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Clinical Characteristics and Treatment Outcomes of Patients with Primary Mediastinal Germ Cell Tumors: 10-Years' Experience at a Single Institution with a Bleomycin-Containing Regimen

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Germ cell tumors · Treatment · Bleomycin

Summary
Background: Cisplatin-based chemotherapy followed by surgical resection of the residual tumor remains the standard of care for patients with mediastinal germ cell tumors (MGCTs). To prevent pulmonary complications, a non-bleomycin-containing regimen is generally preferred. This study aims to review the clinical characteristics and outcomes of these patients. **Methods:** A retrospective chart review was undertaken in patients treated for MGCTs between 2003 and 2013. **Results:** A total of 40 patients were enrolled; 7 patients were diagnosed with seminoma, while 33 patients had non-seminoma. 92% of patients received chemotherapy as a first treatment modality: 87% bleomycin, etoposide and cisplatin; 13% etoposide and cisplatin, with an objective response rate of 61.3%. Among these, 44% achieved a complete serological response. 17 patients underwent surgical resection of the residual tumor. No patient suffered from pulmonary complications after surgery. The 5-year overall survival (OS) was 71.4 and 27.3% in seminoma and non-seminoma patients, respectively (p = 0.051). For those who received chemotherapy followed by surgical resection with no viable tumor or only mature teratoma detected, the 5-year OS was 72.7% compared with 20.7% in patients not treated with surgery (p = 0.02). **Conclusion:** Our study confirmed the importance of a multimodality approach with primary chemotherapy followed by surgical resection of the residual tumor. A bleomycin-containing regimen can be safely used in this setting.

Introduction

Mediastinal germ cell tumors (MGCTs) are relatively rare neoplasms accounting for only 1–4% of all mediastinal tumors [1], and less than 1% of all mediastinal tumors are malignant germ cell tumors (GCTs) [2]. In adults, MGCTs show a noticeable predilection toward males [3]. Compared to gonadal GCTs, MGCTs have the same histologic classification (seminomatous and non-seminomatous). Nevertheless, there are obvious differences in terms of clinical features and aggressiveness, which indicates that these tumors are biologically dissimilar. Patients with MGCTs have a worse prognosis when compared to those with gonadal primaries, especially in the case of non-seminomatous GCTs (NSGCTs) [1]. The most common type of MGCT is teratoma (44%), followed by seminoma (16–37%) [3–5]. The histogenesis of MGCTs is not clearly defined, but the tumors are thought to derive from primordial germ cells that fail to complete the normal migration along the urogenital ridge to the gonadal ridges during embryogenesis, or to be the result of reverse migration of an occult gonadal GCT [6].

Cisplatin-based chemotherapy followed by potential resection of the residual tumor is the standard of care for patients with MGCTs. With this current approach, outcome has improved, with overall survival (OS) rates of 40–50% [7, 8] and 88–90% [9–12] for NSGCTs and seminomas, respectively. To prevent pulmonary complications secondary to extensive thoracic surgery, a non-bleomycin-containing regimen is generally preferred [13].

The objective of this study was to review the clinical characteristics and outcomes of patients with MGCTs treated at our institution between 2003 and 2013.

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Patients and Methods

A retrospective chart review was performed for all patients with newly diagnosed MGCTs, who were treated at Songklanagarind Hospital, Prince of Songkla University, between January 1, 2003 and December 31, 2013. The major inclusion criteria were: a diagnosis of GCTs (either elevated serum tumor markers or histologically confirmed) and a primary tumor located at the mediastinum with no evidence of a testicular or ovarian mass, detected by either clinical or radiological assessment. The variables extracted from the database included: patient information (date of birth, sex, vital status, and date of death or last follow-up), diagnosis (date), presenting symptoms, histologic type, sites of metastasis, tumor markers including α-fetoprotein (AFP), β-human chorionic gonadotropin (β-hCG) and lactate dehydrogenase (LDH), treatment (chemotherapy, radiotherapy, and surgery), and radiological response to chemotherapy. Ethics approval was obtained, and all patient information was de-identified.

Statistical Analysis

Statistical analysis was performed using SPSS, version 17.0 (IBM Corp., Armonk, NY, USA). Duration of follow-up and survival were calculated from the date of diagnosis until the date of last follow-up or death from any cause. OS was calculated from the date of diagnosis to the date of death from any cause. The data of patients who were alive and of those who were free of progression were censored at the last date of follow-up. Survival was calculated using the Kaplan-Meier method. Comparisons were made using the log-rank test. A p value of 0.05 or less was considered statistically significant. All reported p values were two-sided.

Results

Between 2003 and 2013, 40 patients were diagnosed with primary MGCTs. Table 1 summarizes the demographics and baseline disease characteristics for the patient cohort. The median age at the time of diagnosis was 24 years (range 15–52 years). Only 1 patient was female (diagnosed with mature cystic teratoma). The median tumor size was 13 cm. All 39 patients with retrievable data had tumor-related symptoms at the time of the initial diagnosis, with superior vena cava (SVC) syndrome being the most common (36.4%). Approximately one-third experienced fever with significant weight loss. The majority of the patients (66.7%) had no evidence of distant metastasis at the time of the initial diagnosis. Baseline serum tumor marker levels, including AFP, β-hCG, and LDH, are shown in table 1. 6 (85.7%) of 7 patients with pure seminoma had elevated β-hCG. Among these, all had β-hCG levels of less than 100 mIU/ml, with the exception of 1 patient who had a β-hCG level of 165.9 mIU/ml.

Stratified by histology, 7 (17.5%) patients were diagnosed with pure seminoma, while 33 (82.5%) patients had non-seminoma. Details of the histology results are shown in table 2. Based on the criteria of the International Germ Cell Cancer Collaborate Group (IGCCCG), 6 of the 7 seminoma patients were categorized as 'good-risk', whereas all 33 patients with NSGCTs were classified as 'high-risk'.

A total of 37 (92.5%) patients received chemotherapy as a first treatment modality, whereas 3 (7.5%) patients underwent upfront surgery. All patients received cisplatin-based chemotherapy: 87% BEP regimen (bleomycin 30 mg intravenous (IV) days 1, 8 and 15; etoposide 100 mg/m^2 IV days 1–5; cisplatin 20 mg/m^2 IV days 1–5; every 3 weeks); and 13% EP regimen (etoposide 100 mg/m^2 IV days 1–5; cisplatin 20 mg/m^2 IV days 1–5; every 3 weeks). 29 (72.5%) of the 40 patients completed the 3–4 planned cycles of chemotherapy. Reasons for early discontinuation included intolerable toxicities (n = 3), disease progression (n = 3), and unknown reasons due to loss to follow-up (n = 5). Among the 3 patients who progressed during BEP chemotherapy, 1 patient with a yolk sac tumor underwent primary partial tumor removal (postoperative serum AFP 6,887 ng/ml) followed by adjuvant chemotherapy with clinical and radiological progression after 3 cycles. Another yolk sac tumor patient received upfront chemotherapy with rising serum AFP after 2 cycles (from 1,789 ng/ml to 13,379 ng/ml), and the third patient with choriocarcinoma (pretreatment β-hCG = 71,601 mIU/ml) received upfront chemotherapy with radiologically confirmed progressive lung metastasis after 3 cycles.

We were able to assess 31 patients for radiological responses after they had received chemotherapy: 3.2% complete response (CR), 58.1% partial response (PR), 29% stable disease (SD), and 9.7% progressive disease (PD), according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. 44% of the patients achieved a complete serological response with chemotherapy. 17 patients underwent surgical resection of the residual tumor after chemotherapy; the histology details of the resected tumors are shown in table 3. Among these, a viable tumor was seen in 35% (6/17 patients). None of the patients suffered from clinically significant pulmonary complications after thoracic surgery. Only 8 (20%) patients received salvage chemotherapy. 2 patients received paclitaxel with ifosfamide plus a cisplatin (TIP), while 6 patients received vinblastine with ifosfamide plus a cisplatin (VeIP). None of the patients in our cohort underwent high-dose chemotherapy and peripheral blood stem cell transplantation (PBSCT).

A total of 3 patients were diagnosed with teratoma with somatic malignant transformation (SMT; 2 adenocarcinomas and 1 spindle cell sarcoma). Median survival was 6.0 months.

After a median follow-up time for all patients of 13 months (range 1–132 months), 24 (72.7%) patients with NSGCTs and 2 (28.6%) patients with pure seminoma were confirmed as deceased. The 5-year OS of patients with seminoma was 71.4% as compared with 27.3% in those with non-seminoma (p = 0.051) (fig. 1). For those who received chemotherapy followed by surgical resection with no viable tumor or only mature teratoma detected (n = 11), the 5-year OS was 72.7% as compared with 20.7% in those who did not undergo resection (p = 0.02) (fig. 2).

Discussion

In the present study, we analyzed the clinical features and outcomes of 40 consecutive patients with MGCTs, who had been treated at our institution over a 10-year period. Of our patient population, only 1 patient was female with mature cystic teratoma, which is in accordance with the male predilection found in previ-

Table 1. Patient demographics and baseline disease characteristics

Variables	Total	Pure seminoma	Non-seminoma[a]
Patients, n (%)	40	7 (17.5)	33 (82.5)
Age, years			
Median	24	28	22
Range	15–52	15–33	16–52
Sex, n (%)			
Male	39 (97.5)	7 (100)	32 (97)
Female	1 (2.5)	0 (0)	1 (3)
Tumor size, cm			
Median	13	12.9	13
Range	5.0–23.3	9.6–14.5	5.0–23.3
Presenting symptoms, n (%)			
SVC syndrome	16 (40)	4 (57.1)	12 (36.4)
Chest pain	10 (25)	1 (14.3)	9 (27.3)
Dyspnea	6 (15)	0 (0)	6 (18.2)
Chronic cough	4 (10)	1 (14.3)	3 (9.1)
Pleuritic chest pain	1 (2.5)	0 (0)	1 (3)
Hemoptysis	1 (2.5)	0 (0)	1 (3)
Flank pain	1 (2.5)	1 (14.3)	0 (0)
Missing	1 (2.5)	0 (0)	1 (3)
Significant weight loss, n (%)			
Yes	12 (30)	2 (28.6)	10 (30.3)
No	27 (67.5)	5 (71.4)	22 (66.7)
Missing	1 (2.5)	0 (0)	1 (3)
Fever, n (%)			
Yes	14 (35)	2 (28.6)	12 (36.4)
No	25 (62.5)	5 (71.4)	20 (60.6)
Missing	1 (2.5)	0 (0)	1 (3)
Metastasis at time of diagnosis, n (%)			
Yes	13 (32.5)	2 (28.6)	11 (33.3)
No	27 (67.5)	5 (71.4)	22 (66.7)
Site of metastasis, n (%)			
Lung only	5 (38.5)	1 (50)	4 (36.4)
Lung and/or other visceral organs	8 (61.5)	1 (50)	7 (63.6)
AFP level, n (%)			
Normal	12 (30)	7 (100)	5 (15.2)
High	27 (67.5)	0 (0)	27 (81.8)
Range, ng/ml		–	47 – >35,350
Median, ng/ml		–	10,440
Missing	1 (2.5)	0 (0)	1 (3)
β-hCG, n (%)			
Normal	20 (50)	1 (14.3)	19 (57.6)
High	19 (47.5)	6 (85.7)	13 (39.4)
Range, mIU/ml		23.49–165.9	7.04–71,601
Median, mIU/ml		37.63	206.8
Missing	1 (2.5)	0 (0)	1 (3)
LDH, n (%)			
Normal	2 (5)	0 (0)	2 (6.1)
High	34 (85)	6 (85.7)	28 (84.8)
Range, U/l		818–2,192	320–7,560
Median, U/l		1,514	1,059
Missing	4 (10)	1 (14.3)	3 (9.1)

[a]11 patients with mixed histology, and 3 patients with teratoma with malignant transformation (2 adenocarcinomas, 1 sarcoma).
SVC = Superior vena cava; AFP = α-fetoprotein; β-hCG = β-human chorionic gonadotropin; LDH = lactate dehydrogenase.

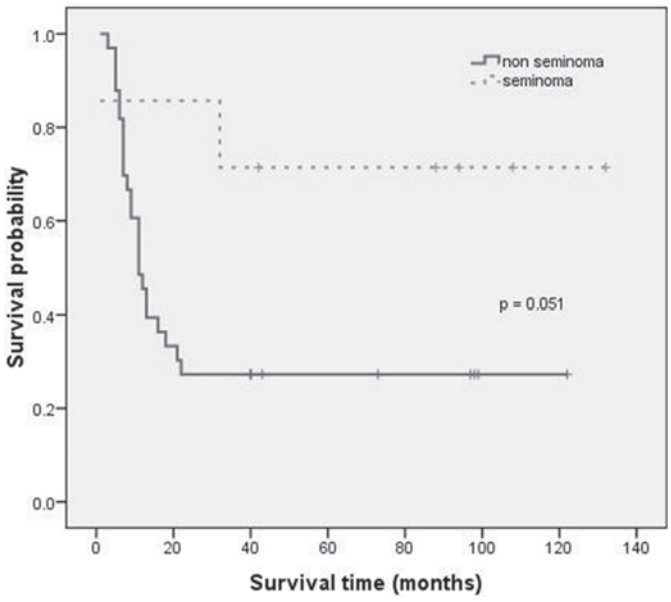

Fig. 1. Overall survival according to histology; non-seminoma (n = 33) and seminoma (n = 7).

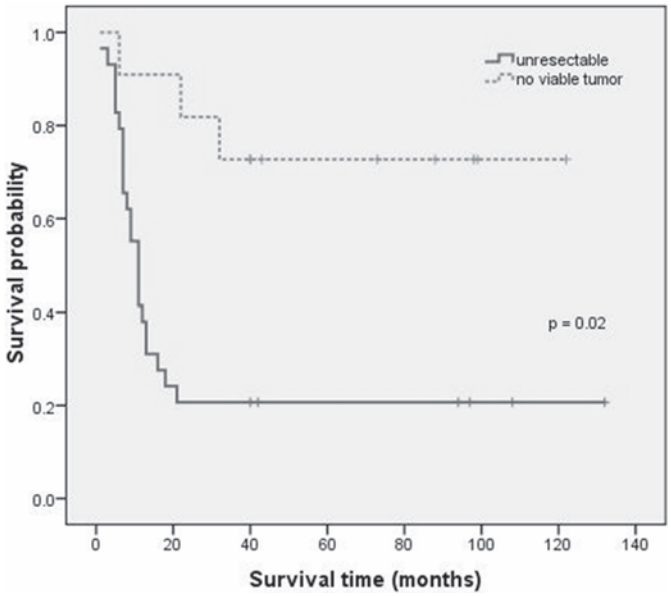

Fig. 2. Overall survival in patients who received chemotherapy followed by surgical resection with no viable tumor or only mature teratoma present (n = 11) compared to those without surgery (n = 29).

ous reports [14, 15]. SVC syndrome, a group of symptoms arising from reduced blood flow from the SVC to the right atrium, was the most common presenting symptom in our cohort (n = 16, 40%), which concurred with relatively large tumor sizes at the time of diagnosis (median tumor size 13 cm). Although dyspnea is one of the symptoms associated with SVC syndrome, this was only seen in 6 (15%) patients from our cohort, which is similar to previous reviews which showed that only half of the patients with SVC syndrome had dyspnea (range 23–74%) [16]. Interestingly, around one-third of the patients in the present study experienced fever

Table 2. Histologic details

Histology	Patients, n
Pure seminoma	7
Non-seminoma	33[a]
Mature teratoma	3
Tetatoma with malignant transformation	3[b]
Yolk sac tumors	8
Embryonal carcinoma	1
Choriocarcinoma	1
Mixed histology	11
Hepatoid variant	1
Poorly-differentiated carcinoma	1
Missing	4[c]

[a]1 tumor with a mixed seminoma and non-seminoma histology was classified as non-seminoma.
[b]2 adenocarcinomas, 1 sarcoma.
[c]Highly elevated serum α-fetoprotein.

Table 3. Surgical resection of residual tumor after chemotherapy, and histology of the resected tumor

Surgery after chemotherapy (n)	Histology of the resected tumor (n)
Complete resection	
Pure seminoma (1)	necrosis (1)
Non-seminoma (8)	necrosis (4)
	mature teratoma (3)
	marure teratoma with malignant transformation (1)
Incomplete resection	
Pure seminoma (1)	necrosis (1)
Non-seminoma (3)	viable germ cell tumors (3)
Unresectable disease	
Pure seminoma (1)	not applicable
Non-seminoma (3)	not applicable

with significant weight loss, which are known to be systemic symptoms seen in patients with lymphoma. It is therefore important to note that MGCTs cannot be completely ruled out in young males with an anterior mediastinal mass coupled with B symptoms, even in the setting of normal serum tumor markers (β-hCG and AFP).

Malignant MGCTs are divided into seminomatous and non-seminomatous GCTs. Histologic details varied among previous studies. Some reported 40% of cases to have been seminomas [14, 17], whereas others reported only 10–16% [12, 18]. In our cohort, 17.5% of patients had seminoma. Among those with NSGCTs, a mixed histology was most commonly seen in the present study (n = 11). This was followed by yolk sac tumors (n = 8) and teratoma (n = 6; 3 cases of mature teratoma and 3 cases of mature teratoma with SMT), which is similar to the report by Wang et al. [14] (8 mixed histology, 5 yolk sac tumors, and 5 immature teratomas, among 21 cases with NSGCTs). In contrast, Takeda et al. [12] and Knapp et al. [19] presented distinct data showing that embryonal carcinoma and choriocarcinoma were the 2 most common subtypes.

Cisplatin-based chemotherapy is the standard treatment, leading to survival improvement in MGCT patients. More than 90% of the patients in our cohort received chemotherapy as a frontline treatment, with BEP being the most commonly used regimen (87%). Approximately one-quarter of the patients were not able to complete the 3–4 planned cycles of chemotherapy due to various reasons (intolerable toxicities (n = 3), disease progression (n = 3), and unknown reasons due to loss to follow-up (n = 5)). This was similar to a previous study conducted in Malaysia showing that 20% of patients received less than 4 cycles of BEP [20].

A total of 40% of the patients in our cohort presented with SVC syndrome; nevertheless no patient received upfront radiation therapy. Although radiotherapy is often used to treat symptomatic patients with malignancy-related SVC syndrome, this treatment modality may not be urgently needed. This is especially true for those diagnosed with chemosensitive tumors without emergent conditions secondary to the SVC syndrome (specifically increased intracranial pressure and upper airway obstruction) [16, 21, 22]. Instead, if available, systemic chemotherapy should be the first treatment modality. However, upfront radiotherapy might be required in cases where definite types of chemosensitive tumors cannot be confirmed.

In terms of efficacy, 44% of the patients achieved a complete serological response with chemotherapy. Among the 31 patients who were able to undergo a radiological evaluation, the objective response rate was 61.3% (3.2% CR, 58.1% PR) and the overall response rate was 90.3% (additionally, 29% of patients had SD) with cisplatin-based chemotherapy. Azrif et al. [20] reported an objective response rate of 70% (30% CR, 40% PR) in patients with extragonadal GCTs treated with the BEP regimen, which was higher compared to our study. However, more than 66% of their patients were reported to have gonadal primaries, whereas all patients in our study had primary tumors of the mediastinum. This might highlight the impact of tumor location on the response to chemotherapy.

In comparison to seminomas, NSGCTs appear to be less chemosensitive and have a more unfavorable prognosis. In our study, the 5-year OS of patients with seminoma was longer than that of those with non-seminoma (71.4 vs. 27.3%). Although not statistically significant (p = 0.051), this could probably be explained by the small sample size. Hence, it is uncertain whether this survival difference was clinically meaningful. Survival was inferior in our study compared to previous studies demonstrating a 5-year OS of 36.7–83% in NSGCT and 87.4–100% in seminoma [14, 15]. This might be explained by multiple factors: First, the larger tumor size (median 13 cm) which correlated with the SVC obstruction seen in about one-third of patients in our study (compared to a median of 9.2 cm in previous case series) [15]; second, only 20% of our patients received salvage chemotherapy, and no patient underwent high-dose chemotherapy and PBSCT, which could potentially have had an impact on survival outcome; lastly, and most importantly, only one-third of the patients in our cohort underwent at least partial tumor resection, whereas 50–100% of the patients in other studies were able to undergo tumor removal [14, 15]. Kuwano et al. [15] reported a high 5-year OS in 11 cases of MGCT (83.7% in NSGCT and 100% in seminoma) all treated with a multimodality approach with preoperative chemotherapy followed by total tumor removal. Moreover, those with viable GCT in the resected specimens were subsequently treated with additional chemotherapy. Rivera et al. [23] reported a multivariate analysis demonstrating that surgery is one of the independent prognostic factors for MGCT. The 5-year OS for those who received treatment with or without surgery were 65.6 and 25%, respectively. In our cohort, patients who received chemotherapy followed by surgical resection with no viable tumor or only mature teratoma detected had significantly longer 5-year OS compared to the non-surgical group (72.7 and 20.7%, respectively). This was comparable to other reports. Previous studies reported the presence of viable GCTs or teratoma in the resected specimens at a range of 45–88% [15, 23, 24], which was similar to our result of 54% (7/13 resected cases). Altogether, this emphasizes the importance of a multimodality approach with preoperative chemotherapy followed by surgical resection of the residual tumor in patients with MGCTs.

To prevent pulmonary complications secondary to extensive thoracic surgery, a non-bleomycin-containing regimen is generally preferred, especially in the U.S. [13]. Kesler et al. [24] reported surgery-associated deaths in 6% of patients who received a bleomycin-containing regimen, and 18% developed postoperative complications. In comparison, in the last 2 years of their study (2005–2006), none of the 17 patients treated with non-bleomycin-containing regimens experienced pulmonary complications. These results were in contrast to data from our study as well as that by Kuwano et al. [15], which showed no clinically significant pulmonary complications or deaths to have occurred after thoracic surgery despite the use of preoperative chemotherapy coupled with a bleomycin-containing regimens.

A total of 3 patients in our study were diagnosed with teratoma with SMT (2 adenocarcinomas and 1 spindle cell sarcoma). Surgery is the mainstay of treatment for teratoma with SMT given its chemoresistant nature, especially in patients with localized disease. In the advanced setting, it remains unclear whether the optimal chemotherapy comprises the regimen used for GCTs or that used for the transformed histology. However, there have been a few reports that demonstrated good responses along with long-term survival with chemotherapy directed toward the transformed histology limited to a single cell type [25, 26]. Patients with teratoma with SMT have a varying prognosis. Patients able to undergo complete resection of the malignant component were reported to have had an excellent outcome [27], whereas a median OS of only 9 months was reported for those with metastatic disease [28]. In our cohort, the median OS was only 6 months. Hence, this highlights the aggressiveness of this rare type of tumor.

Our study is limited by its retrospective design, unavoidably leading to missing data (particularly baseline clinicopathologic characteristics). In addition, a pulmonary function test was not routinely performed for patients without clinically significant pulmonary dysfunction. Although none of the patients in our cohort experienced significant pulmonary complications using a bleomycin-containing regimen, whether such cases had any adverse effects from bleomycin cannot be determined.

In conclusion, our study confirmed the importance of a multimodality approach with primary chemotherapy followed by surgical resection of the residual tumor. Additionally, a bleomycin-containing regimen can be safely used in this setting. Nevertheless, prospective studies closely monitoring pulmonary function in MGCT patients receiving a bleomycin-containing regimen are required to confirm the safety profile of this chemotherapy regimen in these patients.

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Disclosure Statement

No author has any financial conflict of interest with respect to this project.

References

1 Kubota K, Yamada S, Kondo T, et al.: PET imaging in primary mediastinal tumours. Br J Cancer 1996;73:882–886.

2 Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC (eds): World Health Organization Classification of Tumor Pathology and Genetics, Tumors of the Lung, Pleura Thymus and Heart. Lyon, France, IARC Press, 2004.

3 Malagon HD, Montiel DP: Mediastinal germ cell tumours. Diagnostic Histopathology 2010;16:228–236.

4 Dulmet EM, Macchiarini P, Suc B, Verley JM: Germ cell tumors of the mediastinum. A 30-year experience. Cancer 1993;72:1894–1901.

5 Moran C, Suster S: Germ-cell tumors of the mediastinum. Adv Anat Pathol 1998;5:1–15.

6 Oosterhuis JW, Stoop H, Honecker F, Looijenga LHJ: Why human extragonadal germ cell tumours occur in the midline of the body: old concepts, new perspectives. Int J Androl 2007;30:256–264.

7 No authors listed: International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J ClinOncol 1997;15:594–603.

8 Kesler KA, Rieger KM, Hammoud ZT, et al.: A 25-year single institution experience with surgery for primary mediastinal nonseminomatous germ cell tumors. Ann Thorac Surg 2008;85:371–378.

9 Rivera C, Arame A, Jougon J, et al.: Prognostic factors in patients with primary mediastinal germ cell tumors, a surgical multicenter retrospective study. Interact Cardiovasc Thorac Surg 2010;11:585–589.

10 Bokemeyer C, Nichols CR, Droz JP, et al.: Extragonadal germ cell tumors of the mediastinum and retroperitoneum: results from an international analysis. J Clin Oncol 2002;20:1864–1873.

11 Hartmann JT, Nichols CR, Droz JP, et al.: Prognostic variables for response and outcome in patients with extragonadal germ-cell tumors. Ann Oncol 2002;13:1017–1028.

12 Takeda S, Miyoshi S, Ohta M, et al.: Primary germ cell tumors in the mediastinum: a 50-year experience at a single Japanese institution. Cancer 2003;97:367–376.

13 Albany C, Einhorn LH: Extragonadal germ cell tumors: clinical presentation and management. Curr Opin Oncol 2013;25:261–265.

14 Wang JL, Yu H, Guo Y, et al.: A single institution, retrospective study of treatment experience in primary mediastinal germ cell tumors: elucidating the significance of systemic chemotherapy. Chin Med J 2012;125:626–630.

15 Kuwano H, Tsuchiya T, Murayama T, et al.: Outcomes of combined modality therapy for patients with stage III or IV mediastinal malignant germ cell tumors. Surg Today 2014;44:499–504.

16 Wilson LD, Detterbeck FC, YahalomJ: Clinical practice. Superior vena cava syndrome with malignant causes. N Engl J Med 2007;356:1862–1869.

17 Moran CA, Suster S, Przygodzki RM, Koss MN: Primary germ cell tumors of the mediastinum: II. Mediastinal seminomas – a clinicopathologic and immunohistochemical study of 120 cases. Cancer 1997;80:691–698.

18 Joly C, Deblock M, Desandes E, Geoffrois L: Primary mediastinal germs cells tumors: a twenty years experience in a comprehensive cancer center. Bull Cancer 2014;101:1067–1073.

19 Knapp RH, Hurt RD, Payne WS, et al.: Malignant germ cell tumors of the mediastinum. J Thorac Cardiovasc Surg 1985;89:82–89.

20 Azrif M, Leong YK, Aslan NM, et al.: Bleomycin, etoposide and cisplatinum (BEP) chemotherapy for metastatic germ cell tumours: treatment outcomes at UKM Medical Centre, Malaysia. Asian Pacific J Cancer Prev 2012;13:2467–2471.

21 Halfdanarson TR, Hogan WJ, Moynihan TJ: Oncologic emergencies: diagnosis and treatment. Mayo Clin Proc 2006;81:835–848.

22 Behl D, Hendrickson AW, Moynihan TJ: Oncologic emergencies. Crit Care Clin 2010;26:181–205.

23 Rivera C, Arame A, Jougon J, et al.: Prognostic factors in patients with primary mediastinal germ cell tumors, a surgical multicenter retrospective study. Interact Cardiovasc Thorac Surg 2010;11:585–589.

24 Kesler KA, Rieger KM, Hammoud ZT, et al.: A 25-year single institution experience with surgery for primary mediastinal nonseminomatous germ cell tumors. Ann Thorac Surg 2008;85:371–378.

25 Donadio AC, Motzer RJ, Bajorin DF, et al.: Chemotherapy for teratoma with malignant transformation. J Clin Oncol 2003;21:4285–4291.

26 Dechaphunkul A, Bigras G, Sawyer M: Response to 5-fluorouracil-based chemotherapy in a patient with metastatic colonic-type adenocarcinoma arising in a primary mediastinal teratoma. Case Rep Oncol Med 2012;2012:729278.

27 Sakurai H, Miyashita Y, Oyama T: Adenocarcinoma arising in anterior mediastinal mature cystic teratoma: report of a case. Surg Today 2008;38:348–351.

28 Khurana A, Mehta A, Kamboj M: Colonic-type adenocarcinoma (somatic-type malignancy) arising in a mediastinal mature cystic teratoma: a case report of a rare entity. Indian J Pathol Microbiol 2011;54:199–200.