Management of Primary Malignant Germ Cell Tumor of the Mediastinum

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Background: Primary mediastinal malignant germ cell tumors (GCTs) are rare and have a worse prognosis than their gonadal counterparts. Although multimodality treatment is a standard therapeutic strategy in mediastinal GCTs, the clinical implications of surgical intervention remain unclear.

Methods: Forty-eight patients with primary mediastinal malignant GCT who were treated at the National Cancer Center Hospital, Tokyo, from 1962 to 2002 were studied retrospectively with regard to their histology and clinical profile.

Results: Mediastinal GCT occurred predominantly in young males, with a mean age of 28.8 years at the time of diagnosis. There were 46 males (96%) and two females (4%). Histologically, seven patients (15%) were diagnosed as having pure seminoma and 41 (85%) had non-seminomatous GCT. Treatment consisted of surgery alone in nine patients, surgery followed by chemotherapy in two, and chemotherapy followed by surgery in 20. The other 17 patients received chemotherapy and/or radiotherapy without surgery. Of these latter 17 patients, 14 developed progressive disease and three were followed up with a sustained partial response. Among the 31 patients who underwent surgery, complete resection was performed in 27 (87%) and incomplete resection was performed in four (13%). Twelve (41%) patients had elevated serum tumor marker levels preoperatively. Among the 20 patients who received preoperative chemotherapy, viable cells were found in the resected specimen in six (30%). With regard to tumor recurrence in patients with surgical intervention, the preoperative serum tumor marker levels and the presence of viable cells in the resected specimen were significantly associated with recurrence. There was no significant association between surgical curability and recurrence. The 5-year overall survival rate in all 48 patients was 45.5%.

Conclusions: Surgical intervention for mediastinal GCT may be needed to remove a chemotherapy-refractory tumor or to assess the pathological response to chemotherapy to determine the indications for further chemotherapy.

Key words: mediastinum – mediastinal neoplasms – germ cell tumor – tumor markers

INTRODUCTION

Although the most common location for malignant germ cell tumors (GCTs) is the gonads, they can also arise in extragonadal regions such as the mediastinum, retroperitoneum and pineal gland (1). It has been speculated that they occur in such unusual locations due to the abnormal migration of germ cells during embryogenesis (2,3). The histologic characteristics of extragonadal tumors are similar to those of gonadal GCTs, and both are chemosensitive. The mediastinum is the most common site of primary extragonadal GCTs (4). Primary malignant GCTs of the mediastinum account for 1–6% of all mediastinal tumors (5–8). Primary extragonadal GCTs, especially primary mediastinal tumors, are considered to have a poor prognosis (9–16). Although they have similar histologic features, mediastinal GCTs are clinically and biologically distinct from their testicular counterparts.

Malignant GCTs are closely related to serum tumor markers, especially alpha-fetoprotein (AFP) and/or the beta subunit of human chorionic gonadotropin (HCG). Measurement of these serum tumor markers is important in diagnosis of the disease, and in the management and follow-up of patients with GCTs.

Chemotherapy for malignant GCTs has become standard practice since the introduction of cisplatin-based combination
therapy, the clinical significance and indications of salvage
with mediastinal GCT.

chemotherapy in the late 1970s (11,17–19). High-dose che-
mochemistry with peripheral blood stem cell transplantation
(PBSCT) has also been used for refractory tumors (20–22).
Patients with these tumors have not usually been considered as
candidates for primary surgery because of the presumed sys-
temic nature of the disease. Thus, all resections for GCTs have
been performed as ‘salvage surgery’, which is considered to be
a therapeutic challenge for this type of tumor in a large population.

Several issues must be addressed in the management of
malignant GCT: preoperative normalized serum tumor marker
levels, the relationship between prognosis and the presence of
persistent viable cells in post-chemotherapy resected speci-
mens, the significance of the completeness of resection and the
operative risk, especially after high-dose chemotherapy with
PBSCT. Due to the rarity of GCTs arising in the mediastinum,
there have been few reports on the clinical outcome after ther-
apeutic challenge for this type of tumor in a large population.

This report describes our experience with managing patients
with mediastinal GCT.

PATIENTS AND METHODS

PATIENTS

In the 41-year period from 1962 through 2002, 48 patients with
malignant GCT of the mediastinum were treated at the
National Cancer Center Hospital, Tokyo. Three patients were
referred to us after surgical resection of the tumor as the initial
treatment of choice at another institute. The clinicopathologi-
cal characteristics of these 48 patients were examined in this
retrospective study. The patients were considered to have pri-
mary mediastinal GCT when a bulky anterior mediastinal mass
was present in the absence of any clinically detectable testicu-
lar or ovarian masses at any time during the course of the
disease (24). The diagnosis of mediastinal GCT was defined
clinicopathologically in all patients. Serum tumor markers,
especially AFP and/or HCG, were measured preoperatively in
29 patients.

TREATMENT

The treatments used in the 48 patients with mediastinal GCTs
are summarized in Fig. 1. All patients who received che-
mochemistry initially or postoperatively were treated with a regimen
containing cisplatin. The chemotherapy regimen used in each
case was one of those sequentially developed throughout the
study period at our institute for the management of germ cell
tumors. Mainly, the patient was treated with either a com-
bination of cisplatin and etoposide (PE) or a combination of
cisplatin, bleomycin and etoposide (BEP), whether for semino-
matous or non-seminomatous GCT. The PE chemotherapy
consisted of intravenous cisplatin (120 mg/m²) and intravenous
etoposide (100 mg/m²) given on days 1–5. The BEP chemo-
therapy consisted of intravenous cisplatin (20 mg/m² of body-
surface area) given daily for 5 days, intravenous bleomycin (30
U) given on days 2, 9 and 16, and intravenous etoposide (100
mg/m²) given on days 1–5. The patients received two to four
courses of the chemotherapy given at 3-week intervals. Of
these 48 patients, 23 received multimodality treatment while
25 received only one form of treatment, such as chemotherapy,
surgery or radiotherapy. Thirty-four patients received che-
mochemistry, 11 received radiotherapy and 31 underwent surgery.
Three patients received high-dose combination chemotherapy
with PBSCT: one underwent high-dose chemotherapy follow-
ing the initial chemotherapy and surgical resection, and the
others underwent the initial high-dose chemotherapy followed
by surgical resection.

Based on previous reports (3,13,25), the response criteria
were defined as follows: complete remission (CR) was
recorded when serum tumor markers normalized and complete
resolution of tumor masses occurred. CR was also documented
when resection of a residual mass revealed only necrosis.
Partial remission (PR) was defined as a >50% decrease in bi-
dimensional tumor measurements and ≥50% decline in serum
tumor markers. A radiological increase in tumor dimensions or
an elevation of marker levels indicated progressive disease
(PD).

Operative reports were reviewed and the curability of resec-
tion (complete resection or incomplete resection) and outcome
(mortality and morbidity) were recorded. Complete resection
was defined as no macroscopic or microscopic residual tumor,
and incomplete resection was defined as evident macroscopic
or microscopic residual tumor. Operative death was defined as
any death within 30 days of the operation or during hospitali-
ization. Preoperative serum tumor markers, AFP and HCG,
were defined as normal or elevated on the basis of marker
levels collected before the operation and approximately 4–6
weeks from the date of the last chemotherapy.

Post-chemotherapy resected specimens were categorized as
follows. Specimens that showed the histological appearance of
GCTs such as embryonal carcinoma, yolk sac carcinoma, immature or mature teratoma, choriocarcinoma or seminoma were regarded as having viable cells. Specimens that included only necrosis, based on histologic findings of necrotic debris without any viable cells, were regarded as having no viable cells.

STATISTICS
A chi-square test was used to compare the frequencies among different groups. Survival curves were estimated by the Kaplan–Meier method using the date when treatment began as the starting point and the date of recurrence, death or last follow-up as the endpoint. A \( P \)-value of <0.05 was considered statistically significant.

RESULTS

CLINICAL FINDINGS
Malignant GCT of the mediastinum occurred predominantly in young adults, with a mean age of 28.8 years at the time of diagnosis (range, 13–68). There was a male preponderance: 46 (96%) males and two (4%) females. Thirty-six (75%) of the 48 patients showed a symptom that could be related to the tumor at the initial examination. These symptoms were non-specific and resulted from the expanding tumor encroaching on surrounding structures (Table 1). The remaining 12 (25%) patients were asymptomatic and the tumors were found based on evidence of an anterior mediastinal mass on a routine chest radiograph. Klinefelter syndrome was also found in a 13-year-old patient with an immature teratoma.

DIAGNOSIS AND HISTOLOGY
The histologic diagnosis of these 48 malignant GCTs was confirmed in resected specimens taken by thoracotomy (13 patients, 27%), incisional biopsy of the tumor (six patients, 13%), percutaneous needle biopsy (27 patients, 56%), or autopsy (two patients, 4%). Although biopsy specimens were taken in the two autopsy cases, they were not of diagnostic significance. The histologic subtype could not be determined in one patient because of total necrosis of the resected tumor after cisplatin-based chemotherapy, and, therefore, no histologic type could be specified. However, since the pre-chemotherapy serum tumor markers were markedly elevated, a diagnosis of non-seminomatous GCT was made. Seven patients (15%) were diagnosed as having pure seminoma and 41 (85%) had non-seminomatous GCT, containing non-seminomatous elements.

TREATMENT AND RESPONSE
Among these 48 patients, nine underwent surgical resection alone. Two patients underwent surgical resection followed by chemotherapy and 20 patients received chemotherapy followed by surgical resection. Seventeen patients received chemotherapy and/or radiotherapy without surgery. Of these latter 17 patients, 14 developed PD and three were followed up with sustained PR. With regard to the initial treatment, 11 patients underwent surgical resection and 37 received chemotherapy and/or radiotherapy. Among these latter 37, 14 (38%), all of whom had non-seminomatous lesions, developed PD, and 20 (54%) were followed by surgery with PR. The remaining three patients (8%) (one was diagnosed as having non-seminomatous lesion and two were seminoma) were followed up without surgical resection because of sustained good PR (tumor measured 3 cm or less in diameter on CT).

For the 31 patients who underwent surgical resection, complete resection was performed in 27 patients (87%) and incomplete resection was performed in four (13%). Twelve (41%) of the 29 patients whose serum tumor markers were measured had elevated tumor markers prior to resection. Nine of these 12 patients had elevated AFP and five had elevated HCG. Both tumor markers were elevated in only two patients. In the remaining 17 patients (59%), serum tumor markers were within the normal range.

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Among the 20 patients who received preoperative chemotherapy, six (30%) had viable cells in the resected specimen and 14 (70%) had no viable cells.

PROGNOSIS
The median follow-up period was 6.5 years. The 5-year relapse-free survival rate in 34 patients, excluding the 14

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of patients (%)</th>
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<tbody>
<tr>
<td>Chest radiograph abnormality (asymptomatic)</td>
<td>12 (25)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>18 (38)</td>
</tr>
<tr>
<td>Cough</td>
<td>11 (23)</td>
</tr>
<tr>
<td>Back pain</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Bloody sputum</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fever</td>
<td>1 (2)</td>
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</table>

Figure 2. Relapse-free survival in 34 patients, excluding 14 who developed progressive disease after initial chemotherapy. The 5-year relapse-free survival rate was 63.2%. Bars indicate 95% confidence intervals.
patients who developed PD after initial chemotherapy, was 63.2% (Fig. 2). Among the 29 patients whose preoperative serum tumor markers were measured, 17 had normal serum tumor marker levels and two (12%) of these had recurrence. The remaining 12 had elevated levels and nine (75%) of these had recurrence. Thus, the prevalence of recurrence in patients with preoperative elevated serum tumor markers was significantly higher than that in patients with preoperative normal serum tumor markers ($P = 0.001$). In the three patients with preoperative elevated serum tumor markers who had no recurrence (Table 2), the histological diagnosis was non-seminomatous GCT. Two of these three patients received chemotherapy followed by surgery and had no viable cells in their resected specimens, and one of these two received postoperative high-dose chemotherapy with PBSCT because of pulmonary disseminated disease on CT. These two patients both survived relapse-free for more than 5 years. The other patient underwent initial surgery followed by chemotherapy. This patient was lost on the 285th postoperative day due to secondary malignancy (acute leukemia).

Among the 31 surgical resections, there were 27 complete resections and four incomplete resections. Among the 27 complete resections, there were 10 cases (37%) with recurrence and 17 (63%) without recurrence. On the other hand, there were two cases (50%) with recurrence and two (50%) without recurrence in the four incomplete resections. There was no significant difference between curability and recurrence ($P = 0.633$).

With regard to the relationship between recurrence and the presence of viable cells in the resected specimen (Table 3), among the 20 patients who underwent preoperative treatment (chemotherapy and/or radiotherapy), six had viable cells and 14 had no viable cells. Four (67%) of the six patients with viable cells, all of whom had been diagnosed as having non-seminoma, had recurrence. Two (14%) of the 14 patients (five seminomas, nine non-seminomas) with no viable cells had recurrence. There was a significant difference between recurrence and the presence of viable cells in the resected specimen ($P = 0.018$).

The 5-year overall survival rate in the 48 patients was 45.5% (Fig. 3). Among the 23 deaths following treatment, 21 were caused by either recurrence or progression of the disease (tumor-related death). The remaining two patients were lost on the 7th and 285th postoperative days because of multiple organ failure due to disseminated intravascular coagulation (DIC) and secondary malignancy (acute leukemia), respectively. Surgical mortality and morbidity are shown in Table 4. Among the 31 patients who underwent surgical resection, there was one (3%) operative death caused by DIC. Postoperative morbidity was found in 13% of patients.

**DISCUSSION**

Although the general histologic and serologic characteristics of mediastinal malignant GCTs are similar to those of testicular GCTs, mediastinal GCTs have been reported to have a worse prognosis than gonadal GCTs (15,16). Furthermore, the clear differences in clinical behavior suggest that these tumors are biologically distinct. Some investigators have proposed that

<table>
<thead>
<tr>
<th>Table 2. Relapse-free patients with preoperative elevated serum tumor marker levels</th>
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</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

Chemo, conventional chemotherapy; Viable cells, viable cells present in the resected specimen; High-dose, high-dose chemotherapy with PBSCT; NED, no evidence of disease.

<table>
<thead>
<tr>
<th>Table 3. Relationship between recurrence and the presence of viable cells in the resected specimen</th>
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</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Seminoma ($n = 5$)</td>
</tr>
<tr>
<td>Non-seminoma ($n = 15$)</td>
</tr>
<tr>
<td>Total*</td>
</tr>
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* $P = 0.018$.

**Figure 3.** Survival in all 48 patients with primary mediastinal germ cell tumor. The 5-year overall survival rate was 45.5%. Bars indicate 95% confidence intervals.
mediastinal GCTs arise from cells of a different embryologic origin than testicular primaries (10). Others have suggested that the poor outcome of treatment for mediastinal GCTs reflects the advanced stage of the disease usually present at the time of diagnosis and that there is little intrinsic difference between mediastinal and gonadal GCTs with respect to their response to chemotherapy (26). However, the reasons for the observed differences in the clinical characteristics and behavior of mediastinal GCT are unknown. In addition, some reports have suggested that patients with Klinefelter syndrome have a slightly increased predisposition of having mediastinal GCT (27,28). One patient (2%) in the present study had Klinefelter syndrome. The pathogenesis of the association between mediastinal GCT and Klinefelter syndrome remains unclear.

With regard to the treatment of mediastinal malignant GCTs, the current consensus is that initial systemic chemotherapy should be followed by aggressive complete resection of all macroscopic residual tumor when necessary (4,18,24,29–31). As in most series, patients treated with this approach had a superior outcome to those treated with initial resection, even though these tended to be smaller tumors. Our study also ended in disaster for the prognosis. Nine of the 11 patients who underwent surgery as initial treatment had recurrence (distant organ) within one year after surgery, three of whom received adjuvant chemotherapy; the remaining two were survivors for more than 10 years, one of whom received adjuvant chemotherapy and the other, diagnosed as having immature teratoma, underwent only surgery for treatment. However, the clinical implications of surgical resection in the multimodality treatment of mediastinal GCTs are not yet clear.

The management of patients with elevated serum tumor marker levels after chemotherapy is controversial. The degree of the elevation of serum tumor markers, especially AFP and HCG, plays a crucial role in defining the outlook (6,15,16,32,33). In the present study, patients with preoperative normal tumor marker levels had significantly better survival than those with preoperative elevated tumor marker levels. Surgical resection for patients whose markers have not normalized with chemotherapy is usually futile (4,6,34–36). Dulmet and colleagues also stated that normalizing serum tumor marker levels before surgical resection was a significant favorable prognostic factor (7). On the other hand, Vuky and associates found a tendency for shorter survival in patients with elevated and increasing tumor markers compared to patients with normal or elevated-but-declining markers before surgical resection (37). In our series, two patients with chemo-refractory marker-elevated GCTs achieved a prolonged relapse-free status with salvage surgery and they had no viable cells in the resected specimens. These two patients had elevated, but markedly declining, marker levels before surgical resection. In addition, both these two patients had no viable cells in the resected specimens pathologically. These might be due to a half-life of tumor markers and the possibility of a few viable cells besides sections examined microscopically in spite of the diagnosis of no viable cells. Thus, selected patients, such as patients with elevated but declining marker levels before surgery, might be considered as candidates for surgery (33,38).

The histopathologic findings of post-chemotherapy resected specimens are important prognostically (30,33,37). The presence of persistent GCT in the resected specimen is a poor prognostic factor. In the present study, four (67%) of six patients with viable cells in the resected specimen had recurrent disease despite the resection of persistent GCT, whereas two (14%) of 14 patients with no viable cells had recurrence. One definite purpose of surgery is careful evaluation of the tumor after chemotherapy to see whether or not any viable cells remain. Further chemotherapy in the adjuvant setting may be considered in patients who show viable tumor. On the other hand, patients with residual tumor such as mature teratoma are commonly found because of the histological heterogeneity of GCTs. Residual teratomas must be completely removed, since they can compress or invade surrounding mediastinal structures, and dedifferentiation into carcinoma is possible (39).

In the present study, histology influenced the treatment outcome. Patients with pure seminoma achieved a high pathologic CR rate and an excellent prognosis (5-year survival rate, 100%). Several reports have confirmed the good prognosis of mediastinal pure seminoma compared with non-seminomatous

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Initial treatment</th>
<th>Histology</th>
<th>Viable cells</th>
<th>Postoperative treatment</th>
<th>Prognosis (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>Chemo</td>
<td>Non-seminoma</td>
<td>Negative</td>
<td>High-dose</td>
<td>6.2, alive, NED</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>High-dose</td>
<td>Non-seminoma</td>
<td>Positive</td>
<td>None</td>
<td>1.9, dead, WD</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>High-dose</td>
<td>Non-seminoma</td>
<td>Positive</td>
<td>None</td>
<td>0.8, dead, WD</td>
</tr>
</tbody>
</table>

Chemo, conventional chemotherapy; High-dose, high-dose chemotherapy with peripheral blood stem cell transplantation; Viable cells, viable cells present in the resected specimen; NED, no evidence of disease; WD, with disease.
GCTs (7–9,13,15,29,31,40–42). The Southeastern Cancer Study Group reported excellent sustained remissions with initial chemotherapy in all patients with mediastinal seminomas (19). In our study, five patients with seminoma, who received chemotherapy followed by surgery, all had CR without any viable cells in the resected specimen. Motzer and colleagues proposed that close observation without surgery is possible for seminoma patients with a post-chemotherapy residual tumor of 3 cm or less in diameter because none of the patients with a residual tumor of this size had viable cells in the resected specimen (43). In the present study, two patients with pure seminoma also had sustained post-chemotherapy good PR (tumor size, 3 cm or less in diameter on CT) without tumor relapse. On the other hand, GCTs could have a mixed histology, with both seminomatous and non-seminomatous components (40). Accordingly, elevated serum tumor markers in patients with GCT might indicate a non-seminomatous component even if biopsied specimens reveal only pure seminoma. A diagnosis of seminoma based on small biopsy specimens should be considered clinically as well as histopathologically.

High-dose chemotherapy was introduced to improve the outcome in patients with refractory GCTs, based on the fact that the response rate of non-seminomatous GCT increases with the intensification of chemotherapy (21,22). Some reports have suggested that high-dose chemotherapy with PBSCT may have curative potential in refractory GCTs (22,44). In the present study, three patients were treated with high-dose carboplatin and etoposide with PBSCT (Table 5). All three patients underwent surgical intervention. Two of them received two or more regimens of conventional chemotherapy prior to high-dose chemotherapy followed by surgery, with viable cells in the resected specimens. Ultimately, both died of relapse disease in less than 2 years. The other patient received high-dose chemotherapy for disseminated disease (lung disease) after conventional chemotherapy followed by reduction surgery, and remains free of disease at 74 months. Some investigators have proposed that the use of high-dose chemotherapy with PBSCT does not produce durable remission in patients with refractory mediastinal GCT with a poor prognosis (45,46). The efficacy of high-dose chemotherapy, in conjunction with surgical resection when necessary, in the treatment of refractory mediastinal GCTs must be further evaluated.

In conclusion, surgical resection for mediastinal GCT may be required to remove chemotherapy-refractory tumor for local control or assess the pathological response to chemotherapy. Although whether a gross chemotherapy refractory tumor includes pathologically viable cells or is not unknown, if there are any, it might lead to a hotbed of local relapse, which can life-threateningly compress mediastinal structures such as the heart, aorta and superior vena cava. The presence of viable cells in the resected specimen may suggest a necessity for additional chemotherapy because of the presumed systemic nature of the disease. On the other hand, patients with preoperative elevated increasing tumor marker levels and/or progressive disease after initial chemotherapy are no longer candidates for surgery for local control because of their extremely poor prognosis. However, the clinical implications and indications of surgical resection must be investigated further. Additionally, more appropriate and effective therapeutic strategies are needed in the treatment of patients with mediastinal GCT to achieve better survival rates.

References
minged with extragonadal nonseminomatous germ cell tumors. The Indiana University experience.


