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Review

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Expert consensus on the diagnosis and treatment of germ cell tumors of the mediastinum

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Abstract

Germ cell tumors of the mediastinum (GCTM) are a type of extragonadal tumor, accounting for < 5% of both mediastinal tumors and germ cell tumors. Based on histopathological classification, GCTMs can be divided into three major types: teratomas, seminomatous germ cell tumors, and non-seminomatous germ cell tumors, which can be further subdivided into subtypes such as yolk sac tumors and choriocarcinomas. Due to the scarcity and diversity of GCTMs, there is a lack of clear international standards in diagnosis and treatment, leading to clinical challenges such as high misdiagnosis rates and non-standardized treatment. To promote the standardization of GCTM management, experts from the Pan-Yangtze River Delta Alliance of Research for Thymomas (PRD-ART) conducted panel discussions, integrating the medical evidence in pathology, molecular biology, and new drug development, to create clinical recommendations for diagnosis, treatment, and follow-up. This expert consensus: (1) emphasizes molecular testing in clinical management; (2) encourages multidisciplinary consultation to facilitate personalized therapies;(3) promotes international collaboration to validate novel biomarkers and therapies; and (4) suggests the use of real-world, umbrella trial designs to address the scarcity and heterogeneity problems. These measures aim to standardize and improve the clinical management of GCTMs.

Keywords: Diagnosis, germ cell tumor of the mediastinum, treatment

INTRODUCTION

Germ cell tumor of the mediastinum (GCTM) is a rare extragonadal tumor with diverse histopathological subtypes. The lack of clear international diagnosis and treatment standards has led to clinical problems in GCTM such as high misdiagnosis rates and non-standardized treatment. To promote standardized management of GCTMs and provide research directions to address the aforementioned clinical challenges,

experts from the Pan-Yangtze River Delta Alliance of Research for Thymomas (PRD-ART) conducted panel discussions, integrating currently available medical evidence from pathology, molecular biology, and new drug development to create clinical recommendations for diagnosis, treatment, and follow-up of GCTM[1]. This consensus is updated based on our previously released version of consensus, focusing on the diagnosis and treatment of thymic epithelial tumor[2].

INCIDENCE, ETIOLOGY, AND SCREENING

GCTMs are the most common type of extragonadal germ cell tumor (GCT). Compared to their gonadal counterparts, which occur in the testes or ovaries, GCTMs are rarer, constituting only about 4% of mediastinal tumors and approximately 3% of all GCTs[3]. GCTMs primarily occur in the anterior mediastinum, with very rare cases reported in the middle and posterior mediastinum[4,5]. In general, GCTMs are predominantly benign (about 80%-85%), with a roughly equal male-to-female ratio[6]. In contrast, malignant GCTMs occur more frequently in males, with a male-to-female ratio of as high as 9:1[7]. While extragonadal GCTs in adolescents also show a male predominance, pediatric extragonadal GCTs are relatively more common in female patients[8]. The rarity of GCTMs means most clinical studies are limited to single-center and retrospective settings, which makes it difficult to perform a large-scale systematic analysis to support clinical decisions.

GCTMs are considered to arise from the erroneous retention of germ cells in the mediastinal position as they migrate along the midline during embryogenesis[9,10]. In fact, the vast majority of extragonadal GCTs occur in the midline, such as the mediastinum and retroperitoneum. Similar to GCTs, GCTMs can be divided into three major types according to histopathological typing: teratoma, seminomatous germ cell tumor (SGCT), and non-seminomatous germ cell tumor (NSGCT). Among them, teratoma is the most common type, accounting for approximately 60%-70% in GCTMs. Depending on whether the tumor contains typical immature components during fetal development, teratomas can be further divided into mature teratoma and immature subtypes, most of which are benign tumors[7]. Unlike teratomas, both SGCTs and NSGCTs are malignant tumors. Based on the latest fifth edition of the World Health Organization classification[11], NSGCTs can be subdivided into embryonal carcinoma, yolk sac tumor (YST), choriocarcinoma, and mixed GCT according to their histopathological morphology. Two independent subtypes, teratoma with somatic-type malignancies and GCT with associated hematological malignancy, are also described in the classification. There is a certain correlation between the GCTM subtype and the age of onset. As reported in previous studies, the median ages of onset for mediastinal SGCT and mediastinal NSGCT were 33 and 28 years, respectively[12]. In contrast, the peak ages of onset for pediatric patients were infancy and after 10 years of age[8]. It was also pointed out in a study that prepubertal patients primarily have mediastinal teratoma and YST, while the vast majority of postpubertal female patients have mediastinal teratoma[13]. As there is a high misdiagnosis rate due to the variety of GCTM subtypes, they are easily confused with other tumors such as thymoma and lymphoma.

Beyond the issues of case scarcity and subtype diversity, the concomitant diseases also complicate the diagnosis and treatment of GCTMs. Concomitant diseases like chromosomal abnormalities and hematological malignancies are common in GCTM patients. Statistics showed that about 16% of GCTM patients had trisomy 8, and 14% had Klinefelter syndrome[14]. Approximately 6% of patients with mediastinal NSGCT had leukemia, of which acute megakaryoblastic leukemia (AML-M7) was the most common[15-20]. Regarding the cause of concomitant leukemia for GCTMs, it is widely believed that the hematological malignancies are not treatment-induced secondary tumors but rather originate from a common clonal origin. Although treatment with topoisomerase II inhibitors is known to potentially induce hematological malignancies[21,22], cytogenetic analyses indicate that GCTM and acute myeloid leukemia generally share common driver mutations and cellular morphology[23-25], supporting the notion that both cancers share a common cell origin.

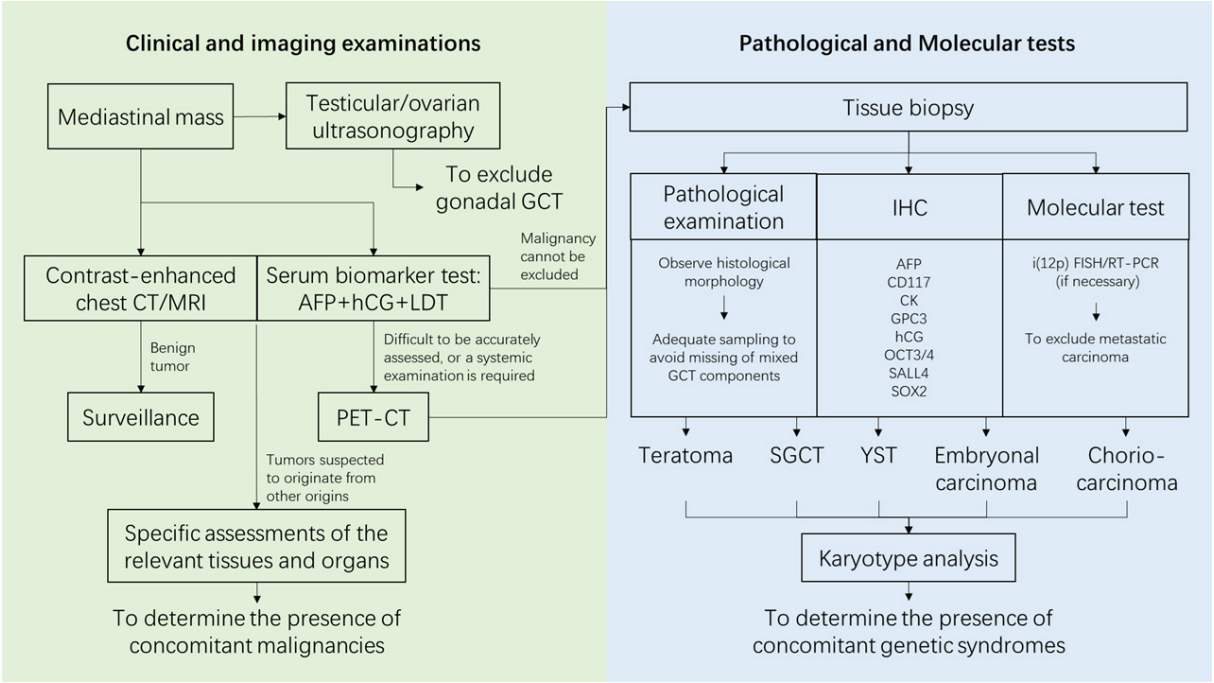

Figure 1. Flowchart of the diagnostic workflow of GCTM.The flowchart delineates the clinical pathway from initial radiological suspicion to definitive histopathological diagnosis and risk-stratified management. The decision node between primary resection and biopsy depends on the patient's biochemical profile and anatomical risk. GCT: Germ cell tumor; CT/MRI: computed tomography/magnetic resonance imaging; AFP: alpha-fetoprotein; hCG: β-human chorionic gonadotropin; LDH: lactate dehydrogenase; PET-CT: positron emission tomography-computed tomography; IHC: immunohistochemistry; CK: cytokeratin; GPC3: glypican-3; SALL4: spalt-like transcription factor; i(12p): isochromosome 12p; FISH/RT-PCR: fluorescence in situ hybridization/reverse transcription-polymerase chain reaction; SGCT: seminomatous germ cell tumor; YST: yolk sac tumor; GCTM: germ cell tumor of the mediastinum.

Consensus 1: GCTM is the most common extragonadal GCT, characterized by its scarcity, subtype diversity, and high rate of concomitant diseases. Clinical diagnosis should be performed carefully to avoid misdiagnosis or missed diagnosis. (Recommended)

DIAGNOSIS

Clinical diagnosis

Most GCTMs are accidentally detected by imaging examinations. Patients may be either asymptomatic or symptomatic, with common symptoms such as chest pain, cough, dyspnea, fever, night sweats, and weight loss[26]. A mediastinal mass has various possible etiologies; besides GCTs, it could be other tumors like thymic tumors, lymphoma, or metastatic carcinoma, or non-neoplastic diseases such as thyroid goiter, thymic cysts, or aortic aneurysms. Because treatment differs, all mediastinal masses should undergo a comprehensive evaluation process, which typically includes imaging, laboratory/molecular tests, and histopathological assessment, to guide treatment decisions [Figure 1].

Imaging diagnosis

For mediastinal nodules found in physical examination, especially asymptomatic, small anterior mediastinal nodules less than 3 cm in diameter, benign cysts are the main form, and most of the nodules remain unchanged during follow-up[27]. To avoid unnecessary surgery, it is recommended to determine the type of a nodule based on the imaging characteristics of contrast-enhanced chest computed tomography (CT) and magnetic resonance imaging (MRI). Serum biomarker tests can be used to supplement to the diagnosis of suspected cases. Patients considered to have benign tumors should undergo regular follow-up to observe changes in the nodules.

Contrast-enhanced chest CT is the main imaging modality for evaluating mediastinal tumors. It can reveal the tumor's morphology, blood supply, and relationship to surrounding vasculature[28]. Three-dimensional reconstruction can be performed if necessary. For suspected vascular tumors or mediastinal tumors that invade or compress major vessels, angiography can be used for further evaluation[7,29]. Additionally, MRI can reveal the relevant characteristics of the lesion by showing its morphology, border, cystic or solid nature, relationship with adjacent tissues/organs, and *etc.*, which helps differentiate thymic hyperplasia, cysts, and malignant thymic neoplasms. For patients with contraindications to iodine-based contrast agents, MRI can serve as an alternative method for assessing mediastinal tumors[7,29]. Positron emission tomography-CT (PET-CT) can be used for systemic evaluation in patients with mediastinal tumors, helping to determine the presence of recurrent or metastatic lesions. It is also a relatively effective tool for staging and assessing treatment response[30,31]. One study indicated that PET-CT also has utility in assisting with the differential diagnosis of benign versus malignant lesions and in distinguishing between mediastinal SGCT and NSGCT[32].

Consensus 2: Patients with mediastinal tumors found by physical examination or by accident are recommended to routinely receive contrast-enhanced chest CT/MRI scans and serum biomarker tests. If a tumor is assessed as benign, a CT/MRI re-examination is recommended to be performed after 3-6 months, and once every 1-2 years thereafter. Patients with suspected malignancies, abnormal serum biomarkers, and/or symptoms are recommended to receive the tissue biopsy as soon as possible to clarify the nature of the lesion. PET-CT may be considered for patients with mediastinal tumors that are difficult to accurately assess by conventional CT/MRI, or those who need a systemic examination and assessment. (Strongly recommended)

All male patients with suspected GCTMs should undergo testicular ultrasonography to rule out a primary gonadal tumor[7]. Similarly, ovarian ultrasonography should be performed in suspected female patients. Some tumors may lead to inspiratory flow limitation, so pulmonary function tests are required for patients scheduled for surgery. If necessary, additional cardiopulmonary exercise testing may also be performed with reference to the preoperative assessment of lung surgery[33]. For tumors suspected to originate from other sites, corresponding imaging examinations should be performed, for example, radioactive iodine scanning to assess activity in an intrathoracic goiter and a ^{99m}Tc-isotope scan for a possible retrosternal parathyroid adenoma[7].

Consensus 3: Any suspected GCTM should undergo adequate clinical and imaging examination to exclude the possibility of mediastinal metastasis from gonadal or retroperitoneal tumors or metastatic carcinoma from non-mediastinal primary sites. For tumors suspected to originate from other origins, specific imaging examinations of the relevant tissues and organs are routinely recommended. (Strongly recommended)

LABORATORY TESTS

In terms of laboratory tests, all patients with mediastinal tumors should undergo routine blood tests[7]. Patients with suspected GCTMs are recommended to undergo testing for at least 3 serum biomarkers, i.e., alpha-fetoprotein (AFP), β-human chorionic gonadotropin (hCG), and lactate dehydrogenase (LDH). Among them, positive AFP and hCG results represent a high probability of malignant NSGCTs, while a significant elevation of LDH indicates the possibility of lymphoma[34]. Specifically, in the context of a characteristic mediastinal mass, significantly elevated AFP or HCG typically guides the treatment approach towards systemic therapy or resection without preoperative biopsy. In contrast, marker-negative cases or those with a high surgical risk should prioritize image-guided biopsy to rule out lymphoma or other malignancies. For tumors suspected to originate from other sites, corresponding biomarkers should be

tested to aid diagnosis. For example, for suspected thyroid diseases, thyroid function and cortisol should be tested; for suspected thymic epithelial tumors, CYFRA 21-1 and CA125 should be tested; for suspected thymoma with myasthenia gravis, antibody tests for acetylcholine receptor, muscle-specific kinase, and lipoprotein receptor-related protein 4 should be performed[35-37]. Additionally, for suspected mediastinal tuberculosis, the T-spot test can be performed. For suspected mediastinal infections, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) tests can also be performed.

Consensus 4: Routine blood tests should be performed to aid in the differential diagnosis of patients with suspected GCTMs. Among them, the serum biomarkers to be tested should at least include AFP, hCG, and LDH. For tumors suspected to originate from other origins, specific tumor marker tests on the relevant tissues and organs are routinely recommended to be performed. (Strongly recommended)

Pathological and molecular diagnosis

Although most of the mediastinal diseases are benign, there is still a possibility of a variety of malignant diseases, especially in patients who have already developed symptoms. Therefore, all mediastinal masses where the possibility of malignancy cannot be excluded should be subject to tissue biopsy. It is useful in obtaining tumor samples to determine the nature of the lesion through pathological examination. Options for diagnostic tissue biopsy include transdermal core needle biopsy, transbronchial needle aspiration, mediastinoscopy, mediastinotomy, and thoracoscopic surgery[38]. For patients with suspected lymphoma, surgery is not routinely preferred due to the significant tumor heterogeneity, and tissue biopsy is an indispensable diagnostic method[39]. When lymphoma is suspected, image-guided core needle biopsy with multiple passes is the preferred initial approach over fine-needle aspiration to ensure adequate tissue for IHC and flow cytometry. However, for resectable lesions that are highly suspected to be thymoma based on clinical manifestations and imaging features, biopsy should be avoided due to the risk of tumor capsule disruption and potential seeding. Sufficient tissue specimens for pathological and molecular examinations should be obtained in a single biopsy attempt. Additionally, all patients with confirmed GCTMs should undergo karyotype analysis to determine the presence of concomitant genetic syndromes[40].

Consensus 5: Patients with mediastinal tumors where the possibility of malignancy cannot be excluded by typical imaging features and serum biomarkers are routinely recommended to receive tissue biopsy to carefully determine the nature of the lesion through pathological examination. An appropriate biopsy method should be selected based on the needs, and sufficient tissue specimens required for pathological examination and molecular testing should be obtained in a single biopsy attempt. If a CT-guided biopsy is performed, specimens containing necrotic margins should be adequately sampled. (Strongly recommended)

Consensus 6: Patients with pathologically confirmed GCTMs should be subjected to karyotype analysis to determine the presence of concomitant genetic syndromes. (Strongly recommended)

Different subtypes of GCTMs exhibit distinct pathological and molecular characteristics that facilitate their specific classification[41]. Special attention should be taken for mixed GCTM, as non-teratomatous components may regress after neoadjuvant therapy, potentially inducing "growing teratoma syndrome", where the residual teratoma overgrows[42]. Therefore, it is necessary to collect sufficient samples during the pathological examination, carefully observe for the existence of other GCT components, and make the judgment in combination with treatment history to exclude the possibility of mixed GCTMs.

Consensus 7: Any suspected GCTM should be adequately sampled, and the possibility of mixed GCTM should be carefully judged in combination with the treatment history. (Strongly recommended)

In the differential diagnosis, the emphasis on evidence of pathology, immunohistochemistry (IHC), and molecular detection varies with different subtypes of GCTMs. For mediastinal teratoma, since there are no specifically elevated serum biomarkers, the differential diagnosis mainly depends on tissue biopsy and pathological examination. Histologically, mature mediastinal teratoma is manifested as phenotypically well-differentiated tissues deriving from one of the three germinal layers (e.g., skin with skin appendages, teeth or bone, and cartilage), with components such as keratinized or non-keratinized squamous epithelium, skin appendages (e.g., hair, sweat glands, and sebaceous glands), respiratory epithelium, fat, and cartilage commonly observed, and a high incidence of pancreatic tissues[43]. Other lesions that need to be differentiated from mediastinal teratomas include multilocular thymic cysts[44] and somatic-type malignant tumors[45]. The former shows xanthogranulomatous inflammation and myofibroblastic inflammation, while the latter often presents as well-circumscribed nodules with significant cellular atypia and invasive growth.

Compared to benign mediastinal teratoma, organoid morphology is less common, while cellular atypia is more common in malignant mediastinal teratoma. A study on 34 cases of GCTMs provided some pathological characteristics that could aid in the diagnosis of benign or malignant mediastinal teratoma[46]: (1) Compared to benign teratoma, organoid structures were relatively rare in malignant teratoma (83% *vs.* 27%), with no pancreatic differentiation; (2) The incidence of glial tissue was also higher in malignant teratoma (11% *vs.* 63%); (3) If cartilage was present, it could be used to assess less obvious atypia in the epithelium, where malignant tumors feature frequent multinucleation, proliferation, and apoptosis. Additionally, comparative genomic hybridization techniques can also assist in the differential diagnosis of mediastinal GCTs. Mature teratomas have a normal genetic profile with no 12p abnormalities[47], whereas malignant mediastinal GCTs often exhibit gains/losses of chromosomal arms[48]. For malignant GCTM patients under 8 years old, their genomic features are more similar to those of testicular GCTs of the same age. Common genomic variations observed include gains of 1q, 3, and 20q, as well as losses of 1p, 4q, and 6q. Conversely, adolescent and adult patients commonly show gains of 12p. Other reported genome variations include loss of chromosome 13 and gain of chromosome 21/X[47]. Universal thresholds for genomic variations such as i(12p) have not yet been standardized for mediastinal GCTs.

Consensus 8: Any suspected mediastinal teratoma found in pathological examination should be adequately sampled and determined for the benign or malignant nature in combination with treatment history, and be subjected to differential diagnosis with multilocular thymic cysts and somatic-type malignant tumors to avoid misdiagnosis. Although the differential diagnosis of mediastinal teratomas is primarily based on pathological morphology, IHC is routinely recommended as an adjunctive test to prevent missing occult components. For immature mediastinal teratoma with uncertain differential diagnosis, supplemental 12p fluorescence in situ hybridization (FISH) or reverse transcription-polymerase chain reaction (RT-PCR) testing can be considered to assist in determining germ cell origin. (Strongly recommended)

Mediastinal SGCTs should be subjected to differential diagnosis with other GCTMs or mediastinal tumors such as thymic epithelial tumors, mediastinal B-cell lymphomas, and metastatic melanomas through histomorphology and IHC. Particularly, metastatic SGCTs from the testis are prone to misdiagnosis due to similar features. The possibility of primary testicular seminoma should be excluded based on clinical history, physical examination, and imaging features[49]. Tumor cells of mediastinal SGCTs are arranged in sheets or nested form, with a homogeneous cell morphology, and are characterized by unique fibrovascular septa and lymphocytic infiltration. It is worth noting that inflammation can mask tumor cells. Additionally, scattered multinucleated syncytiotrophoblast cells may also appear in mediastinal SGCTs, so choriocarcinoma should not be diagnosed unless mononuclear cytotrophoblast cells are present. Unlike thymic carcinoma, mediastinal SGCT presents as discrete epithelioid cells that express CD117 in IHC[43]. Mediastinal SGCTs with positive CAM5.2 are prone to being misdiagnosed as carcinoma, so differential

diagnosis is required in combination with OCT3/4 and 12p tests[50]. Besides IHC, some molecular characteristics are also considered valuable for the auxiliary diagnosis of mediastinal SGCTs. A retrospective study found that *TP53* mutations occurred only in mediastinal NSGCTs but not in mediastinal SGCTs (72.2% *vs*. 0%)[51]. Two other studies pointed out that there were differences in frequencies of p53 expression (31% *vs*. 77%), *KIT* exon 17 mutations (50% *vs*. 0%), and *KRAS* mutations (8% *vs*. 15%) between mediastinal SGCTs and testicular SGCTs, suggesting that they could assist in the differentiation of primary and metastatic SGCTs[52,53].

Consensus 9: Mediastinal SGCTs should be subjected to differential diagnosis with other GCTMs or mediastinal tumors through histomorphology and IHC, and at least 3 biomarkers: CD117, OCT3/4, and SOX2 (negative) should be tested. Meanwhile, the possibility of primary testicular seminoma should be excluded based on clinical history, physical examination, and imaging features. If necessary, additional genetic testing may be performed to assist in the diagnosis. (Strongly recommended)

YSTs exhibit diverse morphologies. Common patterns include reticular, myxomatous, endodermal sinus, polyvesicular-vitelline, and solid, while rarer patterns include hepatoid, spindle cell, enteric, and endometrioid. IHC is a crucial method for the differential diagnosis of YSTs. Co-expression of AFP, glypican-3 (GPC3), and spalt-like transcription factor 4 (SALL4) can help differentiate YSTs from metastatic carcinoma[54]. However, due to the lack of specificity of the above biomarkers, a comprehensive diagnosis is still needed based on pathological morphology, clinical factors, and imaging features, such as identifying typical YST areas like Schiller-Duval bodies. Other tumor subtypes that are easily confused and require differential diagnosis include: primary thymic carcinoma, which can be differentiated by positive CD5; seminoma, which can be differentiated by positive OCT3/4, CD117, and D2-40, and by negative GPC3[45]; embryonal carcinoma, which can be differentiated by positive CD30 and OCT3/4, and cell atypia; sarcoma, which can be differentiated by negative keratin staining and positive staining of mesenchymal markers; multilocular thymic cyst, which can be differentiated by the absence of YST cells[41]. It is important to note that YSTs may contain focal syncytiotrophoblast cells, which should not be over-interpreted as choriocarcinoma.

Embryonal carcinomas are solid, adenoid, or papillary in arrangement, with significant cellular atypia, and are accompanied by extensive necrosis. They should be carefully differentiated from other GCTs and malignant tumors. Compared with SGCTs, embryonal carcinoma exhibits more cellular atypia and more blurred cell borders, often with common positive CD30[41]. Compared with YSTs, embryonal carcinoma shows a relatively greater degree of cellular atypia, but typical PAS-positive hyaline bodies (a characteristic of YST) can still be observed in some pediatric cases[34]. Similar to choriocarcinoma, embryonal carcinoma shows large syncytial cells[55] and an appliqué pattern of degenerative change at the periphery of nests[9]. Compared with thymic carcinoma or other metastatic carcinomas, although the cellular atypia is similar, IHC can effectively assist in the differential diagnosis[41]. Finally, compared to other hematological malignancies such as anaplastic large-cell lymphoma, both CD30 and epithelial membrane antigen (EMA) can be positive, so epithelial structures such as glandular or papillary morphology should be carefully observed for differential diagnosis[41].

For choriocarcinoma, a "biphasic cell" population of syncytiotrophoblast cells and cytotrophoblast cells, together with the villous-like spatial configuration formed by multinucleated cells surrounding mononuclear cells, is its key characteristic. It can be easily confused with pleomorphic carcinoma of the lung, as both exhibit multinucleated and syncytial cells, with the production of hCG. Characteristics such as multiple tumor masses invading the lung, a second population of cytotrophoblast cells, and a younger age of onset are helpful in diagnosing choriocarcinoma[56]. Additionally, characteristics such as the absence of

significant atypia, a biphasic cell population, and hCG staining are necessary for differentiation from thymic carcinoma.

Consensus 10: The diagnosis of mediastinal NSGCTs should be based on the comprehensive consideration of IHC and histomorphology, clinical factors, and imaging features, and differential diagnosis should be performed with other GCTs, malignant tumors, or metastatic carcinoma. For YSTs, at least 3 biomarkers: AFP, GPC3, and SALL4, should be tested; for embryonal carcinoma, at least 3 biomarkers: CD30, OCT3/4, and SOX2, should be tested; for choriocarcinoma, at least hCG should be tested; if necessary, tests for other markers should be added. (Strongly recommended)

Common genetic variations in GCTM include mutations or deletions of *TP53*, activating mutations of *KRAS/NRAS*, loss of *PTEN*, and *etc.*[57]. These variations may be helpful for the differential diagnosis of subtypes and primary sites of GCT. Among them, common gene mutations in mediastinal NSGCT include: *TP53* (46%), *KIT* (18%), *KRAS* (18%), *PTEN* (11%), *NRAS* (4%), and *PIK3CA* (4%)[58,59]. Compared with testicular GCT and SGCT (both gonadal and extragonadal), mediastinal NSGCT has a higher frequency of mutations in *TP53*, PIK3CA pathways (e.g., *PTEN*, *PIK3CA*), and cell cycle-related genes (e.g., *CCND1/2/3*, *CDK4/6*, *CDKN2A/B*, *RB1*), while the frequency of gene mutations in RAS-RAF (e.g., *KRAS*, *NRAS*), RTK (e.g., *KIT*), and DNA damage response (e.g., *BRCA1/2*, *ATM*, *CHEK2*, *MUTYH*) pathways does not differ significantly[58,60].

Teratoma with somatic-type malignancies refers to GCT containing non-germ cell-derived malignant components such as sarcoma or carcinoma. Common sarcomas include rhabdomyosarcoma and angiosarcoma. There are also case reports of colon adenocarcinoma, glioblastoma, melanoma, carcinoid, neuroendocrine carcinoma, and other concomitant cancers[41]. Although these cells retain their respective morphology and phenotype, their mutational and methylation profiles are close to those of GCT[61,62] and differ significantly from the molecular characteristics of the primary tumor[63]. The concomitant somatic-type malignancies generally retain chromosome 12p aberrations[64,65], which is a key factor in distinguishing teratoma with somatic-type malignancies from metastatic cancer. Furthermore, for adenocarcinoma components that are easily confused with embryonal carcinoma, IHC for embryonal carcinoma-specific CD30 and OCT3/4 may aid in differential diagnosis[66].

Consensus 11: Teratoma with somatic-type malignancies should be differentiated from metastatic carcinoma through 12p FISH/RT-PCR testing. If any adenocarcinoma component is detected, IHC for CD30 and OCT3/4 is recommended to differentiate from embryonal carcinoma. (Strongly recommended)

For GCT with associated hematological malignancy, differential diagnosis should be mainly performed with chemotherapy-related hematological malignancies[17]. The former has a clonal isochromosome 12p [i(12p)], and the hematological malignancy typically appears earlier, with a median time of only 4.8 months[67], whereas chemotherapy-related hematological malignancies typically occur 25-60 months after chemotherapy[45].

Consensus 12: GCT with associated hematological malignancy should be differentiated from chemotherapy-related hematological malignancies through 12p FISH/RT-PCR testing and considering the time of onset. (Strongly recommended)

Tables 1 and 2 outline the IHC and molecular markers useful for the differential diagnosis of GCTM, respectively[60,68]. IHC markers specific to lymphoma (e.g., CD30) and epithelial cells [e.g., Cytokeratin

Table 1. IHC markers for GCTM subtyping

	Teratoma	SGCT	YST	Embryonal carcinoma	Choriocarcinoma
AFP		Negative	Positive	Negative	Negative
CD117 (c-kit)	Negative	Positive	Negative	Negative	Negative
CD30	Negative	Negative	Negative	Positive	Negative
CK	Positive	Positive (dot-like)	Positive	Positive	Positive
EMA	Positive				
GPC3		Negative	Positive	Negative	
hCG			Negative	Negative	Positive
NANOG	Negative	Positive	Negative	Positive	Negative
OCT3/4	Negative	Positive	Negative	Positive	Negative
PLAP		Positive			Negative
SALL4	Positive	Positive	Positive	Positive	Positive
SOX2		Negative	Negative	Positive	Negative

IHC: Immunohistochemistry; SGCT: seminomatous germ cell tumor; YST: yolk sac tumor; AFP: alpha-fetoprotein; CK: cytokeratin; EMA; epithelial membrane antigen; GPC3: glypican-3; hCG: β-human chorionic gonadotropin; SALL4: spalt-like transcription factor.

(CK)] can be used to rule out tumors of other origin. Stem cell markers such as NANOG, OCT3/4, SALL4, and SOX2 are crucial for the differential diagnosis of GCT subtypes. Specifically, SGCT generally expresses KIT and OCT3/4, but SOX2 is negative; YST generally expresses AFP, GPC3, and SALL4; Embryonal carcinoma generally expresses OCT3/4 and SOX2; hCG is specifically expressed in choriocarcinoma[41,60,68]. To accurately diagnose the subtypes of GCTM, a combination of pathological morphology and at least 3 IHC markers is required to obtain a reliable diagnosis[68]. Furthermore, novel biomarkers have been confirmed to have been confirmed to have value in the diagnosis of specific subtypes of GCT, such as glial cell line-derived neurotropic factor receptor alpha-1 (GFRA-1) specifically expressed in immature teratoma[69], CAM5.2 positive in mediastinal SGCT but not in testicular SGCT[70], LIN28 positive in SGCT and YST but negative in teratoma[71], and HNF1-β and ZBTB16 specifically expressed in YST[72,73].

Consensus 13: IHC is important for determining the pathological subtypes of GCTMs. All patients with suspected GCTMs are recommended to be tested for AFP, CD117, CK, GPC3, hCG, OCT3/4, SALL4, and SOX2. When the differential diagnosis is still uncertain, testing of relevant novel biomarkers may be considered. (Strongly recommended)

Molecular testing is also a key to differential diagnosis of GCTM. Chromosome 12p abnormalities, such as i(12p) or increased 12p copy number, are classic molecular characteristics of GCT. i(12p) is associated with the strong tumor aggressiveness of GCT. Genes located in the short arm of this chromosome may be associated with the occurrence and development of GCT, including *KRAS*, *Cyclin D2*, *FGF6*, and *etc.*, but the pathogenic mechanism is still unclear[60]. Except in pediatric and benign GCTs[74,75], 12p abnormalities are prevalent in malignant GCTs, regardless of subtype[76,77]. For cases where the origin of germ cells is difficult to determine, additional testing of 12p status may be considered to differentiate mediastinal GCT from other mediastinal tumors such as thymoma and lymphoma, and to differentiate primary mediastinal tumors from metastatic gonadal tumors[68,78,79].

Consensus 14: For cases where germ cell origin is uncertain, additional 12p FISH/RT-PCR testing should be considered to differentiate mediastinal GCTs from other mediastinal tumors such as thymoma and lymphoma, and to distinguish primary mediastinal tumors from metastatic gonadal tumors. (Strongly recommended)

Table 2. Molecular markers of different GCTM subtypes

Differential diagnosis	12p aberrations	(1) 12p aberrations are prevalent in malignant GCT (except for pediatric GCT) and can be used to differentiate other non-GCT mediastinal tumors (2) Teratoma with somatic-type malignancies generally retains 12p aberrations, which can be used to differentiate metastatic cancer (3) GCT with associated hematological malignancies generally retains 12p aberrations, which can be used to differentiate chemotherapy-related hematological malignancies
	Genomic variations	Increases in 1q, 3, and 20q and decreases in 1p, 4q, and 6q are common in pediatric patients < 8 years old and can be used to differentiate pediatric GCT
	TP53 mutations	(1) *TP53* mutations only occur in mediastinal NSGCT but not in mediastinal SGCT, and can be used to differentiate mediastinal NSGCT and SGCT. (2) Within GCTM subtypes, *TP53* mutations are more common in mediastinal NSGCT and mediastinal GCT with associated hematological malignancies.
	Mutation frequency	(1) There is a difference in the mutation frequency of p53 expression (31% *vs.* 77%), *KIT* exon 17 mutations (50% *vs.* 0%), and *KRAS* mutations (8% *vs.* 15%) between mediastinal SGCT and testicular SGCT, which can be used to differentiate metastatic gonadal tumors (2) Compared to testicular GCT and SGCT, mediastinal NSGCT has a higher mutation frequency in *TP53*, PIK3CA pathways (e.g., *PTEN*, *PIK3CA*), and cell cycle-related genes (e.g., *CCND1/2/3*, *CDK4/6*, *CDKN2A/B*, *RB1*), which can be used to differentiate mediastinal NSGCT
Predicting platinum resistance	*TP53* mutations	*TP53* mutations play an important role in cisplatin resistance of GCT cells
	MYCN amplification	*MYCN* amplification is another potential factor in chemotherapy resistance
	miRNA	miRNA expression profiling can effectively identify cisplatin-resistant cell strains
Guiding treatment options	DDR gene mutations	Predicts radiotherapy response
	NRAS mutations	Predicts MEK inhibitor response
	RET amplification	Predicts sunitinib response
	TMB	Mediastinal NSGCT has a relatively higher incidence of high TMB, which may be a potential biomarker for predicting the efficacy of immunotherapy
Disease monitoring	miRNA	miR-371-373 and miR-302 clusters are widely expressed in malignant GCTs and may be used for dynamic monitoring of tumor burden and recurrence
Prognostic evaluation	*TP53* mutations	*TP53* mutation carriers have significantly shorter survival

GCT: Germ cell tumor; NSGCT: non-seminomatous germ cell tumor; SGCT: seminomatous germ cell tumor; GCTM: germ cell tumor of the mediastinum; DDR: DNA damage response; TMB: tumor mutation burden.

TREATMENT STRATEGIES

Due to the rarity of GCTM, almost all studies exploring treatment modalities are single-center, retrospective studies, resulting in a lack of consistent treatment standards and limited effective treatment options for high-risk subtypes. Based on the available clinical evidence, our recommended standard treatment modalities for GCTM are shown in Figure 2.

Benign, pure mature teratomas are insensitive to chemotherapy, thus, surgical resection is required as soon as possible[80]. Patients with this type of GCTM have an excellent prognosis after complete surgical resection, but there is still a possibility of recurrence, so close follow-up monitoring is necessary[81]. For high-risk patients found to have postoperative malignant components, adjuvant chemotherapy can be considered.

Consensus 15: Mediastinal teratoma should be treated surgically as soon as possible once diagnosed, because it is difficult to determine whether the teratoma is benign or malignant before surgery, and it has the potential to become malignant and penetrate adjacent tissues. (Strongly recommended)

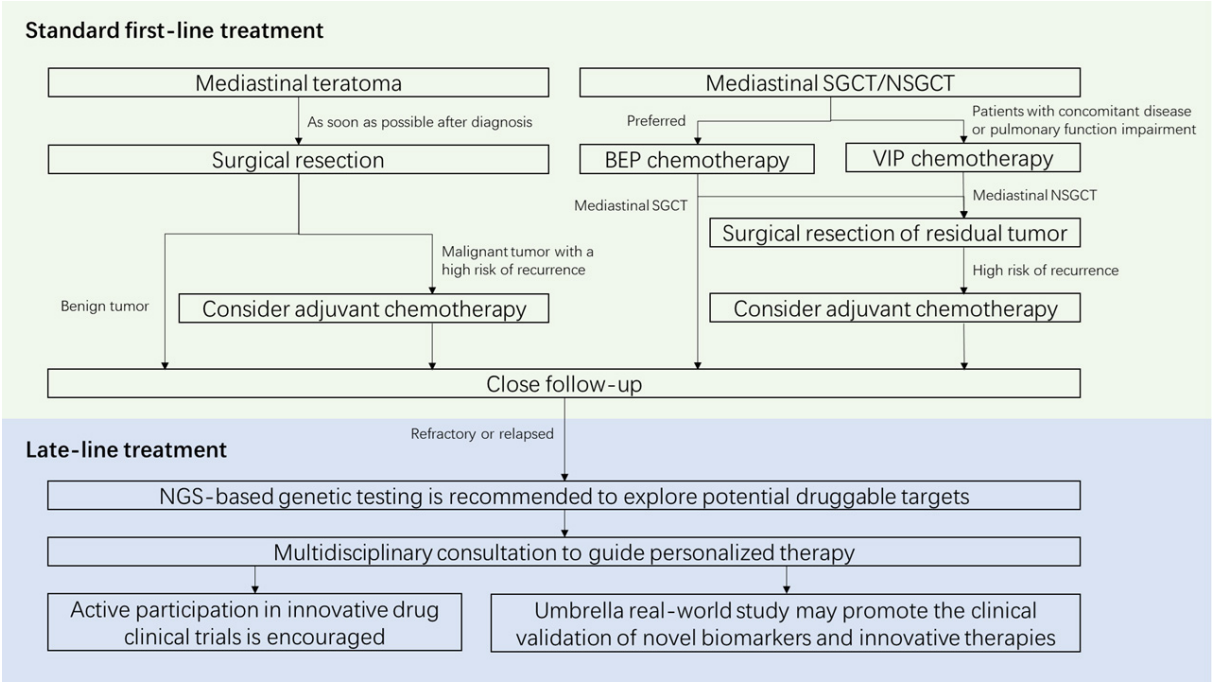

Figure 2. Flowchart of the treatment of GCTM. Brief legend describing key visual indicators or differential diagnostic points shown in the images. SGCT: seminomatous germ cell tumor; NSGCT: non-seminomatous germ cell tumor; BEP: bleomycin + etoposide + cisplatin; VIP: etoposide + ifosfamide + cisplatin; NGS: next-generation sequencing; GCTM: germ cell tumor of the mediastinum.

For other GCTM subtypes, multimodal therapy based on platinum-based chemotherapy and surgery is the current standard of care. The chemotherapy regimen typically consists of 4 cycles of BEP (bleomycin, etoposide, and cisplatin) or VIP (etoposide, ifosfamide, and cisplatin), followed by surgical resection for persistent residual tumor lesions after chemotherapy[3,80]. SGCTs are highly sensitive to platinum-based chemotherapy, and most patients can achieve a complete response, so platinum-based chemotherapy is the preferred treatment, and surgery can be omitted[82]. Furthermore, extragonadal SGCTs are also sensitive to radiotherapy[83]. Radiotherapy is also an option to be considered for patients who are intolerant to chemotherapy.

Consensus 16: For confirmed mediastinal SGCT, platinum-based chemotherapy is preferred. (Strongly recommended)

Patients with NSGCT have a significantly worse prognosis compared to SGCT with an excellent prognosis of up to 70%-100% 5-year overall survival (OS) rate[84-90]. Because cure is difficult for NSGCT with chemotherapy alone, surgical resection of residual tumor lesions is required to improve patient prognosis[91,92]. Retrospective multivariate analysis showed that surgical resection was an independent factor for improving the prognosis of mediastinal NSGCT[93,94]. Any visible residual tumor, even if less than 1 cm, needs to be resected to minimize the risk of recurrence[95]. Adjuvant chemotherapy may be considered for NSGCT patients with high postoperative risk.

Consensus 17: For confirmed mediastinal NSGCT, platinum-based chemotherapy is preferred, followed by resection of residual tumors. (Strongly recommended)

Regarding the choice of chemotherapy regimen, although studies indicated that the prognosis of patients receiving BEP and VIP regimens is similar[96], the risk of severe pulmonary complications with BEP chemotherapy is significantly higher[97-100], therefore, if BEP chemotherapy is selected, patients should be

reasonably evaluated for pulmonary toxicity, and the drug should be discontinued promptly when symptoms such as decreased diffusion capacity or respiratory failure occur[101]. It should be noted that chemotherapy complications are more frequent in elderly patients over 50 years old[102], and close monitoring is required during treatment. In pediatric cases, treatment strategies must carefully balance oncological efficacy against long - term toxicity. Specifically, it concerns cisplatin - induced ototoxicity and nephrotoxicity, which might require dose adjustments or alternative treatment regimens for younger children. If a patient has concomitant lung disease or pulmonary function impairment, VIP chemotherapy is preferred over BEP chemotherapy[96]. First-line high-dose chemotherapy (HDCT) shows better efficacy for mediastinal NSGCT compared to the same used in later-line treatment, and thus can be considered for patients with a good performance status[103,104]. However, the effectiveness of HDCT is still controversial in some studies[105], so it should be used with caution. Additionally, a single-center study using radiotherapy in the initial treatment of mediastinal NSGCT showed that radiotherapy can significantly reduce the risk of local recurrence and is a treatment option to be considered, but further validation is needed[106].

Consensus 18: BEP is the preferred chemotherapy regimen, and patients should be closely monitored for pulmonary toxicity during treatment. If a patient has concomitant lung disease or pulmonary function impairment, VIP chemotherapy is preferred over BEP chemotherapy. (Strongly recommended)

Resistance to platinum-based chemotherapy is one of the main causes of failure to standard of care in GCT. It has been suggested that *TP53* mutations play an important role in the cisplatin resistance of GCT cells[107-109]. *TP53* mutations are more common in mediastinal NSGCT (56%-72%) and mediastinal GCT with associated hematological malignancies (91%), and mutation carriers have significantly shorter survival[64,79,110]. *MYCN* amplification occurs in approximately 5% of platinum-resistant patients and is mutually exclusive with *TP53*/*MDM2* mutations, representing another potential factor contributing to chemotherapy resistance[51]. A cell experiment revealed that the expression of the miR-371-373 clusters was associated with cisplatin resistance in GCT, suggesting that miRNA detection may help identify patients who are resistant to cisplatin[111].

Consensus 19: *TP53* mutations are a key contributor to resistance to platinum-based chemotherapy in GCTM. Detecting *TP53* gene mutations and miRNA expression shows promise to monitor drug resistance in GCTM, but further clinical study validation is still required. (Recommended)

There is currently no effective treatment regimen for patients with refractory or relapsed GCTM. HDCT has shown some efficacy as a second-line palliative treatment for GCT[112], but is less effective for GCTM[113,114], and most patients may not be eligible for treatment due to disease progression and poor performance status[115]. The outcomes of single-agent chemotherapy regimens are also unsatisfying. A single-center study demonstrated that either suramin, all-transretinoic acid, topotecan, pyrazoloacridine, temozolomide, ixabepilone, or sunitinib had extremely limited efficacy in the treatment of refractory or relapsed GCTM[116]. Genetic testing has certain clinical significance in guiding individualized treatment. Some studies have identified potentially targetable gene variations related to drug resistance in GCT through whole-exome sequencing, including those associated with RTK, RAS, PI3K/mTOR, cell cycle, and other pathways[51]. Individualized medication targeting these variations is worthy of further clinical exploration. We encourage patients for whom no suitable treatment is available to undergo genetic testing and to actively participate in clinical trials for new drugs.

Consensus 20: There is currently no effective treatment regimen for patients with refractory or relapsed GCTM. Next-generation sequencing for common genetic variations in GCTM subtypes is recommended to explore the possibility of personalized therapy. (Recommended)

Table 3. Summary of treatment strategy studies in refractory or relapsed GCTM

Regimen	Number of patients	Outcome
*Guadecitabine and cisplatin[117]	2 GCTM out of 14 GCT	A mediastinal YST patient receiving forth-line guadecitabine + cisplatin achieved 5-month PFS and 16-month OS
5-Azacitidine and cisplatin[118]	Cell line experiments	Partial restoration of cisplatin sensitivity at nanomolar concentrations
Pembrolizumab[119]	1 GCTM out of 12 GCT	No objective responses were observed
Tivantinib (a MET-TKI)[120]	3 GCTM out of 27 GCT	No objective responses were observed
Oxaliplatin and bevacizumab[121]	5 GCTM out of 29 GCT	ORR: 27.6% including 1 CR; Median DoR: 5 months
Temozolomide[122]	3 GCTM out of 20 GCT	ORR: 10% including 2 PR lasting 9 and 3.5 months; Median TTP: 1.5 months; Median OS: 3.1 months
*TI-CE regimen[123]	21 NSGCTM out of 107 GCT	With a median follow-up of 61 months, five (24%) mediastinal NSGCT patients remain disease-free and six (29%) patients are still alive
*IPO followed by topotecan-based high-dose therapy[124]	5 GCTM out of 28 GCT	ORR: 80% (4/5); Three GCTM patients received HDCT, of whom two are progression-free for 15 and 27 months
Gemcitabine and oxaliplatin[125]	4 GCTM out of 30 GCT	ORR: 46% (16/35); Seven (44%) responses occurred in cisplatin-refractory patients
Irinotecan[126]	3 GCTM out of 15 GCT	No objective responses were observed

*Studies reporting treatment outcomes specific for GCTM. GCTM: Germ cell tumor of the mediastinum; GCT: germ cell tumor; YST: yolk sac tumor; PFS: progression-free survival; OS: overall survival; ORR: objective response rate; CR: complete response; DoR: duration of response; PR: partial response; TTP: time to progression; TI-CE: paclitaxel + ifosfamide followed by high-dose carboplatin + etoposide; IPO: irinotecan + paclitaxel + oxaliplatin; HDCT: high-dose chemotherapy.

Table 3 lists some study data on alternative treatment options for refractory or relapsed GCTM[117-126]. Chemotherapy regimens such as irinotecan + paclitaxel + oxaliplatin (IPO) and paclitaxel + ifosfamide, followed by carboplatin + etoposide (TI-CE) have shown favorable efficacy[123,124], but more evidence is still needed to support their clinical use. Based on the theory that high DNA methylation levels contribute to platinum resistance[127-129], a study investigated the efficacy of the demethylating agent 5-azacitidine as an epigenetic modulator in combination with cisplatin in the treatment for NSGCT. In cell experiments, 5-azacitidine could at least partially restore the sensitivity of GCT cells to cisplatin, which preliminarily validated the feasibility of this treatment regimen[119]. Another study found that VIRMA, a protein in the methyltransferase complex, led to cisplatin resistance in GCT by interfering with DNA repair and proposed that the m^{6}A methyltransferase complex was a potential therapeutic target for platinum-resistant GCT[130].

Consensus 21: Methylation is a potential mechanism of platinum resistance in GCTs, and the efficacy of second-line treatment of GCTM by demethylating agents or targeting related methyltransferases deserves further investigation. (Recommended)

Biomarker-driven precision therapy is a feasible future direction for the treatment of GCTM. Results of the phase III clinical trial GETUG 13 showed that when AFP and hCG levels did not decline after BEP chemotherapy, switching to a dose-dense chemotherapy regimen significantly improved the 3-year progression-free survival (PFS) rate compared to continuing BEP chemotherapy (59% *vs.* 48%, hazard ratio = 0.66)[131]. Regarding the predictive value of IHC for the efficacy of second-line TIP (paclitaxel + ifosfamide + cisplatin) chemotherapy, a phase II single-center prospective study showed that the expressions of ERCC1, topoisomerases 1 and 2A, HER2, and p53 were not effective in predicting the effectiveness of chemotherapy[132]. Together, these findings suggest that the predictive value for IHC remains unclear, but changes in serum biomarker levels have the potential to guide the individualized chemotherapy for high-risk GCT.

The therapeutic effect of targeted therapy for GCTM is also worth exploring. A genomic study identified

numerous potentially druggable alterations in platinum-resistant GCT, including those affecting the TP53/MDM2, Wnt/β-catenin, PI3K, and MAPK signaling pathways[133]. Although many druggable targets are available, most of them still lack sufficient clinical evidence. A phase II clinical trial demonstrated that imatinib had poor efficacy in treating KIT-expressing metastatic GCT[134]. Another phase II clinical trial showed that sunitinib was effective in treating refractory or relapsed GCT, and identified *RET* amplification as a potential predictive biomarker for sunitinib efficacy[135]. A case report also indicated that a mediastinal YST patient harboring a *BRCA2* germline mutation was sensitive to radiotherapy, suggesting that mutations in DNA damage repair genes may be helpful to screen GCTM patients suitable for radiotherapy[136]. Additionally, a GCTM patient with *NRAS* somatic mutation and associated leukemia responded to MEK inhibitor therapy[137]. More novel targeted agents and predictive biomarkers await research and development.

For immunotherapy, immune checkpoint inhibitors such as pembrolizumab have poor efficacy in the treatment of GCT, and the predictive value of PD-L1 expression is questionable. Ongoing trials are exploring combination strategies and the role of the tumor microenvironment in overcoming chemoresistance[120]. However, in testicular GCT, it has been reported that some patients with *KRAS* mutations responded to immunotherapy[138]. Additionally, some studies have shown that microarray testing can select patients who are more likely to respond to immunotherapy[139], underscoring the need to develop predictive biomarkers for immunotherapy efficacy in GCTM. Currently, no GCTM patients with microsatellite instability high have been reported[140]. However, it has been suggested that mediastinal NSGCT has a relatively higher incidence of high tumor mutation burden (TMB, ≥ 10 mutations/Mb) compared to testicular NSGCT (11.4% *vs.* 4.7%), so TMB may be a potential biomarker for predicting immunotherapy efficacy[58].

Consensus 22: Dynamic changes in serum biomarkers have certain potential for monitoring and guiding personalized chemotherapy for high-risk GCTs. Currently, there is a lack of sufficient clinical evidence to support biomarker-driven targeted therapy, and predictive biomarkers (such as TMB) used to guide immunotherapy still require further clinical trial validation. (Recommended)

Prognosis and surveillance

GCTM has a worse prognosis than GCT occurring in other sites (5-year PFS rate of 35% *vs.* 77% and 5-year OS rate of 40% *vs.* 82% for mediastinal NSGCT compared to testicular GCT), and mediastinal SGCT has a better prognosis than mediastinal NSGCT (5-year PFS rate of 80% *vs.* 35% and 5-year OS rate of 85% *vs.* 40%)[10,87]. For pediatric patients, GCTM also has a worse prognosis compared to other sites (5-year OS rate of 49% *vs.* 89%[141]), but patients with malignant GCTM have a relatively better prognosis compared to adults, with a 5-year survival rate of approximately 60%[142]. It should be noted that patients with certain subtypes of GCTM have an extremely poor prognosis. For example, the median cancer-specific survival is only 12 months for choriocarcinoma and embryonal carcinoma[141], whereas the median survival is only 6 months for GCTM patients with associated hematological malignancies[17].

Prognostic evaluation is helpful in guiding treatment decision for GCTM. The International Germ Cell Cancer Collaborative Group (IGCCCG) classification is a classic prognostic model for GCT[143]. For NSGCT, primary mediastinal tumor, elevated AFP/hCG/LDH, and visceral metastasis outside the lung (e.g., liver, bone, brain) are independent factors for poor prognosis. For SGCT, visceral metastasis other than the lung is the main adverse prognostic factor. By combining the aforementioned prognostic factors, GCT patients can be effectively stratified according to prognosis. Subsequent studies have further identified other factors for more precise patient prognosis stratification. A study found that in the IGCCCG poor-prognosis subgroup, patients with primary mediastinal tumors and lung metastases experienced

worse outcomes, while patients without visceral metastases had a relatively better prognosis[144]. Another study also indicated that in IGCCCG high-risk NSGCT, a subset of patients with a better prognosis can be identified based on the presence of an embryonal carcinoma component, high Ki-67 expression, low apoptotic protein levels, and low p53 expression[145]. For GCTM, Moran and Suster established a staging system based on lesion location and extent of tumor involvement, which can further subdivide the prognosis of patients on the basis of pathological subtypes[146]. Other reported factors associated with the prognosis of GCTM include age, tumor size, number of metastatic sites, completeness of surgical resection, presence of complete tumor necrosis after chemotherapy, and ratio of neutrophil to lymphocyte[93,147-151]. For teratomas not covered by IGCCCG, studies have shown that the presence of digestive tract tissue, immature neuroectodermal cells, or somatic malignant transformation suggests a higher tumor aggressiveness[152-154].

Consensus 23: The IGCCCG classification can be utilized for prognostic stratification of GCT patients, but there remains room for optimization. *TP53* mutations, expression of Ki-67, and the ratio of neutrophil to lymphocyte may also contribute to the prognosis of GCTM patients. (Recommended)

Because patients with a history of GCTM are at higher risk of subsequent AML-M7 development[14] and have a 10% chance of developing metachronous testicular cancer (for male patients) within 10 years[155], long-term follow-up after treatment is recommended for all GCTM patients. Serum biomarkers such as AFP and hCG are important for post-treatment monitoring and can be used to assess the presence of residual tumor after surgery and the risk of postoperative recurrence[156]. Nonetheless, these biomarkers perform poorly in identifying residual tumor after chemotherapy[157]. Studies have found that miR-371-373 and miR-302 clusters are widely expressed in malignant GCTs and are potential biomarkers for dynamic monitoring of tumor burden and recurrence[158]. A case report has shown that although elevated serum AFP made the differential diagnosis more challenging in a patient with mediastinal NUT carcinoma, miR-371a-3p levels were negative, suggesting a high specificity of this biomarker[159].

Consensus 24: For mediastinal SGCT with a good prognosis, it is recommended to perform annual CT/MRI examination, testicular/ovarian ultrasound, and serum biomarker testing as follow-up after surgical therapy until 10 years postoperatively. For mediastinal NSGCT with a poor prognosis, it is recommended to perform CT/MRI examinations, testicular/ovarian ultrasound, and serum biomarker testing every 6 months as follow-up within 3 years after surgical therapy, then change to annual re-examination. Special attention should be paid to evaluating the occurrence of hematological malignancies. If necessary, testing of miRNA levels may be considered as a means of monitoring tumor status. (Strongly recommended)

FUTURE PROSPECTS

Guiding personalized treatment through molecular subtyping will be an important direction for precision medicine in GCTM. A comprehensive analysis of genomics, epigenetics, and proteomics can not only further explore the different pathogenesis of GCTM, but also support individualized medication. For example, guiding immunotherapy by differentiating cold and hot tumors based on their immune microenvironment, and validating the efficacy of pan-KRAS inhibitors in *KRAS*-mutant tumors. Liquid biopsy also holds promise for breaking through the limitations of traditional biomarkers, such as AFP and hCG, and achieving timely treatment of GCTM. For instance, early detection of platinum resistance by *TP53* mutations, and dynamic monitoring of tumor burden by circulating tumor DNA or miRNA.

However, in the case of GCTM, the study progress is severely limited by the scarcity of patients and the lack of standardized practices across study sites. To accelerate study progress and the implementation of new

drugs, particularly for refractory or relapsed mediastinal NSGCT and pediatric patients, establishing a global collaborative international research consortium may be considered to promote standardized diagnosis and treatment, as well as the conduct of large cross-regional clinical trials. The clinical validation of novel biomarkers and innovative therapies can be conducted through umbrella real-world studies. Considering the clinical complexity of GCTM, we encourage multidisciplinary team discussion to explore the most appropriate treatment strategies by integrating pathological, molecular, imaging, and clinical factors. Patients are encouraged to actively participate in clinical trials to gain access to new drugs. In the future, with the development of molecular diagnosis, real-time monitoring, and international resources, the diagnosis and treatment for GCTM are expected to shift from "empirical chemotherapy" towards "precision intervention", ultimately improving long-term survival for high-risk patients.

Consensus 25: To promote the development of innovative therapies and predictive biomarkers for GCTM, the construction of international collaborative platforms is encouraged to facilitate the clinical validation of new technologies through umbrella real-world studies. (Recommended)

Consensus 26: Complicated cases are encouraged to undergo molecular-based multidisciplinary consultation to discuss the most appropriate treatment strategy, integrating pathological, molecular, imaging, and clinical factors. (Strongly recommended)

DECLARATIONS

Authors' contributions

Participated in the design of the expert consensus: Ji Q, Hao Y, Wang Q, Wang W

Conceived of the expert consensus and participated in its design: Xu C, Zhu Y, Lu Y, Fang M

Other authors coordination and helped to draft the expert consensus.

All authors read and approved the final manuscript.

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Conflicts of interest

Xu C, Song Z, and Pu X are Editorial Board members of *International Open Medical Journal*. They were excluded from editorial decision-making related to the acceptance of this article for publication in *International Open Medical Journal*. The other authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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