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G. 知的財産権の出願・登録状況(予定含)

1．特許取得

なし

2．実用新案登録

なし

3．その他

なし

研究成果の刊行に関する一覧表

書籍：該当なし

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ORIGINAL REPORT

Outcomes of Fertility-Sparing Surgery for Stage I Epithelial Ovarian Cancer: A Proposal for Patient Selection

Toyomi Satoh, Masayuki Hatae, Yoh Watanabe, Nobuo Yaegashi, Osamu Ishiko, Shoji Kodama, Satoshi Yamaguchi, Kazunori Ochiai, Masashi Takano, Harushige Yokota, Yosuke Kawakami, Sadako Nishimura, Daiki Ogishima, Shunsuke Nakagawa, Hiroaki Kobayashi, Tanri Shiozawa, Toru Nakanishi, Toshiharu Kamura, Ikuo Konishi, and Hiroyuki Yoshikawa

From the Department of Obstetrics and Gynecology, University of Tsukuba, Tsukuba; Department of Obstetrics and Gynecology, Kagoshima City Hospital, Kagoshima; Department of Obstetrics and Gynecology, Tohoku University, Sendai; Department of Obstetrics and Gynecology, Osaka City University Graduate School of Medicine; Department of Obstetrics and Gynecology, Osaka City General Hospital, Osaka; Department of Gynecology, Niigata Cancer Center Hospital, Niigata; Department of Gynecologic Oncology, Hyogo Cancer Center, Akashi; Department of Obstetrics and Gynecology, The Jikei University School of Medicine; Department of Obstetrics and Gynecology, Juntendo University School of Medicine; Department of Obstetrics and Gynecology, University of Tokyo, Tokyo; Department of Obstetrics and Gynecology, National Defense Medical College, Saitama; Department of Gynecology, Saitama Cancer Center, Ina; Department of Obstetrics and Gynecology, National Hospital Organization Kure Medical Center/Chugoku Cancer Center, Kure; Department of Gynecology and Obstetrics, Kyushu University, Fukuoka; Department of Obstetrics and Gynecology, Shinshu University School of Medicine, Matsumoto; Department of Gynecology, Aichi Cancer Center Hospital, Nagoya; Department of Obstetrics and Gynecology, Kurume University School of Medicine, Kurume; Department of Gynecology and Obstetrics, Kyoto University Graduate School of Medicine, Kyoto, Japan.

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Corresponding author: Toyomi Satoh, MD, PhD, Department of Obstetrics and Gynecology, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki 305-8575, Japan; e-mail: toyomi-s@md.tsukuba.ac.jp.

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ABSTRACT

Purpose
The objective of this study was to assess clinical outcomes and fertility in patients treated conservatively for unilateral stage I invasive epithelial ovarian cancer (EOC).

Patients and Methods
A multi-institutional retrospective investigation was undertaken to identify patients with unilateral stage I EOC treated with fertility-sparing surgery. Favorable histology was defined as grade 1 or grade 2 adenocarcinoma, excluding clear cell histology.

Results
A total of 211 patients (stage IA, n = 126; stage IC, n = 85) were identified from 30 institutions. Median duration of follow-up was 78 months. Five-year overall survival and recurrence-free survival were 100% and 97.8% for stage IA and favorable histology (n = 108), 100% and 100% for stage IA and clear cell histology (n = 15), 100% and 33.3% for stage IA and grade 3 (n = 3), 96.9% and 92.1% for stage IC and favorable histology (n = 67), 93.3% and 66.0% for stage IC and clear cell histology (n = 15), and 66.7% and 66.7% for stage IC and grade 3 (n = 3). Forty-five (53.6%) of 84 patients who were nulliparous at fertility-sparing surgery and married at the time of investigation gave birth to 56 healthy children.

Conclusion
Our data confirm that fertility-sparing surgery is a safe treatment for stage IA patients with favorable histology and suggest that stage IA patients with clear cell histology and stage IC patients with favorable histology can be candidates for fertility-sparing surgery followed by adjuvant chemotherapy.

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INTRODUCTION

The standard surgical treatment for early-stage epithelial ovarian cancer (EOC) is total hysterectomy plus bilateral salpingo-oophorectomy with peritoneal and lymph-node sampling. Fertility-sparing surgery that includes unilateral salpingo-oophorectomy and optimal surgical staging is an option available to young women with stage I EOC. However, the recommended indications for such treatment remain controversial.

Fertility-sparing surgery for reproductive-age patients with invasive EOC has been adopted for stage IA and non-clear cell histology grade 1 (G1)/grade 2 (G2) according to the 2007 guidelines of the American College of Obstetrics and Gynecology (ACOG)[1] and for unilateral stage I tumor without dense adhesions showing favorable histology (ie, non-clear cell histology G1/2) according to the 2008 guidelines of the European Society for Medical Oncology (ESMO).[2] In Japan, fertility-sparing surgery has been recommended for patients with stage IA tumor or unilateral stage IC tumor on the basis of intraoperative capsule rupture [IC(b)] and favorable histology, according to the 2004 guidelines[3] and the 2007 guidelines[4] of the Japan Society of Gynecologic Oncology (JSGO). EOC with clear cell or grade 3 (G3) histology and with bilateral ovarian involvement has been excluded from indications for fertility-sparing surgery in all three guidelines. The recommendations regarding fertility-sparing surgery for unilateral and stage IC EOC differ widely among these guidelines, although those for unilateral and stage IA EOC with favorable histology are common to all three guidelines.

The number of published studies concerning fertility-sparing surgery in young EOC patients who wish to preserve the possibility of pregnancy is

limited,[4-14] and each study included fewer than 60 patients, too small a population to allow consensus regarding recommendations for patient selection for fertility-sparing surgery in stage I EOC. This study attempted to determine selection criteria for fertility-sparing surgery in stage I EOC patients on the basis of clinical outcomes for more than 200 stage I EOC patients who underwent fertility-sparing surgery.

PATIENTS AND METHODS

Patients

Between 1985 and 2004, patients with stage I invasive EOC who underwent fertility-sparing surgery in 30 institutions belonging to the Gynecologic Cancer Study Group of the Japan Clinical Oncology Group or who were referred to these hospitals immediately after fertility-sparing surgery performed elsewhere were enrolled onto this study. Patients were eligible if they had stage I, G1, G2, or G3 EOC; if they were treated using fertility-sparing surgery (conservation of the uterus and contralateral ovary and fallopian tube); and if they were ≤ 40 years of age at the time of fertility-sparing surgery. Four patients (stage IB, n = 2; stage IC, n = 2) who showed microscopic metastases in biopsy specimens from the opposite ovary were excluded from this study because of the small number of patients and the insufficient durations of follow-up.

Reassessment of histologic cell type and tumor differentiation was performed in each institution according the WHO criteria before enrollment onto the present study. Histologic differentiation was defined as G1, well differentiated; G2, moderately differentiated; or G3, poorly differentiated. Staging was determined according to the International Federation of Gynecology and Obstetrics (FIGO) classification (1987). In this study, stage IC patients were classified into three subgroups: stage IC(b), intraoperative capsule rupture with negative peritoneal cytology; IC(a), preoperative capsule rupture and/or tumor on ovarian surface with negative peritoneal cytology; and IC(1/2), malignant cells in ascites or peritoneal washings. Institutional review board approval was obtained from each institution before initiating this investigation.

Factors for Analysis

Mucinous, serous, endometrioid, and mixed epithelial adenocarcinoma were classified by histologic grade (G1, G2, or G3). Clear cell histology was not graded in this study. We defined G1/2 non-clear cell adenocarcinoma as showing favorable histology.

Stage IA or IC patients with unilateral ovarian involvement were divided into six subgroups to determine patient selection for fertility-sparing surgery, as follows: stage IA and favorable histology, stage IA and clear cell histology, stage IA and G3, stage IC and favorable histology, stage IC and clear cell histology, or stage IC and G3.

We defined lethal recurrence (LR) as recurrence showing lesions outside the remaining ovary, because a considerable number of previous reports[15] have suggested that patients with recurrence exclusively within the remaining ovary show much better prognosis following salvage surgery compared with patients displaying other patterns of recurrence. Outcomes for patients were analyzed using overall survival (OS), recurrence-free survival (RFS), and lethal recurrence–free survival (LRFS). We also investigated reproductive outcomes after fertility-sparing surgery in patients who provided the information.

Statistical Analysis

Statistical analysis of data was performed using the JMP Statistics package (SAS Institute, Cary, NC). Two-sided probability values were calculated throughout and considered to be significant at the level of $P < .05$. Survival estimates were generated using Kaplan-Meier methods. Differences between groups were tested using log-rank testing.

RESULTS

Patient Characteristics

A total of 211 patients with unilateral stage I EOC (stage IA, n = 126; stage IC, n = 85) were entered onto the study. Table 1 summarizes the main characteristics of patients and tumors. Mean patient age was 29 years (range, 14 to 40 years). Median duration of follow-up after excluding patients who died was 78 months from initial fertility-sparing surgery (range, 3 to 270 months).

Surgical Treatments

Of the 211 patients, 23 (10.9%) patients underwent restaging laparotomy because of inadequate staging or cytoreduction at initial surgery. Nine of the 23 patients underwent unilateral ovarian cystectomy at initial surgery (laparoscopy, n = 4; laparotomy, n = 5) and unilateral salpingo-oophorectomy at restaging laparotomy. As a result, 205 patients underwent unilateral salpingo-oophorectomy. The

Table 1. Patient Characteristics (N = 211)

Characteristic	No.	%
Age, years		
Median	29	
Range	14-40	
Parity		
Parous	26	12.3
Nulliparous	185	87.7
FIGO stage		
IA	126	59.7
IC	85	40.3
Substage		
IC(b)	55	26.1
IC(a)	18	8.5
IC(1/2)	12	5.7
Cell type		
Mucinous	126	59.7
Serous	27	12.8
Endometrioid	27	12.8
Clear cell	30	14.2
Mixed epithelial	1	0.5
Histologic differentiation		
Well (G1)	160	75.8
Moderate (G2)	15	7.1
Poor (G3)	6	2.8
Not classified (clear cell)	30	14.2
FIGO stage and histologic differentiation		
IA		
G1	95	47.3
G2	13	6.2
G3	3	1.4
Clear cell	15	7.1
IC		
G1	65	30.8
G2	2	0.9
G3	3	1.4
Clear cell	15	7.1

Abbreviations: G(1/2/3), non-clear cell histology grade (1/2/3); FIGO, International Federation of Gynecology and Obstetrics; IC(b), intraoperative capsule rupture with negative peritoneal cytology; IC(a), preoperative capsule ruptured and/or tumor on ovarian surface with negative peritoneal cytology; IC(1/2), malignant cells in ascites or peritoneal washings.

Table 2. Types of Surgery in Initial Treatment

Surgery Type	No. of Patients
Unilateral salpingo-oophorectomy	205
Alone	64
BO	43
OM	16
RLND	5
BO + OM	27
BO + RLND	5
OM + RLND	18
BO + OM + RLND	26
Unknown	1
Unilateral ovarian cystectomy	6
BO	3
RLND	1
BO + OM	1
Unknown	1

Abbreviations: BO, biopsy from the opposite ovary; OM, partial omentectomy; RLND, retroperitoneal lymph node dissection or biopsy.

remaining six patients underwent unilateral ovarian cystectomy at initial laparotomy, not followed by restaging surgery. As for other surgeries, 105 patients underwent biopsy (wedge resection) of the opposite ovary, 88 patients underwent partial omentectomy, and 55 patients underwent retroperitoneal lymph node dissection or biopsies. Table 2 provides details of surgical treatments.

Surgical staging included careful inspection and palpation of peritoneal surfaces with biopsies of any suspect lesions and peritoneal washing cytology. No patients received endometrial curettage during surgery, although most patients had endometrial cytology or biopsy before surgery. If optimal surgical staging required at least omentectomy in addition to unilateral salpingo-oophorectomy, 87 (41.2%) of the 211 patients were optimally staged and 124 (58.8%) were nonoptimally staged. Only 74 (35.1%) patients were optimally staged in one-step surgery.

Adjuvant Chemotherapy

Platinum-based adjuvant chemotherapy was administered to 125 (59.2%) patients, with a mean number of four cycles (range, 1 to 12 cycles). The most common chemotherapy regimens were cisplatin + cyclophosphamide ± doxorubicin (57 of 125; 45.6%) and carboplatin + paclitaxel (46 of 125; 36.8%). Fifteen (7.1%) patients received adjuvant chemotherapy without platinum (including oral medication). The remaining 71 (33.6%) patients received no adjuvant treatment after initial surgery.

Clinical Outcomes

Recurrence was identified during the follow-up period for 18 (8.5%) of 211 patients. Of these 18 patients, five showed recurrence exclusively in the remaining ovary (non-LR; Table 3) and 13 had LR in sites other than the remaining ovary (Table 4). At the end of this investigation, eight patients were alive with no evidence of disease, five patients were alive with disease, and five patients had died of disease. All five patients with non-LR were treated with salvage surgery and showed no evidence of disease.

Stage IA and favorable histology. This subgroup included 108 stage IA patients with favorable histology. Of these, 44 (40.7%) patients received platinum-based adjuvant chemotherapy after surgery, and the 5-year OS, RFS, and LRFS were 100%, 97.8%, and 99.1%, respectively. Three patients with mucinous histology G1 developed LR at 14, 70, and 73 months after fertility-sparing surgery (Table 4). Median duration of follow-up for this group was 79 months.

Stage IA and clear cell histology. This subgroup included 15 stage IA patients with clear cell histology. Of those, nine (60%) patients were treated with platinum-based adjuvant chemotherapy. The 15 patients showed rates of 100% for 5-year OS, RFS, and LRFS. Median duration of follow-up for these patients was 78 months.

Stage IA and G3. One of the three stage IA patients with G3 received platinum-based adjuvant chemotherapy and was alive without recurrence 256 months after fertility-sparing surgery. Two patients without any adjuvant chemotherapy had LR at 25 and 31 months after fertility-sparing surgery (Table 4), although both were alive with disease at the end of this investigation (duration of follow-up, 65 and 90 months).

Stage IC and favorable histology. This subgroup included 67 stage IC patients with favorable histology. Platinum-based adjuvant chemotherapy was administered to 57 (85.1%) patients following surgery. The 5-year OS, RFS, and LRFS were 96.9%, 92.1%, and 95.4%, respectively. As for subgroups of stage IC [IC(b), n = 43; IC(a), n = 14; IC(1/2), n = 10], the 5-year RFS was 92.9%, 91.7%, and 90.0%, respectively. Three (4.5%) of 67 patients developed LR, with one stage IC(b) patient with endometrioid histology G1, one stage IC(b) patient with mucinous histology G1, and one IC(1/2) patient with serous histology G1 developing LR at 20, 8, and 3 months after fertility-sparing surgery, respectively (Table 4). Median duration of follow-up for this group was 76.5 months.

Table 3. Characteristics of Patients With Recurrence in the Residual Ovary Alone (non-lethal recurrence)

Patient No.	Age (years)	Stage	Histologic Type	Grade	Platinum-Based Chemotherapy	Time to Recurrence (months)	Follow-Up After Recurrence (months)	Status
1	18	IA	Mucinous	1	No	83	119	NED
2	26	IA	Serous	1	Yes	52	164	NED
3	26	IC(b)	Endometrioid	1	No	7	45	NED
4	36	IC(b)	Clear cell	Not graded	No	21	124	NED
5	26	IC(a)	Mucinous	1	Yes	43	16	NED

Abbreviations: NED, no evidence of disease; IC(b), intraoperative capsule rupture with negative peritoneal cytology; IC(a), preoperative capsule ruptured and/or tumor on ovarian surface with negative peritoneal cytology.

Table 4. Characteristics of Patients Showing Recurrence With Lesions Outside the Residual Ovary (lethal recurrence)

Patient No.	Age (years)	Stage	Histologic Type	Grade	Platinum-Based Chemotherapy	Site of Recurrence	Time to Recurrence (months)	Follow-Up After Recurrence (months)	Status
1	19	IA	Mucinous	1	No	Peritoneum	70	149	NED
2	27	IA	Mucinous	1	No	Lung	73	34	DOD
3	29	IA	Mucinous	1	No	Abdominal wall	14	39	AWD
4	22	IA	Serous	3	No	Residual ovary, ascites	25	231	NED
5	40	IA	Endometrioid	3	No	Para-aortic lymph nodes	31	34	NED
6	15	IC(b)	Mucinous	1	Yes	Peritoneum	8	18	AWD
7	31	IC(b)	Endometrioid	1	Yes	Liver	20	6	DOD
8	29	IC(b)	Clear cell	Not graded	No	Para-aortic lymph nodes	15	86	AWD
9	29	IC(b)	Clear cell	Not graded	Yes	Residual ovary, ascites, peritoneum	11	19	DOD
10	36	IC(b)	Clear cell	Not graded	Yes	Liver	46	8	AWD
11	33	IC(a)	Endometrioid	3	Yes	Not recorded	1	5	DOD
12	26	IC(1/2)	Serous	1	Yes	Peritoneum	3	22	DOD
13	38	IC(1/2)	Clear cell	0	No	Residual ovary, pelvic lymph nodes, peritoneum	21	29	AWD

Abbreviations: NED, no evidence of disease; DOD, died of disease; AWD, alive with disease; IC(b), intraoperative capsule rupture with negative peritoneal cytology; IC(a), preoperative capsule ruptured and/or tumor on ovarian surface with negative peritoneal cytology; IC(1/2), malignant cells in ascites or peritoneal washings.

Stage IC and clear cell histology. This subgroup included 15 stage IC patients with clear cell histology. Eleven (73.3%) of these patients were treated with platinum-based adjuvant chemotherapy. LR occurred in two patients with and in two patients without platinum-based adjuvant chemotherapy (Table 4). These 15 patients showed rates of 93.3%, 66.0%, and 72.7% for 5-year OS, RFS, and LRFS. In particular, 5-year RFS of 11 stage IC(b) patients resembled that of the other four stage IC patients (63.6% *v* 75.0%, respectively). Median duration of follow-up for the 14 survivors was 64 months.

Stage IC and G3. All three stage IC patients with G3 were treated using platinum-based chemotherapy after surgery, but one patient developed LR and died of disease 6 months after fertility-sparing surgery. The remaining two patients were alive without recurrence 58 and 230 months after fertility-sparing surgery.

Comparison of Clinical Outcomes Among Subgroups

We compared OS and RFS among the four subgroups except for the two subgroups (stage IA and G3, or stage IC and G3) consisting of only three patients. In terms of OS, no significant differences were seen among the four subgroups. Significant differences in RFS were seen between the following three pairs of subgroups: stage IA favorable histology versus stage IC clear cell histology (97.8% *v* 66.0%; $P < .001$), stage IC favorable histology versus stage IC clear cell histology (92.1% *v* 66.0%; $P = .008$), and stage IA clear cell histology versus stage IC clear cell histology (100% *v* 66.0%; $P = .02$).

Figure 1 shows OS and RFS curves in those with good prognosis (group I: stage IA favorable histology [n = 108]), those with fairly good prognosis (group II: stage IA clear cell histology or stage IC favorable histology [n = 82]), and those with poor prognosis (group III: stage IA G3, stage IC clear cell histology, or stage IC G3 [n = 21]). No significant differences in OS were seen between groups I and II ($P = .21$) or between groups II and III ($P = .29$), whereas significant differences were identified between groups I and III ($P = .02$). No significant differences in RFS were apparent between groups I and II ($P = .65$), but significant differences were noted between groups I and III ($P < .001$) and between groups II and III ($P < .001$).

Reproductive Outcomes

After fertility-sparing surgery with or without adjuvant chemotherapy, 182 (96.8%) of 188 patients who gave information on menstruation had almost the same cycle of menstruation as before treatment. Six (5.0%) of 121 patients who received platinum-based adjuvant chemotherapy showed continued secondary amenorrhea for 6, 48, 66, 72, 172, and 224 months following two to six cycles of chemotherapy (median, four cycles).

Of the 195 patients who gave reproductive outcomes at the end of the investigation, 55 (28.5%) patients achieved 76 pregnancies and 53 gave birth to 66 healthy children after fertility-sparing surgery. Five (9.1%) of 55 patients had received some kind of infertility treatment before pregnancy. These patients and their babies showed no clinical problems during the perinatal period. Four (9.4%) of 53 patients who gave birth to children underwent completion surgery, including hysterectomy and contralateral salpingo-oophorectomy, after childbearing.

Forty-five (53.6%) of 84 patients who were nulliparous at fertility-sparing surgery and married at the end of the follow-up period had achieved 65 pregnancies, and 43 had given birth to 56 healthy children during follow-up (mean follow-up, 8.8 years). Of the 84 patients, the remaining 39 patients had not conceived during follow-up (mean follow-up, 7.2 years), and mean age was 37 years (range, 25 to 54 years) at the end of the investigation.

DISCUSSION

In this series, recurrence rate among the 211 stage I EOC patients after fertility-sparing surgery was 8.5% (18 of 211), falling within the 5.4% to 30.3% reported previously.[5,6,10,12,14] Of the 18 patients with recurrence, five (2.4%) patients showing recurrence exclusively in the residual ovary achieved no evidence of disease. According to data from five studies[5,6,10,12,14] that investigated relationships between sites of recurrence and clinical outcomes, eight of 10 patients with recurrence limited to the residual ovary achieved no evidence of disease following salvage therapy, whereas only three of 21 patients with recurrence at

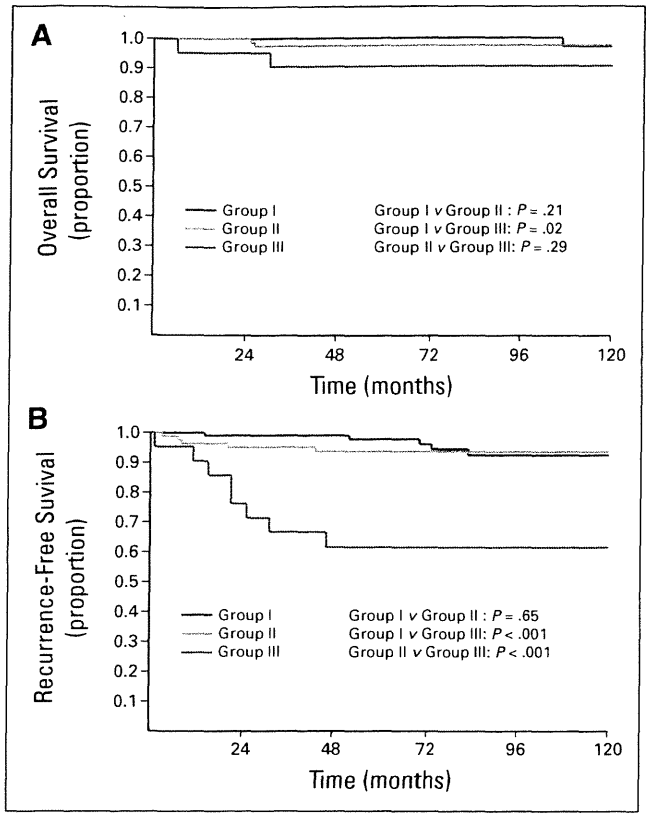

Fig 1. (A) Overall survival curves for patients with good prognosis (group I), fairly good prognosis (group II), and poor prognosis (group III). Group I: stage IA and favorable histology; group II: stage IA and clear cell histology, or stage IC and favorable histology; group III: stage IA and clear cell histology grade 3 (G3), stage IC and clear cell histology, or stage IC and G3. (B) Recurrence-free survival curves for groups I, II, and III.

extra-ovarian sites achieved no evidence of disease. We thus evaluated LRFS in addition to OS and RFS in this study.

The 108 stage IA patients with favorable histology showed a 5-year RFS of 97.8% and a 5-year LRFS of 99.1% (5-year recurrence rate, 2.2%; 5-year LR rate, 0.9%), although only 40.7% of these patients received platinum-based adjuvant chemotherapy after surgery. Stage IA patients with favorable histology were always included in selection criteria for fertility-sparing surgery in previous reports and in various guidelines.[1-14] The recurrence rate for stage IA patients with favorable histology in four previous reports[5,10,12,14] was 0% to 22.2% during follow-up. Our data confirm fertility-sparing surgery as a safe treatment option for stage IA patients with favorable histology, even when fertility-sparing surgery is not followed by adjuvant chemotherapy.

In this study, 15 stage IA patients with clear cell histology showed no recurrence, with lymph node biopsy or dissection performed in six (40%) patients and adjuvant platinum-based chemotherapy given to nine (60%) patients. Our data correspond with that in a recent report by Kajiyama et al[16] showing no recurrence in four stage IA patients with clear cell histology who had undergone fertility-sparing surgery. Other investigations,[10,12,14] however, have reported three recurrences among eight stage IA patients with clear cell histology after fertility-sparing surgery. These data suggest that stage IA patients with clear cell histology may be candidates for fertility-sparing surgery, including optimal staging followed by adjuvant chemotherapy.

In our series, only one of three stage IA patients with G3 survived for 5 years without recurrence. The recurrence rate for the 17 stage IA patients with G3 from six investigations[5,7,10-12,14] who underwent fertility-sparing surgery was 35.3% (6 of 17), although some reports classified clear cell histology into G3. These data suggest that fertility-sparing surgery cannot be recommended for stage IA patients with G3.

The 67 stage IC patients with favorable histology had a 5-year RFS of 92.1% and a 5-year LRFS of 95.5%. Outcomes seem to be better in our study compared with the recurrence rate of 12.8% (5 of 39) in previous studies.[7,10-12,14] Platinum-based adjuvant chemotherapy was more frequently given to this group compared with the stage IA and favorable histology group (85.1% *v* 40.7%; $P < .001$). In our series, no significant difference in 5-year RFS was seen among 43 IC(b) patients, 14 IC(a) patients, or 10 IC(1/2) patients with values of 92.9%, 91.7%, and 90.0%, respectively. Our data suggest that stage IC patients with favorable histology in the unilateral ovary can be candidates for fertility-sparing surgery, including optimal staging followed by adjuvant chemotherapy.

Our series included 15 stage IC patients with clear cell histology. These patients showed a 5-year RFS of 66.0% and a 5-year LRFS of 72.7%, even when 11 (73.3%) patients were treated with platinum-based adjuvant chemotherapy. Kajiyama[16] reported that one stage IC(2) patient among the six stage IC patients with clear cell histology experienced relapse and died of the disease. Five-year RFS was 63.6% for 11 IC(b) patients, 100% for two IC(a) patients, and 50% for two IC(1/2) patients. These data suggest that stage IC patients with clear cell histology cannot be candidates for fertility-sparing surgery.

Our series included three stage IC patients with G3. One patient developed LR and died of the disease 6 months after fertility-sparing surgery, although all three patients had been treated with platinum-based adjuvant chemotherapy. In previous reports,[10-14] four of nine stage IC patients with G3 who underwent fertility-sparing surgery displayed recurrence. These data suggest that fertility-sparing surgery cannot be recommended for stage IC patients with G3.

In addition to the study patients, during the study period, we managed four patients with unilateral stage I EOC treated with fertility-sparing surgery elsewhere, who were referred to these hospitals for treatment of lethal recurrent disease and died of the disease. These four patients included one stage IA patient with clear cell histology, one stage IA patient with G3, and two stage IC patients with G3. Clinical outcomes for these patients support our recommendations regarding fertility-sparing surgery for unilateral stage I EOC.

In our series, 5% of patients with platinum-based adjuvant chemotherapy developed secondary amenorrhea and infertility, suggesting that we should not administer adjuvant chemotherapy to patients with stage IA and favorable histology without serious consideration. As for the reproductive outcome, we confirmed that most married but nulliparous EOC patients undergoing fertility-sparing surgery can give birth to children within several years after fertility-sparing surgery.

In conclusion, this study confirmed that stage IA EOC patients with favorable histology can be safely treated with fertility-sparing surgery not followed by platinum-based adjuvant chemotherapy. We would thus propose that fertility-sparing surgery be considered

Table 5. Recommendation for Fertility-Sparing Surgery in Young Patients With Unilateral Stage I Ovarian Cancer

Stage	Histology/Grade		
	FH	CCH	G3
1A	Offer FSS	Consider FSS + CT	No FSS
1C	Consider FSS + CT	No FSS	No FSS

Abbreviations: FH, favorable histology (mucinous, serous, endometrioid, or mixed histology and grade 1 or 2); CCH, clear cell histology; G3, clear cell histology grade 3; FSS, fertility-sparing surgery; CT, adjuvant chemotherapy.

for stage IA EOC patients with clear cell histology and for stage IC EOC patients with unilateral ovarian involvement and favorable histology, under conditions of performing complete staging surgery and platinum-based adjuvant chemotherapy (Table 5). Conversely, fertility-sparing surgery cannot be recommended for patients with stage IA with G3 histology or stage IC with clear cell or G3 histology. Theoretically, a randomized controlled trial may be needed to compare conservative surgery with radical surgery for young patients with EOC to achieve high-quality evidence. However, such trials may not be ethically feasible. Confirming the decision of patient criteria for selection in a phase II trial would be appropriate.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Toyomi Satoh, Hiroyuki Yoshikawa
Administrative support: Toyomi Satoh
Provision of study materials or patients: Toyomi Satoh, Masayuki Hatae, Yoh Watanabe, Nobuo Yaegashi, Osamu Ishiko, Shoji Kodama, Satoshi Yamaguchi, Kazunori Ochiai, Masashi Takano, Harushige Yokota, Yosuke Kawakami, Sadako Nishimura, Daiki Ogishima, Shunsuke Nakagawa, Hiroaki Kobayashi, Tanri Shiozawa, Toru Nakanishi, Toshiharu Kamura, Ikuo Konishi
Collection and assembly of data: Toyomi Satoh, Masayuki Hatae, Yoh Watanabe, Nobuo Yaegashi, Osamu Ishiko, Shoji Kodama, Satoshi Yamaguchi, Kazunori Ochiai, Masashi Takano, Harushige Yokota, Yosuke Kawakami, Sadako Nishimura, Daiki Ogishima, Shunsuke Nakagawa, Hiroaki Kobayashi, Tanri Shiozawa, Toru Nakanishi
Data analysis and interpretation: Toyomi Satoh, Toshiharu Kamura, Ikuo Konishi, Hiroyuki Yoshikawa
Manuscript writing: Toyomi Satoh, Hiroyuki Yoshikawa
Final approval of manuscript: Toshiharu Kamura, Ikuo Konishi, Hiroyuki Yoshikawa

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The Optimal Debulking after Neoadjuvant Chemotherapy in Ovarian Cancer: Proposal Based on Interval Look During Upfront Surgery Setting Treatment

Takashi Onda[1,2], Hiroyuki Yoshikawa[1,3], Toshiharu Yasugi[1,4], Koji Matsumoto[1,3] and Yuji Taketani[1]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, University of Tokyo, [2]Division of Gynecologic Oncology, National Cancer Center Hospital, Tokyo, [3]Department of Obstetrics and Gynecology, University of Tsukuba, Ibaraki and [4]Department of Gynecology, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Tokyo, Japan

For reprints and all correspondence: Takashi Onda, Division of Gynecologic Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: taonda@ncc.go.jp

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Objective: The optimal goal of interval debulking surgery (IDS) following neoadjuvant chemotherapy (NAC) remains undefined. The aim of this study was to determine the optimal goal of IDS following NAC on the basis of long-term survival by the disease status at the end of interval look surgery (ILS) or IDS during the treatment in the setting of upfront primary debulking surgery (PDS).

Methods: From January 1986 through December 2000, we performed treatment in the setting of upfront PDS in 128 patients with Stage III/IV epithelial ovarian cancer. Sixty-six patients with residual disease (RD) at PDS underwent interval surgery (IS) such as ILS or IDS; 4 patients after two cycles of chemotherapy and 62 after three or more cycles. We investigated how disease status at the end of IS was associated with overall survival (OS).

Results: The 5-year OS rates for no, minimal and gross RD were not available ($n = 0$), 67% ($n = 3$) and 0% ($n = 1$) after two cycles, and 47% ($n = 42$), 0% ($n = 18$) and 0% ($n = 2$) after three or more cycles, respectively. No visible tumors at the end of IS after three or more cycles of chemotherapy were necessary for 5-year survival.

Conclusions: If the optimal goal of IDS is defined as the surgery that is expected to result in long-term survival in the NAC setting treatment, our data on the assessment of peritoneal findings during the upfront PDS setting treatment suggest that only complete resection with no RD could be the optimal goal of IDS in the NAC setting treatment.

Key words: ovarian cancer – neoadjuvant therapy – gynecol-surg – chemo-gynecology

INTRODUCTION

Primary debulking surgery (PDS) followed by chemotherapy is a standard treatment for ovarian cancer. For patients with advanced ovarian cancer, the goal of PDS is optimal cytoreduction, usually defined as surgery with residual disease (RD) <1 or <2 cm in diameter. Proportion of patients who achieved optimal surgery or size of RD is one of the important prognostic factors for the patients with advanced ovarian cancer (1–4). Unfortunately, optimal cytoreduction for advanced ovarian cancer is achieved in only 30–60% of the patients at most institutions (5,6). One reason for this low rate is that patients with advanced ovarian cancer are often poor candidates for aggressive surgery because of low performance status (PS) caused by massive ascites, pleural effusion and large abdominal tumors. Another reason is that some patients have unresectable tumors at the time of primary surgery.

Thus, because of recent advances in chemotherapy, neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) and further chemotherapy has become an alternative treatment for patients with low PS and those with apparently unresectable tumors evaluated with computed

tomography (CT) or laparoscopy. Several retrospective studies revealed comparable results by the NAC setting treatments with standard treatment (7–9), and a few prospective Phase II (10) or feasibility study (11,12) revealed promising results by NAC setting treatment. Taking into account these favorable outcomes of NAC setting treatment, several prospective clinical trials are now under way to compare this treatment with the standard treatment for advanced ovarian cancer, not only in patients with low PS or unresectable tumors (13,14). Most previous studies have emphasized that the greatest advantage of the treatment in the setting of an NAC is a higher rate of optimal cytoreduction at IDS (7,9,10). These studies used the same definition of optimal cytoreduction at IDS as that at PDS. At the time of PDS, optimal cytoreduction indicates an optimal goal of surgery that lengthens survival. However, there is limited information on the survival of patients in relation to the size of RD after IDS. Thus, the appropriate definition of 'optimal cytoreduction' at the time of IDS in the setting of NAC is undetermined.

Since 1986, we have performed interval look surgery (ILS) for patients who have minimal RD (<2 cm in diameter) at PDS or IDS for patients who have gross RD (≥2 cm in diameter) at PDS after two to six cycles (mostly three or four cycles) of chemotherapy. We investigated how peritoneal findings at the end of interval surgery (IS) are associated with the overall survival (OS) of patients. These associations should help us to clarify the optimal goal of IDS in the setting of NAC for advanced ovarian cancer.

PATIENTS AND METHODS

Patients

From January 1986 through December 2000, we treated 230 patients with epithelial ovarian cancer, including 128 patients with Stage III–IV disease, at the Department of Obstetrics and Gynecology, University of Tokyo Hospital. According to the International Federation of Gynecology and Obstetrics (FIGO) staging, disease was classified as Stage IIIB in 14 patients, Stage IIIC in 89 patients and Stage IV in 25 patients. Histologic type was serous in 94 patients, clear cell in 18 patients, endometrioid in 6 patients, mucinous in 5 patients, transitional cell in 2 patients, mixed epithelial in 2 patients and undifferentiated in 1 patient. Median age at the time of PDS was 54 years, with a range of 29–78 years. Median follow-up period after PDS, excluding patients who died, was 94 months, with a range of 8–201 months. All but two surviving patients were followed up for >5 years.

Our standard surgical treatment for advanced ovarian cancer at the time of PDS consists of total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic or total omentectomy, and debulking of peritoneal tumor masses with maximum efforts. Patients with no or minimal RD (<2 cm in diameter) also underwent systematic retroperitoneal lymphadenectomy, except for patients with severe medical complications, low PS or long operation time. Retroperitoneal lymphadenectomy included both the pelvic and aortic lymph nodes.

In principle, our primary management for ovarian cancer was performed as follows according to the outcome of PDS: (i) patients with no RD received six cycles of chemotherapy and underwent no additional surgery, (ii) patients with minimal RD (<2 cm in diameter) received three or four cycles of chemotherapy followed by ILS and two to four cycles of additional chemotherapy, (iii) patients with gross RD (≥2 cm in diameter) received two to four cycles of chemotherapy until a favorable response was obtained and underwent IDS followed by four to five cycles of additional chemotherapy.

Cisplatin-based regimens, such as CAP or TC, were used for post-operative chemotherapy. From 1986 through 1997, we used the CAP regimen, consisting of 400–600 mg/m^2 of cyclophosphamide, 30–40 mg/m^2 of doxorubicin and 50–75 mg/m^2 of cisplatin. Thereafter, we used the TC regimen consisting of paclitaxel (175 mg/m^2 infused over 3 h) and an area under the curve 6 of carboplatin.

Statistical Methods

OS was measured from the day of starting primary treatment. The survival curves were determined with the Kaplan–Meier product-limit method. Differences in survival were analyzed with the log-rank test and Cox proportional-hazard regression model using the SPSS program ver. 11.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Survival of all Patients in Relation to the Size of RD at PDS

In 128 patients with Stage III or IV ovarian cancer, complete resection of all visible tumors was achieved in 37 patients (28.9%), minimal RD remained in 52 patients (40.6%) and gross RD remained in 39 patients (30.5%). Figure 1 shows the OS of all 128 patients with Stage III/IV disease in relation to the largest size of RD at PDS. Median OSs and 5-year OS rates of the above three groups were 112 months and 65%, 50 months and 40%, and 22 months and 13%. The difference in OS among the three groups was statistically significant ($P < 0.0001$ with log-rank test). In particular, the difference in OS between patients with minimal RD and gross RD was more significant than that between patients with no RD and minimal RD ($P < 0001$ vs. $P = 0.02$). Hazard ratio and 95% confidence interval (CI) for patients with minimal RD and gross RD against patients with no RD were 1.92 (1.08–3.42) and 5.43 (2.98–9.89), respectively.

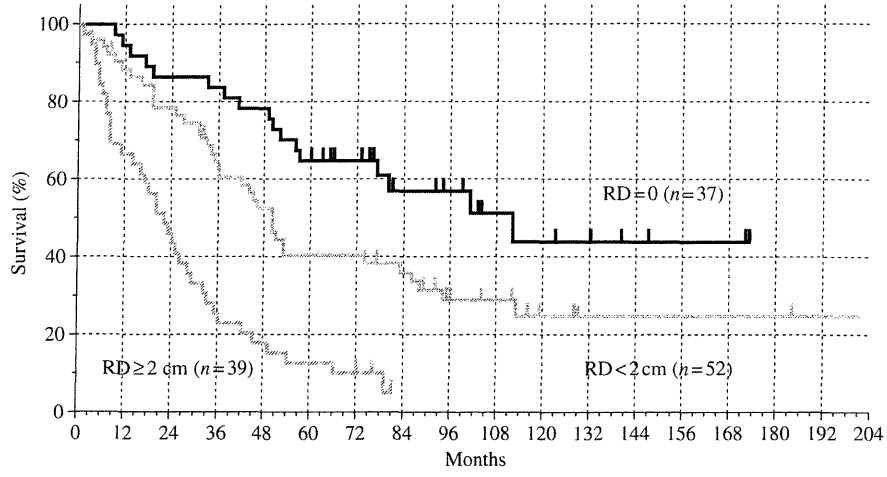

Figure 1. Overall survival of the patients with Stage III/IV ovarian cancer according to the size of largest RD at the time of PDS. RD, residual disease; PDS, primary debulking surgery.

Performance of IS

For Patients with Minimal RD at PDS

Of the 52 patients with minimal RD at PDS, 29 underwent ILS after three or four cycles of post-operative chemotherapy. Nine patients underwent ILS after five or six cycles of chemotherapy. The remaining 14 patients did not undergo ILS due to the following reasons: progressive disease in 2 patients, unfavorable response in 2 patients, entry to clinical trial in 4 patients, patient refusal in 1 patient, medical complications in 4 patients and unknown reason in 1 patient.

For Patients with Gross RD at PDS

Of 39 patients with gross RD at PDS, 28 underwent IDS after two to six cycles of post-operative chemotherapy. Four patients underwent IDS after two cycles of chemotherapy because of early partial responses, 20 patients underwent IDS after three or four cycles of chemotherapy and 4 patients underwent IDS after six cycles of chemotherapy. The remaining 11 patients did not undergo IDS because of progressive disease in 9 patients and medical complications in 2 patients.

RD at the end of IS and OS

IDS after Two Cycles of Chemotherapy

Four patients underwent IDS after two cycles of chemotherapy. Three patients had minimal RD and one patient had gross RD at the end of IDS. Median OSs and 5-year OS rates were 66 months and 67% in patients with minimal RD and 8 months and 0% in a patient with gross RD. The mean number of chemotherapy cycles after IDS was 5.3 (range, 3–6) for patients with minimal RD and 1 (range, 1–1) for a patient with gross RD. Two patients with minimal RD after IDS survived >5 years.

ILS and IDS after Three or More Cycles of Chemotherapy

Thirty-eight patients underwent ILS after three or more cycles of chemotherapy. At the end of ILS, 32 patients had no RD, 5 had minimal RD and 1 had gross RD. Median OSs and 5-year OS rates were 83 months and 55% in patients with no RD, 16 months and 0% in patients with minimal RD and 11 months and 0% in a patient with gross RD. The mean number of chemotherapy cycles after ILS was 2.8 (range, 0–5) for patients with no RD, 2.8 (range, 0–6) for patients with minimal RD and 2 (range, 2–2) for a patient with gross RD.

Twenty-four patients underwent IDS after three or more cycles of chemotherapy. At the end of IDS, 10 patients had no RD, 13 had minimal RD and 1 had gross RD. Median OSs and 5-year OS rates were 28 months and 20% in patients with no RD, 23 months and 0% in patients with minimal RD and 8 months and 0% in a patient with gross RD. The mean number of chemotherapy cycles after IDS was 3.4 (range, 0–5) for patients with no RD, 4.1 (range, 2–7) for patients with minimal RD and 1 (range, 1–1) for a patient with gross RD.

Overall, 42 patients had no RD, 18 had minimal RD and 2 had gross RD at the end of IS such as ILS and IDS after three or more cycles of chemotherapy. Median OSs and 5-year OS rates were 53 months and 47% in patients with no RD, 23 months and 0% in patients with minimal RD and 11 months and 0% in patients with gross RD. The difference in OS among the three groups was statistically significant ($P < 0.0001$ with the log-rank test, Fig. 2). The difference in OS between patients with no RD and minimal RD was much more significant than that between patients with minimal RD and gross RD ($P < 0.0001$ vs. $P = 0.04$). None of these patients with RD at the end of IS after three or more cycles of chemotherapy survived >5 years. Hazard ratio and 95% CI for patients with minimal RD and gross RD against

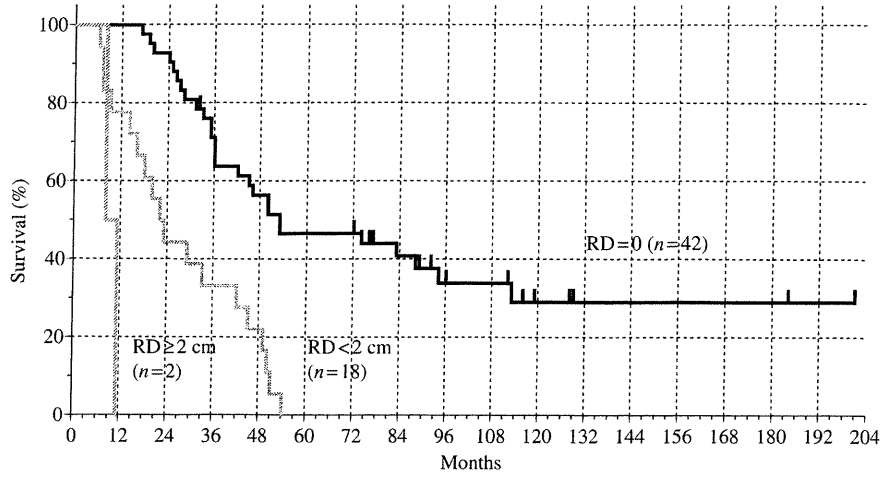

Figure 2. Overall survival of the patients who underwent IS after three or more cycles of chemotherapy according to the size of largest RD at the end of IS. IS, interval surgery.

patients with no RD were 3.99 (2.11–7.55) and 32.78 (5.67–189.55), respectively.

DISCUSSION

NAC setting treatment for advanced ovarian cancer has lately attracted much attention and randomized controlled trials are now under way comparing the outcome with the treatment in the setting of upfront PDS (13,14). However, because of the paucity of the data, optimal goal of IDS in the NAC setting treatment has not yet determined. For our management of advanced ovarian cancer, we performed ILS for patients with minimal RD to assess the peritoneal findings mainly after three to four cycles of chemotherapy separate from IDS for patients with gross RD. Although our data are not based on the treatment results of NAC setting treatment, we thought that the disease status at the time of IDS or ILS in patients who had good outcomes would be useful for determining the optimal goal of IDS following NAC from the standpoint of cell biology. Similar assessments may be possible by the data of two large Phase III studies of IDS after suboptimal PDS for advanced ovarian cancer (15,16). However, it is regrettable that these studied did not address the issue.

Patients with Stage III/IV disease in our series had relatively good outcomes: a median OS of 46 months and a 5-year OS rate of 39%. We used RD < 2 cm in diameter as the definition of optimal cytoreduction at PDS because our study is a retrospective analysis of patients treated from 1980s. Among these patients, those with no RD had good outcomes: a median OS of 112 and a 5-year OS rate of 65%, whereas patients with minimal RD also had good outcomes: a median OS of 50 months and a 5-year OS rate of 40%. However, patients with gross RD had much poorer outcomes: a median OS of 22 months and a 5-year OS rate of 13% (Fig. 1). Patients who underwent optimal debulking at PDS survived significantly longer than those who underwent suboptimal debulking at PDS (median OS of 74 vs. 22 months, 5-year OS rate of 51% vs. 13%, $P < 0.0001$ with the log-rank test). Hazard ratio of the patients with suboptimal debulking against optimal debulking was 3.65 (95% CI: 2.31–5.71). In agreement with previous reports, our present study confirmed that the optimal goal at PDS is cytoreduction with no or minimal RD.

To determine the optimal goal of IDS following NAC, OS in relation to the size of RD after surgery should be known. However, at present, we have little information on the relation between the outcome of IDS following NAC and long-term survival. A recent analysis of NAC and IDS by Le et al. (17) has found that progression-free survival was significantly improved in patients with complete resection at IDS and did not differ significantly among patients with various sizes of macroscopic RD (<1, 1–2 or >2 cm). However, Le et al. could not find significant improvement in OS of patients with complete resection, likely because of the small number of patients in each group and the short median follow-up time of 19 months. In the present study, we tried to determine the optimal goal of IDS following NAC using peritoneal findings at corresponding timing in patients undergoing treatment in the setting of upfront PDS and having fairly good outcomes. The optimal goal of IDS following NAC should be a favorable status that leads to good long-term survival. The present study suggests that no RD at the end of IS after three or more cycles of chemotherapy can lead to fairly good survival. Although the survivals are not identical following ILS or IDS, combined survival of the patients with no RD at ILS or IDS is comparable to that achieved with minimal RD at PDS in the setting of upfront PDS (median OS of 53 and 50 months and 5-year OS rate of 47% and 40%, Figs 2 and 1, respectively). The survival of the patients with no RD was much better than the patients with any RD, especially in 5-year OS rate (median OS of 53 vs. 22 months, 5-year OS rate of 47% vs. 0%, $P < 0.0001$

with the log-rank test). Hazard ratio of the patients with any RD against no RD was 4.26 (95% CI: 2.27–7.96). However, if IDS is performed after good response to two cycles of chemotherapy, even patients with minimal RD may be expected to obtain good long-term survival (median OS of 66 months and 5-year OS rate of 67%).

In the setting of upfront PDS, RD is chemo-naive and will be exposed to at least six cycles of post-operative chemotherapy. However, in the treatment of NAC and IDS, RD is not chemo-naive, and the number of chemotherapy cycles given after IDS is limited (usually three to four cycles), suggesting that residual cancer cells are less likely to disappear completely following IDS than following PDS. In our series, patients with minimal RD at the end of IS after three to six cycles of chemotherapy received, an average, 3.9 cycles of additional chemotherapy and a total of 8.0 cycles of chemotherapy, which are slightly more than those received by patients with no RD at the end of IS (2.9 and 7.1 cycles, respectively). Previous reports have shown that additional cycles of chemotherapy after six cycles do not improve survival (18,19). Thus, the OS might not improve with an increased number of chemotherapy cycles in patients with minimal RD at the end of IS.

Because of long study period and retrospective nature of the study, we used the definition of <2 cm as minimal RD at IDS. Thus, there may be a room to discuss about survival of patients with much smaller RD. However, our result showed that none of the 20 patients with any RD at the end of IS after three or more cycles of chemotherapy survived >5 years. Because we tried to define the optimal surgery mainly by the condition that leads patients to long-term survival, the results may be similar even if we could divide the patients at smaller RD such as <0.5 or <1 cm.

From our results, we believe that OS of patients with no RD after IDS in the setting of NAC is comparable to that of patients with minimal RD after PDS and is slightly inferior to that of patients with no RD after PDS in the setting of upfront PDS. Therefore, to obtain better OS by the NAC setting treatment compared with standard treatment, complete resection with no RD at IDS by the NAC setting treatment should be higher than the rate of cytoreduction with no or minimal RD at PDS by the upfront PDS setting treatment. Recent presentation of the results of Phase III study conducted by European Organization for Research and Treatment of Cancer (13) at the meeting of International Gynecologic Cancer Society (Bangkok, Thailand, October 2008) showed that OSs for patients treated with PDS or NAC setting treatment are similar (29 vs. 30 months), irrespective of much higher rate of achieving residual tumor <1 cm in IDS compared with PDS (83% vs. 48%). These results may support our result that definition of the optimal surgery for PDS and IDS should be different.

In conclusion, on the basis of long-term follow-up data in patients undergoing upfront PDS setting treatment and having assessment of peritoneal findings during chemotherapy, we propose that the optimal goal of the IDS following three or more cycles of NAC is only complete resection of all visible tumors. However, our study was a retrospective analysis and included only a small number of patients. The definition of optimal cytoreduction at PDS has been established on the basis of long-term clinical data. Similarly, accumulation of data regarding IDS outcomes and OSs in the setting of NAC may be necessary for wide spread acceptance of our proposal.

Conflict of interest statement

None declared.

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特集 卵巣がんに関する最新トピックス

進行卵巣癌に対するNAC化学療法への期待

恩田貴志*

進行卵巣癌の予後改善を目指した治療法の一つとして，術前化学療法（NAC）が注目されている。これまでの多くのretrospective studyの結果に加え，近年，過去の治療成績を解析したmeta-analysisの結果や，prospectiveな第Ⅱ相試験の結果がいくつか論文発表され，また，第Ⅲ相比較試験の途中経過も学会発表され，進行卵巣癌に対するNAC療法の役割が明らかとなりつつある。本稿では，進行卵巣癌に対するNAC療法の治療成績について解説し，今後の検討課題について提案する。

はじめに

術前化学療法（neoadjuvant chemotherapy；NAC）は，シスプラチン（cisplatin；CDDP）やカルボプラチン（carboplatin；CBDCA）などのプラチナ製剤の出現，さらにはパクリタキセル（paclitaxel；PTX）やドセタキセル（docetaxel；DTX）などのタキサン系薬剤の出現など，卵巣癌に対する化学療法の進歩とともに，進行卵巣癌の予後改善を目指す治療法の一つとして，注目されてきた。これまで，術前化学療法で始まる化学療法先行治療（以下，NAC療法と呼ぶ）の治療成績は，retrospectiveな解析による治療成績がほとんどであった。近年，多くの過去の治療成績を解析したmeta-analysisの結果や，prospectiveな第Ⅱ相試験の結果がいくつか論文発表され，また，第Ⅲ相比較試験の途中経過も学会発表され，いよいよ進行卵巣癌に対するNAC療法の役割が明らかとなりつつある。本稿では，進行卵巣癌に対するNAC療法について解説する。

*Takashi ONDA（医長）
国立がん研究センター中央病院婦人腫瘍科
〒104-0045　東京都中央区築地5-1-1

Ⅰ. 進行卵巣癌に対する標準治療とNAC療法

卵巣癌の治療は，主として手術と化学療法の組み合わせで行われる。現在の標準治療は，疾患の診断，進行期の診断を目的に最初に手術を行い，術後に化学療法を追加する治療である。進行卵巣癌においては，初回手術での残存腫瘍径が重要な予後因子であり，残存腫瘍径<1 cmのoptimal surgeryを目指して，転移病巣の可及的摘出が試みられ，この初回手術はprimary debulking surgery（PDS）と呼ばれる。化学療法は，タキサン系薬剤とプラチナ製剤との併用が標準であり，主としてTC療法（PTX+CBDCA）が，進行卵巣癌には3週ごとに6～8コース行われる（ただし，毎週投与法や腹腔内化学療法も第Ⅲ相比較試験の結果，有効性が示されている）。

しかしながら，進行卵巣癌においてはoptimal surgeryは一般に40～60%程度しか達成できず，optimal surgeryが達成できないsuboptimal症例に関しては，良好な予後を得るのは困難であった。そこで，初回手術が試験開腹に

終わった症例，CTや腹腔鏡診断で，腫瘍進展のため初回手術ではoptimal surgeryの達成が困難な症例，合併症や高齢，PS不良のため，初回手術が安全もしくは十分に行えない症例に対して，化学療法を数コース施行し（NAC），腫瘍の縮小あるいはPSの改善が得られた時点で，interval debulking surgery（IDS）と呼ばれる腫瘍縮小手術を行い，さらに化学療法を追加する治療（NAC療法）が，代替治療として行われてきた。この治療成績を，標準治療を行いえた症例の治療成績と比較した多くの報告により，進行した症例や高齢者を対象としながら，標準治療に比して劣らないことが示され，同時に手術に伴う侵襲が少ないことも示された。NAC療法は，切除不能症例や，手術困難例に限らず，Ⅲ/Ⅳ期進行卵巣癌全体に対する標準治療の候補として期待が集まり，prospectiveな臨床試験も実施されるようになった。

Ⅱ．NAC療法の治療成績

1．メタアナライシスによるNAC療法の治療成績の解析（表1）

Bristowら[1]は，1989～2005年に報告された，卵巣癌Ⅲ/Ⅳ期に対するNAC療法の論文21本をmeta-analysisにより解析した。生存期間中央値（median survival time；MST）は24.5 M，optimal surgery（残存腫瘍径≤2 cm）達成率は65%であった。NAC療法の治療成績は，論文の年代，PTXの使用割合，optimal症例の割合，Ⅳ期症例の割合，NAC療法のコース数と有意に相関が認められた。optimal症例の割合は，10%増えるごとに1.9 Mの予後の改善が認められたが，NACのコース数は，1コース増えるごとに4.1 Mの生存期間の短縮が認められた。著者らは，Gynecologic Oncology Group（GOG）による臨床試験で，PDSでsuboptimalとなった症例のMSTが24 Mであることと比較して，NAC療法のMST 24.5 Mは，これらsuboptimal症例と同等であるとして，NAC療法に否定的な見解を示している。

一方，Kangら[2]は，1989～2008年に報告された論文21本を用いて同様の解析を行った。年代以外の論文の選択基準はほぼ同様であるが，7本の論文が除外され，新しい年代の論文が7本追加され，違う解析の手法が用いられた。MSTは27.5 M，optimal surgery達成率は70%であった。この論文では，論文の年代，PTXの使用割合，optimal症例の割合は，治療成績と相関がみられたが，Ⅳ期症例の割合，NAC療法のコース数とは相関を認めなかった。さらに，NAC療法を標準治療と比較した論文を解析し，NAC療法により，手術でsuboptimalとなるriskは有意に減少し，optimal達成率を上げることができると，NAC療法を評価している。解析に含まれる論文の違いや，解析方法の違いにより，解析の結果が異なっており，NAC療法の有用性に関して結論は出せないが，解析に含まれる報告の多くは，前述のように，PS不良やoptimal surgeryが期待できない症例に対する治療成績であり，否定的見解のBristowら[1]の結果から判断しても，少なくともNAC療法により，治療成績が損なわれることはないと考えられる。

2．NAC療法と手術先行治療のnon-randomized比較試験

NAC療法の治療成績を標準治療と比較した多くの報告のうち，無作為試験ではないものの，prospectiveに施行された報告を紹介する（表2）。Kuhnら[3]は，多量の腹水貯留を認める卵巣癌ⅢC期症例を対象にNAC療法と標準治療のnon-randomizedの比較試験を行った。臨床試験に同意が得られなかった人に標準治療を行った。手術侵襲や合併症に有意差は認めなかったが，NAC群で84%，標準療法群で63%と，NAC群で有意に（$p=0.04$）高率にoptimal surgeryが達成でき，MSTにおいてNAC群42 M，標準治療群23 Mと有意な（$p=0.007$）予後改善を認めた。Hegazyら[4]は，試験開腹や腹腔鏡診断による切除不能例にNAC療法を施行，標準治療群との比較を行った。NAC群は，より進行した症例と考えられ，年齢は有意に高