INVITED REVIEW ARTICLE

Nagoya J. Med. Sci. **68**. 19 ~ 26, 2006

ADVANCES IN TREATMENT OF EPITHELIAL OVARIAN CANCER

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ABSTRACT

Since most cases of epithelial ovarian cancer are advanced at diagnosis, this disease is one of the most lethal malignancies of the female genital tract. In recent years, aggressive cytoreductive surgery and chemotherapy have been employed in an attempt to improve the survival rate in patients with epithelial ovarian cancer. Introduction of platinum anticancer drugs increased survival rate, and several randomized studies have been tried to establish the better combination of anticancer drugs. As a result, the combination of paclitaxel and carboplatin was considered as standard regimen for the first-line treatment of patients with advanced ovarian cancer. Since International Federation of Gynecology and Obstetrics (FIGO) accepted a postoperative staging system in 1988, staging laparotomy needs hysterectomy, bilateral adnexectomy, omentectomy, and pelvic and para-aorta lymphadenectomy. However, the influence of lymphadenectomy on survival still remains controversial. Complete resection of the tumor is often difficult since the disease has spread to the abdominal cavity. In such cases, interval debulking surgery is performed after chemotherapy to remove tumors completely. The effectiveness of neoadjuvant chemotherapy and interval debulking surgery still remains unclear. This review will describe the advances in surgical procedures and chemotherapy in treatment of ovarian cancer patients.

Key Words: Ovarian cancer, Chemotherapy, Prognosis, Surgery

INTRODUCTION

Epithelial ovarian cancer is the second most lethal cancer of the reproductive system, and the incidence of this disease has been increasing over the past 50 years in Japan. The causes of ovarian cancer are poorly understood, but the change to a more western lifestyle appears to be increasing its incidence. In contrast to other gynecologic cancers, this disease often exhibits no specific symptoms in the early stages. Since the ovary is in the abdominal cavity, ovarian cancer can easily spread to other parts of the peritoneal cavity. This disease is not easily diagnosed until the tumor size increases to more than 10 cm, which causes abdominal distension and discomfort. Thus, at diagnosis of this disease, more than 50% of ovarian cancers are found to be stage III or higher. As a result, curative and complete surgical resection is not an option for most patients. Chemotherapy is another weapon in the treatment of ovarian cancer, since complete resection is often impossible in patients in the advanced stage of the disease. Before the introduction of

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cisplatin, chemotherapy showed little effect on survival. However, administration of cisplatin has improved the survival rate by 10 to 20%. Chemotherapy has advanced remarkably over the last two decades because of the introduction of new anticancer and supporting drugs. This paper presents a review of published data on the clinical relevance of ovarian cancer treatment and summarizes the history of chemotherapy in treating this disease.

HISTOLOGY

Ovarian tumors include many histologic types, causing difficulty and complexity in understanding the characteristics of the disease. Epithelial ovarian cancer consists mainly of 4 major histologic types: serous, mucinous, endometrioid, and clear cell adenocarcinoma. The epithelium

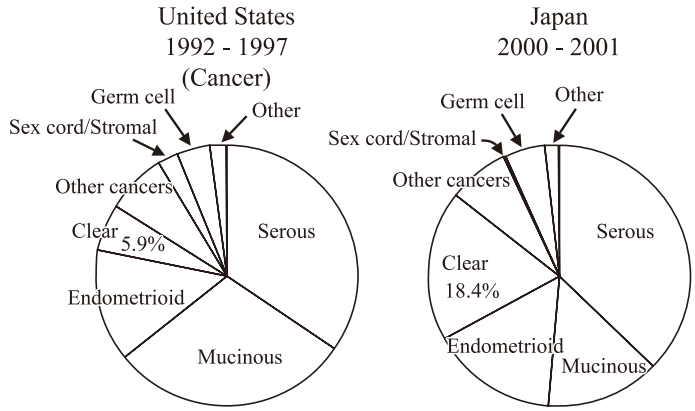

Fig. 1 Distribution of epithelial ovarian cancer by histologic types in US and Japan.

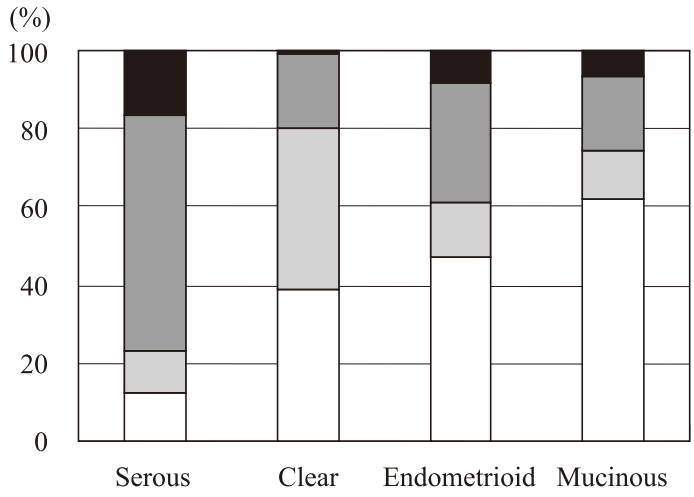

Fig. 2 Stage distribution of epithelial ovarian cancer by histologic types. White columns, stage I; light gray columns, stage II; dark gray columns, stage III; black columns, stage IV.

that characterizes serous tumors resembles the lining of a normal fallopian tube. Mucinous tumors are lined with cells that generally resemble typical mucinous cells lining the endocervix, and are usually diagnosed by traditional morphology. The tumors present as sheets of cells, often in a cribriform pattern, or as tumor cells invading the stroma. Endometrioid adenocarcinoma resembles adenocarcinoma of the endometrium. Clear cell adenocarcinoma is characterized by both clear and "hobnail" cells, and the clear appearance of the cytoplasm is due to the dissolution of glycogen. The rates of histologic types are shown in figure 1. The serous type is the most common histology in both the United States and Japan. The rate of clear cell adenocarcinoma is low in the United States, while in Japan it is the second most common histology. Clinical characteristics are quite different among these 4 histologies; mucinous and clear histologies show resistance to anticancer drugs, whereas serous and endometrioid histologies are sensitive to them. Fortunately, about 80% of clear and mucinous carcinoma is stage I or II, although at diagnosis more than 50% of epithelial ovarian cancers have spread to the peritoneal cavity (Fig. 2).

SURGICAL PROCEDURE

The surgical procedure for ovarian cancer was the simplest among gynecologic cancers before Burghardt first reported lymph node metastasis in ovarian cancer[1)] and the International Federation of Gynecology and Obstetrics (FIGO) accepted a postoperative staging system in 1988. Since then, staging laparotomy has included hysterectomy, bilateral adnexectomy, omentectomy, and pelvic and para-aortic lymphadenectomy, as shown in figure 3. Although the diagnostic significance of pelvic and para-aortic lymphadenectomy in obtaining an accurate assessment of each stage has

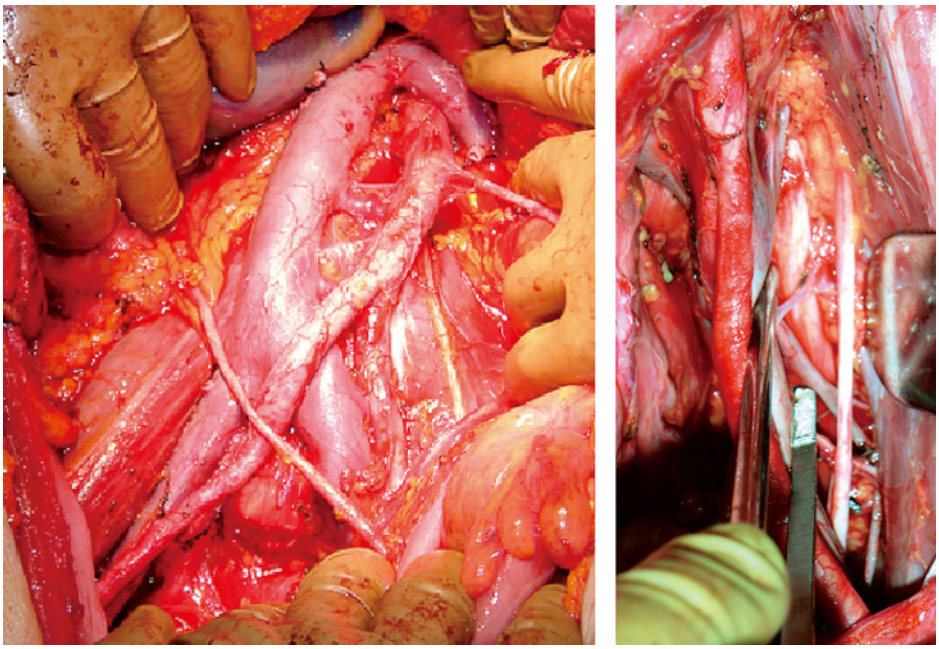

Fig. 3 Photographs after lymphadenectomy. Left photo shows para-aortic region. Right photo shows pelvic region.

been established, whether or not lymphadenectomy improves survival remains controversial.[2,3] If an ovarian malignant tumor is suspected based on clinical findings, exploratory laparotomy is necessary to confirm whether or not the tumor is malignant as well as to determine its histologic type and stage. Surgical staging provides important information that can guide postoperative chemotherapy. In addition, maximal tumor debulking is a valuable component of initial surgery. Meta-analyses have suggested that reduction to a small volume of residual tumors after initial cytoreductive surgery was associated with improved survival.[4,5] Although none of these studies involved patients randomly assigned or not assigned to debulking surgery, the value of that procedure is recognized by gynecologic oncologists. Residual tumor size significantly affects survival time as many papers have reported, and several trials has been conducted to determine whether a favorable outcome associated with small volume residual tumors was indeed the result of debulking surgery. However, none of these studies have clearly demonstrated any improvement in survival time associated with a small volume of residual tumor size after initial cytoreductive surgery. A randomized trial would be essential to provide convincing evidence. However, such a trial does not appear feasible, since most gynecologic oncologists have already accepted the value of initial debulking surgery.

Complete resection of ovarian cancer is often impossible due to the extent of the disease. In such cases, interval debulking surgery is performed after chemotherapy to facilitate a response to subsequent chemotherapy and thus improve survival. The theoretical advantage of this approach is the increased rate of optimal cytoreduction. The European Organization for Research and Treatment of Cancer (EORTC) reported that interval debulking surgery significantly lengthened the progression-free and overall survival time.[6] Contradictory results reported by the Gynecologic Oncology Group (GOG 152) indicated that interval debulking surgery failed to impact either of those outcomes.[7] The reason for these two disparate results is the use of different chemotherapy regimens and different residual tumor diameters after initial surgery.

CHEMOTHERAPY

Before platinum anticancer drugs were available, patients with advanced ovarian cancer were treated with alkylating drugs such as cyclophosphamide, melphalan, chlorambucil, and thiotepa as monotherapy, but the outcome was miserable. Wiltshaw and Kroner reported a phase II study of cisplatin with a response rate of 26.5% in 34 patients resistant to conventional alkylating drugs.[8] Lambert and Berry reported the first randomized study showing a significantly longer survival time and response duration in patients receiving cisplatin compared to those receiving cyclophosphamide.[9] Subsequently, several reports showed that cisplatin achieved superior survival times as well as response rates compared to those of alkylating drugs, thus establishing the effectiveness of a combination chemotherapy using cisplatin with alkylating drugs as the standard regimen.[10-12] A'Hern and Gore, in a meta-analysis of 10 trials, reported that the CAP regimen (cyclophosphamide, adriamycin, cisplatin) showed a significant improvement in survival compared with the CP regimen (cyclophosphamide, cisplatin).[13] Although most European and Japanese gynecologic oncologists have accepted the CAP regimen for advanced ovarian cancer, it has not been adopted in the United States because one of the critical adverse drug reactions of adriamycin is cardiotoxicity.

In 1996, McGuire et al. reported findings of the GOG 111 (Gynecologic Oncology Group) based on a randomized controlled trial of CP (cyclophosphamide, cisplatin) *vs* TP (paclitaxel, cisplatin) in stage III and IV ovarian cancer.[14] They concluded that incorporating paclitaxel into first-line chemotherapy improves the duration of progression-free survival and of overall survival

in women with a residual tumor after initial surgery. Furthermore, another randomized controlled trial (OV10) reported by the European-Canadian Intergroup[15] confirmed the findings of the GOG 111 and indicated that the combination of paclitaxel and cisplatin confers a survival advantage over that of cyclophosphamide and cisplatin.

Cisplatin produces severe side effects such as neurotoxicity, ototoxicity, and nephrotoxicity in addition to myelosuppression and severe nausea. Carboplatin, an analogue of cisplatin, is less toxic than the parent drug, while showing equal efficacy against ovarian cancer.[16,17] Two randomized studies were performed to compare survival rates and adverse effects between TP (paclitaxel, cisplatin) and TJ (paclitaxel, carboplatin).[18,19] Although myelosuppression results were contradictory in each study, the TJ regimen showed a lower frequency of gastrointestinal and neurologic toxicity than the TP regimen in both. As a result, the combination of paclitaxel and carboplatin was accepted as standard therapy for the first-line treatment of patients with advanced ovarian cancer. Docetaxel is a novel semi-synthetic taxane with significant antitumor activity and manageable toxicity of myelosuppression. A randomized trial was performed to compare the efficacy and adverse effects of the DJ (docetaxel, carboplatin) with those of the TJ (paclitaxel, carboplatin) regimen,[20] in which the two appeared to show a similar efficacy. However, the adverse effects of the two regimens were different. The DJ regimen was associated with significantly more myelosuppression but significantly less neurotoxicity than the TJ regimen during both therapy and follow-up. Although the former cannot yet be considered a standard therapy due to only a 3-year follow-up, it should be viewed as an alternative to the TJ regimen in the future.

Since ovarian cancer has often spread to the abdominal cavity at diagnosis or surgery, optimal cytoreduction surgery (residual tumor size; < 2 cm) may be difficult to achieve due to the extent of the tumor. Furthermore, there are no conclusive reports of a clear survival benefit in patients with residual tumors larger than 2 cm in diameter following initial cytoreductive surgery. Since about 80% of ovarian cancers are chemosensitive and neoadjuvant chemotherapy may significantly reduce the tumor burden, this chemotherapy used before surgery may facilitate an easier optimal cytoreduction. Although many retrospective studies have reported that neoadjuvant chemotherapy reduced perioperative morbidity and improved the quality of life in patients with advanced ovarian cancer, no firm conclusions can be drawn as yet. Definitive conclusions regarding prognosis must await the findings of a randomized controlled trial currently being conducted by EORTC.

Advances in supportive therapy have developed over the last two decades. Granulocyte colony stimulating factor (G-CSF) is a strong weapon in treating patient with decreased granulocytes, by facilitating aggressive chemotherapy and reducing the death rate from severe infection. Severe nausea and vomiting due to cisplatin is most distressing to patients. Several serotonin receptor antagonists have been developed and introduced. The further development of supportive drugs could ease the pain and anxiety caused by chemotherapy, rendering patients more tolerant and allowing doctors to be more aggressive in the treatment of cancer.

SURVIVAL IN OUR STUDY GROUP

In 1979, we established the Tokai Ovarian Tumor Study Group centering on Nagoya University Hospital and affiliated hospitals to improve prognoses and clarify clinical characteristics of malignant ovarian tumors, since they consist of many histologic types. The protocol of chemotherapy and the surgical procedure were listed in Table 1. More than 2,000 cases were recorded in this study group, and we reported the usefulness of tumor markers, importance of lymphadenectomy, poor prognoses for clear cell and mucinous adenocarcinomas, and low values of maintenance

Table 1 Changes in chemotherapy and surgical procedure

Protocol No.		Chemotherapy	Surgical Procedure
1	1979 Jun – 1881 Jul	Mitomycin C, 5-FU, Cytarabine	Adnexectomy, Hysterectomy, Omentectomy
2	1981 Aug – 1982 Sep	Mitomycin C, 5-FU, Cytarabine, Cisplatin	Adnexectomy, Hysterectomy, Omentectomy
3	1982 Oct – 1985 Dec	Cyclophosphamide, Adriamycin, Cisplatin	Adnexectomy, Hysterectomy, Omentectomy
4	1986 Jan – 1989 Apr	Cyclophosphamide, Adriamycin, Cisplatin or Cisplatin, Vinblastin, Bleomycin	Adnexectomy, Hysterectomy, Omentectomy in some cases Pelvic Lymphadenectomy
5	1989 May – 1991 Dec	Cyclophosphamide, Adriamycin, Cisplatin	Adnexectomy, Hysterectomy, Omentectomy Pelvic Lymphadenectomy in some cases Para-aortic Lymphadenectomy
6	1992 Jan – 2000 Mar	Cisplatin, Vinblastin, Bleomycin or Cisplatin, Carboplatin	Adnexectomy, Hysterectomy, Omentectomy Pelvic and Para-aortic Lymphadenectomy
7	2000 Apr – 2002 Dec	Taxol, Carboplatin	Adnexectomy, Hysterectomy, Omentectomy Pelvic and Para-aortic Lymphadenectomy
8	2003 Jan –	Taxol, Carboplatin or Taxotere, Carboplatin	Adnexectomy, Hysterectomy, Omentectomy Pelvic and Para-aortic Lymphadenectomy

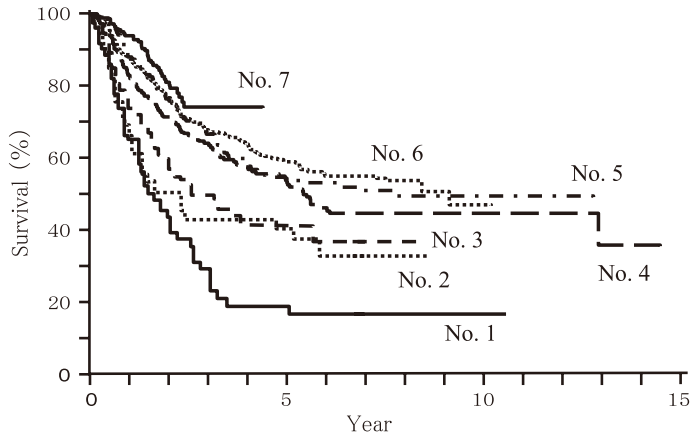

Fig. 4 Survival curves according to protocol of the Tokai Ovarian Tumor Study Group.

chemotherapy and second look operations.[21-24] Survival rates have been improved according to the protocol shown in figure 4. Improved prognoses are mainly due to the introduction of new anticancer drugs and aggressive cytoreductive surgery. Standard chemotherapy and surgical procedures have been established, although the optimal procedure and timing of surgery remain debatable.

REFERENCES

1) Burghardt, E., Pickel, H., Holzer, E. and Lahousen, M.: The significance of lymphadenectomy in therapy of ovarian carcinoma. *Am. J. Obstet. Gynecol.*, 146, 111–112 (1983).

2) Di Re, F. and Baiocchi, G.: Value of lymph node assessment in ovarian cancer: Status of the art at the end of the second millennium. *Int. J. Gynecol. Cancer*, 10, 435–442 (2000).
3) De Poncheville, L., Perrotin, F., Lefrancq, T., Lansac, J. and Body, G.: Does paraaortic lymphadenectomy have a benefit in the treatment of ovarian cancer that is apparently confined to the ovaries? *Eur. J. Cancer*, 37, 210–215 (2001).
4) Bristow, R.E., Tomacruz, R.S., Armstrong, D.K., Trimble, E.L. and Montz, F.J.: Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J. Clin. Oncol.*, 20, 1248–1259 (2002).
5) Allen, D.G., Heintz, A.P. and Touw, F.W.: A meta-analysis of residual disease and survival in stage III and IV carcinoma of the ovary. *Eur. J. Gynaecol. Oncol.*, 16, 349–356 (1995).
6) Van Der Burg, M.E., Van Lent, M., Buyse, M., Kobierska, A., Colombo, N., Favalli, G., Lacave, A.J., Nardi, M., Renard, J. and Pecorelli, S.: The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N. Engl. J. Med.*, 332, 629–634 (1995).
7) Rose, P.G., Nerenstone, S., Brady, M.F., Clarke-Pearson, D., Olt, G., Rubin, S.C., Moore, D.H. and Small, J.M.: Secondary surgical cytoreduction for advanced ovarian carcinoma. *N. Engl. J. Med.*, 351, 2489–2497 (2004).
8) Wiltshaw, E. and Kroner, T.: Phase II study of cis-dichlorodiammineplatinum(II) (NSC-119875) in advanced adenocarcinoma of the ovary. *Cancer Treat. Rep.*, 60, 55–60 (1976).
9) Lambert, H.E. and Berry, R.J.: High dose cisplatin compared with high dose cyclophosphamide in the management of advanced epithelial ovarian cancer (FIGO stages III and IV): report from the North Thames Cooperative Group. *Br. Med. J. (Clin. Res. Ed.)*, 290, 889–893 (1985).
10) Neijt, J.P., Ten Bokkel Huinink, W.W., Van Der Burg, M.E., Van Oosterom, A.T., Vriesendorp, R., Kooyman, C.D., Van Lindert, A.C., Hamerlynck, J.V., Van Lent, M., Van Houwelingen, J.C. *et al.*: Randomised trial comparing two combination chemotherapy regimens (Hexa-CAF vs CHAP-5) in advanced ovarian carcinoma. *Lancet*, 2, 594–600 (1984).
11) Omura, G., Blessing, J.A., Ehrlich, C.E., Miller, A., Yordan, E., Creasman, W.T. and Homesley, H.D.: A randomized trial of cyclophosphamide and doxorubicin with or without cisplatin in advanced ovarian carcinoma. A Gynecologic Oncology Group Study. *Cancer*, 57, 1725–1730 (1986).
12) Williams, C.J., Mead, G.M., Macbeth, F.R., Thompson, J., Whitehouse, J.M., Macdonald, H., Harvey, V.J., Slevin, M.L., Lister, T.A., Shepherd, J.H. *et al.*: Cisplatin combination chemotherapy versus chlorambucil in advanced ovarian carcinoma: mature results of a randomized trial. *J. Clin. Oncol.*, 3, 1455–1462 (1985).
13) A'hern, R.P. and Gore, M.E.: Impact of doxorubicin on survival in advanced ovarian cancer. *J. Clin. Oncol.*, 13, 726–732 (1995).
14) Mcguire, W.P., Hoskins, W.J., Brady, M.F., Kucera, P.R., Partridge, E.E., Look, K.Y., Clarke-Pearson, D.L. and Davidson, M.: Cyclophosphamide and cisplatin versus paclitaxel and cisplatin: a phase III randomized trial in patients with suboptimal stage III/IV ovarian cancer (from the Gynecologic Oncology Group). *Semin. Oncol.*, 23, 40–47 (1996).
15) Piccart, M.J., Bertelsen, K., James, K., Cassidy, J., Mangioni, C., Simonsen, E., Stuart, G., Kaye, S., Vergote, I., Blom, R., Grimshaw, R., Atkinson, R.J., Swenerton, K.D., Trope, C., Nardi, M., Kaern, J., Tumolo, S., Timmers, P., Roy, J.A., Lhoas, F., Lindvall, B., Bacon, M., Birt, A., Andersen, J.E., Zee, B., Paul, J., Baron, B. and Pecorelli, S.: Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. *J. Natl. Cancer. Inst.*, 92, 699–708 (2000).
16) Alberts, D.S., Green, S., Hannigan, E.V., O'toole, R., Stock-Novack, D., Anderson, P., Surwit, E.A., Malvlya, V.K., Nahhas, W.A. and Jolles, C.J.: Improved therapeutic index of carboplatin plus cyclophosphamide versus cisplatin plus cyclophosphamide: final report by the Southwest Oncology Group of a phase III randomized trial in stages III and IV ovarian cancer. *J. Clin. Oncol.*, 10, 706–717 (1992).
17) Swenerton, K., Jeffrey, J., Stuart, G., Roy, M., Krepart, G., Carmichael, J., Drouin, P., Stanimir, R., O'connell, G., Maclean, G. *et al.*: Cisplatin-cyclophosphamide versus carboplatin-cyclophosphamide in advanced ovarian cancer: a randomized phase III study of the National Cancer Institute of Canada Clinical Trials Group. *J. Clin. Oncol.*, 10, 718–726 (1992).
18) Ozols, R.F., Bundy, B.N., Greer, B.E., Fowler, J.M., Clarke-Pearson, D., Burger, R.A., Mannel, R.S., Degeest, K., Hartenbach, E.M. and Baergen, R.: Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J. Clin. Oncol.*, 21, 3194–3200 (2003).
19) Du Bois, A., Luck, H.J., Meier, W., Adams, H.P., Mobus, V., Costa, S., Bauknecht, T., Richter, B., Warm,

M., Schroder, W., Olbricht, S., Nitz, U., Jackisch, C., Emons, G., Wagner, U., Kuhn, W. and Pfisterer, J.: A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J. Natl. Cancer Inst.*, 95, 1320–1329 (2003).

20) Vasey, P.A., Jayson, G.C., Gordon, A., Gabra, H., Coleman, R., Atkinson, R., Parkin, D., Paul, J., Hay, A. and Kaye, S.B.: Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J. Natl. Cancer Inst.*, 96, 1682–1691 (2004).

21) Kikkawa, F., Matsuzawa, K., Arii, Y., Kawai, M., Kobayashi, I., Nakashima, N. and Mizutani, S.: Randomized trial of cisplatin and carboplatin versus cisplatin, vinblastine and bleomycin in ovarian cancer. *Gynecol. Obstet. Invest.*, 50, 269–274 (2000).

22) Kikkawa, F., Kawai, M., Tamakoshi, K., Suganuma, N., Nakashima, N., Furuhashi, Y., Kuzuya, K., Hattori, S., Arii, Y. and Tomoda, Y.: Mucinous carcinoma of the ovary. Clinicopathologic analysis. *Oncology*, 53, 303–307 (1996).

23) Kikkawa, F., Ishikawa, H., Tamakoshi, K., Suganuma, N., Mizuno, K., Kawai, M., Arii, Y., Tamakoshi, A., Kuzuya, K. and Tomoda, Y.: Prognostic evaluation of lymphadenectomy for epithelial ovarian cancer. *J. Surg. Oncol.*, 60, 227–231 (1995).

24) Morikawa, Y., Kawai, M., Kano, T., Kikkawa, F., Oguchi, H., Nakashima, N., Ishizuka, T., Furuhashi, Y., Hattori, S.E., Kuzuya, K. *et al.*: Clinical remission criteria for epithelial carcinoma of the ovary. *Gynecol. Oncol.*, 48, 342–348 (1993).