Original Article

rare tumors

Rare Tumors
Volume 12: 1–9

DOI: 10.1177/2036361320972220
journals.sagepub.com/home/rtu
SAGE

Primary mediastinal germ cell tumors: Survival outcomes and prognostic factors – 10 years experience from a tertiary care institute

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Abstract

Primary Mediastinal Germ Cell Tumor (PMGCT) is a rare and heterogeneous entity. These tumors are typically diagnosed in young adults and carry a poor prognosis. We conducted this study to evaluate the role of radiotherapy on treatment outcomes and prognostic factors in PMGCT that may allow a more adapted treatment strategy to improve survival. Case records of patients who presented with PMGCT over a period of 10-years from January-2009 to December-2019 were retrospectively evaluated. Survival analyses were calculated using Kaplan-Meier (Log-rank) method. Poor prognostic factors for survival were evaluated with Multivariate analysis using Cox-regression method. A total of 46-patients data was analyzed, the majority of the patients were males (95.7%) with a median age of 25-years (range, 17–62). Non-seminomatous histology was predominant (60.9%). Sixteen-patients (34.7%) presented with complications at their initial presentation. Majority of the patients were treated with multimodality approach using chemotherapy, surgery, and/or radiotherapy. At a median follow-up of 40.8 months, the 1, 3, and 5-year overall survival (OS) was 69.6%, 52.2%, and 44.7% respectively. Patients who received radiotherapy in first-line treatment showed significant improvement in 5-year OS (72% vs 30%, $p = 0.004$) and disease-free survival (70% vs 24%, $p = 0.007$) in comparison with patients who did not receive. Multivariate analysis revealed that radiotherapy, chemotherapy, surgery, and complications at presentation were independent prognostic factors for OS. PMGCTs are aggressive neoplasms especially in patients presenting with disease-related complications. Dual modality management (radiotherapy as local therapy along with chemotherapy) had shown improvement in survival.

Keywords

Germ cell tumors, mediastinum, treatment outcomes

Date received: 31 May 2020; accepted: 19 October 2020

Introduction

Germ cell tumors (GCTs) are neoplasms that are derived from germ cells. Majority of the GCT arise from gonads (more commonly from the testes than ovaries) and often seen in the adolescents/young adults. Extragonadal GCTs (EGCTs) arise outside the gonads, typically midline in location and constitutes for only 2% to 5% of all GCTs.[1] Most common sites of EGCTs in adults are retroperitoneum

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followed by mediastinum, pineal gland (supra-sellar region) and the coccyx.[2] The primary mediastinal GCTs are derived from aberrantly migrated primitive germ cells along with urogenital ridge during embryogenesis.[3] The primary mediastinal GCTs accounts for 10% to 15% of all mediastinal malignancies and 1% to 3% of all GCTs.[4] These tumors have similar histopathological characteristics, cytogenetic abnormalities, and tumor marker expression as it counterparts in gonads, though diverse clinical and prognostic features exist.[5]

Two thirds of mediastinal GCT are non-seminomatous in histology as compared to the gonadal counterpart where seminomas exceeded non-seminomas.[6] According to the International Germ cell Cancer Collaborative Group (IGCCCG), non-seminoma mediastinal GCTs have poorer prognosis as compared to its gonadal and retroperitoneal analogue.[7] The 5-year survival rate of seminomatous mediastinal GCT was 80% to 85% and non-seminomatous histology was 40% to 45%.[7,8] However, these clinical outcomes linked to their disease extension at the time of diagnosis and very aggressive clinical behaviour of seminomatous mediastinal GCTs has been reported.

Owing to the rarity, there are no consensus guidelines for the management of primary mediastinal GCT. The treatment has evolved over last 30 years,[9–11] and varies based on histology and associated complications during initial presentation (superior vena cava obstruction syndrome). Primary surgery is not effective except in mature teratoma. For most of the other histologies, literature supports cisplatin-based chemotherapy followed by consolidative local therapy with surgery or radiotherapy.[8,12] Only few retrospective institutional publications exist in past 20 years describing the mediastinal GCTs in pediatric and adult population, and queries remain regarding the treatment outcomes and prognostic factors.[8,13]

In this paper, we are reporting our institute experience of mediastinal GCT patients who were managed using chemotherapy, radiotherapy and/or surgery.

Materials and methods

Medical records of patients with primary mediastinal GCTs treated at our institute from January-2009 to December-2019 were analyzed. The diagnosis of primary mediastinal GCT was made clinic-pathologically by the definition when a mediastinal mass was present with absence of clinically detectable testicular or ovarian mass, as determined by physical examination or scrotal ultrasound. Clinical parameters including age, sex, symptoms, KPS, comorbidities, histology, disease extension, staging, tumor markers, treatment intent, and modality, number of chemotherapy cycles, radiotherapy dose and fractionation, treatment toxicity, response to first line treatment, and second line treatment modalities were entered on a structured pro forma. Survival status was confirmed through telephonic conversation and outpatient follow-up records.

Serum tumor markers (STM) especially alpha fetoprotein (AFP), β-human chorionic gonadotrophin (β-HCG), and lactate dehydrogenase (LDH) were measured before and after treatment. Imaging modalities such as contrast enhanced computed tomography (CECT) of chest & abdomen was used to measure the disease extension. In males, ultrasound scrotum was done to rule out testicular lesions. Pathological diagnosis was made through excisional biopsy or fine needle aspiration cytology and was confirmed by immunohistochemistry (IHC) markers, specifically used markers were AFP, β-HCG, PLAP, OCT4, SALL4, LCA, and Chromogranin-A. Clinical staging was done using Moran and Suster staging system.[14] Base line investigations like hemogram, kidney function test, liver function test, and viral screening were done.

Most commonly used chemotherapy regimen regimens as first line treatment were a combination of bleomycin, etopside, and cisplatin (BEP) and etopside and cisplatin (EP). During relapse or refractory disease conventional second line chemotherapy was given with combination of paclitaxel, ifosfamide, and cisplatin (TIP). Patients with immature teratoma with malignant mesenchymal component (small round blue cell tumor) received second line chemotherapy with vincristine, adriamycin, and cyclophosphamide (VAC) combination. Response to chemotherapy and operability was assessed by CECT scan.

External beam radiation therapy (EBRT) was delivered using 6 MV (mega voltage) or 15 MV photons from linear accelerator. Conventional fractionation regimen (1.8-2 Gy per fraction, five fractions per week) was used in all radically treated patients. Three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT) planning techniques were utilized for radiation execution. Palliative radiotherapy (RT) was delivered by conventional two-dimensional RT (2D-RT) using two parallel opposed antero-posterior portals. For conformal techniques, the target volumes were defined as clinical target volume (CTV) and planning target volume (PTV). The CTV was defined as tumor bed/residual mass visible in post chemotherapy images plus 0.5 cm isometric margin and 2 cm superior & inferior to tumor, ipsilateral supraclavicular fossa was included if the tumor extends beyond the mediastinum. Isometric 0.5 to 1 cm margin was given to CTV to generate PTV. EBRT dose was prescribed to PTV at 36-50.4 Gy in 18-28 fractions, delivered over 3½ to 5½ weeks. EBRT planning was done in Eclipse treatment planning system (TPS) Varian Associates, Palo Alto, CA, USA workstation.

Assessment of toxicity was done during the period of chemotherapy and radiotherapy. Toxicity was graded according to the CTCAE (Common terminology criteria for Adverse Events) version 3.0. The response assessment was done after 6 weeks to 2 months of treatment completion with serum tumor markers and CECT chest using RECIST criteria version 1.1.[15] Patients were followed up every 3 months for the first 3 years and 6 months thereafter with 3 monthly tumor markers and yearly CECT chest & abdomen.

Statistical analysis

Statistical analysis was done by SPSS (Statistical Package for Social Sciences) version 23. Descriptive statistics were used to quantify the qualitative data. Chi-square test was applied to quantify the association between two groups of clinical parameters. Survival analysis was computed using life table method and Kaplan-Meier method. The Univariate influence of various prognostic factors on survival outcomes was analyzed using Log-Rank test. Independent prognostic factors for survival outcomes were analyzed using Multivariate analysis with Cox-proportional hazard model. A p-value less than 0.05 was considered as significant. Overall survival (OS) and progression-free survival (PFS) were determined from the time of pathological diagnosis to the date of death or last follow-up or recurrence as the end point.

Results

Patient's demographic details, clinical and treatment characteristics are tabulated in Tables 1 and 2. A total of 46 patients were included in this analysis. Majority of them were males (44 men vs 2 women) with a median age at presentation of 25 years (range; 17–62 years). Median duration of symptoms was 3 months (range; 1–12 months), with chest pain (34.8%), shortness of breath (30.4%), and cough (17.4%) as predominant symptoms. Sixteen patients (34.8%) were presented with disease-related complications, superior vena cava obstruction (SVCO) in 10 patients, SVCO with malignant pericardial effusion and spinal cord compression in three patients each. Eighteen and 28 patients were seminoma (39.1%) and non-seminoma GCTs (NSGCT) (60.9%) respectively. Among NSGCTs sub-type; mature teratoma in three patients (6.5%), immature teratoma (IT) with other malignant component in 12 patients (26.1%) yolk sac tumor in six patients (13%), and mixed GCTs in seven patients (15.3%). 14 patients (30.4%) had stage II disease, 20 (43.5%) had stage IIIA, and 12 (26.1%) had stage IIIB (metastatic disease). Stage I & II were classified as limited stage (LS) disease and stage IIIA & IIIB as extensive stage (ES).

In primary treatment, 40 patients were treated with radical intent and six patients (13%) were managed with palliative intent (palliative EBRT was given to three seminoma patients and three NSGCTs patients). Among the radical treatment, triple modality (surgery, EBRT, and chemotherapy) was used in nine patients (19.5%), dual modality (EBRT and chemotherapy) in 16 patients (34.8%), and single modality (surgery ($n = 3$) or chemotherapy ($n = 12$)) in 18 patients (39.2%). Surgery was performed in 12 patients (26%) through median sternotomy (three patients of seminoma and nine patients of NSGCT). Because of bulky mediastinal disease and baseline metastasis (stage IIIB) only 12 patients underwent surgery. Nine patients received adjuvant chemotherapy followed by radiation in view of gross residual disease. Three patients were kept under observation because of mature teratoma histology and complete resection. A total of 37 patients (80.4%) received first line chemotherapy. BEP was the commonest regimen ($n = 34$) followed by EP ($n = 3$). Ten patients received second line chemotherapy in view of stable / progressive disease

Table 1. Baseline patient and disease characteristics.

Characteristics	Number of patients ($N = 46$) (%)
Age; Median: 25 years (range; 17–62)	
⩽30 years	34 (73.9)
>30 years	12 (26.1)
Sex	
Males	44 (95.7)
Females	2 (4.3)
Major symptoms	
Shortness of breath	15 (32.6)
Chest pain	16 (34.8)
Cough	8 (17.4)
Fever	5 (10.8)
Backache and lower limb weakness	2 (4.3)
Complication at presentation	
SVCO	10 (21.7)
SVCO & Cardiac tamponade	3 (6.5)
Spinal cord compression	3 (6.5)
Comorbidities	
Yes	16 (34.8)
No	30 (65.2)
Type of Co-morbidity	
Pulmonary tuberculosis	8 (17.4)
Hypertension	5 (10.8)
Diabetes mellitus	3 (6.50
HIV	2 (4.3)
Hepatitis-B	2 (4.3)
Maximum tumor size	
⩽10 cm	20 (43.5)
>10 cm	26 (56.5)
Stage	
II	14 (30.4)
III A	20 (43.5)
III B	12 (26.1)
Extension	
Limited stage (I & II)	14 (30.4)
Extensive stage (III A & III B)	32 (59.6)
Location	
Superior & Anterior mediastinum	36 (78.3)
Posterior	6 (13)
Middle	4 (8.7)
Serum AFP ($N = 43$)	130.6 ± 3994 (Mean ± Standard deviation)
Serum beta-HCG ($N = 43$)	44.7 ± 108.5 (M ± SD)
Serum LDH ($N = 43$)	562.2 ± 362.2 (M ± SD)

Table 2. Histology, treatment characteristics and toxicity.

Characteristics	Number of patients (*N* = 46) (%)
Histology:	
Seminoma	18 (39.1)
Non-seminoma (NSGCT)	3 (6.5)
Mature teratoma	
Immature teratoma with NSGCT (type-I)	10 (21.7)
Immature teratoma with mesenchymal tumor (type-III)	2 (4.4)
Mixed NSGCT	7 (15.3)
Yolk sac tumor	6 (13)
Primary treatment:	
Radical intent	
Surgery alone	3 (6.5)
Surgery + chemotherapy + EBRT	9 (19.5)
Chemotherapy + EBRT	16 (34.8)
Chemotherapy alone	12 (26.1)
Palliative intent:	
Palliative EBRT	6 (13)
Toxicity:	
Hematological (18/46 patients)	
Anemia (Grade ⩽3)	8 (17.4)
Thrombocytopenia (Grade ⩽3)	6 (13)
Leucopenia (Grade ⩽3)	8 (17.4)
Febrile neutropenia (Grade = 3)	4 (8.87)
Non-hematological (9/46 patients)	
Dysphagia (Grade ⩽3)	7 (15.2)
Pneumonitis (Grade = 2)	2 (4.3)
Number of cycles of chemotherapy	4.4 ± 1.6 (M ± SD) (range; 2–6)
EBRT dose (radical only)	36–50.4 Gy

clinically and biochemically; eight patients were treated with conventional TIP regimen and two patients given with VAC regimen. Rest of the patients with complete / partial response received radical radiotherapy.

Twenty-five patients received EBRT in primary treatment as radical intent; definitive RT was given in 16 patients for residual disease after initial chemotherapy and adjuvant RT was given in nine patients who underwent initial surgery followed by chemotherapy. Median RT dose in seminoma and non seminoma was 36 and 45 Gy respectively. Radical RT was delivered with IMRT technique in 14 patients and 3D CRT in 11 patients. Six patients were received palliative RT due to huge tumor mass compressing major vessels in mediastinum (SVCO and pericardial effusion with cardiac tamponade) and poor performance status. Palliative EBRT was executed by 2D technique with two parallel opposed fields. Palliative EBRT was given to metastatic bone lesions with the same 2D technique.

Acute toxicity during the course of primary treatment was divided into hematological and non hematological. 18 patients had experienced haematological toxicity; notably four patients had grade 3 febrile neutropenia. No patient developed grade 4 hematological toxicity. Treatment breaks were observed in eight patients due to haematological toxicity. Among non-hematological toxicity; seven patients had grade ⩽3 acute dysphagia and two patients had grade ⩽2 acute pneumonitis. No other late toxicities were reported during follow-up and no treatment related deaths were observed.

The median follow-up was 40.8 months, ranging from one to 98 months. The one, three, and 5-year OS and PFS were 69.6%, 52.2%, 44.7%, and 60.9%, 44.7%, 35.8% respectively. At last follow-up, 20 patients were alive and 26 patients were dead. All relapses or local disease progression occurred within 2 years of primary treatment. Median time to progression was 20 months. Six patients with SVCO or pericardial effusion received palliative radiation and expired during their first 3 months of follow-up. Fourteen patients had developed distant metastasis at last follow-up; common sites were lungs, liver and bone.

Disease-related complications during initial presentation showed significant detrimental effect on survival outcomes. The five-year OS was 25% in patients who presented with complications as compared to 53.3% in those who did not ($p = 0.001$). Five-year OS and PFS of patients with seminomatous GCTs was 37.5% and 35%, while that of NSGCTs was 28% and 26.5% ($p = 0.562$ and $p = 0.619$), respectively (Figure 1). Primary tumor location in mediastinum had showed significant impact on survival; superior and anterior mediastinal location showed significantly better survival to that of middle and posterior mediastinal location (Table 3). Limited stage patients had significantly higher survival than extensive stage patients (5-year OS: 85.7% vs 25%, $p = 0.000$). Elevated STM at the time of diagnosis was not significantly associated with survival outcomes. In contrast, 5-year OS was 100% of patients with decrease level or normalization of STM after first line treatment in comparison to 36.4% in patients with non-decreasing or raising STM ($p = 0.011$). The 5-year OS of 39.1% was obtained in patients who received chemotherapy as compared to 22.2% in those who did not ($p = 0.003$). Inclusion of surgery into the primary treatment has showed trend towards significance in survival outcomes for entire study patients. Furthermore, subset analysis of extensive stage patients showed that surgery did not appear to have impact on OS or PFS.

Patients who received radical radiotherapy as a part of primary treatment had a significant survival advantage over individuals who did not receive (5-year OS: 72% vs 30%, $p = 0.004$). (Figure 2) Similar results were observed for 5-year PFS (70% vs 24%, $p = 0.007$). Subset analysis of extensive stage patients showed significant difference in 3-year OS between individuals who received and did not receive EBRT (60% vs 37.5%, $p = 0.015$), but there was no difference in 3-year PFS. Multivariate analysis was done to know the prognostic factors, which revealed that the complications at the time of presentation (hazard ratio [HR] 0.35, 95% confidence interval [CI] 0.14–0.86, p = 0.002), stage, mediastinal location, surgery, chemotherapy (HR

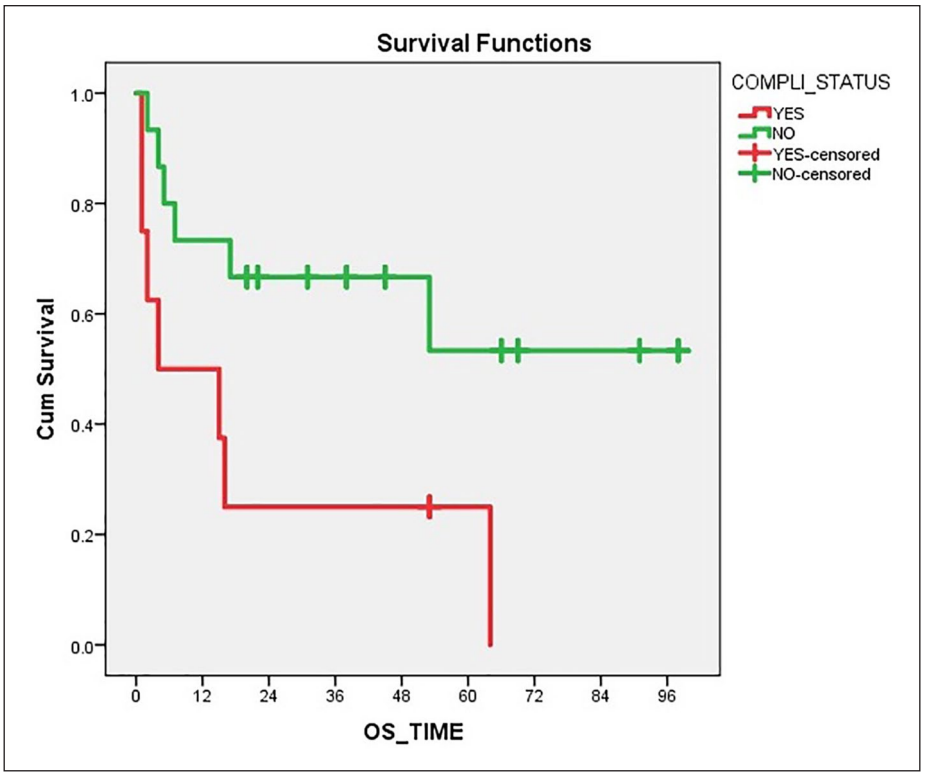

Figure 1. Overall survival with complication status at initial presentation $p = 0.001$.

Table 3. Overall survival (OS) and progression free survival (PFS) computed by log rank test.

Characteristics		5-year OS%	*p*-value	5-year PFS%	*p*-value
Tumor size	⩽10 cm	60	0.132	60	0.123
	>10 cm	34.6		17.3	
Mediastinal location	Superior & anterior	50.9	0.001	50	0.002
	Posterior	33.3		0	
	Middle	0		0	
Stage	Limited	85.7	0.000	85.7	0.000
	Extensive	25		0	
Histology	Seminoma	37.5	0.562	35	0.619
	NSGCT	28		26.5	
Surgery	Yes	62.5	0.085	61.2	0.075
	No	38		25	
EBRT	Yes	72	0.004	70	0.007
	No	30		24	
Chemotherapy	Yes	39.1	0.003	36.8	0.084
	No	22.2		33.3	

2.1, 95% CI 0.9–4.1, p = 0.071), radiotherapy (HR 3.6, 95% CI 0.4–3.6, p = 0.008), and response to primary treatment were independent prognostic factors for OS (Table 4).

Discussion

In this retrospective analysis of 46 patients with primary mediastinal GCTs, a paramount frequency of disease-related complications was identified at the time of presentation. The median age of the whole group was 25 years, of whom 35 patients were aged more than 20 years. According to Schneider et al.[16] an epidemiological analysis of GCTs, the peak incidence for gonadal GCTs was around 15 years, and for mediastinal GCTs it was greater than their analogue in gonads. These tumors occurs more in men than women. In this study 44 patients were males and two were females. This age tendency and gender difference was supported by literature evidence and reported by other authors.

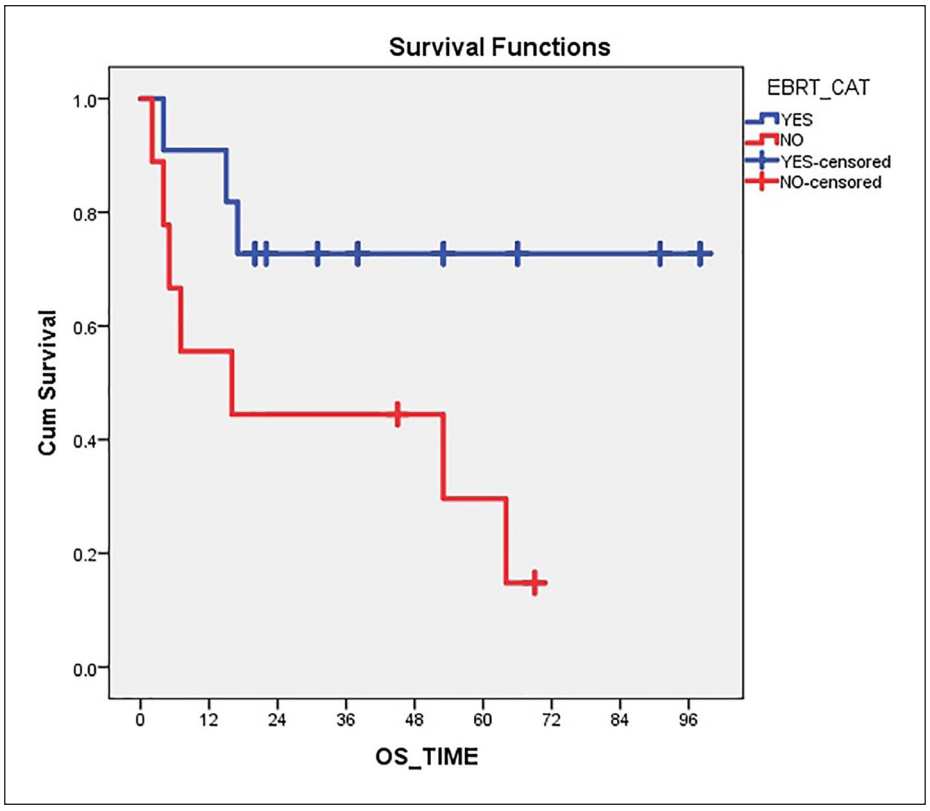

Figure 2. Overall survival with radiotherapy $p = 0.004$.

A significant number of patients presented with complaints of chest pain (34.8%) and shortness of breath (30.4%), while others presented with non-specific complaints like cough, fever, and backache with limb weakness. As many as 34.7% presented with disease related complications like SVCO (21.7%), pericardial effusion (6.5%) and compression of spinal cord (6.5%) which showed a statistically significant poor OS (p = 0.001) compared to the patients without complications. The duration of symptoms ranges from one to 12 months, as initial non-specific symptoms could have delayed the diagnosis allowing an uninterrupted proliferation of the tumour and hence presenting with an extensive disease. Hence, an aggressive treatment strategy and early intervention is warranted in these patients.

Mediastinal GCTs commonly arise in the anterior mediastinum[6] as was correlated with our study showing an occurrence of 78.3%. Patients with anterior or superior mediastinal tumors were performed better than middle and posteriorly located tumors. The 5-year survival for anterior/superior, middle, and posterior locations were 50.9%, 33.3%, and 0 respectively ($p = 0.001$). In present study, 43.5% of the patients presented with an extra-mediastinal disease and particularly extra-thoracic disease with chest wall and lungs were the most common sites (17.4%) followed by liver and bones (13%). Five-year OS of patients who had tumors localized to mediastinum was 57.7% compared to 30% in patients who had extra-mediastinal disease ($p = 0.003$), supporting the Moran and Suster staging system.

Serum tumor markers like AFP, β-HCG, and LDH are recommended to use for staging and monitoring the relapse in seminoma and non-seminomatous GCTs. They are not recommended while deciding the management strategies and screening purpose.[17] Decrease in STM level or normalization after chemotherapy plays as an independent prognostic factor.[18,19] According to Ebi et al.,[20] assessment of STM after 7 days of chemotherapy initiation might be useful prognostic factor for OS. In present study, baseline elevated tumor markers did not show any impact over OS. However, patients with normalization or decreased STM after primary treatment had significantly better OS than non-decreasing or raising STM (5-year OS 100% vs 36.4%, $p = 0.011$). Histological subgroup analysis showed no statistically significant difference in OS even though literature reports a better OS in patients with seminomatous mediastinal GCTs.[21] According to IGCCCG risk classification, extra-gonadal seminoma without non-pulmonary visceral metastasis categorised to good-risk, whereas non-seminomatous GCTs categorised as intermediate or poor-risk group.[7] Poor survival in seminoma group in present study may be attributed to the reason that majority (44.4%) of seminoma patients presented with complications.

With regard to management strategies, previous authors reported their experiences with surgery, chemotherapy, radiotherapy, and high-dose chemotherapy (HDCT) with stem cell transplant in first line treatment using small samples.[8–13,22,23]

Table 4. Prognostic factors for overall survival and progression free survival calculated with multivariate (cox proportion hazard model) analysis.

Factor	Overall survival (OS)			Progression free survival (PFS)		
	Hazard ratio (HR)	95% confidence interval (CI)	*p*-value	HR	95% CI	*p*-value
Tumor size	1.8	0.7–4.2	0.153	1.8	0.7–3.7	0.125
Stage	2.1	1.1–3.8	0.001	2.3	1.4–3.5	0.010
Site	1.9	1.2–3.4	0.002	2.1	1.3–3.8	0.003
Complications at presentation	0.3	0.1–0.8	0.002	1.3	0.4–1.8	0.025
Elevated tumor markers at presentation	0.7	0.2–2.1	0.582	0.7	0.2–2.2	0.619
Histology	0.7	0.5–1.0	0.084	2.1	0.9–3.9	0.078
Surgery	2.1	1.4–4.1	0.009	1.8	1.4–4.0	0.007
Chemotherapy	1.8	0.9–4.1	0.071	1.9	0.8–3.4	0.110
EBRT	2.6	0.4–3.6	0.008	1.7	0.4–4.1	0.005
1st Follow up response	2.7	1.4–4.5	0.003	2.3	1.3–4.4	0.003

They recommend a dual modality management; chemotherapy plus local therapy with surgery or radiotherapy as the reasonable options. Liu et al.[8] evaluated 55 patients of primary mediastinal GCTs over 22 years and concluded that dual modality management has the longest survival time. According to IGCCCG, recommended first line treatment consists of three to four cycles of BEP regimen depending on risk category.[7] Some authors prefer to avoid bleomycin, due to its lung toxicity and substituting with ifosfamide in bulky thoracic disease.[24] Feldman et al.,[25] investigated TIP regimen as first line treatment in a phase-II study with 16 patients of intermediate and poor risk group and reported 62% of 3-year estimated survival. Motzer al.,[26] a phase-III trial evaluated HDCT with autologous stem cell rescue as first line treatment in intermediate and poor risk group and compared with BEP regimen. This study concluded that routine use of HDCT in first line treatment did not improve clinical outcomes and recommended local therapy for residual disease following first line BEP chemotherapy. In present study, 74% of patients received BEP chemotherapy as first line management and achieved 5-year survival of 44.7%.

GCTs are sensitive to chemotherapy and radiotherapy, but optimal radiation dose and technique to improve survival is unknown. In past radiotherapy has been used for microscopic (R1) or macroscopic (R2) residual disease after surgery and unresectable disease. In spite of advanced radiation execution, no evaluation has been undertaken on substantial benefit of radiotherapy in mediastinal GCTs. Nowadays, modern radiotherapy techniques allow for precise small field delivery and limited dose to surrounding vital organs. Massie et al.[27] evaluated the role of radiotherapy (radiation dose of 45 Gy) to residual tumor after chemotherapy, later underwent surgical resection in two patients and found that no viable malignant cells or necrosis in specimen. These patients were alive and disease free for 14 years. Wang et al.[28] represents the largest study of mediastinal non-seminomatous GCTs with 61 patients over 21 years, used radiotherapy in 22 patients as local treatment strategy. The 5-year OS was 68.2% in patients who received RT compared to 38.5% in patients not received RT ($p = 0.036$). This study concluded that radiotherapy was an effective local treatment option and an independent prognostic factor of final outcomes. In present study, 22 patients received radiation as local therapy in primary management and showed improved OS and PFS. Five-year OS was 72.7% in patients who received radiotherapy as compared to 30% in those who did not receive RT Radiotherapy was found to be an independent prognostic factor for treatment outcomes according to multivariate analysis.

Radiation delivery with advanced techniques may provide eloquent alternative to surgical salvage for refractory and relapsed tumors. Complete en-block resection (R0) should be achieved for better survival and local control. Patient selection always plays a major role while deciding for surgery; assessment of resectability is based on radiological findings and performance status of patients. Extensive stage disease may require assistance of cardiopulmonary bypass or a great vessel replacement; hence, experience of surgical oncology or cardiovascular surgery team also plays a crucial role while going for surgery.[29,30] In contrast, radiotherapy can be delivered to lower performance status patients.

This study has several limitations, including single-center, retrospective study design, and small sample size. We did not measure the seventh day STMs following chemotherapy as recommended for predictive factor. But, decreasing or normalized levels of STMs following primary management showed significant survival difference. A significant difference in survival outcomes was seen between patients who received and those who not-received radiotherapy.

Conclusion

Primary mediastinal GCTs are challenging to treat because of their rarity and diversity. The treatment outcomes in present study were heterogeneous and comparable with recent

literature. Our data provides considerable evidence to choose dual modality management with platinum-based chemotherapy and accompanying radiotherapy to local residual disease, as an effective option.

Contributorship

All the authors had contributed for the conception & study design, data acquisition & interpretation, and drafting the article. All authors critically reviewed the manuscript for its content, contributed to the interpretation and presentation of the review, and approved the final version of the same before submission.
Specific contributions by the authors individually have been highlighted below:

1. Dr. Narendra Kumar – study concepts and design, manuscript preparation, manuscript editing.
2. Dr. Renu Madan – conceptualization, manuscript preparation, manuscript editing.
3. Dr. Chinna Babu Dracham – conceptualization, guarantor of integrity of the entire study, experimental studies / data analysis, statistical analysis, manuscript preparation and editing.
4. Dr. Vigneshwaran Chandran – literature research, supervision, manuscript preparation.
5. Dr. Arun Elangovan – literature research, clinical studies, experimental studies / data analysis, supervision.
6. Dr. Divya Khosla – manuscript preparation, manuscript editing, supervision.
7. Dr. Budhi S Yadav – literature research, manuscript preparation, manuscript editing.
8. Dr. Rakesh Kapoor – clinical studies, literature research, manuscript editing.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval to report this case series was obtained from "INSTITUTIONAL ETHICS COMMITTEE (IEC), PGIMER, CHANDIGARH, INDIA" (INT/IEC/2019/342).

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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