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Testicular Carcinoma: Molecular Pathogenesis, Diagnostic Advances, and Evolving Therapeutic Strategies

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Abstract

Testicular carcinoma is the most common solid tumor in young male patients. Despite a high rate of survival, current treatments come with significant long-term toxicities, highlighting the need for more precise diagnostics and therapies. The current review focuses on the molecular pathogenesis, diagnostic development and evolving treatments of testicular germ cell tumors (TGCTs). TGCTs arise from the precursor lesion germ cell neoplasia of unclassified type or in situ (GCNIS) and consist of key genetic changes including isochromosome 12p along with changes affecting KIT/KITLG, Wnt/β-catenin, PI3K/AKT events. Recent developments in molecular and multi-omics profiling sow important differences between seminomatous and non-seminomatous subtypes and enable molecular taxonomy of the tumor as well as discovery of new targeted therapies. There is a change in the diagnostic landscape with the arrival of highly sensitive liquid biomarkers, specifically microRNA-371a-3p and circulating tumor DNA that enable precise, non-invasive monitoring and risk classification over time. Radical orchiectomy, chemotherapy and radiotherapy remain cornerstone treatments, but the field is rapidly evolving towards body- and function-sparing management. These include personalized medicine, immunotherapy, risk-stratified therapy and fertility preservation. Furthermore, we believe that the convergence of AI with molecular data improves prognostication and therapeutic decision making, ultimately guiding the field to less toxic and more effective patient-quality care.

Key words testicular carcinoma, germ cell tumors, molecular pathogenesis, biomarkers, mir-371a-3p, precision diagnostics, targeted therapy, immune-oncology

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Introduction

Testicular cancer is the most common solid tumor of young men 95% among most patients), the large number men affected and association between aggressive-acting metastases, long-term toxicities of standard treatments such as chemotherapy and radiotherapy have meant that Pca remains a significant clinical burden [1]. Such concerns have further raised the significance in understanding biological pathways that drive testicular carcinogenesis and devising more accurate, less harmful, techniques for early detection/treatment [2].

The majority of testicular carcinoma develops from germinoma neoplasia in situ (GCNIS), a precursor lesion reflecting perturbed embryonic germ cell differentiation [3]. The germ cell developmental biology, with its robust pluripotency, epigenetic plasticity and sensitivity to hormonal and environmental influences are instrumental in tumor initiation [4]. Consistent genetic changes and anomalies have been recapitulated at the level of protein mutations in testicular germ cell tumors (TGCTs), namely, i(12p), KIT and its ligand (KITLG) mutations as well as the Wnt/β-catenin and PI3K/AKT pathways activation [5]. This discovery clarifies the lineage of both seminomatous and non-seminomatous histology highlighting the heterogeneous nature of TGCTs that will likely have important implications for therapeutic response, and clinical outcomes [3].

The diagnostic terrain for testicular cancer has developed greatly in parallel with the molecular knowledge [2]. Historically, diagnosis was made based on physical examination findings along with scrotal ultrasound and serum tumor markers including b-HCG, LDH, and AFP [6]. However, sensitiveness and specification of these markers are poor and then they have driven the search for a better non-invasive marker [7]. Novel approaches, such as circulating tumor DNA and blood-based microRNA miR-371a-3p, have shown excellent diagnostic performance exceeding that of conventional markers for the diagnosis of recurrent disease, treatment monitoring, and active cancer detection [8]. Intermittent and irregular clinical biomarkers have largely enabled personalized disease monitoring [9]. In addition, imaging techniques represented by CT, MRI and PET are useful for staging and post-treatment residual disease evaluation or choosing the treatment options; in turn, high-resolution ultrasound has also made early detection of testicular masses possible [10]. More recently, research on radiomics and the application of artificial intelligence (AI) has been used to improve diagnostic accuracy by revealing subtle imaging patterns related to tumor biology, risk of recurrence or response to systemic therapy [11]. Testicular carcinoma is still one of the success stories in oncology with curative treatment. The mid-late 20th century administration of cisplatin-containing chemotherapy led to a dramatic increase in survival, including at the metastatic stage [12]. Current treatment strategies, comprising risk-adapted chemotherapy (e.g., Single agents based on the BEP regimen), targeted radiation and radical inguinal orchiectomy. show optimal cure rates [13]. Nevertheless, considerations concerning side-effects especially long-term sequelae like infertility, metabolic disorders, cardiovascular diseases or secondary cancers have stimulated an increased interest to optimize treatment concepts [14]. It is in this field that new strategies, such as molecular targeted agents, immune checkpoint inhibitors and reduced-intensity or watch-and-wait approach, seek to achieve a combination of curative potential and long-term survival. Fertility preservation and psychosocial care are some of the cornerstones of care, especially given that most patients are very young [15]. These new treatments including sperm banking, and testicular tissue preservation, as well as new developments in IUI provides novel strategies for the preservation of reproductive capacity.

We summarize existing data on the molecular pathogenesis of testicular carcinoma, recent advances in diagnosis and treatment. To this end, combining new advances in tumor biology, biomarker science, imaging and new precision oncology approaches aimed at more precisely tailoring treatment to each patient's individual risk profile we hope to provide a full spectrum overview of the disease and emergent strategies towards increasing cure rates and reducing long term toxicities. This review highlights the need for a multidisciplinary, patient-centered approach as testicular carcinoma treatment moves forward from its era of personalized medicine.

Histologic and clinical subclassification of testicular carcinoma

Testicular carcinoma includes several malignant tumors originating from germ cells in most cases and a minority arising from sex-cord stromal elements, or uncommon cell types [16]. World health organization (WHO) recognizes testicular tumors as: germ cell tumors (GCTs) and non-testicular GCTs that accounts for >95% of malignant neoplasms; whereas pure sex cord stromal, Sertoli cell-only tumor are classified as non–germ cell tumors which also include adnexal neoplasm, para-testicular liposarcoma associated with embryonal rhabdomyosarcoma, primary leiomyosarcoma of the tunica vaginalis and adenomatoid tumor [17]. It is essential to understand these subtypes because they are biologically distinct entities characterized by different treatment responses and clinical outcomes. Germ cell tumors (GCTs) are classified in seminomas and non-seminomatous germ cell tumors (NSGCTs), with separate histological, molecular, and clinical features found for each subclassification [18].

Seminomas originate from GCNIS and resemble primordial germ cells. Presentation is common at age 30-40 years, with a slow growth and radio-sensitivity of these tumors [19]. Seminomas usually present with homogeneous, well-circumscribed hypoechoic masses on US. From the molecular point of view, some of these cells often show expression of OCT3/4, SOX17, PLAP, CD117 (KIT), indicating the retention of their germ cell phenotype (Damjanov 2021). Despite their radiosensitivity, seminomas have an excellent prognosis with a cure rate of over 95%, even in the context of metastatic disease [20].

NSGCTs, however, primarily occur in younger men (20–30-year-old males) and are more biologically aggressive [21]. This category includes embryonal carcinoma, YST, choriocarcinoma, teratoma and mixed germ cell tumors representing two or more histological types [3]. Most of NSGCTs secrete tumor markers into the blood, including alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (b-hCG), so multimodal treatment such as chemotherapy plus surgery is required [7]. They are heterogeneous and differentiate to become part of the embryonic (embryonal carcinoma), yolk sac, chorionic (choriocarcinoma) or somatic teratoma lineages [3].

Non-germ cell neoplasms and are very uncommon yet have serious diagnostic as well as therapeutic implications (1994). Sex-cord stromal tumors are usually benign but can cause metastasis in rare occasions, including Leydig cell tumor and Sertoli cell tumor [22]. Steroid production may give rise to hormonal effects, such as gynecomastia and precocious puberty [23]. Rare para-testicular tumors include gonadoblastoma (a tumor of the genital ridge associated with chromosomal anomalies e.g. gonadal dysgenesis), primary testicular lymphoma (the most common testicular malignancy in older men), and supportive soft tissue sarcomas originating from the scrotal wall [16].

To guide the treatment decision-making, it is important to determine accurately what kind of classification it is. Seminomas and NSGCT show striking differences in the treatment sensitivity,

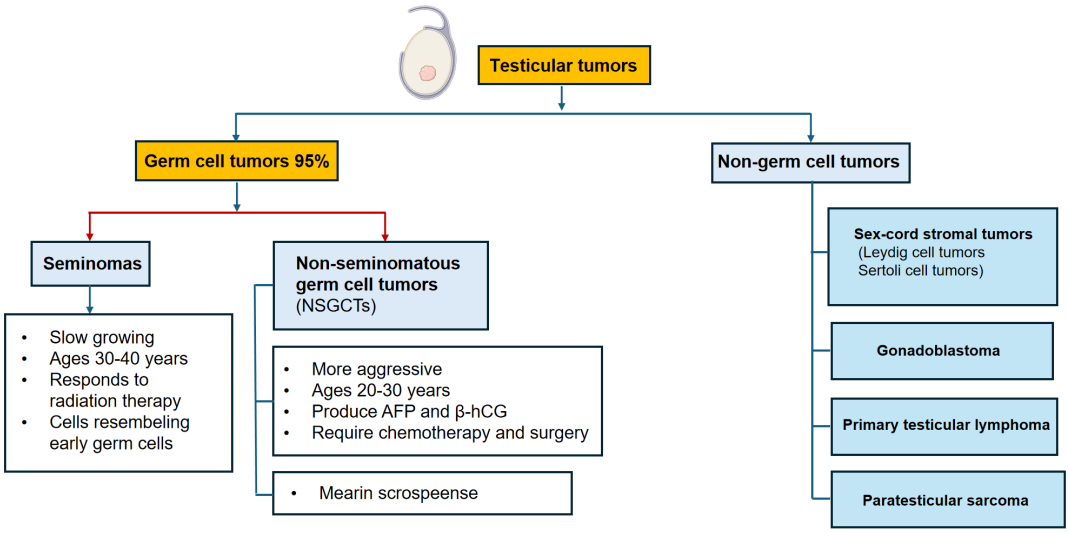

Figure 1. The histologic and clinicopathologic spectrum of testicular tumor. An illustration for seminoma and NSGCT. The seminoma panel shows a homogenous, well-circumscribed mass while the NSGCT panel exhibits a heterogeneous mass containing areas of hemorrhage and necrosis reflecting its aggressive mixed histology.

with seminomas responding well to radiotherapy but patients with sinonasal anal plastic carcinoma (SNAC) patients get treated with chemotherapy and other material surgery cases at least one adjuvant therapy [24]. For mixed tumors, surgery must be directed towards most the aggressive component. The advent of molecular profiling is further shaping this classification by providing information on treatment response and relapse risk. The International Germ Cell Cancer Collaborative Group (IGCCCG) system categorizes metastatic germ cell tumors into 3 risk categories-low, intermediate, and poor-based on tumor markers and sites of metastases. This is the framework upon which chemotherapy intensity and long-term survival estimates are based. A comparative schematic of seminoma and NSGCT histology is shown in **Figure 1**.

Molecular and cellular etiology of testicular carcinoma

Testicular cancer, and especially testicular germ cell tumors (TGCTs), is the consequence of an original carcinogenesis pathway that distinguishes it from other solid tumors [25]. They arise from precursors of primordial germ cell origin, and they maintain features of pluripotency, epigenetic sensitivity and responsiveness to endocrine/endogenous factors among others [26]. The molecular underpinning of their conversion is crucial to explain inherent clinical heterogeneity of the patients and significant sensitivity toward systemic therapies. The majority of TGCTs are derived from GCNIS, a precursor lesion that reflects disturbance in the normal developmental program of fetal germ cells [4]. Germ cells develop into the genital ridge during embryogenesis, proliferate and undergo epigenetic resetting in preparation for differentiation [27]. Derailment of this controlled mechanism by way of genetic susceptibility, hormonal deregulation, or environmental exposure leads to retention of embryonic-like germ cells in the post pubertal testis [28]. However, GCNIS cells do express key pluripotency genes such as Oct3/4, Nanog, Sox17 and c-KIT but do not initiate spermatogenesis. Although not yet fully understood, these cells undergo additional changes over time that ultimately result in the formation of either seminomatous or non-seminomatous tumors [29]. Such CIN, including the presence of isochromosome 12p [i(12p)], affecting as was shown for i(12p) in TGCTs the majority of invasive tumors, represents a specific molecular feature of TGCTs [30].

This deviation is the consequence of duplication of the short arm of chromosome 12, which results in an overexpression of genes involved in cell proliferation and stemness (such as KRAS, CCND2, NANOG and BCAT1) [30]. The initial stimuli leading to the development of i(12p) are largely unknown but represent a key transition between GCNIS and invasive cancer [31]. Gains of chromosomes 7, 8 and 21, and losses of chromosome 11 and 13-Are additional events contributing to treatment resistance. The relatively low somatic mutation burden in TGCTs as compared with other adult cancers indicates that oncogenic process is mainly mediated by chromosomal and epigenetic changes [32]. Epigenetic control is a main contributor to explaining the differential biological behavior of seminomas and NSGCTs. Seminomas display a globally undermethylated DNA profile much like the pattern demonstrated by PGCs, which correspond to their higher degree of undifferentiation. In contrast, NSGCTs present with increased DNA methylation and unique histone modifications that reflect differentiation into EC, YST, choriocarcinoma (CH), or teratoma [33]. The extent to which these epigenetic differences contribute to tumor biology is demonstrated by the phenotypic differences between tumors: while seminomas generally grow slowly and are radiosensitive, NSGCTs proliferate quickly with a degree of lineage heterogeneity showing differential sensitivities to treatment [32]. Continued activity of OCT3/4-, NANOG-, LIN28- and other stemness factor-regulated transcriptional networks drives tumorigenesis by promoting the retention of embryonic-like features [34]. Several important signaling pathways are involved in the process of development and progress of TGCT [5]. Alterations in KIT/KITLG pathway (such as c-KIT alterations and KITLG amplification) will have brought about the survival

Table 1. Comparison of testicular germ cell tumors: seminoma vs NSGCT.

Feature	Seminoma	Non-Seminomatous germ cell tumor (NSGCT)	Clinical / Pathological significance
Epigenetics	Hypomethylated	Hypermethylated	Seminomas: simpler epigenetic profile; NSGCTs: more complex
Markers	OCT3/4, SOX17, KIT	OCT3/4, SOX2, SALL4	Useful for immunohistochemistry diagnosis
Biology	Less differentiated	Highly heterogeneous	NSGCTs: mixed histology; Seminomas: more uniform
Treatment sensitivity	Radio- and chemosensitive	May require aggressive multimodal therapy	Seminomas: respond well to radiotherapy; NSGCTs: need combo therapy
Age of onset	30–40 years	20–30 years	Younger patients more often have NSGCT
Histology	Uniform, sheets of cells	Mixed: embryonal carcinoma, yolk sac, choriocarcinoma, teratoma	Guides pathologic diagnosis
Metastatic pattern	Lymph nodes primarily	Lymphatic and hematogenous spread	NSGCTs: lungs, liver, brain
Tumor growth rate	Slow-growing	Rapid-growing	NSGCTs can progress quickly
Prognosis	Generally excellent	Variable; depends on subtype and stage	Seminomas: very high cure rates
Serum tumor markers	Usually none or mild β-hCG elevation	AFP, β-hCG, LDH may be elevated	Useful for diagnosis and monitoring
Molecular alterations	KIT mutations common	TP53, KRAS, diverse mutations	Can influence targeted therapy research
Histological variants	Classic, spermatocytic	Embryonal carcinoma, teratoma, yolk sac tumor, choriocarcinoma	Helps with subtype-specific management
Key Clinical Features	Painless testicular mass, slow progression	Rapidly enlarging testicular mass, sometimes with symptoms from metastases	Guides clinical suspicion and workup

Abbreviations: NSGCT, non-seminomatous germ cell tumor; AFP, alpha-fetoprotein; β-hCG, beta-human chorionic gonadotropin; LDH, lactate dehydrogenase.

and proliferation advantage of GCPs, which are prevailing in seminomas [35]. The PI3K/AKT/mTOR pathway is frequently activated in seminomatous and non-seminomatous tumors enabling growth, metabolic adaption, and resistance to apoptosis [36]. Activation of the RAS/MAPK signaling pathway - often through KRAS activation or 12p amplification - enhances cell proliferation and has also been identified as a driver of invasiveness [37]. In addition, the increased expression of Wnt/β-catenin pathway in NSGCT s helps for the differentiation to embryonal carcinoma and teratomatous component [38]. The TME plays a large role in the biology of TGCT. Seminomas are frequently associated with marked lymphocytic infiltration, in which the activated Th1- and Ts-type T-cells could contribute to radiosensitivity. In contrast, NSGCTs usually present with a more immunosuppressive microenvironment, marked by the presence of tumor-associated macrophages [39]. Disparate expression of immune checkpoint molecules, such as PD-1 and PD-L1 reflects opportunities for development of immunotherapeutic measures in the future although their therapeutic application to the clinic is currently being worked on. Although originating from GCNIS, seminomas and NSGCTs show extensive dissimilarity in terms of their molecular and biological characteristics.

Seminomas are associated with a hypomethylated epigenetic profile, express both SOX17 and KIT, and present as relatively undifferentiated, which renders them highly sensitive to radiation and chemotherapy [40]. In contrast, NSGCTs are hypermethylated and express SOX2 and SALL4, suggesting they have a complex differentiation pattern that may warrant aggressive multimodal therapy [33]. These differences underlie modern risk stratification and therapeutic decision making. Recent multi-omics studies have improved our understanding of TGCT biology. Genomic studies show a low mutational load, with recurrent chromosomal gains and losses. Transcriptomic studies reveal high expression levels of pluripotency-related genes in seminomas, and lineage specific signatures in NSGCTs [41]. Proteome-based studies could reveal essential biomarkers, in particular microRNA miR-371a-3p, having high potential for the diagnosis and follow-up of the disease. Metabolomic profiling uncovers that seminomas are dependent on glycolysis, whereas NSGCTs are more oxidative in metabolism due to their distinct energy demands and differentiation status [42]. Together, these multi-omics results support the development of personalized tools for diagnosis and therapy to one step closer toward precision oncology in testicular cancer. Key molecular pathways in TGCT pathogenesis are illustrated in **Figure 2**. A summary of the distinguishing features between seminomas and NSGCTs is provided in **Table 1**.

Clinical implications of diagnosis and treatment of testicular germ cell tumors

Molecular and cellular differences between seminoma and non-seminomatous germ cell tumors (NSGCTs) result in distinct clinical behavior, diagnostics, and therapies [18]. Among males 30-40 years of age, seminomas usually appear as a painless

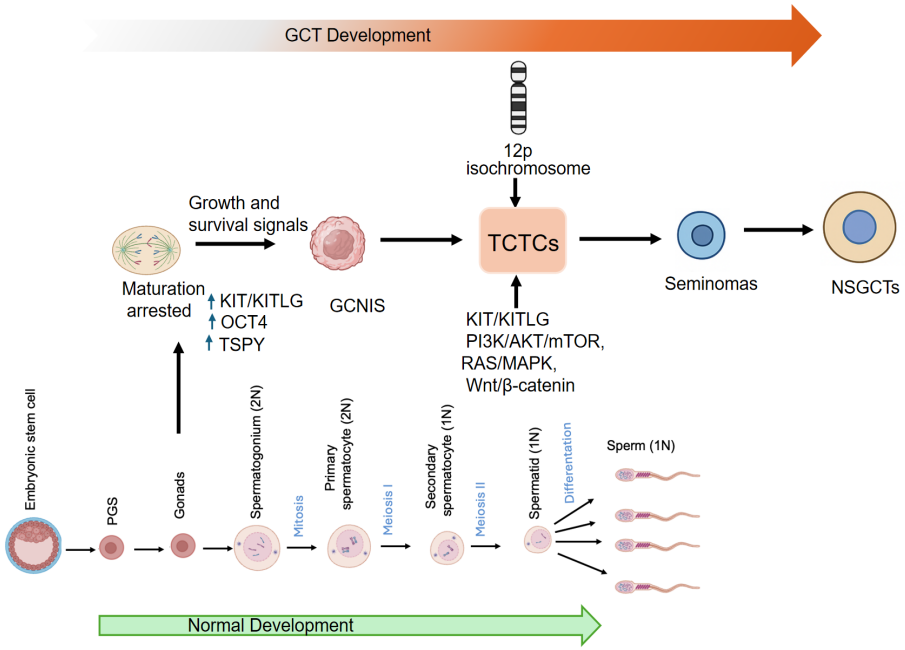

Figure 2. The cellular and molecular pathogenesis of TGCT. Schematic summarizing the process from a PGC to GCNIS and separate line of development towards either seminoma or non-seminomatous germ cell tumors (NSGCT). Various molecular fingerprints are mentioned, such as gains of i(12p), dysregulation of signaling pathways (KIT, PI3K/AKT and Wnt/β-catenin) or the differences in the epigenetic landscapes with global hypomethylation in seminoma versus hypermethylation in NSGCT.

testicular mass while NSGCTs tend to occur in younger males and grow rapidly with symptoms suggestive of local invasion or distant spread [43]. Tumor subtypes, treatment response, and tumor recurrence are all distinguished with the help of serum tumor markers [44], like AFP (α-fetoprotein), β-HCG (β-human chorionic gonadotropin), LDH (lactate dehydrogenase). Increased AFP concentration is rare in seminomas, whereas NSGCTs characteristically have a high elevation of both AFP and β-hCG as a manifestation of their mixed cellular lineage and aggressive nature [7]. Imaging modalities such as scrotal ultrasound scanning and computed tomography are important for localizing tumors, staging, and evaluating the presence of metastatic disease [45]. Moreover, FDG-PET can be helpful in the assessment of residual post-chemotherapy masses, especially for seminomas that are known to be highly radiosensitive [46]. Surgical treatment typically starts with radical inguinal orchiectomy that is diagnostic and therapeutic [47]. Because seminomas are highly radiosensitive, adjuvant radiotherapy is sometimes used in certain cases. Although both seminomas and NSGCTs are sensitive to cisplatin-based chemotherapy, a more aggressive multifaceted treatment approach is often justified for NSGCT because of its rapid growth rate and increased likelihood of hematogenous spread [32]. Risk stratification according to tumor stage, histology, serum markers and molecular characteristics is essential for directing the intensity of treatment and follow-up regimens. Long-term follow-up consists of serial imaging and tumor markers given the fact that late relapses, despite being infrequent in seminomas, may happen specially in patients with residual NSGCT elements. Features comparison as shown in **Table 2**, which summarizes important differences of management, outcome and follow-up of seminomas vs. non-seminoma germ cells tumors three different studies are suggestive of the association between tumor biology and therapy.

Recent findings from multi-omics research and immunological profiling are informing the creation of personalised therapeutic approaches. Research is ongoing into immune checkpoint inhibitors and targeted therapies aimed at specific molecular alterations, including KIT or RAS/MAPK pathway mutations, to enhance outcomes in high-risk non-seminomatous germ cell tumors (NSGCTs) and to mitigate treatment-related toxicity in seminomas [48]. The integration of molecular knowledge with clinical and histopathological data facilitates accurate risk assessment, personalised therapy, and enhanced survival outcomes in patients with testicular germ cell tumors.

Prognostic factors, new treatment strategies and future perspectives

Today, the outlook for testicular germ cell tumors (TGCTs) has been dramatically changed with improved molecular understanding, early detection and multimodal therapy strategies [49]. Seminomas generally have a good prognosis, with cure rates at over 95% for early-stage disease. On the other hand, non-seminomatous germ cell tumors (NSGCTs) are characterized by a much wider spectrum of clinical behavior that depends on histologic subtype, stage at presentation and response to therapy [50]. Several prognostic factors affect patient prognosis, such as tumor size, vascular invasion serum tumor markers levels, disease burden and histologic type. High AFP or β-hCG pretreatment concentrations as well as non-pulmonary visceral metastases predict a greater risk of relapse and are part of the risk stratification criteria according to International Germ Cell Cancer Collaborative Group (IGCCCG) [51]. Molecular features (such as KIT mutations

Table 2. Clinical management and prognosis of seminomas vs NSGCTs.

Clinical feature	Seminoma profile	NSGCT Profile
Typical presentation	Painless testicular mass, slow-growing	Rapidly enlarging mass, sometimes symptomatic metastases
Serum tumor markers	Usually none or mild β-hCG elevation	AFP, β-hCG, LDH often elevated
Initial management	Radical inguinal orchiectomy	Radical inguinal orchiectomy
Adjuvant therapy	Radiotherapy for stage I–II in selected cases; chemotherapy if higher stage	Chemotherapy (BEP: bleomycin, etoposide, cisplatin) for stage II–III; surgery for residual masses
Chemotherapy sensitivity	High (cisplatin-based)	Variable; often requires aggressive multimodal therapy
Radiotherapy sensitivity	Highly sensitive	Generally resistant
Prognosis	Excellent; >95% cure in early-stage disease	Good overall, dependent on subtype and stage; higher relapse risk in aggressive variants
Metastatic pattern	Lymph nodes primarily	Lymphatic and hematogenous (lungs, liver, brain)
Surveillance	Serial imaging, serum markers; follow-up for 5–10 years depending on stage	Intensive surveillance post-chemotherapy; imaging and serum markers for at least 5 years; longer in high-risk cases
Recurrence risk	Low; typically late if it occurs	Higher; often early, especially in high-risk NSGCTs
Emerging therapies	Targeted therapies and immunotherapy under study; currently mainly standard chemo/ radiotherapy	Targeted therapies (KIT, RAS/MAPK) and immune checkpoint inhibitors under investigation

Abbreviations: NSGCT, non-seminomatous germ cell tumor; BEP, bleomycin, etoposide, and cisplatin; AFP, alpha-fetoprotein; β-hCG, beta-human chorionic gonadotropin; LDH, lactate dehydrogenase.

in seminomas or TP53, KRAS and other chromosomal alterations in NSGCTs) may allow for a more accurate prognosis and offer targets of interest. New treatments and rational approaches are expected to result in considerable progress [52]. Immunotherapy, including immune checkpoint inhibitors directed against PD-1/ PD-L1, has demonstrated some early efficacy especially in tumors with marked lymphocytic infiltrates, for instance seminomas [53]. Selective inhibitors targeting distinct molecular aberrations in NSGCTs such as RAS/MAPK, PI3K/AKT/mTOR pathways, have been developed and are being investigated. Multi-omics profiling, including genomics, transcriptomics, proteomics and metabolomic approaches have led to the identification of new candidate biomarkers such as circulating miR-371a-3p [48]. This biomarker can be used for early detection, to monitor the efficacy of chemotherapy and to predict relapse with more accuracy than traditional serum markers. Recent advances focus on minimizing treatment-related morbidity without compromising cure. Tactics being explored involve modified oncologic therapy application, tailored radiotherapy treatment, and organ-preserving surgery. As molecular classification is combined to clinical staging, it may refine patient stratification to attenuate overtreatment in low-risk cases and intensified therapy for high-risk NSGCTs (non-seminomatous germ cell tumors [54]. These interaction studies during TME, epigenetic regulation and pluripotency networks will continue to elucidate TGCT biology guiding the next generations of therapies [55]. These breakthroughs are likely to have an impact on overall survival and QoL in T-GCT patients. A conceptual diagram of future precision medicine approaches in TGCT is shown in **Figure 3**.

Surveillance, survivorship, and long-term considerations

The care for testicular germ cell tumors (TGCTs) does not finish with primary therapy: long-term surveillance and survivorship issues are major factors to enhance outcome in patients with cancer [56]. A well-structured follow-up plan assures early relapse detection, treatment-related side effects control and attends to the psychosocial and reproductive concerns of survivors; importantly in view of high cure rates with seminomas [57]. Surveillance regimens generally involve intermittent physical examinations, measurement of serum tumor markers and imaging studies at tailored intervals for a defined period based on the dominant lesion type, stage/regional extent and risk category. The follow-up duration of seminomas is, in general, approximately ten years post-diagnosis, namely among the stage III patients [20]. However, compared with NSGCTs prefer strict surveillance for the first 5 years10 because of an increased risk of earlier relapse. Late-effects and survivorship are becoming more integrated into the care [58]. Risk of secondary malignancies, cardiovascular disease, nephrotoxicity and pulmonary complications are associated with exposure to chemotherapy and radiotherapy (Fung et al., 2018). A conservative approach is to consider fertility preservation before the onset of treatment for all men, as both orchiectomy and systemic treatments can impair spermatogenesis [59]. Psychological support is paramount, because survivors may suffer from anxiety, depression and quality-of-life issues regarding sexual functioning, body image and changes in career or lifestyle. Counseling and support services referral can assist in short-term management of these difficulties and improve posttraumatic stress overall [60]. Novel surveillance approaches are combining molecular and imaging biomarkers for enhancing sensitivity of detection and minimizing radiation exposure.

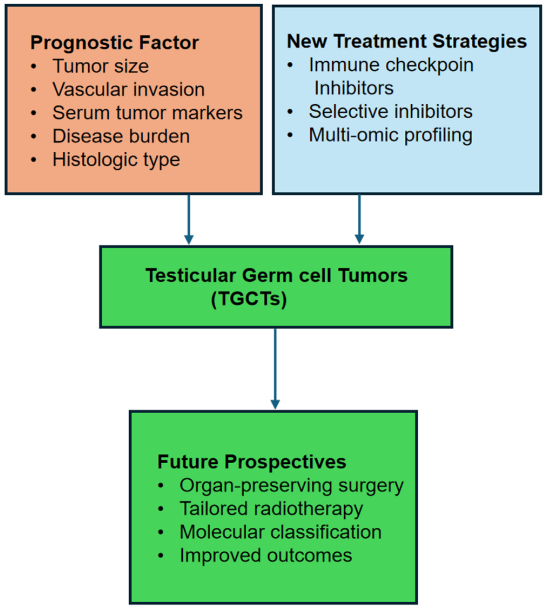

Figure 3. Next steps in TGCT care and precision medicine model. This figure provides an overview of the main factors that determine prognosis, new treatment approaches, and potential clinical paths for testicular germ cell tumours (TGCTs). It emphasises how risk assessment and treatment customisation are changing because of molecular profiling, targeted agents, and immunotherapy. Multi-omics biomarkers like miR-371a-3p should be included to enhance early identification and enhance patient outcomes.

Circulating microRNAs from one example miR-371a-3p, provide a noninvasive approach for the early diagnosis of relapse and may decrease the need for multiple computer tomography imaging [61]. Moreover, risk-adapted follow-up guided done on tumor biology and initial response to therapy is more and more applied to individualize care for the patient, reduce overtreatment, and long-term morbidity. In summary, ongoing care for TGCT survivors includes vigilant observation, potential administrative of late effects and consideration of fertility and psychosocial concerns, as well as the use of up-and-coming molecular-based tools [57]. By addressing oncologic control with long-term QoL, physicians can be sure that the high cure rates in TGCT are reflected by sustainable survivorship results thus exemplifying the conversion to patient-centered cancer care.

Challenges, limitations, and future perspectives

Although substantial strides have been made in the management of testicular germ cell tumors (TGCTs), there remain unmet clinical needs which require further investigation and development for patient benefit [49]. The heterogeneity of non-seminomatous germ cell tumors (NSGCTs) is a major obstacle for the diagnosis, risk stratification and planning treatment for this disease [54]. The mixed histology and molecular heterogeneity require personalized treatment approaches; however, standard protocols might be unable to cover the complexity of the tumor biology with overtreatment for some patients or undertreatment in a high-risk group [62]. Moreover, despite the generally high cure rate of seminomas there is still a small proportion that will relapse late after treatment and less sensitive for chemotherapy indicating in need for better prognostic markers identifying patients at risk. Another restriction is the late side effects of treatment. Chemotherapy (e.g., cisplatin) and radiotherapy have considerably advanced survival, but are associated with high risks of renal, cardiac and neurotoxicity, secondary malignancies as well as infertility [63]. New strategies are developing to reduce these effects but balancing between efficacy and safety is a relevant issue. Furthermore, inconsistencies exist in Fertility Preservation and psychosocial support availability across survivorship care. Recent developments in genomics, RNA expression, proteomics, and metabolomics are identifying novel biomarkers and the potential for new therapeutic targets to guide improved patient selection and risk-adapted therapy [64]. Circulating microRNAs, immune profiling and tumor microenvironment characterization represent important resources for early relapse detection and personalized therapy [65]. Sustained interdisciplinary cooperation between biologist at molecular level and clinicians/epidemiologists is needed to translate these findings into better patient results [66]. With a focus on the issues of tumor heterogeneity, treatment toxicity and discrepancies in survivorship, this puts the field forward for evolution into a targeted personalized approach to TGCT management thus ensuring maximal prolongation of life with best possible quality of life for our patients worldwide.

Conclusion and key takeaways

Testicular germ cell tumors (TGCTs) are a unique group of cancers defined by their embryonic origins, molecular plasticity, and high treatment sensitivity [3]. The distinctions between seminomas and NSGCTs are observed at multiple levels, including epigenetic landscapes, expression of pluripotent markers, histological composition, tumor behavior, and treatment response. Seminomas are characterized by homogeneous histology, hypomethylated DNA, and high radiosensitivity, which underpin their excellent prognosis. In contrast, NSGCTs are heterogeneous, exhibit hypermethylation, have a propensity for early metastasis, and

frequently require aggressive, multimodal treatment, necessitating a focus on risk stratification and personalized care.

Molecular features provide insight into TGCT biology. At the same time, multi-omics profiling and circulating biomarkers like miR-371a-3p are improving early diagnosis, assessment of treatment response, and relapse prediction, with implications for both established treatments and novel strategies such as immunotherapy and targeted agents. Comprehensive management should encompass oncologic care, follow-up surveillance, fertility preservation, psychological support, and efforts to minimize treatment-related toxicities. As precision medicine becomes more integrated into TGCT management, personalized, risk-adapted treatment strategies are being implemented to maximize efficacy while minimizing toxicity. In summary, the integration of clinical and molecular data provides a strong foundation for understanding, diagnosing, and treating TGCT. While both major subtypes originate from GCNIS, they are distinct entities in terms of biology, prognosis, and treatment, underscoring the necessity for accurate differentiation. Ongoing progress in molecular biology, multi-omics, and personalized therapy positions TGCT as a paradigm for precision oncology in curable cancers, with the goal of further improving survival and quality of life.

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Ethical policy

Non applicable.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

Aadhira Aiyar and Alina Roos contributed to design of the work, data collection, and drafting the article.

Competing interests

The author declares no competing interests.

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