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A retrospective study for investigating the relationship between old and new staging systems with prognosis in ovarian cancer using gynecologic cancer registry of Japan Society of Obstetrics and Gynecology (JSOG): disparity between serous carcinoma and clear cell carcinoma

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ABSTRACT

Objective: International Federation of Gynecology and Obstetrics (FIGO) staging for ovarian, fallopian tube, and peritoneal cancers was revised in 2014. The aim of this study is to clarify whether the revised FIGO2014 staging reflects the prognosis of patients with ovarian cancer by histological type in Japan.

Methods: We extracted 9,747 patients who were diagnosed with ovarian cancer since 2004 until 2008 and who could be classified into appropriate stages from the Gynecologic Cancer Registry of Japan Society of Obstetrics and Gynecology. These cases were analyzed after revision to FIGO2014 based on the pTNM classification.

Results: Among stage I, the 5-year overall survival rate (5y-OS) in FIGO2014 was 94.9% in stage IA, 92.3% in stage IC1, 86.1% in IC2, and 84.9% in IC3 with significant differences between stages IA and IC1 ($p=0.012$), IC1 and IC2 ($p<0.001$). There was a significant difference between stages IA and IC1 in clear cell and mucinous carcinoma but not in serous and endometrioid carcinoma. Among stage III, the 5y-OS was 75.6% in stage IIIA1, 68.9% in IIIA2, 58.6% in IIIB, and 44.4% in IIIC, with significant differences between stages IIIA2 and IIIB ($p=0.009$), IIIB and IIIC ($p<0.001$). Among stage IV, the 5y-OS was 43.1% in stage IVA* and 32.1% in IVB with a significant difference ($p=0.002$).

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: Y.M., A.D.; Data curation: N.S.; Formal analysis: Y.M.; Investigation: I.K., H.T., M.M.; Methodology: Y.M., N.S., T.F.; Project administration: N.S.; Supervision: E.T., K.H., A.D.; Writing - original draft: Y.M.

Conclusion: The results suggest that changes in classification for stage III and stage IV are appropriate, but the subclassification for stage IC might be too detailed. There was a discrepancy of prognosis by histological type between stage IA and IC1.

Keywords: Ovarian Cancer; Prognosis; Cancer Staging; Serous Carcinoma; Clear Cell Carcinoma

INTRODUCTION

International Federation of Gynecology and Obstetrics (FIGO) staging for ovarian, fallopian tube, and peritoneal cancers was revised in 2014 [1]. The staging is periodically revised to reflect prognosis more correctly based on the latest findings. The major changes to the staging were the focus on fallopian tube and peritoneal cancers, in addition to ovary cancer; subdivision of stage IC into stage IC1, IC2, and IC3; the elimination of stage IIC; classification of node-positive patients into stage IIIA1, rather than the conventional stage IIIC; subdivision of stage IV into stage IVA and IVB; and classification of patients who were positive in cytological diagnosis of pleural effusion into stage IVA [1].

The main treatments for ovarian cancer are surgery and chemotherapy, and the effect of treatment affects the prognosis. In Japan, the incidence of ovarian clear cell carcinoma, which is resistant to chemotherapy, is higher than that in the West [2-4]. This raises the question of whether FIGO staging created mainly in Western countries with a large number of patients with chemosensitive serous carcinoma is useful in Japan, in which there is a large number of patients with chemoresistant clear cell carcinoma.

In Japan, the Japan Society of Obstetrics and Gynecology (JSOG) maintains a gynecological cancer registry (GCR) to collect information on clinicopathological factors and prognosis of patients with ovarian cancer and ovarian borderline malignant tumor [2,3]. Based on the registered patients in the GCR, the JSOG member facilities have extensive therapeutic experience in gynecological cancer treatment. The aim of this study is to clarify whether the revised FIGO2014 staging reflects the prognosis of patients with ovarian cancer in Japan.

MATERIALS AND METHODS

1. Patients

Clinicopathological factors and prognoses were obtained for 20,563 patients who were histopathologically diagnosed with ovarian cancer or ovarian borderline malignant tumor, received treatment for this cancer in the 5 years from 2004 to 2008 at JSOG medical facilities, and were registered in the GCR. Approval was obtained from the JSOG and the Ethics Boards of Keio University (approval No. 20170261). Among the 20,563 patients, those with missing prognostic data were excluded, leaving 14,204 patients for analysis, including 10,810 patients with epithelial ovarian cancer and 9,747 patients who could be classified into appropriate stages (**Fig. 1**).

2. Methods

The 4 major changes from FIGO1988 to FIGO2014 were 1) stage IC was subdivided into stage IC1, IC2, and IC3; 2) stage IIC was eliminated; 3) node-positive patients with no peritoneal dissemination were classified as stage IIIA1, and those with lymph node metastasis only were

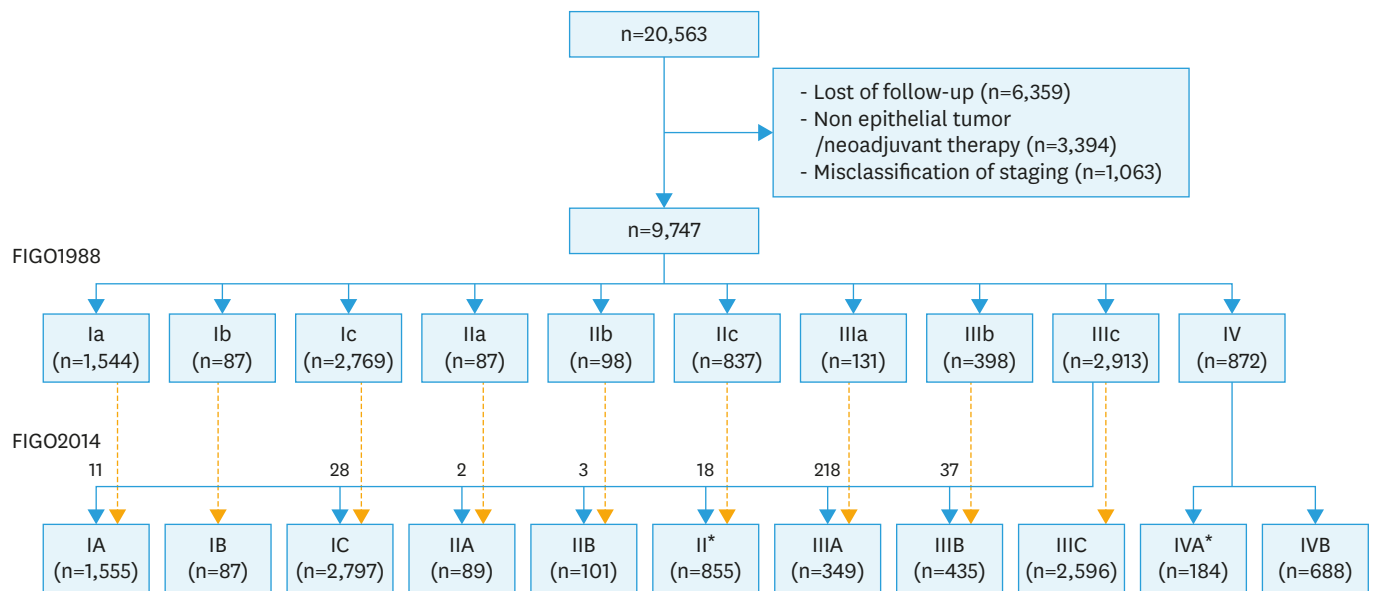


Fig. 1. Re-classification of ovarian cancer post-surgical staging from FIGO1988 to FIGO2014. Of the 317 cases in stage IIIc (FIGO1988), 11 cases were reclassified into stage IA, 28 into stage IC, 2 into stage IIA, 3 into stage IIB, 18 into stage unclassified II, 218 into stage IIIA and 37 into stage IIIB (FIGO2014), respectively. Of the 872 cases in stage IV (FIGO1988) 184 cases were classified into stage IVA and 688 in stage IVB (FIGO2014), respectively. FIGO, International Federation of Gynecology and Obstetrics.

not classified as stage IIIC; and 4) among patients with distal metastasis, those who were positive in cytological diagnosis of pleural effusion were classified as stage IVA. The JSOG GCR data include stages classified using FIGO1988, and among the changes, subclassified data for stage IC and stage III could be analyzed. Furthermore, FIGO1988 was modified to register patients subdivided into stage Ic and stage IIc in Japan. Cases were registered as (a) spontaneous capsular rupture, (b) intraoperative capsular rupture, (1) positive in peritoneal lavage cytology, or (2) positive in ascitic fluid cytology. These cases were analyzed after revision to FIGO2014 based on the TNM classification and the former subclassification of stage IC.

In detail, stage IC(b) was reclassified into stage IC1, stage IC(a) into stage IC2, and stage IC(1) or stage IC(2) into stage IC3; and pT1-2N1M0 was reclassified into stage IIIA1, pT3aN0-1M0 into stage IIIA2, pT3bN0-1M0 into stage IIIB, and pT3cN0-1M0 into stage IIIC. Patients who were included in the N1 group based only on the results of palpation with no pathological confirmation of metastasis were not classified as stage IIIA1. Patients in stage IIC could not be classified as stage IIA or stage IIB, and it was impossible to identify patients with a single positive cytological diagnosis of pleural effusion from those in stage IV. Therefore, a correct analysis could not be performed for such patients. However, since distal metastasis sites in patients in stage IV were recorded, this could be used to compare patients with pleural dissemination only with other patients in stage IV. Thus, they were analyzed as “deemed stage IVA” (stage IVA*). Regarding the histological type, serous carcinoma + endometrial carcinoma was defined as the S+E group, and clear cell carcinoma + mucinous carcinoma as the C+M group for analysis because it is known that S+E group cancer is often chemosensitive, whereas C+M group cancer is often chemoresistant [5].

3. Statistical analysis

Clinicopathological factors were analyzed by χ^2 test, Fisher exact test, and Mann-Whitney U test. Survival rate was determined using the Kaplan-Meier method and examined by Log rank

test. All analyses were performed using SPSS ver. 24 (IBM Corp., Armonk, NY, USA), with $p < 0.05$ considered to be significant.

RESULTS

1. Background of the study population

The median age of the patients was 56 years (range: 13–93 years). The median observation period was 1946 days (range: 3–2,531 days). In the FIGO1988 classification, 4,400 patients were classified as stage I (1,544 as stage Ia, 87 as stage Ib, and 2,769 as stage Ic), 1,022 as stage II (87 as stage IIa, 98 as stage IIb, and 837 as stage IIc), 3,442 as stage III (131 as stage IIIa, 398 as stage IIIb, and 2,913 as stage IIIc), and 872 as stage IV. In the histological classification, 3,290 cases were classified as serous carcinoma, 2,470 as clear cell carcinoma, 1,869 as endometrioid carcinoma, 1,312 as mucinous carcinoma, 251 as mixed carcinoma, 212 as undifferentiated carcinoma, and 343 as others. After reclassification based on FIGO2014, the data were transformed as shown in **Fig. 2**. As a result, 4,439 patients were classified as stage I (1,555 as stage IA, 87 as stage IB, and 2,797 as stage IC), 1,045 as stage II (89 as stage IIA, 101 as stage IIB, and 855 as unclassified stage II), 3,380 as stage III (203 as stage IIIA1, 146 as stage IIIA2, 435 as stage IIIB, and 2,596 as stage IIIC), and 872 as stage IV (184 as stage IVA and 688 as stage IVB) (**Table 1**).

2. Comparison of 5-year survival rates between FIGO1988 and FIGO2014

Stage I to stage IV

The 5-year survival rates in FIGO1988 were 91.4% in stage I, 77.1% in stage II, 48.9% in stage III, and 33.4% in stage IV, with significant differences between all stages (**Fig. 2A**, $p < 0.001$ between

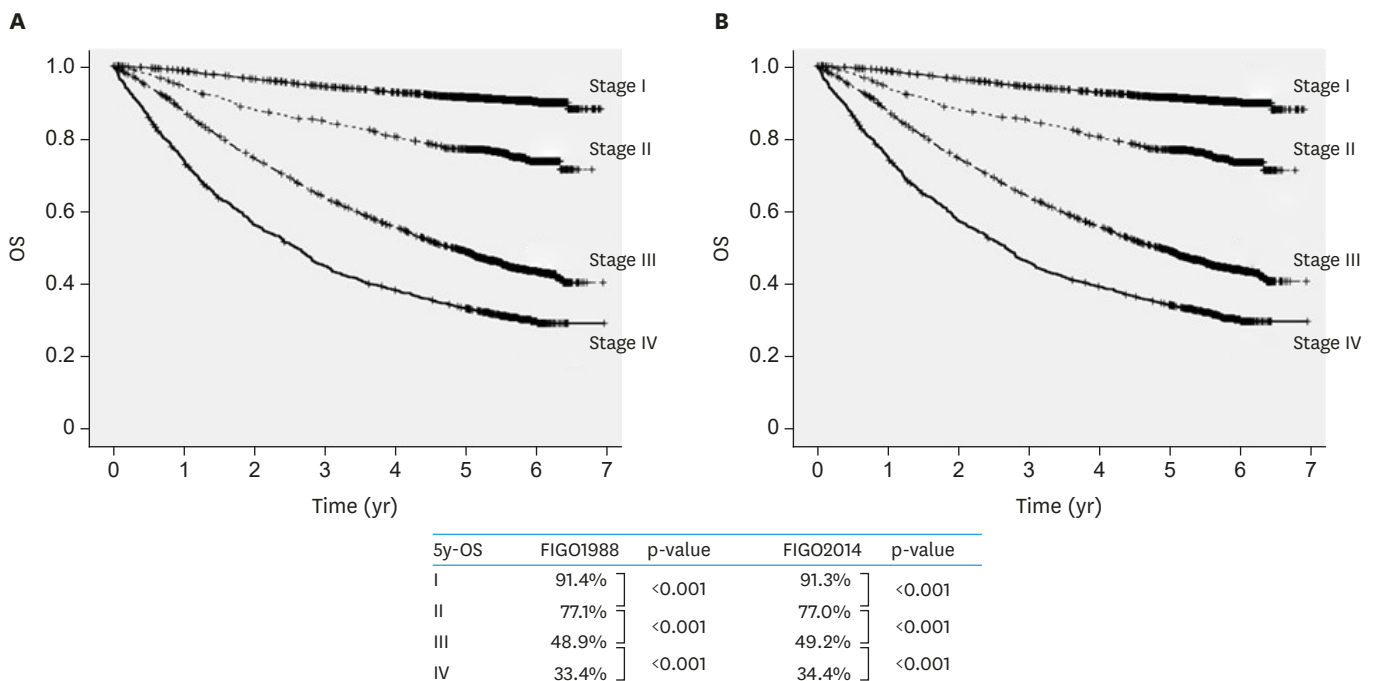


Fig. 2. OS in patients with stage I to IV ovarian cancer. (A) FIGO1988 staging system, (B) FIGO2014 staging system. 5y-OS in FIGO2014 were similar to that in FIGO1988 staging system. There were significant differences between all stages in FIGO1988 and FIGO2014. 5y-OS, 5-year overall survival rate; FIGO, International Federation of Gynecology and Obstetrics; OS, overall survival.

Table 1. Clinicopathological characteristics in our study

Characteristics	Value
Age (yr)	56 (13–93)
Observation period (days)	1,946 (3–2,531)
FIGO 1988 staging	
I	4,400 (45.2)
II	1,022 (10.5)
III	3,442 (35.4)
IV	872 (9.0)
FIGO 2014 staging	
I	4,439 (45.6)
II	1,045 (10.7)
III	3,380 (34.7)
IV	872 (9.0)
Histological type	
Serous	3,290 (33.8)
Endometrioid	1,869 (19.2)
Clear	2,470 (25.4)
Mucinous	1,312 (13.5)
Others	806 (8.2)

Values are presented as number (%).

any 2 stages); and those in FIGO2014 were 91.3% in stage I, 77.0% in stage II, 49.2% in stage III, and 34.4% in stage IV, also with significant differences between all stages (**Fig. 2B**, $p < 0.001$ between any 2 stages).

In the S+E group, the 5-year survival rates in FIGO1988 were 93.3% in stage I, 81.2% in stage II, 53.5% in stage III, and 36.8% in stage IV, while those in FIGO2014 were 93.2% in stage I, 82.0% in stage II, 53.5% in stage III, and 37.6% in stage IV. In the C+M group, the 5-year survival rates were 90.6% in stage I, 68.7% in stage II, 35.7% in stage III, and 28.7% in stage IV, while those in FIGO2014 were 90.5% in stage I, 67.2% in stage II, 36.9% in stage III, and 29.3% in stage IV. In both FIGO1988 and FIGO2014, the prognosis of patients in stages I to IV in the S+E group was significantly more favorable than that in the C+M group.

Stage IC

The 5-year overall survival rate (5y-OS) in FIGO1988 were 94.8% in stage Ia, 92.6% in stage Ic(b), 86.5% in stage Ic(a), 84.6% in stage Ic(1), and 85.0% in stage Ic(2), with significant differences between Ia and Ic(b) ($p = 0.041$), or Ic(b) and Ic(a) ($p < 0.001$). There was no significant difference between stages Ic(a) and Ic(1) ($p = 0.704$), or Ic(1) and Ic(2) ($p = 0.915$) (**Fig. 3A**); and those in FIGO2014 were 94.9% in stage IA, 92.3% in stage IC1, 86.1% in stage IC2, and 84.9% in stage IC3, with significant differences between IA and IC1 ($p = 0.012$), or IC1 and IC2 ($p < 0.001$). There was no significant difference between stages IC2 and IC3 ($p = 0.490$) (**Fig. 3B**).

The 5-year survival rates in the S+E group in FIGO1988 were 95.4% in stage Ia, 95.2% in stage Ic(b), 90.2% in stage Ic(a), 89.1% in stage Ic(1), and 86.5% in stage Ic(2), with significant differences between Ic(b) and Ic(a) ($p = 0.007$). There was no significant difference between stages Ic(a) and Ic(1) ($p = 0.884$), Ic(1) and Ic(2) ($p = 0.109$). The 5-year survival rates in the S+E group in FIGO2014 were 95.4% in stage IA, 94.9% in stage IC1, 89.8% in stage IC2, and 87.1% in stage IC3, with significant differences between IC1 and IC2 ($p = 0.008$). There was no significant difference between stages IA and IC1 ($p = 0.745$), or IC2 and IC3 ($p = 0.219$).

The 5-year survival rates in the C+M group in FIGO1988 were 94.8% in stage Ia, 91.2% in stage Ic(b), 83.9% in stage Ic(a), 82.3% in stage Ic(1), and 84.2% in stage Ic(2), with

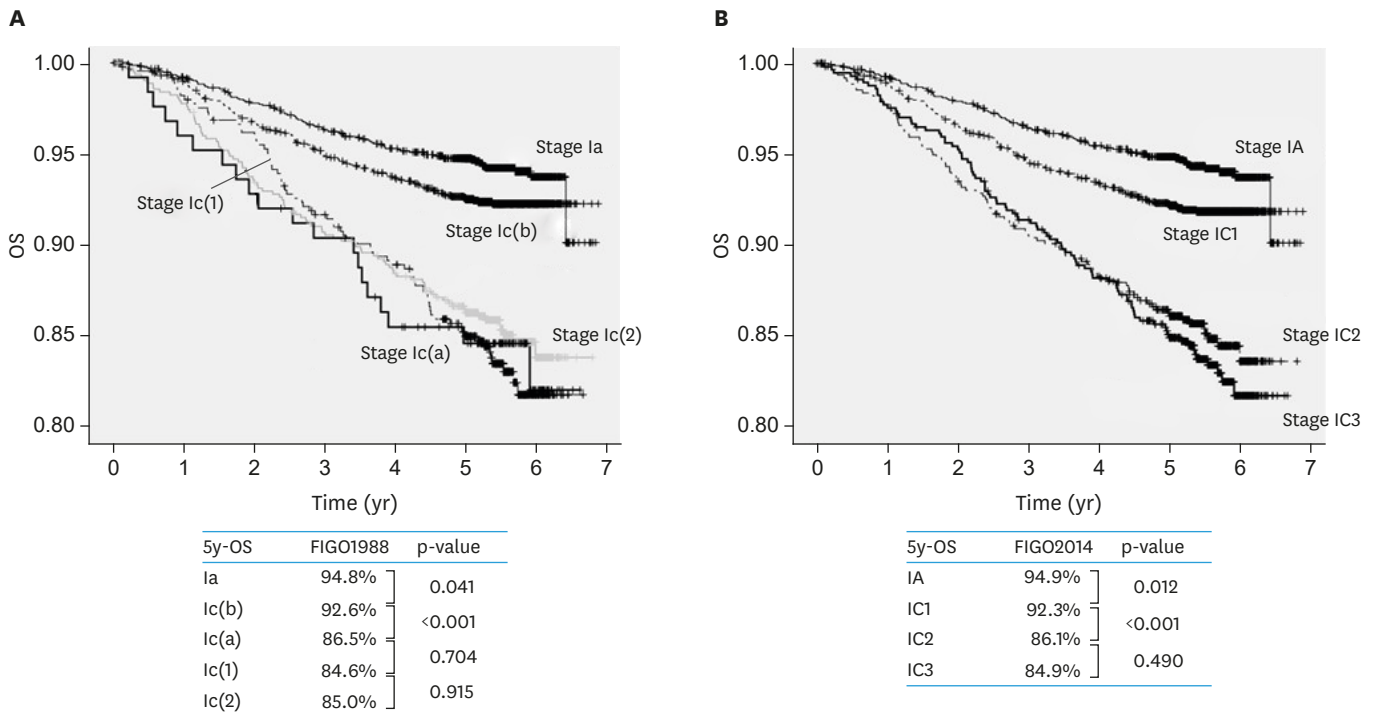


Fig. 3. OS in patients with stage IA and IC ovarian cancer. (A) FIGO1988 staging system. There were significant differences of 5y-OS between stage Ia and Ic(b), or Ic(b) and Ic(a). There was no significant difference between stage Ic(a) and Ic(1), or Ic(1) and Ic(2). (B) FIGO2014 staging system. There were significant differences of 5y-OS between stage IA and IC1, or IC1 and IC2. There was no significant difference between stage IC2 and IC3. 5y-OS, 5-year overall survival rate; FIGO, International Federation of Gynecology and Obstetrics; OS, overall survival.

significant differences between Ia and Ic(b) ($p=0.010$), Ic(b) and Ic(a) ($p<0.001$). There was no significant difference between stages IC(a) and Ic(1) ($p=0.850$), or Ic(1) and Ic(2) ($p=0.800$). The 5-year survival rates in the C+M group in FIGO2014 were 95.0% in stage IA, 90.9% in stage IC1, 84.0% in stage IC2, and 83.8% in stage IC3, with significant differences between IA and IC1 ($p=0.003$), IC1 and IC2 ($p<0.001$). There was no significant difference between stages IC2 and IC3 ($p=0.877$).

Stage IIIA1 and stage IIIC

The 5-year survival rates in FIGO1988 were 69.5% in stage IIIa, 59.0% in stage IIIb, and 46.6% in stage IIIc, with significant differences between IIIa and IIIb ($p=0.009$), IIIb and IIIc ($p<0.001$) (**Fig. 4A**); and those in FIGO2014 were 75.6% in stage IIIA1, 68.9% in stage IIIA2, 58.6% in stage IIIB, and 44.4% in stage IIIC, with significant differences between IIIA2 and IIIB ($p=0.009$), IIIB and IIIC ($p<0.001$). There was no significant difference between stages IIIA1 and IIIA2 ($p=0.153$) (**Fig. 4B**).

The 5-year survival rates in the S+E group in FIGO1988 were 81.0% in stage IIIa, 66.6% in stage IIIb, and 51.0% in stage IIIc, with significant differences IIIa and IIIb ($p<0.001$), IIIb and IIIc ($p<0.001$); and those in FIGO2014 were 80.6% in stage IIIA1, 79.9% in stage IIIA2, 67.6% in stage IIIB, and 48.5% in stage IIIC, with significant differences between IIIA2 and IIIB ($p=0.012$), IIIB and IIIC ($p<0.001$). There was no significant difference between stages IIIA1 and IIIA2 ($p=0.841$).

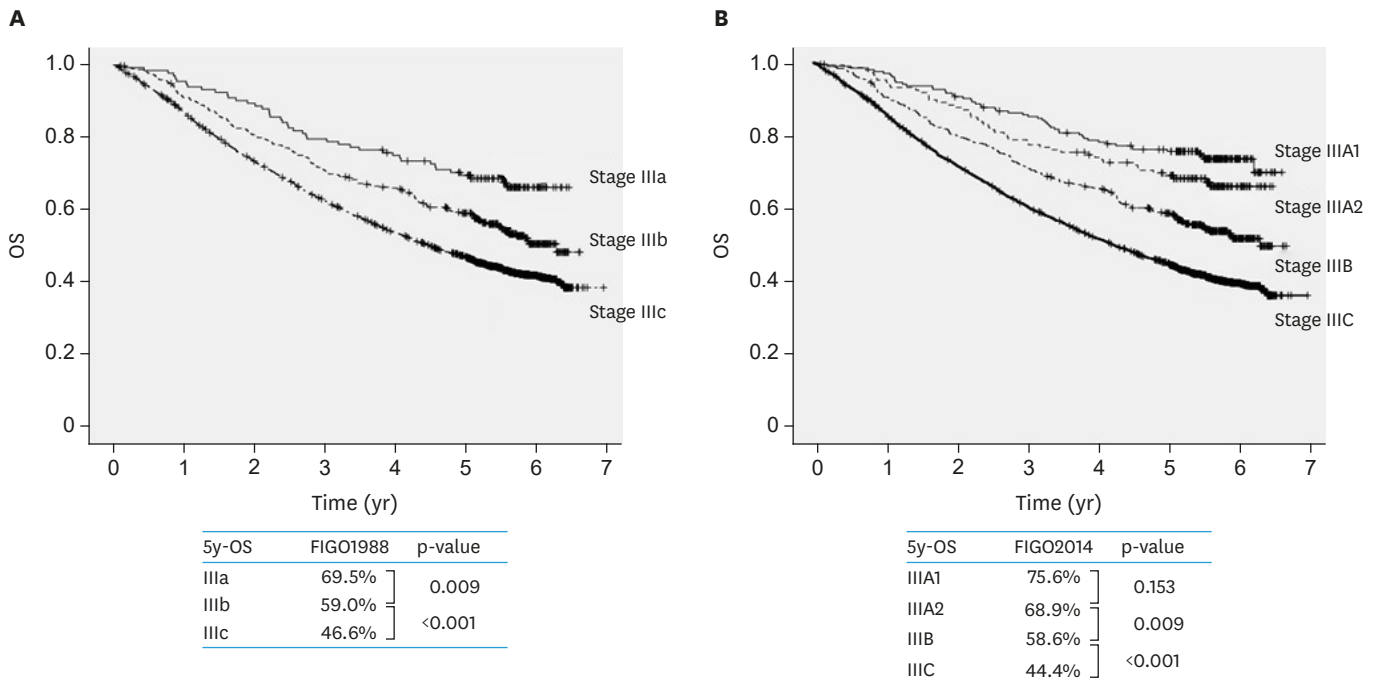


Fig. 4. OS in patients with stage III ovarian cancer. (A) FIGO1988 staging system. There were significant differences of 5y-OS between IIIa and IIIb, or IIIb and IIIc. (B) FIGO2014 staging system. There were significant differences of 5y-OS between IIIA2 and IIIB, or IIIB and IIIC. There was no significant difference between IIIA1 and IIIA2.

5y-OS, 5-year overall survival rate; FIGO, International Federation of Gynecology and Obstetrics; OS, overall survival.

The 5-year survival rates in the C+M group in FIGO1988 were 53.3% in stage IIIa, 41.2% in stage IIIb, and 33.1% in stage IIIc, with significant differences IIIa and IIIb ($p=0.008$), IIIb and IIIc ($p=0.047$); and those in FIGO2014 were 65.2% in stage IIIA1, 53.2% in stage IIIA2, 36.7% in stage IIIB, and 30.4% in stage IIIC, with a significant difference between IIIA2 and IIIB ($p=0.017$). There was no significant difference between stages IIIA1 and IIIA2 ($p=0.212$), IIIB and IIIC ($p=0.060$).

Lymph node enlargement on palpation and histopathological lymph node metastasis

In FIGO2014, lymph node enlargement confirmed on palpation is not classified as lymph node metastasis. However, if patients in stage IA to stage IIB with suspected lymph node metastasis after lymph node enlargement found on palpation are defined as stage IIIA1*, the 5-year survival rates in stage IIIA1* and stage IIIA1 were 71.8% and 75.8%, respectively, with no significant difference ($p=0.216$). The 5-year survival rates were 83.3% and 80.6%, respectively, in the S+E group, and 57.3% and 65.2%, respectively, in the C+M group, with no significant difference between the stages in either group ($p=0.670, 0.527$).

Stage IVA and stage IVB*

In FIGO1988, the 5-year survival rates in stage IV were 33.4% in all patients, 36.8% in the S+E group, and 28.7% in the C+M group. In FIGO2014, the 5-year survival rates in stage IVA* and IVB were 43.1% and 32.1%, with a significant difference ($p=0.002$) (Fig. 5); 44.3% and 35.7% in the S+E group, with no significant difference ($p=0.059$); and 45.0% and 25.2%, in the C+M group, with a significant difference ($p=0.022$).

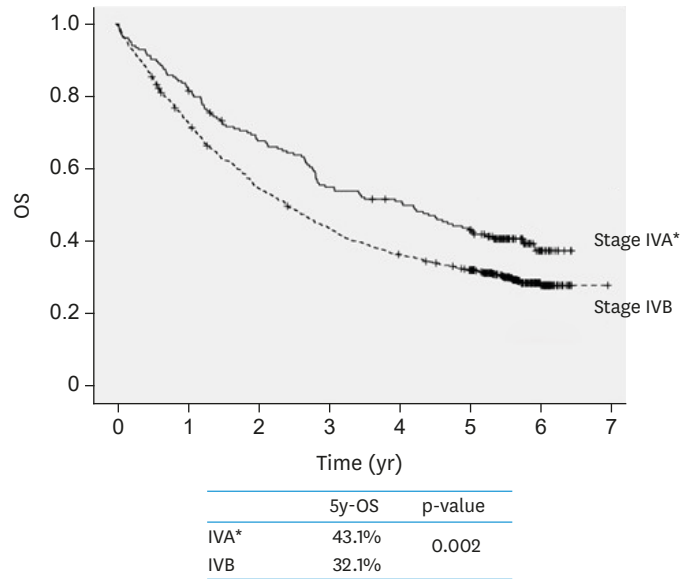


Fig. 5. OS in patients with stage IV ovarian cancer. 5y-OS of stage IVB were significantly poorer than that of stage IVA* in FIGO 2014 staging system for ovarian cancer. 5y-OS, 5-year overall survival rate; FIGO, International Federation of Gynecology and Obstetrics; OS, overall survival.

DISCUSSION

In this study, we analyzed data from the GCR of JSOG, and thus the study includes a large number of patients with ovarian cancer in Japan. The GCR of JSOG includes about 70% of cancer patients in Japan, and gynecological oncologists register patients at medical facilities where they provide treatment for a gynecological tumor.

Of the characteristics of the FIGO2014 classification, we mainly analyzed the validity of the revised subclassification of stage IC, changes in weighting of lymph node metastasis in stage III, and the subclassification of stage IV. Since this was a retrospective study using data collected for 5 years from 2004 to 2008 before the FIGO stages were revised, some clinical data required for reclassification to FIGO2014 were not available. Therefore, most patients who were classified in stage IIc in FIGO1988 could not be reclassified, and had to be considered as unclassified in stage II. In FIGO2014, patients with lymph node metastasis based on cytological or histological diagnosis are classified into stage IIIA1 or higher, but those found to have an enlarged lymph node based on touch or diagnostic imaging are not considered positive for lymph node metastasis. Based on this, patients diagnosed with lymph node metastasis based only on palpation or diagnostic imaging in the GCR were reclassified into stage IIB or lower. Regarding stage IV, since cytopathologic examinations of pleural fluid are not included in the GCR, patients with pleural dissemination only were reclassified into stage IVA* for convenience, and this incorrect classification is a limitation of this study. In addition, only OS is recorded for prognosis in the GCR, and progression free survival is not entered. Therefore, only OS was analyzed for prognosis in this study. Despite these limitations, the study has an advantage over previous similar reports due to the larger number of subjects [6,7].

There was a significant difference in 5-year OS among stage I, II, III, and IV in FIGO1988 and FIGO2014, suggesting that both classifications clearly reflect the prognosis. Regarding stage IC, there were no significant differences in 5y-OS among stage Ic(a), Ic(1), and Ic(2) in FIGO1988,

and between stage IC2 and IC3 in FIGO2014. Sartorius et al. found no significant difference in prognosis between stage IA and IC [8], while Suh et al. suggested significant differences among all of stage IC1, IC2, and IC3 [9], indicating that various findings are possible. In our study, prognosis in stage IC1 differed significantly compared to stage IC2 and IC3, but those in stages IC2 and IC3 were similar. The prognosis did not differ significantly between stages IA and IC1 in the S+E group, but was significantly different in the C+M group, and thus we believe that the stage IC1 classification is important because there are many patients with clear cell carcinoma especially in Japan. Intraoperative capsular rupture (stages Ic[b] and IC1) has been discussed as a factor in a poor prognosis [10]. Ovarian cancer may exhibit strong adhesions with surrounding tissues, and this is particularly common in ovarian clear cell carcinoma. All intraoperative ruptures due to strong adhesions have generally been classified as stage IC, but the FIGO guidelines describe “Dense adhesions with histologically proven tumor cells justifying upgrading to stage II” [1]. Therefore, some cases registered as stage IC1 may have been more appropriately diagnosed as stage II.

Regarding stage III, patients with lymph node metastasis who were classified into stage IIIc in FIGO1988 were reclassified into stage IIIA1 in FIGO2014. Prognosis did not differ significantly between stages IIIA1 and IIIA2 in FIGO2014, but was significantly different between stages IIIB and IIIC. Based on this, it is appropriate for patients with lymph node metastasis to be classified into stage IIIA1, rather than stage IIIC. The results of our study support previous reports in which patients with lymph node metastasis only had a more favorable prognosis than those with peritoneal metastasis [11,12]. In contrast, there was no significant difference between patients diagnosed with lymph node metastasis based on touch, or diagnostic imaging and those with a pathological diagnosis of lymph node metastasis. Therefore, for staging, lymph node metastasis diagnosed by touch and diagnostic imaging may be considered similar to that based on cytological or histological diagnosis.

Regarding stage IV, the prognosis of patients with pleural dissemination was better than that of other patients, especially in the C+M group. Since the prognosis of patients who are positive in a cytopathologic examination of pleural fluid may be better than that with pleural dissemination, it is appropriate to subclassify patients in stage IV. However, it reported that there was no significant difference in prognosis between stages IVA and IVB [13], and thus it was a limitation of our study that we could not extract patients who were positive in cytopathologic examination of pleural fluid.

The strength of this study is that we were able to clarify the characteristics of ovarian cancer in Japanese patients as a whole by using data from the gynecologic cancer registry in Japan. The limitation of this analysis is that all prognostic factors for ovarian cancer could not be included. The gynecologic cancer registry of JSOG includes age, progression, histology, and simple treatment methods, but does not include representative prognostic factors for ovarian cancer such as PS, surgical procedure, chemotherapy regimen and cycle, and presence or absence of residual tumor. Therefore, multivariate analysis including these prognostic factors could not be performed. Instead, univariate analysis was performed for each histological type with or without chemosensitivity.

The results of our study suggest that changes in classification for stage III and stage IV are appropriate, but that the subclassification for stage IC might be too detailed. The finding that histological type can affect the prognosis of patients in individual stages was also useful. Since stage II could not be subclassified based on the GCR of JSOG, we hope to confirm its validity by analyzing the prognosis of patients who will be newly classified in the future.

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