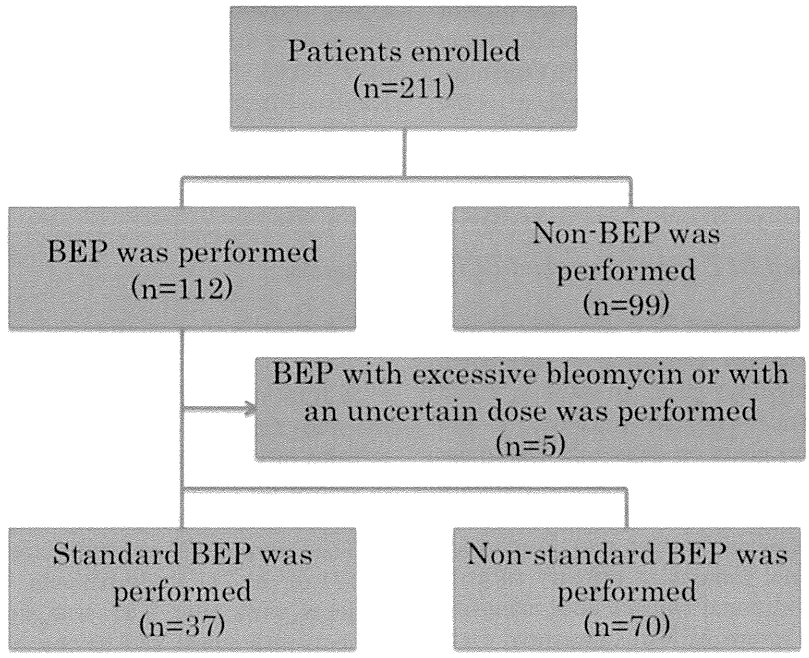

Fig. 1. CONSORT diagram.

eight (25%) relapsed patients in non-standard BEP group had long-term progression-free survival after receiving salvage therapy and the remaining 31 patients died of disease within 44 months.

As for the two rescued patients in the non-BEP group, one patient with stage Ic who had three courses of platinum-based non-BEP after surgery progressed the disease and the patient received six courses of PVB and had complete remission. Another patient with stage 1c who received five courses of platinum-based non-BEP after surgery, recurrent tumour developed in the contralateral ovary 128 months after surgery. She underwent the tumour resection from the ovary, fertility-sparing surgery, followed by three courses of VAC.

As for the two rescued patients in the non-standard BEP group, one patient with stage IIIa who received three courses after surgery had recurrent tumour in the pelvis 17 months after surgery. She received three courses of non-standard BEP after the recurrent tumour was removed surgically. Another patient with stage IIIc who received five courses after surgery had recurrent tumour in a paraaortic lymph node 42 months after surgery. The tumour was completely removed by surgery. She did not receive postoperative chemotherapy because the pathological diagnosis of the removed tumour was mature cystic teratoma with a very small part of YST.

These four patients were alive without disease 85, 68, 60 and 52 months after salvage therapy, respectively.

3.2.1. Analysis of prognostic factors

Table 3 shows the results of univariate and multivariate analyses for OS. In the univariate analysis, five variables—age $\geqslant$ 22 years, FIGO stage III/IV, AFP $\geqslant$ 33,000 ng/ml, residual tumour at primary surgery, and chemotherapy regimens other than BEP were significantly associated with poor OS. Subsequently, we performed multivariate analysis using the above significant five variables in the univariate analysis. In the multivariate analysis, age $\geqslant$ 22, AFP $\geqslant$ 33,000 ng/ml, residual tumour at primary surgery, and regimens other than BEP were independently and significantly associated with poor OS of patients with YST.

3.2.2. BEP and non-BEP

There were 112 patients who received BEP and 99 patients who received non-BEP. Non-BEP chemotherapy regimens were PVB ($n = 33$), peplomycin + etoposide + cisplatin ($n = 20$), paclitaxel + carboplatin ($n = 8$), vinblastine + actinomycin D + bleomycin ($n = 7$), VAC ($n = 4$), peplomycin + vinblastine + cisplatin ($n = 4$), etoposide + cisplatin ($n = 4$), other regimens with platinum ($n = 16$) and other regimens without platinum ($n = 3$). Of 99 patients who received non-BEP, 72 patients who gave substantial information received additional 0–7 cycles (median: 2) of chemotherapy after AFP normalisation. As shown in Table 3, BEP was significantly superior to non-BEP with respect to 5-year OS (93.6% versus 74.6%, $P = 0.0004$). In 71 patients with stage III/IV, 5-year OS was 94.0% with BEP ($n = 35$), 66.7% with PVB ($n = 9$), 50.0% with PEP ($n = 6$) and 43.5% in other regimens ($n = 21$) (Fig. 2A). The 5-year OS of 56 patients with residual tumour at primary surgery was 91.8% with BEP ($n = 25$), 50% with PVB ($n = 8$), 40.0% with PEP ($n = 5$) and 33.3% with the other regimens ($n = 18$) (Fig. 2B). In

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Table 1
Patient characteristics ($n = 211$).

Median age (range)	23 (11 months-68 years)
FIGO stage	
I	123 (58.3%)
II	17 (8.1%)
III	60 (28.4%)
IV	11 (5.2%)
Ascites	
Present	163 (77.3%)
⩾500 ml	50 (23.7%)
<500 ml	89 (42.2%)
Unknown	24 (11.4%)
Absent	44 (20.9%)
Unknown	4 (1.9%)
Histological features	
Pure YST	144 (68.2%)
Mixed YST	67 (31.8%)
Proportion of YST in mixed YST	
YST component ⩾50%	21 (31.3%)
YST component <50%, ⩾5%	29 (43.3%)
YST component <5%	5 (7.5%)
Unknown	12 (17.9%)
Median AFP level before treatment	
Pure YST ($n = 117$)	22,829 (403–540,000)
Mixed YST	
YST component ⩾50% ($n = 18$)	22,318 (1,399–146,665)
YST component <50%, ⩾5% ($n = 25$)	7,350 (136–80,300)
YST component <5% ($n = 5$)	228 (36–1,488)
YST component: unknown ($n = 9$)	5,145 (308–55,700)
Postoperative chemotherapy regimen in primary treatment	
BEP (Bleomycin + Etoposide + Cisplatin)	112 (53.1%)
PVB (Cisplatin + Vinblastine + Bleomycin)	33 (15.6%)
PEP (Peplomycin + Etoposide + Cisplatin)	20 (9.5%)
TC (Paclitaxel + Carboplatin)	8 (3.8%)
VAB (Vinblastine + Actinomycin D + Bleomycin)	7 (3.3%)
PVP (Peplomycin + Vinblastine + Cisplatin)	4 (1.9%)
VAC (Vinblastine + Actinomycin D + Cyclophosphamide)	4 (1.9%)
EP (Etoposide + Cisplatin)	4 (1.9%)
Other	19 (9.0%)
Fertility-sparing therapy at initial treatment (n = 196)	
Yes	157 (80.1%)
No	39 (19.9%)

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; YST, yolk sac tumor; NAC, neoadjuvant chemotherapy followed by surgery.

addition, BEP was significantly superior to platinum-based non-BEP in 5-year OS (93.6% versus 75.9%, $P = 0.0009$, Table 3).

3.2.3. Standard BEP and non-standard BEP

In this comparison, we excluded five patients as described earlier. Of the remaining 107 patients who received BEP, six patients died of YST at 5–44 months after primary surgery, and one patient died of breast cancer (the same patient described in 'Clinical Outcomes'). The median duration of follow-up after excluding the seven patients who died was 80.5 (4–178) months from the day of primary surgery. Median number of cycles is four (3–6) for standard BEP and four (1–6) for non-standard BEP.

Median (range) total doses of bleomycin, etoposide and cisplatin at the first course of non-standard BEP group were 35 (3–60) mg/course or 21 (15–60) mg/m^2/course, 500 (80–775) mg/m^2/course and 80 (15–150) mg/m^2/course, respectively, and median (range) cycles of non-standard BEP is 4 (1–6).

Table 4 shows a comparison of the 5-year OS between the standard BEP group and the non-standard BEP group; 100% of the standard BEP group survived to 5 years, and 91.0% of the non-standard BEP group survived to 5 years ($P = 0.049$) (Fig. 3A). Considering the dose of each drug, <75% of the standard dose of bleomycin and <50% of the dose of etoposide were significantly associated with poor 5-year OS (100% versus 89.4%, $P = 0.02$, and 96.9% versus 62.5%, $P = 0.0002$) (Fig. 3B, C). Regarding the administration schedule of BEP, the non-standard administration schedule of bleomycin was associated with poor 5-year OS (97.2% versus 88.0%, $P = 0.02$) and the non-standard administration

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Table 2
Proportion of patient characteristics in each regimen.

Patient characteristics	BEP group ($n = 112$)	Non-BEP group ($n = 99$)	P-Value	Standaard BEP group ($n = 37$)	Non-standard BEP group ($n = 70$)	P-Value
Median age (range)	23 (1 months - 57 years)	22 (7 years - 68 years)	0.73	22 (12 years - 39 years)	23 (11 months - 57 years)	0.73
FIGO stage			0.55			0.49
IA	28	17 (58.3%)		10	17	
IC	41	35		16	22	
I unknown substage	0	2		0	0	
II	8	9 (8.1%)		2	6	
III	31	29 (28.4%)		7	23	
IV	4	7 (5.2%)		2	2	
Histological features			0.64			0.72
Pure YST	78	66		24	41	
Mixed YST	34	33		13	19	
Median AFP (range, [n]), ng/ml	18,273 (36.3–367,464, [98])	21,490 (101–540,000, [76])	0.76	19,549 (198.8–344,880, [32])	18,048 (36.3–367,464, [63])	0.74

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; YST, yolk sac tumor; BEP, Combination chemotherapy with Bleomycin, Etoposide and Cisplatin.

schedule of etoposide tended to be associated with poor 5-year OS (96.3% versus 87.5%, $P = 0.054$).

All patients who received standard BEP became normalised in AFP levels, whereas two of 70 (2.9%) patients who received non-standard BEP failed to be normalised in AFP levels because of residual tumour.

Three patients suffered from pulmonary fibrosis caused by bleomycin. Two of the three patients were diagnosed at 3 or 4 months after the last cycle of BEP, and the other patient developed pulmonary fibrosis after the first cycle of BEP. In all three patients, the pulmonary fibrosis was successfully treated by steroid hormone therapy after the completion of chemotherapy. The patient who developed the pulmonary fibrosis after the first cycle was treated by chemotherapy only with etoposide and cisplatin without bleomycin. All three patients had no evidence of recurrence.

As for the five patients excluded from the present study, one of the two patients who received an excessive dose of bleomycin died of pulmonary fibrosis after the 4th cycle of BEP. The other patient developed pulmonary fibrosis, however she recovered, and is alive without disease. The other three of the five patients who received uncertain doses of drugs are alive without disease.

3.3. Reproductive outcomes of the patients with BEP and non-BEP

We excluded 38 patients from the 112 patients who received the BEP regimen and 64 patients from the 99 patients who received the non-BEP regimen for the following reasons: primary amenorrhea, age > 40 years at diagnosis, non-FSS, death during the study period and loss of information. Therefore, we assessed the reproductive safety and outcomes in 74 patients who received the BEP and 35 patients who received the non-BEP. As for the menstruation, 106 of 109 patients recovered almost the same cycles as before treatment within 6 months ($n = 85$, 78.0%), 7–12 months ($n = 19$, 17.4%) and over 12 months ($n = 2$, 1.8%) after treatment, two patients (1.8%) had menarche, and a patient (0.9%) who received irradiation for metastatic pelvic and para-aortic lymph nodes after chemotherapy did not recover menstruation.

Sixteen of 23 patients (70.0%) receiving BEP who were nulliparous at FSS and married at the end of the study period achieved 26 pregnancies and gave birth to 21 healthy children during follow-up. Thirteen of 17 patients (76.5%) receiving the non-BEP who were nulliparous at FSS and married at the end of the study period achieved 20 pregnancies; 12 gave birth to 19 healthy children during follow-up.

4. Discussion

In univariate and multivariate analyses, we revealed that age ⩾ 22, AFP ⩾ 33,000 ng/ml, residual tumours at primary surgery, and non-BEP were independently and significantly associated with poor OS of patients with YST.

Regarding malignant ovarian germ cell tumours, Chan [18] reported that older age (age > 40) predicted poorer survival. In the present study, we also confirmed that the elder age was one of prognostic factors. However, the cut-off level (age ⩾ 22) was younger compared with Chan's results. These results might be due to that this study was focused on YST histology alone.

The prognostic value of the high level of pretreatment AFP in patients with YST has not been well evaluated. In two studies [19,20] including non-YST germ cell tumours in most of the study patients, a high AFP level was a significantly poor prognostic factor, using 1000 ng/ml as the cut-off level. Three other studies reported that preoperative AFP levels had no significant

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Table 3
Univariate and multivariate analyses of prognostic factors for OS.

Variables	Univariate analysis			Multivariate analysis	
	Number of patients	5-year OS (%)	*P* value	Hazard ratio (95% CI)	*P* value
Age					
<22	91	93.4	0.001	Reference	
⩾22	120	77.8		3.02 (1.18–9.27)	0.02
FIGO stage					
I, II	140	92	<0.0001	Reference	
III, IV	71	70		1.12 (0.34–3.88)	0.85
Period at initial treatment					
1980–2000	109	83.3	0.61		
2001–2007	102	86.0			
Ascites					
Absent	44	88.2	0.39		
Present	163	83.2			
Serum AFP level before treatment (ng/ml)					
<33,000	118	93.1	0.004	Reference	
⩾33,000	56	76.4		3.58 (1.48–9.16)	0.005
Histology					
Pure YST	144	83.8	0.82		
Mixed YST	67	86.3			
Fertility-sparing surgery					
All stages					
Yes	157	90.2	0.41		
No	39	84.5			
Stage III/IV					
Yes	39	76.5	0.84		
No	23	78			
Residual tumor at primary surgery					
All stages					
Absent	150	92.5	<0.0001	Reference	
Present	56	62.4		3.93 (1.25–13.2)	0.02
Stage III/IV					
Absent	23	95.7	0.002		
Present	46	56.4			
Postoperative chemotherapeutic regimen in initial treatment (versus BEP)					
All stages			(versus BEP)		
BEP	112	93.6		Reference	
Non-BEP	99	74.6	0.0004	4.35 (1.71–13.3)	0.002
PVB	33	87.5	0.43		
PEP	20	85.0	0.29		
TC	8	62.5	0.003		
VAB	7	85.7	0.61		
Non-BEP with platinum	92	75.9	0.0009		
Non-BEP without platinum	7	57.1	0.003		
Stage III/IV					
BEP	35	94.0			
Non-BEP	36	47.2	<0.0001		
PVB	9	66.7	0.02		
PEP	6	50.0	0.0009		
TC	4	25.0	<0.0001		
VAB	4	75.0	0.17		
Presence of residual tumor at initial surgery					
BEP	25	91.8			
Non-BEP	31	38.7	<0.0001		
PVB	8	50.0	0.004		
PEP	5	40.0	0.002		

Abbreviations: PFS, progression-free survival; OS, overall survival; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; AFP, alpha-fetoprotein; YST, yolk sac tumor; BEP, combination chemotherapy with bleomycin, etoposide and cisplatin; PVB, combination chemotherapy with cisplatin, vinblastine and bleomycin; PEP, combination chemotherapy with peplomycin, etoposide and cisplatin; TC, combination chemotherapy with paclitaxel and carboplatin; VAB, combination chemotherapy with vinblastine, actinomycin D, cisplatin, bleomycin and cyclophosphamide.

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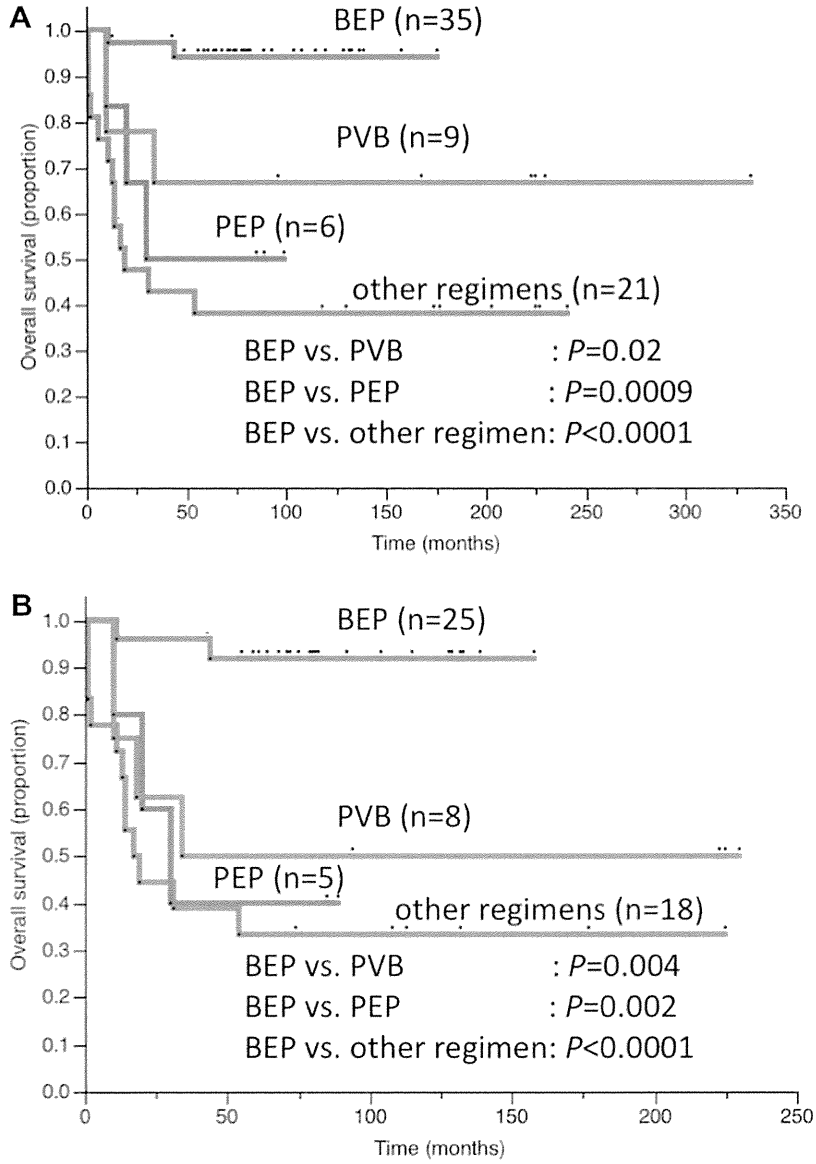

Fig. 2. (A) Overall survival curve for patients with stage III-IV disease who received BEP and non-BEP. The 5-year OS was 94.0% with BEP ($n = 35$), 66.7% with PVB ($n = 9$), 50.0% with PEP ($n = 6$) and 43.5% with other regimens ($n = 21$) ($P < 0.0001$). (B) Overall survival curve for patients with residual tumor at initial surgery who received BEP or non-BEP. The 5-year OS of 56 patients with residual tumor at primary surgery was 91.8% with BEP ($n = 25$), 50% with PVB ($n = 8$), 40.0% with PEP ($n = 5$) and 33.3% with other regimens ($n = 18$) ($P < 0.0001$). *Abbreviations:* BEP, bleomycin + etoposide + cisplatin; OS, overall survival; PVB, cisplatin + vinblastine + bleomycin; PEP, peplomycin + etoposide + cisplatin.

correlation with prognosis [7,21,22]. The recent study which reviewed 84 patients with YST revealed that 5-year OS was 93% in 32 patients with AFP < 1000 ng/ml and 79% in 41 patients with AFP > 1000 ng/ml, although the difference was not significant [21]. Our data suggest that higher pretreatment AFP level may be a poor prognostic factor in YST when 33,000 ng/ml is used as the cut-off level (Table 3).

Most reports regarding prognostic factors in patients with YST have concluded that residual tumour at primary surgery is a poor prognostic factor [7,21–23]. These data suggest that complete surgery without residual tumours is important in YST, although there is no solid evidence that debulking surgery with maximum effort is necessary in YST.

All patients who had a relapse after initial treatment received salvage therapy, but their prognosis was poor as a previous study [24] reported.

In the present study, BEP was significantly superior to non-BEP with respect to 5-year OS. The superiority of BEP compared with non-BEP was clearly confirmed in the following subset groups with poor prognosis: patients with stage III/IV and patients with residual tumour at primary surgery (Table 3). Some previous reports have suggested that BEP should be selected for patients with YST, because the OS was >90% in patients

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Table 4
Comparison of 5-year overall survival (OS) between standard BEP and non-standard (reduced-dose) BEP.

Variables	Number of patients	5-year OS (%)	*P* value
Standard BEP			
Yes	37	100	0.049
No	70	91.0	
Percentage of the standard dose administered at the first cycle			
Bleomycin			
100%	44	100.0	0.02
<100%	63	90.0	
⩾75%	48	100.0	0.02
<75%	59	89.4	
⩾50%	75	97.3	0.08
<50%	32	86.6	
Administration on a day/week, 3 times (standard schedule)			
Yes	71	97.2	0.02
No	36	88.0	
Etoposide			
100%	71	95.7	0.22
<100%	36	91.1	
⩾75%	85	96.4	0.15
<75%	22	84.7	
⩾50%	98	96.9	0.0002
<50%	9	62.5	
Administration on day 1–5 (standard schedule)			
Yes	81	96.3	0.054
No	26	87.5	
Cisplatin			
100%	70	95.6	0.21
<100%	37	91.5	
⩾75%	87	95.2	0.52
<75%	20	89.5	
⩾50%	105	94.1	0.73
<50%	2	100.0	
Administration on day 1–5 (standard schedule)			
Yes	73	95.8	0.22
No	34	91.0	

Abbreviations: OS, overall survival; BEP, combination chemotherapy with bleomycin, etoposide and cisplatin.

who were treated with BEP [9,10,23]. Cicin showed that the cumulative survival rate in 27 patients with BEP was 76%, whereas the rate in five patients treated with options other than the BEP regimen was 20% ($P = 0.016$) [23]. A report stated that the 5-year OS was 94% in 52 patients who received BEP, which was significantly better than 67% in 32 patients who received non-BEP ($P = 0.001$) [22]. These data confirm that BEP should be the standard chemotherapeutic regimen for postoperative chemotherapy in treating patients with YST, because BEP has the clear advantage for better prognosis of patients with YST.

In the present study, standard BEP was significantly superior to non-standard BEP with respect to 5-year OS (100% versus 91.0%, $P = 0.049$). Reduced doses (<75% dose of bleomycin and < 50% dose of etoposide) at the first cycle of BEP were significant factors for poor prognosis. A randomized clinical trial in male patients with germ cell tumours showed that four cycles of non-standard BEP (100 mg/m^2 of cisplatin on day 1, 120 mg/m^2 of etoposide on days 1–3 and 30 kU bleomycin on day 1, repeated every 21 days) (Regimen B) could be responsible for a poorer outcome compared with three cycles of standard BEP (20 mg/m^2 of cisplatin on days 1–5, 100 mg/m^2 of etoposide on days 1–5, and 30 kU bleomycin on days 1,8 and 15, repeated every 21 days) (Regimen A) [25]. Compared with Regimen A, Regimen B had a lower total dose and dose-intensity of bleomycin and a lower dose-intensity of etoposide. Furthermore, an updated analysis of this randomized trial showed that the survival benefit of three cycles of Regimen A over Regimen B was maintained during long-term follow-up [26]. These data suggest that standard-dose BEP should be administered to patients with ovarian YST.

As for the safety of BEP for ovarian function, no patients lost their menstrual cycles among 74 patients in the present study who received BEP and provided information on menstruation. Kang claimed that the cumulative high-dose BEP regimen did not seem to impair ovarian function [27]. We reported that six of 121 patients (5.0%) with epithelial ovarian cancer stage

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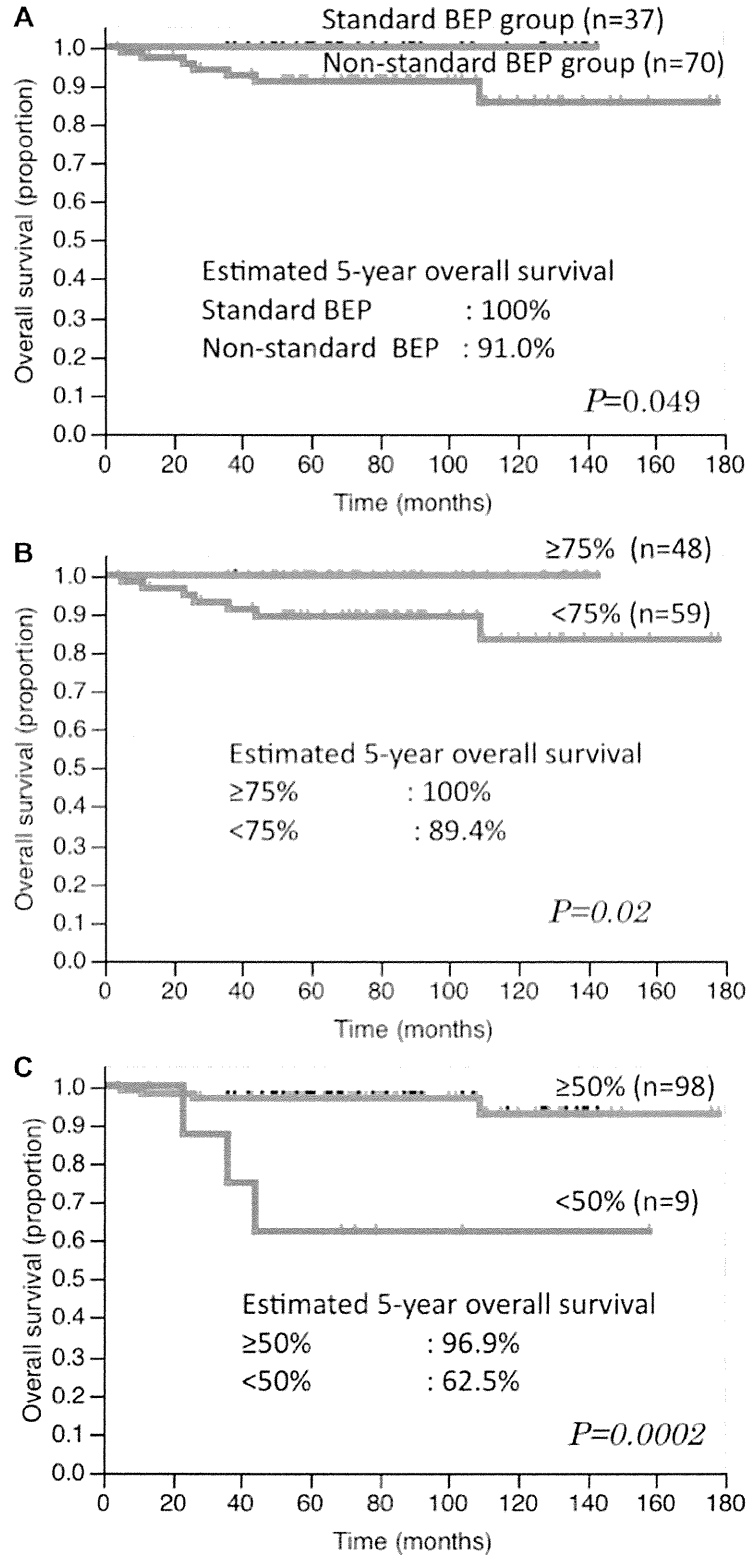

Fig. 3. (A) Overall survival curves in patients who received BEP. Standard BEP was significantly superior to non–standard BEP in 5-year OS (100% versus 91.0%, $P = 0.049$). (B) Overall survival curve for patients with BEP who received ⩾75% and <75% of the standard dose of bleomycin. A reduced dose (<75%) of the standard dose of bleomycin was significantly associated with poor 5-year OS (100% versus 89.4%, $P = 0.02$). (C) Overall survival curve for patients with BEP who received ⩾50% and <50% of the standard dose of etoposide. A reduced dose of <50% of the dose of etoposide was significantly associated with poor 5-year OS (96.9% versus 62.5%, $P = 0.0002$). *Abbreviations:* BEP, bleomycin + etoposide + cisplatin; OS, overall survival.

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I who received platinum-based adjuvant chemotherapy after FSS showed continued secondary amenorrhea [28]. BEP for YST may be safer for ovarian function compared with the platinum-based regimen for epithelial ovarian cancer. As for reproductive outcome, 16 of 23 patients (70.0%) who attempted conception gave birth to 21 healthy children within several years after treatment, keeping with de La Motte Rouge's report that pregnancy was achieved in 12 of 16 (75%) women after they underwent FSS and BEP therapy [29]. Most patients who receive BEP can preserve normal ovarian function and childbearing ability.

The study has several limitations. This study is a retrospective series where pathology was not centrally reviewed, assays to measure tumour markers were different, staging procedures may have differed between institutes so staging data may be variable in quality. Nevertheless, we believe that the present study may give some useful suggestions for clinical practice.

In conclusion, the data from the present study suggest that standard BEP should be used as postoperative chemotherapy for patients with ovarian YST. Theoretically, a randomized controlled trial may be needed to establish that standard BEP is superior to both non-BEP and non-standard BEP for treatment of patients with YST. However, such trials may not be ethically feasible. The ovarian toxicity of BEP was not serious, and the probability of childbearing after treatment was $\geqslant$70% in patients with YST who received BEP.

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The funding source had no role in the study concept and design, data acquisition, statistical analysis, data interpretation, manuscript preparation, editing or review.

Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

A survey of the practice patterns of gynecologic oncologists dealing with hereditary cancer patients in Japan

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Abstract Hereditary breast and ovarian cancer syndrome (HBOC) is a significant type of familial ovarian cancer. A survey of gynecologic oncologists was conducted in order to characterize the state of care and awareness of information provision for HBOC in Japan and to identify information necessary to enhance HBOC care. All gynecologic oncologists certified by the Japan Society of Gynecologic Oncology (JSGO) as specialists in the treatment of ovarian cancer were included. They were sent a 44-question questionnaire dealing with the background of the respondent, the facilities at the respondent's medical institution, how the family history interview is conducted, awareness of and practice behavior toward HBOC, performance of genetic testing, and performance of risk-reducing salpingo-oophorectomy (RRSO). The response rate was 50.1 %. About 60 % of respondents stated that "I administer care with HBOC in mind" and "I want to be involved in the care of HBOC." However, only 2 in 3 doctors was able to explain HBOC to patients, fewer than 1 in 5 doctors was able to give counseling to patients, 1 in 10 doctors provided printed information to patients suspected of having a hereditary cancer, and 1 in 7 doctors recommended that patients suspected of having a hereditary cancer visit the department of genetics. The provision of information to patients, recommending that patients visit the department of genetics, and the performance of genetic testing were dependent on whether a department of genetics was present in the respondent's institution. The survey also found that RRSO is not widely performed in Japan.

Keywords Hereditary breast and ovarian cancer syndrome · Gynecologic oncologists · Survey · Genetic testing

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Introduction

Hereditary breast and ovarian cancer syndrome (HBOC) is a significant type of familial ovarian cancer. The Clinical Practice Guidelines in Oncology of the National Comprehensive Cancer Network (NCCN) present HBOC testing criteria based on the disease and family histories of the patient and call for personalized risk assessment, genetic counseling, and management for HBOC when applicable [1]. Western countries offer comprehensive programs for hereditary cancer, which include genetic counseling and cancer genetic testing. Surveillance, chemoprevention, and risk-reducing surgery aimed at reducing cancer morbidity and mortality are implemented and have been shown to be beneficial [2]. Although no such comprehensive programs are widely available in Asian countries, a nationally operated, large-scale study called the Korean Hereditary Breast Cancer (KOHBRA) study was begun in 2007 [3],