Cancer Center Hospital); Hiroaki Iwase (National Hospital Organization Nagoya Medical Center); Masashi Yamamoto (Nagoya Ekisaikai Hospital); Atsushi Watanabe (Anjo Kosei Hospital); Hiroshi Saito (Aichi Cancer Center Aichi Hospital); Yoshimasa Tanikawa (Kamo Hospital); Takuya Ikeda (Yokkaichi Municipal Hospital); Hidenori Ibata (National Hospital Organization Mie Chuo Medical Center); Hiroshi Hara (Kyoto Second Red Cross Hospital); Taketoshi Shimada (Kyoto Prefectural University of Medicine Hospital); Yoshiyuki Sasaki (National Hospital Organization Kyoto Medical Center); Mitsuo Nonomura (Kyoto-Katsura Hospital); Atsuo Sato (National Hospital Organization Minami-Kyoto Hospital); Shinzo Kudo (Osaka City University Hospital); Takashi Yana (Federation of National Public Service Personnel Mutual Aid Associations Otemae Hospital); Fumio Imamura (Osaka Medical Center for Cancer and Cardiovascular Diseases); Tatsuya Ioka (Osaka Medical Center for Cancer and Cardiovascular Diseases); Michiyuki Usami (Osaka Medical Center for Cancer and Cardiovascular Diseases); Shinji Atagi (National Hospital Organization Kinki-Chuo Chest Medical Center); Kaoru Matsui (Osaka Prefectural Medical Center for Respiratory and Allergic Diseases); Kazuhiko Nakagawa (Kinki University Hospital); Tatsuhiko Kashii (Osaka City General Hospital); Yoshihiro Nishimura (Kobe University Hospital); Takashi Nishimura (Kobe City General Hospital); Shunichi Negoro (Hyogo Medical Center for Adults); Shigemichi Iwae (Hyogo Medical Center for Adults); Nobuyuki Katakami (Institute of Biomedical Research and Innovation); Shuichi Yano (National Hospital Organization Matsue National Hospital); Takeshi Isobe (Shimane University Hospital); Kenichi Gemba (Okayama Rosai Hospital); Minoru Fukuda (Kawasaki Medical School Hospital); Takuo Shibayama (National Hospital Organization Minami-Okayama Medical Center); Isao Murakami (National Hospital Organization Higashihiroshima Medical Center); Akihito Yokoyama (Hiroshima University Hospital); Yukio Kimura (National Hospital Organization Iwakuni Clinical Center); Jun Araki (Yamaguchi Grand Medical Center); Keisuke Aoe (National Hospital Organization Sanyo Hospital); Tetsu Shinkai (National Hospital Organization Shikoku Cancer Center); Fumitaka Ogushi (National Hospital Organization Kochi National Hospital); Sadamu Ando (Kitakyushu Municipal Medical Center); Hiroshi Matsuura (Saiseikai Fukuoka General Hospital); Kentaro Watanabe (Fukuoka University Hospital); Akito Yamaguchi (Harasanshin Hospital); Koichi Takayama (Kyushu University Hospital); Hiroshi Aso (National Hospital Organization Fukuoka National Hospital); Masayuki Kawasaki (National Hospital Organization Fukuoka-Higashi Medical Center); Shinichiro Hayashi (Saga University Hospital); Hiroaki Kikukawa (National Hospital Organization Kumamoto Medical Center); Mitsuhiro Matsumoto (Kumamoto University Hospital); Eiji Moriyama (National Hospital Organization Kumamoto Saishunso National Hospital); Hideki Yokoyama (National Hospital Organization Beppu Medical Center); Mutsuo Kuba (National Hospital Organization Okinawa National Hospital).

Acknowledgments

This study was designed and funded by Ono Pharmaceutical Co., Ltd, and Merck & Co., Inc., the manufacturer of aprepitant.

Disclosure Statement

The authors have no conflict of interest.

References

1 Grunberg SM, Hesketh PJ. Control of chemotherapy-induced emesis. *N Engl J Med* 1993; **329**: 1790–6.
2 Bender CM, McDaniel RW, Murphy-Ende K *et al.* Chemotherapy-induced nausea and vomiting. *Clin J Oncol Nurs* 2002; **6**: 94–102.
3 Tavorath R, Hesketh PJ. Drug treatment of chemotherapy-induced delayed emesis. *Drugs* 1996; **52**: 639–48.
4 Kris MG, Cubeddu LX, Gralla RJ *et al.* Are more antiemetic trials with a placebo necessary? Report of patient data from randomized trials of placebo antiemetics with cisplatin *Cancer* 1996; **78**: 2193–8.
5 Gralla RJ, Osoba D, Kris MG *et al.* Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. *J Clin Oncol* 1999; **17**: 2971–94. Erratum in: *J Clin Oncol* 1999; **17**: 3860. *J Clin Oncol* 2000; **18**: 3064.
6 de Wit R, Schmitz PIM, Verweij J *et al.* Analysis of cumulative probabilities shows that the efficacy of $5HT_3$ antagonist prophylaxis is not maintained. *J Clin Oncol* 1996; **14**: 644–51.
7 de Wit R, van den Berg H, Burghouts J *et al.* Initial high anti-emetic efficacy of granisetron with dexamethasone is not maintained over repeated cycles. *Br J Cancer* 1998; **77**: 1487–91.
8 Kris MG, Gralla RJ, Tyson LB, Clark RA, Cirrincione C, Groshen S. Controlling delayed vomiting: double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. *J Clin Oncol* 1989; **7**: 108–14.
9 Hesketh PJ, Grunberg SM, Gralla RJ *et al.* The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin–the Aprepitant Protocol 052 Study Group. *J Clin Oncol* 2003; **21**(22): 4112–9. Epub 2003 Oct 14.
10 Poli-Bigelli S, Rodrigues-Pereira J, Carides AD *et al.* Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer* 2003; **97**(12): 3090–8.
11 Chawla SP, Grunberg SM, Gralla RJ *et al.* Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. *Cancer* 2003; **97**(9): 2290–300.
12 Warr DG, Hesketh PJ, Gralla RJ *et al.* Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. *J Clin Oncol* 2005; **23**: 2822–30.
13 American society of clinical oncology, Kris MG, Hesketh PJ, Somerfield MR *et al.* American society of clinical oncology guideline for antiemetics in oncology: update 2006. *J Clin Oncol* 2006; **24**: 2932–47.
14 Roila F, Hesketh PJ, Herrstedt J. Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC). . Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. *Ann Oncol* 2006; **17**: 20–8.
15 NCCN Clinical Practice Guidelines in OncologyTM. Antiemesis V.1. 2007.
16 Warr DG, Grunberg SM, Gralla RJ *et al.* The oral NK_1 antagonist aprepitant for the prevention of acute and delayed chemotherapy-induced nausea and vomiting: pooled data from 2 randomised, double-blind, placebo controlled trials. *Eur J Cancer* 2005; **41**(9): 1278–85.
17 Nygren P, Hande K, Petty KJ *et al.* Lack of effect of aprepitant on the pharmacokinetics of docetaxel in cancer patients. *Cancer Chemother Pharmacol* 2005; **55**(6): 609–16.
18 Loos WJ, de Wit R, Freedman SJ *et al.* Aprepitant when added to a standard antiemetic regimen consisting of ondansetron and dexamethasone does not affect vinorelbine pharmacokinetics in cancer patients. *Cancer Chemother Pharmacol* 2007; **59**(3): 407–12.
19 McCrea JB, Majumdar AK, Goldberg MR *et al.* Effects of the neurokinin$_1$ receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. *Clin Pharmacol Ther* 2003; **74**(1): 17–24.
20 Nakade S, Ohno T, Kitagawa J *et al.* Population pharmacokinetics of aprepitant and dexamethasone in the prevention of chemotherapy-induced nausea and vomiting. *Cancer Chemother Pharmacol* 2008; **63**: 75–83. Epub 2008 Mar 4.

Med Oncol (2010) 27:1371–1377
DOI 10.1007/s12032-009-9389-3

ORIGINAL PAPER

Clinical characteristics and outcomes of women with stage IV endometrial cancer

M. Tanioka · N. Katsumata · Y. Sasajima · S. Ikeda · T. Kato · T. Onda · T. Kasamatsu · Y. Fujiwara

Received: 1 December 2009 / Accepted: 3 December 2009 / Published online: 19 December 2009

Abstract Treatment strategies for patients with stage IV endometrial cancer (EC) remain controversial. Some studies have suggested that optimal cytoreduction improves survival. We retrospectively analyzed the clinical characteristics and outcomes of 41 women with stage IV EC. The results of preoperative cytologic evaluation and biopsy of the endometrium were reviewed by a single pathologist for patients in whom stage IV EC was diagnosed preoperatively. Of the 41 patients with stage IV EC (median age, 62 years), 31 had surgical stage IV disease and 10 had clinical stage IV disease. Twenty-eight patients were diagnosed of stage IV EC before surgery or without surgery. Progression-free survival and overall survival were 10.4 and 21.3 months, respectively. On univariate analysis, grade 1 or 2 endometrioid subtype, 0 or 1 sites of extraperitoneal metastasis, and hormonal therapy were associated with good outcomes. Multivariate analysis revealed that grade 1 or 2 endometrioid subtype ($P = 0.005$, hazard ratio [HR] 0.23 [0.08–0.65]) and 0 or 1 sites of extraperitoneal metastasis ($P = 0.001$, HR 0.24 [0.10–0.57]) were independent predictors of survival. Neither surgery as primary therapy nor optimal cytoreduction was significantly related to overall survival in either the 28 patients in whom stage IV was diagnosed preoperatively or in all 41 patients. In women with stage IV EC, histologic features and extent of disease are more important determinants of outcomes than any kind of treatment. The indication for surgery should be carefully considered in this subset of patients.

Keywords Endometrial cancer · Stage IV · Outcome · Prognostic factor · Endometrioid · Metastatic site · Hormonal sensitivity

M. Tanioka · N. Katsumata · Y. Fujiwara
Division of Breast and Medical Oncology, National Cancer Center Hospital Tokyo, Tsukiji 5-1-1, Chuo-ku, Tokyo, Japan

M. Tanioka (✉)
Department of Medical Oncology, Hyogo Cancer Center, 13-70 Kitaoji-cho, Akashi, Hyogo 673-8558, Japan
e-mail: tanioka@hp.pref.hyogo.jp

Y. Sasajima
Pathology Section, National Cancer Center Hospital Tokyo, Tokyo, Japan

S. Ikeda · T. Kato · T. Onda · T. Kasamatsu
Division of Gynecology, National Cancer Center Hospital Tokyo, Tokyo, Japan

Introduction

Endometrial carcinoma (EC) is one of the most common female pelvic malignancies. The Japanese Gynecologic Oncology Committee estimated that 4,600 new cases were diagnosed in 2005. Stage IV disease accounts for only 6% of all cases (stage IVa, 0.5%; stage IVb, 5.6%). Among patients with stage IV disease, 72% have surgical stage IV disease and 28% have clinical stage IV disease [1]. According to the International Federation of Gynecology and Obstetrics (FIGO) 6th Annual Report on the Results of Treatment in Gynecological Cancer, the rate of survival at 5 years is 19% in patients with stage IV disease, when compared with 80% in all patients with EC [2]. The low incidence and the varied presentations of stage IV EC contribute to difficulties in diagnosis and treatment. Some studies have suggested that optimal cytoreductive surgery improves overall survival [3–6], but conclusive evidence is lacking.

The primary objective of this study was to identify clinically significant prognostic variables in patients with

stage IV EC. The secondary objective was to evaluate the impact of residual disease on survival after cytoreductive surgery in patients with surgical as well as clinical stage IV disease.

Methods

After an institutional review board approval, we retrospectively reviewed the medical charts of patients who were given a diagnosis of EC, excluding carcinosarcoma, between 1995 and 2006 at National Cancer Center Hospital Tokyo, Japan. A total of 41 patients who met the FIGO criteria for stage IV disease were studied. Four patients had Stage IVa disease and 37 had Stage IVb disease. Ten patients did not undergo primary surgical exploration.

Individual patient data were collected from inpatient charts, operative reports, pathology charts, discharge summaries, and outpatient records. We abstracted data on Eastern Cooperative Oncology Group (ECOG) performance status, date of surgery, tumor grade, histologic subtype, and other important findings. Intraoperative data included the sites and distribution of metastatic disease. The results of surgery were obtained from the patients' surgical records and were therefore subject to bias, because the operators' evaluation of the extent of resection was used. For patients in whom resection status was not available, optimal surgery was defined as residual disease less than or equal to 1 cm in maximal diameter, and suboptimal surgery was defined as residual disease greater than 1 cm in maximal diameter.

At initial diagnosis, the primary gynecologist suspected preoperative stage IV disease in 28 patients. These patients had extrapelvic disease or invasion of the rectum on computed tomography, magnetic resonance imaging, and barium enema examination. The results of preoperative cytologic evaluation and biopsy of the endometrium were reviewed by a single pathologist (Dr. Sasajima), who was blinded to all postoperative information.

Statistical analyses were performed using Dr. SPSS II (SPSS Inc., Chicago, IL). Overall survival was defined as the interval from the date of diagnosis to the date of death from any cause. Progression-free survival was defined as the interval from the date of diagnosis to the date of disease recurrence, disease progression, or death from any cause. For the survival analysis, data on surviving patients without disease recurrence or progression were censored on the date of their last follow-up examination. Survival curves were generated using the method of Kaplan–Meier, based on the interval from the date of diagnosis to the date of last contact or death. The log-rank test was used to compare differences between survival curves. Multivariate analysis with a Cox proportional-hazards model was used to identify independent predictors of survival. Models were selected by stepwise forward selection, retaining variables significant at the $\alpha = 0.05$ level for our final model.

Results

The disease stage was surgical stage IV in 31 patients and clinical stage IV in 10. Stage IV disease was clinically diagnosed before surgery in 18 of the 31 patients with surgical stage IV disease. Table 1 shows the clinical characteristics of the 41 patients. Median age was 62 years (range, 38–80 years). Performance status was 0 or 1 in 38 patients. The 3 other patients had a performance status of 2. On postoperative evaluation, the histologic subtype of EC was endometrioid in 23 patients and serous in 7. Four patients were given a diagnosis of "adenocarcinoma" or "carcinoma," and the subtype was not classified; however, primary stage IV EC was diagnosed clinically.

The distribution of disease was evaluated at surgery or by computed tomography. The most common sites of metastasis were the pelvis (68%), pelvic lymph nodes (37%), paraaortic lymph nodes (34%), omentum (31%), and peritoneum (31%). Metastases to multiple extrapelvic regions were documented in 85% of the patients. Metastases to the rectum were pathologically confirmed in 6 patients (15%), 4 of whom had stage IVa disease. Extraperitoneal metastases were documented in 18 patients (44%). Sites of extraperitoneal metastasis included the liver and extra abdominal organs. In this paper, the number of sites of extraperitoneal metastasis was defined as the number of metastasis of lymph nodes and organs. For example, multiple lung metastases or multiple subclavicular lymph node metastases are considered as one site of extraperitoneal metastasis.

As initial treatment, 31 patients underwent surgery, 6 received chemotherapy, 2 received hormonal therapy, and 1 received radiotherapy. The remaining patient died of septic shock secondary to pyometra before receiving any treatment.

On examination of biopsy specimens from 28 patients given a preoperative diagnosis of stage IV disease, the histologic subtype was endometrioid in 16 patients and serous in 5 (Table 2). Four specimens were not assessable.

Surgical results

Thirty-one patients experienced surgery as primary treatment and 2 experienced surgery after neoadjuvant chemotherapy. Total 33 patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, staging, and maximal cytoreduction as indicated. Three patients underwent low anterior resection of the

Table 1 Patient characteristics ($n = 41$)

Age (years) median (range)	62 (38–80)
PS 0/1/2	15/23/3
Histology	No.
Endometrioid adenocarcinoma (grade 1/2/3)	24 (6/8/10)
Serous adenocarcinoma	8
Small cell carcinoma	2
Poorly differentiated adenocarcinoma	2
Others*	5
Distribution of disease	
Genital organs	28
Pelvic lymph nodes	15
Paraaortic lymph nodes	14
Omentum	13
Peritoneum	13
Rectum	6
Diaphragm	3
Extraperitoneal metastasis	
Lymph node**	9
Lung	8
Liver	4
Bone	3
Spleen	2
Other (brain, eye)	2
Initial treatment	
Surgery	31
Chemotherapy	6
Hormonal therapy	2
Radiotherapy	1
No therapy	1

* Clear cell carcinoma, neuroendocrine carcinoma, mucinous adenocarcinoma, adenocarcinoma, carcinoma

** Supraclavicular, neck, mediastinum, groin lymph

Table 2 Histologic subtypes in 28 patients with a preoperative diagnosis of stage IV disease

Histology	$n = 28$ No.
Endometrioid adenocarcinoma	16
Grade 1/2/3	5/4/7
Serous adenocarcinoma	5
Carcinosarcoma	1
Adenocarcinoma	2
Not accessable	4

rectosigmoid colon to achieve complete resection of locally advanced pelvic disease. Overall, primary surgery was completed with optimal disease status in 23 (69%) of the 33 patients.

Chemotherapy

A total of 29 patients (71%) received chemotherapy. Six patients (15%) received chemotherapy as primary treatment, including 2 who received neoadjuvant chemotherapy in a clinical-trial setting. Twenty patients (49%) received adjuvant chemotherapy, including 8 in whom residual tumor was the target lesion. All patients were given platinum-based regimens. Twenty-three patients (56%) received doxorubicin and cisplatin with or without cyclophosphamide (CAP or AP). Five patients (12%) received carboplatin and paclitaxel, given weekly or every 3 weeks.

Hormonal therapy

All 7 patients (18%) who received hormonal therapy were postmenopausal women and had progesterone receptor positive tumors on immunohistochemical analysis and were given medroxyprogesterone acetate (MPA) at a dose of 600 mg three times daily. Two patients received MPA as primary therapy. Three of 5 patients with a preoperative histologic diagnosis of grade 1 or 2 endometrioid subtype responded to hormonal therapy (Table 3).

Radiation

A total of 7 patients (18%) received whole pelvic radiation, with or without periaortic radiation. Four patients with stage IVb disease received postoperative radiotherapy.

Analysis of all 41 patients with stage IV disease

Median progression-free survival and overall survival in the study group as a whole were 10.4 months (range 0.6–79.7 months) and 21.3 months (range 1.3–115.4 months), respectively. Twenty-eight patients had died and 13 were alive at the time of chart review.

Grade 1 or 2 endometrioid subtype and 0 or 1 sites of exraperitoneal metastasis were predictors of survival on univariate analysis (Table 4). Hormonal therapy was also significantly related to better survival. In contrast, neither chemotherapy nor whole pelvic radiotherapy was a significant predictor of survival. There was no association of survival with surgery as primary treatment or surgery as a whole. Optimal cytoreduction also was not significantly related to survival ($P = 0.066$).

Multivariate analysis was used to simultaneously examine independent effects of prognostic factors on survival in all 41 patients. Variables tested for inclusion in the model were age, performance status, 0 or 1 sites of extraperitoneal metastasis, grade 1 or 2 endometrioid subtype,

Table 3 Hormonal therapy

No.	Age	Histology at diagnosis	Grade	Surgery	Role of therapy	Response	Survival (months)
1	52	Endometrioid	1	+	Palliative	CR	115.4**
2	68	Endometrioid	1	+	Palliative	CR	84.0**
3	55	Endometrioid	1	+	Adjuvant	SD*	52.6
4	61	Endometrioid	2	–	Primary	PR	33.6**
5	60	Endometrioid	2	–	Palliative	SD	6.4
6	80	Endometrioid	3	–	Primary	PD	35.3**
7	65	Not accessale		+	Palliative	SD	15.0**

* The patient had residual tumor

** Alive

Table 4 Univariate analysis of study group as a whole ($n = 41$)

	Factor	No.	Survival	
			Median (months)	*P*
Age	>60	20	14.8	0.65
	≦60	21	22.7	
PS	0	15	19.8	0.72
	1–4	26	22.7	
Stage	IVa	4	(*)	0.11
	IVb	37	17.3	
Histology	Endometrioid grader 1or 2	14	(*)	0.0001
	Other	27	11.9	
Extraperitoneal sites	0–1	33	24.8	>0.0001
	2–4	8	3.5	
Liver metastasis	+	4	6.4	0.09
	–	37	22.7	
Lung metastasis	+	8	6.4	0.12
	–	33	24.7	
Surgery	+	33	22.7	0.33
	–	8	6.4	
Primary therapy	Surgery	31	22.7	0.32
	Other	10	17.3	
Residual disease	≦1 cm (optimal)	23	25.9	0.066
(operative cases)	>1 cm (suboptimal)	10	11.7	
Chemotherapy	+	29	21.3	0.36
	–	12	19.8	
Hormonal therapy	+	7	(*)	0.042
	–	34	17.3	
Whole abdominal radiation	+	7	12.6	0.70
	–	34	22.7	

(*) Median survival was not reached

hormonal therapy, and surgery as primary treatment. After controlling for these factors, grade 1 or 2 endometrioid subtype ($P = 0.001$, hazard ratio [HR] 0.19 [0.07–0.52]) and 0 or 1 sites of extraperitoneal metastasis ($P = 0.001$, HR 0.24 [0.10–0.57]) retained significance as independent predictors of good outcomes. Surgery as primary treatment was not a significant predictor of survival.

Analysis of 28 patients with a preoperative diagnosis of stage IV disease

These 28 patients were diagnosed of stage IV EC before surgery or without surgery. Similar to the result of all patients with stage IV disease, univariate analysis revealed that grade 1 endometrioid subtype, 0 or 1 sites of

Table 5 Univariate analysis of patients with a peroperative diagnosis of stage IV disease ($n = 28$)

	Factor	No.	Survival	
			Median (months)	*P*
Age	>60	17	17.3	0.38
	≦60	11	26.2	
PS	0	7	11.7	0.10
	1–4	21	24.7	
Stage	IVa	4	(*)	0.10
	IVb	24	15.0	
Histology	Endometrioid grade 1	5	(*)	0.006
	Other	23	15.0	
Extraperitoneal sites	0–1	20	24.8	>0.0001
	2–4	8	3.5	
Liver metastasis	+	4	6.4	0.12
	–	24	22.7	
Lung metastasis	+	8	6.4	0.20
	–	28	24.7	
Surgery	+	20	22.7	0.42
	–	8	6.4	
Primary therapy	Surgery	18	22.7	0.38
	Other	10	17.3	
Residual disease	≦1 cm (optimal)	13	24.7	0.46
(operative cases)	>1 cm (suboptimal)	7	11.6	
Chemotherapy	+	20	17.3	0.08
	–	8	(*)	
Hormonal therapy	+	7	(*)	0.028
	–	21	17.3	
Whole abdominal radiation	+	5	17.3	0.75
	–	23	22.7	

(*) Median survival was not reached

extraperitoneal metastasis, and hormonal therapy were predictors of survival in patients with a preoperative diagnosis of stage IV disease. Surgery as primary treatment (for 18 patients) and optimal cytoreduction were not significantly related to survival (Table 5).

Long-term or short-term survivors

While 7 patients survived for 48 months or longer, 7 patients survived for only 6 months or shorter. Their clinical characteristics are summarized in Table 6. Age and performance status were similar in both groups. At the last follow-up examination, all long-term survivors were alive: 3 were alive without disease and 4 were alive with disease. All long-term survivors had only 0 or 1 site of extraperitoneal metastasis, whereas 5 of the short-term survivors had 2 or more sites of extraperitoneal metastasis. Grade 1 or 2 endometrioid adenocarcinoma was diagnosed in 5 of the long-term survivors, but in only 1 of the short-term survivors.

Discussion

We believe that our study is one of the large retrospective series to evaluate clinical outcomes specifically in patients with stage IV EC compared with past studies [3–5] because of their rarity. Our findings suggest that cytoreductive surgery may not improve survival among patients with a preoperative diagnosis of stage IV EC.

Because of the rarity of stage IV EC, prognostic factors and treatment strategies remain unclear. Alvarez et al. [7] studied 356 patients with advanced (stage III and IV) EC and suggested that a combination of adjuvant chemotherapy and radiation improves survival. However, patients with stage IV disease accounted for only about one-third of their study group, and results were not reported separately for this stage. Several other studies have assessed treatment strategies for advanced EC, but patients with stage III disease far outnumbered those with stage IV disease [8–10].

Table 6 Characteristics of long- and short-term surviors

	Age	PS	Stage	Histology	Grade	Number of extraperitoneal sites	Survival (months)	Dead or alive
Long-term survivors								
1	49	2	IVa	Endometrioid	1	0	115.4	AWD*
2	67	1	IVb	Endometrioid	1	1	84.0	AWD*
3	51	1	IVb	Endometriod	1	0	79.9	AOD*
4	66	0	IVb	Endometrioid	3	0	66.7	AWD*
5	63	1	IVb	Endometrioid	2	0	52.6	AWD*
6	52	0	IVb	Endometrioid	2	0	51.7	AOD*
7	56	1	IVa	Serous		0	49.6	AOD*
Short-term survivors								
1	53	1	IVb	Adenocarcinoma		4	1.3	Dead
2	58	1	IVb	Neuroendocrine		4	1.7	Dead
3	49	0	IVb	Endometrioid	3	2	3.1	Dead
4	64	1	IVb	Small cell		0	3.3	Dead
5	48	1	IVb	Small cell		4	3.5	Dead
6	62	0	IVb	Clear cell		0	6.3	Dead
7	60	1	IVb	Endometrioid	1	3	6.4	Dead

* *AWD* alive with diesase, *AOD* alive withot disease

In our study of 41 patients with stage IV EC, grade 1 or 2 endometrioid subtype and 0 or 1 sites of extraperitoneal metastasis were independent predictors of good outcomes. Hormonal therapy was also related to survival, whereas surgery as primary therapy and optimal surgery were not. Our results suggest that histologic features and extent of disease are more important determinants of outcomes than any kind of treatment and raise the question of whether surgery is justified in all patients with stage IV EC.

The presence of very short- and long-term survivors in our study suggests that stage IV disease is heterogeneous and that therapy needs to be customized for individual patients. Ideally, a randomized controlled study should be performed to objectively determine whether primary optimal surgery improves outcomes in patients with a preoperative diagnosis of stage IV EC when compared with a control group not receiving surgery. However, the very low incidence of stage IV EC would result in slow patient accrual, making such a clinical trial impractical. Moreover, the results of such a long-term trial would be subject to the effects of many confounding factors, such improvements in diagnostic and treatment techniques. Retrospective studies of course also have major limitations, but are currently considered the best means of comparing treatment outcomes in this rare disease.

Although the role of surgery is well established in early-stage EC, its role in stage IV disease remains controversial. Some studies have concluded that the residual volume of disease after primary surgery influences survival [3–6], but prospective, randomized controlled trials are lacking. The mean number of extraperitoneal metastatic sites at preoperative diagnosis was 0.1 in patients who underwent optimal surgery, 1.0 in those who underwent suboptimal surgery, and 2.3 in those who did not undergo surgery. Given this difference in the prevalence of distance metastasis, the survival of the patients who underwent optimal surgery would most likely have been longer than that of the patients who underwent suboptimal surgery, even if no surgery had been performed. If the sample size of our study were larger, surgery would be a significant prognostic factor. However, that result might be affected by several factors such as the extent of the disease, performance status and preoperative histology. Considering these factors, the indication for surgery should be carefully discussed in this subset of patients.

Outcomes of the 28 patients in whom stage IV disease was diagnosed preoperatively were similar to those of the study group as a whole. Neither surgery as primary therapy nor optimal surgery was a significant predictor of survival. However, our results indicated that hormonal therapy improved overall survival in the patients with a preoperative diagnosis of stage IV EC, as well as the study group as a whole. Ramirez et al. reported that the majority (76%) of patients with well-differentiated endometrioid adenocarcinoma who receive conservative treatment with a progestational agent respond to therapy [11]. Furthermore, hormonal therapy is an active treatment with an overall response rate of 27–33% in women with advanced or recurrent EC [12–14]. These results support our finding that 3 of 5 patients with grade 1 or 2 endometrioid subtype responded to hormonal therapy.

Our study had several important limitations. It was retrospective and lacked sufficient patients to allow us to make firm recommendations for any one therapeutic

regimen. And the statistical analyses included both pretreatment and posttreatment factors as prognostic variables. Despite these limitations, some general conclusions can be made. First, grade 1 or 2 endometrioid subtype and 0 or 1 sites of extraperitoneal metastasis appear to be important determinants of survival in patients with stage IV EC. Second, surgery or optimal surgical outcomes might not convey a survival advantage in patients with a preoperative diagnosis of stage IV EC. Finally, hormonal sensitivity might be an important factor when deciding the optimal treatment for women with stage IV disease.

Acknowledgment We thank Marika Hochi, PhD (Kitazato University), for statistical consultation and helpful comments on the article. *Sources of support*: Grants for Cancer Clinical Research (63) from Ministry of Health, Labor and Welfare, Japan.

References

1. Annual report on patients with endometrial cancer in 2005. Gynecologic cancer committee in japan society of obstetrics and gynecology ed. 2005.
2. Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, et al. Carcinoma of the corpus uteri. FIGO 6th annual report on the results of treatment in gynecological cancer. Int J Gynaecol Obstet. 2006;95 Suppl 1:S105–143.
3. Ayhan A, Taskiran C, Celik C, Yuce K, Kucukali T. The influence of cytoreductive surgery on survival and morbidity in stage IVB endometrial cancer. Int J Gynecol Cancer. 2002;12:448–53.
4. Bristow RE, Zerbe MJ, Rosenshein NB, Grumbine FC, Montz FJ. Stage IVB endometrial carcinoma: the role of cytoreductive surgery and determinants of survival. Gynecol Oncol. 2000; 78:85–91.
5. Chi DS, Welshinger M, Venkatraman ES, Barakat RR. The role of surgical cytoreduction in stage IV endometrial carcinoma. Gynecol Oncol. 1997;67:56–60.
6. Goff BA, Goodman A, Muntz HG, Fuller AF Jr, Nikrui N, Rice LW. Surgical stage IV endometrial carcinoma: a study of 47 cases. Gynecol Oncol. 1994;52:237–40.
7. Alvarez Secord A, Havrilesky LJ, Bae-Jump V, Bae-Jump V, Chin J, Calingaert B, et al. The role of multi-modality adjuvant chemotherapy and radiation in women with advanced stage endometrial cancer. Gynecol Oncol. 2007;107:285–91.
8. Bruzzone M, Miglietta L, Franzone P, Gadducci A, Boccardo F. Combined treatment with chemotherapy and radiotherapy in high-risk FIGO stage III-IV endometrial cancer patients. Gynecol Oncol. 2004;93:345–52.
9. Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler J, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a gynecologic oncology group study. J Clin Oncol. 2006;24:36–44.
10. Sutton G, Axelrod JH, Bundy BN, Roy T, Homesley HD, Malfetano JH, et al. Whole abdominal radiotherapy in the adjuvant treatment of patients with stage III and IV endometrial cancer: a gynecologic oncology group study. Gynecol Oncol. 2005; 97:755–63.
11. Ramirez PT, Frumovitz M, Bodurka DC, Sun CC, Levenback C. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. Gynecol Oncol. 2004;95: 133–8.
12. Fiorica JV, Brunetto VL, Hanjani P, Lentz SS, Mannel R, Andersen W. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a gynecologic oncology group study. Gynecol Oncol. 2004;92: 10–4.
13. Singh M, Zaino RJ, Filiaci VJ, Leslie KK. Relationship of estrogen and progesterone receptors to clinical outcome in metastatic endometrial carcinoma: a gynecologic oncology group study. Gynecol Oncol. 2007;106:325–33.
14. Whitney CW, Brunetto VL, Zaino RJ, Lentz SS, Sorosky J, Armstrong DK, et al. Phase II study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma: a gynecologic oncology group study. Gynecol Oncol. 2004;92:4–9.