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Multimodality treatment outcome in patients with primary malignant mediastinal germ cell tumor in adults

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Abstract

Background: Malignant mediastinal germ cell tumor (MGCT) is rare and has poor outcomes even after multimodality treatment. Data from resource-poor countries are scarce in the literature.

Aims: To evaluate the clinicopathologic features and treatment outcome of primary malignant MGCT at our center.

Methods and Results: Single institutional data review of patients aged ≥18 years, treated with a diagnosis of malignant MGCT between Nov'2013 and Nov'2019. Risk stratification was done as per International Germ Cell Cancer Collaborative Group (IGCCCG) classification. Patients were treated with platinum based chemotherapy and surgical resection for the residual disease was performed in non-seminomatous histology.28 patients had MGCT with a median age of 25 years (range:18-36) and all were male. Seven patients had superior vena cava obstruction (SVCO) at diagnosis and pre-treatment histological diagnosis was available in 23 (82%) patients. Seven (25%) patients had seminoma histology, all were of good risk as per IGCCCG risk criteria, whereas others had non-seminoma histology with poor-risk group. Seven patients with seminoma histology achieved a complete response after initial treatment. Six patients with non-seminoma histology underwent complete resection of residual disease post-chemotherapy and five revealed residual viable tumors. After a median follow-up of 10.8 months (range:2.9-75), 3-year progression-free survival (PFS) and overall survival (OS) estimate was 61.2% and 94.7% in the whole cohort, respectively and 3-year PFS and OS estimate was 100% in patients with seminoma histology.

Conclusions: This is the largest data set of MGCT patients' outcomes reported from India with multi-modality treatment. All patients were male and one-fourth had SVCO

at presentation. Seminoma histology patients had a 100% outcome after initial platinum based chemotherapy. But, those with non-seminoma histology had a poor outcome even with chemotherapy and surgery.

KEYWORDS
mediastinal germ cell tumor, residual disease, seminoma, superior vena cava obstruction

1 | INTRODUCTION

Mediastinal germ cell tumor (MGCTs) are some heterogeneous mixtures of benign and malignant tumor identical to their testicular or ovarian counterpart. They probably arise from primitive germ cells due to interrupted migration during embryogenesis and account for 1%-3% of all GCTs.[1] MGCT constitute 3%-15% of all mediastinal tumors in different published literature.[2,3]

A diagnostic difficulty may arise due to mimickers like - lymphoma and thymic neoplasms and often they are diagnosed after a mediastinoscopic biopsy. The teratomatous tumor forms the major bulk of MGCTs followed by seminoma and making non-seminomatous GCTs (NSGCT) or mixed GCTs the least sub-types. Primary malignant MGCTs constitute only 10% of the whole group of MGCTs and almost invariably occur in males with a male: female ratio of 9:1.[4]

There is no standard TNM staging available for MGCT and the majority of the case series or larger publications followed staging system proposed by Moran et al[4] whereas they are risk grouped as per International Germ Cell Cancer Collaborative Group (IGCCCG) classification.[5] Treatment usually consists of a platinum based polychemotherapy regimen followed by surgery of residual disease in case of NSGCT sub-types, if indicated. The outcome remains inferior to their gonadal counterpart being a poor risk disease due to the location in the case of NSGCT variety. In contrast, the outcome is much better with seminoma histology.

Due to the rarity and non-familiarity of primary malignant MGCT, there is a paucity of data in the literature, particularly from India.[6-14] Here, we have evaluated the clinico-pathological features, treatment pattern, and outcome of patients diagnosed and treated as primary malignant MGCT in our institution over the last 6 years.

2 | MATERIALS AND METHODS

2.1 | Patients

This is a retrospective study of MGCT patients aged ≥18 years registered and treated at our center. Patients were searched from a prospective database of hospital management services from Nov'2013 to Nov'2019. Patients who did not take any further treatment after initial staging and evaluation were excluded from survival analysis. Ethical clearance was taken from Institute Review Board and the patient consent waiver was obtained because of the retrospective nature of this study.

2.2 | Diagnosis and staging

All eligible patients underwent testing for routine biochemical blood parameters, baseline tumor markers - alpha-fetoprotein (AFP), beta-human chorionic gonadotrophin (b-HCG), lactate dehydrogenase (LDH), testicular ultrasound, computed tomography (CT) of the chest and whole abdomen. A bone scan was performed if clinically indicated or with high serum alkaline phosphatase. An attempt was made to do core needle biopsy for diagnostic confirmation to rule out somatic differentiation or *NUT* midline carcinoma,[15] especially in those with normal tumor marker or mild elevation in b-HCG and also to rule out thymic malignancy or lymphoma from pure seminoma. Patients with elevated serum AFP and/or high b-HCG and/or histological features of yolk sac tumor, embryonal carcinoma, immature teratoma, or mixed features were treated as NSGCT. Risk stratification was done as per the IGCCCG classification.[5]

2.3 | Treatment protocol, response evaluation and follow-up

Patients were counseled for semen analysis and sperm banking if unmarried or family not completed. Patients were treated with bleomycin, etoposide, and cisplatin (BEP) or etoposide and cisplatin (EP) depending upon the IGCCCG risk stratification. Etoposide, cisplatin and ifosfamide (VIP) based chemotherapy was preferred over the BEP regimen wherever possible.[16,17] Serial serum tumor marker was monitored before each cycle of chemotherapy.

Response assessment was done by RECIST v 1.1[18] wherever applicable. FDG PET-CT was performed to look for residual disease after normalization of serum marker (if elevated at baseline) in seminoma histology and radiotherapy was offered for metabolically active residual tumor. For non-seminomatous histology, post-chemotherapy resection of residual disease was done when required.[19] Patients with residual disease on the resected specimen of non-seminomatous MGCT were offered 2 cycles of additional EP regimen. Patients were followed-up with CT chest with tumor marker, if elevated baseline, every 4 months for initial 2-years, and then 6 monthly for the next 3-5 years. Patients were followed up for

acute and long-term treatment-related toxicities as well as for recurrence.

2.4 | Statistical analysis

Descriptive statistics were used for demographics and clinico-pathological characteristics. A Chi-square test was used to detect the association between categorical variables. Student's *t* test was applied to compare continuous variables between groups. Survival was estimated by the Kaplan-Meier method and compared using the log-rank test. Data were censored on 31 January 2020. Progression-free-survival (PFS) with the Standard error (SE) was calculated from the date of diagnosis to date of disease relapse. Overall survival (OS) with the SE was calculated from the date of diagnosis to the date of death from any cause. Patients who were lost to follow-up or had treatment abandonment were also included for PFS and OS analysis and outcome in these patients was confirmed by telephonic contact. Treatment abandonment was included for survival analysis in the present study as it has been proposed that non-compliant and treatment abandonment patients should be included in survival analysis for studies from developing nations to provide a true picture of outcome from these countries.[20] STATA/SE 11.0 (StataCorp LP, Texas) was used for statistical analysis.

3 | RESULTS

3.1 | Baseline characteristics

Out of a total of 270 patients with a diagnosis of extra-cranial GCT over the study period at our center, a total of 28 MGCT patients were included in this analysis with a median age of 25 years (range:18-36). All patients were male with a median symptom duration of 2 months (range:0.5-12 months) and cough was the most common symptom (Table 1). Seven patients (28%, n = 7/25) had features suggestive of superior vena cava obstruction. The baseline tumor marker was - S1 marker in 9 (32%), S2 marker in 12 (43%), and S3 marker in 7 (25%); three patients had normal serum tumor marker and were classified as S1 marker (Table 2). Image-guided trucut biopsy was done in 23 patients (82%) and 16 patients had non-seminoma histology (Table 3). Nine (32%) patients had metastasis at presentation and out of which two had extra-thoracic metastasis.

3.2 | Treatment details and toxicities

Seven (25%) patients had good risk disease and 21 (75%) patients had the poor-risk disease as per IGCCCG risk classification. Four patients defaulted before initiation of treatment and rest 24 patients received systemic chemotherapy as follows - BEP in 11 patients, EP in seven patients, and VIP in 6 patients. After 4 cycles of chemotherapy, the responses were - complete response in 5 (21%), partial response in 16 (67%), stable disease in 2 (8%), and one patient had progressive disease (had an initial response after second cycle). Ten patients (42%) required in-patient care for grade 3 or 4 toxicities as - febrile neutropenia in 4, vomiting in 2, hyponatremia in one, acute kidney injury in one, decreased lung function in two patients. Four patients had features of metabolic syndrome, five patients had mild peripheral neuropathy (grade1 or 2) and two patients had SVC thrombus.

TABLE 1 Clinicopathologic characteristics

Variable	N	%
Superior vena cava obstruction	07	25
Tumor marker		
S1	09	32
S2	12	43
S3	07	25
Pre-treatment biopsy	23	82
Histology types		
Seminoma	07	25
Non-seminomatous	21	75
IGCCC risk group		
Good	07	25
Intermediate	00	00
Poor	21	75
Chemotherapy protocols (n = 24)		
Bleomycin, Etoposide, Cisplatin	11	54
Etoposide, Cisplatin	07	25
Etoposide, Cisplatin, Ifosfamide	06	21

Abbreviations: IGCCCG, International Germ Cell Cancer Collaborative Group.

3.3 | Post-chemotherapy treatment for residual disease

Two patients with seminoma had residual disease after chemotherapy and received thoracic radiotherapy for that. Subsequently, both of them achieved a complete radiological response. Six patients underwent surgery for complete resection of radiological residual disease in non-seminomatous histology and five patients had residual tumors while one had complete necrosis.

3.4 | Outcome- MGCT with seminoma histology (n = 7)

All patients achieved a complete response after initial treatment and none progressed so far till the last follow-up with PFS of 6, 11, 13.9, 20.6, 35.7, 39.3, and 75.2 months, respectively.

TABLE 2 Classification of tumor marker range/category in germ cell tumor

Tumor marker category	LDH (U/l)	b-HCG (mIU/mL)	AFP (ng/mL)
S1	<1.5 × N and	<5000 and	<1000
S2	1.5-10 × N or	5000-50 000 or	1000-10 000
S3	>10 × N or	>50 000 or	>10 000

Abbreviations: AFP, alpha-fetoprotein; b-HCG, beta-human chorionic gonadotropin; LDH, lactate dehydrogenase; N, upper limit of normal for the LDH assay.

TABLE 3 Pre-treatment histology sub-types (n = 23)

Histology type	N
Seminoma	7
Embryonal carcinoma (EC)	1
Yolk sac tumor (YST)	5
EC + YST	3
YST + seminoma	1
EC + teratoma	1
Teratoma	1
Teratoma + YST	1
Teratoma + YST + sarcoma + adenocarcinoma	1
Immature teratoma	1
Necrosis	1

3.5 | Outcome - MGCT with non-seminoma histology (n = 17)

Seven patients had progressive disease after initial treatment (five had S3 tumor marker) and only three patients received salvage chemotherapy - Ve[vinblastine]IP in one and T[paclitaxel]IP in two patients. One patient died during treatment and 12 patients defaulted for further follow-up.

3.6 | Survival analysis

Twenty-four patients received treatment and were included for survival analysis. Only one patient died during treatment, five patients defaulted after progressive disease and another seven patients defaulted while on treatment. After a median follow-up of 10.8 months (range: 2.9 to 75 months), 3-year PFS and OS estimate was 61.2% and 94.7% in whole cohort, respectively (Figure 1A,B). 2-year PFS and OS estimate in non-seminomatous histology was 33.5% and 91.7%, respectively whereas both 3-year PFS and OS estimate were 100% in the cohort (n = 7) with seminoma histology. There was no statistical difference in PFS or OS among patients with different risk groups or histology (Figure 1C,D).

4 | DISCUSSION

Primary malignant MGCT constitutes 10% of the total GCTs treated at our center and identical to the incidence of 3%-15% in published literature.[1,4,6,16,19,21-29] Diagnosis is sometimes difficult in comparison to their gonadal counterpart due to differential diagnosis of thymic neoplasm, lymphoma, sarcoma, and other mediastinal lesions. Mediastinal NSGCT is more aggressive in presentation with a high volume of disease in the majority of cases and superior vena cava obstruction may present in around 10% of cases but it was much higher (28%) in our series (Table 1) may be due to delayed presentation as supported by symptom duration (10 patients had symptom duration ≥3 months).

Seventy to eighty percent of primary malignant MGCTs are of NSGCT subtype and almost always associated with a rise in AFP and/or b-HCG, LDH. Sometimes they are diagnosed from mediastinal biopsy during the evaluation of an anterior mediastinal mass before detecting elevated tumor marker. It always remains a question whether to rule out a mediastinal metastasis of testicular primary in the first encounter with a malignant MGCT and the current consensus is no need to image the testis in a clinically normal testis as previous studies have ruled out that possibility.[30,31] Tissue diagnosis may not be always required in the case of mediastinal NSGCT with elevated tumor markers, especially AFP. But, it's important to note that somatic differentiation of the tumor especially to the sarcomatous component carries poor prognosis which can be detected only on pre-treatment biopsy as it's difficult to diagnose them on residual disease specimen after chemotherapy-induced tumor necrosis. Histological diagnosis is always recommended with normal tumor marker or mildly elevated b-HCG to differentiate seminoma from NSGCT and other mediastinal diseases. Eighty-two percent (n = 23) of our patients had pre-treatment histological diagnosis (Table 3).

Primary MGCT with non-seminomatous histology has a different biological behavior from their gonadal counterpart. They have an OS of 40%-50% with chemotherapy and surgery.[21,24,32,33] The outcome is far worse with 25% OS in those with extra-thoracic metastasis.[33] On the contrary, mediastinal seminoma has an excellent cure rate of nearly 90% with platinum based chemotherapy.[21,33] In our series, all of the MGCT with seminoma histology achieved a complete response after initial chemotherapy (n=7) and all surviving till date without recurrence. Being mediastinal location, all MGCT with non-seminoma histology are of "poor risk" as per IGCCCG classification and four cycles of BEP is standard chemotherapy regimen. But, there are concerns with bleomycin-induced lung injury and associated increased post-op mortality as reported from Indiana University[16] along with equivalent results of VIP with BEP, there are increasing recent trends in using VIP protocol with MGCT.[17,34] We have used VIP protocol in six patients without any difficulty and good response, mostly in recent times.

Surgical resection is recommended in MGCT with non-seminoma histology as it may contain viable residual germ cell component,

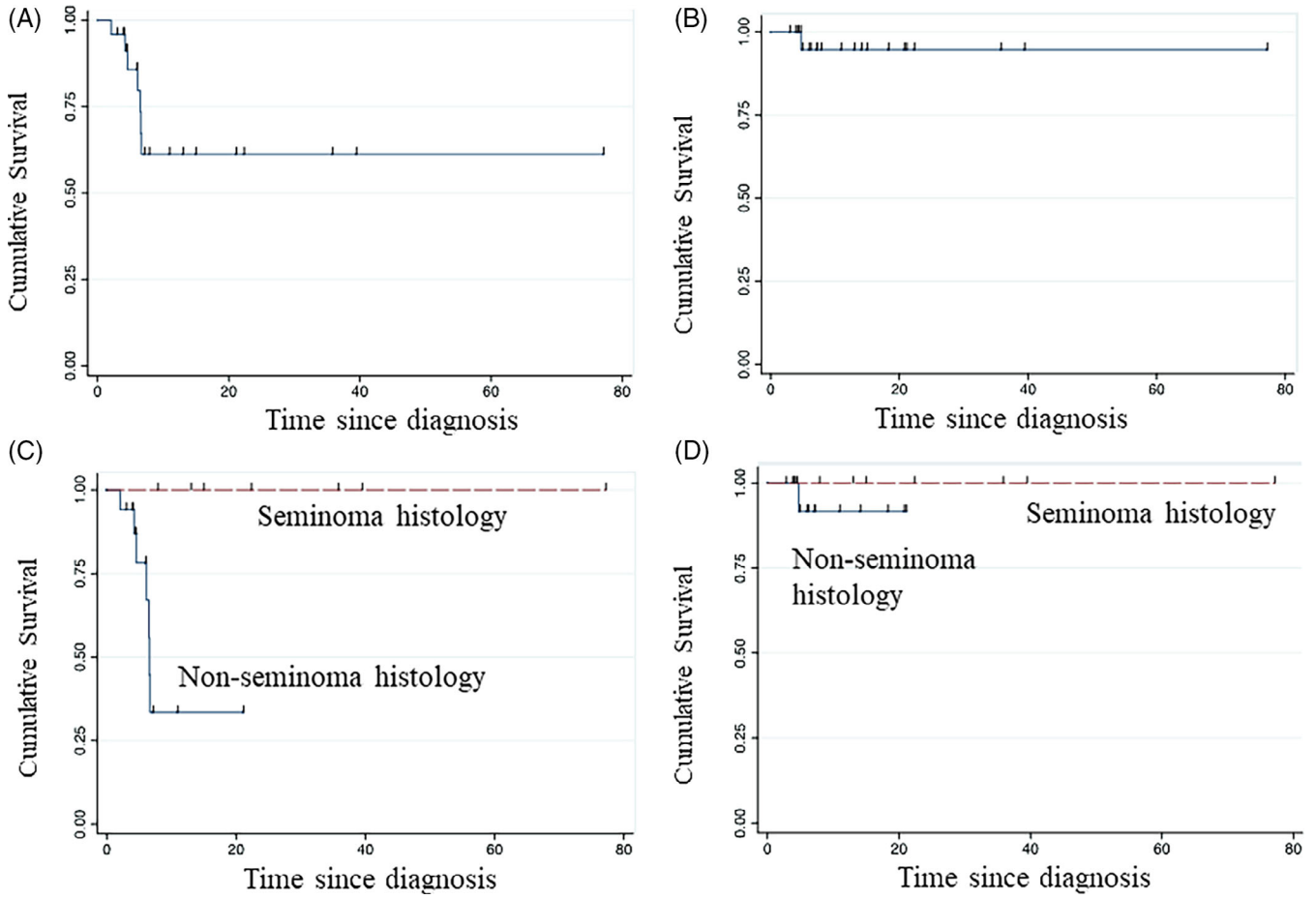

FIGURE 1 Kaplan-Meier progression-free survival (PFS) estimate in the whole cohort A; Kaplan-Meier overall survival (OS) estimate in the whole cohort B; Kaplan-Meier PFS estimate according to histology sub-types C, and Kaplan-Meier OS estimate according to histology sub-types D

immature teratomatous component (which may grow later into "growing teratoma syndrome") and teratoma with a somatic component, like- carcinoma, sarcoma which have prognostic value. On surgically resected specimens of residual non-seminomatous MGCT, 25% showed necrosis, 30% showed teratoma, and viable residual tissue or immature teratoma can be found from 25%-30% of cases.[26,35-37] Six out of 17 patients in our non-seminomatous MGCT cohort had complete resection of residual disease after initial chemotherapy and five patients had residual germ cell components while one patient had only necrosis. Those five patients subsequently received another two cycles of adjuvant EP as recommended. The outcome remains poor despite the full course of chemotherapy and optimal resection of residual tumor,[24] but 5-year PFS is 47% in those with a residual viable tumor on resected specimen compared to 84% in those with necrosis or mature teratoma.[26] Surgery is not recommended for residual disease in case of seminomatous MGCT and they respond to radiotherapy when indicated. Two of our patients received thoracic radiotherapy for FDG avid residual disease and achieved complete response without further relapse.

There are very few Indian publications on MGCT patients and they are limited by small sample size, short follow-up data, and mostly older series without comprehensive treatment details and outcome.[6-14] Many of the publications are from pathological series or too old without multimodality management and very few reported comprehensive data on treatment outcome. To the best of our knowledge, this is the largest cohort of MGCT reported from India with complete clinical profile and treatment outcome after multimodality therapy. Prognostication was not possible due to the relatively small sample size, but patients with seminoma histology had the best outcome.

Being retrospective in nature, there was some data missing on symptomatology and clinical parameters. Three patients lost to follow-up during initial chemotherapy treatment and were not evaluable for treatment response. Due to the relatively small sample size, we were not able to evaluate prognostic factors that can determine the differential outcome. Follow-up was relatively short as many patients lost to follow-up after progression (four out of seven patients) on first line treatment and did not go for subsequent salvage therapy and even patients who were in response (6 out of 17). Compliance with treatment remains a major challenge in cancer treatment in resource-poor countries like-India due to multiple factors - socio-economic, cultural, finance, and access to care. Treatment abandonment leads to poor estimation of disease burden, treatment outcome and remains an unmet need.

5 | CONCLUSIONS

Primary malignant MGCTs are rare and difficulty arises in diagnosis owing to its location and differential diagnoses. Many patients present late with a high volume of disease with/without SVCO as in our cohort (28%). Multimodality treatment is crucial to achieve optimum results as the outcome is still poor in those with non-seminomatous histology and complete resection of residual disease is of paramount importance. Results are excellent in patients with seminoma histology after platinum based chemotherapy and/or radiotherapy for residual disease and our patients achieved a 100% cure rate in this sub-group. VIP based protocol should be preferred over standard BEP based chemotherapy as the majority of non-seminoma histology would undergo future surgery and bleomycin exposure poses a risk to post-operative morbidity and mortality. Adherence to treatment is the key to success with a multimodality approach and patients with MGCT should preferably be treated in a tertiary care cancer center. More familiarity with this entity along with its natural history and multi-modality approach to treatment is a necessity to fulfill the unmet need.

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CONFLICT OF INTEREST

None to declare for each author.

AUTHOR CONTRIBUTIONS

Bivas Biswas: Conceptualization; formal analysis; investigation; methodology; resources; supervision; validation; writing-original draft; writing-review and editing. **Deepak Dabkara:** Conceptualization; formal analysis; supervision; writing-original draft; writing-review and editing. **Moushumi Sengupta:** Conceptualization; formal analysis; writing-original draft; writing-review and editing. **Sandip Ganguly:** Data curation; formal analysis; methodology; supervision; writing-original draft; writing-review and editing. **Joydeep Ghosh:** Conceptualization; formal analysis; methodology; supervision; writing-original draft; writing-review and editing. **Saugata Sen:** Conceptualization; data curation; supervision; writing-original draft; writing-review and editing. **Moses Arunsingh:** Conceptualization; investigation; resources; writing-review and editing.

DATA AVAILABILITY STATEMENT

Data will be shared for peer review & editorial review if required on reasonable ground.

ETHICAL STATEMENT

Ethical clearance was taken from Institute Review Board (IRB) and the patient consent waiver was obtained because of the retrospective nature of this study (IRB protocol waiver no: EC/WV/TMC/27/20).

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