Table 4
Combination chemotherapy for platinum resistant ovarian cancer.

Study	Rx	% of 1 prior Rx	RR (%)	PFS (months)
OVATURE	Cb vs CbPXD	2.8–4.3	1 vs 0	4.7 vs 3.6
OVA301[22]	pD vs pDTr	100	12 vs 13	3.7 vs 4
CARTAXHY[24]	wP vs wPCb vs wPTp	71–74	35 vs 37 vs 39	3.7 vs 4.8 vs 5.4
ASSIST-3[23]	pD vs pDCan	60	8.3 vs 12	3.7 vs 5.6
JCOG0503	E + I	57	21.7	4.1
Buda et al.	P vs PEp	100	37[a] vs 47[a]	6[a] vs 6[a]
AURELIA	wP/pD/Tp vs + BV	57–60	13 vs 31	3.4 vs 6.7
TRINOVA-1	wP vs wPTre	38–41	30[a] vs 38[a]	5.4[a] vs 7.2[a]

Abbreviations. Rx: regimen, Cb: carboplatin, PXD: phenoxidiol, pD: liposomal doxorubicin, Tr: trabectidine, wP: weekly paclitaxel, Tp: topotecan, Can: canfosfamide, E: etoposide, I: irinotecan, P: paclitaxel (every three weeks), Ep: epidoxorubicine, BV: bavacizumab, Tre: trebananib.
[a] Data for patients with platinum free interval less than 12 months.

Regarding toxicity, FN was much more frequent in our study, especially in heavily pretreated patients or elderly patients. Even among patients aged <65 years or those with 1 or 2 prior regimens, FN was still approximately 15%. Therefore, we think that the present regimen is too toxic and cannot be recommended as an option for heavily pretreated patients or elderly patients. Moreover, even when we excluded heavily pretreated patients or elderly patients, RR was similar. Eventually, we decided to discontinue the development of this regimen for patients with platinum-resistant ovarian cancer.

In the OVA301 subset analysis, patients with PFI of 6–12 months are considered good candidates for non-platinum combination chemotherapy [29], and the hypothesis is that platinum chemotherapy after a non-platinum combination can be more effective because of an artificially prolonged PFI. This hypothesis is being tested in the INOVATYON study, which compares trabectedin plus PLD with carboplatin plus PLD in patients with ovarian cancer with PFI of 6–12 months. If the results are positive, then the combination of oral etoposide and intravenous irinotecan, which shows RR of 30.3% in patients with PFI of 3–6 months, can be promising for further investigation for that purpose.

The present study had some limitations. First, pretreatment UGT1A1 assessment was lacking. This issue was discussed at the beginning of this study. Because the dose of irinotecan used in this study is low (140 mg/m^2 per cycle) and because of the negative results of a meta-analysis of the usefulness of such low doses [30], we decided not to use the UGT1A1 assessment. Second, the eligibility criteria allowing heavily pretreated patients are relatively broad compared with those in other trials. This situation can produce a negative bias in both efficacy and safety results. On the other hand, the number of heavily pretreated patients in this study is small, and the subgroup analysis strongly suggested that the conclusions will not change.

In conclusion, this study demonstrates that the combination of oral etoposide and intravenous irinotecan has moderate efficacy in patients with platinum-resistant ovarian cancer. The overall RR was 21.7%. This result did not meet the primary endpoint for a further phase III trial. Because of toxicity, we do not recommend this regimen outside of clinical trials. If such a trial is planned, heavily pretreated patients and elderly patients should be excluded.

Role of funding source

The study was supported in part by the National Cancer Center Research and Development Funds (23-A-16, 23-A-17 and 26-A-4), the Grant-in-Aid for Clinical Cancer Research (17S-1, 17S-5, 18-6, 20S-1, and 20S-6) from the Ministry of Health, Labor and Welfare of Japan.

Conflict of interest statement

Koji Matsumoto participates in the investigation trials and receives clinical investigation expense from Astra Zeneca, Japan Boehringer Ingelheim, Pfizer, and Sanofi. Noriyuki Katsumata receives honorarium from Chugai Pharmaceutical Co. Ltd. and Ono Pharmaceutical Co Ltd. Mayu Yunokawa receives clinical investigation expense from Yakult Honsha Co. Ltd. and Sawai Pharmaceutical Co. Ltd. Taro Shibata, Toyomi Satoh, Motoaki Saitou, Tadao Takano Kenichi Nakamura Toshiharu Kamura and Ikuo Konishi have no relevant financial relationships to disclose.

Participating Hospitals

Iwate Medical University, Tohoku University, Tsukuba University, Jikei Kashiwa Hospital, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital, Jikei University Hospital, Cancer Institute Hospital of Japanese Foundation for Cancer Research, The University of Tokyo Hospital, Kitasato Univerisity School of Medicine, Niigata Cancer Center Hospital, Aichi Cancer Center Hospital, Kyoto University Hospital, Osakacity University Hospital, Osaka Prefectural Hospita Organization Osaka Center for Cancer and Cardiovascular Disease, Osaka City General Hospital, Hyogo Cancer Center, National Hospital Organization Kure Medical Center Chugoku Cancer Center, National Hospital Organization Shikoku Cancer Center, National Kyushu Cancer Center, Kurume University School of Medicine, Kyushu University Hospital, Faculty of Medicine, Saga University, Kagoshima City Hospital, Faculty of Medicine, University of the Ryukyus.

Acknowledgements

We sincerely appreciate the participation of the patients and their families. The authors are also grateful to Dr. Haruhiko Fukuda for his assistance with conducting the trial as well as Ms. Kazumi Kubota and Ms. Harumi Kaba for data management.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2014.10.026.

References

[1] Bookman MA, Brady MF, McGuire WP, Harper PG, Alberts DS, Friedlander M, et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a phase III trial of the Gynecologic Cancer Intergroup. J Clin Oncol 2009; 27(9):1419–25.
[2] Katsumata N, Yasuda M, Takahashi F, Isonishi S, Jobo T, Aoki D, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet 2009; 374(9698):1331–8 [Epub 2009/09/22].
[3] Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol 2001;19(14):3312–22.
[4] Mutch DG, Orlando M, Goss T, Teneriello MG, Gordon AN, McMeekin SD, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. J Clin Oncol 2007; 25(19):2811–8 [Epub 2007/07/03].
[5] Vasey PA, Kaye SB. Combined inhibition of topoisomerases I and II—is this a worthwhile/feasible strategy? Br J Cancer 1997;76(11):1395–7.
[6] Bodurka DC, Levenback C, Wolf JK, Gano J, Wharton JT, Kavanagh JJ, et al. Phase II trial of irinotecan in patients with metastatic epithelial ovarian cancer or peritoneal cancer. J Clin Oncol 2003;21(2):291–7.
[7] Matsumoto K, Katsumata N, Yamanaka Y, Yonemori K, Kohno T, Shimizu C, et al. The safety and efficacy of the weekly dosing of irinotecan for platinum- and taxanes-resistant epithelial ovarian cancer. Gynecol Oncol 2006;100(2):412–6 [Epub 2005/11/22].
[8] Takeuchi S, Dobashi K, Fujimoto S, Tanaka K, Suzuki M, Terashima Y, et al. A late phase II study of CPT-11 on uterine cervical cancer and ovarian cancer. Research groups of CPT-11 in gynecologic cancers. Gan To Kagaku Ryoho 1991;18(10): 1681–9.
[9] Hainsworth JD, Greco FA. Etoposide: twenty years later. Ann Oncol 1995;6(4): 325–41.
[10] Maskens AP, Armand JP, Lacave AJ, De Jager RL, Hansen HH, Wolff JP. Phase II clinical trial of VP-16-213 in ovarian cancer. Cancer Treat Rep 1981;65(3–4):329–30.
[11] Eckhardt S, Hernadi Z, Thurzo L, Telekes A, Sopkova B, Mechl Z, et al. Phase II clinical evaluation of etoposide (VP-16-213, Vepesid) as a second-line treatment in ovarian cancer. Results of the South-East European Oncology Group (SEEOG) study. Oncology 1990;47(4):289–95.
[12] Rose PG, Blessing JA, Mayer AR, Homesley HD. Prolonged oral etoposide as second-line therapy for platinum-resistant and platinum-sensitive ovarian carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 1998;16(2):405–10.

Please cite this article as: Matsumoto K, et al, Phase II trial of oral etoposide plus intravenous irinotecan in patients with platinum-resistant and taxane-pretreated ovarian can..., Gynecol Oncol (2014), http://dx.doi.org/10.1016/j.ygyno.2014.10.026

[13] Kim R, Hirabayashi N, Nishiyama M, Jinushi K, Toge T, Okada K. Experimental studies on biochemical modulation targeting topoisomerase I and II in human tumor xenografts in nude mice. Int J Cancer 1992;50(5):760–6.
[14] Masumoto N, Nakano S, Esaki T, Tatsumoto T, Fujishima H, Baba E, et al. Sequence-dependent modulation of anticancer drug activities by 7-ethyl-10-hydroxycamptothecin in an HST-1 human squamous carcinoma cell line. Anticancer Res 1995;15(2):405–9.
[15] Eder JP, Chan V, Wong J, Wong YW, Ara G, Northey D, et al. Sequence effect of irinotecan (CPT-11) and topoisomerase II inhibitors in vivo. Cancer Chemother Pharmacol 1998;42(4):327–35.
[16] Gronlund B, Engelholm SA, Horvath G, Maenpaa J, Ridderheim M. Sequential topotecan and oral etoposide in recurrent ovarian carcinoma pretreated with platinum-taxane. Results from a multicenter phase I/II study. Cancer 2005;103(7):1388–96.
[17] Yamanaka Y, Katsumata N, Watanabe T, Andoh M, Mukai H, Kitagawa R, Kasamatsu T, et al. A dose finding study of irinotecan in combination with oral etoposide in patients with platinum treated advanced epithelial ovarian cancer. Proc Am Soc Clin Oncol 2002;21(abstr 2521).
[18] Nishio S, Sugiyama T, Shouji T, Yoshizaki A, Kitagawa R, Ushijima K, et al. Pilot study evaluating the efficacy and toxicity of irinotecan plus oral etoposide for platinum- and taxane-resistant epithelial ovarian cancer. Gynecol Oncol 2007;106(2):342–7.
[19] Rustin GJ, Quinn M, Thigpen T, du Bois A, Pujade-Lauraine E, Jakobsen A, et al. Re: new guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). J Natl Cancer Inst 2004;96(6):487–8.
[20] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92(3):205–16.
[21] Green SJ, Dahlberg S. Planned versus attained design in phase II clinical trials. Stat Med 1992;11(7):853–62.
[22] Fotopoulou C, Vergote I, Mainwaring P, Bidzinski M, Vermorken JB, Ghamande SA, et al. Weekly AUC2 carboplatin in acquired platinum-resistant ovarian cancer with or without oral phenoxodiol, a sensitizer of platinum cytotoxicity: the phase III OVATURE multicenter randomized study. Ann Oncol 2014;25(1):160–5 [Epub 2013/12/10].
[23] Monk BJ, Herzog TJ, Kaye SB, Krasner CN, Vermorken JB, Muggia FM, et al. Trabectedin plus pegylated liposomal doxorubicin in recurrent ovarian cancer. J Clin Oncol 2010;28(19):3107–14.
[24] Vergote I, Finkler NJ, Hall JB, Melnyk O, Edwards RP, Jones M, et al. Randomized phase III study of canfosfamide in combination with pegylated liposomal doxorubicin comparedwith pegylated liposomal doxorubicin alone in platinum-resistant ovarian cancer. Int J Gynecol Cancer 2010;20(5):772–80.
[25] Lortholary A, Largillier R, Weber B, Gladieff L, Alexandre J, Durando X, et al. Weekly paclitaxel as a single agent or in combination with carboplatin or weekly topotecan in patients with resistant ovarian cancer: the CARTAXHY randomized phase II trial from Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO). Ann Oncol 2012;23(2):346–52.
[26] Buda A, Floriani I, Rossi R, Colombo N, Torri V, Conte PF, et al. Randomised controlled trial comparing single agent paclitaxel vs epidoxorubicin plus paclitaxel in patients with advanced ovarian cancer in early progression after platinum-based chemotherapy: an Italian collaborative study from the Mario Negri Institute, Milan, G.O.N.O. (Gruppo Oncologico Nord Ovest) group and I.O.R. (Istituto Oncologico Romagnolo) group. Br J Cancer 2004;90(11):2112–7 [Epub 2004/05/20].
[27] Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol 2014;32(13):1302–8 [Epub 2014/03/19].
[28] Monk BJ, Poveda A, Vergote I, Raspagliesi F, Fujiwara K, Bae DS, et al. Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 2014;15(8):799–808 [Epub 2014/06/22].
[29] Poveda A, Vergote I, Tjulandin S, Kong B, Roy M, Chan S, et al. Trabectedin plus pegylated liposomal doxorubicin in relapsed ovarian cancer: outcomes in the partially platinum-sensitive (platinum-free interval 6–12 months) subpopulation of OVA-301 phase III randomized trial. Ann Oncol 2011;22(1):39–48.
[30] Hoskins JM, Goldberg RM, Qu P, Ibrahim JG, McLeod HL. UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters. J Natl Cancer Inst 2007;99(17):1290–5.

Please cite this article as: Matsumoto K, et al, Phase II trial of oral etoposide plus intravenous irinotecan in patients with platinum-resistant and taxane-pretreated ovarian can..., Gynecol Oncol (2014), http://dx.doi.org/10.1016/j.ygyno.2014.10.026

Redistribution of resistance and sensitivity to platinum during the observation period following treatment of epithelial ovarian cancer

YOSHIHITO YOKOYAMA[1], MASAYUKI FUTAGAMI[1], JUN WATANABE[2], NAOKI SATO[3], YUKIHIRO TERADA[3], FUMIHARU MIURA[4], TORU SUGIYAMA[4], TADAO TAKANO[5], NOBUO YAEGASHI[5], TAKANOBU KOJIMAHARA[6], HIROHISA KURACHI[6], HIROSHI NISHIYAMA[7], KEIYA FUJIMORI[7], TORU TASE[8] and HIDEKI MIZUNUMA[1]

[1]Department of Obstetrics and Gynecology, Hirosaki University Graduate School of Medicine, Hirosaki, Aomori 0368562;
[2]Department of Pathologic Analysis, Hirosaki University Graduate School of Health Sciences, Hirosaki, Aomori 0368564;
[3]Department of Obstetrics and Gynecology, Akita University School of Medicine, Akita, Akita 0108543;
[4]Department of Obstetrics and Gynecology, Iwate Medical University School of Medicine, Morioka, Iwate 0208505;
[5]Department of Obstetrics and Gynecology, Tohoku University School of Medicine, Sendai, Miyagi 9808574;
[6]Department of Obstetrics and Gynecology, Yamagata University School of Medicine, Yamagata, Yamagata 9909585;
[7]Department of Obstetrics and Gynecology, Fukushima Medical University, Fukushima, Fukushima 9601295;
[8]Department of Gynecology, Miyagi Cancer Center, Natori, Miyagi 9811293, Japan

Received August 10, 2013; Accepted December 2, 2013

DOI: 10.3892/mco.2013.223

Abstract. The standard postoperative chemotherapy for epithelial ovarian cancer is a combination therapy including platinum and taxanes. The aim this study was to investigate the degree of platinum sensitivity in patients with relapsed epithelial ovarian cancer according to the treatment-free interval (TFI) and the histological tumor type. The medical records of 405 patients diagnosed with stage III/IV ovarian cancer, including 107 patients who relapsed after attaining a clinical complete response with first-line treatment, were retrospectively reviewed. The degree of platinum sensitivity was assessed by comparing the progression-free survival (PFS) following the second-line treatment. In patients with serous/endometrioid adenocarcinoma who were treated with platinum following relapse, there were significant differences in the PFS between the following groups of patients: those who relapsed within 6 months and those who relapsed between 6 and 12 months; those who relapsed between 6 and 12 months and those who relapsed between 12 and 18 months; and those who relapsed between 12 and 18 months and those who relapsed after 18 months. By contrast, in patients with clear cell/mucinous adenocarcinoma who were treated with platinum following a relapse, there were no significant differences in the PFS between patients who relapsed within 6 months and those who relapsed between 6 and 12 months, while there were significant differences in the PFS between those who relapsed between 6 and 12 months and those who relapsed after 12 months. With regard to the patients who relapsed after 12 months, the PFS of those with clear cell/mucinous adenocarcinoma was significantly shorter compared with the PFS of those with serous/endometrioid adenocarcinoma. Therefore, we considered it justified to classify patients with clear cell/mucinous adenocarcinoma who relapsed within 12 months as platinum-resistant and those who relapsed after 12 months as platinum-sensitive.

Correspondence to: Dr Yoshihito Yokoyama, Department of Obstetrics and Gynecology, Hirosaki University Graduate School of Medicine, 5 Zaifu-cho, Hirosaki, Aomori 0368562, Japan
E-mail: yokoyama@cc.hirosaki-u.ac.jp

Key words: relapsed epithelial ovarian cancer, platinum sensitivity, treatment-free interval, progression-free interval, histological type

Introduction

The standard postoperative chemotherapy for epithelial ovarian cancer is currently a combination therapy including platinum and taxanes (1). Although the treatment outcome of epithelial ovarian cancer has improved, it remains unsatisfactory in terms of long-term survival. A recent study demonstrated that bevacizumab administered in combination with paclitaxel/carboplatin (TC) prolongs survival and may be used as maintenance chemotherapy (2). Furthermore, dose-dense weekly TC was reported to be significantly superior to TC therapy regarding progression-free survival (PFS) and overall survival (3). The therapeutic efficacy of intraperitoneal chemotherapy was also verified in a randomized controlled study (4). A combination of molecular-targeted agents or refined regimens has improved the outcome of first-line treatment for epithelial ovarian cancer.

Epithelial ovarian cancer is highly sensitive to chemotherapy and ~75% of patients achieve a clinical complete response (CCR) with first-line treatment. However, several patients relapse, develop chronic disease and ultimately succumb to ovarian

cancer. The disease-free survival of optimal disease (advanced cancer) was reported to be 18-24 months and that of suboptimal disease 18 months (5). Furthermore, a previous study assessing optimal and suboptimal disease reported a disease-free survival of 16-17 months (5). The approximate prevalence of relapse was 10% in low-risk groups, 20% in high-risk groups for early cancer, 60-70% in optimal surgery groups and 80-85% in suboptimal surgery groups for advanced cancer. Thus, ≥60% of patients with ovarian cancer are candidates for second-line treatment (5) and determining the second-line therapeutic options is vital for improving the outcome.

The treatment-free interval (TFI) following the first-line treatment is currently recognized as the most significant parameter for determining the optimal regimen for the treatment of relapsed cancer. Increasing the TFI results in an improved response to platinum (6). Commonly, the treatment regimen is selected for platinum-sensitive tumors with a TFI of ≥6 months and for platinum-resistant tumors with a TFI of <6 months.

However, whether relapsed ovarian cancer with a TFI of 6-12 months may be treated as platinum-sensitive has not been determined. Furthermore, it has not been established whether tumors may be considered drug-sensitive or -resistant according to TFI, regardless of the differences in drug sensitivity according to histological type. In the present study, the medical records of a relatively large number of patients with relapsed stage III/IV epithelial ovarian cancer were reviewed, the PFS was calculated according to the TFI and the degree of platinum sensitivity was retrospectively verified with the TFI. Furthermore, we investigated the degree of platinum sensitivity with TFI according to histological type.

Materials and methods

Study population and inclusion criteria. The study population comprised 747 patients with epithelial ovarian cancer who underwent treatment at seven institutions participating in the Tohoku Gynecologic Cancer Unit between January, 2003 and December, 2007; these were: Hirosaki University Graduate School of Medicine (Hirosaki, Japan), Akita University School of Medicine (Akita, Japan), Iwate Medical University School of Medicine (Morioka, Japan), Tohoku University School of Medicine (Sendai, Japan), Yamagata University School of Medicine (Yamagata, Japan), Fukushima Medical University (Fukushima, Japan) and the Miyagi Cancer Center (Natori, Japan). Of the 747 patients, 405 were diagnosed with stage III/IV epithelial ovarian cancer, including 156 patients with relapsed or recurrent disease. Patients in whom a complete response (CR) was maintained, those who had received neoadjuvant chemotherapy, incomplete first-line chemotherapy or radiotherapy and those with an unknown prognosis were excluded; finally, a total of 107 patients with relapsed epithelial ovarian cancer after attaining a CCR with first-line treatment were assessed. CCR was defined as the cases which became negative for the tumor marker CA125 at the end of first-line treatment, with no lesions detected on computed tomography (CT) and positron emission tomography-CT. Informed consent was obtained from the patients or their family members to collect data, following approval by the Institutional Review Boards of the involved institutions.

Table I. Patient characteristics.

Variables	No. of patients
Age, years [median (range)]	56 (26-78)
Histological type	
Serous	101
Endometrioid	18
Clear cell	26
Mucinous	11
First-line regimen	
TC	135
DC	10
CPT-P	6
CAP	5
No. of first-line chemotherapy cycles [median (range)]	6 (1-13)
Debulking surgery	
Complete	31
Optimal	39
Suboptimal	86
Response to first-line chemotherapy	
Complete response	107
Partial response	26
Stable disease	4
Progressive disease	19
CR according to histological type [CR/non-CR (%)]	
Serous	73/101 (72.3)
Endometrioid	12/18 (66.7)
Clear cell	16/26 (61.5)
Mucinous	6/11 (54.5)
Recurrence sites after CR	
Intraabdominal	45
Intrapelvic	44
Distant	18
Second-line regimen	
Platinum-based	70
Non-platinum-based	37

TC, paclitaxel/carboplatin; DC, docetaxel/carboplatin; CPT-P, irinotecan (CPT-11)/cisplatin; CAP, cyclophosphamide/adriamycin/cisplatin; CR, complete response.

Patient characteristics. The recorded patient characteristics and variables included age, histological type of ovarian cancer, debulking surgery, first-line treatment, response to first-line treatment, time to relapse, site of relapse and second-line treatment (Table I). With regard to debulking surgery, the size of the residual tumor was graded as 0, <1 and ≥1 cm for complete, optimal and suboptimal debulking, respectively. A central pathological review was conducted to assess the histological type.

The TFI was defined as the period from the completion of the first-line treatment to the initiation of second-line treatment after confirming disease relapse on imaging. Increased CA125

Table II. Treatment-free interval (TFI) of patients who relapsed after achieving a complete response.

Histological type	No. of patients	Median TFI[a]
All types	107	11.5
Serous	73	11.5
Endometrioid	12	16.0
Clear cell	16	8.0[b]
Mucinous	6	11.0

[a]In months. [b]Serous vs. clear cell, P<0.02.

Table III. Progression-free survival (PFS) according to the interval from the end of first-line treatment to relapse.

	Interval from the end of first-line treatment to relapse (months)		
Variables	<6	6-12	>12
No. of patients	20	37	50
Median PFS (months)	3.0	5.5	13.0
Second-line treatment			
Platinum-based	6	23	41
Non-platinum-based	14	14	9

Table IV. Interval from the end of first-line treatment to relapse according to histological type.

Histology	No. of patients	Interval from the end of first-line treatment to relapse (months) <6	6-12	>12
Serous	73	10 (14%)	27 (37%)	36 (49%)
Endometrioid	12	3 (25%)	3 (25%)	6 (50%)
Clear cell	16	5 (31%)	6 (38%)	5 (31%)
Mucinous	6	2 (33%)	1 (17%)	3 (50%)

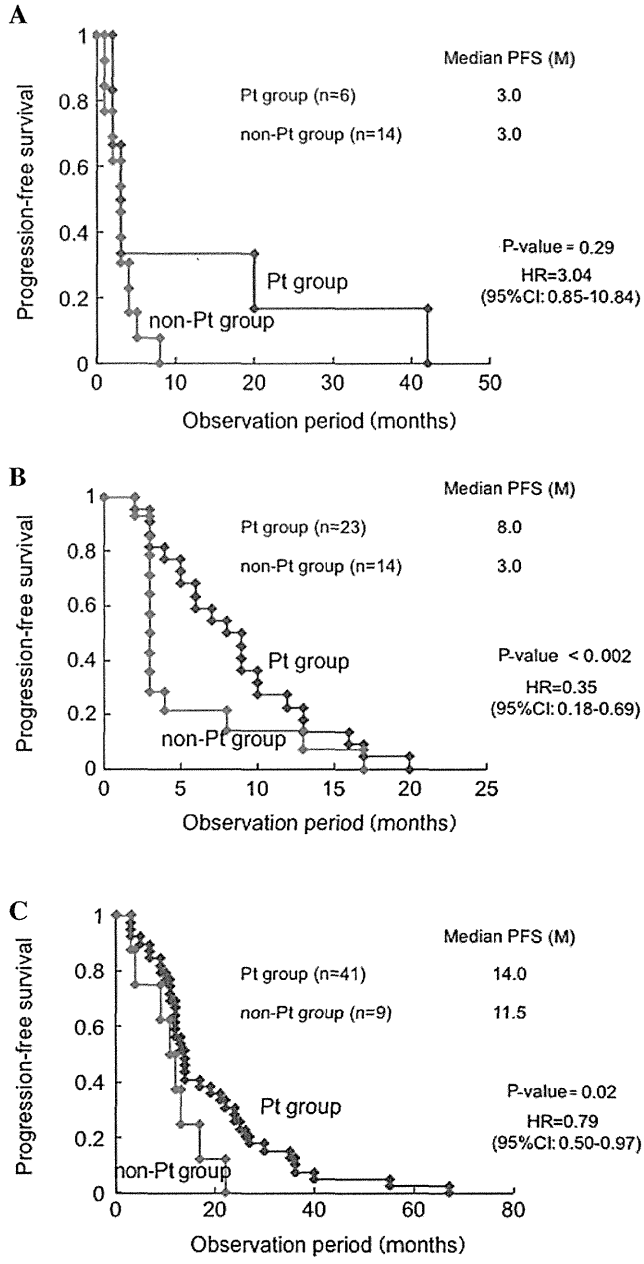

Figure 1. Comparison of progression-free survival (PFS) between the platinum (Pt) and non-Pt groups during the observation period of all histological types. Patients who relapsed (A) <6 months, (B) 6-12 months and (C) ≥12 months after the first-line treatment.

levels alone were not considered to reflect relapse. PFS was defined as the interval from the initiation of second-line treatment for relapsed lesions to confirmed disease progression.

Statistical analysis. The degree of platinum sensitivity was calculated by comparing the PFS values. PFS was estimated using the Kaplan-Meier method and compared using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated with the Cox proportional hazards regression model. P≤0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. The patient characteristics are summarized in Table I. The median age of the patients was 56 years. With regard to histological type, serous adenocarcinoma was diagnosed in 101 patients (65%) and clear cell adenocarcinoma, which was reported to have a measurable incidence in the USA and Europe (7), was identified in 26 patients (17%). The median number of first-line treatment cycles was 6 and the TC regimen was administered to 135 patients (87%), whereas docetaxel/carboplatin was selected for patients with paclitaxel hypersensitivity or peripheral neurotoxicity. As regards debulking surgery, complete or optimal outcomes were achieved in 70 patients (45%). A CR following administration of the first-line treatment was observed in 107 patients (69%). Although the prevalence of CR following administration of the first-line regimen varied by histological type from 72.3% in serous adenocarcinoma to 54.5% in mucinous

Table V. Progression-free survival (PFS) in patients with serous or endometrioid carcinoma and in those with clear cell or mucinous carcinoma treated with a platinum (Pt)-based regimen according to interval from the end of first-line treatment to relapse.

A, Serous/endometrioid group

Interval to relapse after CCR (months)	No. of patients (n=55) with Pt-based regimen	PFS (months)	
<6	4	4.5	
6-12	17	9.0	P=0.01; HR=0.14; 95% CI: 0.03-0.63
12-18	9	12.5	P<0.05; HR=0.56; 95% CI: 0.25-0.93
		P<0.05; HR=0.49; 95% CI: 0.22-0.96	
18-24	9	17.0	P=0.49; HR=1.43; 95% CI: 0.51-4.08
>24	16	19.0	P=0.51; HR=0.35; 95% CI: 0.54-3.34

B, Clear cell/mucinous group

Interval to relapse after CCR (months)	No. of patients (n=55) with Pt-based regimen	PFS (months)	
<6	2	2.5	
6-12	6	5.5	P=0.26; HR, 3.67; 95% CI: 0.38-9.34
>12	7	11.0	P<0.05; HR, 0.33; 95% CI: 0.10-0.97

CCR, clinical complete response; HR, hazard ratio; CI, confidence interval.

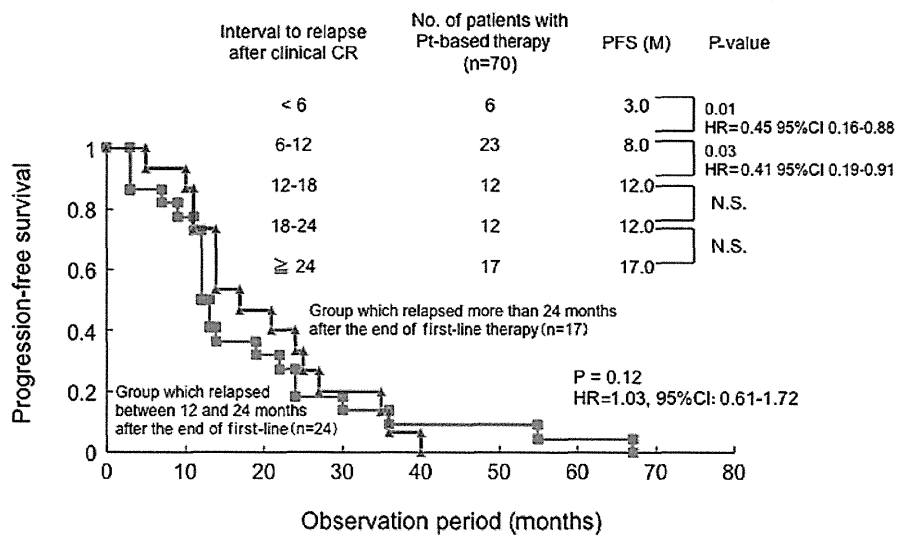

Figure 2. Comparison of the progression-free survival (PFS) by observation period in the platinum (Pt) group alone in all histological types. Patients who relapsed after 12 months were further classified every 6 months. There were no significant differences in the PFS between patients who relapsed between 12 and 24 months and those who relapsed after 24 months. N.S., not significant.

adenocarcinoma, there were no statistically significant differences in the prevalence of CR among the four histological types. The number of relapse sites was similar for abdominal and pelvic cavities. The majority of distant metastases were located in the lungs and in the mediastinal, supraclavicular or inguinal lymph nodes. In patients with a relapse following a CR (70 patients in the platinum and 37 in the non-platinum group), a second-line regimen was initiated.

TFI in relapsed patients following CR. The median TFI in relapsed patients was 11.5 months (Table II). Significant differences in the TFI by histological type were observed between cases with serous adenocarcinoma and those with clear cell adenocarcinoma (HR=0.53; 95% CI: 0.30-0.95; P<0.02) (Table II).

PFS following second-line treatment. A total of 20, 37 and 50 patients relapsed after a CR at <6, 6-12 and ≥12 months, respectively, and the median PFS following administration of a second-line regimen was 3.0, 5.5 and 13.0 months, respectively (Table III). There were no statistically significant differences in the distribution of the interval from the end of first-line treatment to relapse according to the histological type (Table IV). There were no significant differences in the median PFS (3.0 months) between the platinum- and non-platinum-based treatment groups who relapsed within 6 months after CR, when the PFS was compared based on the observation period for all histological types (Fig. 1A). In patients who relapsed between 6 and 12 months, the median PFS was 8.0 and 3.0 months in the platinum- and non-platinum based groups, respectively, with PFS being significantly longer in the platinum group (HR=0.35; 95% CI: 0.18-0.69; P<0.002) (Fig. 1B). In patients who relapsed after 12 months, the median PFS was 14.0 and 11.5 months in the platinum- and non-platinum-based groups, respectively, with the PFS being significantly longer in the platinum group (HR=0.79; 95% CI: 0.50-0.97; P=0.02) (Fig. 1C). Therefore, the platinum group alone was further investigated. Patients who relapsed after 12 months were further classified every 6 months (Fig. 2). There were significant differences in PFS between patients who relapsed within 6 months and those who relapsed between 6 and 12 months (HR=0.45; 95% CI: 0.16-0.88; P=0.01), as well as between those who relapsed between 6 and 12 months and those who relapsed between 12 and 18 months (HR=0.41; 95% CI: 0.19-0.91; P=0.03; Fig. 2). However, there were no significant differences in the PFS between patients who relapsed between 12 and 18 months and those who relapsed between 18 and 24 months, or between those who relapsed between 18 and 24 months and those who relapsed after 24 months (Fig. 2). The patients who relapsed were divided into those who relapsed between 12 and 24 months and those who relapsed after 24 months and the PFS was compared between the groups: no significant differences in PFS were observed between the two groups (HR=1.03; 95% CI: 0.61-1.72; P=0.12).

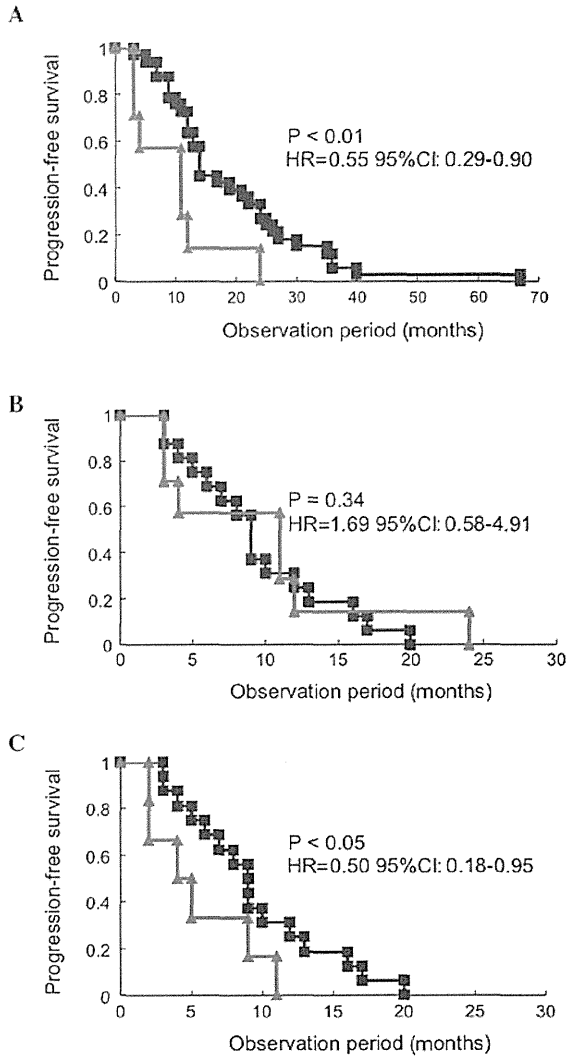

Figure 3. Evaluation of progression-free survival (PFS) of patients and redistribution of sensitivity to platinum according to the histological type. (A) Evaluation of PFS of patients with clear cell/mucinous adenocarcinoma who relapsed after 12 months (n=7, red line). The PFS was significantly shorter compared to that of patients with serous/endometrioid adenocarcinoma who relapsed after 12 months (n=34, blue line). (B) The PFS of patients with clear cell/mucinous adenocarcinoma who relapsed after 12 months (n=7, red line) was similar to that of patients with serous/endometrioid adenocarcinoma who relapsed between 6 and 12 months (n=17, blue line). (C) Comparison of PFS between patients with clear cell/mucinous adenocarcinoma (n=6, red line) and those with serous/endometrioid adenocarcinoma (n=17, blue line) who relapsed between 6 and 12 months.

PFS by histological type following second-line treatment. The differences in PFS by histological type were investigated. The PFS in the serous/endometrioid group treated with platinum after relapse was 4.5, 9.0, 12.5, 17.0 and 19.0 months in patients who relapsed at <6, 6-12, 12-18, 18-24 and ≥24 months, respectively (Table V). There were significant differences in the PFS between patients who relapsed within 6 months and those who relapsed between 6 and 12 months (HR=0.14; 95% CI: 0.03-0.63; P=0.01), as well as between those who relapsed between 6 and 12 months and those who relapsed between 12 and 18 months (HR=0.56; 95% CI: 0.25-0.93; P<0.05) (Table V). Although there were no significant differences in the PFS between those who relapsed between 12 and 18 and those who relapsed between 18 and 24 months, or between those who relapsed between 18 and 24 and those who relapsed after 24 months, there were significant differences in the PFS between patients who relapsed between 12 and 18 and those who relapsed after 18 months (HR=0.49; 95% CI: 0.22-0.96; P<0.05) (Table V). Furthermore, in the clear cell/mucinous adenocarcinoma group treated with platinum as a second-line regimen, there were no significant differences in the PFS between patients who relapsed within 6 months and those who relapsed between 6 and 12 months, while there were significant differences in the PFS between patients who relapsed between 6 and 12 months and those who relapsed after 12 months (HR=0.33; 95% CI: 0.10-0.97; P<0.05) (Table V). In patients who relapsed after 12 months, the PFS in the clear cell/mucinous adenocarcinoma group was significantly shorter compared to that in the serous/endometrioid

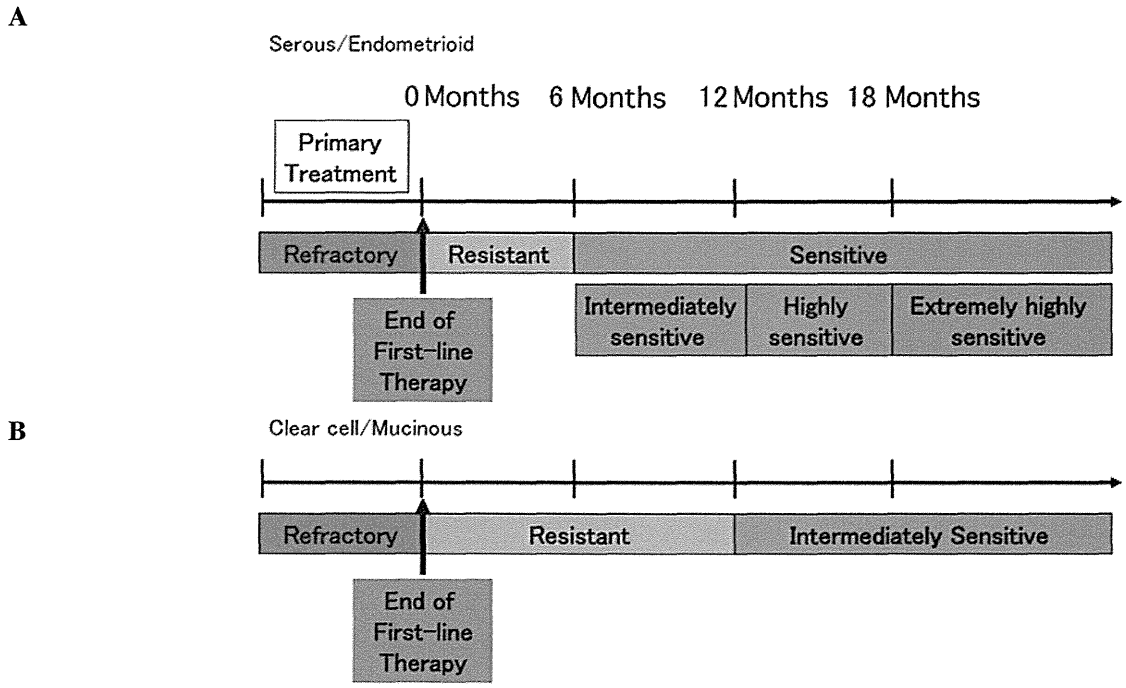

Figure 4. Redistribution of sensitivity to platinum according to the histological type. (A) Serous/endometrioid adenocarcinomas: Patients who relapsed within 6 months were considered to be 'platinum-resistant', those who relapsed between 6 and 12 months were 'intermediately sensitive', those who relapsed between 12 and 18 months were 'highly sensitive' and those who relapsed after 18 months were 'extremely highly sensitive'. (B) Clear cell/mucinous adenocarcinomas: Patients who relapsed within 12 months were considered to be 'platinum-resistant' and those who relapsed after 12 months were 'intermediately sensitive'.

adenocarcinoma group (HR=0.55; 95% CI: 0.29-0.90; P<0.01; Fig. 3A), but similar to that of patients who relapsed between 6 and 12 months in the serous/endometrioid adenocarcinoma group (HR=1.69; 95% CI: 0.58-4.91; P=0.34; Fig. 3B). Furthermore, in patients who relapsed between 6 and 12 months, the PFS of the clear cell/mucinous adenocarcinoma group was significantly shorter compared to that in the serous/endometrioid adenocarcinoma group (HR=0.50; 95% CI: 0.18-0.95; P<0.05; Fig. 3C).

Discussion

The aim of first-line treatment is to cure, whereas the primary goal of second-line treatment is palliation. Accordingly, less toxic and more convenient regimens should be selected, focusing on the balance between toxicity and effectiveness. Quality of life, including improving symptoms and preventing the onset of new symptoms is also preferentially maintained. Therefore, it is crucial to appropriately determine how the sensitivity or resistance to platinum is defined by TFI when selecting a regimen and TFI should also be individualized according to histological type.

Although the TFI of patients who relapsed within 6 months was suggested to indicate platinum sensitivity in this study, the sensitivity to platinum was similar between patients who relapsed between 12 and 24 months and those who relapsed after 24 months for all histological types. However, these results were inconsistent with previous findings reporting a significantly higher response rate in patients with a TFI of ≥24 months (6,8). In this study, the overall proportion of clear cell and mucinous adenocarcinomas, which are relatively refractory to treatment, accounted for ~20% of the cases of ovarian cancer and platinum sensitivity was evaluated according to histological type. In patients with serous/endometrioid adenocarcinoma, the PFS following platinum administration exhibited a significant increase in a stepwise manner depending on the TFI (Table V). These findings suggested a novel distribution of platinum sensitivity classification. The patients who relapsed between 6 and 12 months following the completion of first-line treatment (TFI of 6-12 months) may be classified as 'intermediately sensitive', those with a TFI of 12-18 months as 'highly sensitive' and those with a TFI of ≥18 months as 'extremely highly sensitive', whereas the patients with a TFI of <6 months were considered as platinum-resistant (Fig. 4A).

A significant difference in the PFS was only detected between patients with a TFI of 6-12 and those with a TFI of ≥12 months in the clear cell/mucinous adenocarcinoma group. There were no significant differences in the PFS between patients with a TFI of <6 months and those with a TFI of 6-12 months. However, the PFS of patients who relapsed after 12 months was significantly shorter in the clear cell/mucinous adenocarcinoma group compared to that in the serous/endometrioid adenocarcinoma group and was similar to the PFS of patients who relapsed between 6 and 12 months in the serous/endometrioid adenocarcinoma group. Furthermore, the PFS of patients who relapsed between 6 and 12 months was significantly shorter in the clear cell/mucinous adenocarcinoma group compared to that in the serous/endometrioid adenocarcinoma group. Therefore, it may be rational to classify patients with clear cell/mucinous adenocarcinoma who relapsed within12 months as 'platinum-resistant' and those who relapsed after 12 months as 'intermediately sensitive' (Fig. 4B).

In the 1990s, several studies focused on the identification and differentiation of platinum-sensitive from platinum-resistant relapse (6,8,9). Harries and Gore (10) suggested that

sensitivity and resistance to platinum were separated by a PFS of 6 months. Furthermore, previous studies defined sensitivity and resistance to platinum according to the clinical response, such as the frequency of CR for agents administered to relapsed patients (6,8,9). However, in the present study, drug sensitivity was evaluated by the interval to disease progression (observation period), as well as the PFS of relapsed patients under platinum- and non-platinum-based treatment. It is widely accepted that the patients with a longer time interval between the completion of first-line treatment and the initiation of second-line treatment exhibit a higher response rate to the second-line regimen. In order to avoid ineffective treatment with resistant regimens, the length of the observation period should be considered on an individual basis. The results of the present study suggested that a TFI of <6 and ≥6 months after the completion of first-line treatment may be appropriate for patients with serous/endometrioid adenocarcinoma to determine sensitivity or resistance to platinum as second-line treatment, whereas a TFI of 6 months is too short to apply to patients with clear cell/mucinous adenocarcinoma.

Thus far, an observation period of ≥6 months following the end of first-line treatment has been defined as platinum-sensitive and phase III studies for patients with platinum-sensitive recurrent ovarian cancer have been designed. Although the incidence of relapsed patients with a TFI of ≥12 months was reported to be 60-70% in several randomized controlled studies (11-14), the proportion of patients who relapsed between 6 and 12 months was 30-40%, including those with platinum-resistant clear cell/mucinous adenocarcinoma. Furthermore, in the present study, although the TFI was ≥12 months in the serous/endometrioid adenocarcinoma group, there were significant differences in platinum sensitivity between patients who relapsed between 12 and 18 months and those who relapsed after 18 months. Thus, future clinical studies on the selection of chemotherapy for recurrent ovarian cancer must consider the histological type and platinum sensitivity with TFI.

With regard to taxane sensitivity in recurrent ovarian cancer, it was demonstrated that the number of intervention therapies following relapse, rather than the taxane-free interval, is associated with taxane sensitivity (15). Although there were no differences in the effects of taxanes on recurrent ovarian cancer, regardless of whether the interval between the first and subsequent use of taxanes was ≤12 or ≥24 months, additional intervention therapies resulted in a decreased response to taxanes (15). Similarly, it was previously reported that the taxane-free interval does not affect sensitivity to taxanes (16). Therefore, drug sensitivity to taxanes and platinum must be considered separately.

Novel biological therapies, including anti-angiogenic agents, signaling inhibitors, anti-CA125 antibody and dendritic cell immunotherapy, have been developed for the treatment of recurrent ovarian cancer. Bevacizumab was reported to prolong survival in subjects with recurrent ovarian cancer (17). Molecular-targeted agents are expected to exert additive effects and platinum sensitivity is considered to play a critical role in improving prognosis. Furthermore, maintenance therapy with biological agents may eventually alter the pattern of recurrence and novel characterizations of platinum sensitivity/resistance may emerge. Although TFI is a continuous variable with a wide boundary, it is crucial to determine a definitive criterion of the sensitivity and resistance to platinum in types of ovarian cancer with a prevalence of relapse of ≥60%, in order to enable the selection of the most efficient second-line regimen and design high-quality clinical studies.

References

1. Ozols RF, Bundy BN, Greer BE, *et al*; Gynecologic Oncology Group: 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.
2. Burger RA, Brady MF, Bookman MA, *et al*: Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 365: 2473-2483, 2011.
3. Katsumata N, Yasuda M, Takahashi F, *et al*: Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet 374: 1331-1338, 2009.
4. Armstrong DK, Bundy B, Wenzel L, *et al*: Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 354: 34-43, 2006.
5. Sugiyama T: Second-line treatment using novel chemotherapeutic and biologic agents. Cancer and Chemotherapy 36: 730-735, 2009 (In Japanese).
6. Markman M, Reichman B, Hakes T, *et al*: Responses to second-line cisplatin-based intraperitoneal therapy in ovarian cancer: influence of a prior response to intravenous cisplatin. J Clin Oncol 9: 1801-1805, 1991.
7. Hoskins PJ, Le N, Gilks B, *et al*: Low-stage ovarian clear cell carcinoma: population-based outcomes in British Columbia, Canada, with evidence for a survival benefit as a result of irradiation. J Clin Oncol 30: 1656-1662, 2012.
8. Gore ME, Fryatt I, Wiltshaw E, *et al*: Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds. Gynecol Oncol 36: 207-211, 1990.
9. Blackledge G, Lawton F, Redman C, *et al*: Response of patients in phase II studies of chemotherapy in ovarian cancer: implications for patient treatment and the design of phase II trials. Br J Cancer 59: 650-653, 1989.
10. Harries M and Gore M: Part II: chemotherapy for epithelial ovarian cancer-treatment of recurrent disease. Lancet Oncol 3: 537-545, 2002.
11. Parmar MK, Ledermann JA, Colombo N, *et al*: Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet 361: 2099-2106, 2003.
12. Pfisterer J, Plante M, Vergote I, *et al*: Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol 24: 4699-4707, 2006.
13. Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, *et al*: Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol 28: 3323-3329, 2010.
14. Aghajanian C, Blank SV, Goff BA, *et al*: OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 30: 2039-2045, 2012.
15. McCourt C, Dessie S, Bradley AM, *et al*: Is there a taxane-free interval that predicts response to taxanes as a later-line treatment of recurrent ovarian or primary peritoneal cancer? Int J Gynecol Cancer 19: 343-347, 2009.
16. Rose PG, Blessing JA, Ball HG, *et al*: A phase II study of docetaxel in paclitaxel-resistant ovarian and peritoneal carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 88: 130-135, 2003.
17. Aghajanian C, Blank SV, Goff BA, *et al*: OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 30: 2039-2045, 2012.

Ann Surg Oncol (2014) 21:4246–4255
DOI 10.1245/s10434-014-3880-6

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GYNECOLOGIC ONCOLOGY

Significance of Adenomyosis on Tumor Progression and Survival Outcome of Endometrial Cancer

Koji Matsuo, MD, PhD[1,4], Sigita S. Cahoon, MD[1], Marc Gualtieri, MD[2], Christopher A. Scannell, PhD[3], Carrie E. Jung, MD[1], Tadao Takano, MD, PhD[5], Richard J. Paulson, MD[2], Laila I. Muderspach, MD[1,4], and Lynda D. Roman, MD[1,4]

[1]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Los Angeles County Medical Center, University of Southern California, Los Angeles, CA; [2]Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Los Angeles County Medical Center, University of Southern California, Los Angeles, CA; [3]Keck School of Medicine, Los Angeles, CA; [4]Norris Comprehensive Cancer Center, Los Angeles, CA; [5]Clinical Research, Innovation, and Education Center, Tohoku University, Miyagi, Japan

ABSTRACT

Background. To examine the effects of adenomyosis on tumor progression and survival outcome of endometrial cancer patients.

Methods. This is a retrospective study examining stage I–IV endometrial cancer patients who underwent hysterectomy-based surgical staging (n = 571), and endometrial hyperplasia patients who underwent hysterectomy (n = 213). Clinical demographics, histopathological factors, and survival outcomes were analyzed based on the presence or absence of adenomyosis.

Results. Among the endometrial cancer cohort, adenomyosis was observed in 47.5 % of cases and was significantly associated with lower grade (grade 1–2 tumors, 81.2 vs. 73.3 %; p = 0.028), earlier stage (stage I disease, 74.8 vs. 64.3 %; p = 0.023), and lower likelihood of deep myometrial invasion (19.2 vs. 28.2 %; p = 0.039) and cervical invasion (13.7 vs. 21.2 %; p = 0.024) than those without adenomyosis. In survival analysis, endometrial cancer coexisting with adenomyosis was associated with a significantly better disease-free survival (5-year rate, 89.2 vs. 78.2 %; $p < 0.001$) and overall survival (91.8 vs. 83.9 %; p = 0.004) after hysterectomy. In multivariate analysis, controlling for other significant variables in univariate analysis, presence of adenomyosis remained an independent prognostic factor associated with decreased risk of disease recurrence after surgery (hazard ratio [HR] 0.53; 95 % confidence interval [CI] 0.30–0.92; p = 0.023). Endometrial hyperplasia had a significantly increased incidence of adenomyosis when compared with type I endometrial cancer (grade 1–2 endometrioid adenocarcinoma, n = 411) on multivariate analysis (62.9 vs. 48.9 %; HR 1.88; 95 % CI 1.32–2.69; $p < 0.001$).

Conclusions. Adenomyosis appears to be associated with less aggressive tumor behavior of endometrial cancer, suggesting that it may have inhibitory effects on the progression of this disease.

Endometrial cancer is the most common gynecological cancer and the fourth most common cancer afflicting women overall in the US. In 2013, an estimated 49,560 women were diagnosed with endometrial cancer and 8,190 died of this disease.[1] A large portion of endometrial cancer patients are diagnosed at an early stage which is curable with surgical treatment alone. Surgical staging is the standard approach to endometrial cancer management unless the patient is not a candidate for surgery.[2] The standard procedure includes hysterectomy and bilateral salpingo-oophorectomy, with possible lymphadenectomy/omentectomy. Surgical specimens are valuable to identify the tumors that carry an increased risk of recurrence, and the necessity for postoperative adjuvant therapy with radiotherapy and/or chemotherapy is based on the histopathologic findings.[2]

Adenomyosis is histologically defined as the presence of endometrial tissue in uterine myometrial layers outside the endometrial lining.[3] Adenomyosis is a benign gynecologic

First Received: 28 April 2014;
Published Online: 8 July 2014

K. Matsuo, MD, PhD
e-mail: koji.matsuo@gmail.com

condition which is commonly seen in women of reproductive age. Typical symptoms of adenomyosis include dysmenorrhea, chronic pelvic pain, and dysfunctional uterine bleeding.[3] Adenomyosis is one of the common histopathologic findings in surgical specimens in endometrial cancer patients.[4] In a review of the literature, there seems to be controversy as to whether or not adenomyosis is positively correlated to tumor progression of endometrial cancer. While there are multiple studies presenting endometrial cancer arising from adenomyosis or a positive correlation between adenomyosis and deep myometrial invasion,[5–28] other studies observed no relationship between adenomyosis and endometrial cancer occurrence [29] or concluded that the presence of adenomyosis in endometrial cancer is associated with a decreased risk of nodal metastasis, suggesting better prognosis (protective effect).[30–35] However, the majority of the previous literature was based on level III evidence with case reports, and the sample sizes of cohort studies were relatively small and limited to stage I disease, which made the conclusions of the studies difficult to adapt. The aim of this study was to evaluate the significance of the presence of adenomyosis on tumor progression and survival of endometrial cancer patients in a large-scale comprehensive analysis.

STUDY DESIGN

Eligibility

After Institutional Review Board approval was obtained at the University of Southern California, an institutional database for gynecologic malignancy was utilized to identify the cases. Inclusion criteria included endometrial cancer patients who underwent hysterectomy-based surgical staging at LAC + USC Medical Center between January 2000 and December 2012. Metastatic cancer to the endometrium from another organ site, uterine sarcoma (including carcinosarcoma), and synchronous double primary cancers were excluded from the study. In a separate cohort, consecutive patients of endometrial hyperplasia who underwent surgical treatment with hysterectomy between January 2003 and December 2013 were also collected.

Clinical Information

Among patients eligible for statistical analysis, medical records were further examined to abstract the following variables of interest: (i) patient demographics; (ii) histopathologic findings; (iii) treatment patterns; and (iv) survival outcomes. For patient demographics, variables were obtained from preoperative workup at the time of cancer diagnosis: patient age, ethnicity, parity, body mass index, and past medicosurgical history. For histopathology findings, information obtained from the pathology report included histologic subtype, tumor grade, uterine size, depth of invasion, presence of lymphovascular space invasion, cervical invasion, status of peritoneal washings, nodal metastasis, distant metastasis, presence of adenomyosis and uterine myoma in the myometrial layer, and presence of endometriosis. In our institution, evaluation of the myometrium is routinely performed in a synoptic report. Among tested cases, the results of estrogen and progesterone receptors were also collected. Treatment patterns abstracted from the medical record included type of surgery (type of hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy, and omentectomy), type of postoperative chemotherapy (carboplatin, paclitaxel, or other), and type and location of postoperative radiotherapy (intracavitary vaginal brachytherapy, whole-pelvis radiotherapy, or whole-pelvic radiotherapy with extended field). Survival outcomes included disease-free survival (DFS), which was defined as the time interval between the date of surgery and the date of disease recurrence or the last date of follow-up, and overall survival (OS), which was defined as the time interval between the date of surgery and death or the last date of follow-up.

Statistical Analysis

Continuous variables were assessed for normality (Kolmogorov–Smirnov test) and expressed as appropriate [mean (standard deviation), or median (range)]. Student's t test or Mann–Whitney U test was performed for continuous variables as appropriate. Categorical variables were evaluated with Fisher's exact test or Chi-square test as appropriate, expressed with odds ratio (OR) and 95 % confidence interval (CI). Multivariate analysis with binary logistic regression test was further performed to determine independent risk factors in univariate analysis. Significance of adenomyosis on survival outcomes (DFS and OS) was examined with the log-rank test in univariate analysis. Cox's proportional hazard regression test (conditional backward method) was used to identify the independent prognostic factors of DFS and PS adjusted for all significant variables in univariate analysis. Survival curves were constructed with the Kaplan–Meier method. p values of less than 0.05 were considered statistically significant (all two-tailed). The Statistical Package for Social Science software (SPSS, version 12.0; SPSS Inc., Chicago, IL, USA) was used for all analyses.

RESULTS

Overall, 666 women with endometrial cancer underwent surgical staging during the study period. Of these women, myometrial findings for the hysterectomy specimens were available in 571 (85.7 %) patients who were evaluated for statistical analysis. Patient characteristics are shown in Table 1. Mean age of the study population was 52.7 years. The majority of endometrial cancer patients were hispanic (67.3 %), obese (67.7 %), multiparous (70.8 %), and underwent abdominal hysterectomy (60.6 %). Adenomyosis was diagnosed in nearly half of the endometrial cancer cases (n = 271, 47.5 %; 95 % CI 43.4–51.6), and was not associated with age (p = 0.92), ethnicity (p = 0.65), or body habitus (p = 0.79). Adenomyosis was more commonly seen in multigravidas (OR 1.77; 95 % CI 1.19–2.65; $p < 0.001$) and multiparous (OR 1.72; 95 % CI 1.18–2.51; $p < 0.001$) patients. Incidences of adenomyosis across the extent of parity were as follows: P0, 38.0 %; P1–2, 44.9 %; P3–4, 57.6 %; and $p \geq 5$, 56.4 %, respectively. Patients with adenomyosis were less likely to undergo total laparoscopic hysterectomy when compared with non-adenomyosis patients (24.0 vs. 29.0 %; p = 0.025).

Tumor characteristics of endometrial cancer were examined (Table 2). The majority of the study population had endometrioid histology (83.4 %), grade 1 tumors (52.5 %), and stage I disease (69.3 %). The presence of adenomyosis was significantly associated with a decreased risk of grade 3 tumors (18.8 vs. 26.7 %; p = 0.028) and a higher likelihood of stage I disease (74.8 vs. 64.3 %; p = 0.023) when compared with non-adenomyosis cases. When tumor details were compared, the presence of adenomyosis was significantly associated with a lower likelihood of outer-half myometrial invasion (19.2 vs. 28.2 %; p = 0.039) and a lower likelihood of cervical mucosal/stromal invasion (13.7 vs. 21.2 %; p = 0.024). Uterine myomas were seen in 260 (45.5 %; 95 % CI 41.4–49.6) cases but was not statistically associated with the presence of adenomyosis (p = 0.078). Endometriosis was infrequently seen in concert with endometrial cancer (n = 29, 5.1 %; 95 % CI 3.3–6.9), with the ovary and fallopian tube being the most common site of endometriosis (both 27.6 %). Endometriosis was significantly associated with the presence of adenomyosis in endometrial cancer (8.9 vs. 1.7 %; OR 5.73; 95 % CI 2.16–15.2; $p < 0.001$). Estrogen and progesterone receptors were examined in only 220 (38.5 %) cases; the majority of tested cases of endometrial cancer expressed estrogen receptor (88.6 %) and progesterone receptor (86.8 %) that were not statistically associated with the presence of adenomyosis (p = 0.088 and 0.11, respectively).

Survival outcomes of endometrial cancer were examined. Median follow-up time of all cases after hysterectomy was 26.9 months, and median follow-up time for the adenomyosis group was statistically longer than the non-adenomyosis group (37.3 vs. 23.9 months; p = 0.008). There were 67 events of disease recurrence and 47 events of death due to endometrial cancer. Risk factors for DFS are shown in Table 3. In univariate analysis, endometrial cancer patients with adenomyosis had a significantly improved DFS when compared with endometrial cancer patients with no adenomyosis (5-year DFS rate 89.2 vs. 78.2 %; hazard ratio [HR] 0.42; 95 % CI 0.25–0.70; $p < 0.001$) (Fig. 1a). The presence of uterine myomas (p = 0.22) or endometriosis (p = 0.53) was not associated with DFS. Significant prognosticators for decreased DFS included age ≥60 years (p = 0.01), CA-125 ≥ 35 IU/L ($p < 0.001$), non-endometrioid histology ($p < 0.001$), grade 3 tumors ($p < 0.001$), and stage III–IV disease ($p < 0.001$). Hispanic race ($p < 0.001$) and obesity (p = 0.005) were associated with improved DFS. On multivariate analysis, entering all the significant variables from univariate analysis, the presence of adenomyosis remained an independent significant predictor for improved DFS (HR 0.53; 95 % CI 0.30–0.92; p = 0.023). Other independent prognosticators for decreased DFS included CA-125 ≥ 35 IU/L ($p < 0.001$), grade 3 tumor ($p < 0.001$), and stage III–IV disease ($p < 0.001$). In a subanalysis of type II histology (grade 3 endometrioid, serous and clear cell histology, n = 128), adenomyosis remained an independent predictor for improved DFS (5-year rate 79.1 vs. 46.5 %; HR 0.42; 95 % CI 0.20–0.88; p = 0.022) in multivariate analysis (other independent variables, CA-125 p = 0.007, and stage p = 0.013).

Survival analysis for OS was performed (Table 4). On univariate analysis, endometrial cancer cases with adenomyosis was significantly associated with better OS when compared with non-adenomyosis cases (5-year OS rate 91.8 vs. 83.9 %; HR 0.42; 95 % CI 0.23–0.78; p = 0.004) (Fig. 1b). Variables associated with decreased OS included age ≥60 years (p = 0.013), CA-125 ≥35 IU/L ($p < 0.001$), non-endometrioid histology ($p < 0.001$), grade 3 tumor ($p < 0.001$), and stage III–IV disease ($p < 0.001$). In multivariate analysis, entering all the significant variables in univariate analysis, the presence of adenomyosis did not remain an independent predictor for OS. Similar to the results for DFS, CA-125 ≥ 35 IU/L ($p < 0.001$), grade 3 tumor (p = 0.002), and stage III–IV disease ($p < 0.001$) remained as significant prognostic factors for decreased OS.

To examine the impacts of adenomyosis in the paradigm of tumor genesis/progression in endometrial cancer, endometrial hyperplasia, a known precursor of type I endometrial cancer, was examined in the separate cohort. A total of 213 hysterectomy specimens for endometrial hyperplasia were evaluated for myometrial lesions. Mean

TABLE 1 Patient demographics of endometrial cancer

Subject	All $n = 571$	Adenomyosis (+) $n = 271$ (47.5 %)	Adenomyosis (−) $n = 300$ (52.5 %)	p value
Age, years				0.92
Mean (± SD)	52.7 (10.2)	52.7 (9.6)	52.7 (10.7)	
<60	432 (75.7)	206 (76.0)	226 (75.3)	
≥60	139 (24.3)	65 (24.0)	74 (24.7)	
Race				0.65
Caucasian	63 (11.0)	31 (11.4)	32 (10.7)	
African American	26 (4.6)	10 (3.7)	16 (5.3)	
Hispanic	384 (67.3)	187 (69.0)	197 (65.7)	
Asian	98 (17.2)	43 (15.9)	55 (18.3)	
BMI				0.79
Mean (± SD)	35.6 (10)	35.8 (9.1)	35.5 (10.7)	
<30	170 (32.3)	69 (28.4)	101 (35.6)	
≥30	357 (67.7)	174 (71.6)	183 (64.4)	
Gravidity				<0.001
Median (range)	2 (0–18)	3 (0–13)	2 (0–18)	
Null	133 (24.5)	49 (19.1)	84 (29.5)	
Multi	409 (75.5)	208 (80.9)	201 (70.5)	
Parity				<0.001
Median (range)	2 (0–17)	2 (0–12)	1 (0–17)	
Null	158 (29.2)	60 (23.3)	98 (34.4)	
Multi	384 (70.8)	197 (76.7)	187 (65.6)	
CA-125, IU/L				0.18
Median (range)	18 (2–7,192)	17 (3–7,192)	19 (2–4,068)	
<35	370 (72.4)	179 (75.2)	191 (70.0)	
≥35	141 (27.6)	59 (24.8)	82 (30.0)	
Hysterectomy type				0.025
TAH	346 (60.6)	166 (61.3)	180 (60.0)	
TLH	152 (26.6)	65 (24.0)	87 (29.0)	
LAVH	37 (6.5)	26 (9.6)	11 (3.7)	
TVH	17 (3.0)	9 (3.3)	8 (2.7)	
RH/MRH	16 (2.8)	4 (1.5)	12 (4.0)	
SCH	3 (0.5)	1 (0.4)	2 (0.7)	
Radiotherapy type				0.28
None	374 (65.5)	186 (68.6)	188 (62.7)	
WPRT alone	73 (12.8)	33 (12.2)	40 (13.3)	
WPRT + ICBT	66 (11.6)	31 (11.4)	35 (12.3)	
ICBT alone	58 (10.2)	21 (7.7)	37 (12.3)	
Chemotherapy type				0.14
None	427 (74.8)	213 (78.6)	214 (71.3)	
Carboplatin + paclitaxel	136 (23.8)	55 (20.3)	81 (27.0)	
Others	8 (1.4)	3 (1.1)	5 (1.7)	

Chi-square or Fisher's exact test were used to calculate p values

Data are expressed as n (%) unless specified otherwise

Total number may not equate to 571 due to missing variables

SD standard deviation, *BMI* body mass index, *CA-125* cancer antigen 125, *TAH* total abdominal hysterectomy, *TLH* total laparoscopic hysterectomy, *LAVH* laparoscopy-assisted vaginal hysterectomy, *TVH* total vaginal hysterectomy, *RH* radical hysterectomy, *MRH* modified radical hysterectomy, *SCH* supracervical hysterectomy, *WPRT* whole-pelvis radiotherapy, *ICBT* intracavitary brachytherapy

TABLE 2 Adenomyosis and tumoral factors in endometrial cancer

Subject	All $n = 571$	Adenomyosis (+) $n = 271$ (47.5 %)	Adenomyosis (−) $n = 300$ (52.5 %)	p value
Histology				0.13
Endometrioid	476 (83.4)	229 (84.5)	247 (82.3)	
Serous/clear cell	49 (8.6)	17 (6.3)	32 (10.7)	
Others	46 (8.1)	25 (9.2)	21 (7.0)	
Grade				0.028
1	300 (52.5)	150 (55.4)	150 (50.0)	
2	140 (24.5)	70 (25.8)	70 (23.3)	
3	131 (22.9)	51 (18.8)	80 (26.7)	
Stage				0.023
I	395 (69.3)	202 (74.8)	193 (64.3)	
II	50 (8.8)	18 (6.7)	32 (10.7)	
III	86 (15.1)	38 (14.1)	48 (16.0)	
IV	39 (6.8)	12 (4.4)	27 (9.0)	
Myometrial invasion, %				0.039
0	93 (16.6)	45 (16.9)	48 (16.3)	
1–49	333 (59.5)	170 (63.9)	163 (55.4)	
50–100	134 (23.9)	51 (19.2)	83 (28.2)	
Cervical invasion				0.024
None	443 (82.3)	221 (86.3)	222 (78.7)	
Mucosa	32 (5.9)	11 (4.3)	21 (7.4)	
Stroma	63 (11.7)	24 (9.4)	39 (13.8)	
LVSI				0.34
No	456 (80.4)	222 (82.2)	234 (78.8)	
Yes	111 (19.6)	48 (17.8)	63 (21.2)	
Adnexal/serosa				0.64
No	489 (91.4)	234 (92.1)	255 (90.7)	
Yes	46 (8.6)	20 (7.9)	26 (9.3)	
Peritoneal cytology				0.07
Negative	470 (90.7)	232 (93.2)	238 (88.5)	
Positive	48 (9.3)	17 (6.8)	31 (11.5)	
Nodal metastasis[a]				0.55
No	259 (82.7%)	113 (81.3)	146 (83.9)	
Yes	54 (17.3)	26 (18.7)	28 (16.1)	
Uterine myoma				0.078
No	311 (54.5)	137 (50.6)	174 (58.0)	
Yes	260 (45.5)	134 (49.4)	126 (42.0)	
Endometriosis				<0.001
No	542 (94.9)	247 (91.1)	295 (98.3)	
Yes	29 (5.1)	24 (8.9)	5 (1.7)	
ER				0.088
No	25 (11.4)	7 (7.1)	18 (14.9)	
Yes	195 (88.6)	92 (92.9)	103 (85.1)	
PR				0.11
No	29 (13.2)	9 (9.1)	20 (16.5)	

TABLE 2 continued

Subject	All $n = 571$	Adenomyosis (+) $n = 271$ (47.5 %)	Adenomyosis (−) $n = 300$ (52.5 %)	p value
Yes	191 (86.8)	90 (90.9)	101 (83.5)	

Chi-square or Fisher's exact test were used to calculate p values

Data are expressed as n (%)

Total number may not equate to 571 due to missing variables

LVSI lymphovascular space invasion, *ER* estrogen receptor, *PR* progesterone receptor

[a] Nodal metastasis for pelvic and/or para-aortic lymph nodes

TABLE 3 Risk factors for disease-free survival in endometrial cancer

	No. at risk	5-year survival proportion (%)	Univariate		Multivariate	
			HR (95 % CI)	p value	HR (95 % CI)	p value
Age, years				0.01		
<60	432	85.4	1			
≥60	139	77.2	1.92 (1.16–3.18)			
Race				<0.001		
Non-Hispanic	187	74.2	1			
Hispanic	384	87.6	0.45 (0.28–0.73)			
BMI				0.005		
<30	170	76.6	1			
≥30	357	85.2	0.51 (0.31–0.83)			
Parity				0.28		
Null	158	85.2	1			
Multi	384	83.1	1.38 (0.77–2.46)			
CA-125, IU/L				<0.001		<0.001
<35	370	92.4	1		1	
≥35	141	55.2	7.03 (4.14–11.9)		3.64 (2.06–6.42)	
Histology				<0.001		
Endometrioid	476	89.2	1			
Non-endometrioid	95	57.2	5.61 (3.47–9.06)			
Grade				<0.001		<0.001
1–2	440	91.5	1		1	
3	131	58.5	8.24 (4.94–13.7)		3.74 (2.11–6.62)	
Stage				<0.001		<0.001
I–II	445	94.7	1		1	
III–IV	125	48.7	13.3 (7.60–23.4)		4.38 (2.28–8.40)	
Adenomyosis				<0.001		0.023
No	300	78.2	1		1	
Yes	271	89.2	0.42 (0.25–0.70)		0.53 (0.30–0.92)	
Uterine myoma				0.22		
No	311	87.2	1			
Yes	260	80.3	1.35 (0.83–2.18)			
Endometriosis				0.53		
No	542	84.1	1			
Yes	29	74.6	1.34 (0.54–3.33)			

The log-rank test was used for univariate analysis and Cox's proportional hazard regression test (conditional backward method) was used for multivariate analysis

HR hazard ratio, *CI* confidence interval, *BMI* body mass index, *CA-125* cancer antigen 125

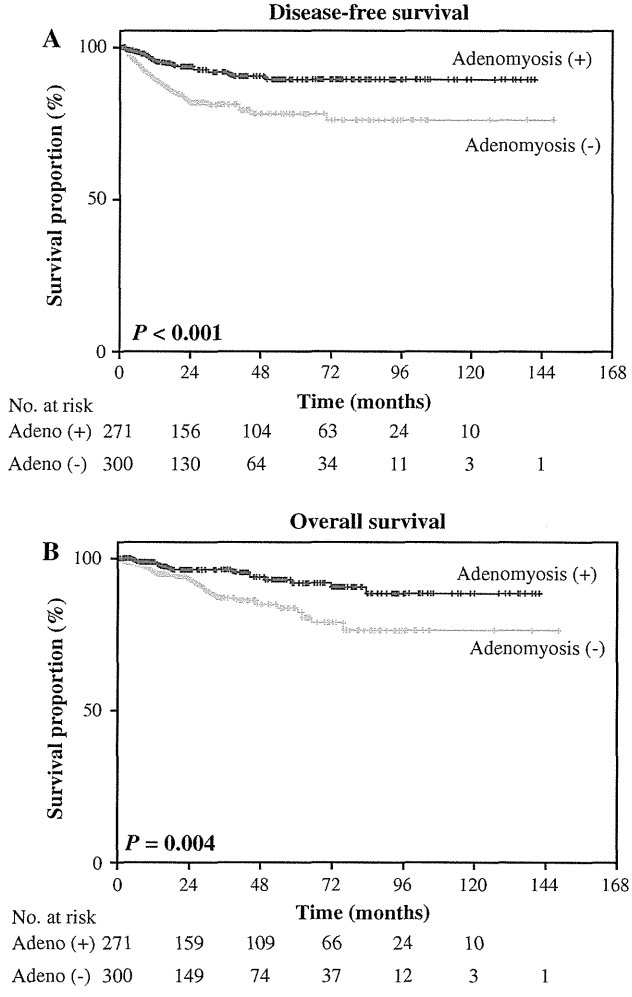

FIG. 1 Adenomyosis and survival outcomes of endometrial cancer. Log-rank test for *p* values. Survival outcomes are shown for **a** disease-free survival and **b** overall survival based on the presence or absence of adenomyosis in endometrial cancer patients. *Adeno* adenomyosis

age of the endometrial hyperplasia patients was 45.5 years (±9.2). Overall, 134 (62.9 %; 95 % CI 56.4–68.4) cases presenting with adenomyosis and 103 (48.4 %; 95 % CI 41.6–55.1) cases presenting with uterine myoma coexisted with endometrial hyperplasia. When endometrial hyperplasia cases were compared with type I endometrial cancer cases (grade 1–2 endometrioid adenocarcinoma, $n = 411$), endometrial hyperplasia was associated with a significantly younger age (mean age, endometrial hyperplasia vs. grade 1–2 endometrioid adenocarcinoma, 45.5 vs. 51.4; $p < 0.001$) and was associated with an increased risk of adenomyosis (62.9 vs. 48.9 %; OR 1.77; 95 % CI 1.26–2.49; $p = 0.001$). The incidence of uterine myoma did not differ between the two groups (48.4 vs. 43.6 %; $p = 0.27$). On multivariate analysis, controlling for age (≥50 vs. <50 years; 50.3 vs. 53.4 %; HR 1.22; 95 % CI 088–1.71; $p = 0.24$), endometrial hyperplasia remained a significant variable associated with increased incidence of adenomyosis when compared with type I endometrial cancer (HR 1.88; 95 % CI 1.32–2.69; $p < 0.001$).

DISCUSSION

Key findings of our results are that (i) the presence of adenomyosis in the myometrial layer of endometrial cancer patients was associated with less aggressive tumor behavior; and (ii) patients with endometrial cancer coexisting with adenomyosis were less likely to develop disease recurrence than those who did not have adenomyosis. In addition, an inverse correlation of adenomyosis occurrence was observed in the continuum of endometrial cancer progression from pre-cancer to cancer. Several key areas deserve further discussion.

The interaction among the triad of endometrial cancer, adenomyosis, and endometrial stromal cells is the important mechanism to understand our findings of adenomyosis in endometrial cancer. Adenomyosis, ectopic endometrium within the myometrium, is characterized by unique patterns of cytokine balance when compared with normal endometrium.[36] Adenomyosis is known to have increased secretions of interferon (IFN)-α, IFN-γ, tumor necrosis factor (TNF)-α, and interleukin (IL)-10.[36,37] Increased level of these cytokines may potentially augment the cancer-immune system (IFN-α and IFN-γ), anti-tumor effect via enhancing apoptosis (TNF-α), and anti-inflammatory cytokine production (IL-10), resulting in protective effects to endometrial cancer progression.[38–41] Adenomyosis is also known to have decreased secretions of various cytokines such as IL-1β, IL-8, and epidermal growth factor (EGF).[36] Because these cytokines play an important role in tumor progression in inflammasome (IL-1β), and in tumor microenviroment (IL-8) and tumor growth factor (TGF),[42,43] a decreased level of oncogenic cytokines/growth factor in adenomyosis may theoretically alleviate endometrial cancer progression.

Another possible link between adenomyosis and lack of endometrial cancer progression is the characteristics of the endometrial stroma of adenomyosis.[44] Previous studies have shown that the endometrial stroma of adenomyosis is associated with rapid cell proliferation under stimulation of estrogen or inflammatory cytokines. As a consequence, it is speculated that thickened endometrial stroma in adenomyosis may contribute to a mechanical block of endometrial cancer invasion in the myometrium. Even though the greatest thickening occurs at the foci of adenomyotic lesions in the deep myometrial tissue,[45] mild thickening of the subendothelial myometrial unit can be seen throughout.[46] Our findings of decreased deep myometrial invasion (≥50 %) strengthen this proposed theory.

TABLE 4 Risk factors for overall survival in endometrial cancer

	No. at risk	5-year survival proportion (%)	Univariate		Multivariate	
			HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Age, years				0.013		
<60	432	89.3	1			
≥60	139	84.0	2.13 (1.16–3.91)			
Race				0.003		
Non-Hispanic	187	80.8	1			
Hispanic	384	91.0	0.44 (0.25–0.77)			
BMI				0.12		
<30	170	83.5	1			
≥30	357	88.1	0.63 (0.35–1.13)			
Parity				0.26		
Null	158	90.6	1			
Multi	384	86.9	1.49 (0.74–3.01)			
CA-125, IU/L				<0.001		<0.001
<35	370	94.7	1		1	
≥35	141	67.6	7.24 (3.80–13.8)		3.49 (1.74–6.99)	
Histology				<0.001		
Endometrioid	476	92.1	1			
Non-endometrioid	95	68.6	4.97 (2.81–8.82)			
Grade				<0.001		0.002
1–2	440	93.9	1		1	
3	131	68.7	6.53 (3.60–11.8)		2.86 (1.48–5.53)	
Stage				<0.001		<0.001
I–II	445	95.8	1		1	
III–IV	125	64.2	14.9 (7.18–30.7)		5.48 (2.39–12.6)	
Adenomyosis				0.004		
No	300	83.9	1			
Yes	271	91.8	0.42 (0.23–0.78)			
Uterine myoma				0.63		
No	311	87.3	1			
Yes	260	88.8	0.87 (0.49–1.54)			
Endometriosis				0.87		
No	542	87.4	1			
Yes	29	96.4	1.10 (0.34–3.55)			

The log-rank test was used for univariate analysis and Cox's proportional hazard regression test (conditional backward method) was used for multivariate analysis

HR hazard ratio, *CI* confidence interval, *BMI* body mass index, *CA-125* cancer antigen 125

Collectively, these unique characteristics of cytokine parameters and local environments seen in adenomyosis may potentially contribute to block the tumor progression of endometrial cancer in a manner of molecular interactions (molecular blockage) or histological interaction (mechanical blockage). Further studies are warranted to elucidate the exact mechanism of the protective effects of adenomyosis in endometrial cancer.

While our data at least suggest there may be a possible protective effect of adenomyosis for endometrial cancer progression, oncogenesis related to adenomyosis is a different entity and needs to be discussed. It is important to note the high rate of adenomyosis seen in our population with endometrial cancer (47.5 %) and hyperplasia (62.5 %), which raises an insight into a possible positive correlation between endometrial cancer and adenomyosis, supporting previous literature proposing adenomyosis-linked endometrial cancer.[5–28] However, the true prevalence of adenomyosis in the general population is difficult to assess due to different criteria for diagnosing

adenomyosis in previous studies or lack of autopsy studies in an unselected population. In a review of previous reported literature including 8,653 cases, a wide range of adenomyosis—from 18 % to 66 %—was noted.[47] Furthermore, our data do not have a control group for non-endometrial cancer in which to compare the incidence of adenomyosis. While it is speculated that a certain fraction of adenomyosis may be a precursor of endometrial cancer,[48] it remains understudied as to whether or not adenomyosis increases the risk of endometrial cancer, and the exact molecular mechanism of oncogenesis in adenomyosis remains unknown. Therefore, further studies are warranted to examine this link.

One of the strengths of our study is that this was one of the largest studies evaluating the significance of adenomyosis in endometrial cancer patients with multivariate analysis. The impact of adenomyosis was further validated in the endometrial hyperplasia cohort. A weakness of the study is that this was a retrospective study that may miss potential confounding factors. Another limitation is that histopathology slides were not reviewed and quantitative analysis based on the severity of adenomyosis was not performed in our study.

CONCLUSIONS

The presence of adenomyosis is a predictor of improved survival outcome of patients with endometrial cancer. Further clinical and pre-clinical studies will be needed to determine the exact mechanism of protective effects of adenomyosis on endometrial cancer progression.

ACKNOWLEDGMENT No funding support was provided for this study.

DISCLOSURE Koji Matsuo, Sigita S. Cahoon, Marc Gualtieri, Christopher A. Scannell, Carrie E. Jung, Tadao Takano, Richard J. Paulson, Laila I. Muderspach, and Lynda D. Roman declare that there are no conflicts of interest for this study.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63:11-30.
2. Wright JD, Barrena Medel NI, Sehouli J, Fujiwara K, Herzog TJ. Contemporary management of endometrial cancer. Lancet. 2012;379:1352–60.
3. Garcia L, Isaacson K. Adenomyosis: review of the literature. J Minim Invasive Gynecol. 2011;18:428–37.
4. Kairi-Vassilatou E, Kontogianni K, Salamalekis M, Sykiotis K, Kondi-Pafitis A. A clinicopathological study of the relationship between adenomyosis and other hormone-dependent uterine lesions. Eur J Gynaecol Oncol. 2004;25:222–4.
5. Winkelman J, Robinson R. Adenocarcinoma of endometrium involving adenomyosis. Report of an unusual case and review of the literature. Cancer. 1966;19:901–8.
6. Hernandez E, Woodruff JD. Endometrial adenocarcinoma arising in adenomyosis. Am J Obstet Gynecol. 1980;138:827–32.
7. Woodruff JD, Erozan YS, Genadry R. Adenocarcinoma arising in adenomyosis detected by atypical cytology. Obstet Gynecol. 1986;67:145–8.
8. Kuwashima Y, Uehara T, Kishi K, et al. Intramural adenocarcinoma of the uterus, arisen from adenomyosis uteri, showing unique histologic appearances. Report of two cases. Eur J Gynaecol Oncol. 1994;15:418–23.
9. Hayata T, Tanaka Y, Miyakawa I. Endometrial cancer associated with adenomyosis. Int J Gynaecol Obstet. 1994;44:76–7.
10. Takai N, Akizuki S, Nasu K, Etoh Y, Miyakawa I. Endometrioid adenocarcinoma arising from adenomyosis. Gynecol Obstet Invest. 1999;48:141–4.
11. Sasaki T, Sugiyama T, Nanjo H, et al. Endometrioid adenocarcinoma arising from adenomyosis: report and immunohistochemical analysis of an unusual case. Pathol Int. 2001;51:308–13.
12. Ichikawa Y, Takano K, Higa S, et al. Endometrial carcinoma coexisting with pregnancy, presumed to derive from adenomyosis: a case report. Int J Gynecol Cancer. 2001;11:488–90.
13. Koshiyama M, Suzuki A, Ozawa M, et al. Adenocarcinomas arising from uterine adenomyosis: a report of four cases. Int J Gynecol Pathol. 2002;21:239–45.
14. Couto D, Mota F, Silva T, de Oliveira C. Adenocarcinoma arising in adenomyosis: report of an unusual case. Acta Obstet Gynecol Scand. 2004;83:406–8.
15. Takeuchi K, Yamanaka Y, Hamana S, Ohara N, Maruo T. Invasive adenocarcinoma arising from uterine adenomyosis involving the rectosigmoid colon. Int J Gynecol Cancer. 2004;14:1004–6.
16. Hsu MI, Chou SY, Lin SE, Liang SJ, Chiu HC, Hsu CS. Very early stage adenocarcinoma arising from adenomyosis in the uterus. Taiwan J Obstet Gynecol. 2006;45:346–9.
17. Izadi-Mood N, Samadi N, Sarmadi S, Eftekhar Z. Papillary serous carcinoma arising from adenomyosis presenting as intramural leiomyoma. Arch Iran Med. 2007;10:258–60.
18. Ismiil ND, Rasty G, Ghorab Z, et al. Adenomyosis is associated with myometrial invasion by FIGO 1 endometrial adenocarcinoma. Int J Gynecol Pathol. 2007;26:278–83.
19. Puppa G, Shozu M, Perin T, et al. Small primary adenocarcinoma in adenomyosis with nodal metastasis: a case report. BMC Cancer. 2007;7:103.
20. Ismiil N, Rasty G, Ghorab Z, et al. Adenomyosis involved by endometrial adenocarcinoma is a significant risk factor for deep myometrial invasion. Ann Diagn Pathol. 2007;11:252–7.
21. Ohta Y, Hamatani S, Suzuki T, et al. Clear cell adenocarcinoma arising from a giant cystic adenomyosis: a case report with immunohistochemical analysis of laminin-5 gamma2 chain and p53 overexpression. Pathol Res Pract. 2008;204:677–82.
22. Motohara K, Tashiro H, Ohtake H, Saito F, Ohba T, Katabuchi H. Endometrioid adenocarcinoma arising in adenomyosis: elucidation by periodic magnetic resonance imaging evaluations. Int J Clin Oncol. 2008;13:266–70.
23. Hirabayashi K, Yasuda M, Kajiwara H, et al. Clear cell adenocarcinoma arising from adenomyosis. Int J Gynecol Pathol. 2009;28:262–6.
24. Kazandi M, Zeybek B, Terek MC, Zekioglu O, Ozdemir N, Oztekin K. Grade 2 endometrioid adenocarcinoma arising from adenomyosis of the uterus: report of a case. Eur J Gynaecol Oncol. 2010;31:719–21.
25. Abushahin N, Zhang T, Chiang S, Zhang X, Hatch K, Zheng W. Serous endometrial intraepithelial carcinoma arising in adenomyosis: a report of 5 cases. Int J Gynecol Pathol. 2011;30:271–81.
26. Kucera E, Hejda V, Dankovcik R, Valha P, Dudas M, Feyereisl J. Malignant changes in adenomyosis in patients with endometrioid adenocarcinoma. Eur J Gynaecol Oncol. 2011;32:182–4.

27. Boes AS, Tousseyn T, Vandenput I, et al. Pitfall in the diagnosis of endometrial cancer: case report of an endometrioid adenocarcinoma arising from uterine adenomyosis. Eur J Gynaecol Oncol. 2011;32:431–4.
28. Quick CM, May T, Horowitz NS, Nucci MR. Low-grade, low-stage endometrioid endometrial adenocarcinoma: a clinicopathologic analysis of 324 cases focusing on frequency and pattern of myoinvasion. Int J Gynecol Pathol. 2012;31:337–43.
29. Hanley KZ, Dustin SM, Stoler MH, Atkins KA. The significance of tumor involved adenomyosis in otherwise low-stage endometrioid adenocarcinoma. Int J Gynecol Pathol. 2010;29:445–51.
30. Hall JB, Young RH, Nelson JH Jr. The prognostic significance of adenomyosis in endometrial carcinoma. Gynecol Oncol. 1984;17:32–40.
31. Jacques SM, Lawrence WD. Endometrial adenocarcinoma with variable-level myometrial involvement limited to adenomyosis: a clinicopathologic study of 23 cases. Gynecol Oncol. 1990;37: 401–7.
32. Mittal KR, Barwick KW. Endometrial adenocarcinoma involving adenomyosis without true myometrial invasion is characterized by frequent preceding estrogen therapy, low histologic grades, and excellent prognosis. Gynecol Oncol. 1993;49:197–201.
33. Koshiyama M, Okamoto T, Ueta M. The relationship between endometrial carcinoma and coexistent adenomyosis uteri, endometriosis externa and myoma uteri. Cancer Detect Prev. 2004; 28:94–8.
34. Musa F, Frey MK, Im HB, Chekmareva M, Ellenson LH, Holcomb K. Does the presence of adenomyosis and lymphovascular space invasion affect lymph node status in patients with endometrioid adenocarcinoma of the endometrium? Am J Obstet Gynecol. 2012;207:417.e1-6.
35. Gun I, Oner O, Bodur S, Ozdamar O, Atay V. Is adenomyosis associated with the risk of endometrial cancer? Med Glas (Zenica). 2012;9:268–72.
36. Sotnikova N, Antsiferova I, Malyshkina A. Cytokine network of eutopic and ectopic endometrium in women with adenomyosis. Am J Reprod Immunol. 2002;47:251–5.
37. Wang F, Li H, Yang Z, Du X, Cui M, Wen Z. Expression of interleukin-10 in patients with adenomyosis. Fertil Steril. 2009;91:1681–5.
38. Ikeda H, Old LJ, Schreiber RD. The roles of IFN gamma in protection against tumor development and cancer immunoediting. Cytokine Growth Factor Rev. 2002;13:95–109.
39. Ferrantini M, Capone I, Belardelli F. Interferon-alpha and cancer: mechanisms of action and new perspectives of clinical use. Biochimie. 2007;89:884–93.
40. van Horssen R, Ten Hagen TL, Eggermont AM. TNF-alpha in cancer treatment: molecular insights, antitumor effects, and clinical utility. Oncologist. 2006;11:397–408.
41. Tagashira Y, Taniguchi F, Harada T, Ikeda A, Watanabe A, Terakawa N. Interleukin-10 attenuates TNF-alpha-induced interleukin-6 production in endometriotic stromal cells. Fertil Steril. 2009;91:2185–92.
42. Zitvogel L, Kepp O, Galluzzi L, Kroemer G. Inflammasomes in carcinogenesis and anticancer immune responses. Nat Immunol. 2012;13:343–51.
43. Palena C, Hamilton DH, Fernando RI. Influence of IL-8 on the epithelial-mesenchymal transition and the tumor microenvironment. Future Oncol. 2012;8:713–22.
44. Yang JH, Wu MY, Chen CD, Chen MJ, Yang YS, Ho HN. Altered apoptosis and proliferation in endometrial stromal cells of women with adenomyosis. Hum Reprod. 2007;22:945–52.
45. Mehasseb MK, Bell SC, Brown L, Pringle JH, Habiba M. Phenotypic characterisation of the inner and outer myometrium in normal and adenomyotic uteri. Gynecol Obstet Invest. 2011;71:217–24.
46. Benagiano G, Habiba M, Brosens I. The pathophysiology of uterine adenomyosis: an update. Fertil Steril. 2012;98:572–9.
47. Vercellini P, Vigano P, Somigliana E, Daguati R, Abbiati A, Fedele L. Adenomyosis: epidemiological factors. Best Pract Res Clin Obstet Gynaecol. 2006;20:465–77.
48. Koike N, Tsunemi T, Uekuri C, et al. Pathogenesis and malignant transformation of adenomyosis (review). Oncol Rep. 2013;29: 861–7.

Int J Clin Oncol
DOI 10.1007/s10147-014-0732-0

ORIGINAL ARTICLE

Evaluation of postoperative chemotherapy in patients with uterine carcinosarcoma: a retrospective survey of the Tohoku Gynecologic Cancer Unit

Ai Otsuki · Takeo Otsuki · Hideki Tokunaga · Hitoshi Niikura · Satoru Nagase · Takashi Sugiyama · Masafumi Toyoshima · Hiroki Utsunomiya · Yoshihito Yokoyama · Hideki Mizunuma · Naoki Sato · Yukihiro Terada · Tadahiro Shoji · Toru Sugiyama · Kenji Nakahara · Tsuyoshi Ohta · Hidekazu Yamada · Toru Tase · Hiroshi Nishiyama · Keiya Fujimori · Tadao Takano · Fumiaki Takahashi · Yoh Watanabe · Nobuo Yaegashi

Received: 2 May 2014 / Accepted: 6 July 2014

Abstract
Background The aim of this study was to evaluate prognostic factors including efficacy of postoperative chemotherapy in Japanese patients with uterine carcinosarcoma.
Methods We conducted a retrospective survey of seven medical facilities in the Tohoku Gynecologic Cancer Unit.
Results A total of 45 patients who had undergone hysterectomy and bilateral salpingo-oophorectomy were enrolled. No significant difference was observed in overall survival according to patient age (≤50 years vs >50 years) or retroperitoneal lymphadenectomy (performed vs. not performed). However, the International Federation of Gynecology and Obstetrics stage (stage I/II vs stage III/IV) and postoperative chemotherapy (provided vs not provided) were significant prognostic factors in both univariate and multivariate analyses for the 25-month median follow-up period.
Conclusions Our results revealed that postoperative chemotherapy should be considered for all uterine carcinosarcoma stages in Japanese patients.

Keywords Uterine carcinosarcoma · Prognostic factor · Chemotherapy · Retrospective study

Introduction

Carcinosarcoma is a rare, aggressive tumor with a poor prognosis and consists of both carcinoma and sarcoma components [1–3]. We previously completed a retrospective study on factors affecting the prognosis of carcinosarcoma, endometrial stromal sarcoma, and leiomyosarcoma [4], and reported that chemotherapy did not significantly predict overall survival for endometrial stromal sarcoma ($p = 0.0714$) or leiomyosarcoma ($p = 0.989$). However,

A. Otsuki · T. Otsuki · H. Tokunaga · H. Niikura · S. Nagase · T. Sugiyama · M. Toyoshima · H. Utsunomiya · T. Takano · Y. Watanabe (✉) · N. Yaegashi
Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, Sendai, Japan
e-mail: watanabe@med.tohoku.ac.jp

Y. Yokoyama · H. Mizunuma
Department of Obstetrics and Gynecology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan

N. Sato · Y. Terada
Department of Obstetrics and Gynecology, Akita University Graduate School of Medicine, Akita, Japan

T. Shoji · T. Sugiyama
Department of Obstetrics and Gynecology, Iwate Medical University, Morioka, Japan

K. Nakahara · T. Ohta
Department of Obstetrics and Gynecology, Yamagata University Faculty of Medicine, Yamagata, Japan

H. Yamada · T. Tase
Department of Gynecology, Miyagi Cancer Center, Sendai, Japan

H. Nishiyama · K. Fujimori
Department of Obstetrics and Gynecology, Fukushima Medical University, Fukushima, Japan

T. Takano · F. Takahashi · Y. Watanabe
Department of Clinical Research Network, Clinical Research, Innovation and Education Center, Tohoku University Hospital, 1-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8574, Japan

Published online: 18 July 2014