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Testicular Cancer in Men: Epidemiological Characteristics, Modern Diagnostic and Treatment Approaches, and Preventive Strategies

Mamarasulova Dilfuzahon Zakirjanovna*, Jalolov Oybek Jamoldinovich

Department of Oncology, Andijan State Medical Institute, Andijan, Uzbekistan

Abstract Background: Testicular cancer is the most common solid malignancy in adolescent and young adult males and demonstrates marked geographic and temporal variation in incidence, with consistently high cure rates due to modern multimodal therapy. Objective: To summarize epidemiological characteristics of testicular cancer in men and present contemporary approaches to diagnosis, treatment, and prevention, emphasizing guideline-based practice and survivorship priorities. Methods: Narrative review of key international guidelines and high-impact evidence describing global epidemiology, risk factors, diagnostic algorithms(ultrasound, serum markers, staging imaging), risk stratification (IGCCCG), primary and post-chemotherapy surgery, systemic therapy (BEP/EP regimens and salvage strategies), and preventive frameworks (primary, secondary, tertiary prevention). Results: Incidence has increased in many regions, particularly in Europe and other high-income settings, while mortality remains low. Cryptorchidism and family history are the most established risk factors. Diagnosis relies on prompt scrotal ultrasound, AFP/β-hCG/LDH assessment, and radical inguinal orchiectomy followed by CT-based staging. Treatment is stage- and histology-adapted: surveillance is preferred for many stage I patients; carboplatin is an option for selected stage I seminoma; one-cycle adjuvant BEP reduces relapse in high-risk stage I non-seminoma; metastatic disease is managed with cisplatin-based chemotherapy with surgery for residual masses when indicated. Survivorship care should address fertility preservation, cardiovascular/metabolic risks, neuro- and ototoxicity, pulmonary toxicity, and psychosocial outcomes. Conclusion: Testicular cancer is a highly curable malignancy when managed according to evidence-based guidelines. Future advances are expected from validated circulating biomarkers and continued treatment de-escalation strategies that preserve cure while reducing late toxicity.

Keywords Testicular cancer, Germ cell tumor, Seminoma, Non-seminomatous germ cell tumor, Cryptorchidism, Epidemiology, Tumor markers, AFP, β-hCG, LDH, Scrotal ultrasound, Radical inguinal orchiectomy, Staging, IGCCCG, BEP, EP, Retroperitoneal lymph node dissection, Surveillance, Fertility preservation, Survivorship

1. Introduction

Testicular cancer is a relatively rare malignancy, accounting for only about 1–1.5% of cancers in men [1]. However, it is the most common solid tumor in adolescent and young adult males (typically ages 15–40) [6]. Over 95% of cases are testicular germ cell tumors (GCTs), broadly classified into seminomas and non-seminomas [1]. Unlike most adult cancers that peak in older age, testicular cancer has an unusual age distribution – incidence peaks in the third decade of life for non-seminomatous tumors and in the fourth decade for pure seminomas [2]. Importantly, advances in therapy (especially the introduction of cisplatin-based chemotherapy in the 1970s) have transformed testicular cancer into a highly curable disease. For example, the cure rate for metastatic GCT improved from ~25% in the early 1970s (pre-cisplatin) to nearly 80% by the 1990s [24]. Today, with evidence-based multimodal management, over 90% of all newly diagnosed cases can be cured [3]. Nevertheless, a subset of patients with platinum-refractory disease still experience fatal outcomes, underscoring the need for continued research and strict adherence to best-practice guidelines.

This article provides a comprehensive overview of testicular cancer epidemiology, modern diagnostic work-up, current treatment protocols, and preventive strategies, emphasizing recent data and guideline recommendations.

2. Epidemiology and Incidence Trends

Rising Incidence: Globally, testicular cancer incidence has been increasing. The worldwide annual case load has roughly doubled in the past 40 years [22]. According to GLOBOCAN 2020 estimates, there were about 74,000 new

* Corresponding author:
dilya2580559@gmail.com (Mamarasulova Dilfuzahon Zakirjanovna)
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cases of testicular cancer worldwide in 2020 [4], making it one of the less common cancers overall (around the 20th most frequent cancer in men) [6]. The global age-standardized incidence rate (ASR) is approximately 1.7 per 100,000 men, but there is striking geographic variation [5,6]. The highest incidence is observed in developed regions – for example, across Europe the ASR is around 6.0–6.5 per 100,000 (with particularly high rates noted in Northern European countries like Norway, Denmark, and Slovenia) [2,6]. Other high-incidence regions include North America and Oceania (Australia/New Zealand), each with ASRs in the ~5 range. In contrast, incidence is much lower in Asia and Africa (often <1 per 100,000), making testicular cancer quite rare in those populations [6]. Notably, people of European ancestry have a higher predisposition regardless of residence – epidemiologic studies find that Caucasian populations maintain elevated rates even after migration, whereas males of African or Asian descent exhibit lower rates even when living in high-incidence countries [40]. Over time, many countries (e.g. the Netherlands, Germany, Canada) have documented a continuing rise in testicular cancer incidence, with some roughly doubling of cases over the past few decades [50]. This persistent increase appears to be a birth-cohort effect, suggesting that early-life or prenatal influences contribute to risk [50]. Despite rising incidence, mortality from testicular cancer has remained very low and relatively unchanged for over 30 years [6]. This reflects the high cure rates achieved with modern treatments – even in metastatic cases, long-term survival exceeds 95% in many populations [3].

Testicular cancer primarily affects young men. The peak incidence for non-seminomatous GCTs is in the late teens to 20s (around age 25–30), whereas seminomas tend to peak in the mid-30s [2]. Indeed, it is the most frequently diagnosed cancer among males ~20–34 years old in a number of countries [6]. There is also a smaller secondary incidence peak of rare spermatocytic tumors in much older men (typically >60 years), but these account for only a tiny fraction of cases.

At diagnosis, about 1–2% of testicular cancers are bilateral (either simultaneous or sequential tumors in both testes) [1]. There are marked racial/ethnic differences in risk: globally, White men have substantially higher incidence than Black or Asian men, and this disparity holds even within the same geographic regions [40]. The lifetime risk of developing testicular cancer for the average male is roughly 0.3–0.5% (approximately 1 in 200–250) – low compared to most other malignancies.

Several factors have been associated with increased risk of testicular GCT, although only a few are strongly predictive. The clearest risk factor is a history of cryptorchidism (undescended testis). Men with an undescended testicle have about a 3.7–7.5-fold higher risk of developing testicular cancer than those with normally descended testes [40]. Risk is highest for intra-abdominal testes and for men who undergo orchiopexy (surgical placement of the testis into the scrotum) after puberty, whereas early orchiopexy (before ~1 year of age) appears to partially mitigate the risk [40,41,42]. Another important risk factor is a positive family history of testicular cancer – particularly an affected father or brother. Having a brother with testicular cancer may increase one's risk by roughly 8–10-fold, and having an affected father confers a 4–6-fold risk, reflecting familial or genetic susceptibility [40]. (However, known genetic factors thus far explain only a minority of this familial clustering [22], implying undiscovered genetic loci or shared environmental exposures might be involved.) The concept of testicular dysgenesis syndrome (TDS) has been proposed as an underlying predisposition to GCT – TDS links developmental abnormalities like cryptorchidism, hypospadias, and impaired fertility to a common etiologic pathway that also leads to germ-cell neoplasia [41]. Consistent with this, infertility or subfertility is associated with a 2–3-fold higher risk of testicular cancer [22]. Increased adult height (tall stature) has also been modestly linked to higher risk [22] – a dozen studies found that above-average height correlates with elevated incidence, supporting a hypothesis that childhood nutrition and growth factors might influence risk [40]. Additionally, various environmental exposures are under investigation. For example, some studies implicate early pesticide or organochlorine exposures with about a threefold increased risk of testicular cancer [22]. Ongoing discussions also center on whether prenatal exposure to endocrine-disrupting chemicals (e.g. excess estrogens or anti-androgens) could be contributing to the rising incidence, though definitive environmental risk factors remain unproven [42,43,44]. On the other hand, clearly protective factors are not well established (aside from early correction of cryptorchidism potentially lowering risk). It's important to note that except for cryptorchidism, most identified risk factors (family history, genetics, etc.) are not modifiable. Fortunately, even as incidence varies by population, the survival rate for testicular cancer is excellent worldwide. In the United States, for example, the 5-year relative survival is ~95% overall – around 99% for localized disease and ~73% even for distant metastatic disease [18]. Similar outcomes are seen in other high-income countries, making testicular cancer one of the most curable solid malignancies.

Clinical Presentation and Diagnosis

The majority of men with testicular cancer present with a painless mass or swelling in one testis. Often the patient (or partner) notices a unilateral testicular enlargement or nodule, sometimes described as a feeling of heaviness in the scrotum. Indeed, most cases are detected by the patient rather than on routine physical exams [18].

Classically the mass is firm and non-tender; acute pain is an uncommon presentation (occurring in a minority of cases, usually due to hemorrhage or infarction within a rapidly growing tumor). Because a cancerous testicular mass is often asymptomatic, the swelling may initially be mistaken for benign conditions like a hydrocele or epididymal cyst. It is not unusual for young men to delay seeking evaluation, attributing the testicular change to trauma or infection. Any persistent testicular abnormality, however, warrants prompt assessment. In a small subset of patients, secondary signs of testicular cancer can manifest: for example, gynecomastia (breast tenderness or enlargement) occurs in ~5–10% of GCT

cases due to tumor secretion of hormones – notably, elevated hCG from certain tumors can stimulate breast tissue [22]. Some patients (especially those with extensive disease) first come to attention because of symptoms from metastases – for instance, back pain from bulky retroperitoneal lymph node masses, cough or dyspnea from pulmonary metastases, or rarely neurologic symptoms from brain metastases. Because testicular cancer initially metastasizes to the retroperitoneal (paraaortic) lymph nodes, very large abdominal nodal tumors can develop before causing symptoms; thus, an advanced case may present with a massive retroperitoneal mass and associated weight loss or abdominal pain despite a relatively small testicular primary tumor [22].

On physical exam, the classic finding is a firm, fixed, intratesticular mass that does not transilluminate (unlike a fluid-filled hydrocele). A thorough exam of both testes is essential, and one should also palpate for supraclavicular or inguinal lymphadenopathy and examine the abdomen (for hepatomegaly or palpable nodal masses) as part of staging the extent of disease.

Diagnostic Work-Up: The evaluation of a suspected testicular tumor involves clinical examination, scrotal imaging, and laboratory studies, followed by surgical confirmation. A high-frequency scrotal ultrasound is the imaging modality of choice for any testicular mass. Ultrasound can readily distinguish an intratesticular solid tumor from extratesticular benign lesions (such as hydroceles, spermatoceles, or epididymal cysts) [1]. It has excellent sensitivity for even small intratesticular tumors, often appearing as a solid hypoechoic intratesticular lesion with increased vascular flow on Doppler. Ultrasound is so sensitive that it can detect impalpable tumors; therefore, guidelines recommend performing a testicular ultrasound if the physical exam is equivocal or if a patient presents with retroperitoneal metastases of an unknown primary (to search for a small testicular tumor) [1]. Once an intratesticular tumor is confirmed by imaging, tumor marker tests should be obtained. The standard serum tumor markers for testicular GCTs are alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (β-hCG), and lactate dehydrogenase (LDH). These markers are measured before orchiectomy and repeated after orchiectomy, as they aid in diagnosis, histologic inference, and staging [1]. Elevated AFP or β-hCG levels can support the diagnosis of a GCT and may even hint at the tumor subtype – for example, a markedly elevated AFP is produced by yolk sac elements and thus indicates a non-seminomatous component (pure seminomas never produce AFP) [1]. β-hCG can be elevated in both seminomas and non-seminomas (especially choriocarcinoma, which causes very high hCG levels), while LDH is a non-specific marker correlating with tumor bulk. It is important to note that normal tumor marker levels do not rule out testicular cancer – roughly 15–20% of non-seminomatous GCTs have normal preoperative markers, and pure seminomas virtually never elevate AFP and only occasionally cause a modest hCG elevation [1]. Nevertheless, if markers are elevated pre-orchiectomy, their persistence after removal of the tumor indicates occult metastatic disease.

Post-orchiectomy marker half-life kinetics (AFP and hCG should drop at characteristic rates) are tracked; persistently elevated or rising marker levels after removal of the testis imply residual cancer and help assign the clinical stage [1]. Markers are also invaluable for monitoring treatment response and for detecting relapse during follow-up [1]. In addition to these conventional markers, new biomarkers are under active investigation: for example, circulating microRNAs (notably the miR-371~373 cluster) have shown promise in detecting viable germ cell tumor cells with high sensitivity [15,16]. Early studies indicate that serum miR-371a-3p is elevated in ~90% of all GCTs and clears rapidly after orchiectomy, potentially outperforming the traditional markers in diagnosing and monitoring disease [15,16,17,18,19,20,21,22,23]. These miRNA assays are still in clinical trials and not yet part of routine practice pending further validation [15].

After imaging and blood tests, the definitive diagnostic step is a surgical exploration and orchiectomy. When testicular cancer is suspected, a radical inguinal orchiectomy is performed – this involves an incision in the groin and removal of the entire testis together with the spermatic cord up to the internal inguinal ring. A trans-scrotal approach (biopsy or orchiectomy via the scrotum) is contraindicated, as it could spill tumor cells into the scrotal subcutaneous tissues or alter the lymphatic drainage – the inguinal approach is the standard of care [1]. The orchiectomy specimen is sent for comprehensive pathological examination. Histology confirms the tumor type (seminoma vs. the various non-seminomatous elements such as embryonal carcinoma, yolk sac tumor, choriocarcinoma, teratoma, or mixed GCT). About 40% of cases are pure seminoma, while ~60% involve at least some non-seminomatous components (mixed tumors) [1]. Pathology reports also document features like the tumor's T stage, the presence of lymphovascular invasion (LVI, which is prognostically significant in stage I disease), and whether carcinoma in situ is present in adjacent parenchyma.

Clinical staging of testicular cancer is completed with imaging of the typical metastatic landing zones. A contrast-enhanced CT scan of the abdomen and pelvis is obtained to evaluate the retroperitoneal lymph nodes – the primary site of spread for testicular GCTs. Chest imaging is also needed: a chest CT is more sensitive for small pulmonary metastases, but in low-stage cases a plain chest X-ray may suffice to check for lung nodules (since the lungs are the next most common site of metastasis). Current guidelines recommend at least an abdominal/pelvic CT for staging, generally prior to or shortly after orchiectomy [20]. If there are known lung metastases, very high hCG levels (>5,000 mIU/mL), or any neurologic symptoms, a brain MRI is obtained to exclude intracranial metastases [1]. (Brain metastases are relatively rare in testicular cancer – occurring mostly in choriocarcinoma or very advanced disease.) There is no role for bone scan in routine staging, as bone metastases are uncommon except in very late-stage cases [1]. Similarly, FDG-PET scanning is not recommended for initial staging of testicular cancer [1]. (PET has a niche role later in management: for post-chemotherapy seminoma patients with residual masses >3

cm, an FDG-PET can help distinguish fibrosis from active tumor, and guide further treatment [45]. This is considered during follow-up rather than at diagnosis.) Once orchiectomy and staging work-up are completed, the cancer is assigned a stage: Stage I (disease confined to the testis), Stage II (spread to retroperitoneal lymph nodes), or Stage III (distant metastases such as lung, liver, brain, etc). In addition, metastatic germ cell tumors are stratified by the International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic classification into Good, Intermediate, or Poor risk categories based on markers and extent of disease [7,8].

This risk group (for advanced disease) guides therapy intensity. For example, IGCCCG "good-risk" patients have very high expected cure rates and can be given slightly less intensive therapy, whereas "poor-risk" patients (e.g. those with very high marker levels or non-pulmonary visceral mets) require the most aggressive therapy. (The original IGCCCG model was defined in 1997 [7]; in recent years it has been refined with updated data, improving prognostication for modern patients [21].

In summary, the diagnostic approach to a testicular tumor includes prompt imaging (scrotal ultrasound) of any suspicious testis, serum tumor markers, and an inguinal orchiectomy for pathologic confirmation. A contralateral testis ultrasound is also recommended to screen for an asymptomatic contralateral tumor or intratubular neoplasia (GCNIS) in the opposite testicle [1]. With these steps, staging and risk stratification can be completed, which sets the stage for appropriate treatment planning.

Treatment Approaches

Modern management of testicular cancer is multidisciplinary and often multimodal, involving surgery, chemotherapy, and (in select cases) radiation therapy. The treatment strategy is guided by tumor histology and stage, following standardized protocols developed by expert groups like the NCCN, EAU, and others. Orchiectomy is the initial therapeutic step for all testicular tumors, and beyond that, therapy is risk-adapted to maximize cure while minimizing long-term toxicity in low-stage disease. Cure rates are outstanding: even patients with metastatic disease are often cured with appropriate systemic therapy. Below we outline the main treatment modalities and recommendations.

Surgical Treatment

Radical Orchiectomy: Inguinal orchiectomy is not only the diagnostic procedure but also the primary treatment for the localized tumor. Removing the affected testis (with its spermatic cord) achieves definitive local control and in many Stage I cases is curative as sole therapy [1]. After orchiectomy, the need for further surgical intervention depends on the situation.

Retroperitoneal Lymph Node Dissection (RPLND): The retroperitoneum is the first site of spread for testicular germ cell tumors (especially non-seminomas). RPLND is a surgical removal of the retroperitoneal lymph nodes. Its role in management varies by histology. For seminoma, RPLND is rarely utilized – seminomas are extremely radiosensitive and chemosensitive, so systemic therapy (or radiotherapy) is favored if additional treatment is needed. For non-seminomatous GCT (NSGCT), RPLND can be employed in two settings:

1. Primary RPLND in early-stage disease – historically this was a management option for clinical Stage I or IIA non-seminomas, particularly at some centers in the United States, as an alternative to adjuvant chemotherapy or surveillance. However, primary RPLND is now typically reserved for highly selected cases (e.g. a patient with Stage I NSGCT who is unable to comply with surveillance and prefers to avoid chemotherapy). Current guidelines emphasize surveillance or adjuvant chemotherapy over routine RPLND in Stage I NSGCT, but do allow that a meticulous nerve-sparing RPLND by an experienced surgeon is an option for those unwilling or unsuited for surveillance and adjuvant chemo [1]. Notably, a German randomized trial demonstrated that one cycle of BEP chemotherapy yields a significantly lower relapse rate than RPLND in high-risk Stage I NSGCT, establishing 1×BEP as a preferred strategy in those patients [12,13]. As a result, primary RPLND is infrequently chosen today.
2. Post-chemotherapy RPLND – this is a standard recommendation for advanced non-seminomas with residual masses. After first-line chemotherapy, any residual retroperitoneal masses >1 cm on CT in NSGCT should be surgically resected. This is because residual NSGCT masses often contain either persistent cancer or teratoma.

Teratoma, in particular, does not respond to chemo and can continue to grow or even undergo malignant transformation; therefore, surgical removal of all residual masses is critical. Thus, all patients with metastatic NSGCT receive a post-chemotherapy RPLND if imaging shows remaining retroperitoneal lesions (and sometimes additional surgery to resect residual lung or liver metastases, if present) [27,28]. For seminoma patients, routine post-chemo RPLND is not indicated – if a residual seminoma mass remains after chemotherapy, management can be observation (if PET scan is negative) or surgical removal if PET is positive and resection is feasible, but often these residual masses are just fibrotic tissue [45].

Surgical techniques for RPLND have evolved. Modern nerve-sparing RPLND techniques aim to preserve the sympathetic nerves that control ejaculation, in order to prevent retrograde ejaculation and maintain fertility potential. In experienced hands, a bilateral nerve-sparing RPLND can preserve antegrade ejaculation in ~90–95% of patients, even when done after chemotherapy [26]. Additionally, some centers have explored minimally invasive approaches (laparoscopic or robotic-assisted RPLND) in select cases, with the goal of reducing morbidity while achieving similar oncologic control. Minimally invasive RPLND is feasible for low-volume disease in expert hands, but open surgery

remains standard for post-chemotherapy dissections or extensive disease [26].

Apart from RPLND, other surgical considerations include testis-sparing surgery (TSS) and use of testicular prostheses. Partial orchiectomy (TSS) is rarely indicated in testicular cancer – it is considered only in very specific scenarios, such as in men with bilateral tumors or a tumor in a solitary testis, or when a small intratesticular lesion (<1 cm) is highly suspected to be benign (e.g. certain Leydig cell tumors). If a testis-sparing approach is attempted, an intraoperative frozen section is done; if malignancy is confirmed, an orchiectomy should be completed. In all patients undergoing orchiectomy, offering a testicular prosthesis (silicone implant) for cosmetic /psychological reasons is considered part of standard care.

Another preventive surgical measure is a contralateral testicular biopsy in high-risk individuals. About 5% of patients will have carcinoma in situ (CIS/GCNIS) in the opposite testis. The EAU guidelines recommend discussing a contralateral biopsy in those at elevated risk for an occult CIS – such as men with a history of cryptorchidism, markedly atrophic testes, or those <40 years old. If intratubular neoplasia (GCNIS) is found in the opposite testis, options include low-dose radiation therapy to the remaining testis or prophylactic orchiectomy to prevent progression to invasive cancer, balanced against the goal of preserving hormonal and fertility function.

Finally, fertility preservation is an important aspect of the management of testicular cancer. Because surgery (orchiectomy) removes one testis and chemotherapy can transiently or permanently impair spermatogenesis, sperm banking prior to starting chemotherapy is strongly recommended for virtually all patients who may want to father children in the future [36,37]. Centers follow established ASCO/AUA guidelines that advise offering semen cryopreservation to young men with cancer before treatment whenever possible [36].

Chemotherapy

The introduction of cisplatin-based combination chemotherapy revolutionized testicular cancer treatment in the 1970s [24]. Germ cell tumors are highly sensitive to platinum agents, and chemotherapy is the cornerstone of curative therapy for advanced disease. The standard first-line regimens are BEP (Bleomycin + Etoposide + Cisplatin) and EP (Etoposide + Cisplatin). Use of chemotherapy is tailored by stage and prognostic group.

Stage I Disease (Localized to Testis): Management of Stage I is risk-adapted. Many Stage I patients – especially those with seminoma or low-risk NSGCT – can be managed with surveillance alone after orchiectomy, thereby avoiding chemotherapy unless relapse occurs. The relapse rate on surveillance is about 15% for Stage I seminoma and ~30% for Stage I NSGCT without LVI [14]. Any relapses are then treated at that time with curative intent. However, certain patients with higher risk of relapse may be offered a short course of adjuvant chemotherapy upfront to pre-empt recurrence. In Stage I seminoma, current guidelines recommend surveillance as the preferred option if reliable follow-up is available, given the low relapse rate (~15%) and the fact that nearly all relapses are cured with chemotherapy at that time. If adjuvant therapy is desired (for example, in a patient anxious about relapse or with risk factors like tumor size >4 cm or rete testis invasion), a single dose of carboplatin (AUC 7) can be given – evidence shows that one cycle of carboplatin is as effective as retroperitoneal radiation in reducing seminoma recurrences [9,10,11]. Notably, routine adjuvant radiotherapy is no longer recommended for Stage I seminoma due to concerns about long-term toxicities (e.g. increased risks of secondary malignancies and cardiovascular disease) [39]. Radiation is now reserved only in unusual cases who cannot undergo surveillance or chemotherapy. In Stage I NSGCT, surveillance is also often preferred for low-risk patients (those with no LVI in the primary tumor) [14]. If pathological risk factors are present – such as lymphovascular invasion or other features of Stage IB (e.g. >T2) – then adjuvant chemotherapy with one cycle of BEP can be offered. One cycle of BEP reduces the relapse risk from ~30% down to ~3% [13]. Indeed, current practice (per NCCN and EAU guidelines) is to either closely observe or give a single cycle of BEP in Stage I NSGCT. A recent large trial ("111 Study") confirmed that one cycle of BEP is highly effective at preventing relapse in high-risk Stage I patients, with relapse rates ~1–2% and minimal toxicity [13, p. 346-351]. Consequently, many centers have adopted one-cycle BEP as the standard adjuvant regimen for high-risk Stage I NSGCT. Primary RPLND is an alternative in Stage I non-seminoma for those who wish to avoid chemo and are willing to undergo surgery, but as noted earlier this approach has become less common today [12].

Metastatic Disease (Stages II and III): For metastatic testicular cancer, systemic chemotherapy is the cornerstone of treatment. The choice of regimen and number of cycles is determined by the IGCCCG prognostic risk group. Good-risk metastatic GCT (which includes most Stage IIA/IIB and low-volume Stage III disease, as well as all pure seminomas without nonpulmonary visceral metastases) is typically treated with either 3 cycles of BEP or 4 cycles of EP – clinical trials have shown these to be equivalent options for good-risk patients [38]. Most centers use 3 ×BEP as first-line, reserving 4 ×EP for situations where bleomycin is contraindicated (e.g. significant pulmonary comorbidity) [38]. Intermediate-risk and Poor-risk metastatic disease (e.g. very high tumor marker levels, or nonpulmonary visceral metastases in NSGCT) is treated with 4 cycles of BEP as the standard regimen [1]. BEP chemotherapy involves cisplatin and etoposide administered daily for 5 days, with bleomycin given weekly; each cycle lasts 3 weeks. These regimens are highly effective: long-term cure rates are on the order of ~90% for good-risk and ~70–75% for poor-risk patients with first-line therapy [21].

(The IGCCCG update analysis found 5-year overall survival of 96% in good-risk, 89% in intermediate, and ~67% in poor-risk in the modern era– a significant improvement for poor-risk patients compared to the original 1990s data.)

If residual masses remain after first-line chemo (particularly in NSGCT), adjunct surgeries like RPLND (and resection of residual lung or liver lesions) are performed as discussed above. In seminoma, any residual mass >3 cm is evaluated with PET; if PET-positive, surgical resection or second-line therapy is considered [45].

Salvage Therapy: Approximately 10–20% of patients have disease that is refractory to first-line chemotherapy or that relapses after an initial remission. Fortunately, even many relapsed cases can be successfully salvaged. Common second-line salvage regimens include TIP (Paclitaxel + Ifosfamide + Cisplatin) and VeIP (Vinblastine + Ifosfamide + Cisplatin). For patients with more aggressive or multiply relapsed disease – especially those with initial poor-risk features – high-dose chemotherapy with autologous stem cell transplant is sometimes used (for example, high-dose carboplatin/etoposide following TIP induction, known as the TICE protocol). Overall, about half of patients who relapse can still be cured with these sequential salvage approaches [33,34,35]. Notably, seminoma that relapses after initial therapy can often still be cured with standard platinum-based chemo if it was not given previously (seminomas are highly chemo-responsive even in relapse).

Radiation Therapy

Radiotherapy plays a limited but specific role in testicular cancer management. Seminomas are extremely radiosensitive tumors. In the past, the standard management of Stage I seminoma was orchiectomy followed by adjuvant radiotherapy to the para-aortic (and ipsilateral pelvic) lymph nodes (the classic "dog-leg" field). This produced excellent tumor control – relapse rates were only ~4% – but decades of follow-up revealed small increases in secondary malignancies and cardiovascular disease among survivors. Consequently, adjuvant radiation is no longer recommended for Stage I seminoma. Guidelines explicitly state do not routinely perform adjuvant radiotherapy for Stage I seminoma. If any post-orchiectomy therapy is needed in Stage I, a single course of carboplatin is used instead, which carries fewer long-term risks.

Radiotherapy does still have a role in some advanced seminomas. For Stage II seminoma (disease spread to retroperitoneal nodes), radiation to the lymph nodes is one option. In Stage IIA (minimal nodal spread, nodes <2 cm), radiation to the para-aortic and ipsilateral pelvic lymph nodes (~20–30 Gy) yields cure rates around 95%. In Stage IIB (nodal masses ~2–5 cm), a higher dose (~36 Gy) can be used, achieving approximately 75–85% cure rates. However, many oncologists now favor primary chemotherapy (typically 3×BEP) for Stage IIB seminoma, especially if there are multiple nodes or larger volume disease, since chemo may slightly improve relapse-free survival and avoids the long-term side effects of radiation [39]. For Stage IIC or Stage III seminoma (extensive disease), radiation is not used – systemic chemotherapy is the preferred treatment. Non-seminomatous tumors are not treated with radiation in curative settings, because NSGCTs are less radiosensitive and systemic chemotherapy is far more effective. The only exceptions are brain metastases: if a patient has metastatic GCT involving the brain, therapy may include surgical resection or stereotactic radiosurgery for isolated lesions and/or whole-brain radiotherapy in addition to chemotherapy. (Prophylactic cranial irradiation is not utilized, unlike in some other cancers.) Radiotherapy can also be used for palliation of incurable disease – for example, to alleviate bone pain or other symptoms in a chemo-refractory patient.

In summary, radiotherapy's use is now mainly confined to certain seminoma scenarios (Stage II disease in select patients) and the occasional palliative setting, while the majority of testicular cancer patients are cured without needing any radiation exposure.

3. Survivorship and Late Effects

Through a combination of these modalities, the outcomes for testicular cancer are superb. It is often cited that testicular GCT is a model of a curable cancer – even with metastatic disease, the majority of patients achieve complete remission. Management should be delivered in a multidisciplinary setting (involving urology, medical oncology, and when appropriate radiation oncology and fertility specialists) and in accordance with expert-developed guidelines. Studies have shown that strict adherence to evidence-based guidelines maximizes cure rates while minimizing toxicity in testicular cancer care [20].

With cure rates now exceeding 95% in early-stage disease and >80% even in advanced disease, increasing attention has turned to survivorship and minimizing long-term treatment sequelae. Patients who receive chemotherapy and/or radiotherapy may experience late complications years after treatment. For example, cisplatin-based chemotherapy is associated with a higher long-term risk of cardiovascular disease (e.g. premature coronary artery disease) and metabolic syndrome [30,31,32]. Chemotherapy (especially cumulative dose of etoposide >2 g/m²) slightly increases the risk of secondary malignancies such as leukemia [29], and any prior radiotherapy raises the risk of secondary solid tumors in the irradiated field over time [29,30,39]. Additionally, many survivors have residual peripheral neuropathy or ototoxicity (high-frequency hearing loss) from cisplatin [47,48]. Bleomycin can cause pulmonary fibrosis – usually an acute toxicity, but it can lead to chronic lung changes and reduced pulmonary reserve in a subset of patients [46]. Fortunately, modern treatment protocols try to limit these risks: for instance, bleomycin is omitted for patients with lung compromise, and the trend has been to use the minimum effective number of chemo cycles (e.g. 3 cycles instead of 4 for good-risk disease). Clinical trials have confirmed that 3 cycles of BEP is sufficient for good-risk metastatic GCT, avoiding the toxicity of a 4th cycle without compromising cure [38]. Ongoing research is exploring predictive biomarkers (such as microRNAs) to better identify which early-stage patients can safely undergo surveillance versus needing adjuvant

therapy [15]. There is also interest in novel agents (targeted therapies or immunotherapy) for the rare patients with multiply relapsed GCT, but so far these tumors have not shown actionable mutations or robust response to checkpoint inhibitors – thus, conventional chemotherapy remains the gold standard.

Testicular cancer survivors should be followed long-term for monitoring of relapse and late effects. For recurrence surveillance, patients undergo a scheduled follow-up program with periodic tumor markers and imaging for at least 5–10 years after treatment (most relapses occur within 2–3 years of diagnosis) [25]. Follow-up intensity is tailored to initial stage and treatment – for example, those on surveillance or with higher-stage disease get more frequent CT scans in the first few years, whereas those who received adjuvant therapy or had low-stage disease require fewer scans [20]. This intensive surveillance can be viewed as a form of secondary prevention, aiming to catch any relapse early when it is highly curable. Survivorship care also includes counseling on healthy lifestyle and monitoring for late toxicities.

Young men cured of testicular cancer should have regular primary care to watch for cardiovascular risk factors (since cisplatin may increase risks) [30], and be assessed for psychosocial well-being and hormonal status (some survivors develop hypogonadism requiring testosterone replacement). Patient-reported outcomes generally show high quality of life years after treatment, but some survivors report anxiety about cancer, sexual or fertility issues, and peripheral neuropathy symptoms [49]. Support groups and counseling can be beneficial.

4. Preventive Strategies

Primary Prevention: Unlike many adult malignancies, there are no proven lifestyle changes that definitively prevent testicular cancer. This reflects the fact that the etiologic factors largely involve fixed genetic or developmental causes. Nevertheless, some preventive actions relate to known risk factors. The clearest example is early orchiopexy for cryptorchidism. Boys born with an undescended testis should undergo surgical correction in infancy – not only does this improve fertility potential, it also appears to lower (though not eliminate) the later risk of developing testicular cancer. A meta-analysis confirms that orchiopexy before puberty significantly reduces cancer risk compared to leaving the testis undescended or fixing it after puberty. Therefore, one preventive health measure is ensuring timely management of cryptorchidism (ideally by ~age 1). Apart from that, broad recommendations are less concrete. It is sensible to avoid or reduce exposure to environmental chemicals that are suspected to interfere with testicular development (e.g. certain endocrine-disrupting pesticides), though data on causation remain inconclusive [42]. There is no evidence that specific diets, supplements, or medications influence testicular cancer risk. Given the likelihood that testicular germ cell tumors have in utero origins, primary prevention at the individual level is challenging.

Screening and Early Detection: The goal with testicular cancer is early detection, since virtually all patients can be cured if the disease is caught at an early stage. However, routine population screening is not recommended by major guidelines (e.g. the U.S. Preventive Services Task Force and the American Cancer Society). The USPSTF reaffirms that screening asymptomatic males – whether by clinician testicular exam or patient self-examination – has no proven benefit in reducing mortality, given the cancer's low incidence and the excellent outcomes even when cancers present clinically [18,19]. In addition, universal screening could lead to unnecessary anxiety and interventions due to false positives. Therefore, formal screening programs are not advocated. Instead, emphasis is placed on awareness and prompt evaluation of any testicular changes. Young men (especially those in the highest-risk age group of 15–35) should be educated about the normal size and feel of their testes and encouraged to seek medical attention if they detect any lump, swelling, or persistent pain in a testicle [18]. Some clinicians advise a monthly self-exam for high-risk men (such as those with a history of cryptorchidism or family history), although this is optional. The key message is that early presentation leads to virtually 100% cure, so delays should be avoided. Public and provider education efforts continue to play a role in ensuring that testicular tumors are recognized and treated early.

5. Conclusions

Testicular cancer is a highly curable malignancy when managed with modern evidence-based approaches – a true "oncologic success story" in young adult males. Continued efforts in research, guideline implementation, and survivor care will ensure that this success is sustained and even further improved in the future.

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