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Complete Resection of Post-Chemotherapy Residual Tumor Could Improve the Prognosis in Extragonadal Germ Cell Tumor

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Abstract

Background: We investigate the effects of chemotherapy and surgical treatment on the extragonadal germ cell tumor of which poor prognosis has been reported.

Methods: We analyzed the prognosis of 31 patients with extragonadal germ cell tumor treated at Kanagawa Cancer Center by factors including patient background, the condition of disease, and treatments.

Result: As the prognostic factors for the overall survival, pulmonary metastasis at the first visit (p=0.011), no normalization of tumor markers after induction chemotherapy (p=0.014) and no residual tumor resection irrespective with (p=0.03) or without (p=0.001) normalized tumor makers were significantly poor prognosis in the univariate analysis. On the other hand, patients who underwent residual tumor resection with un-normalized tumor markers (desperation surgery) tended to show a better prognosis compared to previous reports.

Conclusion: Although this was an investigation in a rather small group, regardless of the tumor markers normalization, resection of a residual tumor showed the tendency of improving the prognosis of extragonadal germ cell tumor. It was considered that resection of a residual tumor with a high degree of expertise could lead to better treatment outcomes.

Keywords: Male neoplasms; Germ cells; Embryonal prognosis; Surgery testicular neoplasms

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Abbreviations

ADP: α-Fetoprotein; BEP: Bleomycin, Etoposide, and Cisplatin; EGGCT: Extragonadal Germ Cell Tumor; HCG: Human Chorionic Gonadotropin; IGCCC: The International Germ Cell Consensus Classification; LDH: Lactate Dehydrogenase; NSGCT: Non-Seminomatous Germ Tumor; OS: Overall Survival; SGCT: Seminomatous Germ Cell Tumor; TIP: Paclitaxel, Ifosfamide, and Cisplatin; VIP: Etoposide, Ifosfamide, and Cisplatin

Background

Germ cell tumor is the most common malignant tumor among 15 to 35 years old men. The major primary lesion is testicle, but 5% of them occur extragonadal [1]. Extragonadal Germ Cell Tumor (EGGCT) often occurs in mediastinum and retroperitoneum, and histologically they are divided into Seminomatous Germ Cell Tumor (SGCT) and Non-Seminomatous Germ Tumor (NSGCT). Since EGGCT tends to be detected in the advanced stage and the malignant potential may be worse, it has been considered that the prognosis is poorer compared to those with testicular primary, so the NSGCT with mediastinal primary is classified as the poor prognosis group in the International Germ Cell Consensus Classification (IGCCC) [2]. Its first-line treatment is chemotherapy similarly to those with testicular primary, and residual tumor resection is performed after normalization of tumor markers in principle. However, when the tumor markers do not normalize even after continuous chemotherapy, residual tumor resection with elevated tumor marker (desperation surgery) may be performed. In this situation, complete resection is essential for the curability [3,4], but resection of residual tumor is frequently tricky, which requires a high degree technique of specialized surgeon. In this paper, we conducted a clinical analysis of the extragonadal germ cell tumors treated at our hospital and especially investigated the significance of resection of residual

tumors.

Methods

Subjects were 31 cases with extragonadal germ cell tumor who were treated at the Department of Urology, Kanagawa Cancer Center between February 1994 and April 2018. As the prognostic factor, we analyzed age, histological type, IGCCC, primary lesion, presence of metastasis, site of metastasis, pre-treatment tumor marker value, normalization of tumor markers after chemotherapy, presence of residual lesions after chemotherapy, and residual tumor resection. The analysis was conducted using log-rank test, and the continuous variable was analyzed using a binary variable with the median value as the cutoff value.

Results

The cases consisted of 5 SGCTs, 22 NSGCTs and 4 GCTs which was determined by tumor marker, though the histological type was unknown (Table 1). In NSGCTs, single histological types observed were 4 embryonal carcinomas, 4 yolk sac tumors, 3 choriocarcinomas, and 2 immature teratomas, and multiple histological types were observed in 6 cases. The median age was 29 (15 to 61) years old and there was no significant difference between SGCT and NSGCT (median 28 and 30 years old). The primary lesions of SGCT and NSGCT were 4 and 12 cases in mediastinum and 1 and 10 cases in retroperitoneum, respectively. The metastasis sites other than mediastinum and retroperitoneum at the diagnosis were 12 lungs, 6 cervical lymph nodes, and 3 livers. The cases are classified as 4 good, 5 intermediates and 16 poor prognoses by the IGCCC. The median value of pre-treatment tumor markers were 525 (168-3082) U/L in Lactate Dehydrogenase (LDH), 79.6 (1.8-190000) ng/mL in α-Fetoprotein (AFP), and 71.8 (0.4-707700) mIU/mL in Human Chorionic Gonadotropin (HCG). Five cases underwent surgical resection as the primary treatment; these were cases who underwent surgery in other hospitals then referred to hour hospital. Those who underwent the primary treatment at our hospital were all received chemotherapy as the first line. In general, BEP (Bleomycin, Etoposide, and Cisplatin) regimens were applied as the induction treatment, but five cases over 40 years old were applied VIP (Etoposide, Ifosfamide, and Cisplatin) regimen. When the normalization of tumor markers after induction chemotherapy did not achieve, in principle, TIP (Paclitaxel, Ifosfamide, and Cisplatin) was applied as the salvage chemotherapy. Among IGCCC poor prognosis cases, two cases underwent auto-peripheral blood stem cell transplantation accompanied by high-dose chemotherapy (ifosfamide, carboplatin, and etoposide) as the salvage chemotherapy. The surgical resections after chemotherapy were performed for 11 mediastinal tumor, 5 retroperitoneal lymph nodes and 1 cervical lymph node. During the median observation period of 30.7 months (2.7 to 227.0 months), 21 survivals, 8 cancer deaths, and 2 treatment-related deaths (one septic shock and one interstitial pneumonia) were observed (Table 2). The 5-year Overall Survival (OS) rate was 71.8% (Figure 1). The 5-year OS of patients with SGCT was 80%, retroperitoneum NSGCT was 67% and mediastinum NSGCT was 80%.

Table 1: Patients characteristics.

	Whole	Seminoma	Non-seminoma
No. of patients (n)	31	5 (16.1%)	22 (71.0%)
Median age (years)	29 (15-61)	28 (22-47)	30 (15-61)
Primary site (n)	18	4	12
Mediastinal	13	1	10
Retroperitoneal	0	0	0
Unknown			
The median value of pre-treatment	525 (168-3082)	304 (220-350)	1070 (223-3082)
Tumor markers	79.6 (1.8-190000)	3.8 (1.8-6.2)	438 (2-190000)
LDH (U/l)	71.8 (0.4-707700)	6.3 (1-120)	110.7 (0.4-300000)
AFP (ng/ml)			
HCG (ng/ml)			
IGCCC prognosis (n)	4	4	0
Good	6	0	5
Intermediate	19	0	16
Poor	2	1	1
Unknown			
No. of metastatic sites (n)	15	5	9
0	8	0	6
1	7	0	6
≥ 2			
Type of treatment (n)	13	3	7
Chemotherapy	17	2	14
Chemotherapy + Surgery	1	0	1
Unknown			

Compared to report of many cases from Europe and the US [5], the 5-year OS rate was similar, but the normalization of tumor markers after chemotherapy among the group of mediastinal NSGCT was lower (30% *vs.* 64%). On the other hand, the recurrence rate (52% *vs.* 10%), and the 5-year survival rate (80% *vs.* 45%) were better (Table 3).

When we analyzed the prognostic factors (Table 4), the presence of pulmonary metastasis at the first visit (p=0.011), and no normalization of tumor markers after induction chemotherapy (p=0.014) were related to significantly poor prognosis. When the

Table 2: Outcome (n=31).

	Whole	Seminoma	Non-seminoma
Median observation time (months)	30.7 (2.7-227.0)	30.6 (15.1-123.3)	42.2 (2.7-227.0)
Alive (n)	21	4	15
Dead (n)	10	1	7

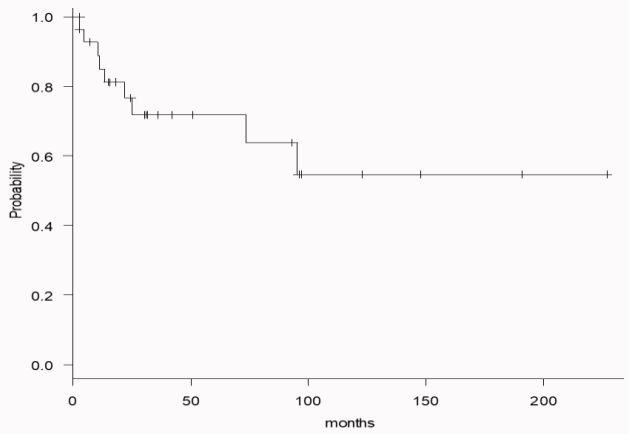

Figure 1: Kaplan-Meier curve for overall survival of 31 patients.

Table 3: International analysis and this study for extragonadal germ cell tumors.

		5-year survival (%)	Tumor marker normalization (%)	Relapse (%)
Bokemeyer et al.	Mediastinal SGCT	88	94	6
n=635	Retroperitoneal SGCT	88	88	17
	Mediastinal NSGCT	45	64	52
	Retroperitoneal NSGCT	62	68	50
This study	SGCT	80	100	0
n=31	Mediastinal NSGCT	80	30	10
	Retroperitoneal NSGCT	67	80	50

Table 4: Possible prognostic factors in extragonadal germ cell tumors.

	No. of patients (n)	5-year survival (%)	P-value
Seminoma	5	75	0.795
Non-seminoma	22	78.4	
Primary mediastinal	18	74	0.747
Primary retroperitoneal	12	72.7	
Presence metastatic site	15	63.5	0.121
Absence metastatic site	15	83.6	
Presence of pulmonary metastasis	12	53	0.011
Absence of pulmonary metastasis	18	86.9	
Presence of metastatic site except for pulmonis	9	77.8	0.691
Absence of metastatic site except for pulmonis	21	71.4	
Age >29 years	14	56.4	0.273
Age ≤ 29 years	16	85.6	
The value of pre-treatment tumor markers			
LDH>525 U/l	10	64.8	0.144
LDH ≤ 525 U/l	12	90	

Table 5: Patients who did not obtain the normalization of tumor markers after chemotherapy (n=10).

	Age (years)	Un-normalized marker	Site of residual tumor	Desperation surgery	Complete resection	Histological type	Adjuvant chemotherapy	5-year dead or alive
Case 1	26	AFP	Mediastinal	+	+	Viable cell	-	Alive
Case 2	29	AFP	Mediastinal	+	+	Teratoma	+	Alive
Case 3	31	AFP	Mediastinal	+	+	Teratoma	-	Alive
Case 4	20	AFP	Mediastinal	+	+	Necrosis	-	Alive
Case 5	32	AFP	Mediastinal	+	+	Necrosis	-	Alive
Case 6	22	HCG	Retroperitoneal	+	+	Necrosis	-	Alive
Case 7	32	AFP	Mediastinal	-	*	*	*	Dead
Case 8	47	HCG	Mediastinal	-	*	*	*	Dead
Case 9	18	HCG	Retroperitoneal	-	*	*	*	Dead
Case 10	51	HCG	Retroperitoneal	-	*	*	*	Dead

normalization of tumor markers and surgery were analyzed together, the 5-year survival rates were better in the surgery group irrespective of with (p=0.003) or without (p=0.001) tumor marker normalization.

Discussion

The 5-year survival rate of EGGCT in SGCT has been reported 88%, which means the prognosis is relatively good [5], but in NSGCT, it is 63% in the retroperitoneum and 45% in the mediastinum, indicating poor prognosis [6]. Among a few reports from Japan [7,8], Kakimoto et al. summarized 51 cases in which the 5-year survival rate was 68% in all cases, 92% in SGCT, 81% in retroperitoneal NSGCT, and 43% in mediastinal NSGCT [8]. The poor prognosis of mediastinal NSGCT in the previous reports [5-8], is identical to the IGCCC that classified mediastinal NSGCT as poor prognosis [2]. In our cases, the 5-year survival rate of mediastinal NSGCT was 80%, which was better than the other reports. As shown in Table 3, although the non-normalization rate of tumor markers after chemotherapy of mediastinal NSGCT was worse than the other reports, the recurrence rate of our cases was relatively low. Discrepancy of this result probably depends on the surgery of the post chemotherapy residual tumors. In

Table 6: Possible prognostic factors in patients who did not obtain the normalization of tumor markers after chemotherapy (n=10).

		Dead (n=4)	Alive (n=6)	5-year survival (%)	P-value
Un-normalized marker	AFP	1	5	83.3	0.119
	HCG	3	1	25	
Site of residual tumor	Mediastinal	2	5	71.4	0.524
	Retroperitoneal	2	1	33.3	
Desperation surgery	Complete resection	0	6	100	0.001
	Un-complete resection	0	0	0	
	Not done	4	0		
Histological type	Viable cell	*	1		
	Teratoma	*	2		
	Necrosis	*	3		
Adjuvant chemotherapy	+	*	1		
	-	*	5		

mediastinal NSGCT, resection of the residual tumors after inductive chemotherapy has shown a 30% to 60% long term survival rate [9]. As the prognostic factors for the residual tumor resection, no remaining viable cell, complete resection, and the normalized pre-operative tumor markers are listed [10]. In general, surgery to the residual tumor without normalization of tumor markers (desperation surgery) is often leaded to poor outcome. However, even by the desperation surgery, complete resection could prolong survival [3]. In our cases, as shown in Table 4, 5, the desperation surgery in the mediastinal NSGCT potentially contributes to the better outcome. Among 10 cases who did not obtain the normalization of tumor markers after chemotherapy, complete resection of residual tumors achieved in 6 cases and all the 6 cases survived long term. In these 10 cases, the cases of complete resection of residual tumors were significantly better prognosis compared to cases without surgery (p=0.001) and AFP positive cases were tended to be better prognosis compared to HCG positive cases (p=0.119), (Table 6). Although there must be a bias that the cases without surgery were far progressed diseases, performing desperation surgery was suggested to have clinical significance in cases that were judged to resect completely. The reason for the better outcomes of our mediastinal NSGCT compared to other authors were presumably depends on the skills of surgeon who actively perform the residual tumor resection with highly specific techniques to achieve the complete resection. On the other hand, in 4 cases with non-normalization of tumor markers and did not receive resection of the residual tumors, 2 cases died from progressive disease, and 2 cases died from adverse events of chemotherapy (one septic shock, and one interstitial pneumonia). Improvement of the treatment for these cases is considered to be the future task.

Conclusion

We investigated EGGCT cases treated at our hospital. In addition to no pulmonary metastasis at the first presentation and normalization of tumor markers after inductive chemotherapy, resection of the residual tumors irrespective of presence or absence of normalization of tumor markers, tended to be the prognostic factor. Our cases with mediastinal NSGCT who received chemotherapy showed a lower normalization rate of tumor markers compared to other authors. However, the recurrence-free survival rate was better than the others, possibly due to complete surgical resection of the residual tumor. The desperation surgery, especially in the AFP positive cases, showed better outcome, suggesting this surgery as an effective treatment strategy in EGGCT.

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