Full title

Impact of surgical staging in stage I clear cell adenocarcinoma of the ovary

Short title

Surgical staging in stage I CCC of the ovary

Authors' full names, highest academic degrees and affiliations

Kayo Suzuki, M.D. *, Satoshi Takakura, M.D., Ph.D. †, Motoaki Saito, M.D., Ph.D. †, Asuka Morikawa, M.D. ‡, Jiro Suzuki, M.D. §, Kazuaki Takahashi, M.D. †, Chie Nagata, M.D., Ph.D., M.P.H. †, Nozomu Yanaihara, M.D., Ph.D. †, Hiroshi Tanabe, M.D., Ph.D. *, Aikou Okamoto, M.D., Ph.D. †

* Department of Obstetrics and Gynecoloy, The Jikei University Kashiwa Hospital, Kashiwa, Japan

† Department of Obstetrics and Gynecology, The Jikei University School of Medicine, Tokyo, Japan

‡ Department of Obstetrics and Gynecology, The Jikei University Daisan Hospital, Tokyo, Japan

§ Department of Obstetrics and Gynecology, The Jikei University Katsushika Medical Center, Tokyo, Japan

Address correspondence and reprint requests to:

Satoshi Takakura, Department of Obstetrics and Gynecology, The Jikei University School of Medicine, 3-25-8 Nishi-shinbashi, Minato-ku, Tokyo 105-8461, Japan.
Tel.: +81 3 3433 1111, ext 3521; Fax: +81 3 3433 1219; E-mail: stakakur@jikei.ac.jp

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Disclosure

The authors declare that there is no conflict of interest.

Abstract

Aim: The aim of this study was to evaluate the impact of surgical staging in stage I clear cell adenocarcinoma of the ovary (CCC).

Methods: We performed a retrospective review of 165 patients with stage I CCC treated with optimal or non-optimal staging surgery.

Results: The median follow-up period in this study was 67 months. No significant difference was detected in recurrence-free survival (RFS) or overall survival (OS) between patients optimally and non-optimally staged (RFS: p=0.434; OS: p=0.759). The estimated 5-year RFS and OS rates were 92.1% and 95.3% in patients with stages IA/IC1 and 81.0% and 83.7% in stages IC2/IC3, respectively. The multivariate analysis indicated that stages IC2/IC3 predicted worse RFS and OS than stages IA/IC1 in stage I CCC patients (RFS: p=0.011; OS: p=0.011). Subsequently, we investigated the impact of surgical staging, respectively, in stages IA/IC1 and stages IC2/IC3. Significant differences were observed in PFS and OS between patients optimally and non-optimally staged with stages IA/IC1 (RFS: p=0.021; OS: p=0.024), but no significant difference was found in those with stages IC2/IC3. The multivariate analysis indicated that non-optimal staging surgery predicted worse RFS than the optimal staging surgery in stages IA/IC1 CCC patients (p=0.033). Additionally, we investigated the impact of surgical staging for stages IA/IC1 in the adjuvant chemotherapy group. The 5-year RFS and OS rates in patients optimally and non-optimally staged with stages IA/IC1 in the adjuvant chemotherapy group were 97.8% and 100%, and 85.2% and 89.4%, respectively. The multivariate analysis indicated that non-optimal staging surgery predicted worse RFS than the optimal staging surgery for stages IA/IC1 patients in the adjuvant chemotherapy group (p=0.019).

Conclusion: The prognosis for women with stage 1A/IC1 is very good. Surgical staging category was the only independent prognostic factor for RFS in stages IA/IC1 CCC.

Key words: Ovarian cancer, Clear cell carcinoma, Surgical staging, Lymphadenectomy, Adjuvant chemotherapy

Introduction

Clear cell adenocarcinoma of the ovary (CCC) has been recognized as a distinct histologic entity under the World Health Organization (WHO) classification of ovarian tumors since 1973. It is characterized by its association with endometriosis and frequent mutations of ARID1A and PIK3CA.[1] CCC is the second most common type of the epithelial ovarian cancer (EOC) in Japan, representing 23.7% of ovarian malignancies.[2] Women with CCC are more likely to present at a younger age, to be diagnosed with stage I–II disease, and have a poorer prognosis compared to serous adenocarcinoma. (SC) [3]

Trimbos JB et al. [4] performed a preplanned combined analysis of two parallel randomized clinical trials [International Collaborative Ovarian Neoplasm 1 (ICON1) and European Organisation for Research and Treatment of Cancer-Adjuvant ChemoTherapy In Ovarian Neoplasm (EORTC-ACTION)] in early-stage EOC that compared platinum-based adjuvant chemotherapy with observation following initial surgery. Adjuvant chemotherapy improved overall survival (OS) and recurrence-free survival (RFS) at 5 years in patients with early-stage EOC.[4-6] EORTC-ACTION trial was performed to test the efficacy of adjuvant chemotherapy for early-stage EOC, with emphasis on the extent of surgical staging. [5] Among the patients in the observation arm, optimal staging was associated with a statistically significant improvement in OS and RFS, whereas no such association was observed in the chemotherapy arm. In the non-optimally staged patients, adjuvant chemotherapy was associated with statistically significant improvements in survivals.[5] Furthermore, staging adequacy was an independent prognostic factor for survival.[5] It was concluded that the survival benefit of adjuvant chemotherapy was apparently limited to patients with non-optimal surgical staging, that is, to patients who were at higher risk of unappreciated residual disease.[5] The proportion of patients with CCC was only 14%.[5]

A staging laparotomy is an important part of early management for EOC [7]. As outlined by the 1988 International Federation of Gynecology and Obstetrics (FIGO), recommended staging procedures include assessment for metastasis through biopsies of suspicious and benign appearing tissues in the abdominal cavity and within retroperitoneal lymphatic channels alongside pelvic and the para-aortic lymph bearing tissues. [8, 9] The extent of lymphadenectomy which is required to adequately presume early-stage EOC is not well defined. [9] The FIGO

recommendations state that staging should include “selected lymphadenectomy of the pelvic and para-aortic lymph nodes, at least ipsilateral if the malignancy is unilateral”. [7] In fact, the optimal staging that was defined in EORTC-ACTION trial included only iliac and periaortic lymph node sampling, but that did not included systematic pelvic lymphadenectomy (PEL-LNX) or para-aortic lymphadenectomy (PAO-LNX). On the other hand, comprehensive staging surgery including PEL-LNX and PAO-LNX is recommended by several recent guidelines and often upstages women presumed to have early-stage disease. [10-11] It was reported that the mean incidence of lymph node metastases in clinical stage I-II EOC and CCC were 14.2% and 14.4%, respectively.[12]

To evaluate the impact of surgical staging in stage I CCC, we retrospectively reviewed outcomes in 165 stage I CCC patients who underwent optimal or non-optimal surgical staging.

Patients and Methods

Patients

Between 2000 and 2009, 165 patients with stage I CCC were identified by reviewing the medical records of the four hospitals affiliated to The Jikei University School of Medicine. A diagnosis of pure-type CCC was made in all these patients. Pure-type CCC was diagnosed as previously described. [13] Surgical staging was assessed according to the FIGO (approved by the FIGO Executive Board in October 2012 and published in January 2014). [14] In the new FIGO classification, stage IC1 was defined as tumor limited to 1 or both ovaries with only intraoperative capsule rupture (no surface involvement and negative cytology), stage IC2 was defined as that with surface involvement or with preoperative capsule rupture (negative cytology), and stage IC3 was defined as that with malignant cells in the ascites or peritoneal washings. [14]

Surgical staging

For surgical staging, upon entering the abdominopelvic cavity, the peritoneal fluid was taken for cytological examination (peritoneal fluid cytology). In the absence of ascites, irrigation was performed and washings were taken for cytological examination (peritoneal washing cytology). Further, surgical staging was consisting of at least examination to look for capsular rupture of ovarian tumor, and careful inspection and palpation of all peritoneal surfaces, with biopsies of any

suspected lesions, such as adhesions adjacent to the ovarian tumor. In addition, we defined three types of the surgical staging categories; optimal, minimal, and inadequate (Table 1). In addition, we defined non-optimal staging surgery as minimal or inadequate staging surgeries. Surgeries with selected lymphadenectomy of the pelvic and/or para-aortic lymph nodes were belonged to minimal or inadequate staging surgery, but not to optimal. In principle, the choice between systematic and selected lymphadenectomy in each patient was determined by the institutional treatment policy in staging surgery for presume early stage EOC at the time of surgery. The number of lymph nodes which were removed and pathologically examined was not considered for the completion of the lymphadenectomy.

Adjuvant chemotherapy

In 165 patients, 146 (88.5%) were treated postoperatively with the adjuvant chemotherapy; 96 (58.2%) with taxane plus platinum (TP), 46 (27.9%) with irinotecan hydrochloride plus cisplatin (CPT-P), 2 (1.2%) with conventional platinum-based chemotherapy, and 2 (1.2%) with irinotecan hydrochloride plus mitomycin-C. Nineteen (11.5%) patients did not receive the adjuvant chemotherapy due to older age, the patients' wishes, or the decision of each institution.

Follow-up and analysis

At the end of treatment, all patients underwent regular follow-up, consisting of clinical checkups such as a pelvic examination, ultrasonographic scan, CA125 evaluation, and periodic CT scan. Survival information was available on all patients. OS was assessed from the date of initial surgery to the time of death or last contact. RFS was defined as the time from initial surgery until recurrence or last contact. We designed present study to evaluate the impact of surgical staging by the univariate and multivariate analysis in the whole sample for stage I CCC and in the two-subgroups for stages IA/IC1 and stages IC2/IC3 separately because several previous reports revealed that CCC patients with stages IC2/IC3 showed poor RFS and OS than those with stages IA/IC1. [15-17] Patient survival was calculated by using the Kaplan-Meier method and the difference between groups was assessed by the log-rank test. The multiple Cox regression model was used to explore the impact of specific prognostic factors on OS and RFS. Stat View software version 5.0 (SAS, Cary, N.C., USA) was used to analyze the data.

Results

Patient characteristics

In 165 patients, 80 were staged with optimal staging surgery, 74 with minimal staging surgery, and 11 with inadequate staging surgery. Median age in patients optimally and non-optimally staged were 52 years (range: 33-74) and 54 (range: 30-99), respectively (p=0.114). Of the 80 optimally staged women, 13 were stage IA, 43 stage IC1, 6 stage IC2 and 18 stage IC3 , while in the 85 non-optimally staged women, 29 were stage IA, 43 stage IC1, 7 stage IC2 and 6 stage IC3 (p=0.007). All 80 women optimally staged underwent systematic PEL-LNX and PAO-LNX and 59 of 85 women non-optimally staged underwent selected lymphadenectomy. Meanwhile, 26 of 85 women non-optimally staged did not receive lymphadenectomy due to the patients' wishes or the decision of each institution (p<0.001). Seventy-eight of 80 (97.5%) patients optimally staged and 68 of 85 (80.0%) non-optimally staged were treated with adjuvant chemotherapy (p=0.001). (Table: patient characteristics in supplemental digital content)

Prognostic factors and survival in all stage I patients

The median follow-up period in this study was 67 months (range: 3-148 months). Recurrence of disease was observed within and over 2 years after staging surgery in 5 and 2 of 80 patients optimally staged and 6 and 6 of 85 non-optimally staged, respectively. In 1 patient optimally staged and 4 non-optimally staged, first relapse occurred in the pelvic and/or para-aortic lymph nodes within 2 years after staging surgery. In addition, recurrence of disease was observed in 17 of 146 patients in the chemotherapy group and 2 of 19 in the observation group. One patient without recurrence died of leukemia.

The 5-year RFS and OS rates in 165 stage I patients by each category are summarized in Table 2. The significance of the RFS and OS distribution in each group as assessed by the log-lank test is also summarized in Table 2. In the whole population, no significant difference was detected in RFS or OS between patients optimally and non-optimally staged (RFS: p=0.434; OS: p=0.759). There were significant differences in RFS and OS between patients with stages IA/ IC1 and stages IC2/IC3 (RFS: p=0.017; OS: p=0.012) (Figure 1). No significant difference was found in RFS or OS by age or adjuvant chemotherapy.

Multivariate analysis using the Cox regression model was performed to further assess the factors targeted, and the results are shown in Table 2. The analysis indicated that stages IC2/IC3 predicted worse RFS and OS than stages IA/IC1 [RFS: p=0.011, Relative risk (RR) 3.321, 95% Confidence interval (CI) 1.313-8.403;

OS: p=0.011, RR 4.202, 95%CI 1.384-12.755]. Stage was the only independent prognostic factor for RFS and OS in stage I CCC (Table 2).

Since the patients were treated with adjuvant chemotherapy more frequently in the optimally staged group (97.5%) than in the non-optimally staged group (80.0%), we performed a subset analysis in patients treated with adjuvant chemotherapy. Among 146 patients received adjuvant chemotherapy, no significant difference was observed in RFS or OS between patients optimally and non-optimally staged (RFS: p=0.432; OS: p=0.919), aged <50 years or ≥50 years (RFS: p=0.240; OS: p=0.330) or treated with TP and CPT-P (RFS: p=0.523; OS: p=0.929). There was a significant difference in RFS and OS between patients with stages IA/ IC1 and stages IC2/IC3 (RFS: p=0.010; OS: p=0.004). The multivariate analysis indicated that stages IC2/IC3 predicted worse RFS and OS than stages IA/IC1 (RFS: p=0.008, RR 3.802, 95%CI 1.423-10.152; OS: p=0.006, RR 5.470, 95%CI 1.636-18.282). As a result, stage was the only independent prognostic factor for RFS and OS in the adjuvant chemotherapy group while surgical staging category, age, or regimen of adjuvant chemotherapy was not.

Prognostic factors and survival in patients with stages IA/IC1

The 5-year RFS and OS rates in 128 stages IA/IC1 patients by each category are summarized in Table 3. The significance of the RFS and OS distribution in each group as assessed by the log-lank test is also summarized in Table 3. In patients with stages IA/IC1, significant differences were observed in PFS and OS between patients optimally and non-optimally staged (RFS: p=0.021; OS: p=0.024; Figure 2). No significant difference was found in RFS or OS by age, stage or adjuvant chemotherapy.

Multivariate analysis using the Cox regression model for RFS was performed to further assess the factors targeted, and the results are shown in Table 3. The analysis indicated that non-optimal staging surgery predicted worse RFS than the optimal staging surgery (p=0.033, RR 9.551, 95% CI 1.194-76.355). As a result, surgical staging category was the only independent prognostic factor for RFS in stages IA/IC1 CCC (Table 3). Multivariate analysis for OS could not be performed due to no event in patients optimally staged.

As with the analysis in the whole population, we added a subset analysis for the impact of surgical staging in patients with stages IA/IC1 in the adjuvant chemotherapy group. The 5-year RFS and OS rates were 97.8% and 100% in 55 stages IA/IC1 patients optimally staged and 83.3% and 91.7% in 56 stages IA/IC1patients non-optimally staged, respectively (Figure 3). Significant

differences were observed in PFS and OS between patients optimally and non-optimally staged (RFS: p=0.021; OS: p=0.033; Figure 3), while no significant difference was observed in RFS or OS between patients aged <50 years or ≥50 years (RFS: p=0.290; OS: p=0.329), stage IA or IC (RFS: p=0.193; OS: p=0.590) and treated with TP or CPT-P (RFS: p=0.939; OS: p=0.549). The multivariate analysis indicated that non-optimal staging surgery predicted worse RFS than the optimal staging surgery (p=0.019, RR 13.495, 95%CI 1.543-117.647) for stages IA/IC1 patients in the adjuvant chemotherapy group. As a result, surgical staging category was the only independent prognostic factor for RFS in stages IA/IC1 CCC patients treated with adjuvant chemotherapy, while age, stage or regimen of adjuvant chemotherapy was not. Multivariate analysis for OS could not be performed due to no event in patients optimally staged.

Prognostic factors and survival in patients with stages IC2/IC3

In patients with stages IC2/IC3, no significant difference was observed in RFS or OS between patients optimally and non-optimally staged (RFS: p=0.417; OS: p=0.923), aged <50 years and ≥50 years (RFS: p=0.774; OS: p=0.229), or with stage IC2 and IC3 (RFS: p=0.623: OS: p=0.196). Survival differences between the adjuvant chemotherapy group and the observation group were not assessed since only 2 patients were in the observation group.

As with the analysis in patients with stages IA/IC1, we added a subset analysis for the impact of surgical staging in patients with stages IC2/IC3 in the adjuvant chemotherapy group. The 5-year RFS and OS rates were 73.0% and 72.1% in 23 stages IC2/IC3 patients optimally staged and 83.3% and 91.7% in 12 stages IC2/IC3 patients non-optimally staged, respectively (Figure 3). In patients with stages IC2/IC3, no significant difference was observed in RFS or OS between patients optimally or non-optimally staged (RFS: p=0.436; OS: p=0.238; Figure 3), aged <50 years or >50 years (RFS: p=0.370; OS: p=0.391), with stage IC2 or IC3 (RFS: p=0.542; OS: p=0.161), or treated with TP or CPT-P (RFS: p=0.615; OS: p=0.561).

Discussion

We retrospectively reviewed 165 stage I CCC patients consisting of 42 (25.5%) with stage IA, 86 (52.1%) with stage IC1, 13 (7.9%) with stage IC2 and 24 (14.5%) with stage IC3. The distribution of sub-stage in our study was similar to several previous reports for Japanese patients with stage I CCC. [16-17] However, the

incidence of stage IA (60.9%) in the Surveillance, Epidemiology and End Results Program (SEER) data was higher than that in our report and previous reports for Japanese patients. [3,16-17] It has long been recognized that CCC is associated with endometriosis. [1] In keeping with the higher incidence of CCC in Asian women, some studies have reported higher prevalence rates of endometriosis in Asian women. [1] In fact, firm adhesion of tumor capsule to the retro-peritoneum and/or the rectum due to endometriosis is commonly observed in Japanese patients with CCC. High incidence of IC1 (intraoperative capsule rupture) in our report and previous reports for Japanese patients was likely due to the adhesion.

Taxane and platinum adjuvant chemotherapy is recommended by several guidelines for stage I CCC patients disregarding the surgical staging category.[18-19] On the other hand, EORTC-ACTION demonstrated that completeness of surgical staging was an independent prognostic factor in early-stage EOC patients, and that adjuvant chemotherapy in early-stage EOC was not effective after optimal surgical staging.[5] It was suggested that adjuvant chemotherapy in early-stage EOC was predominantly effective in patients with occult residual disease and that its effectiveness was dependent on the likelihood of remaining ovarian cancer spread.[5] In terms of lymph node assessment, the optimal staging defined in EORTC-ACTION included only lymph node sampling, but that did not include systematic PEL-LNX and/or PAO-LNX. *Takano M* et al. [20] reported that the incidence of lymph node metastases in patients with clinical stage I CCC who underwent complete PEL-LNX and PAO-LNX was 7.5%. In this study, we detected lymph node metastases in 5 out of 85 patients with clinical stage I CCC who underwent complete PEL-LNX and PAO-LNX (5.9%; data not shown). In addition, first relapse were detected in the pelvic and/or para-aortic lymph nodes within 2 years in 4 non-optimally staged patients, suggesting that they had occult residual disease in lymph nodes at presentation. *Mahdi* et al. [21] reported that there was a trend toward an improved survival when more extensive lymphadenectomy is performed in stage I CCC patients with histologically negative nodes (1-10 vs >10 nodes), although it did not reach statistical significance (p=0.064). Conversely, *Chan JK* et al. [22] demonstrated that lymphadenectomy improved the survival in patients with non–clear cell EOC but not in those with CCC. To evaluate the impact of surgical staging in stage I CCC, we retrospectively reviewed outcomes in 165 stage I CCC patients who underwent optimal staging surgery including systematic PEL-LNX and PAO-LNX or non-optimal staging surgery, but no significant difference was observed in RFS or OS (Table 2, Figure 1). We also

demonstrated that stages IA/IC1 was the only independent predictor of poor RFS and OS in stage I CCC, but that surgical staging category was not (Table 2). *Takano M* et al. [20] retrospectively reviewed outcomes in both 124 CCC patients with pT1pN0M0 and 10 with pT1pN1M0 who underwent complete surgical staging procedures including PEL-LNX and PAO-LNX and 65 with pT1pNxM0 who were assessed for lymph nodes metastases by exploration or sampling. It was reported that peritoneal cytology status was the only independent prognostic factor for RFS, but that completion of surgical staging procedures was not. [20] *Higashi M* et al [17] reported that no significant difference was observed in RFS or OS of CCC patients between IA and IC1, but that CCC patients with IC2/IC3 showed a poorer RFS and OS than those at IC1, and that the capsule status was an independent prognostic factor of a poor RFS and OS. Our results were similar to those previous reports.

In accordance with plans, we also assessed the impact of surgical staging, in stages IA/IC1 and stages IC2/IC3 separately. Significant differences were observed in PFS and OS between patients optimally and non-optimally staged with stages IA/IC1, but no significant difference was found in those with stages IC2/IC3 (Table 3, Figure 2). Moreover, we indicated for the first time that surgical staging category was the only independent prognostic factor for RFS in stages IA/IC1 CCC (Table 3).

Since the patients were treated with adjuvant chemotherapy more frequently in the optimally staged group (97.5%) than in the non-optimally staged group (80.0%), we performed a subset analysis in patients treated with adjuvant chemotherapy. Results in this subset analysis were similar results in all patients. In a subset analysis, the 5-year RFS and OS rates in 55 patients optimally staged with stages IA/IC1 in the adjuvant chemotherapy group were 97.8% and 100%, respectively, and survival were longer than those in 56 stages IA/IC1patients non-optimally staged (Figure 3). We indicated that surgical staging category was the only independent prognostic factor for RFS in stages IA/IC1 CCC patients treated with adjuvant chemotherapy. On the other hand, we cannot compare the outcome associated with adjuvant chemotherapy in each group due to small sample size of the observation group, although no significant difference was observed in RFS or OS by adjuvant chemotherapy and that was not independent prognostic factor in stage I CCC. *Mizuno M* et al [16] reported that the 5-year RFS rates in CCC patients received comprehensive surgical staging and treated with/without adjuvant chemotherapy were 93.8% (n=16) and 100% (n=25) for stage IA, 86.6% (n=75) and 94.1% (n=18) for stage IC1, respectively, and concluded the routine

adjuvant chemotherapy after comprehensive surgical staging may be unnecessary for patients with at least stage IA. *Takada T* et al [23] reported outcome of stage I CCC patients received comprehensive surgical staging consisting of 4 with stage IA and 11 with stage IC1 who received adjuvant chemotherapy, 16 with stage IA and 16 with stage IC1 received no additional therapy. It was reported that no recurrence was observed in stage IA patients, and that the 5-year RFS and OS rates in stage IC1 patients were 87.5% and 100% in the adjuvant chemotherapy group and 74.0% and 76.4% in the observation group, respectively, and suggested that postoperative adjuvant chemotherapy is not necessary for stage IA CCC patients, but that adjuvant chemotherapy suppressed recurrence for stage IC CCC. Our results and previous reports show that the outcome in patients with stages IA/IC1 who received optimal surgical staging and adjuvant chemotherapy are favorable. However, survival benefit of adjuvant chemotherapy in patients with stages IA/IC1, especially in those with stage IC1, is controversial. At the present, Japanese Gynecologic Oncology Group (JGOG) is performing a randomized phase III trial of the necessity of adjuvant chemotherapy in stage I [stage IA/IB with grade2/3 or CCC, stage IC1] EOC after comprehensive staging surgery (JGOG3020, UMIN000008481), and the results are eagerly awaited.

No survival benefit from optimal staging surgery including systematic PEL-LNX and PAO-LNX was found in stages IC2/IC3 patients who received adjuvant chemotherapy in the present study (Figure 3). These results suggest the existence of intra-abdominal micro-dissemination which includes chemoresistant clones in these patients. We could not assess the survival benefit of adjuvant chemotherapy for stages IC2/IC3 in this trial due to small sample size of the observation group. However, *Takada M* [23] et al reported that the 5-year RFS and OS rates in stages IC2/IC3 patients were 69.6% and 75.0% in the adjuvant chemotherapy group and 34.6% and 70.0% in the observation group, respectively suggesting that adjuvant chemotherapy suppressed recurrence in stages IC2/IC3). In this study, there was no significant difference in RFS and OS between stages IC2/IC3 patients treated with TP and CPT-P therapy as adjuvant chemotherapy. *Takakura S* et al. [24] reported a randomized phase II trial of paclitaxel and carboplatin (TC) therapy versus CPT-P therapy as first line chemotherapy for CCC (JGOG3014). No significant difference was observed in progression-free survival for patients with no residual disease between the two treatment groups. [24] *Kajiyama H* et al. [25] found no significant difference in RFS or OS between stages I/II CCC patients who received TC and various conventional cisplatin-based

chemotherapies. So to improve the prognosis of these patients, effective new antineoplastic agents and molecularly-targeted agents should be evaluated in prospective clinical trials. Since more than 80% of CCC show activation of the AKT-mTOR pathway, exploration of the potential benefit of mTOR inhibitors is of great interest.[26] At present, the Gynecologic Oncology Group (GOG) is performing a phase II trial of temsirolimus in combination with TC followed by temsirolimus consolidation as first-line therapy in the treatment of stage III-IV CCC (GOG-0268, NCI-2011-02653).

In this retrospective study, the prognosis for women with stage 1A/IC1 CCC is very good. Furthermore, surgical staging category was the only independent prognostic factor for RFS in stages IA/IC1 CCC. The necessity of adjuvant chemotherapy for CCC patients optimally staged with stages IA/IC1 should be verified by a prospective randomized trial.

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Figure legends

Figure 1 Kaplan–Meier curves for recurrence-free survival (RFS: A) and overall survival (OS: B) in patients with stages IA/IC1 and stages IC2/IC3.

Significant differences were observed in RFS and OS between patients with stages IA/ IC1 and stages IC2/IC3 (RFS: p=0.017; OS: p=0.012)

Figure 2 Kaplan–Meier curves for recurrence-free survival (RFS: A) and overall survival (OS: B) in patients with stages IA/IC1 by surgical staging category.

Significant differences were observed in RFS and OS between patients optimally and non-optimally staged (RFS: p=0.021; OS: p=0.024).

Figure 3 Kaplan–Meier curves for recurrence-free survival (RFS) and overall survival (OS: B) in patients received adjuvant chemotherapy by both stage and surgical staging category

Significant difference were observed in RFS and OS between stages IA/IC1 patients optimally and non-optimally staged (RFS: p=0.021; OS: p=0.033), while no significant difference was observed in those between stages IC2/IC3 patients optimally or non-optimally staged (RFS: p=0.436; OS: p=0.238).

Table 1. Surgical staging categories

Surgical staging categories	Requirements for surgical staging
Optimal	Examination to look for capsular rupture of ovarian tumor; inspection and palpation of all peritoneal surfaces; biopsies of any suspected lesions; peritoneal fluid cytology or peritoneal washing cytology; total abdominal hysterectomy; bilateral salpingo-oophorectomy; subtotal (infra-gastroepiploic vessels) omentectomy; pelvic lymphadenectomy†; para-aortic lymphadenectomy.
Minimal	Less than optimal staging but at least examination to look for capsular rupture of ovarian tumor; inspection and palpation of all peritoneal surfaces; biopsies of any suspected lesions; peritoneal fluid cytology or peritoneal washing cytology; total abdominal hysterectomy; bilateral salpingo-oophorectomy; infracolic or subtotal (infra-gastroepiploic vessels) omentectomy.
Inadequate	Less than minimal staging but at least examination to look for capsular rupture of ovarian tumor; inspection and palpation of all peritoneal surfaces; biopsies of any suspected lesions; peritoneal fluid cytology or peritoneal washing cytology; unilateral salpingo-oophorectomy (e.g. fertility-sparing surgery).

† Pelvic lymphadenectomy was the removal of the common, external, and internal iliac nodes, and the obturator node groups to the level of the inguinal ligament; ‡ Para-aortic lymphadenectomy was the removal of node bearing tissues along aorta and vena cava to the level of the renal veins.

Table 2 The recurrence-free and overall survival rates and relative risk of recurrent and death in all patients

Variable (number of patients)	Recurrence-free survival							Overall survival						
	5-year rate (%)	Univariate analysis			Multivariate analysis			5-year rate (%)	Univariate analysis			Multivariate analysis		
		Risk ratio	95% Cl†	P-value	Risk ratio	95% Cl†	P-value		Risk ratio	95% Cl†	P-value	Risk ratio	95% Cl†	P-value
Age														
<50 years (n=63)	91.1	1.367	0.558-3.412	0.484	1.606	0.651-3.966	0.304	91.1	1.273	0.433-3.794	0.653	1.503	0.505-4.470	0.464
≥50 years (n=102)	87.3	1			1			97.5	1			1		
FIGO‡ stage														
IA and IC1 (n=128)	92.1	1			1			95.3	1			1		
IA (n=42)	97.6							97.6						
IC1 (n=86)	89.5							94.2						
IC2 and IC3 (n=37)	81.0	2.782	1.254-10.225	0.017	3.321	1.313-8.403	0.011	83.7	3.499	1.416-17.637	0.012	4.202	1..384-12.755	0.011
IC2 (n=13)	83.9							90.9						
IC3 (n=24)	75.0							74.5						
Surgical staging category														
Optimal (n=80)	92.5	1		0.434	1		0.197	93.7	1		0.759	1		0.463
Non-optimal (n=85)	87.0	1.427	0.489-3.419		1.856	0.726-4.746		91.7	1.179	0.412-3.367		1.527	0.494-4.724	
Minimal (n=74)	87.8							91.9						
Inadequate(n=11)	81.8							90.9						
Adjuvant chemotherapy														
Chemotherapy (n=146)	89.7	1.129	0.279-4.530	0.870	1.169	0.262-5.220	0.838	92.4	1		0.723	1		0.642
Observation (n=19)	89.4	1			1			94.7	1.309	0.257-7.067		1.443	0.307-6.775	

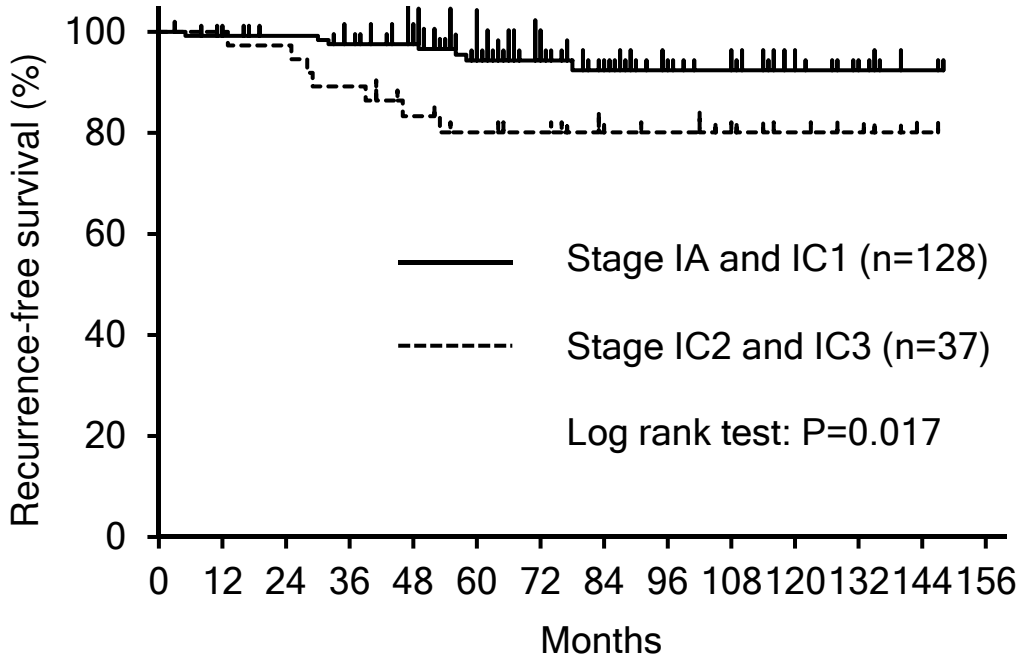
†CI: Confidence interval; ‡: FIGO: International Federation of Gynecology and Obstetrics

Table 3 The recurrence-free and overall survival rates and relative risk of recurrent and death in patients with stages IA and IC1

Variable (number of patients)	Recurrence-free survival							Overall survival			
	5-year rate (%)	Univariate analysis			Multivariate analysis			5-year rate (%)	Univariate analysis		
		Risk ratio	95% Cl†	P-value	Risk ratio	95% Cl†	P-value		Risk ratio	95% Cl†	P-value
Age											
<50 years (n=51)	88.1	1.313	0.393-4.447	0.652	1		0.898	91.4	1.188	0.260-5.461	0.821
≥50 years (n=77)	92.9	1			1.108	0.325-3.602		96.0	1		
FIGO‡ stage											
IA (n=42)	97.6	1		0.071	1		0.058	97.6	1		0.262
IC1 (n=86)	89.5	5.389	0.906-10.803		7.564	0.935-61.350		94.2	3.150	0.517-11.015	
Surgical staging category											
Optimal (n=56)	98.2	1		0.021	1		0.033	100			0.024
Non-optimal (n=72)	87.5	7.679	1.228-13.348		9.551	1.194-76.335		91.6			
Adjuvant chemotherapy											
Chemotherapy (n=111)	92.7	1		0.649	1		0.8305	95.4	1		0.257
Observation (n=17)	88.2	1.423	0.264-8.425		1.187	0.248-5.685		94.1	2.492	0.403-29.646	

†CI: Confidence interval; ‡: FIGO: International Federation of Gynecology and Obstetrics

A


Recurrence-free survival (%)
100
80
60
40
20
0
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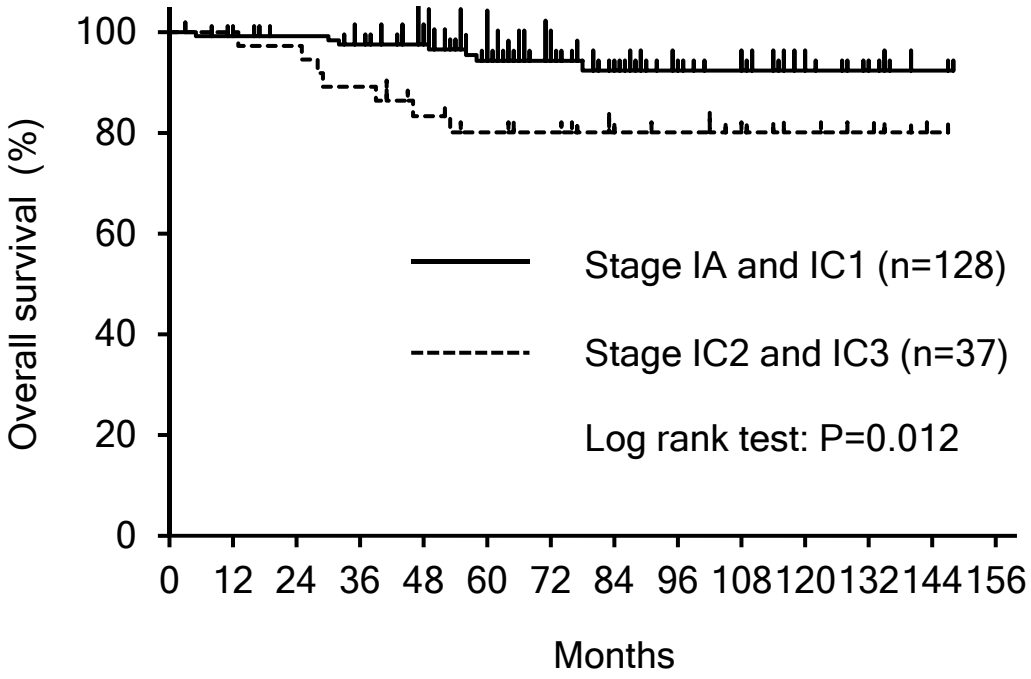
Months
Stage IA and IC1 (n=128)
Stage IC2 and IC3 (n=37)
Log rank test: P=0.017

B


Overall survival (%)
100
80
60
40
20
0
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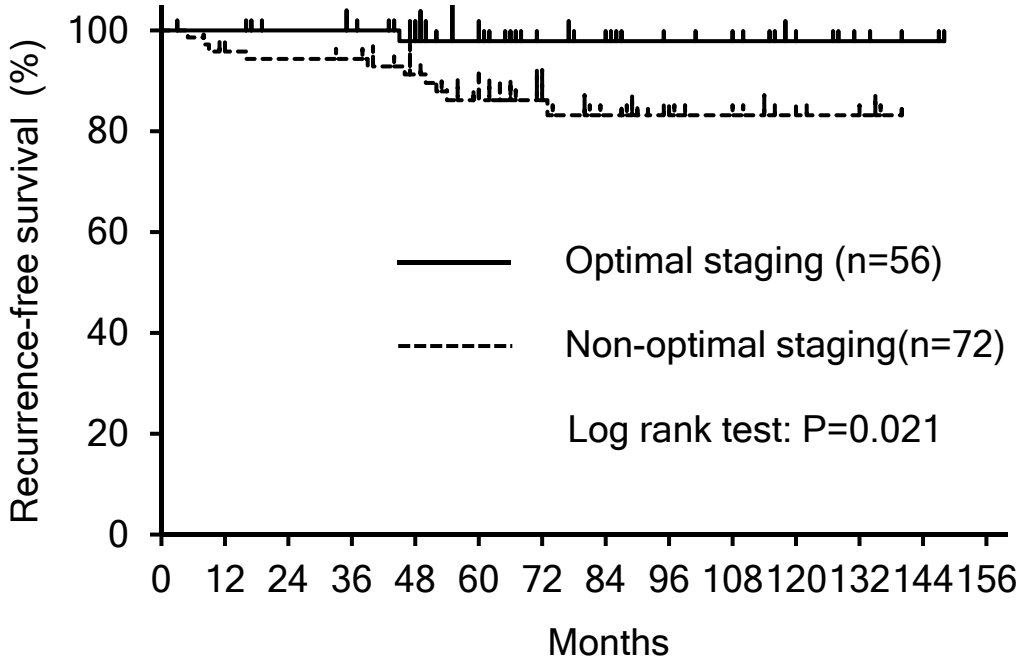
Months
Stage IA and IC1 (n=128)
Stage IC2 and IC3 (n=37)
Log rank test: P=0.012

A


Recurrence-free survival (%)
100
80
60
40
20
0
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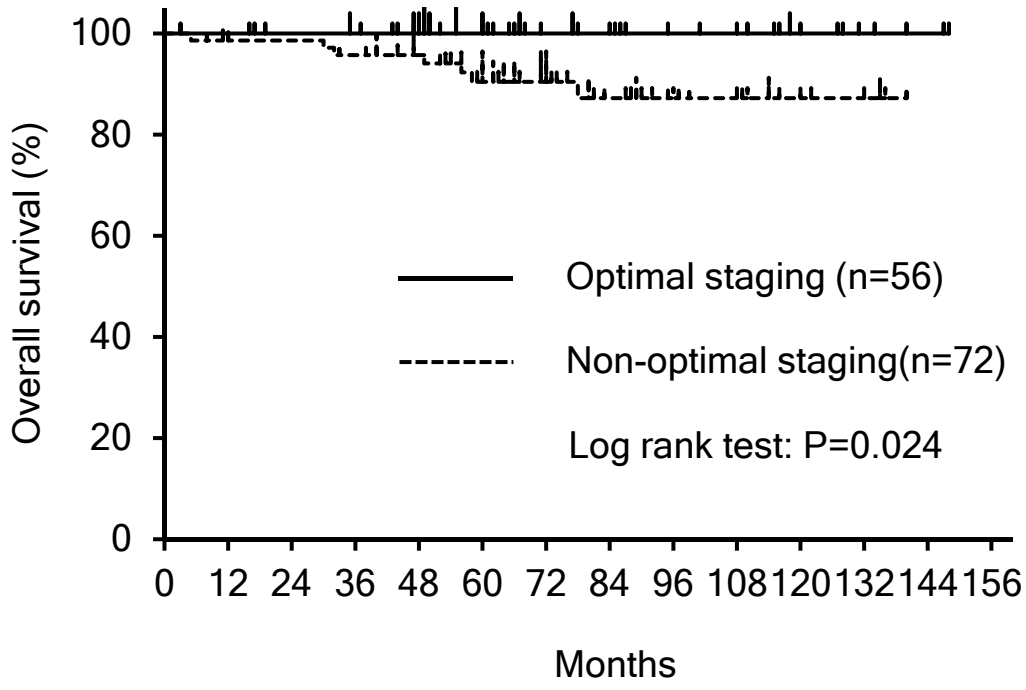
Months
Optimal staging (n=56)
Non-optimal staging(n=72)
Log rank test: P=0.021

B


Overall survival (%)
100
80
60
40
20
0
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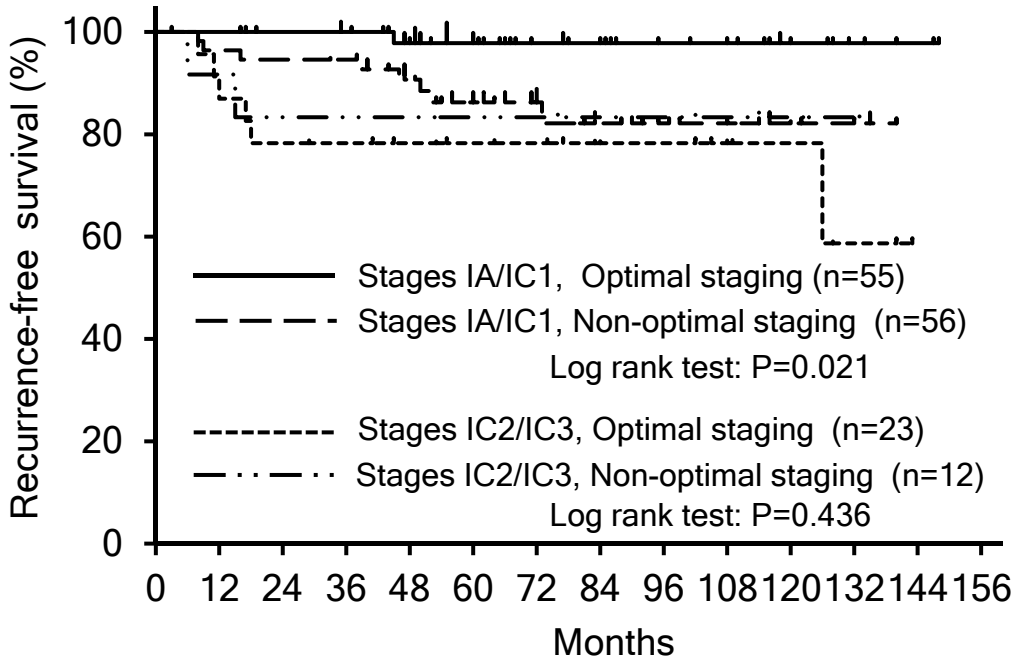
Months
Optimal staging (n=56)
Non-optimal staging(n=72)
Log rank test: P=0.024

A


Recurrence-free survival (%)
100
80
60
40
20
0
Stages IA/IC1, Optimal staging (n=55)
Stages IA/IC1, Non-optimal staging (n=56)
Log rank test: P=0.021
Stages IC2/IC3, Optimal staging (n=23)
Stages IC2/IC3, Non-optimal staging (n=12)
Log rank test: P=0.436
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Months

B

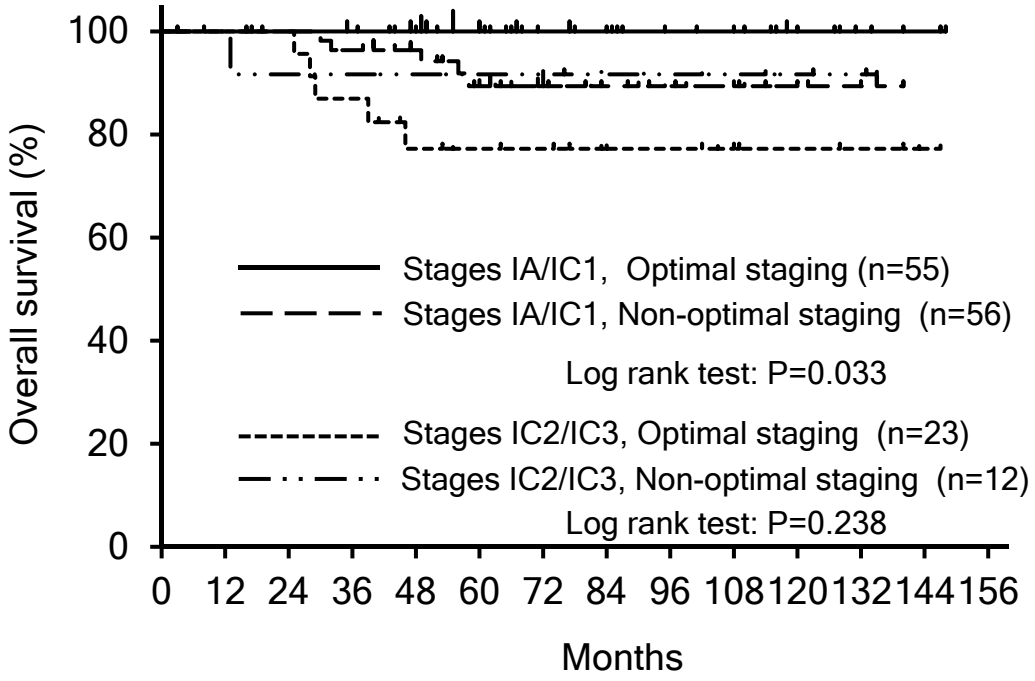
Overall survival (%)
100
80
60
40
20
0
Stages IA/IC1, Optimal staging (n=55)
Stages IA/IC1, Non-optimal staging (n=56)
Log rank test: P=0.033
Stages IC2/IC3, Optimal staging (n=23)
Stages IC2/IC3, Non-optimal staging (n=12)
Log rank test: P=0.238
0 12 24 36 48 60 72 84 96 108 120 132 144 156
Months

Table. Patient characteristics

Characteristic	Total	Optimal staging surgery	Non-optimal staging surgery	P-value
Age				
Median age (range), years		52 (33-74)	54 (30-99)	0.114
<50 years	63	32	31	0.641
≥50 years	102	48	54	
FIGO† stage				
IA	42	13	29	0.007
IC1	86	43	43	
[IA and IC1]	[128]	[56]	[72]	[0.024]
IC2	13	6	7	
IC3	24	18	6	
[IC2 and IC3]	[37]	[24]	[13]	
Lymphadenectomy				
(Number of lymph nodes: median, range)				
Systematic‡	80(41, 14-89)	80(41,14-89)	0	<0.001
Selected§	59(11, 1-44)	0	59 (11, 1-44)	
Not done	26(0)	0	26(0)	
Adjuvant chemotherapy				
Chemotherapy	146	78	68	0.001
Observation	19	2	17	
Total	165	80	85	

† FIGO: International Federation of Gynecology and Obstetrics; Systematic: ‡ systematic lymphadenectomy of the pelvic and para-aortic lymph nodes; § Selected: lymphadenectomy of the pelvic and/or para-aortic lymph nodes