cases in primary RPLND and ~90% of cases in post-chemotherapy RPLND.[79–81] Right-sided tumor location and tumor size >5cm constitute negative prognostic factors for ejaculatory function recovery.[82]

Unilateral template dissection achieves 92% recurrence-free survival with in-field recurrence rates below 2% and major complication rates of only 1–2%. Ejaculatory function preservation exceeds 90% with unilateral nerve-sparing approaches compared to 30–40% with bilateral non-nerve-sparing techniques.[80,82–85] Post-chemotherapy RPLND carries an elevated complication risk (intraoperative ~15%, postoperative ~25-45%) and retrograde ejaculation rates of 21–75% and 2–15% for bilateral and unilateral approaches, respectively.[86–89]

Chemotherapy

Chemotherapy in CS I - Seminoma

For patients with CS I seminoma who decline surveillance or for whom it is deemed unsuitable, chemotherapy with 1 or 2 cycles of carboplatin is recommended. The MRC TE19 trial, which randomized patients to receive either RT or one cycle of carboplatin, demonstrated the non-inferiority of single-dose carboplatin compared with RT, with similar RFS rates at 5 years (96% vs 95% for RT and carboplatin respectively).[90,91] Two cycles of adjuvant carboplatin show similar relapse reduction,[92] however, due to lack of comparative randomized data one cycle remains the standard.

Chemotherapy in CS I - NSGCT

In patients with CS I NSGCT, where surveillance is not the preferred approach, a single cycle of BEP is considered the standard chemotherapy option. This is based on the UK single-arm 111 study, which demonstrated a relapse rate of 3% and one death across 49 months of follow-up in patients with LVI receiving one cycle of BEP.[93]

Chemotherapy in CS IIA/IIB Seminoma

Chemotherapy with three cycles of bleomycin, etoposide, and cisplatin (BEPx3) or four cycles of etoposide and cisplatin (EPx4) are the standard treatment option for CS IIA and CS IIB (lymph nodes <3cm) seminoma, along with RT. To date, no trials have compared the oncologic or toxicity benefits of these treatment modalities head to head. However, a meta-analysis found both treatments effective in reducing recurrence and disease-specific survival approaching 100%.[94,95] CS IIB patients with bulky disease (lymph nodes >3cm) are thought to be at higher risk of distant recurrence and, thus, chemotherapy (BEPx3 or EPx4) is recommended over RT.[16,96]

Given the impact of long-term toxicity and late effects for survivors associated with chemotherapy, the SEMITEP nonrandomized Phase 2 trial investigated de-escalating chemotherapy in 98 patients with IGCCCG good prognosis.[97] Specifically, after EPx2, patients who had negative FDG-PET/CT received one cycle of carboplatin, while those with positive FDG-PET/CT received two additional cycles of EP. Patients experienced comparable PFS at three years (90% with EPx4, 91% with carboplatin x1), reported lower rates of neuropathy and avoided bleomycin-related toxicity. However, this strategy has the drawback of diminishing the natural prognostic separation, as patients with negative PET scans (those with the best prognosis) end up with outcomes similar to those with positive scans (those with a poorer prognosis).

Chemotherapy in CS IIC/III - Seminoma

Patients with advanced GCT should be referred for consultation at an experienced center.[65] The first-line chemotherapy options for patients with advanced metastatic GCT are based on the IGCCCG risk classification, which is determined by histology, site of primary disease, and tumour marker elevation (AFP, β-HCG, and LDH) after orchiectomy. Patients with CS IIC, IIIA and IIIB seminoma are classified as IGCCCG good-prognosis and should receive BEPx3 or EPx4.[98–100] CS IIIC is considered intermediate-risk, and patients should receive BEPx4 or VIPx4.[65]

Chemotherapy in CS IIC/ III - NSGCT

Recently, IGCCCG survival rates for NSGCT were updated and demonstrated improved five-year OS across all groups (96%, 89%, and 67% for good, intermediate, and poor risk, respectively).[101] Good-risk treatment, as previously covered, consists of BEPx3 or EPx4. Patients with intermediate-risk and high-risk disease should be treated with BEPx4 (recommended) or VIPx4 for patients at increased risk of bleomycin-related complications.[16]

Treatment of Relapsed Disease

Relapse remains potentially curable but requires risk-adapted salvage therapy in experienced centres. CS I seminoma relapsing after adjuvant carboplatin and confined to the retroperitoneum can be treated with radiotherapy or cisplatin-based chemotherapy.

Extra-retroperitoneal relapse and relapse after locoregional therapy requires management as de novo metastatic disease per the IGCCCG risk classification.[65]

For relapse after first-line cisplatin-based chemotherapy (≥3 cycles), treatment follows the International Prognostic Factors Study Group (IPFSG) scoring.[14,102] Conventional-dose salvage chemotherapy (CDCT) with paclitaxel–ifosfamide–cisplatin (TIP) or vinblastine–ifosfamide–cisplatin (VeIP) plus GCSF is preferred for very low- and low-risk disease. High-dose chemotherapy (HDCT) with carboplatin and etoposide followed by autologous stem-cell rescue represents standard for intermediate- and high-risk relapse and after CDCT failure, with non-randomized data showing improved survival in these groups.[65,103] The international Phase 3 TIGER clinical trial (NCT02375204), completed recruitment in 2022, will prospectively compare HDCT versus CDCT to determine the best approach to salvage therapy.[104]

Patients with a second or subsequent relapse after CDCT should receive HDCT if not previously given. Those relapsing post-HDCT or ineligible for it may receive palliative regimens such as paclitaxel, gemcitabine, or oxaliplatin, although long-term remission remains rare. Complete surgical resection of isolated chemo-refractory or late (>2 years) relapses is crucial, as such disease is often chemo resistant but potentially curable. All salvage therapy should be centralized in high-volume germ cell tumour programs, with early sperm banking and consideration of clinical trials encouraged.[16,65,103]

Radiotherapy

Radiotherapy in CS I - Seminoma

Seminoma is a highly radiosensitive tumor, establishing radiotherapy as a critical therapeutic modality. In CS I seminoma, adjuvant RT was historically utilized to reduce recurrence risk. However, surveillance is now preferred as 80–85% of patients achieve cure with orchiectomy alone.[65,68] Moreover, nearly all relapses remain salvageable, while RT carries potential acute and long-term toxicities, which is particularly relevant in populations with excellent survival outcomes.[11,15,16]

When indicated for CS I seminoma, para-aortic lymph nodes require 20 Gy in 10 fractions. Fossa et al demonstrated that patients with intact inguinal drainage receiving para-aortic-only versus combined para-aortic and inguinal RT showed equivalent recurrence rates with reduced toxicity in the para-aortic-only cohort.[105] Para-aortic-only treatment requires pelvic surveillance for nodal recurrence, whereas combined para-aortic and ipsilateral pelvic treatment (dog-leg or modified dog-leg) eliminates requirements for routine pelvic monitoring.

The MRCTE18 trial established equivalent recurrence rates with improved tolerance at 20 Gy versus 30 Gy.[106] Post-adjuvant RT relapse rates range 1–5%, predominantly occurring outside irradiated fields.[105,107,108] Most relapses manifest within 2 to 3 years, though late presentations are documented.[107]

Radiotherapy in CS II - Seminoma

RT is endorsed by the current guidelines as an option for CS IIA and non-bulky CS IIB seminoma.[11,16,65] Non-bulky definitions remain unstandardized; while some guidelines suggest RT contraindication for lymph nodes ≥3 cm, contemporary data demonstrate favorable outcomes following radiotherapy for lymph nodes ≤5 cm (encompassing all CS IIB disease). Princess Margaret Cancer Centre retrospective data revealed 5-year relapse rates of 12% for CS IIA and 5% for CS IIB disease following RT, which were statistically equivalent to chemotherapy outcomes.[109]

CS II disease treatment encompasses RT of para-aortic and ipsilateral pelvic lymph nodes, incorporating left gonadal vessel nodal regions for left-sided tumors.[96,110] This modified dog-leg configuration extends from T11/T12 superior margins to ipsilateral acetabular superior borders.[110] Gross disease typically receives 30–36 Gy total dose for CS IIA/B presentations. Standard prescription delivers 25 Gy in 20 daily fractions to modified dog-leg volumes, with additional 10 Gy to gross lymphadenopathy, though randomized dose-fractionation validation remains absent.[96,110]

The SAKK 01/10 Phase II randomized trial investigated reduced-volume "involved node radiotherapy (INRT)", incorporating gross lymphadenopathy plus margin without elective nodal treatment, combined with single-cycle carboplatin for de-escalated chemoradiotherapy.[111] Primary endpoint achievement (95% 3-year progression-free survival) failed, though 3-year progression-free survival reached 94% with favorable short-term toxicity profiles. Long-term oncologic and toxicity outcomes, including combination therapy effects, remain pending evaluation. SAKK 01/18 represents ongoing investigation combining cisplatin/etoposide with INRT as potential therapeutic optimization over SAKK 01/10 protocols.

Treatment Considerations and Toxicity of Radiotherapy

RT for seminoma requires 3-dimensional conformal techniques rather than intensity-modulated RT to minimize hypothetical secondary malignancy risk from increased low-dose exposure.[112,113] Proton therapy may offer potential for further low-dose splash reduction.[114–117] Treatment protocols require empty bladder positioning, contralateral testicular shielding with clamshell protection, and penile positioning outside treatment fields.[110] Sperm banking should precede radiotherapy if not completed pre-orchiectomy.

RT is generally well-tolerated, with acute toxicities including nausea, emesis, and fatigue.[118] Late toxicities include secondary malignancies, cardiac events (perhaps less relevant in modern era with adjustment of superior field border), and infertility.[118,119] Analysis of 10,534 seminoma patients revealed overall relative risk of 2.0 (95% CI 1.8–2.2) for secondary malignancy, with elevated risks for gastric, colorectal, pancreatic, prostatic, bladder, and other cancers.[120]

Prognosis, Surveillance and Management

Prognosis is determined by CS, incorporating primary tumor pathological features, metastatic extent, and post-orchiectomy serum tumor marker levels.[121]

In CS I Seminoma patients reach nearly 100% survival. Post-orchiectomy relapse occurs in 15–30%.[122] Risk factors include tumor size >4 cm and rete testis invasion, with 5-year relapse-free survival ranging 87–96% (≤4 cm) versus 73–83% (>4 cm).[123,124] Wagner et al reported 16% overall relapse rate, ranging from 6% (no risk factors) to 62% (four factors).[125] Boormans et al proposed refined stratification: low-risk (8% relapse), intermediate-risk (20%), and high-risk (44%) groups.[18] For NSGCT CS I relapse rates 20–30% and cancer-specific survival 97–99%.[15,63,122,126] Risk factors include lymphovascular invasion, embryonal predominance, and adjuvant therapy receipt.[124,127,128]

In CS II seminoma (~15-20% at presentation) 90–100% 5-year overall survival is achieved.[14,15] CS IIA/B Nonseminoma cancer-specific survival approaches 98% with guideline-based treatment. Primary RPLND demonstrates 10% relapse rates (pathological stage IIA) and 35–50% (IIB).[73,129–131] Primary chemotherapy yields 4–9% (IIA) and 10–15% (IIB) relapse rates.[68,132]

In CS III seminoma distant metastases are managed per IGCCCG classification. Good-risk patients achieve 89% 5-year progression-free survival and 95% overall survival; intermediate-risk patients achieve 79% and 88%, respectively.[133] No pure seminoma falls into poor-risk category.[101,133] CS IIC/III NSGCT is managed with IGCCCG-classified chemotherapy. Updated data demonstrate 5-year survival rates of 96% (good), 89% (intermediate), and 67% (poor-prognosis) groups.[101]

Follow-Up

Follow-up in TGCT after curative treatment should be conducted for five to ten years and focuses on the early detection of recurrence and the close monitoring of disease progression through structured surveillance.[11]

Follow-up encompasses systematic monitoring with tumor markers (AFP, β-hCG, LDH) and scheduled imaging protocols. Surveillance frequency and intensity vary according to histology, disease stage, treatment modality.[11,16,65,68]

Some follow-up protocols have evolved to reduce visit intensity, to omit tumor markers and chest imaging in seminoma surveillance, to use low-dose CT or MRI instead of standard imaging, and to apply conditional survival estimates to tailor follow-up intensity.[134–137]

MRI vs CT

The use of ionizing radiation during follow-up imaging should be critically considered in the young testicular cancer population. The TRISST trial, a randomized Phase III study, compared abdominal MRI and CT for surveillance in CS I seminoma and included nearly 700 patients. The results demonstrated that MRI was noninferior to CT with no compromise in disease-free or overall survival. These findings have been used to support MRI as a preferred monitoring modality CS I seminoma.[138] However, the study has been criticized as the primary endpoint was set as very large (CS IIC) relapses and thus the study is underpowered with only 0.6–2.6% of patients having an endpoint event. MRI is a promising modality for reducing radiation exposure in surveillance, though resource constraints may limit its widespread adoption.

Radiation Dose Reduction in CT

To minimize radiation exposure, low-dose abdominal CT has been identified as a reliable alternative to standard-dose CT for the surveillance in CS I germ cell tumors. Low-dose CT offers a comparable accuracy in detecting retroperitoneal relapse with minimal difference in nodal measurements and significant reduction in radiation dose by ~55%.[139] These results are promising, however radiation exposure remains a concern and the long-term effects are not fully understood.

Long-Term Sequela and Quality of Life

Testicular cancer and its therapeutic interventions, though associated with excellent survival outcomes, significantly impact quality of life through diverse adverse health outcomes (AHOs) manifesting in short-term and long-term periods.

Chemotherapy administration correlates with peripheral neuropathy, ototoxicity, cardiovascular disease, and secondary malignancy development; radiotherapy increases gastrointestinal and cardiovascular complications alongside secondary cancer risk; while retroperitoneal lymph node dissection may precipitate surgical complications and anejaculation.[15,89,140,141]

Mental health outcomes demonstrate significant impairment, with testicular cancer survivors exhibiting elevated mental health service utilization compared to general population controls, predominantly for anxiety and depression management.[142] Clinical surveillance protocols should incorporate systematic monitoring for these potential adverse effects during routine follow-up assessments. Survivor education regarding possible complications and active care participation represents essential components of comprehensive management.

Long-term care delivery optimally utilizes multidisciplinary approaches, with evidence-based interventions such as structured exercise programs demonstrating measurable benefits for cognitive and cardiometabolic health parameters.[143] Despite substantial AHO burden, longitudinal follow-up analyses reveal overall quality of life metrics among testicular cancer survivors remain largely comparable to general population standards, though subgroups receiving high-dose chemotherapy protocols maintain elevated impairment risk.[144]

Socio-Economic Impact

Testicular cancer creates substantial socio-economic challenges, as it primarily affects men in their prime working years. Population-based Canadian data indicate that the mean 5-year net cost of testicular cancer care is <$25,000 CAD, placing it among the lowest-cost major malignancies.[145] In the United States (U.S), treatment costs vary markedly by clinical stage and histology, with advanced-stage seminoma costing $48,877 USD and nonseminoma $51,592 compared to early-stage seminoma at $17,283 USD and nonseminoma $26,190 USD.[146] Interestingly, in a large US cohort each additional mile between a patient's residence and the treating hospital increased the odds of CS II/III presentation by 7%, highlighting the impact of geographic barriers that can eventually result in higher costs.[147] Regarding overall hospitalization rates for testicular cancer, a decrease from 1.8 per 100,000 in 1994 to 1.4 per 100,000 in 2000 has been reported, reflecting a shift of care to outpatient settings that may lead to lower costs.[148]

Notably, the most important gains in cost-effectiveness have come from therapy de-escalation in early-stage disease. Surveillance after orchiectomy for seminoma increased from 56% to 84% between 2000 and 2010, while adjuvant radiotherapy use decreased from 38% to 8%, with stable long-term outcomes (5- and 10-year overall survival 97% and 96%, cancer-specific survival 98% at both time points).[149]

For CS IIA seminoma, an analysis published in 2024 demonstrated that RPLND constitutes the most cost-effective approach at $58,469 USD per patient with 41 quality-adjusted life years (QALYs), compared to radiotherapy ($98,783 USD, 41 QALYs) and chemotherapy ($104,096 USD, 39 QALYs).[150] The superior cost-effectiveness of RPLND derives from avoiding the chronic toxicities and secondary malignancies associated with systemic therapy and radiation while preserving near-equivalent quality-adjusted survival.

Conclusion, Challenges and Future Directions

In contrast to many other areas of oncology, testicular cancer remains a setting in which prognosis across most disease stages is exceptionally strong. While a subset of patients may benefit from treatment-intensification strategies, such as dose-escalated chemotherapy, the overall high cure creates a distinct challenge in balancing the risks of overtreatment and their associated long-term toxicities in a predominantly young patient population.

Current academic and clinical priorities revolve around two closely connected themes. The first is the pursuit of more accurate diagnosis and prognostication to guide individualized management. Improvements in imaging and more selective surgical approaches have enhanced diagnostic precision while reducing morbidity. Chemotherapy regimens continue to deliver excellent cure rates, yet a growing awareness of long-term toxicities has amplified interest in treatment de-escalation for low- and intermediate-risk disease. Recent advances in testicular cancer research have also expanded opportunities to incorporate novel biomarkers, which show promise in refining risk assessment across multiple clinical settings, from CS I surveillance and relapse detection to the evaluation of post-chemotherapy residual masses and the management of small testicular mass. These tools may ultimately support safer reductions in treatment intensity and follow-up, lessening the burden of therapy-related morbidity. Continued investigation and the thoughtful integration of evidence-based findings into routine care represent the next essential steps.

The second priority is a deeper understanding of quality-of-life and survivorship outcomes, including the socio-economic pressures experienced by individuals diagnosed with and treated for testicular cancer. Data on long-term physical, psychological, fertility-related, and financial impacts remain incomplete, limiting the ability to provide fully informed counseling and to identify patients who may benefit from additional support.

Even with these gaps, the trajectory of progress is encouraging. Ongoing laboratory and clinical advancements continue to broaden the diagnostic, therapeutic and supportive-care landscape, setting the stage for the next decade of innovation in testicular cancer management.

Funding

The authors have no funding sources to report.

Disclosure

Dr Rachel Glicksman reports grants and/or personal fees from TerSera, Astellas, Tolmar, Knight, Bayer, and Abbvie, outside the submitted work. The authors report no other conflicts of interest in this work.

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