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DIAGNOSIS AND TREATMENT OF EARLY-STAGE TESTICULAR CANCER: AUA GUIDELINE (Published 2019; Amended 2023)

Guideline Panel

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SUMMARY

Purpose

Testis cancer is the most common solid malignancy in young males. Testis cancer is a relatively rare malignancy, with outcomes defined by specific cancer- and patient-related factors. The vast majority of men with testis cancer have low-stage disease (limited to the testis and retroperitoneum; clinical stages I-IIB); survival rates are high with standard therapy. A priority for those patients with low-stage disease is limiting the burden of therapy and treatment-related toxicity without compromising cancer control. Thus, surveillance has assumed an increasing role among those with cancer clinically confined to the testis. Likewise, paradigms for management have undergone substantial changes in recent years as evidence regarding risk stratification, recurrence, survival, and treatment-related toxicity has emerged.

Methodology

The systematic review utilized to inform this guideline was conducted by a methodology team at the Johns Hopkins University Evidence-based Practice Center. Scoping of the report and review of the final systematic review to inform guideline statements was conducted in conjunction with the Testicular Cancer expert panel. The methodology team searched using PubMed®, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1980 through August 2018. The team developed a search strategy by using medical subject heading (MeSH) terms and key words relevant to the diagnosis and treatment of early-stage testicular cancer. The evidence review team also reviewed relevant systematic reviews and references provided by the panel to identify articles that may have been missed by the database searches. Searches were updated using the same methodological protocol to capture literature published through March 2023.

GUIDELINE STATEMENTS

INITIAL MANAGEMENT

Diagnosis and Initial Consultation

1. A solid mass in the testis identified by physical exam or imaging should be managed as a malignant neoplasm until proven otherwise. (Clinical Principle)

2. In a man with a solid mass in the testis suspicious for malignant neoplasm, serum tumor markers (AFP, hCG, and LDH) should be drawn and measured prior to any treatment, including orchiectomy. (Moderate Recommendation; Evidence Level: Grade C)

3. Prior to definitive management, patients should be counseled about the risks of hypogonadism and infertility (Moderate Recommendation; Evidence Level: Grade C) and should be offered sperm banking, when appropriate. In patients without a normal contralateral testis or with known subfertility, this should be considered prior to orchiectomy. (Clinical Principle)

4. Scrotal ultrasound with Doppler should be obtained in patients with a unilateral or bilateral scrotal mass suspicious for neoplasm. (Strong Recommendation; Evidence Level: Grade B)

5. Testicular microlithiasis in the absence of solid mass and risk factors for developing a germ cell tumor (GCT) does not confer an increased risk of malignant neoplasm and does not require further evaluation. (Moderate Recommendation; Evidence Level: Grade C)

6. Patients with normal serum tumor markers (hCG and AFP) and indeterminate findings on physical exam or testicular ultrasound for testicular neoplasm should undergo repeat imaging in six to eight weeks. (Clinical Principle)

7. Magnetic Resonance Imaging (MRI) should not be used in the initial evaluation and diagnosis of a testicular lesion suspicious for neoplasm. (Moderate Recommendation; Evidence Level: Grade C)

Orchiectomy

8. Patients with a testicular lesion suspicious for malignant neoplasm and a normal contralateral testis should undergo a radical inguinal orchiectomy; testis-sparing surgery (TSS) is not recommended. Transscrotal orchiectomy is discouraged. (Strong Recommendation; Evidence Level: Grade B)

9. Testicular prosthesis should be discussed prior to orchiectomy. (Expert Opinion)

10. Patients who have undergone scrotal orchiectomy for malignant neoplasm should be counseled regarding the increased risk of local recurrence and may rarely be considered for adjunctive therapy (excision of scrotal scar or radiotherapy) for local control. (Moderate Recommendation; Evidence Level: Grade C)

Testis-Sparing Surgery

11a. TSS through an inguinal incision may be offered as an alternative to radical inguinal orchiectomy in highly selected patients wishing to preserve gonadal function with masses <2cm and (1) equivocal ultrasound/physical exam findings and negative tumor markers (hCG and AFP), (2) congenital, acquired or functionally solitary testis, or (3) bilateral synchronous tumors. (Conditional Recommendation; Evidence Level: Grade C)

11b. Patients considering TSS should be counseled regarding (1) higher risk of local recurrence, (2) need for monitoring with physical examination and ultrasound, (3) role of adjuvant radiotherapy to the testicle to reduce local recurrence, (4) impact of radiotherapy on sperm and testosterone production, and (5) the risk of testicular atrophy and need for testosterone replacement therapy, and/or subfertility/infertility. (Moderate Recommendation; Evidence Level: Grade C)

11c. When TSS is performed, in addition to the suspicious mass, multiple biopsies of the ipsilateral testicle normal parenchyma should be obtained for evaluation by an experienced genitourinary pathologist. (Moderate Recommendation; Evidence Level: Grade C)

GCNIS Counseling and Management

12. Clinicians should inform patients with a history of GCT or GCNIS of risks of a second primary tumor while rare is significantly increased in the contralateral testis. (Moderate Recommendation; Evidence Level: Grade B)

13a. In patients with GCNIS on testis biopsy or malignant neoplasm after TSS, clinicians should inform patients of the risks/benefits of surveillance, radiation, and orchiectomy. (Moderate Recommendation; Evidence Level: Grade C)

13b. Clinicians should recommend surveillance in patients with GCNIS or malignant neoplasm after TSS who prioritize preservation of fertility and testicular androgen production. (Moderate Recommendation; Evidence Level: Grade C)

13c. Clinicians should recommend testicular radiation (18-20 Gy) or orchiectomy in patients with GCNIS or malignant neoplasm after TSS who prioritize reduction of cancer risk taking into consideration that radiation reduces the risk of hypogonadism compared to orchiectomy. (Moderate Recommendation; Evidence Level: Grade C)

STAGING

Serum Tumor Markers

14. Nadir serum tumor markers (AFP, hCG, and LDH) should be repeated at appropriate T1/2 time intervals after orchiectomy for staging and risk stratification. (Moderate Recommendation; Evidence Level: Grade B)

15. For patients with elevated AFP or hCG post-orchiectomy, clinicians should monitor serum tumor markers to establish nadir levels before treatment only if marker nadir levels would influence treatment. (Clinical Principle)

16. For patients with metastatic GCT (Stage IIC or III) requiring chemotherapy, clinicians must base chemotherapy regimen and number of cycles on the IGCCCG risk stratification. IGCCCG risk stratification is based on nadir serum tumor marker (hCG, AFP and LDH) levels obtained prior to the initiation of chemotherapy, staging imaging studies, and tumor histology following radical orchiectomy (Strong Recommendation; Evidence Level: Grade A). Any post-pubertal male, regardless of age, should be treated according to adult treatment guidelines. (Moderate Recommendation; Evidence Level: Grade B)

17. For patients in whom serum tumor marker (AFP and hCG) levels are borderline elevated (within 3x upper limit of normal) post-orchiectomy, a rising trend should be confirmed before management decisions are made as false-positive elevations may occur. (Clinical Principle)

Imaging

18. In patients with newly diagnosed GCT, clinicians should obtain cross-sectional imaging of the abdomen and pelvis with IV contrast or MRI if CT is contraindicated. (Strong Recommendation; Evidence Level: Grade B)

19a. In patients with newly diagnosed GCT, clinicians must obtain chest imaging. (Clinical Principle)

19b. In the presence of elevated and rising post-orchiectomy markers (hCG and AFP) or evidence of metastases on abdominal/pelvic imaging, chest x-ray or physical exam, a CT chest should be obtained. (Strong Recommendation; Evidence Level: Grade C)

19c. In patients with clinical stage I seminoma, clinicians should preferentially obtain a chest x-ray over a CT scan. (Moderate Recommendation; Evidence Level: Grade B)

19d. In patients with non-seminomatous germ cell tumors (NSGCT), clinicians may preferentially obtain a CT scan of the chest over a chest x-ray and should prioritize CT chest for those patients recommended to receive adjuvant therapy. (Conditional Recommendation; Evidence Level: Grade C)

20. In patients with newly diagnosed GCT, clinicians should not obtain a positron emission tomography (PET) scan for staging. (Strong Recommendation; Evidence Level: Grade B)

21. Patients should be assigned a TNM-s category to guide management decisions. (Strong Recommendation; Evidence Level: Grade B)

MANAGEMENT

Principles of Management

22. Management decisions should be based on imaging obtained within the preceding 4 weeks and serum tumor markers (hCG and AFP) within the preceding 10 days. (Expert Opinion)

23. Management decisions should be made in a multidisciplinary setting involving experienced clinicians in urology, medical oncology, radiation oncology, pathology, and radiology. (Clinical Principle)

24. Expert review of pathologic specimens should be considered in clinical scenarios where treatment decisions will be impacted. (Moderate Recommendation; Evidence Level: Grade C)

25. In patients with normal serum tumor markers (hCG and AFP) and equivocal imaging findings for metastasis, clinicians may consider repeat imaging in six to eight weeks to clarify the extent of disease prior to making a treatment recommendation. (Clinical Principle)

Seminoma Management – Surveillance/RPLND/Chemotherapy/Radiation

26. Clinicians should recommend surveillance after orchiectomy for patients with stage I seminoma. Adjuvant radiotherapy and carboplatin-based chemotherapy are less preferred alternatives. (Strong Recommendation; Evidence Level: Grade B)

27a. For patients with stage IIA or IIB seminoma with a lymph node ≤3cm, clinicians should recommend RT or multi-agent cisplatin-based chemotherapy based on shared decision-making. (Moderate Recommendation; Evidence Level: Grade B)

27b. For patients with stage IIA or IIB seminoma with a lymph node ≤3cm who wish to avoid the long-term toxicities associated with chemotherapy or radiation therapy, RPLND may be offered as an appropriate and effective treatment option. (Moderate Recommendation; Evidence Level: Grade B)

27c. For patients with IIB seminoma with a lymph node >3 cm, chemotherapy is recommended. (Moderate Recommendation; Evidence Level: Grade B)

Non Seminoma Management – Surveillance/RPLND/Chemotherapy/Radiation

28. Clinicians should recommend risk-appropriate, multi-agent chemotherapy for patients with NSGCT with elevated and rising post-orchiectomy serum AFP or hCG (i.e. stage TanyN1-2S1). (Strong Recommendation; Evidence Level: Grade B)

29. Clinicians should recommend surveillance for patients with stage IA NSGCT. RPLND or one cycle of bleomycin, etoposide, and cisplatin chemotherapy are effective and appropriate alternative treatment options for patients who decline surveillance or are at risk for non-compliance. (Moderate Recommendation; Evidence Level: Grade B)

30. For patients with stage IB NSGCT, clinicians should recommend surveillance, RPLND, or one or two cycles of bleomycin, etoposide, and cisplatin chemotherapy based on shared decision-making. (Strong Recommendation; Evidence Level: Grade B)

31. Patients with stage I NSGCT and any secondary somatic malignancy (also known as teratoma with malignant transformation) in the primary tumor at orchiectomy should undergo RPLND. (Expert Opinion)

32. Clinicians should recommend RPLND or chemotherapy for patients with stage IIA NSGCT with normal post-orchiectomy serum (S0) AFP and hCG. (Moderate Recommendation; Evidence Level: Grade B)

33. In patients with clinical stage IIB NSGCT and normal post-orchiectomy serum AFP and hCG, clinicians should recommend risk-appropriate, multi-agent chemotherapy. (Moderate Recommendation; Evidence Level: Grade B). Clinicians may offer RPLND as an alternative to chemotherapy to select patients with clinical stage IIB NSGCT with normal post-orchiectomy serum AFP and hCG. (Conditional Recommendation; Evidence Level: Grade C)

34. Among patients who are candidates for RPLND, it is recommended clinicians consider referral to an experienced surgeon at a high-volume center. (Moderate Recommendation; Evidence Level: Grade C)

35. Surgeons with experience in the management of GCT and expertise in minimally invasive surgery may offer a minimally-invasive RPLND, acknowledging the lack of long-term data on oncologic outcomes. (Expert Opinion)

36. Primary RPLND should be performed with curative intent in all patients. RPLND should be performed with adherence to the following anatomical principles, regardless of the intent to administer adjuvant chemotherapy. These principles are applied to both open and minimally-invasive approaches. (Moderate Recommendation; Evidence Level: Grade B).

    - A full bilateral template dissection should be performed in patients with suspicious lymph nodes based on CT imaging or intraoperative assessment and in those with somatic-type malignancy in the primary tumor.
    - A full bilateral template or modified template dissection may be performed in patients with clinically negative lymph nodes.

- A right modified template dissection may omit the para-aortic lymph nodes below the inferior mesenteric artery. Omission of para-aortic lymph nodes above the inferior mesenteric artery is controversial.
- A left modified template dissection may omit paracaval, precaval, and retrocaval lymph nodes. Omission of interaortocaval lymph nodes is controversial.
- Nerve-sparing should be offered in select patients desiring preservation of ejaculatory function.
- Nerve-sparing attempts should not compromise the quality of the lymph node dissection.
- A complete retroaortic and/or retrocaval lymph node dissection with division of lumbar vessels should be performed when within the planned template.
- The ipsilateral gonadal vessels should be removed in all patients.
- The cephalad extent of the dissection is the crus of the diaphragm to the level of the renal arteries. The caudad extent of disease is the crossing of the ureter over the ipsilateral common iliac artery.

37. After primary RPLND, clinicians should recommend surveillance or adjuvant chemotherapy in patients with NSGCT who have pathological stage II disease that is not pure teratoma. (Moderate Recommendation; Evidence Level: Grade B)

- For patients with pN1 and/or pN1-3 pure teratoma, surveillance is preferred.
- For patients with pN2-3 at RPLND, multi-agent cisplatin-based chemotherapy is preferred.

Surveillance for Stage I Testicular Cancer

38. For patients with clinical stage I seminoma choosing surveillance, clinicians should obtain a history and physical examination and perform cross-sectional imaging of the abdomen with or without the pelvis, every 6 months for the first 2 years, and then every 6-12 months in years 3-5. Routine surveillance imaging of the chest and serum tumor marker assessment can be obtained as clinically indicated. (Strong Recommendation; Evidence Level: Grade B)

39. In patients with stage I NSGCT undergoing surveillance after orchiectomy, clinicians should perform a physical examination and obtain serum tumor markers (AFP, hCG +/- LDH) every 2-3 months in year 1, every 2-4 months in year 2, every 4-6 months in year 3, and every 6-12 months for years 4 and 5. (Moderate Recommendation; Evidence Level: Grade C)

40. In patients with stage I NSGCT undergoing surveillance after orchiectomy, radiologic assessment (chest x-ray and imaging of the abdomen with or without the pelvis) should be obtained every 3-6 months in year 1 starting at 3 months, every 4-12 months in year 2, once in year 3, and once in year 4 or 5. (Moderate Recommendation; Evidence Level: Grade B) Men at higher risk of relapse (e.g., lymphovascular invasion) should be imaged with shorter intervals. (Expert Opinion)

41. Patients who relapse on surveillance should be fully restaged and treated based on their TNM-s status. (Moderate Recommendation; Evidence Level: Grade C)

42. Clinicians should inform patients with stage I GCT on surveillance of the ≤1% risk of late relapse after 5 years. (Moderate Recommendation; Evidence Level: Grade B) Annual serologic and radiographic assessment may be performed thereafter as indicated based upon clinical concerns. (Clinical Principle)

ADDITIONAL SURVIVORSHIP

43. Clinicians should refer patients to a survivorship clinic appreciating the long-term risks and potential sequelae of prior treatment among patients with GCT, with the integration of screening and monitoring for potential medical issues which may arise (Expert Opinion) including:

    - Monitoring for signs and symptoms of hypogonadism. If present, serum AM testosterone and luteinizing hormone (LH) levels should be measured.
    - Patients with a history of GCT whose treatment has included radiation therapy, chemotherapy, or both should be advised of the elevated risk of cardiovascular disease and should establish regular care with a primary care physician so that modifiable risk factors for cardiovascular disease (e.g., diet, exercise, smoking, serum lipid levels, blood pressure, serum glucose) can be monitored.
    - Patients with a history of GCT whose treatment has included radiation therapy, chemotherapy, or both should be advised of the elevated risk of secondary malignancy and should establish regular care with a primary care physician for appropriate health care maintenance and cancer screening as appropriate.

INTRODUCTION

PURPOSE

Testis cancer is the most common solid malignancy in young males. The vast majority of men with testis cancer have low-stage disease (limited to the testis and retroperitoneum; clinical stages I-IIB); survival rates are high with standard therapy. A priority for those patients with low-stage disease is limiting the burden of therapy and treatment-related toxicity without compromising cancer control. Thus, surveillance has assumed an increasing role among those with cancer clinically confined to the testis. Testis cancer is a relatively rare malignancy, with outcomes defined by specific cancer- and patient-related factors. Likewise, paradigms for management have undergone substantial change in recent years as evidence regarding risk stratification, recurrence, survival, and treatment-related toxicity has emerged.

Urologists are frequently the initial treating clinician for men with newly diagnosed testis cancer and thus play a crucial role in counseling and treatment decision making. This clinical practice guideline provides evidence-based recommendations for clinicians regarding the diagnosis, staging, treatment selection, and post-treatment surveillance of patients with clinical stages I, IIA, and IIB seminoma and nonseminomatous germ cell tumor (NSGCT). Please also refer to the associated Low-Stage Testis Cancer Treatment Algorithm.

METHODOLOGY

Panel Formation and Process

The Testicular Cancer Panel was created in 2017 by the American Urological Association Education and Research, Inc. (AUAER). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chairs who in turn appointed the additional panel members based on specific expertise in this area. The Panel included specialties from urology, oncology, and radiology. In 2023, an update review assessing abstracts from new studies published since the publication of the 2019 Guideline was completed.

Peer Review and Document Approval

An integral part of the guideline development process at the AUA is external peer review. The AUA conducted a thorough peer review process to ensure that the document was reviewed by experts in the diagnosis and treatment of testicular cancer. In addition to reviewers from the AUA PGC, Science and Quality Council (SQC), and Board of Directors (BOD), the document was reviewed by representatives from American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Urologic Oncology as well as external content experts. Additionally, a call for reviewers was placed on the AUA website from December 14-28, 2018 to allow any additional interested parties to request a copy of the document for review. The guideline was also sent to the Urology Care Foundation to open the document further to the patient perspective. The draft guideline document was distributed to 105 peer reviewers. All peer review comments were blinded and sent to the Panel for review. In total, 45 reviewers provided comments, including 30 external reviewers. At the end of the peer review process, a total of 530 comments were received. Following comment discussion, the Panel revised the draft as needed. Once finalized, the guideline was submitted for approval to the AUA PGC, SQC and BOD for final approval.

In 2023, as a part of the amendment process, the AUA conducted a thorough peer review process. A call for peer reviewers was posted in April 2023 and the draft guideline document was distributed to 62 peer reviewers, 16 of which submitted comments. The Amendment Panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the guideline was submitted for approval to the original guideline panel, the PGC and SQC. It was then submitted to AUA BODs for final approval. Panel members received no renumeration for their work.

Search Strategy

The Johns Hopkins University Evidence-based Practice Center team searched PubMed®, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 1980 through August 2018. Searches were updated using the same methodological protocol to capture literature published through March

2023. The team developed a search strategy by using medical subject headings terms and key words relevant to the diagnosis and treatment of early-stage testicular cancer. The evidence review team also reviewed relevant systematic reviews and references provided by the Panel to identify articles that may have been missed by the database searches.

Study Selection and Data Abstraction

Study selection was based on predefined eligibility criteria for the patient populations, interventions, outcomes, and study designs of interest. Two reviewers independently screened titles, abstracts, and full text for inclusion. Differences between reviewers regarding eligibility were resolved through consensus.

Reviewers extracted information on study characteristics, participants, interventions, and outcomes. One reviewer completed data abstraction, and a second reviewer checked for accuracy.

Assessment of Risk of Bias (ROB) and Data Extraction

Two reviewers independently assessed risk of bias for individual studies. The Cochrane Collaboration's tool was used for assessing the risk of bias of randomized controlled trials (RCTs).[1] For non-randomized studies of treatment interventions, the reviewers used the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI). For diagnostic studies, reviewers used the quality assessment tool for diagnostic accuracy studies (QUADAS -2).[2] Differences between reviewers were resolved through consensus. The evidence review team graded strength of evidence on outcomes by adapting the AUA's three predefined levels of strength of evidence.

Determination of Evidence Strength

The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes not only the quality of individual studies but consideration of study design; consistency of findings across studies; adequacy of sample sizes; and generalizability of study populations, settings, and interventions for the purposes of the guideline. The AUA categorizes body of evidence strength as Grade A (well-conducted and highly-generalizable RCTs or exceptionally strong observational studies with consistent findings), Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). By definition, Grade A evidence has a high level of certainty, Grade B evidence has a moderate level of certainty, and Grade C evidence has a low level of certainty (**Table 1**).[3]

AUA Nomenclature: Linking Statement Type to Evidence Strength

The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens **(Table 2)**. ***Strong Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. ***Moderate Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. ***Conditional Recommendations*** are non-directive statements used when the evidence indicates there is no apparent net benefit or harm or when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates the statement can be applied to most patients in most circumstances and that future research is *unlikely to change confidence*. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates the statement can be applied to most patients in most circumstances, but better evidence *could change confidence*. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates the statement can be applied to most patients in most circumstances, but better evidence is *likely to change confidence*. Body of

evidence strength Grade C is only rarely used in support of a Strong Recommendation. Conditional Recommendations can also be supported by any evidence strength. When body of evidence strength is Grade A, the statement indicates benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is *unlikely to change confidence*. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient circumstances, and better evidence *could change confidence*. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens, alternative strategies may be equally reasonable, and better evidence is *likely to change confidence*.

Where gaps in the evidence existed, ***Clinical Principles*** or ***Expert Opinions*** are provided via consensus of the Panel. A ***Clinical Principle*** is a statement about a component of clinical care widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. ***Expert Opinion*** refers to a statement based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature.

TABLE 1: STRENGTH OF EVIDENCE DEFINITIONS

AUA Strength of Evidence Category	GRADE Certainty Rating	Definition
A	High	• Very confident that the true effect lies close to that of the estimate of the effect
B	Moderate	• Moderately confident in the effect estimate • The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C	Low Very Low	• Confidence in the effect estimate is limited • The true effect may be substantially different from the estimate of the effect • Very little confidence in the effect estimate • The true effect is likely to be substantially different from the estimate of effect

TABLE 2: AUA NOMENCLATURE LINKING STATEMENT TYPE TO LEVEL OF CERTAINTY, MAGNITUDE OF BENEFIT OR RISK/BURDEN, AND BODY OF EVIDENCE STRENGTH

Evidence Grade	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm substantial)	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) appears substantial -Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) appears moderate -Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (Net benefit or harm comparable to other options)	-Benefits = Risks/Burdens -Best action depends on individual patient circumstances -Future Research is unlikely to change confidence	-Benefits = Risks/Burdens -Best action appears to depend on individual patient circumstances -Better evidence could change confidence	-Balance between Benefits & Risks/Burdens unclear -Net benefit (or net harm) comparable to other options -Alternative strategies may be equally reasonable -Better evidence likely to change confidence
Clinical Principle	a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature		

BACKGROUND

Epidemiology

In 2019, an estimated 9,500 men will be diagnosed with testis cancer in the United States, and 400 will die from the disease.[4] Testis cancer is the most common solid malignancy among men aged 20 to 40 years. The incidence rate is highest among Caucasians, lowest among African-Americans, and most rapidly increasing in Hispanic populations.[5,6] Age-adjusted incidence has nearly doubled over the last 4 decades for unknown reasons, from 3.7 per 100,000 in 1975 to 6.4 per 100,000 in 2014.[5] A stage migration of GCT has been observed, presumably due to increased awareness and earlier diagnosis. Between 1973 and 2014, the percentage of tumors diagnosed at a localized stage increased from 55% to 68% in the United States. Currently, less than 15% of men present with stage III disease (to the lungs, viscera, or non-regional lymph nodes).

Risk factors for developing testis cancer include germ cell neoplasia in situ (GCNIS), history of undescended testis (UDT)/ cryptorchidism, family history, and a personal history of testis cancer. Infertility is associated with the presence of GCT, though this association is thought to arise from inherent testicular dysfunction.[7,8,9] GCNIS is the precursor lesion from which the majority of GCTs arise. Among men with invasive GCT, GCNIS is found in adjacent testicular parenchyma in 80-90%. Among men with GCNIS, the risk of developing invasive GCT is approximately 50% within 5 years.[10] Men with cryptorchidism have a four to six fold increased risk of developing testis cancer in the affected testicle, but the relative risk (RR) falls to two to three fold if orchiopexy is performed before puberty.[11,12] Studies assessing the cancer risk of UDT in the contralateral testis are conflicting, though a meta-analysis of cryptorchidism studies showed the contralateral descended testis is also at slightly increased risk of developing cancer (RR 1.74; 95% Confidence Interval [CI], 1.01 to 2.98).[13] Men with a first-degree relative with GCT are at an increased risk of developing testis cancer and at an earlier age.[14] Men with a personal history of testis cancer are at a 12-fold increased risk of developing GCT in the contralateral testis, but the 15-year cumulative incidence is only 2%.[15]

Etiology

GCNIS arises from transformed primordial germ cells that develop *in utero* or early infancy that lay dormant until puberty when they are stimulated by increased serum LH and/or testosterone levels.[16] The carcinogenesis of GCNIS and testis cancer is poorly understood. The increase in testis cancer incidence along with other male reproductive disorders (e.g., infertility, hypospadias, UDT) suggests that GCT may arise from 'testicular dysgenesis,' which results from a combination of environmental and/or lifestyle factors (possibly from exposure *in utero*) in combination with genetic susceptibility. The role of genetic factors is supported by the clustering of testis cancer in some families, the extreme difference in the rate of testis cancer in black and white Americans, and the finding of susceptibility loci on chromosomes 5, 6, and 12.[14] Additionally, polymorphisms of certain genes, including the gene encoding c-KIT ligand, have been associated with an increased risk of testis cancer.[17] Gonocytes depend on KIT ligand for survival; the gene for this protein is located on the long arm of chromosome 12, where an increased number of copies is a universal finding in adult GCT.[18] Thus, a connection between mutations or polymorphisms in c-KIT ligand and GCT has biological plausibility. Inherited alterations to susceptibility genes involved in DNA repair may contribute to the development of adult GCT. A multicenter case-control gene-level enrichment analysis of germline pathogenic variants in individuals with GCT relative to cancer-free controls found 22 pathogenic germline DRG variants, one-third of which were in CHEK2. The variant CHEK2 allele was found in 9.8% of cases and associated with a four-fold increased risk of GCT.[19]

Histological Classification

The histological classification of post-pubertal GCT is outlined in **Table 3**.[16] GCT are broadly classified as GCNIS-derived (germ-cell) and non-GCNIS derived (non-germ cell). The vast majority of post-pubertal GCT are GCNIS-derived. GCT are divided into seminoma and NSGCT, with relative distribution of 52-56% and 44-48%, respectively.[20] NSGCT includes embryonal carcinoma, yolk sac tumor, teratoma, and choriocarcinoma subtypes, either alone as pure forms or in combination as mixed GCT with or without seminoma. Most NSGCTs are composed of two or more GCT subtypes (mixed tumors).

GCTs that contain both NSGCT subtypes and seminoma are classified as NSGCT even if the NSGCT component represents a tiny proportion of the tumor.

The classification of GCT into seminoma and NSGCT has histological, biological, and practical implications. Compared to NSGCT, pure seminomas tend to develop at a later age, are of lower stage at diagnosis, and grow at a slower rate.[21] The risk of occult systemic disease for stage I disease is lower for seminoma than for NSGCT. Lastly, pure seminomas are even more highly sensitive to chemotherapy relative to NSGCTs and sensitive to radiation therapy. All these differences have important treatment implications. Among NSGCT, embryonal carcinoma is the most undifferentiated cell type and has totipotential capacity to differentiate into other NSGCT cell types (yolk sac, choriocarcinoma, and teratoma) within the primary tumor and at metastatic sites.

Among NSGCT patients, the potential for teratoma to arise within the primary tumor or at metastatic sites has important management implications. Though histologically benign, teratomas contain many genetic abnormalities frequently found in malignant GCT elements.[22,23] Teratoma typically grows slowly or may be indolent. However, their underlying genetic instability may lead to uncontrollable growth and invasion of surrounding structures (growing teratoma syndrome)[24] or transformation into somatic-type malignancies such as sarcoma or adenocarcinoma.[25] Unlike other GCT subtypes, teratoma is universally resistant to chemotherapy and only curable by surgical resection. This has important implications in treatment selection for all stages of NSGCT.

TABLE 3: 2016 WORLD HEALTH ORGANIZATION CLASSIFICATION OF GERM CELL TUMORS OF THE TESTIS[16]

Germ cell tumors derived from germ cell neoplasia in situ
Non-invasive germ cell neoplasia
Germ cell neoplasia in situ
Specific forms of intratubular germ cell neoplasia
Seminomatous tumors of a single histologic type (pure seminoma)
Seminoma
Seminoma with syncytiotrophoblast cells
Nonseminomatous germ cell tumors of a single histologic type
Embryonal carcinoma
Yolk sac tumor, postpubertal type
Trophoblastic tumors
Choriocarcinoma
Non-choriocinomatous trophoblastic tumors
Placental site trophoblastic tumor
Epithelioid trophoblastic tumor
Cystic trophoblastic tumor
Teratoma, postpubertal type
Teratoma with somatic-type malignancy
Nonseminomatous germ cell tumors of more than one histologic type
Mixed germ cell tumors
Germ cell tumors of unknown type
Regressed germ cell tumors

Serum Tumor Markers

Testis cancer is one of the few malignancies with reliable serum tumor markers (alpha-fetoprotein [AFP], human chorionic gonadotropin [hCG], and lactate dehydrogenase [LDH]) that are essential for diagnosis, prognosis, clinical staging, management, response to therapy, and post-treatment surveillance. AFP is produced by yolk sac and embryonal carcinoma and is elevated in 10-40% of low-stage (clinical stages I, IIA, IIB) NSGCT.[26] Choriocarcinoma and seminoma do not produce AFP. Patients with pure seminoma in the primary tumor with an elevated serum AFP are considered to have NSGCT. The half-life of AFP is five to seven days. Other malignant sources of AFP include cancers of the stomach, pancreas, biliary tract, liver, and lung. Non-malignant sources of AFP include liver disease (infectious, drug-induced, alcohol-induced, autoimmune), ataxia telangiectasia, hereditary tyrosinemia, and heterophile antibodies.[27,28] Hereditary persistence of AFP (HPAFP), a congenital alteration in the hepatic nuclear factor binding site of the AFP gene leads to increased AFP transcription and is a rare cause of elevated AFP.[29] Despite most laboratories considering an AFP level of >8 ng/mL to be abnormally elevated, a proportion of the population may have levels up to 15 or 25 ng/mL in the absence of any pathology.[7] Treatment decisions soley based on “elevated” AFP levels that are stable and <25 ng/mL are discouraged.

hCG levels are elevated in 10-30% of low-stage NSGCT and 10-15% of seminomas.[26] hCG is secreted by choriocarcinoma, embryonal carcinoma, and syncytiotrophoblastic cells found in 10-15% of seminomas. The half-life of hCG is 24-36 hours. hCG levels may be elevated in cancers of the liver, biliary tract, pancreas, stomach, lung, breast, kidney and bladder. The alpha-subunit of hCG is common to several pituitary tumors, thus immunoassays for hCG are directed at the beta-subunit. Similarly, heterophile antibodies, hypogonadism, and possibly some medications can lead to false-positive elevations of hCG.[30-34]

LDH levels are the least relevant and clinically applicable of the serum tumors markers and elevated in approximately 20% of low-stage GCT.[26] LDH is expressed in smooth, cardiac, and skeletal muscle and can be elevated from cancerous (e.g., kidney, lymphoma, GI, breast) or non-cancerous conditions (e.g., heart failure, anemia, HIV). Of the five isoenzymes of LDH, LDH-1 is the most frequently elevated isoenzyme in GCT. The magnitude of LDH elevation correlates with bulk of disease. As a non-specific marker, its main GCT use is in the prognostic assessment at diagnosis. Treatment decisions based solely on LDH elevation in the setting of normal AFP and hCG should be discouraged.

Prognosis and Staging

Prognosis and initial management decisions are dictated by clinical stage, which is based on the pathological stage of the primary tumor, **post-orchiectomy** serum tumor marker levels, and staging as determined by physical examination and imaging. In 1997, an international consensus for GCT staging was developed by the American Joint Committee on Cancer (AJCC) and Union Internationale Contre le Cancer (UICC) (**Table 4**).[35] The AJCC and UICC staging systems for GCT are unique because, for the first time, a serum tumor marker category (S) based on **post-orchiectomy** AFP, hCG, and LDH levels was used to supplement the prognostic stages (**Table 5**). Clinical stage I is defined as disease clinically confined to the testis, clinical stage II indicates regional (retroperitoneal) lymph node metastasis, and clinical stage III represents non-regional lymph node, lung and/or visceral metastasis, although post-orchiectomy serum tumor marker levels can upstage patients from clinical stage II to III.

For patients with low-stage GCT (clinical stage I, IIA, or IIB), long-term survival is 95% or better. As GCT patients are often healthy and young with long estimated life expectancy, reducing the burden of therapy and treatment-related toxicity are particularly important.

TABLE 4: STAGES OF TESTICULAR CANCER [35]

AJCC Stage	Stage grouping	Stage description*
0	**pTis N0 M0 S0**	The cancer is only in the seminiferous tubules (small tubes inside each testicle). It has not grown into other parts of the testicle (pTis). It hasn't spread to nearby lymph nodes (N0) or to distant parts of the body (M0). All tumor marker levels are within normal limits (S0).
I	**pT1-pT4 N0 M0 SX**	The tumor has grown beyond the seminiferous tubules, and might have grown outside the testicle and into nearby structures (pT1-pT4). The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0). Tumor marker test results aren't available, or the tests haven't been done (SX).
IA	**pT1 N0 M0 S0**	The tumor has grown beyond the seminiferous tubules, but is still within the testicle, and it hasn't grown into nearby blood vessels or lymph nodes (pT1). The cancer hasn't spread to nearby lymph nodes (N0) or to distant parts of the body (M0). All tumor marker levels are within normal limits (S0).
IB	**pT2-pT4 N0 M0 S0**	The tumor has grown outside of the testicle and into nearby structures (pT2-pT4). The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0). All tumor marker levels are within normal limits (S0).
IS	**Any pT (or TX) N0 M0 S1-S3**	The tumor might or might not have grown outside the testicle (any pT), or the extent of the tumor can't be assessed for some reason (TX). The cancer has not spread to nearby lymph nodes (N0) or to distant parts of the body (M0). At least one tumor marker level is higher than normal (S1-S3).
II	**Any pT (or TX) N1-N3 M0 SX**	The tumor might or might not have grown outside the testicle (any pT), or the extent of the tumor can't be assessed for some reason (TX). The cancer has spread to 1 or more nearby lymph nodes (N1-N3), but it hasn't spread to distant parts of the body (M0). Tumor marker test results aren't available, or the tests haven't been done (SX).
IIA	**Any pT (or TX) N1 M0 S0 or S1**	The tumor might or might not have grown outside the testicle (any pT), or the extent of the tumor can't be assessed for some reason (TX). The cancer has spread to at least 1 nearby lymph node (but no more than 5, if checked by surgery), and none of the lymph nodes are larger than 2 centimeters (cm) across (N1). The cancer has not spread to distant parts of the body (M0). All tumor marker levels are within normal limits (S0), or at least 1 tumor marker level is slightly higher than normal (S1).
IIB	**Any pT (or TX) N2 M0 S0 or S1**	The tumor might or might not have grown outside the testicle (any pT), or the extent of the tumor can't be assessed for some reason (TX). The cancer has spread to at least 1 nearby lymph node that's larger than 2 cm but no larger than 5 cm, OR it has grown outside of a lymph node, OR more than 5 nodes contain cancer (found during surgery) (N2). The cancer has not spread to distant parts of the body (M0). All tumor marker levels are within normal limits (S0), or at least 1 tumor marker level is slightly higher than normal (S1).
IIC	**Any pT (or TX) N3 M0 S0 or S1**	The tumor might or might not have grown outside the testicle (any pT), or the extent of the tumor can't be assessed for some reason (TX). The cancer has spread to at least 1 nearby lymph node that's larger than 5 cm across (N3). The cancer has not spread to distant parts of the body (M0). All tumor marker levels are within normal limits (S0), or at least 1 tumor marker level is slightly higher than normal (S1).

III	**Any pT (or TX) Any N M1 SX**	The tumor might or might not have grown outside the testicle (any pT), or the extent of the tumor can't be assessed for some reason (TX). The cancer might or might not have spread to nearby lymph nodes (any N). It has spread to distant parts of the body (M1). Tumor marker test results aren't available, or the tests haven't been done (SX).
IIIA	**Any pT (or TX) Any N M1a S0 or S1**	The tumor might or might not have grown outside the testicle (any pT), or the extent of the tumor can't be assessed for some reason (TX). The cancer might or might not have spread to nearby lymph nodes (any N). It has spread to distant lymph nodes or to the lungs (M1a). All tumor marker levels are within normal limits (S0), or at least 1 tumor marker level is slightly higher than normal (S1).
IIIB	**Any pT (or TX) N1-N3 M0 S2**	The tumor might or might not have grown outside the testicle (any pT), or the extent of the tumor can't be assessed for some reason (TX). The cancer has spread to 1 or more nearby lymph nodes (N1-N3), but it hasn't spread to distant parts of the body (M0). At least 1 tumor marker level is much higher than normal (S2).
	OR	
	Any pT (or TX) Any N M1a S2	The tumor might or might not have grown outside the testicle (any pT), or the extent of the tumor can't be assessed for some reason (TX). The cancer might or might not have spread to nearby lymph nodes (any N). It has spread to distant lymph nodes or to the lungs (M1a). At least 1 tumor marker level is much higher than normal (S2).
IIIC	**Any pT (or TX) N1-N3 M0 S3**	The tumor might or might not have grown outside the testicle (any pT), or the extent of the tumor can't be assessed for some reason (TX). The cancer has spread to 1 or more nearby lymph nodes (N1-N3), but it hasn't spread to distant parts of the body (M0). At least 1 tumor marker level is very high (S3).
	OR	
	Any pT (or TX) Any N M1a S3	The tumor might or might not have grown outside the testicle (any pT), or the extent of the tumor can't be assessed for some reason (TX). The cancer might or might not have spread to nearby lymph nodes (any N). It has spread to distant lymph nodes or to the lungs (M1a). At least 1 tumor marker level is very high (S3).
	OR	
	Any pT (or TX) Any N M1b Any S	The tumor might or might not have grown outside the testicle (any pT), or the extent of the tumor can't be assessed for some reason (TX). The cancer might or might not have spread to nearby lymph nodes (any N). It has spread to distant parts of the body other than the lymph nodes or to the lungs (M1b). Tumor marker levels might or might not be higher than normal (any S).

*The following additional category is not listed on the table above:

NX: Nearby lymph nodes cannot be assessed due to lack of information.

TABLE 5: TUMOR MARKER S DESIGNATION LEVELS[35]

SX	Tumor marker levels are not available, or the tests have not been done
S0	Tumor marker levels are normal
S1	At least 1 tumor marker level is above normal. LDH is less than 1.5 times the upper limit of the normal range, beta-hCG is less than 5,000 mIu/mL, and/or AFP is less than 1,000 ng/mL
S2	At least 1 tumor marker level is substantially above normal. This means that LDH is 1.5 to 10 times the upper limit of the normal range, beta-hCG is 5,000 to 50,000 mIu/mL, and/or AFP is 1,000 to 10,000 ng/mL
S3	At least 1 or more tumor marker level is very highly elevated. This means that LDH is more than 10 times the upper limit of the normal range, beta-hCG is more than 50,000 mIu/mL, and/or AFP is more than 10,000 ng/mL

GUIDELINE STATEMENTS

INITIAL MANAGEMENT

Diagnosis and Initial Consultation

1. **A solid mass in the testis identified by physical exam or imaging should be managed as a malignant neoplasm until proven otherwise. (Clinical Principle)**

Testis cancer is the most common solid malignancy among men aged 20-40 years.[36] The typical presentation is a painless, enlarging mass. Acute testicular pain is less common and caused by rapid expansion of the testis due to intra-tumor hemorrhage or infarction caused by rapid tumor growth. A solid testis mass may be distinguished from other disease entities by physical examination and ultrasound. Diagnostic delay is a common phenomenon, with both patients and physicians contributing to this delay, [37, 38] and often leads to unnecessary intensification of therapy and potential compromise in cure rate.

2. **In a man with a solid mass in the testis suspicious for malignant neoplasm, serum tumor markers (AFP, hCG, and LDH) should be drawn and measured prior to any treatment, including orchiectomy. (Moderate Recommendation; Evidence Level: Grade C)**

Serum AFP, hCG, and LDH are essential for characterization and risk stratification and should be obtained in any patient suspected of having testis cancer. As seminomas do not produce AFP, a significantly elevated and rising AFP in a patient with histologically pure seminoma at orchiectomy should be treated as NSGCT.[39] Baseline determinations of AFP, hCG, and LDH prior to orchiectomy are also important to interpret post-orchiectomy changes for staging and to determine the need for subsequent therapy. For patients with persistently elevated post-orchiectomy serum tumor markers, it is essential to know whether these levels are

declining by their respective half-lives or not, or whether they are rising, as this impacts subsequent treatment decisions.

3. **Prior to definitive management, patients should be counseled about the risks of hypogonadism and infertility (Moderate Recommendation; Evidence Level: Grade C) and should be offered sperm banking, when appropriate. In patients without a normal contralateral testis or with known subfertility, this should be considered prior to orchiectomy. (Clinical Principle)**

Impaired spermatogenesis is associated with GCT and both are thought to arise from inherent testicular dysfunction. [7-9] At diagnosis, up to 50% of men have impaired semen parameters, and 10% are azoospermic.[9] Treatments for GCT may adversely impact fertility through the effects of chemotherapy and radiation therapy on the germinal epithelium and the impact of retroperitoneal lymph node dissection (RPLND) on ejaculatory function. Following multi-agent cisplatin-based chemotherapy, virtually all patients will become azoospermic with recovery of spermatogenic function in 50% and 80% of patients within 2 and 5 years, respectively.[40,41] Recovery of spermatogenesis following radiation therapy is highly dose dependent; return to pre-irradiation sperm concentrations may take 9–18 months following radiation with 1 Gy or less, 30 months for 2–3 Gy, and 5 years or more for doses of 4 Gy and above. Irradiation doses exceeding 6 Gy may result in permanent azoospermia.[42] However, doses to the remaining testis can be kept below this threshold using modern techniques including a gonadal shield (mean, 0.026 Gy).[43] RPLND may result in permanent ejaculatory dysfunction in 80% or more of patients, though nerve-sparing techniques, when indicated, may reduce this rate to 10% or less.[44-46] Given the potential impact of treatments on fertility, men who are undecided or planning future paternity should be offered sperm cryopreservation. In patients with an absent or abnormal contralateral testis or in those with known subfertility, sperm banking may be offered prior to orchiectomy.

Patients with GCT are at risk for hypogonadism with elevated LH , elevated FSH, or low testosterone.[47-50] The prevalence of hypogonadism is increased compared to age-matched controls after cisplatin-based chemotherapy (adjusted odds ratio, 4.8-7.9 depending on cumulative dose), radiation therapy (adjusted odds ratio, 3.5), and orchiectomy alone (adjusted odds ratio, 2.0). For patients receiving chemotherapy, the rates of hypogonadism are directly associated with the number of cycles.[48] Over long-term follow-up, up to 10-15% of patients will have low serum testosterone levels or will require testosterone replacement therapy.[47] Consequently, men should be informed of the risks of treatment-related hypogonadism prior to definitive therapy.

4. **Scrotal ultrasound with Doppler should be obtained in patients with a unilateral or bilateral scrotal mass suspicious for neoplasm. (Strong Recommendation; Evidence Level: Grade B)**

Ultrasound is widely available, inexpensive, non-invasive, and has excellent performance characteristics for the diagnosis of testicular cancer.[51,52] Seminomas have a typical hypoechoic and homogenous appearance while NSGCT are often more heterogeneous with irregular margins, cystic areas, and echogenic foci (e.g., calcification, hemorrhage, fibrosis).[53] Therefore, any hypoechoic mass with vascular flow on Doppler ultrasonography is highly suggestive of malignancy; however, the absence of flow does not exclude GCT. Occasionally, men with an advanced testicular GCT will have a normal physical examination, and scrotal ultrasound will detect a non-palpable scar or calcification indicative of a “burned-out” primary tumor.[54]

5. **Testicular microlithiasis in the absence of solid mass and risk factors for developing a germ cell tumor (GCT) does not confer an increased risk of malignant neoplasm and does not require further evaluation. (Moderate Recommendation; Evidence Level: Grade C)**

Testicular microlithiasis is defined as multiple small, similar-sized echogenic non-shadowing with >5 foci per testis.[55] A meta-analysis of 12 cohort and 2 case-control studies including 35,578 men demonstrated an increased risk of testicular cancer in men with testicular microlithiasis compared to the general population (RR: 12.7; 95% CI: 8.18 to 19.71, P<0.001).[56] However, in a prospective study of 1,500 US Army volunteers – regarded as the most informative screening study of testicular microlithiasis –5.6% of men had testicular microlithiasis[57]. With 5-year follow-up, only 1 of 63 (1.6%)

men with microlithiasis developed a testicular cancer. Additional metadata of men with testicular microlithiasis indicates the risk of testicular GCT is only increased in men with an additional risk factor (i.e., cryptorchidism, family history, personal history of GCT, or diagnosis of GCNIS).[58] Therefore, men with incidentally detected microlithiasis should not undergo further evaluation or screening. Men with risk factors and testicular microlithiasis should be counseled about the potential increased risk of GCT, perform periodic self-examination, and be followed by a medical professional.

6. **Patients with normal serum tumor markers (hCG and AFP) and indeterminate findings on physical exam or testicular ultrasound for testicular neoplasm should undergo repeat imaging in six to eight weeks. (Clinical Principle)**

Men with non-palpable, small (<10mm) intra-testicular lesions in the absence of elevated serum tumor markers or evidence of metastatic GCT may represent a diagnostic dilemma. Up to 50-80% of non-palpable masses less than 2 cm are not cancer; they may be benign tumors, testicular cysts, small infarcts, or Leydig cell nodules.[59] The likelihood of a benign mass is inversely associated with the size of the lesion. Management options include observation with serial physical examination and ultrasound, inguinal orchiectomy, and TSS through an inguinal incision with intraoperative frozen-section. Patient preference and shared decision-making should be employed in choosing a management strategy. Antibiotics are inappropriate unless signs and symptoms of epididymo-orchitis (i.e., swelling, tenderness, fever, diffuse hyperemia on ultrasound, urinalysis or culture indicative of infection, history of sexually transmitted, or complex urinary tract infection) are present.

7. **Magnetic Resonance Imaging (MRI) should not be used in the initial evaluation and diagnosis of a testicular lesion suspicious for neoplasm. (Moderate Recommendation; Evidence Level: Grade C)**

A systematic review identified nine studies evaluating MRI in the diagnosis of 220 masses suspected to be testicular GCT.[60-69] Results were inconsistent and did not demonstrate a clear benefit to MRI for the diagnosis of intra-testicular pathology in comparison to the more standard, widely available, cost-effective, and easily interpreted scrotal ultrasound.[53,70] Additional but limited data indicate quantitative enhancement patterns may be able to distinguish benign tumors (i.e., Leydig cell tumors) from GCTs.[60,62] Therefore, MRI can be considered an adjunct to scrotal ultrasound in patients with lesions suspicious for benign etiology but should not delay orchiectomy in patients in whom malignancy is suspected. MRI is often dependent on expert radiology interpretation, and referral to an experienced MRI center is recommended when possible.[65]

Orchiectomy

8. **Patients with a testicular lesion suspicious for malignant neoplasm and a normal contralateral testis should undergo a radical inguinal orchiectomy; testis-sparing surgery (TSS) is not recommended. Transscrotal orchiectomy is discouraged. (Strong Recommendation; Evidence Level: Grade B)**

Radical orchiectomy establishes a diagnosis and primary T stage while being curative for the majority of men with clinical stage I testicular GCT.[69] Ligation of the spermatic cord at the internal inguinal ring is essential for appropriate oncologic control and facilitates complete resection of the spermatic cord if future RPLND is required.[71] Therefore, in the presence of clinical findings suggestive of a testicular malignancy and a normal contralateral testis, radical orchiectomy remains the treatment of choice.

9. **Testicular prosthesis should be discussed prior to orchiectomy. (Expert Opinion)**

Patients may electively choose to have a testicular prosthesis at the time of orchiectomy. Testicular prosthesis is associated with a very low risk of morbidity (primarily infection), malposition, deflation, or need for explant. Overall satisfaction rates are high (> 80%).[72-75] Surveys indicate nearly 50% of patients are not offered testicular prosthesis implantation.[74,76] Decisions to undergo testicular prosthesis should be discussed prior to orchiectomy. Patients may choose to have a delayed prosthesis implantation if it was not offered prior to orchiectomy.

10. Patients who have undergone scrotal orchiectomy for malignant neoplasm should be counseled regarding the increased risk of local recurrence and may rarely be considered for adjunctive therapy (excision of scrotal scar or radiotherapy) for local control. (Moderate Recommendation; Evidence Level: Grade C)

Transscrotal orchiectomy and transscrotal biopsy are not recommended if malignancy is suspected. For patients who experience scrotal violation during surgery, biopsy of a testicular mass through the scrotum, or scrotal exploration leading to an incidental diagnosis of testicular cancer, the rates of local recurrence are significantly higher than for patients undergoing radical inguinal orchiectomy. In a systematic review, 2.5% of patients undergoing scrotal violation had a local recurrence compared to none of the patients who underwent radical inguinal orchiectomy (P<0.001) with a median follow-up of 24 to 126 months.[69] Among patients undergoing excision of the scrotal scar, 9% had residual, viable GCT. Notably, there was no difference in rates of metastatic disease or all-cause mortality based on scrotal violation.[69]

Testis-Sparing Surgery

11a. TSS through an inguinal incision may be offered as an alternative to radical inguinal orchiectomy in highly selected patients wishing to preserve gonadal function with masses <2cm and (1) equivocal ultrasound/physical exam findings and negative tumor markers (hCG and AFP), (2) congenital, acquired or functionally solitary testis, or (3) bilateral synchronous tumors. (Conditional Recommendation; Evidence Level: Grade C)

11b. Patients considering TSS should be counseled regarding (1) higher risk of local recurrence, (2) need for monitoring with physical examination and ultrasound, (3) role of adjuvant radiotherapy to the testicle to reduce local recurrence, (4) impact of radiotherapy on sperm and testosterone production, and (5) the risk of testicular atrophy and need for testosterone replacement therapy, and/or subfertility/infertility. (Moderate Recommendation; Evidence Level: Grade C)

11c. When TSS is performed, in addition to the suspicious mass, multiple biopsies of the ipsilateral testicle normal parenchyma should be obtained for evaluation by an experienced genitourinary pathologist. (Moderate Recommendation; Evidence Level: Grade C)

TSS (or partial orchiectomy) can be considered in men with a high-likelihood of harboring a benign testicular tumor or in men with an anatomically or functionally solitary testicle who desire to preserve hormone and fertility function. Approximately 50-80% of non-palpable masses < 2 cm are benign lesions such as testicular cysts, small infarcts, Leydig cell nodules, or small tumors of sex cord stromal origin (Leydig or Sertoli cell tumors).[77-80] Men with small, non-palpable testicular masses who meet these criteria may consider TSS with frozen-section. Utilizing a pathologist experienced in the histologic assessment of GCT is recommended.[81] The role of an intraoperative frozen section analysis of the primary tumor should be discussed, and determination should be made with the patients preoperatively as to the long-term goals of the remnant testicle if a GCT is diagnosed or suspected on pathological analysis. Specifically, the decision regarding whether the testicle should be removed in its entirety if the diagnosis of a testicular cancer is made or cannot be determined on frozen section should be determined prior to surgery.

TSS is an option for preservation of hormonal function and fertility in patients with congenital, acquired, or functionally solitary testis or bilateral synchronous malignancy. In a meta-analysis of 201 patients undergoing TSS, local recurrence rates were 11%, with higher incidences observed in seminoma compared to NSGCT (16.7% versus 8.1%, respectively).[69, 82-89] Among those not receiving radiation to the ipsilateral testicle or systemic chemotherapy as adjuvant therapy, local recurrences were identified in 20%. Due to these high rates of local relapse, close monitoring with physical examination and ultrasound of the testis are imperative. Complications after TSS include testicular atrophy in 2.8%, and 7% required subsequent androgen replacement therapy for hypogonadism.[69,82-90] Importantly, cancer-specific survival following TSS ranges from 98-100%. Little data exist regarding the long-term rate for preservation of fertility in this population.

The presence of GCNIS informs the likelihood and timing of recurrence and may assist patients and providers about the need for and timing of adjuvant radiotherapy. GCNIS is present in up to 90% of testicular GCT. [83,91] Fifty and seventy percent of men with GCNIS will develop a testicular GCT by 5 and 7 years respectively.[92-95] Therefore, additional sampling of surrounding testicular parenchyma should be evaluated for the presence of GCNIS at the time of TSS. The presence of GCNIS should prompt a discussion with the patient regarding close surveillance or adjuvant therapy. While the absence of GCNIS is reassuring, it is highly likely that GCNIS is present outside of the sampled tissue, and the patient should be followed with serial self-testicular exam, ultrasound, and tumor markers as appropriate.

GCNIS Counseling and Management

12. Clinicians should inform patients with a history of GCT or GCNIS of risks of a second primary tumor while rare is significantly increased in the contralateral testis. (Moderate Recommendation; Evidence Level: Grade B)

Among all patients with testicular cancer, there is a lifetime 2% risk of a contralateral testicular cancer, most commonly metachronous (70%) but also synchronous (30%).[15,96] For a metachronous contralateral cancer, the median time to diagnosis is five to six years.[15,97] The risk of a contralateral primary tumor is increased in the setting of testicular atrophy, cryptorchidism, or younger age at initial presentation.[98,99] A numerical difference in risk of metachronous malignancy was identified between unscreened groups and those who utilized routine contralateral testicular screening, but this difference was not statistically significant (cumulative incidence of 1.9% versus 3.1%, p=0.097).[100] In these patients, routine testicular self-examination is recommended for surveillance and early detection of a contralateral primary tumor.

13a. In patients with GCNIS on testis biopsy or malignant neoplasm after TSS, clinicians should inform patients of the risks/benefits of surveillance, radiation, and orchiectomy. (Moderate Recommendation; Evidence Level: Grade C)

13b. Clinicians should recommend surveillance in patients with GCNIS or malignant neoplasm after TSS who prioritize preservation of fertility and testicular androgen production. (Moderate Recommendation; Evidence Level: Grade C)

13c. Clinicians should recommend testicular radiation (18-20 Gy) or orchiectomy in patients with GCNIS or malignant neoplasm after TSS who prioritize reduction of cancer risk taking into consideration that radiation reduces the risk of hypogonadism compared to orchiectomy. (Moderate Recommendation; Evidence Level: Grade C)

In patients with GCNIS on biopsy, the risk of developing testicular cancer is 50% over the subsequent 5 years.[95] Following TSS (partial orchiectomy) for cancer, 50-80% have concomitant GCNIS in the ipsilateral testicle. [86,91] Management options include surveillance/expectant management, ipsilateral radiation, or orchiectomy. Chemotherapy is not recommended. Clinicians should engage in shared decision-making discussing the risks and benefits with specific attention to the oncologic efficacy, impact on fertility, and hormonal function associated with each option. Sperm banking and treatment of hypogonadism should be discussed with the patient and appropriately implemented as needed.

Expectant management with deferred radiation or orchiectomy may be considered in the patient who desires future paternity without the need for assisted reproductive techniques. Close monitoring in these patients and compliance with follow-up is essential.

Radiation therapy (18-20 Gy radiation; 2 Gy for 9-10 daily sessions) has a low rate of GCNIS on follow-up biopsies (0 - 2.5%). The rationale for radiation therapy is to lower the likelihood of developing cancer while attempting to preserve Leydig cell function and testosterone production. In the largest study of 122 men with GCNIS in the setting of a contralateral testicular cancer treated with 18-20 Gy, 3 participants (2.5%) had GCNIS on follow-up biopsy, and 70% did not require treatment for hypogonadism.[101] Lower rates of radiation (14-16 Gy) have been investigated with similarly low rates of GCNIS on follow-up biopsy (0-7%) and potentially lower rates of hypogonadism.[102] Radiation therapy at either dose eliminates spermatogenesis in that testicle.

Orchiectomy eliminates the risk of developing testicular cancer but can be unnecessary for those unlikely to develop cancer and lead to lower rates of fertility and testosterone levels.

Cisplatin-based chemotherapy is discouraged since 18-100% (median from all reports: 30%) will have GCNIS on follow-up biopsy. Among 81 men with GCNIS treated with 2 or 3 cycles of cisplatin-based chemotherapy, 27 (33%) had GCNIS on follow-up biopsy. [101]

In patients prioritizing preservation of fertility and testicular androgen production after a diagnosis of GCNIS or malignant neoplasm after TSS, surveillance should be recommended as radiation therapy, surgery, and chemotherapy can result in infertility and hypogonadism. Two studies directly compared rates of hypogonadism between patients receiving 20 Gy radiation to the testis to lower doses; one found radiation doses < 20 Gy resulted in lower frequencies of hypogonadism, and the other found no difference.[102,103] In a study comparing testosterone production in men undergoing 16 Gy versus 20 Gy, men treated with 16 Gy therapy had stable testosterone levels (–1.1% per year, p=0.4) following therapy, whereas men treated with 20 Gy had an annual decrease of 2.4%, most pronounced in the first 5 years and subsequently stabilizing (p = 0.008).[103] Androgen therapy was initiated in 11 of 14 (79%) patients treated with 20 Gy radiation compared to 18 of 37 (49%) patients treated with 16 Gy (p=0.03). However, the reduced risk of hypogonadism associated with a lower radiation dose is not firmly established. Another study comparing 14 to 20 Gy showed a stable testosterone decrease (3.6% per year) without statistically significant dose-dependence (20 Gy versus 14 Gy; p=0.33).[102] A total of 10 of 18 (56%) patients in the 20 Gy group, 2 of 3 (67%) in the 18 Gy group, 3 of 9 (33%) in the 16 Gy group, and 5 of 13 (39%) in the 14 Gy group received androgen replacement therapy. Cisplatin-based chemotherapy results in rates of hypogonadism of 13-20%.[99,101] In a comparative study, hypogonadism following chemotherapy (two or three cycles of cisplatin-based chemotherapy, or carboplatin) was significantly lower than in patients receiving 18-20 Gy radiation (16% versus 31%, respectively; p=0.028).[104]

Radiation reduces rates of a second GCT or persistence of GCNIS, eliminates fertility, and is associated with higher rates of hypogonadism compared to surveillance. A clinician should treat the affected testicle with up to 18-20 Gy of radiation therapy. Administration of 18-20 Gy radiation demonstrated the lowest rate of GCNIS on follow-up biopsies (0-2.5%).[99,102,105, 106] The efficacy of doses <18 Gy are poorly defined, but rates of hypogonadism may be lower.

Radical orchiectomy eliminates the risk of GCNIS or malignant neoplasm and is considered the most definitive treatment, but this procedure is associated with higher rates of infertility and hypogonadism.

Chemotherapy is not recommended for GCNIS due to lack of efficacy. Patients receiving cisplatin-based regimens had higher rates of GCNIS on follow-up biopsies compared to radiation, with a median rate of 30% (range 18.2-100%) during a median overall follow-up period of 48 months. [99, 101,105,107] Carboplatin-based regimens had an even higher rate of persistent disease (66-75% of repeat biopsies), as compared to cisplatin-based regimens.[101,107]

STAGING

Serum Tumor Markers

14. Nadir serum tumor markers (AFP, hCG, and LDH) should be repeated at appropriate T1/2 time intervals after orchiectomy for staging and risk stratification. (Moderate Recommendation; Evidence Level: Grade B)

Serum tumor markers (hCG, AFP, and LDH) are an integral part of staging for all patients with GCT.[35] For those with advanced GCT, serum tumor markers are used for risk stratification and appropriate treatment selection.[108] GCTs are the only tumors for which the AJCC adds an “S” stage to the common T (primary tumor stage), N (regional nodal stage), and M (metastasis stage) format (Table 3).[35] Importantly, both the AJCC staging system and International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic model are based on post-orchiectomy rather than pre-orchiectomy tumor markers, underscoring that one’s stage and risk correlates with the levels of markers produced by metastatic sites of disease. Accordingly, a rising AFP or hCG following orchiectomy represents systemic GCT. Use of pre-orchiectomy markers for staging and risk

stratification can lead to over- or under-treatment with resulting excess rates of toxicity or relapse, respectively.

15. **For patients with elevated AFP or hCG post-orchiectomy, clinicians should monitor serum tumor markers to establish nadir levels before treatment only if marker nadir levels would influence treatment. (Clinical Principle)**

Elevated post-orchiectomy serum tumor markers generally indicate systemic disease and the need for subsequent treatment. However, in the absence of obvious metastatic disease requiring chemotherapy, serum tumor markers should be serially measured following orchiectomy to ascertain rise or persistent elevation prior to consideration of subsequent therapy. In patients with declining serum tumor markers post-orchiectomy, staging and treatment decisions are made after adequate time has elapsed to allow for markers to normalize according to their half-life (hCG: 24-36 hours; AFP: 5-7 days).

16. **For patients with metastatic GCT (Stage IIC or III) requiring chemotherapy, clinicians must base chemotherapy regimen and number of cycles on the IGCCCG risk stratification. IGCCCG risk stratification is based on nadir serum tumor marker (hCG, AFP and LDH) levels obtained prior to the initiation of chemotherapy, staging imaging studies, and tumor histology following radical orchiectomy (Strong Recommendation; Evidence Level: Grade A). Any post-pubertal male, regardless of age, should be treated according to adult treatment guidelines. (Moderate Recommendation; Evidence Level: Grade B)**

When chemotherapy is indicated for newly diagnosed advanced testicular GCT, selection of the appropriate regimen (bleomycin, etoposide, cisplatin [BEP]; etoposide, cisplatin [EP]; etoposide phosphate, ifosfamide, cisplatin) and number of cycles (3 versus 4) is based on the IGCCCG prognostic model.[108] A combination of histology (seminoma versus nonseminoma), presence or absence of non-pulmonary visceral metastasis, and serum tumor marker levels (following orchiectomy) are used to classify patients with testicular GCT into good-, intermediate-, and poor-risk groups with significantly different progression-free and overall survival rates.[108] This classification can be found in **Table 6**. In general, patients with good-risk disease are treated with either three cycles of BEP or four cycles of EP, and those with intermediate- or poor-risk disease are treated with four cycles of BEP or etoposide phosphate, ifosfamide, cisplatin.[109-111] Additional information relevant to advanced GCT can be found in the NCCN guidelines.[112] Any post-pubertal male of pediatric age (< 18 years) should be treated according to adult (as opposed to pediatric) treatment guidelines in terms of chemotherapy scheduling and dosing. Recent data suggest inferior outcomes when these patients are treated according to pediatric guidelines for metastatic disease.[113,114]

17. **For patients in whom serum tumor marker (AFP and hCG) levels are borderline elevated (within 3x upper limit of normal) post-orchiectomy, a rising trend should be confirmed before management decisions are made as false-positive elevations may occur. (Clinical Principle)**

It is important to recognize that elevations in the serum levels of AFP and hCG are not always due to GCT. Failure to consider potential etiologies of false-positive marker elevation can lead to treatment in the absence of disease and subjecting the patient to unnecessary acute and long-term toxicities. When low-level elevation of either marker is present, particularly in the absence of metastatic disease on imaging, clinicians should consider one of these alternative etiologies. With elevated AFP or hCG due to metastatic GCT, a consistent marker rise is typically seen, whereas in false-positive etiologies, the marker level is often stable or fluctuates.

TABLE 6: DEFINITION OF THE GERM CELL CONSENSUS CLASSIFICATION [108]

Good Prognosis	
Non-Seminoma	**Seminoma**
Testis/retroperitoneal primary ***and*** No non-pulmonary visceral metastases ***and*** Good markers- all of *AFP < 1000 ng/mL and* *hCG < 5,000 IU/L (1,000 ng/mL) and* *LDH < 1.5 x upper limit of normal* **56% of non-seminomas** **5 year PFS 89%** **5 year Survival 92%**	Any primary site ***and*** No non-pulmonary visceral metastases ***and*** Normal AFP, any hCG, any LDH **90% of seminomas** **5 year PFS 82%** **5 year Survival 86%**
Intermediate Prognosis	
Non-Seminoma	**Seminoma**
Testis/retroperitoneal primary ***and*** No non-pulmonary visceral metastases ***and*** **Intermediate markers- any of:** *AFP≥ 1,000 and ≤ 10,000 ng/mL or* *hCG ≥ 5,000 IU/L and ≤ 50,000 IU/L or* *LDH ≥ 1.5 x N and ≤ 10 x N* **28% of non-seminomas** **5 year PFS 75%** **5 year Survival 80%**	Any primary site ***and*** **Non-pulmonary visceral metastases** ***and*** Normal AFP, any hCG, any LDH **10% of seminomas** **5 year PFS 67%** **5 year Survival 72%**
Poor Prognosis	
Non-Seminoma	**Seminoma**
Mediastinal primary **or** **Non-pulmonary visceral metastases** **or** **Poor markers- any of:** *AFP > 10,000 ng/mL or* *hCG > 50,000 IU/L (10,000 ng/mL) or* *LDH > 10 x upper limit of normal* **16% of non-seminomas** **5 year PFS 41%** **5 year Survival 48%**	**No patients classified as poor prognosis**

Imaging

18. In patients with newly diagnosed GCT, clinicians should obtain cross-sectional imaging of the abdomen and pelvis with IV contrast or MRI if CT is contraindicated. (Strong Recommendation; Evidence Level: Grade B)

The retroperitoneal lymph nodes are the most frequent site of initial metastatic dissemination for both seminoma and NSGCT. Less frequently, metastasis can be found within the retained spermatic cord or involving pelvic lymph nodes (the latter are uncommon in the absence of retroperitoneal lymphadenopathy). As such, imaging of the retroperitoneum and pelvis at diagnosis is paramount for staging and treatment selection. Computed tomography (CT) scan of the abdomen and pelvis has a sensitivity of 67%, specificity of 95%, positive predictive value (PPV) of 87%, negative predictive value (NPV) 73%, and accuracy of 83% with most studies measuring node size in axial (short axis) imaging.[115-120] Experience with MRI in the staging of the retroperitoneal lymph nodes is substantially less than CT and has a sensitivity of 78-98%.[121-124] There is inadequate evidence to support the use of MRI of the abdomen and pelvis over a CT scan at the time of diagnosis. In general, the smaller the size definition of a positive node, the greater the sensitivity and lesser the specificity. CT scans should be performed with IV contrast, if possible, for better tissue differentiation and should be performed in a single phase according to as low as reasonably achievable principles of minimizing ionizing radiation.

19a. In patients with newly diagnosed GCT, clinicians must obtain chest imaging. (Clinical Principle)

19b. In the presence of elevated and rising post-orchiectomy markers (hCG and AFP) or evidence of metastases on abdominal/pelvic imaging, chest x-ray or physical exam, a CT chest should be obtained. (Strong Recommendation; Evidence Level: Grade C)

19c. In patients with clinical stage I seminoma, clinicians should preferentially obtain a chest x-ray over a CT scan. (Moderate Recommendation; Evidence Level: Grade B)

19d. In patients with non-seminomatous germ cell tumors (NSGCT), clinicians may preferentially obtain a CT scan of the chest over a chest x-ray and should prioritize CT chest for those patients recommended to receive adjuvant therapy. (Conditional Recommendation; Evidence Level: Grade C)

The thorax is the most common site of metastatic disease after retroperitoneal lymph nodes for men with GCT; lung metastases represent the most common site of visceral metastases.[125] Hence, imaging studies of the chest are essential for staging purposes. While CT chest has increased sensitivity compared to chest x-ray (median 100% versus 76% in combined seminoma and non-seminoma histology),[126-128] chest x-ray has superior specificity (median 98% versus 93% in combined seminoma and non-seminoma histology).[126,128] When tumor markers are normal, the rate of skip metastasis to the thorax in seminoma approaches zero, and the addition of CT chest to chest x-ray is very unlikely to alter treatment decisions.[127, 128] Skip metastases are more common in non-seminoma than seminoma. A retrospective analysis of low-stage seminoma patients evaluated by CT chest imaging found a high rate of false-positive chest findings in those with normal CT abdomen-pelvis imaging.[127] Sensitivity of CT is superior to chest x-ray in non-seminoma, and understaging by chest x-ray remains a concern. Thus, for patients with clinical stage I NSGCT who are undergoing further treatment with RPLND or chemotherapy, CT chest imaging is recommended to ensure no evidence of metastatic disease in the thorax before proceeding with therapy.

20. In patients with newly diagnosed GCT, clinicians should not obtain a positron emission tomography (PET) scan for staging. (Strong Recommendation; Evidence Level: Grade B)

Positron-emission tomography (PET) scan was demonstrated to have excellent specificity and PPV (100% each) for staging of seminoma with ability to confirm stage I disease but did not lead to substantial alterations in management.[129,130] The potential harms (cost, radiation exposure, and overtreatment due to false-positive findings) without evidence of potential beneficial impact on clinical care, indicate PET should not be used in staging of seminoma. In non-seminoma staging, PET

scan demonstrated a median sensitivity of 71%, specificity 98%, PPV 89%, NPV 80%, and accuracy 80%.[115, 129-131] While some studies showed superior sensitivity and NPV compared to CT scan[129,130], another study showed no benefit over using CT alone.[131] The only prospective and, therefore, highest-quality study identified improved sensitivity, NPV, and accuracy for PET but similar specificity and no significant overall benefit over CT.[115] Given the cost, radiation exposure, and potential anxiety and excess testing resulting from false-positive findings with no significant alteration in management, the harms appear to outweigh the benefits of PET for staging of non-seminoma. Therefore, clinicians should not use PET for initial staging of GCT.

21. **Patients should be assigned a TNM-s category to guide management decisions. (Strong Recommendation; Evidence Level: Grade B)**

Once a diagnosis of GCT is made, clinical staging imaging studies are obtained (including chest, abdominal, and pelvic imaging) and post-orchiectomy nadir levels of AFP, hCG, and LDH are determined, patients should be assigned a TMN-S stage according to the UICC/AJCC staging system (see Tables 3 and 4) and should be managed according to guidelines outlined for their specific TNM-S clinical stage.[35,108]

MANAGEMENT

Principles of Management

22. **Management decisions should be based on imaging obtained within the preceding 4 weeks and serum tumor markers (hCG and AFP) within the preceding 10 days. (Expert Opinion)**

Due to the rapid doubling time of many GCT, particularly NSGCT, there is a risk of disease progression between staging studies and intervention.[132] Therefore, risk adapted management decisions (i.e. RPLND for Stage IIA disease) should be made based on recent imaging and serum tumor marker levels to avoid undertreatment.

23. **Management decisions should be made in a multidisciplinary setting involving experienced clinicians in urology, medical oncology, radiation oncology, pathology, and radiology. (Clinical Principle)**

Optimal management for patients with testis cancer is often enhanced following a multi-disciplinary discussion. When possible, this includes a collaborative discussion including urology, medical oncology, and, for patients with stage I-II seminoma, radiation oncology. Application of a multi-disciplinary disease management team has been demonstrated to significantly decrease the rates of overtreatment, decrease relapse, and improve survival.[133]

24. **Expert review of pathologic specimens should be considered in clinical scenarios where treatment decisions will be impacted. (Moderate Recommendation; Evidence Level: Grade C)**

The evaluation of testicular cancers is challenging due to heterogeneity of tumor and multiple histology elements often present in NSGCT. Review by expert pathologists leads to alterations of histologic subtype in 4-6% of cases with up to 27% of pathology reports revised overall.[134,135] These pathologic changes can affect management and prognosis. For example, the determination of lymphovascular invasion was altered in 20% on genitourinary pathologic review, affecting the stage and risk of recurrence.[136] However, expert review of pathologic specimens may not be necessary in all clinical situations before treatment decisions are made. For example, a patient with elevated and rising post-orchiectomy levels of AFP (with or without clinical evidence of metastases) may be appropriately managed as metastatic NSGCT and initiate chemotherapy before expert pathological review of the orchiectomy specimen.

25. **In patients with normal serum tumor markers (hCG and AFP) and equivocal imaging findings for metastasis, clinicians may consider repeat imaging in six to eight weeks to clarify the extent of disease prior to making a treatment recommendation. (Clinical Principle)**

Many patients with newly diagnosed GCT have equivocal imaging findings, not clearly consistent with localized or metastatic disease. Most often, this manifests as the presence of borderline enlargement (0.8 to 1.5cm) of lymph nodes in the retroperitoneum, sometimes lateralizing to the expected landing zone. In the absence of elevated tumor markers, these findings should be approached cautiously rather than hastily initiating treatment for metastatic disease. Repeating imaging six to eight weeks after the initial CT can be helpful in

establishing the probable etiology. Enlarging lymph nodes are often associated with metastatic disease, while stable or regressing lymph nodes suggest benign etiologies. Such a practice, as employed by the Swedish Norwegian Testicular Cancer (SWENOTECA) group,[137] helps avoid overtreatment with resultant potential for unnecessary toxicity.[112]

Seminoma Management – Surveillance/ RPLND/Chemotherapy/Radiation

26. Clinicians should recommend surveillance after orchiectomy for patients with stage I seminoma. Adjuvant radiotherapy and carboplatin-based chemotherapy are less preferred alternatives. (Strong Recommendation; Evidence Level: Grade B)

For stage I seminoma, patients are candidates for surveillance, adjuvant carboplatin, or adjuvant radiation therapy after orchiectomy. Surveillance is associated with the lowest risk for short- and long-term treatment-related morbidity since more than 80% of patients will not experience recurrence and are cured with orchiectomy alone. Adjuvant carboplatin and radiation reduce the risk of relapse but do not improve cancer-specific survival compared to surveillance.[138]

There is lack of agreement and validation of risk factors for recurrence. The use of tumor size and rete testis involvement is not recommended in determining management of stage I seminoma.[139] Surveillance affords the patient the best opportunity to avoid unnecessary treatment-related toxicity without compromising survival.

Oncologic outcomes after diagnosis of stage I seminoma are favorable regardless of initial management strategy. Although recurrence rates are higher after surveillance (15-20%) compared to either adjuvant radiation or chemotherapy (3-9%), cause specific survival is similar (>98%).[138, 140-143] Adjuvant radiation therapy has been tested for stage I seminoma in randomized trials from the Medical Research Council in the United Kingdom[44,144] showing non-inferiority of 20 Gy to the para-aortic region only compared to a larger dog leg field or higher dose of 30 Gy. Adjuvant chemotherapy has been compared to adjuvant radiation, showing non-inferiority with a single dose of carboplatin (AUC=7).[145] Short term toxicities are common for both radiation therapy and chemotherapy but tend to be mild and self-limited.[44,144,145] Late toxicity of radiation therapy and chemotherapy can involve the cardiovascular,[146] gastrointestinal,[44] and hematologic systems,[147] and may cause infertility[148] and rarely result in secondary malignancy.[149] Long-term impact of a single dose of carboplatin is unknown.

A retrospective study of primary RPLND in stage IA and IB seminoma has shown comparable survival rates to standard treatments with acceptable short-term toxicity. There is insufficient evidence to support its use as a standard treatment alternative to surveillance in these patients.[150]

27a. For patients with stage IIA or IIB seminoma with a lymph node ≤3cm, clinicians should recommend RT or multi-agent cisplatin-based chemotherapy based on shared decision-making. (Moderate Recommendation; Evidence Level: Grade B)

27b. For patients with stage IIA or IIB seminoma with a lymph node ≤3cm who wish to avoid the long-term toxicities associated with chemotherapy or radiation therapy, RPLND may be offered as an appropriate and effective treatment option. (Moderate Recommendation; Evidence Level: Grade B)

27c. For patients with IIB seminoma with a lymph node >3 cm, chemotherapy is recommended. (Moderate Recommendation; Evidence Level: Grade B)

Radiation therapy and multi-agent chemotherapy both result in high rates of cancer specific survival (>97%) in stage II seminoma. Comparative analyses are limited and retrospective but show no apparent survival differences. For patients with stage IIA seminoma, recurrence rates after radiation[151] or chemotherapy[152] are similar (<10%), with radiation therapy prescribed to a dog leg field with doses up to 30 Gy, and chemotherapy given as multi-agent, cisplatin-based therapy including 4 cycles of EP or 3 cycles of BEP. Studies of stage IIB seminoma suggest fewer relapses after chemotherapy compared to radiation therapy.[141] Short-term toxicities are common for both radiation therapy and chemotherapy but tend to be self-limited. Long-term toxicity of therapy can involve the

cardiovascular, gastrointestinal, and hematologic systems[147] and may cause infertility[148] and can rarely result in secondary malignancy.[149] Secondary solid tumors were noted to develop in 5.6% of 40,576 testicular cancer survivors in North America and Europe. Moreover, the risks appear to increase with younger age at testis cancer diagnosis. These cancers include malignant mesothelioma, as well as cancers of the lung, colon, esophagus, bladder, pancreas, and stomach. Compared to carboplatin, multi-agent cisplatin-based chemotherapy may have additional, long-term effects on neurologic, renal, and pulmonary systems.[41, 153-156]

The role of RPLND for early metastatic seminoma has been explored in several recent clinical trials. Surgery in Early Metastatic Seminoma (SEMS), a multi-institutional phase 2 clinical trial, enrolled patients with testicular seminoma and small-volume retroperitoneal disease (<3 cm) with normal tumor markers to undergo primary RPLND. The study accrued 55 patients from 12 institutions and demonstrated 2-yr recurrence-free survival of 81% and overall survival of 100% with only 7% of patients experiencing long-term complications. Patients who developed recurrence were successfully treated with chemotherapy (10/55) or additional surgery (2/55).[157] The PRIMTEST trial included patients with <5 cm retroperitoneal disease and patients with recurrence after single-dose carboplatin. 33 patients were accrued and after median follow-up of 32-month, progression free survival was 70%. In addition, all disease recurrences were successfully managed with systemic therapy.[158] In the COTRIMS trial, Heidenreich et al reported a relapse rate of 9.5% (two of 21) at mean follow-up of 20 month in a cohort undergoing RPLND for stage IIA/B seminoma.[159] These studies demonstrate that RPLND has significant disease-free survival rates which avoids the need for chemotherapy in the majority of patients.

Non Seminoma Management – Surveillance/ RPLND/Chemotherapy/Radiation

28. Clinicians should recommend risk-appropriate, multi-agent chemotherapy for patients with NSGCT with elevated and rising post-orchiectomy serum AFP or hCG (i.e. stage TanyN1-2S1). (Strong Recommendation; Evidence Level: Grade B)

Studies of men with stage I NSGCT of the testis with persistently elevated serum AFP or hCG after orchiectomy have reported high relapse rates after primary RPLND. A multivariable regression analysis of 453 patients undergoing primary RPLND for stage I-II NSGCT at Memorial Sloan Kettering Cancer Center reported that elevated markers at the time of RPLND were associated with substantially elevated risk of relapse (HR = 5.6; 95% CI 2.4 to 12.8, p<.0001).[160] Saxman et al. reported similar findings: among 30 patients with elevated markers undergoing primary RPLND, 5 of 6 patients (83%) with elevated AFP and 6 of 24 patients (25%) with elevated hCG relapsed after RPLND.[161] Another study of 15 patients with clinical stage IS NSGCT reported all 11 treated with RPLND required subsequent chemotherapy, whereas only 1 of 4 treated with primary chemotherapy required subsequent RPLND.[162] Thus, elevated and rising post-orchiectomy levels of AFP and hCG in patients with clinical stage I, IIA, and IIB NSGCT indicate the presence of occult systemic disease for which primary chemotherapy according to IGCCCG risk is recommended.

29. Clinicians should recommend surveillance for patients with stage IA NSGCT. RPLND or one cycle of bleomycin, etoposide, and cisplatin chemotherapy are effective and appropriate alternative treatment options for patients who decline surveillance or are at risk for non-compliance. (Moderate Recommendation; Evidence Level: Grade B)

The relapse rate for patients with clinical stage IA NSGCT is 10-20% in most studies; thus, 80-90% of men are cured with orchiectomy alone.[137,163] Multiple studies have reported lymphovascular invasion and a predominance of embryonal carcinoma as independent risk factors for relapse.[164,165] Predominance of embryonal carcinoma has been defined in a variety of ways, including more embryonal carcinoma than any other individual histology,[166,167] more than 50% embryonal carcinoma, [160, 163,168-170] at least 80% embryonal carcinoma, no more than a microscopic focus of another GCT subtype,[171] and pure embryonal carcinoma.[172,173] Surveillance allows men to reduce their exposure to the risks and side effects of RPLND and chemotherapy without compromising their overall or disease-specific survival. The benefit of

surveillance is greatest for men with a lower risk of relapse.

Representative studies of surveillance published in this century include the following:

- A series of 223 patients treated in British Columbia and Oregon that reported a 5-year disease-specific survival of 100% and a relapse rate among stage IA patient of less than 18%.[163]
- A series of 371 men in Toronto that reported a 5-year disease-specific survival of 99% and a relapse rate of 18.7% among low-risk patients with neither lymphovascular invasion nor pure embryonal carcinoma.[173]
- A Turkish study of 221 consecutive stage I patients followed for a median of 75 months reported a disease-specific survival of 97.6% for all patients and a relapse rate of 17.9% for those with clinical stage IA disease.[165]
- The SWENOTECA group reported that among 338 stage IA NSGCT patients undergoing surveillance, the relapse rate was 13.5%. There were no deaths from testis cancer.[174]
- A Danish study of surveillance for stage I NSGCGT included 513 men with stage IA NSGCT reported that 15-year disease-specific survival was 99.1%. The 5-year relapse rate for men with stage IA disease was 24.6%.[175]

Some men may prefer active treatment with RPLND or one cycle of BEP chemotherapy in order to reduce the risk of relapse and the need for more extensive treatment should a relapse occur on surveillance.[176] Shared decision-making is appropriate so that the clinical decision is attuned to the patient's priorities, values, and medical history.[177-179]

- The SWENOTECA group reported that among 155 men with stage IA NSGCT who underwent treatment with one cycle of BEP chemotherapy, the relapse rate was 1.3%. There were no deaths from testis cancer or complications of treatment.[137]

30. For patients with stage IB NSGCT, clinicians should recommend surveillance, RPLND, or one or two cycles of bleomycin, etoposide, and cisplatin chemotherapy based on shared decision-making. (Strong Recommendation; Evidence Level: Grade B)

Men with clinical stage IB NSGCT of the testis have a higher risk of relapse following orchiectomy compared to men with stage IA. For instance, among men in British Columbia and Oregon undergoing surveillance for clinical stage I NSGCT, 60 tumors had lymphovascular invasion and 30 (50%) relapsed.[163] In the Danish study, the relapse rate on surveillance was 43% with lymphovascular invasion present,[175] while the relapse rate was 54% among men whose tumors had lymphovascular invasion in the Toronto series.[173] When lymphovascular invasion and a predominance of embryonal carcinoma are both present, the risk of relapse may be higher than with either factor alone.[165,175] Men with clinical stage IB NSGCT of the testis may be uncomfortable going on a surveillance protocol given that their risk of relapse is roughly 45-50%; such patients may prefer to undergo RPLND or one cycle of BEP chemotherapy in order to reduce their risk of relapse.[176] Shared decision-making is important so that the treatment plan is consistent with the patient's values and priorities.[177] In addition, the patient's medical history may influence the appropriateness of certain options. Men with prior inguinal surgery, for example, may have altered lymphatic drainage and thus are not ideal candidates for RPLND. Patients with compromised renal function are at increased risk of complications from BEP chemotherapy. Decision-making should take into account all these factors.

31. Patients with stage I NSGCT and any secondary somatic malignancy (also known as teratoma with malignant transformation) in the primary tumor at orchiectomy should undergo RPLND. (Expert Opinion)

Teratoma has the capacity to dedifferentiate into somatic malignancies including sarcomas and carcinomas that are less responsive to chemotherapy than GCT. These tumors are rare, and the literature is limited to relatively small case series. A series of 10 patients with metastatic teratoma with somatic–type malignancy from Memorial Sloan Kettering Cancer Center reported that seven died

with systemic therapy.[180] A European series of 10 men with metastatic transformed GCT reported that 9 died.[181] Median survival for patients with metastatic transformed GCT has been reported as 28 months.[25] Neither GCT-specific nor histology-specific chemotherapy has demonstrated efficacy for these tumors. Given the insensitivity of these tumors to chemotherapy, RPLND is recommended for these patients to remove any retroperitoneal metastases that may exist and reduce the risk of relapse. However, it is important to distinguish transformed GCT from teratomas: the presence of teratoma in the primary tumor is not a specific indication for RPLND, but the rationale for RPLND is stronger when teratoma is present because of concerns about chemotherapy resistance and late recurrence.

32. Clinicians should recommend RPLND or chemotherapy for patients with stage IIA NSGCT with normal post-orchiectomy serum (S0) AFP and hCG. (Moderate Recommendation; Evidence Level: Grade B)

Men with stage IIA NSGCT have an excellent prognosis when treated with either RPLND or chemotherapy. [108,182-184] Therefore, shared decision-making should be used to tailor the treatment decision to the patient's goals, values, and medical history.[177]

The benefits of RPLND for these patients include reduced exposure to chemotherapy, removal of any chemotherapy-resistant teratoma, and a reduced need for serial retroperitoneal imaging. Most men with clinical stage IIA disease will be found to have pathological stage IIA disease, which is associated with a relapse rate of about 10% if adjuvant chemotherapy is not given.[160,185] In addition, some men will be found to have no nodal metastases (pathological stage I disease). One single institution series reported that 49 of 122 men (40%) with clinical stage IIA disease had pathological stage I disease.[160] Another reported that 32 of 140 (23%) patients with clinical stage II disease had pathological stage I disease.[186] Thus, a substantial proportion of men with clinical stage IIA NSGCT are over-staged. However, a minority of men with clinical stage IIA are upstaged to pathological stage IIB and may be advised to receive two cycles of adjuvant chemotherapy in order to reduce their risk of relapse from 35-50% to about 1%.[186-190]

Chemotherapy for good-risk disseminated NSGCT consists of either three cycles of BEP or four cycles of EP. For the good-risk patients, chemotherapy is associated with 90% relapse-free survival, and IIA patients presumably have an even better prognosis compared to men with bulkier good-risk disease.[110] In addition to the short-term side effects of nausea, vomiting, alopecia, and immunosuppression, chemotherapy is associated with an increased rate of infertility, peripheral neuropathy, high-pitch hearing loss, cardiovascular disease, and secondary malignancies.[49,149,191-195]

Certain factors can help guide decision-making. When the primary testis tumor contains teratoma, the rationale for RPLND is stronger due to the chemotherapy resistance of this tumor type. Patients who have had inguinal surgery prior to orchiectomy may have altered lymphatic drainage and chemotherapy is generally preferred.

33. In patients with clinical stage IIB NSGCT and normal post-orchiectomy serum AFP and hCG, clinicians should recommend risk-appropriate, multi-agent chemotherapy. (Moderate Recommendation; Evidence Level: Grade B). Clinicians may offer RPLND as an alternative to chemotherapy to select patients with clinical stage IIB NSGCT with normal post-orchiectomy serum AFP and hCG. (Conditional Recommendation; Evidence Level: Grade C)

Patients with clinical stage IIB NSGCT almost always have pathological stage II disease confirmed if they undergo RPLND and may be advised to undergo two cycles of post-RPLND chemotherapy if non-teratoma GCT is found in the surgical specimen due to the high risk of relapse.[160,186,190] The Memorial Sloan Kettering series reported all 23 clinical stage IIB patients undergoing RPLND had pathological stage II disease confirmed, and clinical stage IIB was a significant predictor of progression (HR = 12.3; p<0001) [160] with 70% of patients with pN2 disease relapsing. Similarly, in a multicenter study of adjuvant chemotherapy for pathological stage II disease, over half of men with pN2 disease relapsed if they did not receive adjuvant chemotherapy.[190] Therefore, chemotherapy is generally preferred over RPLND as initial post-orchiectomy treatment for these patients. Chemotherapy consists of either three cycles of BEP or four cycles of EP because stage IIB NSGCT is classified

as good-risk disease within the standard prognostic classification framework.[108]

For patients with a predominance of teratoma in their primary tumor and patients with a relative contraindication to chemotherapy, RPLND is an effective alternative. RPLND may also be considered for asymptomatic patients with unifocal and small (<3cm) IIB disease based on the same rationale as clinical stage IIA NSGCT.

34. Among patients who are candidates for RPLND, it is recommended clinicians consider referral to an experienced surgeon at a high-volume center. (Moderate Recommendation; Evidence Level: Grade C)

RPLND is a technically complex surgery encompassing removal of retroperitoneal lymph nodes while preserving the great vessels, surrounding organs, and ejaculatory nerves. At the completion of urology residency training in the United States, the average number of RPLND's performed is four, and half of graduates participate in two or less.[196] According to the National Cancer Database, the median number of annual testicular cancer cases per hospital was three. For patients with metastatic disease, treatment at a higher-volume hospital is independently associated with superior overall survival.[197,198] Strong consideration for referral to an experienced testes cancer surgeon or center is advised for RPLND, particularly for large post-chemotherapy masses, which can lead to significant blood loss, adjacent organ resection, and a high level of overall difficulty.

35. Surgeons with experience in the management of GCT and expertise in minimally invasive surgery may offer a minimally-invasive RPLND, acknowledging the lack of long-term data on oncologic outcomes. (Expert Opinion)

The role of minimally invasive RPLND in the management of GCT is controversial. Multiple cohorts have demonstrated feasibility and safety of minimally-invasive RPLND.[199-201] Patients need to be appraised of the potential limitations and consequences of this approach as literature series report low lymph node yields, lower than expected positive node rates, lack of meaningful intermediate- or long-term cancer outcomes, high rates of chylous ascites, or indiscriminate use of adjuvant chemotherapy. Minimally-invasive RPLND can be considered with an experienced surgeon who has a thorough understanding of testicular cancer and the capability to convert to open surgery, if needed. Particular caution should be exhibited in the setting of post-chemotherapy RPLND.

36. Primary RPLND should be performed with curative intent in all patients. RPLND should be performed with adherence to the following anatomical principles, regardless of the intent to administer adjuvant chemotherapy. These principles are applied to both open and minimally-invasive approaches. (Moderate Recommendation; Evidence Level: Grade B)

- **A full bilateral template dissection should be performed in patients with suspicious lymph nodes based on CT imaging or intraoperative assessment and in those with somatic-type malignancy in the primary tumor.**
- **A full bilateral template or modified template dissection may be performed in patients with clinically negative lymph nodes.**
- **A right modified template dissection may omit the para-aortic lymph nodes below the inferior mesenteric artery. Omission of para-aortic lymph nodes above the inferior mesenteric artery is controversial.**
- **A left modified template dissection may omit paracaval, precaval, and retrocaval lymph nodes. Omission of interaortocaval lymph nodes is controversial.**
- **Nerve-sparing should be offered in select patients desiring preservation of ejaculatory function.**
- **Nerve-sparing attempts should not compromise the quality of the lymph node dissection.**
- **A complete retroaortic and/or retrocaval lymph node dissection with division of lumbar vessels should be performed when within the planned template.**
- **The ipsilateral gonadal vessels should be removed in all patients.**
- **The cephalad extent of the dissection is the crus of the diaphragm to the level of the renal arteries. The caudad extent of disease is the**

crossing of the ureter over the ipsilateral common iliac artery.

RPLND should be performed with curative intent; RPLND should not be performed as a staging modality alone. A full, bilateral template includes removal of the para-aortic, retro-aortic, pre-aortic, left common iliac, interoartocaval, pre-caval, para-caval, retro-caval, and right common iliac lymph nodes in addition to the ipsilateral gondal vessels. A full, bilateral template dissection should be performed in patients with suspicious lymph nodes based on CT imaging or intraoperative evaluation and in those with somatic-type malignancy (teratoma with malignant transformation) in the primary tumor. This template is associated with the lowest rates of retroperitoneal recurrence.[160] In appropriate patients, nerve-sparing procedures can be performed in the setting of a full, bilateral template with preservation of ejaculatory function in 90% or more of patients.

In patients with clinically negative lymph nodes, a full, bilateral template or a modified template dissection may be performed. The extent of the dissection for modified templates varies greatly among published series.[202-205] Limiting the extent of the dissection may increase the risk of retroperitoneal recurrence. Modified templates are associated with inferior ejaculatory rates compared to nerve-sparing techniques.[206] For right-sided tumors, an acceptable modified template must include the right common iliac, para-caval, pre-caval, retro-caval, interaortocaval, pre-aortic, and retro-aortic lymph nodes in addition to the right gonadal vessels. There was not consensus among panel members whether omission of [205]para-aortic lymph nodes above the inferior mesenteric artery from the template is acceptable. Studies have reported a 19% rate of positive lymph nodes in this region among patients with right-sided tumors and pathological stage II disease.[204] For left-sided tumors, an acceptable modified template must include the left common iliac, para-aortic, pre-aortic, and retro-aortic lymph nodes. There was not consensus whether the interaortocaval lymph nodes may be safely omitted when performing a left modified template dissection. Rates of lymph node metastases in this region are reported in 22% of patients with left-sided tumors who have pathological stage II disease.[204]

37. After primary RPLND, clinicians should recommend surveillance or adjuvant chemotherapy in patients with NSGCT who have pathological stage II disease that is not pure teratoma. (Moderate Recommendation; Evidence Level: Grade B)

- **For patients with pN1 and/or pN1-3 pure teratoma, surveillance is preferred.**
- **For patients with pN2-3 at RPLND, multi-agent cisplatin-based chemotherapy is preferred.**

Among men having a primary RPLND, options for adjuvant treatment versus surveillance are based on pathologic findings from the surgery. A randomized trial of adjuvant chemotherapy versus observation for pathological stage II disease after primary RPLND showed significant reduction in relapse but no difference in overall survival.[190] For men with no cancer at lymphadenectomy, teratoma, or low-volume nodal metastases (pN1) with negative tumor markers and complete resection, RPLND offers a greater than 90% cure as a single modality.[160] For men with viable non-teratoma at RPLND specimen and pN2, recurrence rates with surveillance were 58% (35 of 60 patients) in a randomized trial and as high as 93% (13 of 14 patients) in a single institution series.[207,208] In a large randomized study evaluating surveillance versus adjuvant chemotherapy following RPLND for pN1-N3 NSGCT, recurrence rates were lowered from 50% to 6% following chemotherapy, but overall survival rates were similar due to the effectiveness of salvage chemotherapy, when needed.[190] Other studies indicate adjuvant chemotherapy (EP x 2 or BEP x 2) reduces recurrence rates to 0-7%.[190,207, 209, 210]

A retrospective study examined 156 patients with PSII NSGCT that received two cycles of EP after RPLND.[210] Thirty (19%) had pathologic N1, 122 (78%) had pathologic N2 (pN2), and four (3%) had pathologic N3 (pN3) disease. One hundred fifty patients (96%) received two cycles of EP, five received one cycle of EP, and one received four cycles of EP. Median follow-up was nine years. Only two patients experienced a relapse, and both responded well to salvage chemotherapy. The 10-year disease-specific, relapse-free, and overall survival rates were 100%, 98%, and 99%, respectively. The study had no comparator group but had long follow-up and supports the current

guideline of multi-agent cisplatin-based chemotherapy for pN2 patients, however the authors concluded that two cycles of EP instead of 2 cycles of BEP is likely sufficient in this patient population.

Surveillance for Stage I Testicular Cancer

38. For patients with clinical stage I seminoma choosing surveillance, clinicians should obtain a history and physical examination and perform cross-sectional imaging of the abdomen with or without the pelvis, every 6 months for the first 2 years, and then every 6-12 months in years 3-5. Routine surveillance imaging of the chest and serum tumor marker assessment can be obtained as clinically indicated. (Strong Recommendation; Evidence Level: Grade B)

The safety of surveillance in clinical stage I seminoma has been well established, with disease-specific survival approaching 100%.[211-214] Relapse rates range from 13-19%.[211] At relapse, good-risk features are identified in 99% of cases, and nearly all relapses are cured with salvage therapy. Accordingly, it remains a central tenant for close monitoring to identify relapses in a timely manner. Adherence to a prescribed regimen of surveillance with office visits, imaging, and laboratory testing when indicated is important to optimize detection and minimize treatment burden and morbidity. There are no randomized trials comparing follow-up schedules for physical examinations and tumor markers for surveillance in stage I seminoma. A phase III, non-inferiority trial of seven (6, 12, 18, 24, 36, 48 and 60 months) versus three (6, 18 and 36 months) CT/MRI scans in the surveillance of stage I seminoma demonstrated that 3 scans was not inferior to 7 in the detection of advanced disease (clinical stage IIC or higher) at relapse (2.8% vs. 0.7%). MRI was also deemed to be non-inferior to CT in the detection of relapses on surveillance and may be substituted for CT if situations prohibit the latter's use.[215]

However, this remains a challenge for many patients and physicians, with up to 30% of patients on surveillance for clinical stage I seminoma receiving no evaluation or assessment during the first year after diagnosis according to a private insurance claims database.[216] The pattern of relapse in early-stage seminoma is relatively predictable. Relapses on surveillance are identified by CT scan in 87% of patients and by serum tumor marker elevation in 3% of patients; nearly all patients with intrathoracic failure had at least one other indicator of relapse (tumor markers or by abdominal scan).[211] The role of routine serum tumor marker assessment in all patients at every visit is of limited value given that the majority of relapsing patients will be identified on imaging. Therefore, consideration for routine assessment with hCG can be limited to only those with elevated hCG prior to orchiectomy; reserving full panel serum tumor marker assessment as clinically indicated in the remaining patients for concerns of new onset symptoms or radiographic changes suggestive of relapse. Timing of relapse occurred at a median of 14 months with 92% of cases identified during the first 3 years of surveillance. Therefore, the first 36 months remains the period of the most intensive assessment. The role for routine imaging of the chest and pelvis remains uncertain. Because isolated chest relapses are rare, chest imaging should be reserved for patients identified with elevated serum tumor markers or radiographic evidence of disease in the retroperitoneal. Routine imaging of the pelvis is also associated with a low yield for identifying isolated relapses in the absence of retroperitoneal disease and can be omitted; such imaging may be obtained when signs of relapse are evident.[211] A suggested follow-up protocol can be found in **Table 7**.

TABLE 7: CLINICAL STAGE I SEMINOMA- ACTIVE SURVEILLANCE FOLLOW-UP

Clinical Stage I Seminoma- Active Surveillance Follow-Up			
	Years 1-2	Years 3-5	> Year 5
History and Physical **CT abdomen +/-pelvis**	Every 6 months	Every 6-12 months	If clinically indicated

39. In patients with stage I NSGCT undergoing surveillance after orchiectomy, clinicians should perform a physical examination and obtain serum tumor markers (AFP, hCG +/- LDH) every 2-3 months in year 1, every 2-4 months in year 2, every 4-6 months in year 3, and every 6-12 months for years 4 and 5. (Moderate Recommendation; Evidence Level: Grade C)

More than 95% of patients with stage I NSGCT on surveillance who experience a recurrence will do so during the first 2 years. [175,211] There are no randomized trials comparing follow-up schedules for physical examinations and tumor markers for surveillance in stage I NSGCT.

Relapses occur in 34-54% of patients with lymphovascular invasion and in 14-26% of patients with no lymphovascular invasion. [171, 173,175,211,217-219] Generally, early relapses[175] and relapses in lymphovascular invasion-positive patients[211] are detected by elevation in serum tumor markers. Based on the higher recurrence rates and earlier recurrences in patients with lymphovascular invasion, a follow-up interval at the more intensive end of the ranges provided is recommended. While relapses after two years are uncommon, they are more likely in patients without lymphovascular invasion.[220,221] A suggested follow-up protocol can be found in **Table 8**.

40. In patients with stage I NSGCT undergoing surveillance after orchiectomy, radiologic assessment (chest x-ray and imaging of the abdomen with or without the pelvis) should be obtained every 3-6 months in year 1 starting at 3 months, every 4-12 months in year 2, once in year 3, and once in year 4 or 5. (Moderate Recommendation; Evidence Level: Grade B) Men at higher risk of relapse (e.g., lymphovascular invasion) should be imaged with shorter intervals. (Expert Opinion)

For men with stage I NSGCT, chest imaging and physical examination detected less than 3% of relapses.[211]

A randomized trial (MRC-TE08) compared frequency of CT chest and abdomen imaging in the surveillance of patients with stage I NSGCT, where 414 patients (10% were lymphovascular invasion-positive) were enrolled from 1998 to 2003, and randomized to either CT at 3 and 12 months or CT at 3, 6, 9, 12, and 24 months.[219] This study found no significant difference in the rate of IGCCCG intermediate-prognosis relapse between the 2 arms (0.8% versus 0.6%, respectively), and no patients recurred with poor-risk disease.[219] While this study shows 2 scans are no worse than 5 scans, it is important to keep in mind that 90% of the patients in this study were classified as low-risk (no lymphovascular invasion).

41. Patients who relapse on surveillance should be fully restaged and treated based on their TNM-s status. (Moderate Recommendation; Evidence Level: Grade C)

TABLE 8: CLINICAL STAGE I NSGCT- ACTIVE SURVEILLANCE FOLLOW-UP

Clinical Stage I NSGCT- Active Surveillance Follow-Up						
	Year 1	Year 2	Year 3	Year 4	Year 5	> Year 5
History and Physical and Tumor markers	Every 2-3 months	Every 2-4 months	Every 4-6 months	Every 6-12 months	Every 6-12 months	If clinically indicated
Chest x-ray and CT abdomen +/- pelvis	Every 3-6 months	Every 4-12 months	Once	Once		If clinically indicated

Among clinical stage I seminoma patients on surveillance, relapses are observed in approximately 13%, the median time to relapse is 14 months, and the site of relapse is the retroperitoneal lymph nodes in the vast majority of patients. Abdominal-pelvic CT imaging is the most common means by which relapses are detected (87%). For clinical stage I NSGCT patients on surveillance, relapses are observed in 19%, and the median time to relapse is 4-8 months. Abdominal-pelvic CT imaging and elevated AFP and/or hCG levels identified relapses in 41-52% and 33-61% of patients, respectively, depending on the presence or absence of lymphovascular invasion.[211,222] Isolated retroperitoneal disease without elevated AFP or hCG is present in 53% of relapsing NSGCT patients. Clinical stage I seminoma and NSGCT patients with evidence of relapse on surveillance should undergo repeat staging imaging studies as for newly-diagnosed GCT, including physical examination (including the contralateral testis), chest-abdominal-pelvic imaging, and serum tumor marker (AFP, hCG, LDH) determinations. Patients should be assigned a new TNM-S clinical stage according to the results of these repeat staging investigations, and they should be treated according to the clinical stage assignment at the time of relapse. Among clinical stage I seminoma and NSGCT patients with relapse, approximately 99% and 90% are classified as IGCCCG good-risk, respectively. For the former, 61% and 32% are treated with cisplatin-based chemotherapy and radiation therapy, respectively, and survival rates exceed 99%. For the latter, 59-89% and 11-38% are treated with cisplatin-based chemotherapy and RPLND, respectively, and survival rates approach 99%.[211,222]

In rare instances, evidence of relapse may arise from a de novo metachronous contralateral primary tumor. This is more likely to be seen among patients who have a palpable mass in the contralateral testis, a long disease-free interval (> 4 years) on surveillance, and/or a pattern of relapse more typical of a contralateral primary tumor (e.g., isolated retroperitoneal disease in the primary landing zone of the non-affected testis). In these patients, a testicular ultrasound should be obtained to rule out a metachronous contralateral primary tumor.

42. Clinicians should inform patients with stage I GCT on surveillance of the ≤1% risk of late relapse after 5 years. (Moderate Recommendation; Evidence Level: Grade B) Annual serologic and radiographic assessment may be performed thereafter as indicated based upon clinical concerns. (Clinical Principle)

Large surveillance studies have shown the rate of late recurrence (>5 years) in patients with stage I GCT is ≤1%.[175,211] Given such a low rate of late recurrence, routine testing after five years is not universally needed, and the decision to perform a physical examination, serum tumor marker testing, and radiologic assessment should be individualized.

ADDITIONAL SURVIVORSHIP

43. Clinicians should refer patients to a survivorship clinic appreciating the long-term risks and potential sequelae of prior treatment among patients with GCT, with the integration of screening and monitoring for potential medical issues which may arise (Expert Opinion) including:

- **Monitoring for signs and symptoms of hypogonadism. If present, serum AM testosterone and luteinizing hormone (LH) levels should be measured.**
- **Patients with a history of GCT whose treatment has included radiation therapy, chemotherapy, or both should be advised of the elevated risk of cardiovascular disease and should establish regular care with a primary care physician so that modifiable risk factors for cardiovascular disease (e.g., diet, exercise, smoking, serum lipid levels, blood pressure, serum glucose) can be monitored.**
- **Patients with a history of GCT whose treatment has included radiation therapy, chemotherapy, or both should be advised of the elevated risk of secondary malignancy and should establish regular care with a primary care physician for appropriate health care maintenance and cancer screening as appropriate.**

Despite an increase in the incidence of GCT globally,[223, 224] the survival rate for patients impacted with this malignancy continues to improve, with most of this resulting as a consequence of the efficacy of cisplatin based chemotherapy.[225] With an overall survival rate at 10 years approximating 95%,[226] there has been an increasing realization that patients diagnosed and treated with GCT using a host of treatment modalities including systemic chemotherapy, radiotherapy, surgery, or a combination of these remain at risk of developing a number of clinical conditions including (but not solely confined to): anxiety, cardiovascular disease, cognitive impairment, chronic fatigue, depression, metabolic syndromes including hypogonadism, nephrotoxicity, neurotoxicity, infertility, ototoxicity, and importantly secondary malignancies.[227, 228] In consequence, the establishment of a comprehensive and long-term survivorship program screening and assessing these patients for these potential sequelae of prior GCT treatment has been shown to be advantageous and something that should be recommended and offered.[227]

FUTURE DIRECTIONS

Biomarkers for Micrometastases in Low-Stage GCT

Practice patterns of patients with clinical stage I seminoma and NSGCT indicate a substantial shift towards surveillance, even among those with risk factors.[229] Lymphovascular invasion is the only parameter that reliably identifies patients at risk for relapse among patients with clinical stage I NSGCT, and the risk of lymphovascular invasion varies from 35-55%.[230,211] Thus, patients who relapse following surveillance are exposed to treatment intensification. Likewise, adjuvant therapy exposes a substantial proportion of patients to treatment and its associated toxicity who were otherwise cured by orchiectomy. Lastly, despite changes to surveillance protocols, patients on surveillance are subject to intensive monitoring. Circulating biomarkers that reliably identify the presence of residual disease may be helpful in selecting clinical stage I patients for adjuvant therapy, identifying which patients with residual masses after chemotherapy benefit from surgical resection, and modifying surveillance schedules.

In early clinical studies, serum microRNA (miRNA) has demonstrated substantial promise as a biomarker. miRNA are small, non-coding RNA molecules that interact with messenger RNA (mRNA) to regulate gene expression at the post-transcriptional stage. In several cancer types, miRNA plays a role in malignant transformation and exhibits aberrant expression.[231,232] In malignant GCT, expression analysis has demonstrated increased expression of several miRNA clusters, specifically miR-371-373 (chromosome 19q13), and miR-302-367 (chromosome 4q25).[233,234] Both of these are specific to GCT and elevated in patients with both seminoma and NSGCT. Of the miRNA clusters, miR-371a-3p has the best performance characteristics as a biomarker in terms of sensitivity, specificity, and accuracy. Serum levels of miR-371a-3p have been shown to correlate with the extent of disease, response to therapy, relapse, and presence of residual malignant GCT elements.[235-237] Serum levels of miR-371a-3p are not elevated in patients with teratoma. On the basis of the accumulating evidence in support of miR-371a-3p, two large intergroup trials are under development to define the role of miR371a-3p as a circulating biomarker in low-stage and advanced GCT to guide subsequent therapy.

Primary Surgical Management of Low-Volume Metastatic Seminoma

Primary RPLND has previously not been considered in the treatment of low-stage seminoma. Favorable outcomes with primary radiotherapy and primary chemotherapy are associated with acceptable acute toxicity and have been considered the standard-of-care for decades. However, concerns about late toxicity of these modalities has stimulated renewed interest in RPLND for clinical stage IIA and IIB seminoma. Primary RPLND has been a standard option for low-stage NSGCT with proven oncological efficacy and favorable short- and long-term morbidity. In comparison with NSGCT, seminoma is well-suited to treatment by RPLND as it is more likely to spread via lymphatic routes and has lower risks of occult systemic disease. RPLND for IIA and IIB seminoma has been evaluated in small studies, and low relapse rates with surgery alone have been reported.[238-240]

ABBREVIATIONS

Alpha-fetoprotein	AFP
American Joint Committee on Cancer	AJCC
American Urological Association	AUA
Bleomycin, Etoposide, Cisplatin	BEP
Board of Directors	BOD
Confidence Interval	CI
Computed tomography	CT
Etoposide, Cisplatin	EP
Germ Cell Neoplasia In Situ	GCNIS
Germ Cell Tumors	GCT
Human Chorionic gonadotropin	hCG
International Germ Cell Cancer Collaborative Group	IGCCCG
Lactate Dehydrogenase	LDH
Luteinizing Hormone	LH
Magnetic Resonance Imaging	MRI
Negative Predictive Value	NPV
Non-seminomatous germ cell tumors	NSGCT
Positron Emission Tomography	PET
Positive Predictive Value	PVV
Practice Guidelines Committee	PGC
Randomized Controlled Trials	RCT
Retroperitoneal Lymph Node Dissection	RPLND
Relative Risk	RR
Science and Quality Council	SQC
Surgery in Early Metastatic Seminoma	SEMS
Testis-Sparing Surgery	TSS
Undescended Testis	UDT
Union Internationale Contre le Cancer	UICC

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DISCLAIMER

This document was written by the Testicular Cancer Panel of the American Urological Association Education and Research, Inc., which was created in 2019. The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chair. Panel members were selected by the Panel and PGC Chair.

Membership of the panel included specialists with specific expertise on this disorder. The mission of the panel was to develop recommendations that are analysis-based or consensus-based, depending on panel processes and available data, for optimal clinical practices in the testicular cancer setting.

Funding of the panel was provided by the AUA. Panel members received no remuneration for their work. Each member of the panel provides an ongoing conflict of interest disclosure to the AUA.

While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses (“off label”) that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not in-tended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management that are too new to be addressed by this guideline as necessarily experimental or investigational.

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