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Yolk Sac Tumor of the Ovary: A Retrospective Multicenter Study of 33 Japanese Women by Tohoku Gynecologic Cancer Unit (TGCU)

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Yolk sac tumor (YST) of the ovary is a rare germ cell tumor comprising about 1% of all ovarian malignancies. YST usually occurs as a rapidly growing unilateral tumor in young women. With the introduction of cisplatin, YST has been changed from a fatal tumor to a curable tumor. The standard treatment of YST consists of fertility-preserving surgery and 3 or 4 courses of adjuvant combination chemotherapy with bleomycin, etoposide, and cisplatin (BEP). However, the long-term prognosis of BEP-treated YST patients has not been well studied. We therefore conducted a retrospective multicenter study to investigate the prognostic factors of 33 YST patients, including 25 patients treated with BEP. The median age at initial treatment was 20 years (range 10-53). There were 15 patients (at stage I), one (stage II), 16 (stage III), and one (stage IV). Nominal and grouped numerical values were analyzed by the Kaplan-Meier method. All patients had unilateral tumor, with right-side predominance (23 patients; $P = 0.02$). Eighteen patients had pure YST, 13 had mixed germ cell tumor with YST component, and other 2 patients were not specified. Twenty-eight patients received fertility-preserving surgery. Twenty-seven patients had optimal surgery with less than 1 cm residual tumor diameter. Median number of chemotherapy courses was 5. Median follow-up period was 49 months. The cumulative 5-year survival rate was 87%. Univariate analysis revealed the following significant prognostic factors ($P < 0.05$): stage, tumor diameter, and residual tumor. Extensive debulking surgery to minimize residual tumor would improve the prognosis.

Keywords: bleomycin; cisplatin; etoposide; retrospective study; yolk sac tumor
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Introduction

Yolk sac tumor (YST) of the ovary, also called endodermal sinus tumor, is a subgroup of malignant ovarian germ cell tumors (MOGCT). YST is a rare malignant tumor comprising about 1% of all malignant ovarian tumors (Dällenbach et al. 2006). In Japan, between 2003 and 2010, among 35,572 malignant ovarian tumors registered, there were 464 patients (1.3%) with YST and mixed germ cell tumors with a YST component (Annual Report of Japan Society of Gynecology and Obstetrics Tumor Registry 2003-2010).

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YST occurs most often in young adults or adolescents whose fertility preservation is of great concern. It mainly presents as abdominal pain and/or a rapidly enlarged abdominal tumor, and sometimes as acute abdomen by torsion of ovarian tumor (Dällenbach et al. 2006). Almost all cases of YST are unilateral in origin (Gershenson 1994). Platinum-containing chemotherapy changed the outcome for YST patients from fatal to potentially curable. Among all subtypes of MOGCT, YST is highly malignant and has a poor prognosis (Mitchell et al. 1999). Today, the standard treatment of MOGCTs is fertility-preserving surgery and three to four cycles of combination chemotherapy with bleomycin, etoposide, and cisplatin (BEP) (Gershenson 1994). Dällenbach et al. (2006) reviewed articles on YST of the ovary up to December 2005, and this remains the most important article on YST.

Prognosis and prognostic factors of BEP-treated YST were analyzed in two studies including 84 and 32 cases. The five-year survival rates of BEP-treated YST patients were 75-100% at Stage I and 63-75% at Stages II-IV (Cicin et al. 2009; de La Motte Rouge et al. 2011). There has been another study including 20 YST patients treated with high-dose BEP; after follow up for a median of 70 months, the overall survival rate was 90% (Kang et al. 2008). These are the only three reports describing more than 10 cases of YST treated with a BEP regimen.

In Japan, there have been three studies of YST that included 29, 41, and 47 patients, respectively (Kawai et al. 1991; Fujita et al. 1993; Nawa et al. 2001), in which non-BEP regimen as adjuvant chemotherapy was given. In addition, Umezu et al. (2008) analyzed 36 patients with YST, among whom10 patients (28%) were treated with BEP. There are no publications with a large series of BEP-treated YST patients in Japan. This is the largest study in Japan that includes 25 YST patients (76% of a total of 33 patients) treated with BEP therapy (24 patients as adjuvant and 1 for recurrence).

The aim of this study is to analyze the survival rate and prognostic factors of YST patients, most of whom were treated with BEP.

Patients and Methods

This is a retrospective multicenter analysis of YST patients who were treated by gynecologic oncologists from the Tohoku Gynecologic Cancer Unit (TGCU). The TGCU consists of 7 tertiary center hospitals in the Tohoku region of Japan.

In this study, we included those patients whose pathological diagnosis was YST (pure type) or YST with another histologic type of germ cell tumor (mixed type). The patients of at least past 10 years were searched for. Pathologists in each TGCU-related hospital had made histopathologic diagnoses, according to the WHO classification (Tavassoli and Devilee 2003).

Clinical and follow-up data were retrieved anonymously from each TGCU-related hospital. The retrieved data were as follows: age at initial treatment, chief complaint, days from onset to first visit, pre-treatment imaging findings, pre-treatment tumor marker levels, days from first visit to initial operation, operatory method, maximal tumor diameter, weight of tumor, histopathologic diagnosis, stage (FIGO, pTNM), volume of ascites, maximal diameter of residual tumor, adjuvant chemotherapy (total course, regimen), days from operation to the first course of chemotherapy, diagnostic modality and site of recurrence (if any), progression-free interval, follow-up period, patient status at the last visit, post-treatment menstrual state, and live birth after the treatment.

Owing to the fact that this is a retrospective analysis, there are some imprecise descriptions of the volume of ascites and residual tumor volume. For the statistical analysis, we coded a "small amount" of ascites as 50 mL, a "large amount" of ascites as 2,000 mL, and a "massive" residual tumor diameter as 10 cm.

Data were processed in Microsoft Excel, and statistical analyses were carried out using the free software R (R Development Core Team (2011); R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria, ISBN 3-900051-07-0, http://www.R-project.org/).

To assess tumor laterality, we performed Fisher's exact test. To analyze the candidate prognostic factors, survival curves were derived using the Kaplan-Meier method and were compared using the log-rank test. Nominal values were assessed by category, and numerical values were divided into two groups by the median. To assess the relationship between two ordinal (or one numerical and one ordinal) variables, such as between stage and tumor diameter, we employed scatter plots and Spearman's rank correlation test. The candidate prognostic factors for multivariate analysis were picked up if the *P*-value was less than 0.10. *P*-values less than 0.05 are considered as significant.

Results

There were 33 patients with YST who were treated in TGCU-related hospitals. The median age at initial treatment was 20 years old (Table 1), and 25 patients (76%) were younger than 25 years (data not shown). Twenty-nine patients (88%) had abdominal/flank pain, abdominal distension, or both, and one patient had lumbago. One patient visited hospital because of dyspnea and increased body weight. Two patients had no symptoms and were diagnosed incidentally.

The median levels of tumor markers were as follows: AFP, 10,000 ng/mL (range 58-320,000 ng/mL); CA125, 160 U/mL (30-850 U/mL); and LDH 610 IU/L (170-4,900 IU/L). There were 15 patients at stage I, one patient at stage II, 16 patients at stage III, and one patient at stage IV (Table 1).

All 33 patients were diagnosed with YST; 18 patients had the pure type, 13 patients had the mixed type, and the type in the remaining 2 patients was not specified. Among

Table 1. Patient Characteristics.

Age at initial treatment (Year)	20	[10-53]	$P = 0.895$	
Serum Tumor Marker				
AFP (ng/mL)	10,000	[51-320,000]	$P = 0.903$	NA2(0)
CA125 (U/mL)	160	[30-850]	$P = 0.868$	NA3(0)
LDH (IU/L)	610	[170-4,900]	$P = 0.555$	NA4(1)
Stage			$P = 0.046$	
I	15			
II	1			
III	16			DOD3
IV	1			DOD1
Histology			$P = 0.494$	
Pure	18			DOD3
Mixed	13			DOD1
Dysgerminoma		3		
Dysgerminoma + Immature Teratoma		2		
Immature Teratoma		4		
Mature Teratoma		4		
Not Assessed	2			
Tumor Laterality			$P = 0.018$	
Right	23			
Left	10			
Tumor Diameter (cm)	18	[5-30]	$P = 0.015$	NA2(0)
Tumor Weight (g)	1,200	[330-5,200]	$P = 0.285$	NA15(3)
Ascites at Operation (mL)	250	[0-3,400]	$P = 0.338$	NA9(3)

NA, not available; DOD, died of disease.
NA4(1) means, among 4 cases with missing values, 1 cases DOD.
P values are the result of univariate analysis for survival.

the 13 patients with mixed type, there were 3 patients with dysgerminoma, 2 with dysgerminoma and immature teratoma, 4 with immature teratoma, and 4 with mature teratoma. All 33 patients had a unilateral tumor, with significant preponderance on the right side (right 23 vs. left 10; Fisher's exact test $P = 0.018$). The median tumor diameter of the 33 patients was 18 cm. Among the 18 patients for whom data on tumor weights were available, the median was 1,200 g. The median of the ascites volume was 250 mL in 25 patients, for whom data were available (Table 1).

The median time from the onset of complaints to their hospital visit was 24 days (data of 31 patients). The median time from their first hospital visit to operation was 15 days (range 1-80 days). The median time from operation to chemotherapy was 17 days (range 1-45 days). Fertility-preserving operations were performed in 28 patients (85%), two of whom had contralateral ovarian biopsy. Radical operation was performed in 5 patients. Omentectomy and appendectomy were performed in 13 patients (39%) and 7 (21%), respectively. Lymph node dissection/biopsy was performed in 10 patients (30%). Twenty-two patients (67%) were completely debulked (no residual tumor), 5 were optimally debulked (residual tumor diameter < 1 cm), and 6 were suboptimally debulked (residual tumor diameter ≥ 1 cm). Among 32 patients who received adjuvant chemotherapy, 24 patients (73%) received BEP-related therapy. The other 8 patients received non-BEP therapy. The median number of courses of chemotherapy was 5 (Table 2). There was a patient who did not receive adjuvant chemotherapy, but received BEP treatment for the recurrent lesion 8 months after the first operation (Table 2, remarks).

The median follow-up period was 49 months (range 1-151 months). Twenty-eight patients (85%) were followed up for longer than 2 years. Kaplan-Meier curve revealed that the cumulative 5-year survival rate was 87% and the progression-free survival rate was 84% (data not shown).

The patients at stage I or II disease had better cumulative 5-year survival than those at stage III or IV (100% vs. 72%; $P = 0.046$) (Fig. 1). Residual tumor diameter ($P < 0.001$) (Fig. 2) and tumor diameter at operation ($P = 0.015$) (data not shown) also affected survival.

There were 3 patients with recurrence and 2 with progressive disease after the first treatment. Among them, four patients died of disease. One patient with residual tumor of

Table 2. Patient Data of Treatment.

Duration [Days]				
Onset – First Visit	24	[1-420]	$P = 0.315$	
First Visit – Operation	15	[1-80]	$P = 0.447$	
Operation – Adjuvant Chemoth	17	[1-45]	$P = 0.806$	NA1
Operation				
Mode of Operation			$P = 0.363$	
Fertility-preserving	28			
Radical	5			
Omentectomy	13		$P = 0.526$	
Appendectomy	7		$P = 0.884$	
Lymph Node			$P = 0.858$	
Dissection				
Paraaortic	2			
Pelvic	1			
Paraaortic + Pelvic	5			
Biopsy				
Paraaortic	1			
Pelvic	1			
Not Performed	23			
Residual Tumor			$P < 0.001$	
No macroscopic lesion	22			
< 1 cm	5			
>=1 cm	6			
Adjuvant Chemotherapy				
Regimen			$P = 0.949$	
BEP*	24			DOD3
non-BEP	8			DOD1
Total Course	5	[0-10]	$P = 0.599$	

NA, not available; DOD, died of disease.

*A patient who did not received adjuvant chemotherapy, and received BEP treatment for the recurrent legion 8 months after first operation is not included.

P values are the result of univariate analysis for survival.

more than 2 cm in diameter remitted completely after 6 courses of postoperative BEP therapy, but intraperitoneal recurrence occurred at 21 months and, despite one course of BEP followed by tumor excision, she died of the disease at 30 months from the first treatment. Three patients had persistent intraperitoneal tumor after postoperative chemotherapy, and died of the disease at 1, 5, and 13 months; among them, the patient who died at 13 months also had liver, paraaortic, and mediastinal lesions. On the other hand, one patient who survived without adjuvant chemotherapy had a recurrence in the pelvis 8 months after unilateral salphingo-oophorectomy, and was treated with 2 courses of BEP followed by tumor excision and 3 courses of BEP. After recurrence treatment, she had no evidence of disease for 60 months.

Among the 28 patients who underwent fertility-preserving operation, data about the postoperative menstrual status were available for 24 patients. Of these 24 patients, 18 had a regular period and two had an irregular period, but in the other four patients, the menstrual cycle was not restored. Thus, 20 out of 24 patients (83%) were potentially fertile. There were a total of five live births in three patients.

Discussion

This is the largest study of BEP-treated YST in Japan to date; it includes 24 out of 33 patients (73%) who were treated with a BEP regimen as adjuvant chemotherapy. Previous analyses from Japan were mostly from the pre-BEP era (Kawai et al. 1991; Fujita et al. 1993; Nawa et al. 2001), and one study reported on 10 BEP-treated patients (Umezu et al. 2008).

To date, the largest study of YST published in English is a retrospective analysis of 84 prospectively registered YST patients, among whom 52 patients (62%) received BEP as adjuvant chemotherapy (de La Motte Rouge et al.

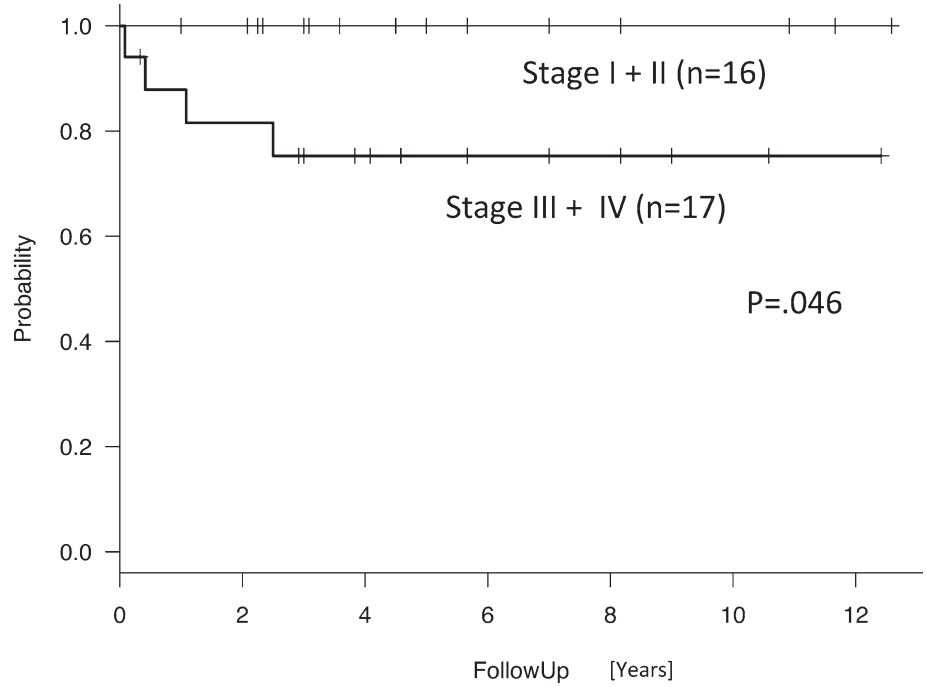

Fig. 1. Kaplan-Meier curves of overall survival by stage.
There is a significant difference in survival between the patients at stage I or II and those at stage III or IV (log-rank test: $P = 0.046$).

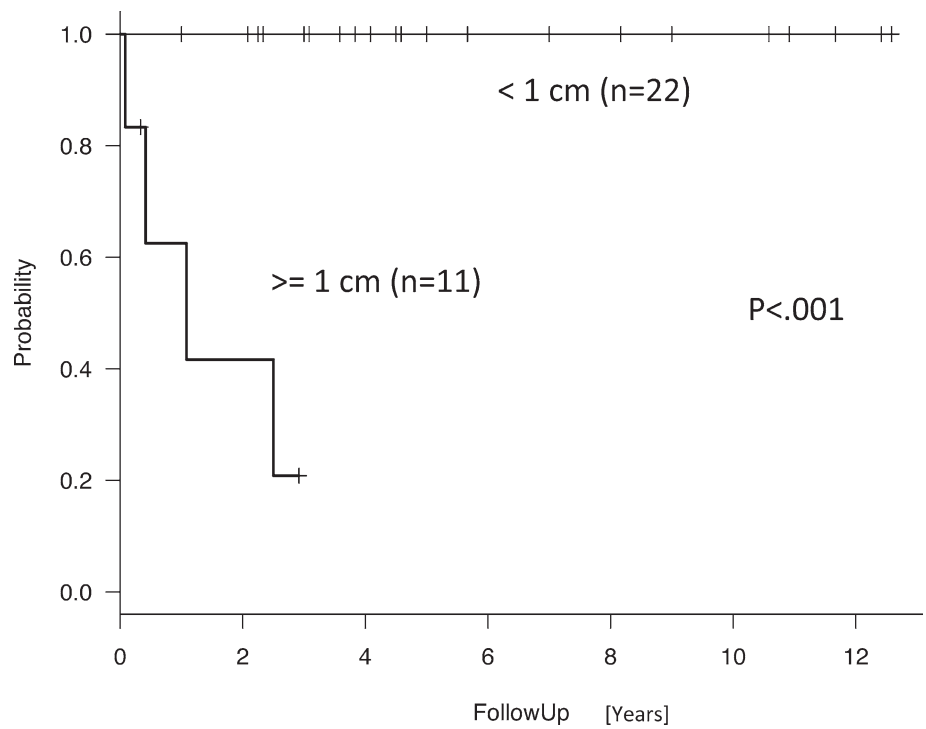

Fig. 2. Kaplan-Meier curves of overall survival by residual tumor diameter.
There is a significant difference in survival between the patients with residual tumor diameter < 1 cm and those with ≥ 1 cm (log-rank test: $P < 0.001$).

2011). Besides the present study, there have been two other retrospective studies with more than 20 BEP-treated YST patients: one study included 27 BEP-treated patients out of 32 YST patients (Cicin et al. 2009) and the other included 20 cumulative high-dose BEP-treated YST patients (Kang et al. 2008). Dällenbach et al. (2006) reviewed the litera-

ture about YST published up to December 2005; most cases received treatment other than BEP, such as PVB (cisplatin, vinblastine, bleomycin) or VAC (vincristine, actinomycin-D, cyclophosphamide). The reported 5-year survival rate of YST at stage I or II is 66-95%, while that at stage III or IV is 20-73%. Even in the BEP-treated group, the 5-year survival of patients at stage III or IV is about 70%. The prognosis of YST is worse than in other common types of MOGCT, such as dysgerminoma (5-year survival 80-90%) and grade 3 immature teratoma (5-year survival 90-100%) (Lee et al. 2011; Anita and Rushdan 2012). In our study, the cumulative 5-year survival rate of our patients at stage I or II was 100%, and that at stage III or IV was 72%. For those at stage I to III, the cumulative 5-year survival rate was 91% (29/32), which is comparable to that of patients treated with cumulative high-dose BEP therapy (Kang et al. 2008). The present study is the largest in Japan that includes as many as 25 YST patients treated with BEP chemotherapy. Our data suggest that the effectiveness of BEP chemotherapy to the Japanese young patient is compatible to that to the Caucasian patients.

To date, the reported prognostic factors of YST are as follows: stage (Kawai et al. 1991; de La Motte Rouge et al. 2011), residual tumor (Kawai et al. 1991; Nawa et al. 2001; Umezu et al. 2008; Cicin et al. 2009), ascites (Kawai et al. 1991; Nawa et al. 2001; Umezu et al. 2008; de La Motte Rouge et al. 2011), cisplatin-containing chemotherapy in advanced cases (Kawai et al. 1991), BEP therapy (Cicin et al. 2009; de La Motte Rouge et al. 2011), AFP half-life (de La Motte Rouge et al. 2011), and time to serum AFP normalization (de La Motte Rouge et al. 2011). In our data, univariate analysis revealed that the candidate prognostic factors were stage ($P = 0.046$), tumor diameter ($P = 0.015$), and residual tumor diameter ($P < 0.001$). Volume of ascites was not a candidate prognostic factor, possibly because the number of events (number of patients who died) was insufficient to detect significance; the data of ascites volume were not available from 3 out of 4 patients who died of the disease. Tumor diameter was a candidate prognostic factor, whereas tumor weight, which is roughly proportional to the third power of diameter, was not a significant prognostic factor. The reason for this may be due to the unavailable data of the 3 patients. We also screened tumor markers, excised tissue, and duration of treatment as surrogate prognostic factors, but found that they were not significant prognostic factors. Because there were only four events out of 33 cases, multivariate analysis is inappropriate.

Cisplatin-containing chemotherapy is one of the prognostic factors (Kawai et al. 1991; Nawa et al. 2001). Among cisplatin-including regimens, BEP is more effective than others (Cicin et al. 2009). Cicin et al. (2009) reported worse 5-year survival at an earlier stage (66%) than others and they described that all patients who were treated with non-BEP chemotherapy had recurrence. We could not prove the superiority of BEP over a pre-BEP regimen in terms of the survival of YST patients, because of the small sample size and the small number of events.

Currently, three courses of BEP are the standard therapy and four courses are recommended in cases of bulky residual disease after surgery (Dällenbach et al. 2006), but the median number of courses of chemotherapy in our cases was 5. The 5-year cumulative survival rates were 100% in stage I-II patients and 72% in stage III-IV patients, slightly better than those reported elsewhere (Cicin et al. 2009). Again, the number of chemotherapy courses was not a significant prognostic factor in our patients.

Among 28 patients who underwent fertility-preserving surgery, information on the menstrual state was available in 24 patients, and 20 out of 24 patients (83%) were potentially fertile. The rate of resumption of the menstrual cycle was previously reported to be 70-100% (Kang et al. 2008; Cicin et al. 2009; de La Motte Rouge et al. 2011); thus, our data are similar to those of the earlier studies. There were 5 live births in 3 patients (3/28; 11%) in our study. Because most of our patients were relatively young for childbearing, this is not a peculiar finding. Cicin et al. (2009) also described that all of their patients who were known to have resumed their menstrual cycle did not attempt to conceive.

The limitations of our study are that a central pathological review was not performed, and that about 40% of patients were of mixed YST type. Although our study involved the third largest number of BEP-treated patients, the number of events was only 4; this is too few to detect independent prognostic factors.

Univariate analysis revealed that the candidate prognostic factors are stage, residual tumor, and tumor diameter. YST patients have a relatively good prognosis in the modern BEP era and its alterable risk factor is residual tumor volume. In order to improve the survival of YST patients, surgical skill for maximal debulking is needed. Large-scale analysis focusing on the optimal number of cycles of chemotherapy and the rational treatment for recurrence, perhaps by multicenter study or by meta-analysis, is also needed.

Conclusion

This is the largest study in Japan that includes as many as 25 YST patients treated with BEP. Our data show that the prognostic factors of YST are stage, tumor diameter, and residual tumor. Extensive debulking surgery to minimize residual tumor would improve the prognosis.

Conflict of Interest

The authors declare no conflict of interest.

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