EJGO European Journal of Gynaecological Oncology

Primary peritoneal cancer: study of 14 cases and comparison with epithelial ovarian cancer

T. Fukuda, K. Imai, M. Yamauchi, M. Teramae, Y. Hashiguchi, T. Ichimura, T. Yasui, T. Sumi

Department of Obstetrics and Gynecology, Osaka City University Graduate School of Medicine, Abeno-ku, Osaka (Japan)

Summary

Purpose of investigation: Primary peritoneal carcinoma (PPC) is histologically similar to ovarian serous carcinoma, but its biochemical features remain obscure. The authors investigated and compared clinical findings, treatments, and outcomes of patients with PPS and those with epithelial ovarian cancer (EOC) patients. *Materials and Methods:* The authors retrospectively reviewed data from 14 patients with PPC and 219 patients with EOC treated at the present hospital from January 2005 to December 2012, including demographic data, pathologic findings, treatments, and outcomes. *Results:* Patients with PPC were significantly older (62.6 ± 8.4 years) than those with EOC (56.3 ± 11.3 years) ($p = 0.045$). There was no significant difference in serum CA-125 levels. The five-year survival rates did not differ significantly between patients with PPC (61.1%) and those with EOC (60.3%; $p = 0.78$); nor between patients with PPC and those with Stage III serous EOC (43.8%; $p = 0.40$). *Conclusions:* Treatment strategies for EOC applied to PPC apparently led to similar survival patterns among the two patient groups. Cytoreductive surgery combined with pre/postoperative platinum-containing chemotherapy may be effective for PPC patients.

Key words: Primary peritoneal cancer; Epithelial ovarian cancer; Cytoreductive surgery; Platinum-containing chemotherapy.

Introduction

Primary peritoneal carcinoma (PPC) was first described by Swerdlow in 1959 [1]. PPC is a malignancy with diffuse involvement of the peritoneal surfaces, involving mostly the omentum with minimal or no ovarian involvement [1, 2]. Histopathologic and clinical similarities have been reported between PPC and ovarian serous carcinoma [3–6]. PPC has been reported in women who underwent oophorectomy for benign disease or prophylaxis [7]. Both differences [3, 8, 9] and molecular similarities [10] have been reported between PPC and ovarian serous carcinoma, although the clinicopathologic features and etiology of PPC are somewhat obscure. As PPC begins from intra-abdominal disease, it is at Stage ≥ 3 at presentation, which is the main reason for its poor five-year survival rate. Management of PPC shadows that of epithelial ovarian carcinoma (EOC), with initial debulking surgery followed by adjuvant platinum-containing chemotherapy. However, optimal cytoreduction is more difficult in PPC than in EOC, as PPC tends to have widespread peritoneal disease.

This study investigated clinical findings, treatment, and prognosis of patients with PPS compared with those with EOC, to improve recognition of this disease.

Materials and Methods

Patients

This retrospective study included 14 patients with PPC and 219 patients with EOC, who were treated at the present hospital between January 2005 and December 2012. Each patient provided written informed consent. Both sets of patients were treated with debulking surgery combined with adjuvant/neoadjuvant chemotherapy.

Definitions

PPC was defined by the following Gynecologic Oncology Group's (GOG'S) inclusionary criteria for PPC [11]: (1) both ovaries must be either physiologically normal in size or enlarged by a benign process; (2) involvement in extraovarian sites must be greater than involvement on the surface of either ovary; (3) microscopically, the ovarian component must be one of the following: (a) non-existent, (b) confined to ovarian surface epithelium with no evidence of cortical invasion, (c) involve ovarian surface epithelium and underlying cortical stroma but with no given tumor size ≥ 5 × 5 mm, or (d) any tumor < 5 × 5 mm within ovarian substance associated with or without surface disease; (4) histological and cytological tumor characteristics must be predominantly of the serous type, i.e., similar or identical to that seen in ovarian serous papillary adenocarcinoma. Diagnoses were based on original pathologic reports, reviewed by two certified pathologists.

Data and treatment

Clinical data were obtained from medical records of each patient included age at diagnosis, presenting symptoms, operative findings, whether primary cytoreductive surgery was optimal or suboptimal, preoperative CA125 levels, International Federation of Gynecology and Obstetrics (FIGO) stage based on clinical/surgical examinations and cytology results, type of chemotherapy, number of

Revised manuscript accepted for publication December 30, 2013

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XXXVI, n. 1, 2015
doi: 10.12892/ejgo2573.2015

7847050 Canada Inc.
www.irog.net

Table 1. — *Clinical characteristics of 14 patients with PPC.*

Case	Age	Histological type	Stage	Chief complaint	CA125*	NAC	Surgery	Prognosis
1	65	Serous adenoca	IIIc	Abdominal distention	1981	–	Suboptimal	NED
2	65	Serous adenoca	IIIc	Abdominal distention	9222	–	Suboptimal	NED
3	68	Serous adenoca	IIIc	Abdominal distention	134	–	Suboptimal	NED
4	74	Serous adenoca	IIIc	Appetite loss	1536	–	Optimal	NED
5	69	Serous adenoca	IIIc	Abdominal distention	577	–	Suboptimal	NED
6	68	Serous adenoca	IIIc	Abdominal distention	9222	–	Suboptimal	AWD
7	61	Serous adenoca	IIIb	Abdominal distention	1885	+	Optimal	AWD
8	65	Serous adenoca	IIIc	Abdominal distention	1443	+	Optimal	AWD
9	65	Serous adenoca	IIIc	Abdominal distention	57030	–	Suboptimal	AWD
10	43	Poorly differentiated	IIIc	Abdominal distention	710	–	Suboptimal	AWD
11	65	Serous adenoca	IIIc	Deterioration of dermatomyositis	1108	-	Suboptimal	DOD
12	63	Serous adenoca	IIIc	Abdominal distention	338	–	Suboptimal	DOD
13	58	Serous adenoca	IIIc	Genital bleeding	270	–	Suboptimal	DOD
14	51	Serous adenoca	IIIb	No symptom	249	–	Optimal	DOD

*U/ml; AWD: alive with disease; DOD: dead of disease; NED: no evidence of disease; Serous adenoca: serous adenocarcinoma.

Table 2. — *Clinical characteristics of PPC and EOC patients.*

	PPC (n=14)	EOC (n=219)	*p*
Mean age (y)	62.6 ± 8	56.3 ± 11.3	0.045
FIGO stage			0.001
I	0 (0%)	82 (37.4%)	
II	0 (0%)	20 (9.1%)	
III	14 (100%)	94 (42.9%)	
IV	0 (0%)	23 (10.5%)	
Histological type			< 0.001
Serous adenoca	12 (85.7%)	60 (27.4%)	
Mucinous adenoca	0 (0%)	37 (16.9%)	
Endometrioid adenoca	0 (0%)	46 (21.0%)	
Clear cell adenoca	0 (0%)	65 (29.7%)	
Poorly differentiated	2 (14.3%)	11(5.0%)	
Mean CA 125 (U/ml)	5,616.8	2,458.2	NS

Adenoca: adenocarcinoma; FIGO: International Federation of Gynecology and Obstetrics; NS: not significant.

Table 3. — *Clinical characteristics of patients with PPC, and patients with Stage III EOC with serous adenocarcinoma or poorly differentiated adenocarcinoma as histologic type.*

	PPC (n=14)	EOC (n=219)	*p*
Mean age (y)	62.6 ± 8.4	58.8± 12	NS
FIGO stage			NS
IIIa	0 (0%)	1 (2.2%)	
IIIb	2 (14.3%)	3 (6.5%)	
IIIc	12 (85.7%)	42 (9.1%)	
Histological type			NS
Serous adenoca	12 (85.7%)	38 (82.6%)	
Poorly differentiated	2 (14.3%)	8 (17.4%)	
Mean CA 125 (U/ml)	5,616.8	6,195.4	NS

Adenoca: adenocarcinoma; FIGO: International Federation of Gynecology and Obstetrics; NS: not significant.

courses, date of tumor recurrence or progression, date of last follow-up, and date of death. Optimal surgery was defined as presence of residual tumor < 1.0 cm in size after surgery. Suboptimal surgery was defined as presence of residual tumor ≥ 1.0 cm after surgery. Tumors were staged according to FIGO criteria for ovarian cancer. Treatment for both PPC and EOC usually consisted of initial debulking surgery followed by adjuvant chemotherapy; patients who seemed unsuitable for initial surgery received a few cycles of neoadjuvant chemotherapy. Standard surgery included total hysterectomy with bilateral salpingo-oophorectomy, partial omentectomy, and lymphadenectomy. For those with large residual disease and/or poor medical condition at surgery, lymphadenectomies were omitted. The chemotherapy regimen consisted of paclitaxel + carboplatin or docetaxel + carboplatin. The authors compared characteristics and prognosis of 14 patients with PPC to those of 219 patients with EOC; the 14 patients with PPC were also compared with 41 patients with Stage III EOC, which histologically shows as serous adenocarcinoma or poorly differentiated adenocarcinoma (i.e., the histology type most similar to PPC).

Statistics

Clinicopathological data were analyzed by Fisher's exact test and the χ^2 test. Survival and disease-free survival probabilities were analyzed using the Kaplan–Meier method. SPSS 21.0 was used for data analyses. A $p < 0.05$ was considered to be significant.

Results

Clinical characteristics of all 14 patients with PPC are detailed in Table 1. Among presenting complaints, ten patients (71.4%) had abdominal distension, and one each (7.1%) had abnormal genital bleeding, appetite loss, or deterioration of dermatomyositis; one (7.1%) had no symptoms but was singled out in a screening. Four of the 14 (28.6%) could undergo optimal surgery; two (14.3%) had a few cycles of neoadjuvant chemotherapy consisting of paclitaxel + carboplatin before undergoing optimal surgery. Follow-up range for PPC patients was 11–96 months (median: 55 months), with 9/14 (64.3%) patients followed for at least five years or until death. By August 31st, 2013, 5/14 (35.7%) were alive free of disease, 5/14 (35.7%) were alive with disease, and 4/14 (28.6%) had died of disease.

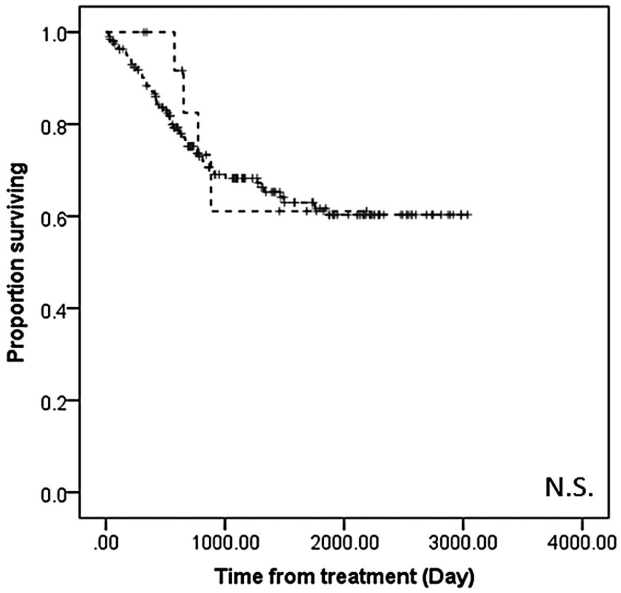

Figure 1. — Kaplan–Meier estimates of overall survival. Dashed line: PPC patients; solid line: EOC patients.

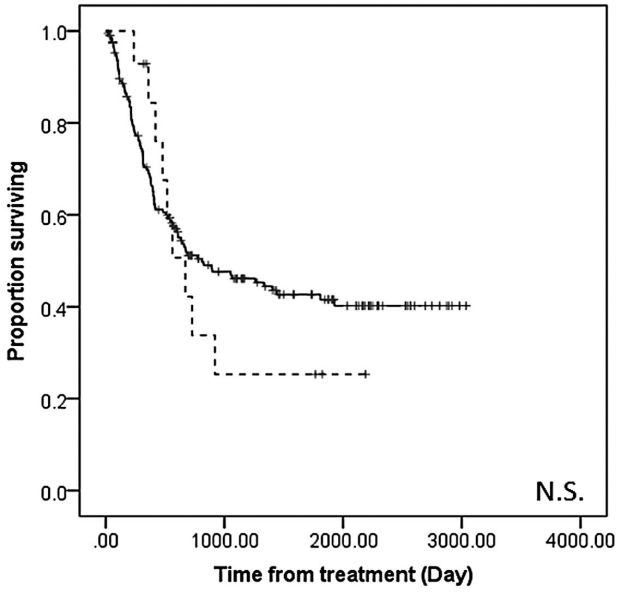

Figure 2. — Kaplan–Meier estimates of time to recurrence. Dashed line: PPC patients; solid line: EOC patients.

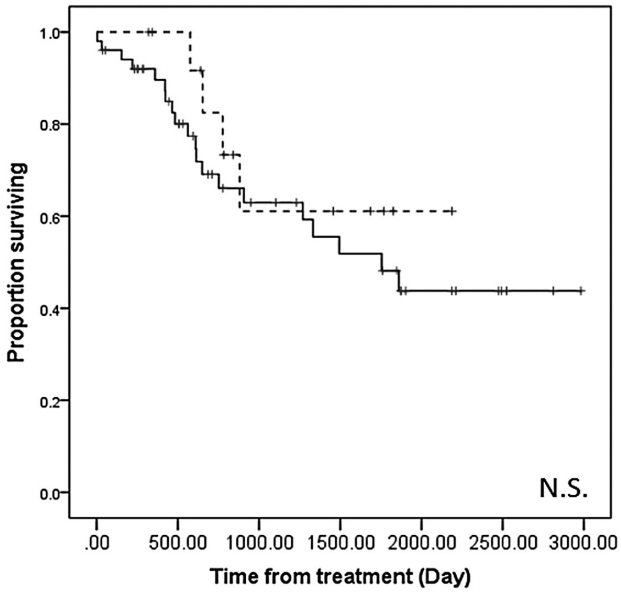

Figure 3. — Kaplan–Meier estimates of overall survival. Dashed line: PPC patients; solid line: Stage III EOC patients with serous adenocarcinoma or poorly differentiated adenocarcinoma as histologic type.

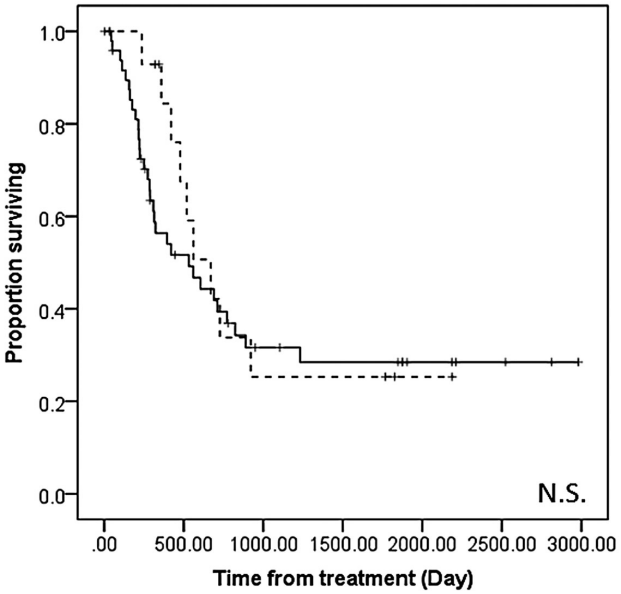

Figure 4. — Kaplan–Meier estimates of time to recurrence. Dashed line: PPC patients; solid line: Stage III EOC patients with serous adenocarcinoma or poorly differentiated adenocarcinoma as histologic type.

The mean age of patients with PPC (62.6 ± 8.4 years) was significantly older than for patients with EOC (56.3 ± 11.3 years, $p = 0.045$; Table 2). All PPC patients had Stage III disease; whereas among the EOC patients, 82 had Stage I, 20 had Stage II, 94 had Stage III, and 23 had Stage IV ($p = 0.001$). Among histologic types, patients with PPC had 12 serous adenocarcinomas and two poorly differentiated adenocarcinoma; those with EOC had 60 serous adenocarcinomas, 37 mucinous adenocarcinomas, 46 endometrioid adenocarcinomas, 65 clear-cell adenocarcinomas and 11 poorly differentiated adenocarcinomas ($P<0.001$). Initial CA125 levels did not differ significantly.

Between PPC patients and those stage III EOC patients with serous adenocarcinoma or poorly differentiated adenocarcinoma as histologic type, mean age, clinical stage, histologic type and initial CA125 level were not significantly different (Table 3).

The two groups did not significantly differ in overall survival ($P = 0.78$; Figure 1) or disease-free survival ($P = 0.73$; Figure 2). Five-year survival was 61.1% for PPC and 60.3% for EOC. Median time to recurrence was 670 days for PPS and 811 days for EOC.

Overall survival of patients with PPC and those with Stage III EOC and serous adenocarcinoma or poorly differentiated adenocarcinoma histology did not significantly differ ($p = 0.40$; Figure 3); five-year survival was 61.1% for PPC and 43.8% for Stage III EOC. Disease-free survival did not significantly differ between PPC patients and Stage III EOC patients ($p = 0.55$; Figure 4). Median time to recurrence was 670 days for PPS and 532 days for Stage III EOC.

Discussion

The clinical and histologic features of PPC are similar to those of EOC, and patterns of spreading, response to chemotherapy, and prognoses are almost the same as EOC [11, 12]. However, PPC can occur after prophylactic oophorectomy, and has been encountered even in a male patient [13]. Histologically, most PPS has serous adenocarcinoma, but other types have also been reported [14, 15]. The etiology, pathogenesis, cell of origin, and clinicopathologic features of PPC remain obscure.

In this study, compared with all EOC patients, PPC patients were older at diagnosis and all had advanced disease (Stage III), which concords with previous studies in terms of age [16, 17] and general disease stage [15]. As PPC begins from intra-abdominal disease, presenting stage must be at least III. Serum CA125 level was elevated in all PPC patients, but did not significantly differ from EOC patients. Most PPC patients had serous adenocarcinoma histology; whereas EOC specimens varied (clear-cell carcinoma; 29.7%, serous adenocarcinoma; 27.4%, endometrioid adenocarcinoma; 21.0%, mucinous adenocarcinoma; 16.9%, poorly differentiated adenocarcinoma; 5.0%). Overall survival and progression-free survival did not significantly differ between the two patient groups. About 30% of EOC patients had clear-cell carcinoma, which has a poor prognosis, and about 60% of EOC patients with other than clear-cell carcinoma had Stage ≥3, which explains why the two types had similar prognoses despite all PPS patients having advanced disease.

When PPC patients and patients with Stage III EOC with serous- or poorly-differentiated adenocarcinoma (i.e., the EOC histology most similar to that of PPC) were compared, mean age, clinical stage, histologic type, initial CA125 level, and prognosis did not significantly differ. Comparative prognoses of PPC and EOC are controversial. Some studies report PPC patients to have significantly worse survival rates than those with EOC [18, 19]; others report that their survival rates are not significantly different [14, 15, 18, 20].

Management of PPC has shadowed that of EOC, with initial debulking surgery followed by adjuvant platinum-containing chemotherapy. Although degree of cytoreductive surgery is reportedly a significant prognostic factor in PPC [21], optimal cytoreduction is more difficult in PPC than in EOC, as PPC tends to develop widespread peritoneal disease. In this study, the optimal cytoreductive rate was only 28.6%, but has been reported as 33–70% [8, 12, 14, 15, 20]. Only 2/14 of the present patients received neoadjuvant chemotherapy, both of whom then underwent optimal cytoreductive surgery. Neoadjuvant chemotherapy might help achieve higher rates of successful cytoreductive surgery.

A standard treatment for PPC has not been established, although such treatment would appear to be similar to that for EOC, as is its prognosis.

References

[1] Swerdlow M.: "Mesothelioma of the pelvic peritoneum resembling papillary cystadenocarcinoma of the ovary; case report". *Am. J. Obstet. Gynecol.*, 1959, *77*, 197.

[2] August C.Z., Murad T.M., Newton M.: "Multiple focal extraovarian serous carcinoma". *Int. J. Gynecol. Pathol*., 1985, *4*, 11.

[3] Bhuyan P., Mahapatra S., Mahapatra S., Sethy S., Parida P., Satpathy S.: "Extraovarian primary peritoneal papillary serous carcinoma". *Arch. Gynecol. Obstet.*, 2010, *281*, 561.

[4] Truong L.D., Maccato M.L., Awalt H., Cagle P.T., Schwartz M.R., Kaplan A.L.: "Serous surface carcinoma of the peritoneum: a clinicopathologic study of 22 cases". *Hum. Pathol*., 1990, *21*, 99.

[5] Resta L., Maiorano E., Zito F.A., Faggiano F., Loizzi P., Ferreri R., Borraccino V., Conte R., Lucisano F.: "Multifocal extraovarian serous carcinoma. A histochemical and immunohistochemical study". *Eur. J. Gynecol. Oncol*., 1988, *9*, 474.

[6]. Raju U., Fine G., Greenawald K.A., Ohorodnik J.M.: "Primary papillary serous neoplasia of the peritoneum: a clinicopathologic and ultrastructural study of eight cases". *Hum. Pathol.*, 1989, *20*, 426.

[7] Tobacman J.K., Greene M.H., Tucker M.A., Costa J., Kase R., Fraumeni J.F. Jr.: "Intra-abdominal carcinomatosis after prophylactic oophorectomy in ovarian-cancer-prone families". *Lancet*, 1982, *2*, 795.

[8] Eltabbakh G.H., Piver M.S., Natarajan N., Mettlin C.J.: "Epidemiologic differences between women with extraovarian primary peritoneal carcinoma and women with epithelial ovarian cancer". *Obstet. Gynecol*., 1998, *91*, 254.

[9] Kowalski L.D., Kanbour A.I., Price F.V., Finkelstein S.D., Christopherson W.A., Seski J.C., Naus G.J., Burnham J.A., Kanbour-Shakir A., Edwards R.P.: "A case-matched molecular comparison of extraovarian versus primary ovarian adenocarcinoma". *Cancer*, 1997, *79*, 1578.

[10] Chen L.M., Yamada S.D., Fu Y.S., Baldwin R.L., Karlan B.Y.: "Molecular similarities between primary peritoneal and primary ovarian carcinomas". *Int. J. Gynecol. Cancer.*, 2003, *13*, 749.

[11] Bloss J.D., Liao S.Y., Buller R.E., Manetta A., Berman M.L., McMeekin S., Bloss L.P., Di Saia P.J.: "Extraovarian peritoneal serous papillary carcinoma: a case-control retrospective comparison to papillary adenocarcinoma of the ovary". *Gynecol. Oncol.*, 1993, *50*, 347.

[12] Killackey M.A., Davis A.R.: "Papillary serous carcinoma of the peritoneal surface: matched-case comparison with papillary serous ovarian carcinoma". *Gynecol. Oncol.*, 1993, *51*, 171.
[13] Shah I.A., Jayram L., Gani O.S., Fox I.S., Stanley T.M.: "Papillary serous carcinoma of the peritoneum in a man: a case report". *Cancer*, 1998, *82*, 860.
[14] Dalrymple J.C., Bannatyne P., Russell P., Solomon H.J., Tattersall M.H., Atkinson K., *et al.*: "Extraovarian peritoneal serous papillary carcinoma. A clinicopathologic study of 31 cases". *Cancer*, 1989, *64*, 110.
[15] Fromm G.L., Gershenson D.M., Silva E.G.: "Papillary serous carcinoma of the peritoneum". *Obstet. Gynecol.*, 1990, *75*, 89.
[16] Jordan S.J., Green A.C., Whiteman D.C., Moore S.P., Bain C.J., Gertig D.M., Webb P.M.: "Serous ovarian, fallopian tube and primary peritoneal cancers: a comparative epidemiological analysis". *Int. J. Cancer*, 2008, *122*, 1598.
[17] Fowler J.M., Nieberg R.K., Schooler T.A., Berek J.S.: "Peritoneal adenocarcinoma (serous) of Müllerian type: a subgroup of women presenting with peritoneal carcinomatosis". *Int. J. Gynecol. Cancer*, 1994, *4*, 43.
[18] Gooneratne S., Sassone M., Blaustein A., Talerman A.: "Serous surface papillary carcinoma of the ovary: a clinicopathologic study of 16 cases". *Int. J. Gynecol. Pathol.*, 1982, *1*, 258.
[19] Rothacker D., Möbius G.: "Varieties of serous surface papillary carcinoma of the peritoneum in northern Germany: a thirty-year autopsy study". *Int. J. Gynecol. Pathol*., 1995, *14*, 310.
[20] Ransom D.T., Patel S.R., Keeney G.L., Malkasian G.D., Edmonson J.H.: "Papillary serous carcinoma of the peritoneum. A review of 33 cases treated with platin-based chemotherapy". *Cancer*, 1990, *66*, 1091.
[21] Eltabbakh G.H., Werness B.A., Piver S., Blumenson L.E.: "Prognostic factors in extraovarian primary peritoneal carcinoma". *Gynecol. Oncol*., 1998, *71*, 230.

Address reprint requests to:
T. FUKUDA, M.D.
Department of Obstetrics and Gynecology,
Osaka City University Graduate School of Medicine,
1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585 (Japan)
e-mail: takeshif@med.osaka-cu.ac.jp