THE JOURNAL OF
Obstetrics and Gynaecology Research

The official Journal of Asia and Oceania Federation of Obstetrics and Gynaecology
Japan Society of Obstetrics and Gynecology

doi:10.1111/j.1447-0756.2011.01826.x J. Obstet. Gynaecol. Res. Vol. 38, No. 7: 1018–1023, July 2012

Is there any association between retroperitoneal lymphadenectomy and survival benefit in advanced stage epithelial ovarian carcinoma patients?

Kotaro Sakai[1,2], Hiroaki Kajiyama[2], Tomokazu Umezu[2], Kiyosumi Shibata[2], Mika Mizuno[2], Shiro Suzuki[2], Michiyasu Kawai[3], Tetsuro Nagasaka[4] and Fumitaka Kikkawa[2]

[1]Department of Obstetrics and Gynecology, Daido Hospital, [2]Department of Obstetrics and Gynecology, Nagoya University Graduate School of Medicine, Nagoya, [3]Department of Obstetrics and Gynecology, Toyohashi Municipal Hospital, Toyohashi, and [4]Department of Medical Technology, Nagoya University School of Health Science, Nagoya, Japan

Abstract

Aim: The effect of systematic retroperitoneal lymphadenectomy (SRL) remains controversial in patients with advanced epithelial ovarian cancer (aEOC) who are optimally debulked.

Material and Methods: Demographic and clinicopathologic data were obtained from the Tokai Ovarian Tumor Study Group between 1986 and 2009. All patients were divided into two groups. Group A ($n = 93$): (i) patients did not undergo SRL; and (ii) lymph node exploration or sampling was optional. Group B ($n = 87$): patients underwent SRL. Survival curves were calculated using the Kaplan–Meier method. Differences in survival rates were analyzed using the log–rank test.

Results: All pT3–4 aEOC patients were optimally debulked (residual tumor <1 cm). The median age was 55 years (range: 18–84). The 5-year progression-free survival (PFS) rates of groups A and B were 46.7 and 41.9%, respectively ($P = 0.658$). In addition, the 5-year overall survival (OS) rates were 62.9 and 59.0%, respectively ($P = 0.853$). Subsequently, there was no significant difference in OS and PFS in the two groups stratified to histological type (serous or non-serous type). Furthermore, there was no significant difference in recurrence rates in retroperitoneal lymph nodes regardless of completion of lymphadenectomy.

Conclusion: Our data suggest that aEOC patients with optimal cytoreduction who underwent SRL did not show a significant improvement in survival irrespective of each histological type.

Key words: advanced ovarian cancer, optimal cytoreduction, stage, survival, systematic lymphadenectomy.

Introduction

Epithelial ovarian carcinoma (EOC) is a major cause of death among gynecological malignancies.[1] EOC has a poor prognosis primarily due to its late symptomatology, frequent association with multiple intraperitoneal disseminations, and high rate of distant metastases. Thus, the 5-year overall survival of the patients diagnosed remains stagnant at approximately 30%.

Primary maximal cytoreductive surgery followed by taxane/platinum-based chemotherapy has been a crucial part of treatment for advanced EOC (aEOC) to reduce the risk of a postoperative residual tumor, which is one of the clinically significant prognostic factors. Indeed, systematic retroperitoneal lymphadenectomy

Received: September 20 2011.
Accepted: October 29 2011.
Reprint request to: Dr Hiroaki Kajiyama, Department of Obstetrics and Gynecology, Nagoya University Graduate School of Medicine, Tsuruma-cho 65, Showa-ku, Nagoya 466-8550, Japan. Email: kajiyama@med.nagoya-u.ac.jp

(SRL) improves the assessment of patients' staging as the involvement of retroperitoneal lymph nodes has been reported at a rate of 13% in only pelvic nodes, and 17% of aortic nodes with aEOC at primary surgery.[2] In fact, although there have been several reports supporting the role of SRL in advanced EOC,[3,4] other studies have not identified a benefit associated with SRL.[5] However, the integral issue of this controversy is whether the removal of lymph nodes leads to the prolongation of survival time, despite the fact that it has been demonstrated to be feasible in the treatment of aEOC. With regard to the long-term prognosis of aEOC, a previous retrospective report showed that the surgical procedure, including a more extended lymphadenectomy, contributed to an improvement in disease-specific survival.[6] Nevertheless, it remains inconclusive whether SRL itself has a therapeutic effect by debulking gross and occult tumor tissues in aEOC, because the meaning of SRL might be influenced by the residual intra-abdominal tumor.

In the present study, we retrospectively analyzed a large number of aEOC patients to evaluate the benefit of SRL in such patients with optimal cytoreduction.

Patients and Methods

One hundred and eighty patients with histologically proven and optimally debulked (residual tumor <1 cm) pT3–4 aEOC diagnosed between 1986 and 2009 were registered and treated by the Tokai Ovarian Tumor Study Group, consisting of Nagoya University Hospital and affiliated hospitals. The study was approved by the ethics committee of Nagoya University. Data were collected from medical records and clinical follow-up visits. All patients were originally diagnosed with aEOC, and histological slides were reviewed by one of the authors with no knowledge of the patients' clinical data, employing the central pathological review system according to World Health Organization (WHO) classification. Clinical staging was assessed according to the International Federation of Gynecology and Obstetrics (FIGO, 1988). All patients were divided into two groups as follows:

Group A ($n = 93$): (i) patients underwent total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and the attempted removal of all macroscopic intra-abdominal tumors; (ii) lymph node exploration or sampling was optional, but all lymph nodes larger than 1 cm in diameter were removed; and (iii) optimal cytoreductive surgery was performed (residual tumor <1 cm).

Groups B ($n = 87$): patients underwent total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, optimal cytoreductive surgery (residual tumor <1 cm) and systematic pelvic and para-aortic lymphadenectomy as the initial operation.

The exploration of regional lymph nodes included SRL, removal of palpable nodes, or removal of all lymphatic tissues surrounding the retroperitoneal vessels, in the absence of clinically obvious disease. Para-aortic lymph node dissection was performed from the bifurcation of the aorta to the origin of the renal vessels. Pelvic node dissection was conducted from the common, internal and external iliac, and obturator vessels to the femoral ring. As the study was a long-term retrospective analysis, there was no evident criterion dividing these patients into each group. Selection of the surgical procedure was influenced by the patients' physical condition, period of treatment, or decision of each institution.

In all aEOC patients, 164 were treated postoperatively with 3–6 cycles of adjuvant chemotherapy; 39 patients received conventional platinum-based chemotherapy, and 125 patients received taxane plus platinum compound chemotherapy. Sixteen patients underwent other or unknown regimens.

Progression-free survival (PFS) was defined as the interval from the date of primary surgery until recurrence or death or last follow-up. The overall survival (OS) duration was determined as the time from the date of primary surgery until death or last follow-up. Progression-free and overall survival curves were calculated using the Kaplan–Meier method, and significance was determined using the log–rank test. Two-tailed tests at P-values of less than 0.05 were considered significant. The prognostic significance concerning pathological variables was assessed using multivariate Cox's proportional hazard analysis. The significance of differences in clinical characteristics between Groups A and B was determined employing the χ^2 test or non-paired Student's t-test (age).

Results

Patient characteristics of Groups A and B are summarized in Table 1. The median age at the time of the diagnosis of patients in Groups A and B was 53 (37–79) and 57 (18–84) years, respectively. There were no significant differences in the age between them ($P = 0.263$). The median follow-up for surviving patients was 49.6 months in Group A and 49.2 months in Group B. No patient was lost to follow-up. Among

Table 1 Patient characteristics

	No.	Group A	Group B	*P*-value
Total	180	93	87	
Age (years)				
Median		53	57	0.263
Range		37–79	18–84	
Histology				
Serous	106	49 (52.7%)	57 (65.5%)	0.403
Clear cell	32	18 (19.4%)	14 (16.1%)	
Endometrioid	22	13 (14.0%)	9 (10.3%)	
Mucinous	11	8 (8.6%)	3 (3.4%)	
Others	9	5 (5.4%)	4 (4.6%)	
pT stage				
3	150	75 (80.6%)	75 (86.2%)	0.317
4	30	18 (19.4%)	12 (13.8%)	
Residual tumor				
None	154	73 (78.5%)	81 (93.0%)	0.250*
<1 cm	16	10 (10.8%)	6 (6.9%)	
Unknown	10	10 (10.8%)	0 (0%)	
Chemotherapy				
Platinum-based	39	18 (19.4%)	21 (24.1%)	0.132
Taxane plus platinum	125	63 (67.7%)	62 (71.3%)	
Unknown or others	16	12 (12.9%)	4 (4.6%)	

*None versus <1 cm.

the total of 180 patients, 106 patients showed serous, 32 clear-cell, 22 endometrioid, and 11 mucinous histology. Nine patients had others histological types (undifferentiated/unclassified). Among the 93 Group A patients, 75 patients (80.6%) had pT3 disease, and 18 (19.4%) had pT4 disease. In addition, among the 87 Group B patients, 75 patients (86.2%) had pT3 disease, and 12 (13.8%) had pT4 disease. The clinical characteristics of the two groups were not significantly different.

The majority of patients received adjuvant chemotherapy, including conventional platinum-based or taxane plus platinum-based chemotherapy (87.1% in Group A and 95.4% in Group B) after cytoreductive surgery. No differences in chemotherapy were found between the two groups ($P = 0.132$).

The 5-year OS rate of all Group A patients was 62.9%, compared with 59.0% in Group B. On Kaplan–Meier analysis, the difference in OS between these groups was non-significant ($P = 0.853$) (Fig. 1a). Moreover, the 5-year PFS rate of all Group A patients was 46.7%, compared with 41.9% in Group B. The difference in PFS between these groups was also non-significant ($P = 0.658$) (Fig. 1b).

In addition, even when confining analysis to patients without residual tumor, there were no significant differences in survival among the two groups (OS [Fig. 1c]: $P = 0.859$; PFS [Fig. 1d]: $P = 0.504$). Similarly, even when confining analysis to serous or non-serous adenocarcinoma patients, there was no significant difference in OS and PFS among the two groups (Serous: $P = 0.492$ [OS]/$P = 0.672$ [PFS], Non-serous: $P = 0.622$ [OS]/$P = 0.396$ [PFS]} (Fig. 2).

In multivariate analyses, age, pT stage (3/4), histological type (serous/non-serous), and SRL (absent/present) were entered into Cox's proportional hazard model. As shown in Table 2, similar to the results of univariate analysis, performance of SRL was not a significant prognostic factor.

We finally examined whether the distributions of sites of recurrence differed among patients showing recurrence in both groups. We identified 46 patients with recurrence in Group A and 53 patients with recurrence in Group B. No difference in the distributions of recurrence sites was found between the two groups (Table 3, $P = 0.759$). Thus, there was no evidence that recurrence around retroperitoneal lymph nodes more frequently occurred in Group A compared to Group B patients.

Discussion

In the present study, we retrospectively analyzed a large number of aEOC patients to evaluate the benefit of SRL in aEOC patients with optimal cytoreduction. As a result, there were no significant differences in the OS and PFS between the SRL and control groups. According to a recent report, Panici *et al*. were the first to perform a multicenter randomized clinical trial that compared OS and PFS in patients who underwent SRL with those undergoing the removal of only pathologically enlarged lymph nodes.[7] In their study, although SRL significantly improved PFS, there were no significant differences in OS between the two groups at 56.3 and 58.7 months, respectively ($P = 0.768$). Certainly, patients in the SRL group achieved a 7-month longer median PFS than those assigned to the control group (29.4 compared with 22.4 months, respectively; $P = 0.022$). Nevertheless, we thought that there might some selection bias because of the rate of patients with stage IV and tumors showing poor differentiation, frequency of larger residual tumors (1–2 cm), and rate of generally chemoresistant tumors (clear-cell and mucinous type) seemed to be higher in the control than in the SRL arm.

The authors stated that in the trial, the follow-up duration might be too short to detect a significant difference between the two groups for assessing

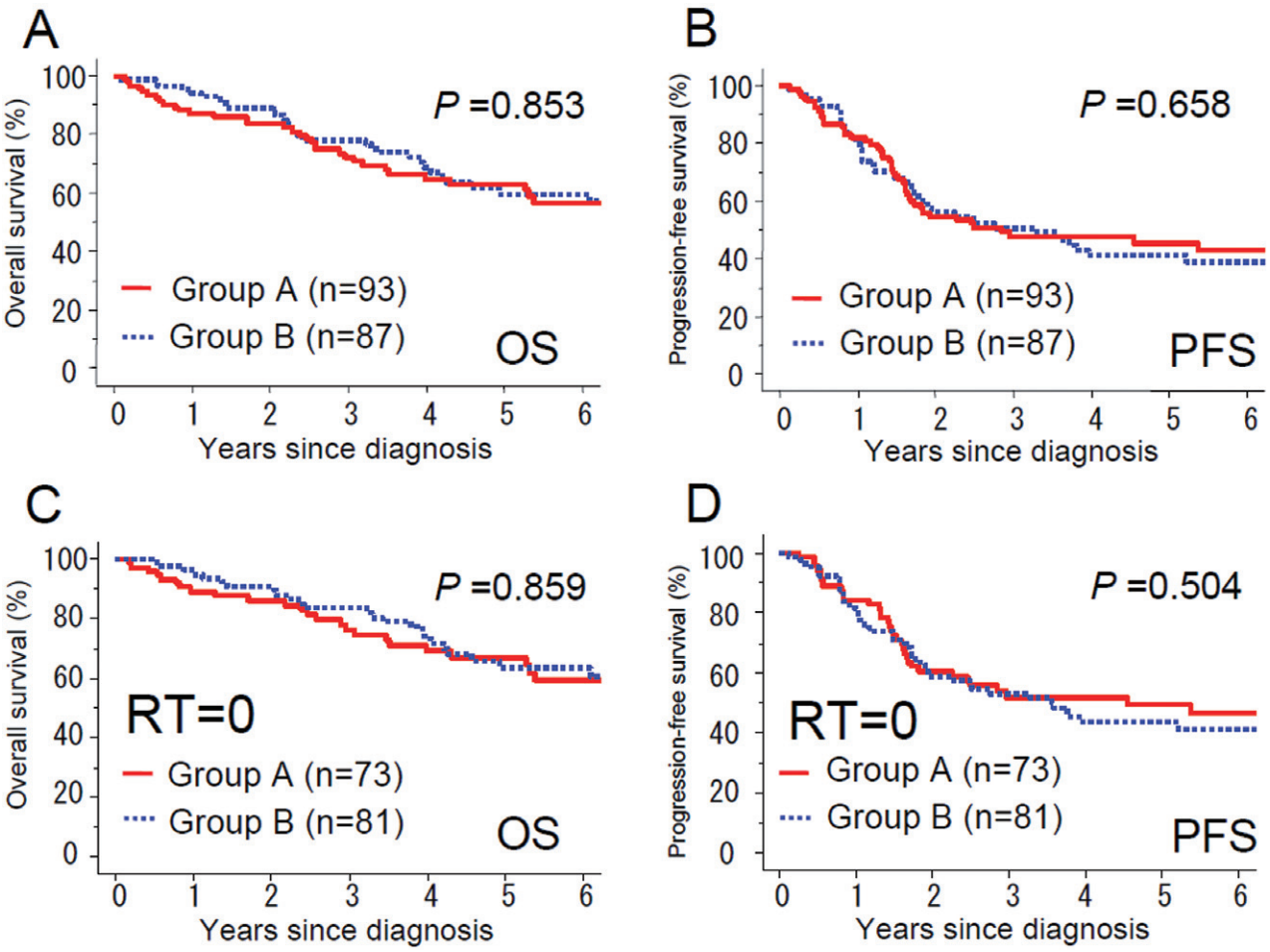

Figure 1 Kaplan–Meier estimated (a) overall survival (OS) or (b) progression-free survival (PFS) in patients with advanced epithelial ovarian cancer (aEOC). Group A (solid line), 93 patients receiving systematic retroperitoneal lymphadenectomy (SRL); Group B (dotted line), 87 patients not receiving SRL. Confining analysis to patients without residual tumor (c) OS and (d) PFS.

long-term survival outcomes. However, they also argued that the reason why SRL did not prolong OS was probably due to effective chemotherapies diluting the impact of SRL on the risk of death.

In a large-scale retrospective analysis, Chan *et al*. reported a positive correlation between more extensive lymphadenectomy and survival benefit of 13 918 EOC patients with stages 3–4.[6] Indeed, as they stated, extensive lymph node resection may lead to improved survival by removing micrometastatic disease within the lymph nodes that may be resistant to chemotherapy. However, their analysis lacked information on the extent of the residual tumor, location of nodal resection, and description of subsequent chemotherapy. Thus, it is possible that a more intensive SRL can be performed when there is a smaller residual tumor presence during cytoreductive surgery, and, consequently, this may result in a better prognosis. According to another retrospective analysis from du Bois *et al*., lymphadenectomy was associated with superior survival in patients without gross residual disease.[8] In patients with or without lymphadenectomy, the median survival time was 103 or 84 months, and 5-year survival rates were 67.4 and 59.2%, respectively ($P = 0.0166$). However, in their analysis, the extent of retroperitoneal lymphadenectomy seemed unclear. Presumably, the differences from our results were in part due to the retrospective nature of the study. Despite the fact that the OS rate was improved by lymphadenectomy, the authors did not support any recommendation for

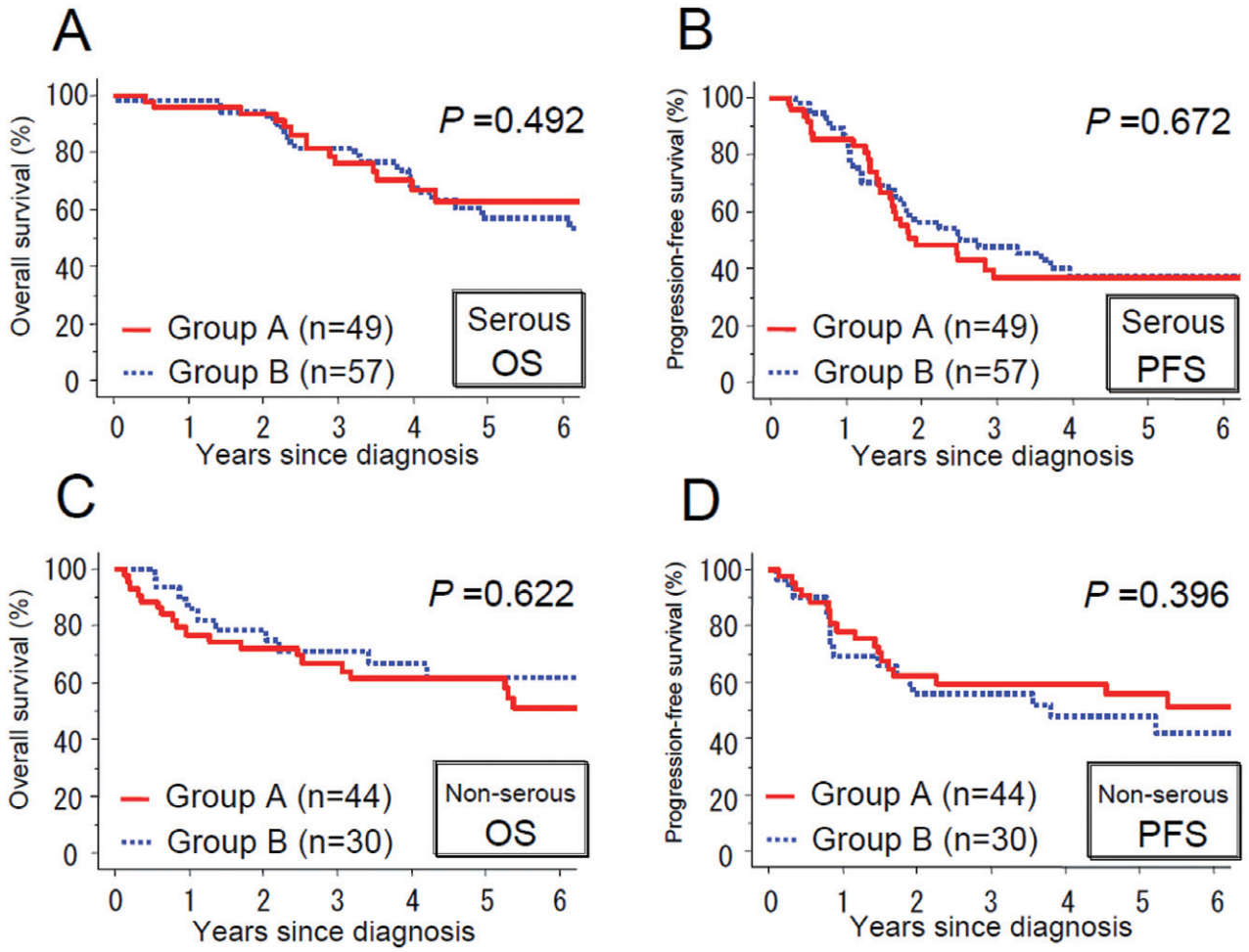

Figure 2 Kaplan–Meier estimated (a) overall survival (OS) or (b) progression-free survival (PFS) in patients with (a,b) advanced serous or (c,d) non-serous adenocarcinoma. (a,b) Serous type: Group A (solid line), 49 patients receiving systematic retroperitoneal lymphadenectomy (SRL); Group B (dotted line), 57 patients not receiving SRL. (c,d) Non-serous type: Group A (solid line), 44 patients receiving SRL; Group B (dotted line), 30 patients not receiving SRL.

Table 2 Multivariate analyses of clinicopathologic parameters in relation to overall survival (OS) and progression-free survival (PFS) of patients

	No.	Progression-free survival (PFS)		Overall survival (OS)	
		Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*-value
Total	180				
Age			0.161		0.234
≥55	92	1		1	
<55	88	1.343 (0.889–2.028)		1.336 (0.829–2.154)	
pT			0.879		0.010
3	150	1		1	
4	30	1.045 (0.595–1.836)		0.356 (0.162–0.780)	
Histological type			0.232		0.128
Serous type	106	1		1	
Non-serous type	74	0.768 (0.499–1.183)		1.454 (0.898–2.352)	
SRL			0.630		0.683
Absent	93	1		1	
Present	87	0.904 (0.598–1.365)		0.902 (0.552–1.476)	

CI, confidential interval; SRL, systematic retroperitoneal lymphadenectomy.

Table 3 Site of disease recurrence by treatment arm

Recurrence site	Group A ($n = 93$)		Group B ($n = 87$)	
	No.	%	No.	%
No recurrence	47	50.5	34	39.1
Recurrence	46	49.5	53	60.9
Pelvic cavity without RPN	26	28	30	34.5
Distant/other without RPN	12	12.9	11	12.6
Including RPN	4	4.3	8	9.2
Unknown	4	4.3	4	4.6

No significant difference in distribution of recurrence sites was found between the two groups ($P = 0.759$). RPN, retroperitoneal lymph nodes.

lymphadenectomy in patients with residual intraperitoneal disease unless node dissection changed the residual disease status from bulky to minimal; in addition, they stated that their results offered only a hypothesis as a prospectively randomized trial. In this regard, our conclusion was essentially the same as theirs and so we agree.

Indeed, according to many investigations, patients with nodal metastases show a poorer prognosis than those with negative lymph nodes.[9] However, is it possible that an attempt to perform maximum SRL to remove occult microscopic tumors leads to a prolongation of disease-specific survival. As the investigations pointed out, the unfavorable prognosis of patients with positive lymph nodes suggests that nodal involvement may be a marker of the tumor's biologic aggressiveness. At least, we have to bear in mind that the therapeutic importance may be separate from its diagnostic significance.

In summary, we did not think that our limited retrospective results would immediately lead to the possibility of omitting lymphadenectomy. As the indication for SRL is still controversial, considering the adverse effects and possible survival benefits, we hope that further investigation involving a larger-scale, prospective, clinical study will be conducted in the future.

Acknowledgments

We sincerely thank Drs Y. Kinoshita (Ogaki Municipal Hospital), K. Sakakibara (Okazaki Municipal Hospital), A. Takeda (Gifu Prefectural Tajimi Hospital), T. Nakanishi (Aichi Cancer Center Hospital), O. Yamamuro (Japanese Red Cross Nagoya Second Hospital), K. Mizuno (Japanese Red Cross Nagoya first Hospital), and K. Matsuzawa (Anjyo Kosei Hospital) who collaborated in data collection.

Disclosure

All authors declare that there are no conflicts of interest. This study was not supported by any grant or funding.

References

1. Brun JL, Feyler A, Chene G, Saurel J, Brun G, Hocke C. Long-term results and prognostic factors in patients with epithelial ovarian cancer. *Gynecol Oncol* 2000; **78**: 21–27.
2. Angioli R, Plotti F, Palaia I *et al*. Update on lymphadenectomy in early and advanced ovarian cancer. *Curr Opin Obstet Gynecol* 2008; **20**: 34–39.
3. Scarabelli C, Gallo A, Zarrelli A, Visentin C, Campagnutta E. Systematic pelvic and para-aortic lymphadenectomy during cytoreductive surgery in advanced ovarian cancer: Potential benefit on survival. *Gynecol Oncol* 1995; **56**: 328–337.
4. Burghardt E, Lahousen M, Stettner H. The significance of pelvic and para-aortic lymphadenectomy in the operative treatment of ovarian cancer. *Baillieres Clin Obstet Gynaecol* 1989; **3**: 157–165.
5. Spirtos NM, Gross GM, Freddo JL, Ballon SC. Cytoreductive surgery in advanced epithelial cancer of the ovary: The impact of aortic and pelvic lymphadenectomy. *Gynecol Oncol* 1995; **56**: 345–352.
6. Chan JK, Urban R, Hu JM *et al*. The potential therapeutic role of lymph node resection in epithelial ovarian cancer: A study of 13918 patients. *Br J Cancer* 2007; **96**: 1817–1822.
7. Panici PB, Maggioni A, Hacker N *et al*. Systematic aortic and pelvic lymphadenectomy versus resection of bulky nodes only in optimally debulked advanced ovarian cancer: A randomized clinical trial. *J Natl Cancer Inst* 2005; **97**: 560–566.
8. du Bois A, Reuss A, Harter P, Pujade-Lauraine E, Ray-Coquard I, Pfisterer J. Potential role of lymphadenectomy in advanced ovarian cancer: A combined exploratory analysis of three prospectively randomized phase III multicenter trials. *J Clin Oncol* 2010; **28**: 1733–1739.
9. Eisenkop SM, Spirtos NM. The clinical significance of occult macroscopically positive retroperitoneal nodes in patients with epithelial ovarian cancer. *Gynecol Oncol* 2001; **82**: 143–149.