Poor Outcomes in Patients with Primary Malignant Mediastinal Germ-cell Tumors

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Primary mediastinal germ-cell tumors (GCTs) without gonadal involvement are rare and can be divided into benign mature teratoma and malignant seminoma or nonseminoma. We describe our experience of malignant mediastinal GCTs and compare the presentations and outcome with those of benign teratomas. Four malignant GCTs (1 seminoma, 1 choriocarcinoma, and 2 yolk-sac tumors) have been treated in our hospital. All patients were men with obvious symptoms before diagnosis. The patient with seminoma was treated with surgery and radiation, while those with nonseminoma tumors were treated with chemotherapy and/or surgery. Two patients died, one with extended pulmonary metastasis and the other with relapsed disease and high levels of tumor markers. Compared with the nine cases of benign teratomas, the four malignant GCTs showed overwhelming male dominance, advanced symptoms at presentation, and poor outcome. These cases highlight the important role of disease staging and tumor-marker levels in malignant GCTs, and suggest that new treatment strategies for malignant GCTs await further investigation.

Key Words: malignant germ-cell tumor, mediastinum, teratoma, seminoma, yolk sac tumor
(*Kaohsiung J Med Sci* 2005;21:561–5)

Most germ-cell tumors (GCTs) are located in the gonads, although about 2–5% arise from extragonadal regions, such as the mediastinum, retroperitoneum, and central nervous system [1,2]. Though gonadal and extragonadal GCTs share similar histologic characteristics and genetic abnormalities, extragonadal GCTs are clinically and biologically distinct from their testicular counterparts [3–5]. The mediastinum is the most common site of primary extragonadal GCTs, and GCTs represent approximately 10–15% of mediastinal tumors [1,6]. It has been suggested that these tumors are derived from primitive germ cells that either mismigrate along the urogenital ridge during early embryogenesis, or are distributed physiologically to the liver, bone marrow, and brain to provide regular functions [7,8].

Primary mediastinal GCTs without gonadal involvement are rare [1,6]. They can be divided into benign mature teratoma and malignant seminoma or nonseminoma. Though the outcome of mature teratoma seems good after surgical intervention, the prognosis of malignant GCTs in the mediastinum is not fully understood, especially that of nonseminomas [9–11]. The situation has shown some improvement since the introduction of platinum-based and high-dose chemotherapy [12–14]. However, the outcome is still poor and there is little data concerning Asian populations. In this study, we describe our experience of malignant mediastinal GCTs and compare the presentations and outcome with those of benign teratoma.

Materials and Methods

Pathology reports from Kaohsiung Medical University Hospital for 1992–2004 were reviewed to find primary mediastinal GCTs. Four malignant GCTs and nine mature teratomas were found and included in this study.

Received: May 3, 2005 Accepted: July 5, 2005
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Clinical presentation, treatment course, and outcome, were retrospectively analyzed.

Diagnostic imaging studies, including chest radiography and computed tomography (CT), were used to confirm the mediastinal mass. Serum tumor markers, including α-fetoprotein (AFP) and β-human chorionic gonadotropin (βHCG), were also checked in some patients. In male patients, normal testes were confirmed by physical examination and ultrasound. Histologic diagnosis was based on the World Health Organization classification criteria [1,15].

Results

Characteristics

Nine cases of benign mature teratoma and four of malignant GCT, including one seminoma, one choriocarcinoma, and two yolk-sac tumors, were included in this study (Table). Among these cases, there were seven male and six female patients with a median age of 24 years (range, 1–44 yrs). Compared with benign teratomas, which occurred across a wide age range, all four malignant GCTs were in adult males. Most patients (69.2%) had symptoms and signs before diagnosis. All malignant GCTs had symptoms, including superior vena cava (SVC) syndrome, severe dyspnea and chest pain, but only five of the nine patients with benign teratomas showed symptoms. No elevation of tumor markers was found in patients with teratomas and the seminoma, while high HCG levels were noted in the patient with choriocarcinoma. High AFP levels were noted in the two cases of yolk-sac tumor.

Treatment and outcome

All patients with teratomas underwent surgical intervention for total tumor removal without further management. The outcomes were good in these patients, with no therapy-related mortality. However, multiple modalities of treatment were prescribed for malignant GCTs. The patient with seminoma underwent surgery for total tumor removal, followed by radiation, and had a good outcome. The two patients with yolk-sac tumors underwent surgery initially, but total tumor removal was not possible. Six courses of chemotherapy with cisplatin, bleomycin, and etoposide were prescribed immediately after surgery. The patient with choriocarcinoma also received cisplatin-based chemotherapy immediately after diagnosis due to multiple lung metastasis, with no obvious response.

Table. Characteristics of malignant and benign germ-cell tumors

Diagnosis (n = 13)	Malignant (n = 4)	Benign (n = 9)
Mature teratoma		9
Seminoma	1	
Yolk-sac tumor	2	
Choriocarcinoma	1	
Median age	23.5 years	20.0 years
Gender		
Male	4	3
Female	0	6
Symptoms		
9 (69.2%)	4 (100%)	5 (55.6%)
Treatment		
Surgery alone		9
Surgery + radiation	1 seminoma	
Surgery + chemotherapy	2 yolk-sac tumors	
Chemotherapy only	1 choriocarcinoma	
Outcome (median follow-up, 8 yrs)		
Death	2 (50%)	0

Compared with malignant GCTs, teratomas had good prognosis without mortality or recurrence (Figure). There were two deaths in the median follow-up of 8 years, one in the choriocarcinoma patient with multiple lung metastasis and no response to chemotherapy, and one in a patient with yolk-sac tumor who did not achieve complete response, as shown by imaging and tumor marker levels after chemotherapy. The second patient suffered from disease recurrence within 1 year without response to salvage chemotherapy and eventually died. Compared with this case of yolk-sac tumor, the other had normal levels of AFP and no residual tumor after chemotherapy, as shown by imaging studies. He had stable disease without recurrence for more than 2 years. The patient with seminoma had a better outcome than other patients with malignant GCTs, with no evidence of disease after management.

Discussion

We retrospectively analyzed cases of primary mediastinal GCTs and compared malignant GCTs with benign teratomas. There were nine benign teratomas (69.2%) and four malignant GCTs (30.8%), including one seminoma and three nonseminomas. The frequency of malignancy was similar to that in Japan [5,16], but slightly lower than that in the USA (39.4%) and Europe (40.8%) [17–19]. There were some differences in clinical characteristics between benign teratomas and malignant GCTs. For example, there was an overwhelming male predominance in malignant GCTs, while in benign teratoma, females outnumbered males. This is the same as in other reports, which show strong male predominance in malignant GCTs, with a near-equivalent sex ratio or a mild female preponderance in patients with benign teratoma [5,6,9,11,20]. In the malignant group, all patients were young adults without children, while in the benign teratoma group, there were three children and one adult aged 44 years, as well as five young adults. In addition, high levels of tumor markers were noted in the malignant GCTs, especially in patients with nonseminomas, while no obvious elevation was found in patients with benign teratomas.

The outcome of malignant GCTs was poor, compared with that of mature teratoma, and nonseminomas had the worst prognosis. Cisplatin-based chemotherapy has recently been shown to improve survival in malignant GCTs [5,9,12, 13]. However, both of the deaths in our study occurred in patients who had received chemotherapy. The death of the patient with choriocarcinoma, who died from respiratory failure, may have been due to the extended multiple pulmonary metastasis. The other death occurred in a patient with yolk-sac tumor without normalized AFP after surgical intervention and chemotherapy, who suffered from relapse of disease within 1 year and died from progressive disease.

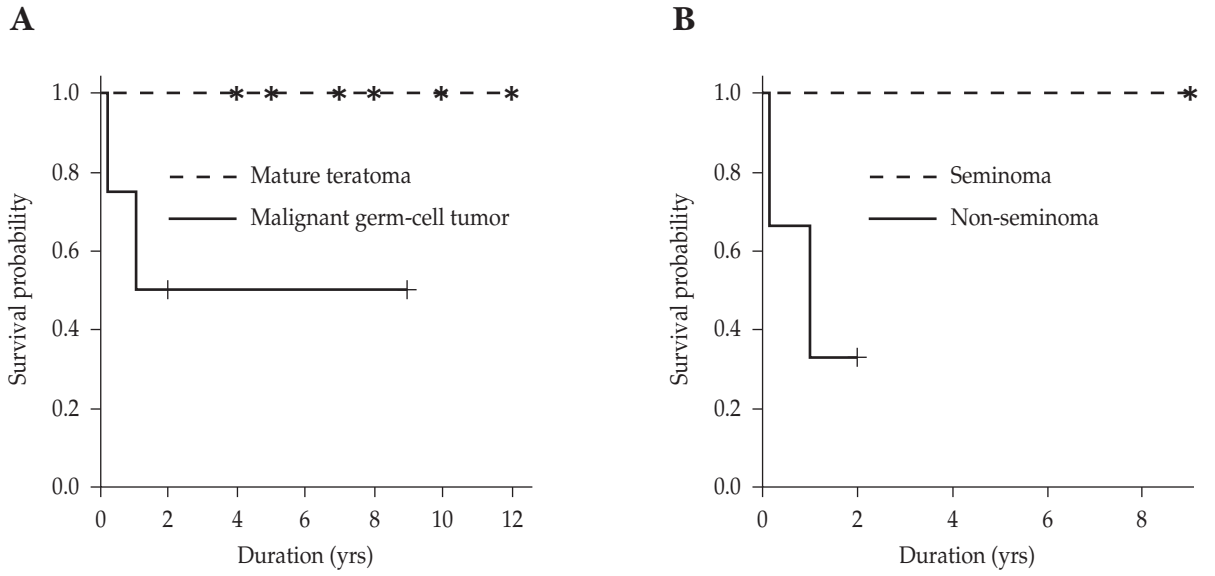

Figure. *Survival curves of patients with primary mediastinal germ-cell tumor (GCT). (A) Compared with mature teratoma, malignant GCTs had a poor prognosis. (B) Of malignant GCTs, nonseminomas had a poorer outcome than seminoma, even after treatment.*

The other patient with yolk-sac tumor had complete response and normalized AFP after treatment, and was alive for 2 subsequent years. These two deaths highlight the important role of extended disease and tumor marker levels in surviving patients [9,11]. In addition to improvements in chemotherapy, high-dose chemotherapy with hematopoietic progenitor cell support shows promise in malignant GCTs with poor risk [5,11,13,14]. Further studies are needed to draw a final conclusion about novel therapies in malignant mediastinal GCTs.

For many years, radiation therapy has been either the primary therapy or one of a combination of therapies after surgery, due to the unique radiosensitive characteristics of seminoma [1,2,21]. Recently, chemotherapy has been introduced into the treatment modalities of seminoma, especially at advanced stages, with good response, while the role of surgical resection is changing [5,10,22]. However, it has also been suggested that patients with mediastinal seminoma have an excellent outcome regardless of treatment approach [23].

In summary, we have reported our experience of malignant mediastinal GCTs. Benign mature teratomas and the seminoma had good response and long-term survival. However, three nonseminomas had poor outcome with two deaths. The poor outcome of malignant cases highlights the important role of advanced disease and tumor-marker levels in survival. Though cisplatin-based chemotherapy improves survival in malignant mediastinal GCTs, new strategies for malignant cases await investigation in the hope of improved survival.

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原發性縱隔腔生殖芽細胞惡性腫瘤病人具不良之預後

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無生殖腺體侵犯之原發性縱膈腔生殖芽細胞腫瘤為罕見之腫瘤，一般分為良性成熟畸胎瘤及包含精細胞瘤和非精細胞瘤在內的惡性腫瘤。在此我們報告惡性縱膈腔生殖芽細胞腫瘤之病患，並和成熟畸胎瘤比較其臨床表現和預後。共有包括一位精細胞瘤、一位絨毛膜癌及兩位卵黃囊瘤在內的四位惡性生殖芽細胞腫瘤的病人於本院治療。此四位病患均為男性成人且皆有明顯之症狀。精細胞瘤的病患以手術加上放射線治療；而其他的非精細胞瘤病患則以化學治療加上開刀治療為主。共有兩位病患死亡，包括一位病患有廣泛的肺部轉移和另一位是有高的腫瘤指數復發病患。和其他九位成熟畸胎瘤病人比較，惡性生殖芽細胞腫瘤的病人有顯著的男性病患傾向，明顯的症狀及較差的預後。這些例子強調疾病晚期和腫瘤指數對惡性生殖芽細胞腫瘤病患預後的重要影響；也認為對惡性生殖芽細胞腫瘤的治療須有更多的研究。

關鍵詞：惡性生殖芽細胞腫瘤，縱膈腔，畸胎瘤，精細胞瘤，卵黃囊瘤

（高雄醫誌 **2005;21:561–5**）

收文日期：**94** 年 **5** 月 **3** 日
接受刊載：**94** 年 **7** 月 **5** 日
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