Considering the likelihood of some ineligible patients among those enrolled, the total number of patients was set to 60.

Primary endpoint, RR, was tested by the exact binomial test and confidence interval of proportion was calculated by the exact method. According to the SWOG's two-stage design, preplanned interim analysis for futility was done after 30 patients enrolled, setting the threshold of the number of minimum responders as four. Then final analysis was conducted with one-sided alphas of 0.02 and 0.055, respectively. OS and PFS curves, median PFS and OS were estimated by Kaplan–Meier method, and confidence intervals for proportion were calculated with Greenwood's formula and median OS and PFS with Brookmeyer and Crowley's method. Exploratory analyses for RR were carried out by Fisher's exact test. All statistical analyses were conducted using SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

### *Interim monitoring*

In-house monitoring was to be performed every 6 months by the Japan Clinical Oncology Group (JCOG) Data Center to evaluate the study progress and to improve study quality.

### *Ethical considerations*

The Protocol Review Committee of JCOG approved the study protocol in January 2009, and the study was initiated in April 2009. The protocol was reviewed and approved at all the participating hospitals. Every patient signed a written informed consent form. This trial was registered at UMIN-CTR as UMIN000001837 (http://www.umin.ac.jp/ctr/).

## Results

### *Patient characteristics*

From April 1, 2009 to July 5, 2010, 30 patients were enrolled and patient accrual was suspended for interim analysis. After the planned interim analysis, the study was resumed on November 22, 2010, and a total of 61 patients were enrolled until January 20, 2012. One patient was ineligible and excluded from this analysis because the days from surgery to registration were shorter than the eligibility criteria. Patient characteristics are summarized in Table 1. There were 14/60 (23.3%) elderly patients, defined as ≥65 years. Eleven of 60 (18.3%) patients had clear cell carcinoma, who were mostly (10 of 11) enrolled in the study after the interim analysis. Among 39 patients with serous carcinoma, two of them (5%) were diagnosed as low grade serous carcinoma. Nine of 60 patients (15%) received ≥3 prior chemotherapy regimens. Twenty-seven of 60 patients (45%) had platinum-refractory disease that progressed during or within 3 months after previous chemotherapy with a platinum-based drug.

### *Treatment administration*

The median number of delivered treatment cycles was 4 (range, 1–6). Twenty-one patients completed 6 cycles of treatment. Thirty-nine patients did not complete treatment because of the following reasons: disease progression ($n = 29$), patient refusal ($n = 5$), adverse event ($n = 3$), intercurrent death ($n = 1$), and earthquake ($n = 1$).

Three treatment-related deaths (TRDs) were reported: interstitial lung disease (judged as a *probable* TRD by the Data and Safety Monitoring Committee), DIC due to infection (judged as a possible TRD), and a recurrent pulmonary embolism (judged as a possible TRD). The first 2 patients listed above were aged ≥65 years.

For etoposide, a median total dose, median dose intensity, and median relative dose intensity were 2852.3 mg/m$^2$, 179.3 mg/m$^2$/week, and 88.9%, respectively. For irinotecan, the median total dose, median dose intensity, and median relative dose intensity were 452.8 mg/m$^2$, 30.7 mg/m$^2$/week, and 88.0%, respectively.

**Table 1**
Patient characteristics.

| Characteristics | | Number of patients (%) | Median | Range |
|---|---|---|---|---|
| Age, years | | | 58 | 31–75 |
| | <65 | 46 (77) | | |
| | ≥65 | 14 (23) | | |
| PS | 0 | 51 (85) | | |
| | 1 | 8 (13) | | |
| | 2 | 1 (2) | | |
| Histology | Serous | 39 (65) | | |
| | (LGS) | 2 (5) | | |
| | Clear cell | 11 (18) | | |
| | Endometrioid | 5 (8) | | |
| | Other | 5 (8) | | |
| Lesion | Measurable | 52 (87) | | |
| | Non-measurable | 8 (13) | | |
| Prior chemo regimens | 1 | 34 (57) | | |
| | 2 | 17 (28) | | |
| | ≥3 | 9 (15) | | |
| PFI | <3 months | 27 (45) | | |
| | ≥3 months | 33 (55) | | |

*Abbreviations.* PS: performance status, PFI: platinum-free interval, chemo: chemotherapy, LGS: low grade serous.

### *Toxicity*

Toxicities are summarized in Table 2. Only treatment-related adverse events (definite, probable, or possible) were counted as toxicities. Grades 3–4 hematological toxicities were: neutropenia (60%), anemia (36.7%), and thrombocytopenia (11.7%). Grades 3–4 non-hematological toxicities were: febrile neutropenia (FN; 18.3%), fatigue (11.7%), anorexia (11.7%), and nausea (11.7%). FN was more frequent in patients aged ≥65 years (28.6%) or those with ≥3 prior chemotherapy regimens (44.4%) compared with patients aged <65 years (15.2%) or those with 1 or 2 prior chemotherapy regimens (13.7%). One patient was diagnosed with acute myeloid leukemia 234 days after completing 6 cycles of the present regimen. She received carboplatin plus paclitaxel for 6 cycles and PLD for 6 cycles before the study entry, and gemcitabine for 3 cycles after this regimen.

### *Efficacy*

One patient achieved CR and 12 patients achieved PR (Table 3); accordingly, RR was 21.7% (13/60) [design-based 89% confidence interval (CI) 13.5–31.9%; 95% CI 12.1–34.2%]. This RR did not exceed the preplanned threshold (one-sided $p = 0.42$ by the exact binomial test for the null hypothesis that RR ≤20%). RR was 30.3% (10/33) in patients with PFI of ≥3 months, while it was 11.1% (3/27) in patients

**Table 2**
Grade 3/4 toxicities affecting >5% of the patients.

| | G1 | G2 | G3 | G4 | % G3–4 |
|---|---|---|---|---|---|
| Leukopenia | 7 | 17 | 26 | 10 | 60 |
| Anemia | 7 | 29 | 12 | 10 | 36.7 |
| Thrombocytopenia | 4 | 2 | 5 | 2 | 11.7 |
| Neutropenia | 7 | 17 | 15 | 21 | 60 |
| Hypoalbuminemia | 30 | 11 | 5 | – | 8.3 |
| Hyponatremia | 13 | – | 4 | 0 | 6.7 |
| Hypokalemia | 18 | – | 1 | 3 | 6.7 |
| Febrile neutropenia | – | – | 11 | 0 | 18.3 |
| Fatigue | 23 | 9 | 7 | 0 | 11.7 |
| Anorexia | 23 | 13 | 7 | 0 | 11.7 |
| Nausea | 20 | 15 | 7 | 0 | 11.7 |
| Vomiting | 13 | 8 | 4 | 0 | 6.7 |
| Diarrhea | 14 | 4 | 3 | 0 | 5 |

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with PFI of <3 months (Fisher's exact test, p = 0.12). RR was 26.5% (13/49) in patients with a non-clear cell histology, while it was 0% (0/11) in patients with a clear cell histology (p = 0.10). Age and the number of prior chemotherapy regimens did not seem to affect RR (21.7 (10/46), 21.4 (3/14), 23.5 (12/51), and 11.1 (1/9) % in young patients, elderly patients (p = 1.00), patients received <3 prior regimen, and patients received ≥3 prior chemotherapy regimens (p = 0.67), respectively).

Median PFS was 4.1 months (95% CI 3.5–4.9 months), and 33.3% of patients (95% CI 21.8–45.2%) survived without progression at 6 months (Fig. 1A). Median PFS was 5.6 months in patients with PFI of ≥3 months, while it was 3.6 months in patients with PFI of <3 months (Fig. 1B). Median PFS was 4.3 months in patients with a non-clear cell histology, while it was 3.6 months in patients with a clear cell histology.

One patient was progression-free at last follow-up (PFS, >1221 days). She was diagnosed with stage 3c ovarian serous adenocarcinoma and was treated with carboplatin plus paclitaxel for 5 cycles. After 16.6 months, she had a recurrent tumor and received carboplatin plus docetaxel for 5 cycles. After 1 month, she experienced platinum-resistant recurrence and was treated with the present regimen; she showed CR.

Median OS was 11.9 months (95% CI 9.4–14.6 m) (Fig. 2A). Median OS was 16.9 months in patients with PFI of ≥3 months, while it was 8.1 months in patients with PFI of <3 months (Fig. 2B). Median OS was 12.4 months in patients with a non-clear cell histology, while it was 10.4 months in patients with a clear cell histology.

## Discussion

This is the first phase II trial evaluating this combination regimen in patients with platinum-resistant ovarian cancer. This study demonstrates that the combination of oral etoposide and intravenous irinotecan has moderate efficacy in patients with platinum-resistant ovarian cancer. The overall RR was 21.7%. Disappointingly, this result does not meet the preplanned criteria for proceeding to a further phase III trial.

Preceding randomized controlled trials of combination chemotherapy against platinum-resistant ovarian cancer are summarized in Table 4. As for efficacy, our study shows a better RR, including CR lasting more than 3 years, compared with OVATURE [22], OVA301 [23] and ASSIST-5 studies [24], although PFS is in the same range. The CARTAXHY trial [25] shows a better RR and PFS compared with other studies, even in a paclitaxel single-agent arm. Nonetheless, this efficacy may not be reproduced in Japan, because weekly paclitaxel has already been adopted as a component of first-line treatment according to the results of JGOG3016 [2]. In addition, an Italian collaborative phase 3 study comparing epidoxorubicine plus paclitaxel with paclitaxel alone for patients with PFI ≤12 months, did not prove the efficacy of cytotoxic doublets in terms of neither PFS nor OS [26]. All these preceding studies concluded that combination chemotherapy utilizing two cytotoxic agents is not effective strategy. Combination chemotherapy utilizing one cytotoxic agent with one biologic agent is a promising strategy. AURELIA [27] has proved the efficacy of bevacizumab for patients with platinum resistant ovarian cancer, showing almost doubled RR and PFS, comparing with monotherapy such as weekly paclitaxel, PLD, or topotecan. Another study, TRINOVA-1 [28], also proved the efficacy of trebananib for patients with PFI ≤12 months.

**Table 3**
Overall response.

| | RECIST (%) | CA-125 (%) | Total (%) |
|---|---|---|---|
| CR | 1 (2) | – | 1 (2) |
| PR | 10 (19) | 2 (25) | 12 (20) |
| SD | 21 (40) | 2 (25) | 23 (38) |
| PD | 16 (31) | 4 (50) | 20 (33) |
| NE | 4 (8) | 0 (0) | 4 (7) |
| Total | 52 | 8 | 60 |

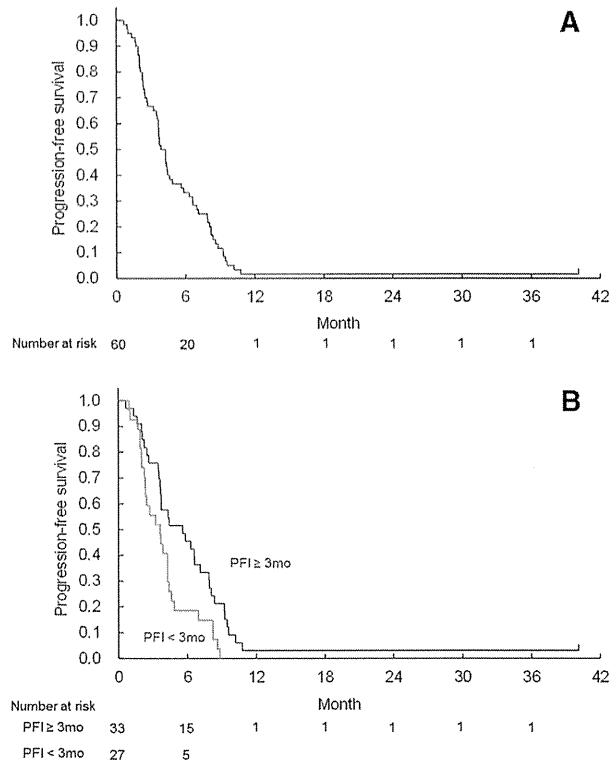


**Fig. 1.** A depicts PFS of all the patients. B depicts PFS by PFI <3 m (pink curve) or ≥3 m (blue curve). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

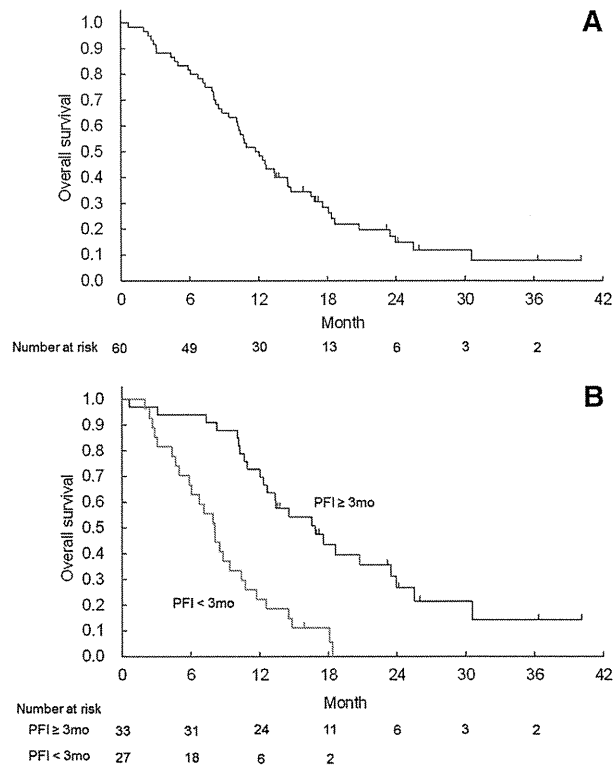


**Fig. 2.** A depicts OS of the patients. B depicts OS by PFI <3 m (pink curve) or ≥3 m (blue curve). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

**Table 4**
Combination chemotherapy for platinum resistant ovarian cancer.

| Study | Rx | % of 1 prior Rx | RR (%) | PFS (months) |
|---|---|---|---|---|
| OVATURE | Cb vs CbPXD | 2.8–4.3 | 1 vs 0 | 4.7 vs 3.6 |
| OVA301[22] | pD vs pDTr | 100 | 12 vs 13 | 3.7 vs 4 |
| CARTAXHY[24] | wP vs wPCb vs wPTp | 71–74 | 35 vs 37 vs 39 | 3.7 vs 4.8 vs 5.4 |
| ASSIST-3[23] | pD vs pDCan | 60 | 8.3 vs 12 | 3.7 vs 5.6 |
| JCOG0503 | E + I | 57 | 21.7 | 4.1 |
| Buda et al. | P vs PEp | 100 | 37[a] vs 47[a] | 6[a] vs 6[a] |
| AURELIA | wP/pD/Tp vs + BV | 57–60 | 13 vs 31 | 3.4 vs 6.7 |
| TRINOVA-1 | wP vs wPTre | 38–41 | 30[a] vs 38[a] | 5.4[a] vs 7.2[a] |

*Abbreviations.* Rx: regimen, Cb: carboplatin, PXD: phenoxidiol, pD: liposomal doxorubicin, Tr: trabectidine, wP: weekly paclitaxel, Tp: topotecan, Can: canfosfamide, E: etoposide, I: irinotecan, P: paclitaxel (every three weeks), Ep: epidoxorubicine, BV: bavacizumab, Tre: trebananib.

[a] Data for patients with platinum free interval less than 12 months.

Regarding toxicity, FN was much more frequent in our study, especially in heavily pretreated patients or elderly patients. Even among patients aged <65 years or those with 1 or 2 prior regimens, FN was still approximately 15%. Therefore, we think that the present regimen is too toxic and cannot be recommended as an option for heavily pretreated patients or elderly patients. Moreover, even when we excluded heavily pretreated patients or elderly patients, RR was similar. Eventually, we decided to discontinue the development of this regimen for patients with platinum-resistant ovarian cancer.

In the OVA301 subset analysis, patients with PFI of 6–12 months are considered good candidates for non-platinum combination chemotherapy [29], and the hypothesis is that platinum chemotherapy after a non-platinum combination can be more effective because of an artificially prolonged PFI. This hypothesis is being tested in the INOVATYON study, which compares trabectedin plus PLD with carboplatin plus PLD in patients with ovarian cancer with PFI of 6–12 months. If the results are positive, then the combination of oral etoposide and intravenous irinotecan, which shows RR of 30.3% in patients with PFI of 3–6 months, can be promising for further investigation for that purpose.

The present study had some limitations. First, pretreatment UGT1A1 assessment was lacking. This issue was discussed at the beginning of this study. Because the dose of irinotecan used in this study is low (140 mg/m$^2$ per cycle) and because of the negative results of a meta-analysis of the usefulness of such low doses [30], we decided not to use the UGT1A1 assessment. Second, the eligibility criteria allowing heavily pretreated patients are relatively broad compared with those in other trials. This situation can produce a negative bias in both efficacy and safety results. On the other hand, the number of heavily pretreated patients in this study is small, and the subgroup analysis strongly suggested that the conclusions will not change.

In conclusion, this study demonstrates that the combination of oral etoposide and intravenous irinotecan has moderate efficacy in patients with platinum-resistant ovarian cancer. The overall RR was 21.7%. This result did not meet the primary endpoint for a further phase III trial. Because of toxicity, we do not recommend this regimen outside of clinical trials. If such a trial is planned, heavily pretreated patients and elderly patients should be excluded.

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### Conflict of interest statement

Koji Matsumoto participates in the investigation trials and receives clinical investigation expense from Astra Zeneca, Japan Boehringer Ingelheim, Pfizer, and Sanofi. Noriyuki Katsumata receives honorarium from Chugai Pharmaceutical Co. Ltd. and Ono Pharmaceutical Co Ltd. Mayu Yunokawa receives clinical investigation expense from Yakult Honsha Co. Ltd. and Sawai Pharmaceutical Co. Ltd. Taro Shibata, Toyomi Satoh, Motoaki Saitou, Tadao Takano Kenichi Nakamura Toshiharu Kamura and Ikuo Konishi have no relevant financial relationships to disclose.

## Participating Hospitals

Iwate Medical University, Tohoku University, Tsukuba University, Jikei Kashiwa Hospital, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital, Jikei University Hospital, Cancer Institute Hospital of Japanese Foundation for Cancer Research, The University of Tokyo Hospital, Kitasato Univerisity School of Medicine, Niigata Cancer Center Hospital, Aichi Cancer Center Hospital, Kyoto University Hospital, Osakacity University Hospital, Osaka Prefectural Hospita Organization Osaka Center for Cancer and Cardiovascular Disease, Osaka City General Hospital, Hyogo Cancer Center, National Hospital Organization Kure Medical Center Chugoku Cancer Center, National Hospital Organization Shikoku Cancer Center, National Kyushu Cancer Center, Kurume University School of Medicine, Kyushu University Hospital, Faculty of Medicine, Saga University, Kagoshima City Hospital, Faculty of Medicine, University of the Ryukyus.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2014.10.026.

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【各論2】子宮体がん

# 子宮体がんⅣ期の治療個別化を模索する

衛藤 貴子　齋藤 俊章

● ⅣB期体がんであっても，類内膜腺癌G1/G2など，予後が比較的良好な症例が存在する．
● 全身状態良好な症例では，遠隔転移の有無にかかわらず，腹腔内腫瘍減量術を考慮すべきである．
● 初回に腫瘍減量術が不可能な症例であっても，術前化学療法が有効であれば，予後改善の可能性がある．

## はじめに

進行子宮体がんは頻度が少ないが予後不良である．日本産科婦人科学会腫瘍委員会報告2012年度患者年報によると，Ⅰ～Ⅳ期の子宮体がん症例数は8,217例で，Ⅳ期は603例（7.3%）であった[1]．2006年治療年報ではⅣ期の5年生存率は24.3%であった[2]．

ⅣB期体がんに対する治療法は確立しておらず，どこまで積極的に治療を行うべきか判断に非常に苦慮する．治療法を検討するにあたり，ⅣB期体がんは頻度が少なくその実態すら明らかでないことや，遠隔転移だけでなく，卵巣がんではⅢ期に相当する上腹部へ進展した腹腔内播種も体がんではⅣB期に分類され，腹腔内播種と遠隔転移の混在した集団であることが重要なポイントであると思われる．

子宮体がんⅣB期についてわれわれが行った調査研究の結果[3,4]とこれまでの文献報告とあわせ，初回治療法や遠隔転移ⅣB期・腹腔内転移ⅣB期に着目して，ⅣB期の治療法の選択について考察したい．

## ⅣB期体がん調査研究の対象と方法

本研究は，厚生労働省がん研究助成金「婦人科悪性腫瘍に対する新たな治療法に関する

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研究」班の一環として行われた．対象は，日本臨床腫瘍グループ（JCOG）関連施設において1996～2005年の10年間に治療開始した肉腫を除く子宮体がんⅣB期426例である．後方視的に，臨床病理学的因子，子宮外進展の部位と大きさ，Ⅳ B期とする転移部位（腹腔内転移/遠隔転移），初回治療法（手術，化学療法，その他），予後について調査した．

## Ⅳ B期の全体像

これまでのⅣB期体がんの文献的報告はほとんどが腫瘍減量術に関するものであるが，それらがⅣB期全体のなかでどれほどの割合を占めるのかも明らかではなかった．本研究では，初回に子宮摘出以上の手術が施行できた症例は，Ⅳ B期体がん426例のうち58%にすぎなかった[4]．化学療法後に子宮摘出を行ったものを含めると71%であった．初回に開腹術が行われなかった症例は35%であった．多くは，全身状態不良や腫瘍の進展著明で腫瘍減量術が不可能であることがその理由であったが，遠隔転移の存在を理由に手術よりも化学療法を優先した症例もみられた．

## Ⅳ B期体がんの臨床病理学的な特徴―初回手術群の検討より

初回手術群は，開腹所見で初めてⅣB期と診断された症例が約半数を占める，比較的全身状態が良い，遠隔転移があっても数が少ないなど，Ⅳ B期全体とは若干異なる集団であることを理解しておく必要がある．しかし，初回手術群でしか，原発巣の組織型や腹腔内病巣などの正確な臨床病理学的所見を得ることはできず，興味深い所見が得られた[3]．

術前と術後の組織型診断が一致したのは60%にすぎず，初回非手術例の治療の際には注意する必要がある．Ⅳ B期に相当する腹腔内播種は小さいことが多く，最大径＞2 cmが55%，2 cm以下が38%，顕微鏡的転移が7%であった．術前の画像診断で検出されていないことが多く，22%は横隔膜に播種を認めることから，開腹時に腹腔内を十分に精査することが重要である．また，一般の集団に比較して予後不良な組織型の頻度が高く，これらは予後不良であるが，類内膜腺癌G1/G2は比較的予後良好であることが示された（**図1**）．

## 子宮体がんの遠隔転移の特徴

Ⅳ B期体がん全体で遠隔転移は54%に認められた[4]．うち6割は遠隔転移が1臓器であった．遠隔転移部位は，卵巣がんではがん性胸水が最も多いが，子宮体がんでは肺が最も多く，肝，鎖骨上リンパ節，縦隔リンパ節，骨の順であった．肺転移はその82%が両側性で，遠隔病巣の多くは切除困難と思われた．実際に遠隔転移病巣がすべて切除された症例は，ごく一部であった[3]．遠隔転移例でも転移臓器数が少ないものはperformance statusも良く，予後も比較的良好であった．初回手術群では，遠隔転移のみのⅣB期症例のほうが腹腔内転移のみのⅣB期よりも，むしろ予後が良好であった．

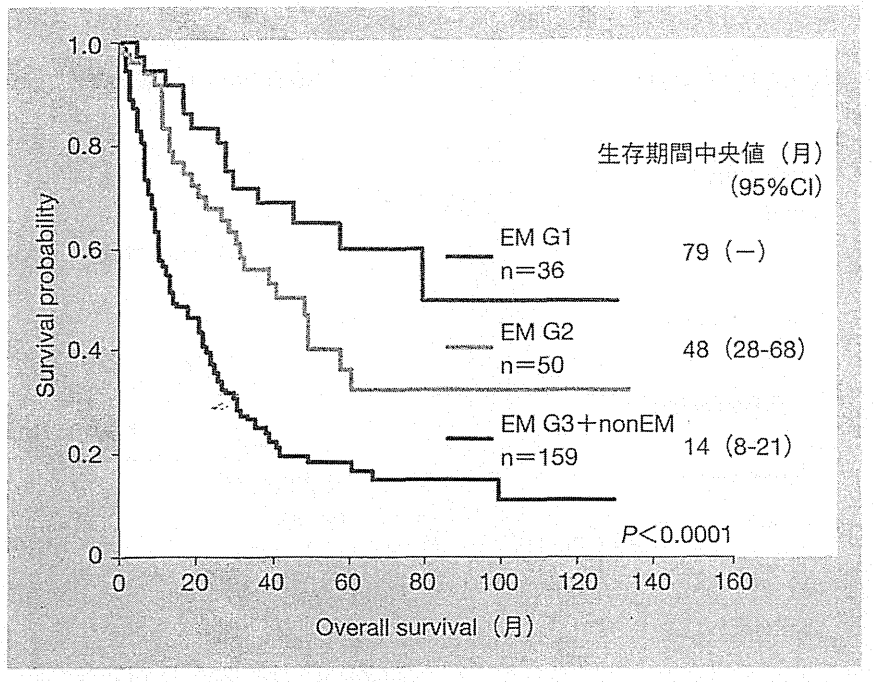


**図1　組織型・分化度と全生存期間**

EM：類内膜腺癌　　（文献10より改変）

## 遠隔転移ⅣB期の治療法

遠隔転移症例の治療法についての報告はほとんどない．これまでのⅣ期体がんの腫瘍減量術に関する報告にも，遠隔転移症例は少数しか含まれていない．NCCNガイドラインでは，緩和的単純子宮全摘出術＋両側付属器摘出術を考慮，± 化学療法，± 放射線療法，± ホルモン療法と記載されている[5]．

本研究の初回手術群の検討では，遠隔転移の有無にかかわらず，開腹術による腹腔内残存なし群が腹腔内残存あり群よりも予後良好であった（**図2**）[3]．腫瘍減量術の効果である可能性，または腫瘍元来の生物学的性質である可能性のいずれもありうる．いずれにしても，切除不能な遠隔転移があっても腫瘍減量術は否定されないことが示唆された．特に遠隔転移が1臓器，performance status良好などの症例では，切除困難な遠隔転移であっても積極的に治療をすべき候補と考えられる．

遠隔転移ⅣB期に対して手術を行わずに化学療法だけで長期生存している症例も認められた．しかし，手術が可能な状態で原発巣は切除せずに化学療法のみ行うことの妥当性は不明である．

## 腹腔内転移ⅣB期の治療法

Ⅳ期体がんに対しても卵巣がん治療のように腫瘍減量術が有用との報告があり，その主なものを表に示す[3,4,6~12]（**表1**）．腹腔内転移ⅣB期症例がほとんどであるが，optimal

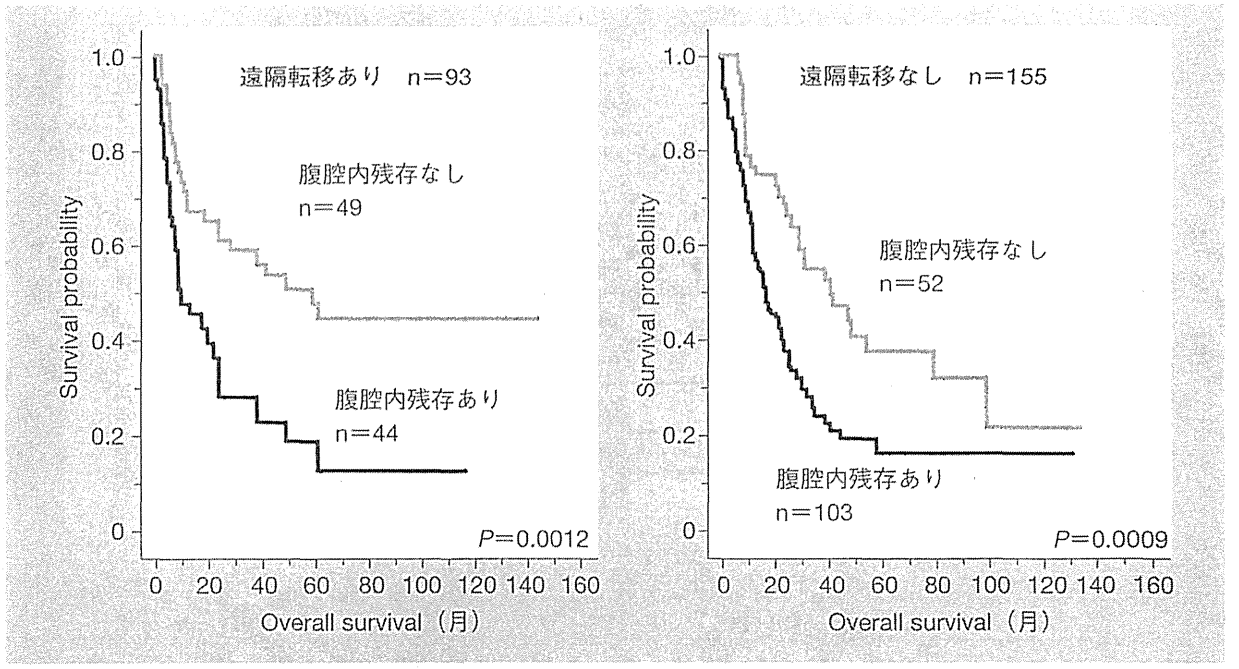


図2　腹腔内残存腫瘍の有無と全生存期間

遠隔転移の有無で層別　（文献10より改変）

表1　Ⅳ期子宮体がんの腫瘍減量術に関する報告

| Author | 報告年 | 症例数 | UPSC/Clear（%） | 遠隔転移症例（%） | Optimal定義 | Optimal手術割合（%） | Optimal例OS中央値（月） | Suboptimal OS中央値（月） | （P-value） |
|---|---|---|---|---|---|---|---|---|---|
| Chi | 1997 | 55 | 24 | 33 | ≦2 cm | 53 | 31 | 12 | ＜0.01 |
| Bristow | 2000 | 65 | 38 | 14 | ≦1 cm | 55 | 34 | 11 | 0.0001 |
| Bristow | 2001 | 31 | 100 | 16 | ≦1 cm | 52 | 26 | 10 | ＜0.001 |
| Ayhan | 2002 | 37 | 13 | 16 | ≦1 cm | 59 | 25 | 10 | 0.01 |
| Moller | 2004 | 49 | 100 | NA | ≦1 cm | 53 | 15 | 8 | ＞0.05 |
| Ueda | 2009 | 33 | 27 | 55 | ≦2 cm | 67 | 43 | 6 | ＜0.0001 |
| Shih | 2011 | 58 | 0 | ≧2 | ≦1 cm | 35 | 42* | 19* | ＜0.001 |
| Eto | 2012 | 248 | 23 | 38 | ≦1 cm | 50 | 34 | 17 | 0.0002 |

UPSC/Clear：漿液性腺癌または明細胞腺癌の割合
*：完全切除例

手術が達成できた群が，suboptimal群よりも予後が良好であったと報告されている．

しかし，手術と術後治療を行った腹腔内転移ⅣB期と腹腔内播種卵巣がんを，年齢と残存病変をマッチさせて比較した研究では，子宮体がんは2年生存率52%で，卵巣がん76%に比し予後不良であった（p=0.008）と報告されている[13]．先に述べたように腹腔内転移ⅣB期は播種病巣の小さいものが多いが，播種が小さいものが予後がよいとは限らないことに注意が必要である．

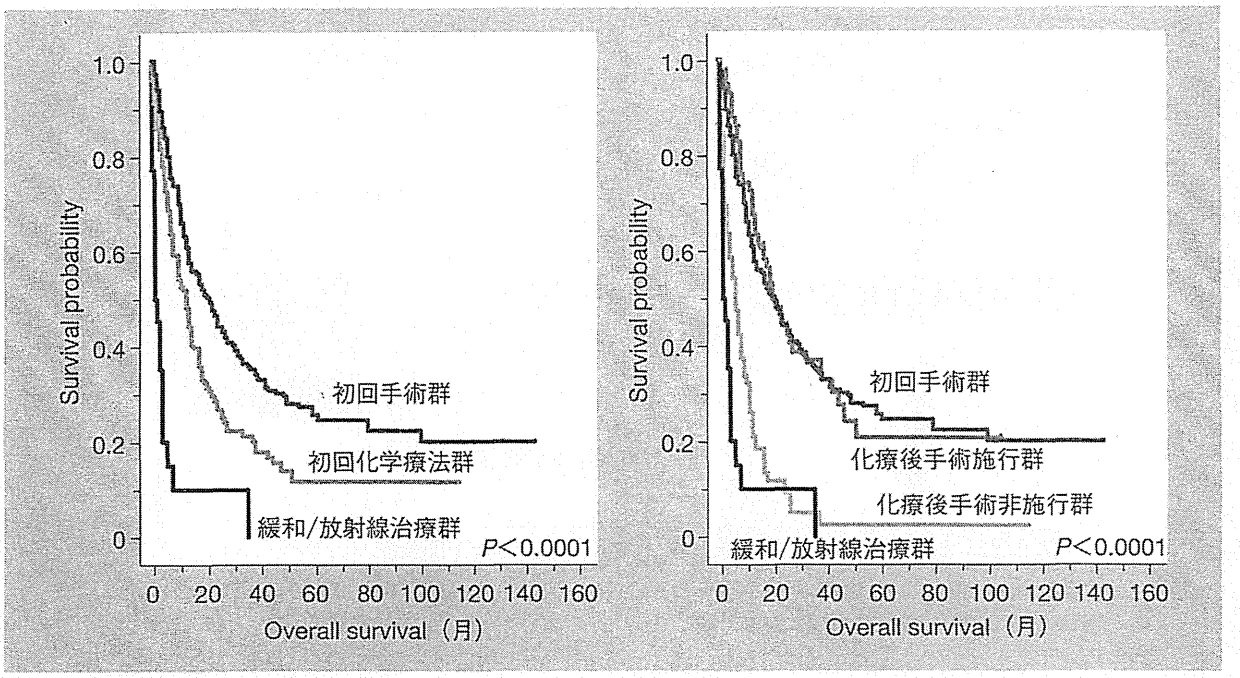


**図3　初回治療法と別の全生存期間**

（文献10より改変）

子宮体がんに対する化学療法の有効性は，卵巣がんのそれに劣り，さらなる化学療法の進歩が望まれる．現時点での試験的研究として腹腔内転移ⅣB期に対してoptimal surgery後に腹腔内化学療法を行うphase Ⅰ studyがGOGで行われている（GOG-9920）．

## neoadjuvant chemotherapyについて

子宮体がんにneoadjuvant chemotherapy（NAC）を試みた報告はきわめて少なく，1報告のみ認められる[14]．腹腔鏡で確認された腹腔内転移ⅣB期30例（漿液性腺癌27例）に対し，化学療法を3～4コース行い，28例に腫瘍減量術が行われ，さらに24例に術後2～5コースの化学療法が追加された．30例の生存期間中央値23か月で，optimal手術達成率80％と高い切除率が得られたと述べている．

われわれが行った研究では，初回化学療法群のなかの症例が，NACを目的としていた症例であったのか，緩和治療に近い症例であったのかを同定することはできなかった．NACを試みる際には，子宮体がんは卵巣がんほど化学療法の奏効率が高くないことに留意する必要がある．結果的に二次的腫瘍減量術を施行したのは初回化学療法群の44％で，それらの予後が初回手術群とほぼ同等であった．この結果から，全身状態不良や大きな転移があるなどの理由で初回手術が不可能な症例には，NACも治療の選択肢となりうると考えられた（**図3**）．

婦人科悪性腫瘍研究機構で臨床試験「臨床的FIGO Ⅳb期子宮体がんに対する寛解導

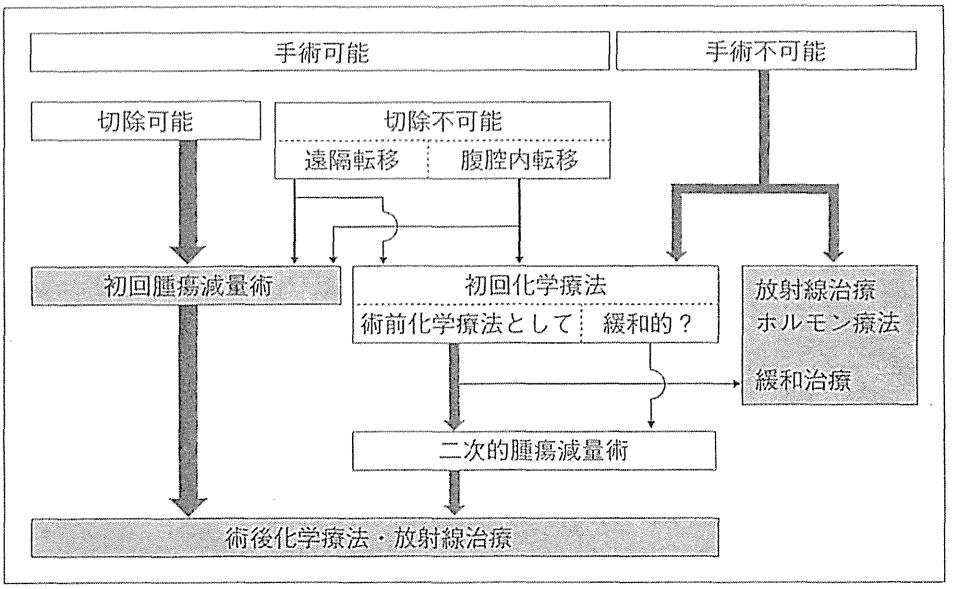


図4　ⅣB期子宮体がんの治療戦略

入化学療法後の腫瘍摘出術に関するFeasibility Study（JGOG2046）」が始まっている．遠隔転移ⅣB期も腹腔内転移ⅣB期も対象とされており，非常に貴重なデータが得られると期待される．

## おわりに

ⅣB期体がんであっても，予後が比較的良好な症例が存在する．治療戦略をフローチャートにしてみた（**図4**）．全身状態良好な症例では，遠隔転移の有無にかかわらず，腹腔内腫瘍減量術を考慮すべきと考えられた．また，全身状態不良など初回に腫瘍減量術が不可能な症例であっても，NACが有効であれば，予後改善の可能性があると考えられた．

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# Administration of standard-dose BEP regimen (bleomycin + etoposide + cisplatin) is essential for treatment of ovarian yolk sac tumour

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**KEYWORDS**
Ovarian yolk sac tumour
BEP regimen
Prognosis
Fertility

**Abstract** ***Aim:*** The aim of this study was to investigate prognostic factors, including postoperative chemotherapy regimen, for the treatment of ovarian yolk sac tumour (YST), and resulting fertility outcome.

***Methods:*** A multi-institutional retrospective investigation was undertaken to identify patients with ovarian pure or mixed YST who were treated between 1980 and 2007. Postoperative chemotherapy regimen and other variables were assessed in univariate and multivariate analyses. Additionally, the reproductive safety of the BEP (bleomycin, etoposide and cisplatin) regimen was evaluated.

***Results:*** There were 211 patients enrolled from 43 institutions. The BEP regimen and a non-BEP regimen were administered to 112 and 99 patients as postoperative chemotherapy, respectively. In univariate and multivariate analyses, age $\geqslant$ 22, alpha-fetoprotein $\geqslant$ 33,000 ng/ml, residual tumours after surgery and non-BEP regimen were independently and significantly associated with poor overall survival (OS). BEP was significantly superior to non-BEP in 5-year OS (93.6% versus 74.6%, $P = 0.0004$). Reduced-dose BEP (<75% standard-dose bleomycin and < 50% etoposide dose) was significantly associated with poorer 5-year OS compared with standard-dose BEP (89.4% versus 100%, $P = 0.02$ and 62.5% versus 96.9%, $P = 0.0002$). All patients who underwent fertility-sparing surgery recovered their menstrual cycles. Sixteen of 23 patients receiving BEP (70.0%) and 13 of 17 patients receiving non-BEP (76.5%) who were nulliparous at fertility-sparing surgery and married at the time of investigation gave birth to 21 and 19 healthy children, respectively.

***Conclusions:*** The results of the present study suggest that standard-dose BEP should be administered for ovarian YST. BEP is as safe as non-BEP for preserving reproductive function.



## 1. Introduction

Until the early 1970s, patients with ovarian yolk sac tumour (YST) had miserable prognosis [1–4]. However, after a triple combination regimen, such as vincristine + actinomycin D + cyclophosphamide (VAC) or cisplatin + vinblastine + bleomycin (PVB), was introduced as postoperative chemotherapy during the 1970s, the survival of patients with YST drastically improved [5–7]. Furthermore, the bleomycin + etoposide + cisplatin (BEP) regimen was developed in the 1980s, and the survival of patients with YST revolutionarily improved [8,9]. However, recent reports have suggested that patients with YST have poorer prognosis than patients with other malignant ovarian germ cell tumours. Peccatori showed that the mortality rates of YST and dysgerminoma were 13.0% (3/23) and 5.3% (3/57), respectively [10]. Mangili reported that the 5-year overall survival (OS) rates were 69.6% and 94.2% for patients with YST and other germ cell tumours, respectively ($P < 0.001$) [11].

The standard strategy for treating YST is administration of BEP following primary surgery in all stages. BEP for patients with YST has been recommended by various guidelines. The recommended dose and administration schedule in the National Comprehensive Cancer Network (NCCN) guideline is bleomycin 30 units per week; etoposide 100 mg/m$^2$/day daily for days 1–5; and cisplatin 20 mg/m$^2$/day daily for days 1–5 for 3–4 cycles [12]. However, the BEP regimen is sometimes administered with a reduced dose of bleomycin and/or etoposide because of the potential for serious adverse reactions such as severe bone marrow suppression, pulmonary fibrosis or secondary leukaemia [13–17]. Therefore, the present study investigated whether the use of BEP, especially standard-dose BEP, is associated with OS in patients with YST, in addition to other prognostic factors.

Fertility-sparing surgery (FSS) is considered for patients with YST, even in advanced disease. Therefore, an additional purpose of the present study was to investigate the reproductive safety of postoperative chemotherapy for YST.

## 2. Methods

### 2.1. Patient population

Between 1980 and 2007, 211 patients with YST who underwent treatment in 43 institutions belonging to the Japan Clinical Oncology Group or who were referred to these institutions immediately after primary surgery performed elsewhere were enrolled into this study. Patients who received preoperative chemotherapy and/or no postoperative chemotherapy were not included in this study.



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Before the study subjects were enrolled into the present study, reassessment of histological type was performed in each institution according to the World Health Organisation criteria. Staging was determined according to the FIGO classification (1987).

Institutional review board approval was obtained from each institution before initiating the present investigation.

### 2.2. Definition of standard BEP and non-standard BEP

In the present study, standard BEP was defined as 3 or 4 cycles of chemotherapy consisting of bleomycin (20 mg/m$^2$/day or 30 mg/day) given on days 2, 9 and 16, etoposide (100 mg/m$^2$/day) given on days 1–5 and cisplatin (20 mg/m$^2$/day) given on days 1–5. The cycles were repeated every 3 weeks. Regarding the standard number of cycles of BEP, we administered three cycles for patients without residual tumour and four cycles for patients with residual tumour at primary surgery, allowing one or two additional courses until achieving normal AFP level. The serum AFP was measured every course of BEP in almost all patients.

Patients who received BEP were divided into the standard BEP group ($n = 37$) and the non-standard BEP group. The non-standard BEP group ($n = 70$) received less than the standard dose and/or less than the standard number of cycles. The following five patients who received BEP were excluded from both the standard BEP and non-standard BEP group: two patients were given an excessive dose of bleomycin, and three patients received BEP with an uncertain dose.

### 2.3. Matters for analysis

We investigated postoperative chemotherapy regimen and other variables as prognostic factors in all 211 patients. Regarding chemotherapy regimen, we compared 5-year OS between BEP and non-BEP, and between standard BEP and non-standard BEP. Other variables were age, stage, tumour size, serum AFP level before treatment, FSS and residual tumour at primary surgery. ROC curve was used for searching cut-off levels for age and AFP and we found the level of age was 22 years and the level of AFP was 33,000 ng/ml. We also investigated whether the doses of bleomycin, etoposide and cisplatin were associated with OS in patients who received BEP.

The reproductive safety of BEP and other regimens was retrospectively reviewed from the medical records of the patients who provided information on menstruation and reproductive outcomes.

### 2.4. Statistical analysis

Statistical analysis of data was performed using the JMP statistics package (SAS Institute, Cary, NC, USA). Two-sided probability values were calculated throughout and considered to be significant at the level of $P < 0.05$. Survival estimates were generated using Kaplan–Meier methods. To test differences between groups, we used log-rank testing for the univariate analysis and the Cox proportional hazard regression method for the multivariate analysis.

## 3. Results

### 3.1. Patient characteristics

A total of 211 patients with YST were entered into the study (Fig. 1). Table 1 summarises the main characteristics of patients and tumours. The median duration of follow-up after excluding patients who died was 93 (4–333) months from primary surgery.

The serum AFP level before treatment was measured in 174 of the 211 study patients. The AFP level of the patients with pure YST was similar to that of the patients with mixed YST having $\geqslant 50\%$ of the YST component, however the level was significantly higher than in the patients with mixed YST having <50% of YST component ($P < 0.01$).

Complete surgical staging was not done like a epithelial ovarian cancer in most patients with YST, therefore staging was determined by limited information from surgical and pathological findings. No residual tumour, residual tumour within 2 cm and residual tumour over 2 cm after initial surgery was 77.7%, 12.5% and 9.8% in BEP group, 68.7%, 10.1% and 21.2 in non-BEP group, 89.1%, 5.4% and 5.4% in standard BEP group and 87.1%, 0% and 12.9% in non-standard BEP group.

Table 2 shows that comparative demographics for the BEP group versus non-BEP group and standard BEP group versus non-standard BEP group were similar.

### 3.2. Clinical outcomes

The estimated 5-year OS of the patients in each stage was 92.5% in stage I, 87.8% in stage II, 74.7% in stage III and 44.5% in stage IV. Overall, 33 deaths (15.6%) occurred from the following causes: disease progression of YST ($n = 31$, 14.2%), pulmonary fibrosis during BEP ($n = 1$, 0.5%) that developed after the patient was given 330 mg of bleomycin in total, and breast cancer ($n = 1$, 0.5%) that occurred 7 years after complete remission following BEP.

Of 99 patients who received non-BEP, 12 patients after remission (normalisation of AFP) and 15 patients without remission progressed their disease. Six patients after remission and 2 patients without remission progressed their disease among 70 patients who received non-standard BEP. We experienced no recurrent patients in the standard BEP group. Only two of 27 (7.4%) relapsed patients in non-BEP group and two of


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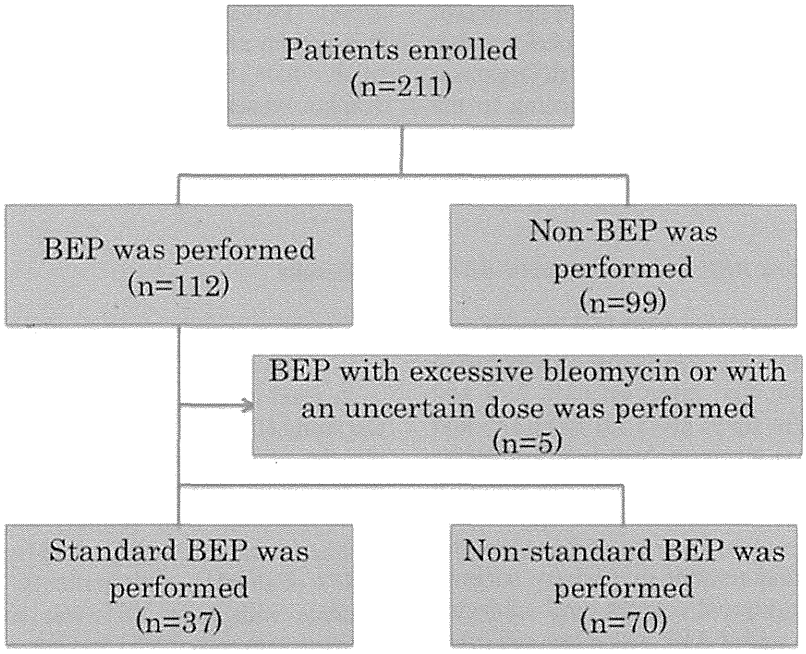


Fig. 1. CONSORT diagram.

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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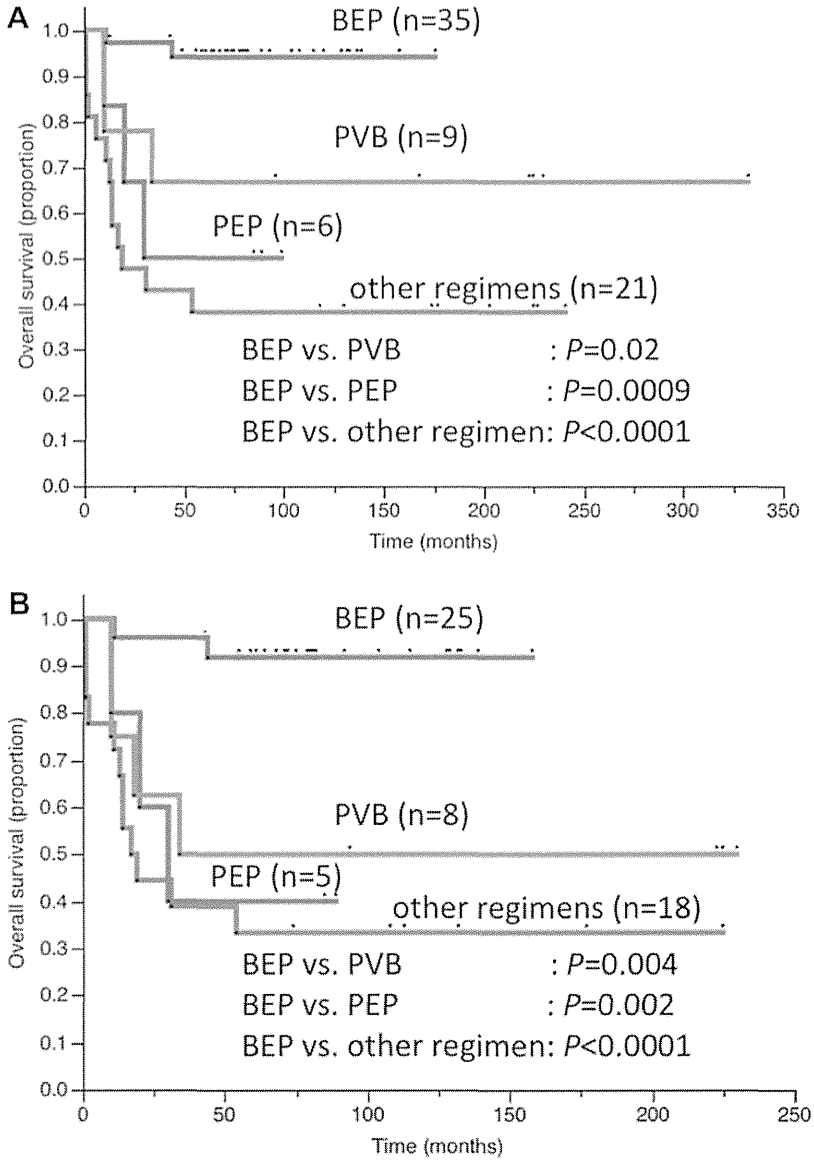


Fig. 2. (A) Overall survival curve for patients with stage III-IV disease who received BEP and non-BEP. The 5-year OS was 94.0% with BEP ($n = 35$), 66.7% with PVB ($n = 9$), 50.0% with PEP ($n = 6$) and 43.5% with other regimens ($n = 21$) ($P < 0.0001$). (B) Overall survival curve for patients with 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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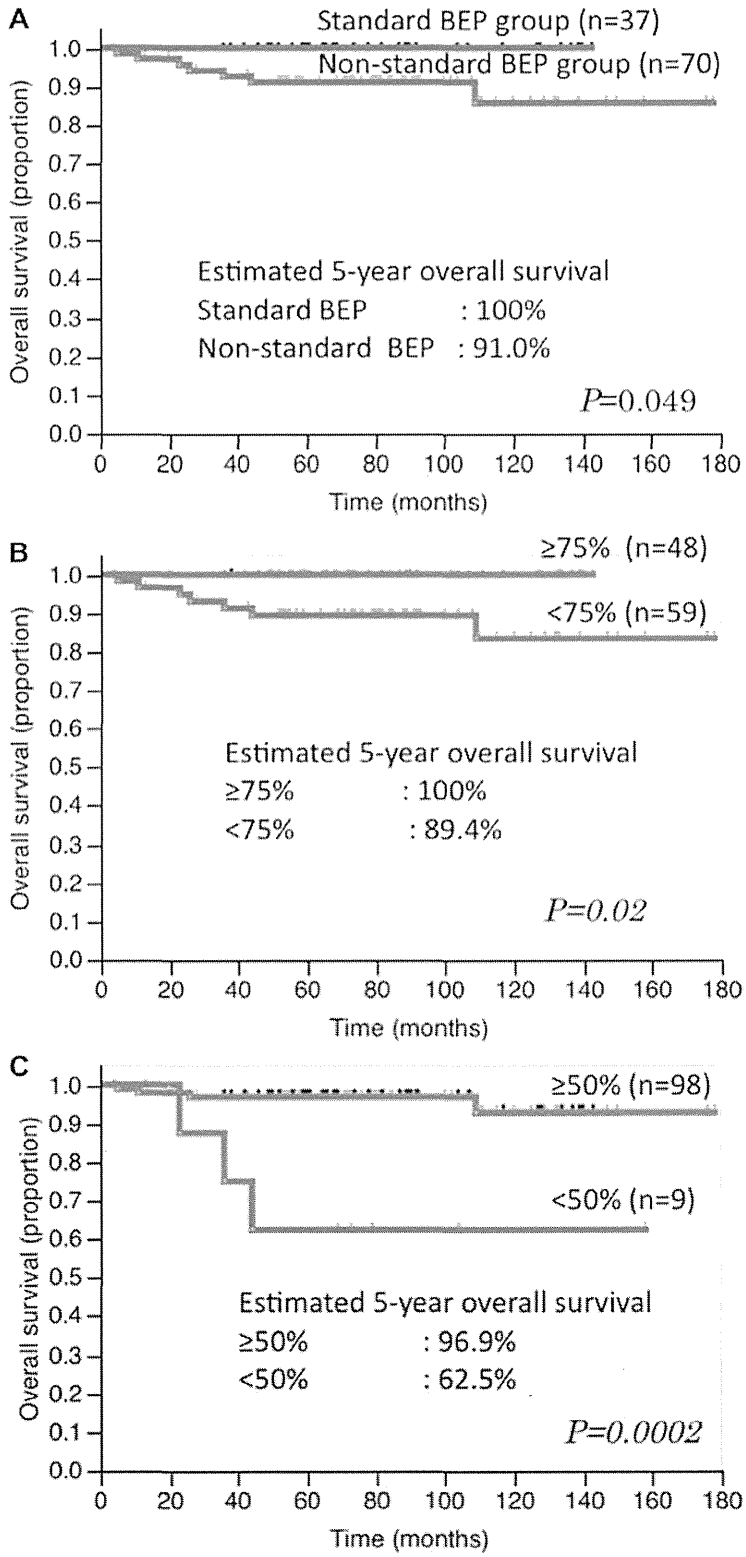


Fig. 3. (A) Overall survival curves in patients who received BEP. Standard BEP was significantly superior to non–standard BEP in 5-year OS (100% versus 91.0%, $P = 0.049$). (B) Overall survival curve for patients with BEP who received ⩾75% and <75% of the standard dose of bleomycin. A reduced dose (<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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