Oncology
and Radiotherapy©
18(9) 2024: 001-006 • REVIEW ARTICLE

Germ cell tumours of the mediastinum: An analysis and comprehensive update research on their pathological, clinical, and molecular characteristics

Ramesh Manmal Oswal[1], Kavina Ganapathy[2], Prabhat Sharma[3], Vikram Shete[4], Heena Baria[5], Sudhanshu Dev[6]

[1] Department of Pathology, Krishna Institute of Medical Sciences, Maharashtra, India
[2] Department of Biotechnology, School of Sciences, (Deemed to be University), Bangalore, India
[3] Centre of Research Impact and Outcome, Chitkara University, Rajpura, Punjab, India
[4] Department of UGDX, ATLAS SkillTech University, Mumbai, Maharashtra, India
[5] Parul Institute of Nursing, Parul University, Vadodara, Gujarat, India
[6] Chitkara Centre for Research and Development, Chitkara University, Himachal Pradesh, India

ABSTRACT

The most frequent Extragonadal Germ Cell Tumours (EGCTs) are Mediastinal Germ Cell Tumours (MGCTs), which tend to develop in men and most frequently appear in the anterior mediastinum. Those with Klinefelter syndrome and probably other genetic diseases are also more likely to receive MGCTs. It is believed that MGCTs, like GCTs at other extragonadal locations, develop from germ cells that migrate incorrectly along the midline during development. The seminomatous and non-seminomatous GCT subtypes of MGCTs are categorized similarly to those seen in the testes. Non-seminomatous MGCTs include embryonal carcinoma, mature or immature teratoma, pure Yolk Sac Tumours (YSTs), mixed GCTs, and choriocarcinoma with any combination of GCT types, including semi-noma. Seminomatous MGCTs are pure semi-noma. Hematologic or somatic cancers may potentially develop concurrently with a primary MGCT. Except for benign teratomas, which simply require surgical removal without chemotherapy, treatment involves neoadjuvant chemotherapy followed by surgical resection of the remaining tumour. It highlights and update the molecular, clinical, and pathologic aspects of MGCTs in this review. There includes a discussion of the Immuno Histochemical (IHC) characteristics of each tumour type and other diagnostic methods.

Keywords: clinical characters, Mediastinal Germ Cell Tumours (MGCTs), pathologic characters, treatment, molecular characters

Address for correspondence:

Ramesh Manmal Oswal

Department of Pathology, Krishna Institute of Medical Sciences, Maharashtra, India

E-mail: drrameshoswal@gmail.com

Word count: 3669 **Tables:** 02 **Figures:** 01 **References:** 15

Received: 14 August, 2024, Manuscript No. OAR-24-145479
Editor Assigned: 17 August, 2024, Pre-QC No. OAR-24-145479(PQ)
Reviewed: 01 September, 2024, QC No. OAR-24-145479(Q)
Revised: 08 September, 2024, Manuscript No. OAR-24-145479(R)
Published: 16 September, 2024, Invoice No. J-145479

INTRODUCTION

The gonads are the primary source of Germ Cell Tumours (GCTs). The testes are the source of more than 90% of GCTs. Moreover, primary extragonadal GCTs account for just 2%-5% of GCTs and are most frequently seen in the mediastinum and retroperitoneum [1]. Their histologies is classified as semi-noma and non-semi-noma and are identical to those of their testicular counterparts. Extragonadal EGCTs still have no recognized cause. There are two main hypotheses. One hypothesis is that embryonic progenitors of germ cells migrate incorrectly and persist in atypical sites. The second holds that throughout development, germ cells are extensively dispersed and eventually give rise to malignancies. About 1% to 3% of all adult GCTs are PMGCTs, making them very uncommon. The development of primary mediastinal semi-noma is rather sluggish and covert [2]. When a primary mediastinal non-semi-noma is first detected, 85%-95% of patients already have at least one metastatic lesion. Moreover, non-semi-nomas have a higher chance of metastasizing than seminos. A large tumour or invasion causes symptoms in more than 90% of patients. Dyspnea, dysphagia, hoarseness, chest discomfort, and cough are the most prevalent symptoms, albeit they are typically vague. Other symptoms that some people may experience include weight loss, fever, weariness, and superior vena cava syndrome [3].

The Serum Tumour Markers (STMs) Beta-Human Chorionic Gonadotropin (β-HCG), Alpha-Fetoprotein (AFP), and Lactate Dehydrogenase (LDH) are shared by PMGCTs and gonadal GCTs. Moreover, both extragonadal and gonadal GCTs exhibit the recognizable genetic aberration known as isochromosome 12p [4]. PMGCTs and gonadal GCTs have comparable Computed Tomography (CT) imaging properties. In a CT scan, semi-noma and non-semi-noma might differ from one another. With the application of contrast, the primary mediastinal semi-noma exhibits homogenous soft tissue attenuation and homogeneous amplification. Primary mediastinal non-semi-noma, on the other hand, is heterogeneous, has uneven boundaries, and may expand into nearby structures [5]. In contrast, non-semi-noma PMGCTs are difficult to treat due to decreased cisplatin sensitivity and a lack of other therapy choices in the first and later lines. For a better treatment strategy, research is being conducted to uncover biomarkers and actionable targets. This essay provides a thorough assessment of the literature on mediastinal germ cell cancers.

LITERATURE REVIEW

In research, 36 male patients with Somatic-Type Malignancies (STM) had their GCTs analysed using a multi-platform molecular approach [6]. Sarcoma and neuroectodermal tumours of the embryonic type, each found in 61% and 31% of patients, correspondingly, were the most prevalent histological forms of SM. To guide how to handle central nervous system germ cell tumours, the author of combined clinical, histological, and genetic data [7]. Understanding of the pathophysiology of the puzzling tumour would be improved by the results about clinical and genetic heterogeneity. To summarize the similarities and differences between the uncommon illness and its gonadal analogs, research intend to compile all molecular data described in the condition [8]. It was currently unclear what mechanisms were at play in their progression, increased resistance to conventional therapy, and modes of development. Few numbers of data were described in the literature for MGCTs, and appropriate multi-omics analysis was currently absent. Histopathological analysis, including diagnostic, grading, immunohistochemistry, and genetic profiling, were discussed in [9]. The cancer group and its associated epidemiology, clinical presentation, and treatment options were also described briefly. The primary emphasis, however, was on analysing the pathologic evaluation process for cancers before and after treatment. At a high-volume facility, patients with PMNSGCTs who were having resection and multidisciplinary therapy were studied for management methods, Progression-Free Survival (PFS), and OS [10]. With a 22% long-term Survival Rate (SR), patients receiving second-line chemotherapy followed by resection have a bad prognosis.

Targeted immunohistochemistry and molecular characterization techniques have significantly enhanced diagnostic biomarkers over the last several decades. The majority of indicators weren't completely sensitive or specific despite these recent developments. In research, they provide a summary of tissue-based biomarkers important to the pathologist, with an emphasis on real-world diagnostic challenges relating to testicular GCT and Sex Cord-Stromal Malignancies (SCST) [11]. The purpose of the research was offered an update on the diagnostic features of malignant ovarian GCT, including their clinical, morphological, immunocytochemical, and, where appropriate, molecular characteristics [12]. Also included are somatic malignancies that contain germ cells, and the new pluripotency indicators that have improved diagnostic accuracy. A late-adolescent teenage boy with a chemotherapy-resistant residual cancerous tumour and an elevated Vasculogenic Mesenchymal Tumour (VMT) was described in the paper [13]. The kid underwent treatment for a mediastinal mixed GCT that included contained YST. The discovery that VMT showed a partially YST-like immunophenotype and inherits the genetic changes of pre-existing mixed GCT might be a factor in the severity of its clinical manifestations.

METHODOLOGY

Using various combinations of mediastinal MGCTs, clinical aspects, prognostic factors, therapy, and molecular features, relevant publications published between 1976 and 2022 were found using a Google Scholar search. By looking through the reference lists of pertinent articles, more papers were found. Studies carried out on animals, publications with a poor level of dependability, and publications published in a language other than English were all disqualified. Depending on how relevant they were to the subject, data were extracted.

Clinical characteristics

The anterior mediastinum has a higher chance of producing MGCTs than the inferior, middle, or posterior mediastinum's. Young males between the ages of 25 years and 35 years who have mediastinal tumours have 15%-20% of them be MGCTs. At the time of diagnosis, symptoms including dyspnea, coughing, chest discomfort, and weight loss are typical. Gynecomastia, haemoptysis, fever, nausea, recurrent laryngeal nerve palsy, and Superior Vena Cava (SVC) syndrome are other symptoms. Mediastinal lymph nodes are where MGCTs most often metastasize. Nevertheless, they may also spread to the retroperitoneum, liver, lungs, heart, bone, and central nervous system. Patients should be staged using the proper diagnostic procedures, which may involve whole-body CT scans since extra-mediastinal metastasis is associated with a worse prognosis.

Thymic disorders, thyroid goiter, NUT carcinoma, metastatic melanoma, sarcomas, lymphomas, and metastatic carcinoma to the mediastinum should all be taken into account while making a differential diagnosis. Moreover, a retroperitoneal primary or a testicular primary is connected to dissemination that follows the thoracic duct's route. To assess testicular primary, more testing should be done. The clinical presentation, symptomatology, and prognosis of MGCTs might vary from those of their gonadal counterparts, although their histological and pathological characteristics are the same as those of gonadal GCTs. Despite treatment and surgery, the prognosis for non-semi-noma MGCTs is dismal, with a 5-years OS of 42% to 54%, as shown in table 1. Non-pulmonary visceral metastases and increased -HCG are independent prognostic variables connected to a shorter SR in non-semi-noma MGCTs. In contrast, semi-noma MGCTs have a fantastic prognosis with an OS of more than 90% when treated with the available curative methods.

Tab. 1. Survival improvements for GCTs at low risk

	5-Year PFS (95% CI)	Years	No of Patients	5-Year OS (95% CI)
Adra et al. [14]	58% (51% to 63%)	1990-2014	273	73% (67% to 78%)
Gillessen et al. [15]	54% (52% to 56%)	1990-2013	2514	67% (65% to 69%)
IGCCCG	41% (35 to 47)	1975-1990	832	48% (42% to 54%)

Tumour markers

Whereas non-semi-noma MGCTs are linked to high levels of AFP, HCG, and LDH and are raised in around 20% of seminomas. In teratoma, YSTs, and embryonal cancer, AFP levels are increased; in embryonal carcinoma, choriocarcinoma, and semi-noma, HCG levels are elevated. LDH lacks specificity, which restricts its therapeutic value. Non-semi-noma components have to be checked out when AFP levels in a semi-noma patient are high and continuing to rise; these patients should be treated as non-semi-noma. There are discoveries of novel circulating micro-RNAs in GCTs, such as miR371a-3p. Compared to the traditional blood tumour markers, AFP, HCG, and LDH, which have a combined

sensitivity of 50%, their sensitivity and specificity are significantly greater. The plasma of PMGCTs with viable functional malignancies that are either non-semi-noma or semi-noma appears to include miR371a-3p, yet it is not seen in patients with mediastinal teratomas. Despite the fact that peripheral blood miRNA synthesis and identification in extramedullary GCT, data are lacking.

Pathological characteristics

The suggested mechanisms for extragonadal GCT development to date include interrupted progenitor germ cell migration during embryogenesis, burnt-out primary, and reverse migration of altered GCs from testes. PMGCTs are categorized as non-seminomas and include semi-noma, mixed germ cell tumours, embryonal carcinoma, choriocarcinoma, GCT with concomitant haematological malignancy, and teratoma. Mature teratoma is the most common histological subtype in adults, whereas prepubertal additional GCTs are mostly composed of teratoma (58%) and YSTs (42%). Without respect to the primary location, GCTs are further divided into 5 categories according to chromosomal alterations and developmental potential. Chromosomes 1p, 4p, and 6q are lost in juvenile teratomas and YSTs. Semi-nomas and non-semi-nomas in adolescent and adult males are classified as type II GCTs. Chromosome losses of 1p, 11p, 13p, and 18p and gains of 7p, 8p, 12p, 21p, and X are frequently observed in these malignancies.

The majority of individuals with primary mediastinal choriocarcinoma are diagnosed with hematogenous spread. Hence, as compared to other histologic subtypes, it has a worse prognosis. Because of their biochemistry and shape, malignant progenitors of embryonal stem cells are thought to be embryonal cancer cells. YSTs usually contain extraembryonic mesenchymal cells and malignant endodermal cells, which are more common in children. A worse prognosis is linked to YSTs and embryonal cancer.

Teratomas develop from the 3 germinal layers and may differentiate into any kind of bodily tissue. Teratoma grading is based on neuroepithelial component quantity and immaturity. Tumours classified as grade 1 must exhibit some degree of immaturity, although only 1 or 2 foci may include neuroepithelium. Grade 3 is described as having considerable neuroepithelial immaturity and having neuroepithelial components in 4 or more fields within individual sections. Between classes one and three is grade 2. In MGCTs, mature teratoma accounts for 63% of teratoma diagnoses, whereas immature teratoma affects 4% of patients. In roughly 33% of instances, teratoma is associated with sarcoma, other malignant GC components, or cancer. The recognized IHC markers for the pathological diagnostic confirmation of GCTs include SALL4, Organic Cation Transporter (OCT) Placental Alkaline Phosphatase (PLAP), Epithelial Membrane Antigen (EMA), CD30, FP, glycan-3, β-HCG, and cytokeratins. IHC antibodies should be employed to identify the proteins since tumor phenotype may often result in varied and localized staining. Contrarily, cytokeratins are virtually invariably present in embryonal cancer. Although PLAP, EMA, CD30, OCT-4, and SALL-4 might also be positive, it is positive in around half of the cases. According to table 2, YSTs are negative for CD30 and c-kit but positive for cytokeratins and SALL-4. In teratoma PMGCTs, non-germ cell malignant transformation which includes sarcoma and differentiation of adenocarcinomas happens more frequently than in primary or gonadal retroperitoneal GCTs.

Tab. 2. IHC in GCTs

	Embryonal Carcinoma	Choriocarcinoma	Immature Teratoma	Seminoma	Yolk Sac Tumour
Positive Markers	Oct 3–4 Sall4 Cd30 Cytokeratin's Sox2 Nanog	Cytokeratin's Hcg Glypican-3 Ema Sall4	Sox2 Sall4 Ema Cytokeratin's	Oct 3–4 Sall4 C-kit Nanog Plap	Cytokeratin's Sall4 Glypican-3 Afp
Negative Markers	Glypican-3 C-kit	C-kit CD30 SOX2 OCT 3-4 NANOG	C-kit NANOG SOX2 OCT 3-4 CD30	Glypican-3 SOX2 CD30	CD30 C-kit SOX2 NANOG OCT 3-4

The following are the characteristics of the post-chemotherapy residual disease:

10%-20% viable GCTs, 30%-40% teratoma, and 40% to 50% clusters of heterogeneous inflammation accompanied by fibrosis and necrosis. The proportion of viable non-teratoma GCTs should be included in a given that pathology reports are among the most significant predictors of long-term results. A positive prognostic sign is the presence of less than 10% viable tumour cells. To better understand the remaining tumour, if there, a large number of samples should be performed.

Molecular characteristics

Irrespective of the histological subtype, the i(12p) is a chromosomal abnormality that is seen in around 80% of MGCTs. The detection of i(12p) in a specimen with a mediastinal mass may help confirm the MGCT diagnosis. Numerous genes on chromosome 12's short arm may have a role in the development of GCTs. The precise molecular processes behind the onset and development of GCT are yet unknown. The sex chromosomes, chromosomes 1p, 1q, and 6q, and other chromosomal abnormalities, are included. In comparison to testicular GCTs, MGCTs have more tumour mutations and particular harmful oncogene changes. The mutations most often seen in MGCTs have been identified (figure 1). Compared to seminomas and non-semi-noma TGCTs, non-seminoma PMGCTs are more likely to have these changes.

A limited amount of research has connected TP53 mutations and MDM2 alterations to cisplatin resistance in GCTs. Testicular GCTs are often the site of TP53 mutations, whereas MDM2 amplifications are primarily seen in the testis. TP53 mutations were found in 16.3% (17/104) of patients in cisplatin-resistant GCTs, according to a retrospective review. Be aware that the research analysis of non-semi-noma MGCT samples revealed TP53 mutations in 72.2% (13/18) of the samples. In a recent multi-institutional approach on MGCTs, 56% of non-semi-noma tumours had

TP53 genomic alterations, and these patients had significantly shorter OS than patients with MGCTs with wild-type TP53. This suggests that patients with MGCTs have a different genomic background, which may help to explain why this patient population has such a poor prognosis. Even more often, TP53 mutations have been seen in 91% of individuals with MGCTs linked to hematologic malignancies.

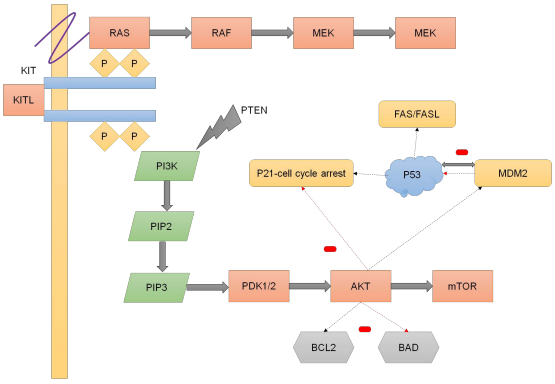

Fig. 1. Molecular aberrations in MGCTs

Diagnosis and pre-treatment evaluation

The differential diagnosis for GCTs in the anterior mediastinum should include thymic diseases, hypothyroidism goiter, and malignancies. Diagnosis and characterization of MGCT might be difficult. Small needle core biopsies are often used to make the diagnosis, and further Immuno Histochemistry (IHC) tests are frequently required for confirmation. Wide-ranging tissue collection and careful diagnostic assessment are crucial since non-diagnostic needle biopsies are a major problem. Before surgery, patients often receive cisplatin-based chemotherapy, thus the first pathologic assessment is crucial. When administering chemotherapy to patients, it is important to determine the presence of somatic differentiation, which portends a poor prognosis since chemotherapy causes tumour necrosis, which can reduce the transformed component. Moreover, a biopsy is required to diagnose the condition since β-HCG in semi-noma and non-seminoma GCTs is within the normal range or modestly increased. In contrast, if the patient has high AFP readings, the condition may not need to be confirmed by biopsy. Get a routine Complete Haemogram (CHG) and blood biochemistry panel including AFP, β-HCG, and LDH. Testicular ultrasound testing is required in cases with clinical suspicion. In cases where the diagnosis is ambiguous, an orchiectomy is required to rule out metastasis from a gonadotropin original. This is true even if the abnormality is likely not a tumor but instead of a blemish lesion in the setting of a damaged malignancy.

Extragonadal GCT staging does not follow any approved AJCC TNM guidelines. Before surgery, a pre-treatment CT imaging/PET scan is necessary to describe the architecture and vascular relationships and to evaluate the disease's spread. When examining neighbouring structural invasion, MRI is a useful tool. Large homogenous soft tissue masses resembling lymphomas characterize seminomas, but non-semi-noma GCTs are inhomogeneous tumours with boundary abnormalities as a result of their invasive activity. Radiological examinations of teratomas reveal a calcified (20%-43%) multi-lobulated soft tissue mass with a rounded appearance. If the patient is showing worrying symptoms, an MRI of the brain and a bone scan might be performed to check for metastasis, which can travel to the brain and vertebrae. Before beginning chemotherapy, patients should get advice on sperm analysis and banking based on their desire to become parents. Chemotherapy may alter sperm count and quality. Also, the inability to conceive puts a person at risk for developing testicular cancer, and DNA repair issues is the cause of the link between poor spermatogenesis and carcinogenesis. More research is needed to determine if cancer screening is necessary for azoospermic males.

Treatment

For MGCT patients, the cure is the end objective of therapy. Treatment is curative in >80% of semi-noma PMGCT patients with the substantial disease, and in 40%-50% of non-semi-noma MGCT patients when adopting a multimodality strategy. As soon as possible, appropriate therapy should be started. Following normalized or decreased blood tumour markers, full or virtually complete surgical excision has a significant influence on the course of treatment for individuals with MGCTs. After initial chemotherapy, factors including full resection, fewer than 10% of live tumour cells remaining in the resection material, and the IGCCCG's categorization of excellent prognosis are suggestive of a favourable outcome. The prognosis is poorer for subgroups of immature teratoma and non-semi-noma.

To prepare for any future thoracic surgery, the VIP protocol (which substitutes ifosfamide for bleomycin) would be preferable to the usual BEP regimen. The use of bleomycin entails a risk for postoperative morbidity the death, and surgical morbidity. In genetically vulnerable individuals, the main factor contributing to the production results of lung problems is oxidation stress, which manifests as interstitial pneumonitis and progresses to fibrosis. The DLCO test is used to quickly and easily show that bleomycin-induced lung damage exists in the subclinical stage. If the diffusion capacity drops under 30%-35% of the original amount, treatment should be stopped, and dosages shouldn't exceed 400 units since doing so increases the risk of pulmonary damage. The anaesthesiologist has to be informed of bleomycin exposure in order for them to take precautionary measures, such as limiting fluid replenishment over the course of the therapy and employing a low proportion of inspired oxygen.

Four chemotherapy rounds followed by post-chemotherapy surgical excision are advised for non-semi-noma histology. Following chemotherapy, surgery is essential because the remaining tumour may still include immature or mature GCs or teratoma with somatic differentiation, all of which are associated with a poor prognosis. Because salvage chemotherapy has a poor response

rate, an increase in malignant tumours following chemotherapy may not exclude effective treatment by surgical excision. The ineffectiveness of normal or high-dose regimens makes treating recurrent illnesses difficult. While it is not used to treat primary non-semi-noma GCTs, radiation treatment is used to treat certain diseases, such as brain metastases. When there is disease development despite tumour markers decreasing after therapy, developing teratoma condition is a medical entity that must be looked at. It is characterized by an expanding mediastinal mass and worsening cardiopulmonary function. For efficient therapy of developing teratoma syndrome, early detection is crucial. Early surgical surgery is advised in these circumstances and is linked to better results. In MGCTs that are resistant to chemotherapy, an aggressive surgical operation could also be necessary.

For individuals with respectable tumours and negative tumour markers, upfront surgery is a possibility. Non-semi-noma MGCT is regarded as a poor prognostic factor, suggesting a poor outcome for patients receiving HDCT and PBSCT. As a result, several specialists do not favor employing HDCT in MGCTs that do not include semi-noma. However, the majority of patients did not respond well to salvage HDCT and PBSCT. Further data on HDCT and PBSCT are required to more accurately identify the individuals who will respond to treatment since this patient group is usually omitted from HDCT trials. Surgery must be done on the remaining masses with a curative purpose after HDCT and PBSCT, perhaps at high-volume facilities to enhance results.

Semi-noma MGCTs patients had a comparable prognosis to gonadal semi-noma patients, with a 5-year SR of more than 90%. IGCCC risk categorization assigns MGCTs without non-pulmonary metastases a favourable risk rating. Semi-noma MGCTs have a favourable prognosis because of their exceptional radiation and chemotherapy sensitivity. Adjuvant chemotherapy in addition to initial surgical excision is a feasible therapeutic option for small, resectable tumours in asymptomatic patients. If initially complete tumour eradication is not achievable, the best course of treatment is chemotherapy, followed by radiation therapy or surgery for the residual tumour. A three-cycle BEP regimen is advised for those with a good IGCCCG risk. A suggested four cycles of BEP and VIP are indicated for individuals with a moderate IGCCCG risk. While chemotherapy is the recommended course of action, radiation treatment to the mediastinum is beneficial for those without a debilitating disease who have strong contraindications to chemotherapy (35-50 Gray).

The histology of the underlying tumor and the extent of the remaining illness determine how post-chemotherapy residual masses should be managed. If the FDG PET scan is negative, it can be useful to rule out any remaining viable semi-noma. The choice of therapy should not, however, be based only on the results of a positive PET scan because of the test's limited positive predictive value and potential for overtreatment. If surgery is not an option, residual viable illness needs chemotherapy or radiation treatment. Progressing lesions after chemotherapy needs either surgery, if feasible, or salvage chemotherapy. Surgery of residual masses is recommended in patients with post-chemotherapy non-semi-noma MGCTs if it is feasible. Due to teratomas' reported low FDG absorption, PET scans in these patients are only of extremely limited benefit.

Surgery alone may successfully treat mature primary mediastinal teratomas, and the prognosis is favourable. Depending on the kind and degree of the changed tumour, teratomas with somatic transformation are either surgically removed or treated with chemotherapy. Before every round of chemotherapy, serum tumour marker testing should typically be done. Above all, referral of patients to centres with experience in handling GCTs should be taken into consideration since such facilities are linked with noticeably improved results when treating patients with poor prognoses.

CONCLUSION

The clinical and molecular characteristics of semi-noma and non-semi-noma MGCTs differ, making MGCTs a heterogeneous entity. Because of their poor chemotherapy sensitivity and high likelihood of recurrence, non-semi-noma MGCTs continue to have one of the worst prognosis outlooks among GCTs. To enhance cure rates in this patient group, integrated, multidisciplinary care is essential. When given a multimodal treatment plan, semi-noma MGCTs have a 5-year OS rate above 90% and a favourable prognosis comparable to that of their gonadal counterpart. To apply treatment techniques and eventually enhance patient outcomes, it would be advantageous to identify biological and genetic markers that predict therapy responses. Moreover, working with facilities experienced in treating GCTs is linked to noticeably improved results.

REFERENCES

1. Takami H, Graffeo CS, Perry A, Ohno M, Ishida J, et al. Histopathology and prognosis of GCTs metastatic to the brain: Cohort study. J Neurooncol. 2021;154:121-130.
2. Lew CZ, Liu HC, Hou JY, Huang TH, Yeh TC. Pediatric extracranial germ cell tumors: Review of clinics and perspectives in application of autologous stem cell transplantation. Cancers. 2023;15:1998.
3. Kubota Y, Seki M, Kawai T, Isobe T, Yoshida M, et al. Comprehensive genetic analysis of pediatric GCTs identifies potential drug targets. Commun Biol. 2020;3:544.
4. Marker DF, Pearce TM. Germ cell tumors of the central nervous system: A brief review and site-specific considerations. Semin Diagn Pathol. 2023;40:47-51.
5. Fonseca A, Lobo J, Hazard FK, Gell J, Nicholls PK, et al. Advancing clinical and translational research in germ cell tumours (GCT): Recommendations from the Malignant Germ Cell International Consortium. Br J Cancer. 2022;127:1577-1583.
6. Wyvekens N, Sholl LM, Yang Y, Tran I, Vasudevaraja V, et al. Molecular correlates of male germ cell tumors with overgrowth of components resembling somatic malignancies. Mod Pathol. 2022;35:1966-1973.
7. Takami H, Fukuoka K, Fukushima S, Nakamura T, Mukasa A, et al. Integrated clinical, histopathological, and molecular data analysis of 190 central nervous system germ cell tumors from the iGCT Consortium. Neurooncol. 2019;21:1565-1577.
8. Urbini M, Schepisi G, Bleve S, Virga A, Gianni C, et al. Primary mediastinal and testicular germ cell tumors in adolescents and adults: A comparison of genomic alterations and clinical implications. Cancers. 2021;13:5223.
9. Sohn A, Moran CA. Primary mediastinal germ cell tumors. Semin Diagn Pathol. 2023;40:37-46.
10. Caso R, Jones GD, Bains MS, Hsu M, Tan KS, et al. Outcomes after multidisciplinary management of primary mediastinal germ cell tumors. Ann Surg. 2021;274:1099-1107.
11. Siegmund SE, Mehra R, Acosta AM. An update on diagnostic tissue-based biomarkers in testicular tumors. Hum Pathol. 2023;133:32-55.
12. Kaur B. Pathology of malignant ovarian germ cell tumours. Diagn Histopathol. 2020;26:289-297.
13. Fujii H, Yamada Y, Yamamura K, Ishida Y, Tsujimura M, et al. A case of vasculogenic mesenchymal tumor in the mediastinum: Whole-exome sequencing reveals origin from pre-existing germ cell tumor. Virchows Arch. 2023;482:923-927.
14. Adra N, Althouse SK, Liu H, Brames MJ, Hanna NH, et al. Prognostic factors in patients with poor-risk germ-cell tumors: A retrospective analysis of the Indiana University experience from 1990 to 2014. Ann Oncol. 2016;27:875-879.
15. Gillessen S, Sauvé N, Collette L, Daugaard G, de Wit R, et al. Predicting outcomes in men with metastatic nonseminomatous germ cell tumors (NSGCT): Results from the IGCCCG update consortium. J Clin Oncol. 2021;39:1563-1574.