disease-free interval from initial surgery of 689 days. One vaginal stump recurrence (0.5%) in stage I/II and six cases of locoregional recurrence (vaginal stump: 1, pelvic cavity: 2, external lymph node: 1, pelvic cavity + vaginal stump: 1, pelvic cavity + abdominal cavity: 1, 9.4%) in stage III/IV were recognized (Table. 1). There were four cases of distant recurrence (1.8%) in stage I/ II. The incidence of local recurrence in stage I/II was extremely lower more than expected. The response rate to chemotherapy or radiotherapy for recurrent diseases was 60.0 (9/15) % (Table. 2). Six cases of locoregional recurrence and nine cases of distant recurrence were treated by radiotherapy and chemotherapy, respectively. Disease control rate (complete response: CR/particular response: PR/stable disease: SD) showed 86.7% (13/15). The response rate to chemotherapy or radiotherapy for recurrence disease was comparatively good. The incidence of recurrence by histological examination was 2.3% (3/129) in grade I, 8.9% (9/101) in grade II, 7.4% (2/27) in grade III, 12.5% (2/16) in adenosqamous carcinoma, 37.5% (3/8) in serous adenocarcinoma and 33.3% (1/3) in clear cell adenocarcinoma (Table 3). The incidence of recurrence was more lower in endometrioid adenocarcinoma grade I than in endometrioid grade 2/3, and there was a high incidence of recurrence in the histological subtypes, adenosquamous carcinoma, serous adenocarcinoma, and clear cell adenocarcinoma. Recurrence risk factors by univariate analysis were menopause ($p=0.0099$), histology ($p=0.005$), FIGO stage ($p<0.0001$), myometrial invasion ($p<0.0001$), adnexal metastasis ($p=0.0009$), lymphvascular space invasion ($p<0.0006$), tumor diameter ($p=0.0076$), peritoneal cytology ($p=0.039$), and RLN metastasis ($p=0.0009$) (Table 4). Cervical involvement ($p=0.3092$) was not recognized as a recurrence risk factor. A multivariate analysis showed that menopause ($p=0.029$) and FIGO stage ($p=0.0369$) were the most significant predictors of recurrence (Table 5). The careful follow-up is always required in endometrial carcinoma with the independent risk factors including menopause and FIGO stage III/IV.

Histological type	No. of Patients	Incidence
Endometrial adenocarcinomas		
Grade I	129	3 (2.3)
Grade II	101	9 (8.9)
Grade III	27	2 (7.4)
Adenosquamous carcinomas	16	2 (12.5)
Serous adenocarcinoma	8	3 (37.5)
Clean cell adenocarcinoma	3	1 (33.3)

Table 3. Incidences of recurrence by histological examination

	No. of Patients Total (N)	Recurrence (%)	p-value
Menopause			
Premenopause	87	1 (1.5)	0.0099
Postmenopause	197	19 (9.6)	
Histology			
G1	129	3 (2.3)	0.005
G2, 3 and others	155	17 (10.9)	
Cervical involvement			
Negative	247	16 (6.5)	0.3092
Positive	37	4 (10.8)	
FIGO stage			
I / II	220	5 (2.3)	<0.0001
III/ IV	64	15 (23.4)	
Myometrial invation			
≦1/2	201	5 (2.5)	<0.0001
>1/2	83	15 (18.1)	
Adenexal metastasis			
Negative	265	14 (5.3)	0.0009
Positive	19	6 (31.6)	
Lymph vascular space invasion			
Negative	166	4 (2.4)	<0.0006
Positive	118	16 (13.6)	
Tumor diameter			
≦4cm	171	6 (3.5)	0.0076
>4cm	113	14 (12.4)	
Peritoneal cytology			
Negative	251	13 (5.2)	0.039
Positive	33	7 (21.2)	
RLN metastasis			
Negative	258	14 (5.4)	0.0009
Positive	26	6 (31.6)	

RLN: Retroperitoneal lymph node

Table 4. Recurrence risk factors by univariate analysis in endometrial carcinoma

	p-value	Odd ratio	95%CI
Menopause Premenopause/ Postmenopause	0.029	9.553	1.295-72.449
Histology G1/G2, 3 and others	0.0663	3.253	0.923-11.460
FIGO stage I, II/III, IV	0.0369	4.017	1.088-14.830
Myometrial invasion ≦1/2 / >1/2	0.2452	1.945	0.633-5.974
Lymph vascular space invasion Negative / Positive	0.2128	2.079	0.657-6.576
Tumor diameter ≦4cm / >4cm	0.1629	2.025	0.751-5.458
RLN metastasis Negative / Positive	0.1773	2.245	0.671-7.265

CI: Confidence interval, RLN: Retroperitoneal lymph node.

Table 5. Recurrence risk factors by multivariate analysis in endometrial carcinoma

5. Conclusion

In modified radical hysterectomy, the uterus should be extirpated with the cardinal ligament allowing an extra 1.5-2.0 cm margin of the vaginal wall. The key point of the technique is formation of a ureteral tunnel during the dissection of the anterior layer of the vesicouterine ligament, while lightly pulling the ureter with tweezers, Cooper scissors and ureteral retractors. Modified radical hysterectomy has a broad range of applications, being positioned in between total hysterectomy and radical hysterectomy. This surgical technique has the advantage that postoperative urinary disturbances and other complications are minimized if the surgical candidates are selected appropriately. This surgical procedure could contribute to reduce locoregional recurrence, especially vaginal stump in stage I/II. It is suggested that management of endometrial carcinoma with risk factors by appropriate surgery and adjuvant chemotherapy is very important for preventing both locoregional and distant recurrence. Thus, further application of this technique is expected.

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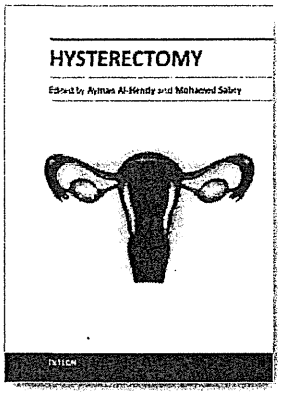

Hysterectomy
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This book is intended for the general and family practitioners, as well as for gynecologists, specialists in gynecological surgery, general surgeons, urologists and all other surgical specialists that perform procedures in or around the female pelvis, in addition to intensives and all other specialities and health care professionals who care for women before, during or after hysterectomy. The aim of this book is to review the recent achievements of the research community regarding the field of gynecologic surgery and hysterectomy as well as highlight future directions and where this field is heading. While no single volume can adequately cover the diversity of issues and facets in relation to such a common and important procedure such as hysterectomy, this book will attempt to address the pivotal topics especially in regards to safety, risk management as well as pre- and post-operative care.

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Clinicopathological prognostic factors and the role of cytoreduction in surgical stage IVb endometrial cancer: A retrospective multi-institutional analysis of 248 patients in Japan

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HIGHLIGHTS

► A total of 248 patients with surgical stage IVb endometrial cancer were reviewed.
► Low grade endometrioid type was a good prognostic factor in this group.
► Cytoreduction and chemotherapy may improve survival even in metastatic disease.

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ABSTRACT

Objective. To evaluate clinicopathological prognostic factors and the impact of cytoreduction in patients with surgical stage IVb endometrial cancer (EMCA).

Methods. The records of 248 patients with stage IVb EMCA who underwent primary surgery including hysterectomy at multiple institutions from 1996 to 2005 were retrospectively analyzed. Data regarding disease distribution, surgical procedures, adjuvant therapy, and survival times were collected. Univariate and multivariate analyses were performed to identify factors associated with overall survival (OS).

Results. The median OS was 24 months. The most common histological types were endometrioid (grade 1: 15%, grade 2: 20%, grade 3: 24%) and serous (17%). The most common sites of intra-abdominal metastases were pelvis (65%), ovaries (58%), omentum (58%), retroperitoneal lymph nodes (52%), and upper abdominal peritoneum (44%). In 93 patients with extra-abdominal metastases, the most common site was the lung ($n=49$). Complete resection of extra-abdominal metastases was achieved in only 13 patients. Complete resection of intra-abdominal metastases was achieved in 101 patients, 52 had ≤1 cm residual disease, and 95 had >1 cm residual disease; the median OS times in these groups were 48, 23, and 14 months, respectively ($p<0.0001$). Multivariate analysis showed that performance status, histology/grade, adjuvant treatment, and intra-abdominal residual disease were independent prognostic factors. Intra-abdominal residual disease was an independent prognostic factor in patients with and without extra-abdominal metastases.

Conclusions. Cytoreductive surgery and adjuvant therapy may improve survival in stage IVb EMCA, particularly in patients with favorable prognostic factors, even in the presence of extra-abdominal metastases.

Introduction

Endometrial cancer (EMCA) is commonly diagnosed at an early stage and has a favorable prognosis [1,2]. The treatment of early-stage EMCA is well established, but the most effective treatment strategies for stage IVb EMCA remain unclear. Stage IVb disease is rare, and the prognosis remains very poor. According to the International Federation of Gynecology and Obstetrics (FIGO) Annual Report, approximately 3% of EMCA patients are classified as stage IV [3]. The 5-year survival rate of surgical stage IVb patients is reportedly 20.1%, and the 4-year survival rate of clinical stage IVb patients is 7.7%. There are no data to

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aid therapeutic decision-making in these patients, and there is no consensus regarding the most effective treatment strategies.

The population of patients with stage IVb EMCA is heterogeneous, as this stage includes patients with upper intra-abdominal dissemination and extra-abdominal metastases. Patients with stage IVb EMCA can therefore be divided into subgroups according to intra- and extra-abdominal disease. However, few published reports have described the specific disease distribution of surgical stage IVb EMCA patients [4–7].

Although the treatment of advanced EMCA is developing in a similar direction to the treatment of ovarian cancer, the role of surgery in the treatment of stage IVb EMCA is unresolved. Recently, several investigators have retrospectively evaluated the role of surgical cytoreduction in patients with stage IVb disease [4,7–12]. A meta-analysis [13] demonstrated that complete cytoreduction is associated with superior overall survival. However, previous studies have been based on populations selected for surgery, with relatively few extra-abdominal metastases. The lung is reportedly the main site of extrapelvic tumor spread, followed by multiple other sites [14]. The effectiveness of intra-abdominal cytoreductive surgery in patients with extra-abdominal metastases considered to be unresectable is unknown.

We hypothesized that clinicopathological characteristics and disease distribution are important when establishing treatment strategies for this disease. We conducted a multicenter study of stage IVb EMCA patients treated in Japan Clinical Oncology Group-related institutions. The primary objective of this study was to clarify the clinicopathological characteristics and disease distribution of surgical stage IVb EMCA patients. The secondary objective was to identify prognostic factors which affect survival and evaluate the impact of cytoreductive surgery on prognosis, including surgery in patients with extra-abdominal metastases.

Methods

Patients

We performed a retrospective review of all patients diagnosed with clinical or surgical FIGO 1988 stage IVb EMCA from 1996 to 2005 who were treated in 30 Gynecologic Cancer Study Group of Japan Clinical Oncology Group-related institutions. Patients with sarcoma were excluded. Patients with stage IVb EMCA who underwent primary surgery including hysterectomy and bilateral salpingo-oophorectomy were eligible.

A case report form was developed using data software (FileMaker-pro Version 6/8) to obtain equivalent data from multiple institutions. The investigation protocol, including the case report form, was approved by the Institutional Review Board of each institution.

Complete clinical data were collected by reviewing inpatient charts, operative records, original pathology reports, and outpatient records from each institution. The demographic data collected included: age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), reproductive history, medical comorbidities, and body mass index (BMI). Pathological information was collected from the pathology reports of the preoperative endometrial biopsy and hysterectomy specimens. The sites and sizes of metastases, surgical procedures, and sites and maximum diameter of residual disease after surgery were collected from radiology reports, intraoperative findings, and pathology reports. Treatment data collected included details of postoperative adjuvant treatment. Follow-up was continued regularly at each institution. Follow-up information included the date and disease status at the last follow-up, or the date and cause of death.

Stage IVb metastases were divided into intra- and extra-abdominal disease. Metastasis to the liver surface was classified as intra-abdominal disease, and metastasis to the liver parenchyma was classified as extra-abdominal disease, following the classification for ovarian cancer. Postoperative residual disease was also divided into intra- and extra-abdominal disease. Remaining retroperitoneal lymphadenopathy and intrapelvic disease were classified as intra-abdominal residual disease. Patient outcomes were analyzed by overall survival (OS) time. OS was calculated from the date of surgery to the date of death or last contact.

Statistical analysis

The Kaplan–Meier method was used to estimate OS curves, and survival was compared among groups using the log-rank test. A p value of <0.05 was considered statistically significant. Multivariate Cox proportional hazards regression analyses were used to identify independent prognostic variables. Factors with a p value of <0.1 in univariate analyses were included in the multivariate analyses. All analyses were performed using SPSS statistical software (11.0.1 J; SPSS Inc., Chicago, IL).

Results

Patients and characteristics

We identified a total of 426 patients with stage IVb EMCA, of which 279 underwent primary surgery with curative intent as the initial treatment. After excluding 31 patients who did not undergo hysterectomy and cytoreductive surgery, 248 patients met the study inclusion criteria.

Detailed clinicopathological characteristics of the patients are listed in Table 1. The median age was 59 years (range: 30–89 years), and 91% had a pretreatment ECOG PS of 0/1. Mean BMI was 23.2 kg/m^2 (range: 15.1–35.8 kg/m^2). Medical comorbidities included hypertension in 19% of patients and diabetes in 9%. The most common histological subtype was endometrioid. There was a high frequency of poor histological factors, with endometrioid grade 3 (EMG3) or non-endometrioid

Table 1
Clinicopathological characteristics (n = 248).

Characteristic	n	(%)
Median age, years (range)	59(30–89)	
ECOG performance status		
0–1	226	(91)
2	17	(7)
3–4	4	(2)
Unknown	1	(<1)
Diabetes mellitus	22	(9)
Hypertension	47	(19)
Histological type		
Endometrioid	149	(61)
Serous	43	(17)
Clear cell	15	(6)
Carcinosarcoma	23	(9)
Other	18	(7)
Grade		
Endometrioid G1	36	(15)
Endometrioid G2	50	(20)
Endometrioid G3	60	(24)
Non-endometrioid	99	(40)
Unknown	3	(1)
Deep myometrial invasion	170	(69)
LVSI	173	(70)
Adjuvant therapy		
CT alone	185	(75)
RT alone	11	(4)
CT + RT	24	(10)
None	28	(11)
Chemotherapy regimen		
Taxane + platinum	115	(46)
AP ± α	79	(32)
Other	15	(6)

ECOG, Eastern Cooperative Oncology Group.
LVSI, lymphovascular space involvement.
CT, chemotherapy; RT, radiotherapy.
AP ± α, doxorubicin + platinum ± other.

histology, deep myometrial invasion, and positive lymphovascular space invasion (LVSI), each found in more than 60% of patients. Only 36 patients (15%) were classified as EMG1. The preoperative histological diagnosis was identical to the postoperative diagnosis in 150 patients (60%). Only 8 of 23 patients (35%) with carcinosarcoma were correctly diagnosed by preoperative endometrial biopsy.

Disease distribution

Disease distribution by anatomical region is shown in Table 2. Extra-abdominal metastases were documented in 93 patients (38%), of whom 71 (75%) had metastasis in only one anatomical region. The most common sites of extra-abdominal metastases were the lungs, supraclavicular lymph nodes, liver, and mediastinal lymph nodes. The majority of lung metastases were bilateral (36/49, 74%) and multiple (40/49, 82%). The diameter of lung metastasis was ≤1 cm in 19 patients, 1–2 cm in 20 patients, >2 cm in 9 patients, and unknown in 1 patient.

Intra-abdominal metastases beyond the pelvis were documented in 191 patients. The diameter of upper intra-abdominal metastases was >2 cm in 105 patients (55%), ≤2 cm in 72 patients (38%), and microscopic in 14 patients (7%). Intra-abdominal stage IVb disease was diagnosed on preoperative imaging in only 47 patients. Other intra-abdominal metastases not categorized as stage IVb disease were also frequently recognized (pelvic peritoneum, positive peritoneal washing cytology, ovaries, and retroperitoneal lymph nodes).

Table 2
Disease distribution.

Site of metastases	n	(%)
Stage IVb disease site		
Intra-abdominal alone	155	(62)
Extra-abdominal alone	57	(23)
Both	36	(15)
Extra-abdominal metastasis	93	(38)
1 region	71	(29)
2 regions	17	(7)
≥3 regions	5	(2)
Lung	49	(20)
Liver	12	(5)
Bone	7	(3)
Brain	3	(1)
Skin, umbilicus, breast	4	(2)
Conjunctiva	1	(<1)
Malignant pleural effusion	5	(2)
Supraclavicular lymph node	15	(6)
Mediastinal/axillary node	12	(5)
Inguinal node	10	(4)
Intra-abdominal metastasis	191	(77)
Sites staged as IVb		
Omentum	143	(58)
Macroscopic	125	(50)
Microscopic	18	(7)
Diaphragm	54	(22)
Peritoneum (upper abdomen)	109	(44)
Colon	7	(3)
Small intestine	3	(1)
Mesentery	6	(2)
Appendix	7	(3)
Sites staged as non-IVb		
Peritoneum (pelvis)	160	(65)
Retroperitoneal node	129	(52)
Para-aortic node	91	(37)
Pelvic node	115	(46)
Peritoneal washing cytology	156	(63)
Bowel mucosa	9	(4)
Bladder mucosa	2	(<1)
Ovary	144	(58)
Parametrium	28	(11)
Vagina	11	(4)

Surgical procedures and results

All 248 patients underwent surgical staging (Table 3). In addition to hysterectomy and bilateral salpingo-oophorectomy, cytoreductive procedures with the intent of maximum cytoreduction were performed in most patients. Resection of the colon, ileum, spleen, or diaphragmatic peritoneum was performed in 19 patients. After surgery, 101 patients (41%) had complete gross intra-abdominal resection and 52 (21%) had ≤1 cm residual disease.

To remove extra-abdominal metastases, some patients underwent resection of inguinal/supraclavicular lymph nodes, the umbilicus, or the abdominal wall. No patients underwent resection of lung or liver metastases. Complete resection of extra-abdominal metastases was achieved in only 13 patients.

Postoperatively, one patient with >2 cm residual disease died of disease progression on postoperative day 26. No major life-threatening complications occurred within 30 days after surgery.

Postoperative adjuvant therapy

Postoperative adjuvant therapy was administered to 220 patients (89%). The majority of these (n = 185) were treated with chemotherapy alone. A variety of chemotherapy regimens were used including paclitaxel, docetaxel, carboplatin, cisplatin, doxorubicin, cyclophosphamide, ifosfamide, etoposide, CPT11, and 5-fluorouracil. The most commonly administered regimen was taxanes + platinum ± doxorubicin (n = 115), followed by doxorubicin + platinum (AP) ± cyclophosphamide ± ifosfamide (n=79). Radiotherapy was administered to 35 patients, including external beam radiotherapy to the whole pelvis (n=23), para-aortic lesions (n=16), neck (n=6), bone (n=3), brain (n=2), and vaginal brachytherapy (n=2).

Clinical and pathological risk factors for survival

The median follow-up time among the censored patients was 41 months, and the median OS was 24 months (95% confidence interval [CI], 20–29 months). The causes of death were EMCA in 157 patients, other diseases in 2, and unknown in 3. At the last follow-up, 48 patients were alive with no evidence of disease, 33 were alive with disease, and 5 were alive with unknown disease status. There were no treatment-related deaths.

Table 3
Surgical procedures performed.

Procedure	n	(%)
Intra-abdominal		
Hysterectomy + BSO	248	(100)
Type of hysterectomy		
Simple	184	(74)
Subtotal	9	(4)
Modified-radical	49	(20)
Radical	6	(2)
Omentectomy/biopsy	157	(63)
Pelvic lymphadenectomy	157	(63)
Para-aortic lymphadenectomy	82	(33)
Resection of peritoneum	90	(36)
Appendectomy	30	(12)
Resection of colon/ileum	17	(7)
Colostomy/ileostomy	3	(1)
Splenectomy	1	(<1)
Diaphragm peritonectomy	1	(<1)
Resection of internal iliac artery	1	(<1)
Extra-abdominal		
Mastectomy	1	(<1)
Resection of umbilicus/skin	3	(1)
Resection of supraclavicular nodes	3	(1)
Resection of inguinal nodes	7	(3)

BSO, bilateral salpingo-oophorectomy.

Table 4
Univariate analyses for overall survival.

Variable	n	(%)[a]	Median OS (months) (95% CI)	Log-rank p^b
Age				
≤59 years	134	(54)	29 (22–36)	
≥60 years	114	(46)	20 (13–28)	0.0675
ECOG performance status				
0–1	226	(91)	25 (20–31)	
2–4	21	(8)	11 (5–16)	0.0150
Stage IVb disease site				
Intra-abdominal alone	155	(62)	24 (19–29)	
Extra-abdominal alone	57	(23)	30 (0–61)	
Both	36	(15)	20 (9–31)	0.1283
Histological type				
Endometrioid	149	(60)	31 (21–40)	
Non-endometrioid	99	(40)	14 (7–22)	<0.0001
Histology and grade				
EMG1	36	(15)	79 (not estimated)	
EMG2	50	(20)	48 (28–68)	
EMG3 + non-EM	159	(64)	14 (8–21)	<0.0001
Myometrial invasion				
≤1/2	59	(24)	40 (28–53)	
>1/2	170	(69)	22 (16–7)	0.0108
LVSI				
Present	173	(70)	24 (19–8)	
Absent	27	(11)	58 (not estimated)	0.0037
Stage IVb disease site				
Extra-abdominal metastasis				
Positive	93	(38)	24 (15–4)	
Negative	155	(62)	24 (19–9)	0.3722
Intra-abdominal metastasis				
Positive	191	(77)	23 (19–27)	
Negative	57	(23)	30 (0–61)	0.0609
Site of metastasis				
Para-aortic lymph node				
Positive	91	(37)	21 (14–27)	
Negative	119	(48)	31 (17–45)	0.0086
Pelvic lymph node				
Positive	115	(46)	21 (14–28)	
Negative	104	(42)	32 (18–47)	0.0134
Omentum				
Positive	143	(58)	24 (20–29)	
Negative	92	(37)	24 (10–38)	0.3877
Diaphragm				
Positive	54	(22)	22 (16–29)	
Negative	172	(69)	25 (18–32)	0.1077
Peritoneum (upper abdomen)				
Positive	109	(44)	18 (12–25)	
Negative	131	(53)	29 (24–35)	0.0070
Bone				
Positive	7	(3)	6 (3–9)	
Negative	241	(97)	25 (20–31)	<0.0001
Parametrium				
Positive	28	(11)	18 (11–26)	
Negative	202	(81)	25 (20–30)	0.0338
Postoperative residual disease				
None	62	(25)	48 (27–69)	
≤1 cm	63	(25)	25 (19–31)	
>1 cm	123	(50)	17 (11–22)	0.0004
Intra-abdominal residual disease				
None	101	(41)	48 (30–66)	
≤1 cm	52	(21)	23 (18–27)	
>1 cm	95	(38)	14 (10–19)	<0.0001
Extra-abdominal residual disease				
None	168	(67)	26 (21–31)	
≤1 cm	24	(10)	38 (0–100)	
>1 cm	56	(23)	21 (8–34)	0.3553
Adjuvant therapy				
Yes	220	(89)	26 (21–31)	
No	28	(11)	6 (4–9)	<0.0001
Type of adjuvant therapy				
CT alone	185	(75)	27 (22–32)	
RT alone	11	(4)	12 (0–50)	
CT + RT	24	(10)	26 (4–48)	0.9816
Chemotherapy regimen				
Taxane + platinum	115	(46)	30 (23–37)	
AP ± α	79	(32)	27 (20–34)	
Other	15	(6)	8 (0–16)	0.0470

Notes to Table 4:
ECOG, Eastern Cooperative Oncology Group; LVSI, lymphovascular space invasion; AP ± α, doxorubicin + platinum ± ifosfamide/cyclophosphamide/5FU/VP16; CT, chemotherapy; RT, radiotherapy.
[a] Numbers may not add up to the total because some data are unknown.
[b] Patients with unknown status were excluded from the calculation of log-rank p-values.

Univariate analyses

Univariate analyses were performed to identify relationships between OS and demographic, clinicopathological, surgical, and therapeutic variables (Table 4). Of the demographic and clinicopathological variables, PS, histology/grade, myometrial invasion, and LVSI were significantly associated with OS. Fig. 1 shows OS curves according to PS, histology/grade, and adjuvant therapy. Median OS was 79 months in patients with EMG1, 48 months in EMG2, and 14 months in EMG3 + non-EM ($p<0.0001$).

Metastases to para-aortic lymph nodes, pelvic lymph nodes, upper abdominal peritoneum/mesentery, bone, and parametrial invasion were inversely related to OS. The median OS according to stage IVb disease site was 30 months in patients with extra-abdominal metastases alone (n = 57) and 24 months with intra-abdominal metastases alone (n = 155). In the 155 patients with intra-abdominal metastases alone, the median OS was 42 months (95% CI, 0–86) in patients with microscopic disease, 24 months (95% CI, 16–33) with ≤2 cm disease, and 20 months (95% CI, 14–27) with >2 cm disease. This was not significantly different among groups ($p = 0.1527$).

Residual disease showed a significant association with OS ($p = 0.0004$). In patients with intra-abdominal residual disease, smaller size of residual disease was associated with longer OS. In contrast, extra-abdominal residual disease was not related to OS. Median OS was 48 months in patients with no gross intra-abdominal residual disease, 23 months with ≤1 cm residual disease, and 14 months with >1 cm residual disease ($p<0.0001$) (Fig. 2A).

Further stratification according to the presence of extra-abdominal metastases showed that patients with no gross intra-abdominal residual disease survived significantly longer than patients with intra-abdominal residual disease, with or without extra-abdominal metastases (Fig. 2B).

Furthermore, stratification by histology/grade showed a survival advantage in patients who underwent cytoreduction of intra-abdominal disease. Among patients with EMG1/EMG2 type, those with no residual intra-abdominal disease had a longer median OS than those with gross residual intra-abdominal disease (79 vs. 36 months, $p = 0.0226$). The results were similar among patients with EMG3/non-EM type (24 vs. 13 months, $p = 0.0022$).

OS was significantly longer in patients who received postoperative adjuvant chemotherapy and/or radiotherapy than patients who did not receive adjuvant therapy (Fig. 1C). In patients who received postoperative chemotherapy, there was no difference in OS between those who received taxanes plus platinum and those who received AP ($p = 0.5658$).

Multivariate analysis

Cox multivariate analysis was used to simultaneously examine the independent effects on OS of age, PS, histology/grade, myometrial invasion, parametrial invasion, para-aortic lymph node metastasis, pelvic lymph node metastasis, upper abdominal peritoneal/mesenteric metastasis, adjuvant therapy, and intra-abdominal residual disease. Bone metastasis showed a strong correlation with poor prognosis by univariate analysis, but was excluded from the multivariate analysis because there were only 7 patients in this group. The results showed that PS, histology/grade, adjuvant therapy, and intra-abdominal residual disease were independent prognostic factors for OS. The significance of these

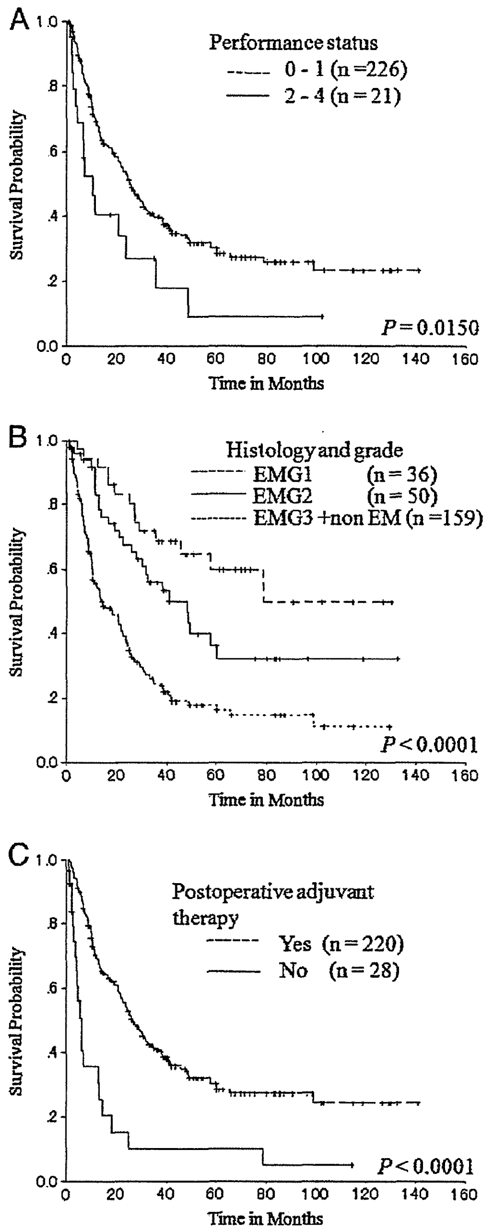

Fig. 1. Kaplan–Meier curves for overall survival (OS). A: Median OS time according to performance status (PS): PS 0–1 (dashed line), 25 months; PS2–4 (solid line), 11 months. B: Median OS time according to histology/grade: endometrioid (EM) grade 1 (dashed line), 79 months; EM grade 2 (solid line), 48 months; EM grade 3 + non-EM (dotted line), 14 months. C: Median OS time according to adjuvant therapy: yes (dashed line), 26 months; no (solid line), 6 months.

variables was as follows: PS (0–1 vs. 2–4) (hazard ratio [HR] = 1.988; 95% CI, 1.108–3.569; $p = 0.021$), histology/grade (EMG1 vs. EMG2 vs. EMG3 + non EM) (HR = 2.245; 95% CI, 1.652–3.050; $p < 0.001$), adjuvant therapy (yes vs. no) (HR = 3.396; 95% CI, 1.898–6.076; $p < 0.001$), and intra-abdominal residual disease (none vs. ≤1 cm vs. >1 cm) (HR = 1.499; 95% CI, 1.203–1.867; $p < 0.001$).

Discussion

Our study is the largest retrospective series exploring the clinical outcome of surgical stage IVb EMCA, including patients with extra-abdominal metastases. Our study also investigated the clinicopathological variables of these patients.

Although surgical staging is the most basic treatment for EMCA [1,2], intra-abdominal metastases are poorly recognized without staging laparotomy. Although several reports have documented disease distribution in surgical stage IVb patients, the reports lacked detailed information, or did not classify patients according to intra- or extra-abdominal disease. Bristow et al. reported that the most common intra-abdominal metastatic sites were the pelvis, peritoneum, omentum, and retroperitoneal nodes [7]. The distribution of metastatic disease sites in our study was comparable with previously reported distributions. In the present study, 77% of surgical stage IVb patients had upper intra-abdominal disease, and 78% had intra-pelvic spread and/or retroperitoneal lymph node metastases. However, most upper intra-abdominal disease was not detected by preoperative imaging studies. Goff et al. reported that preoperatively unrecognized upper intra-abdominal disease occurred in 53% of surgical stage IV patients [8]. In our study, the size of intra-abdominal stage IVb disease was ≤2 cm in half of the patients, which seemed to be smaller than the disseminated disease found in cases of advanced ovarian cancer. This may be one of the reasons why preoperative diagnosis is difficult. Metastasis to the diaphragm was documented in 22% of patients in the present study. This may be valuable information for gynecologic oncologists. The importance of thorough observation of the entire abdominal cavity, including the diaphragm, is stressed.

Few reports of stage IVb EMCA patients have discussed the relationship between survival and histological factors, which is known to be significant in stage I–III patients [1,2]. This is the first study to report a detailed evaluation of histopathological factors in stage IVb EMCA. As the unfavorable histopathological factors such as serous subtype or LVSI have a higher propensity for extrauterine metastasis, patients with these factors are more likely to present with advanced-stage disease. Most patients in the present study had these factors. Univariate analyses showed that non-endometrioid type, high-grade endometrioid type, deep myometrial invasion, and positive LVSI were significantly associated with poor prognosis. Multivariate analysis showed that histology/grade was an independent prognostic factor. Patients with lower-grade endometrioid type are expected to have a longer survival time, even in stage IVb EMCA.

The favorable impact of surgical cytoreduction on survival has been well demonstrated in advanced ovarian cancer [15,16]. Greer and Hamberger first suggested the beneficial effect of cytoreductive surgery and postoperative radiotherapy in advanced EMCA [17]. Subsequently, several reports on advanced EMCA have demonstrated improved OS in patients who undergo optimal cytoreductive surgery, including all histological subtypes [4,7–9,18], endometrioid subtype [10], and serous subtype [11,12,19]. Barlin et al. performed a meta-analysis of 14 retrospective cohort studies including 672 patients with advanced or recurrent EMCA who underwent cytoreductive surgery [13]. Although primary stage IV patients accounted for only 60% of the patients in their analysis, complete cytoreduction to no gross residual disease was associated with superior OS.

Generally, distant metastases are considered to be a poor prognostic factor. The association between extra-abdominal metastases and prognosis has not previously been discussed, because studies have included few patients in this group. In our study, the frequency of extra-abdominal metastases was 38%, which is the highest reported frequency compared with previous reports of surgical stage IVb EMCA. Ayhan et al. reported that the prognosis of patients with extra-abdominal metastases was poor [4]. Bristow et al. reported that optimal debulking was not achieved in patients with extra-abdominal metastases [7]. Most extra-abdominal metastases are unresectable, and in our study complete resection of extra-abdominal metastases was achieved in 13 patients (14%). It is unclear whether laparotomy benefits patients with unresectable extra-abdominal metastases. Recently, Ueda et al. reported a small study which demonstrated that optimal cytoreduction was associated with improved survival even in stage IVb EMCA patients with extra-abdominal metastases [6].

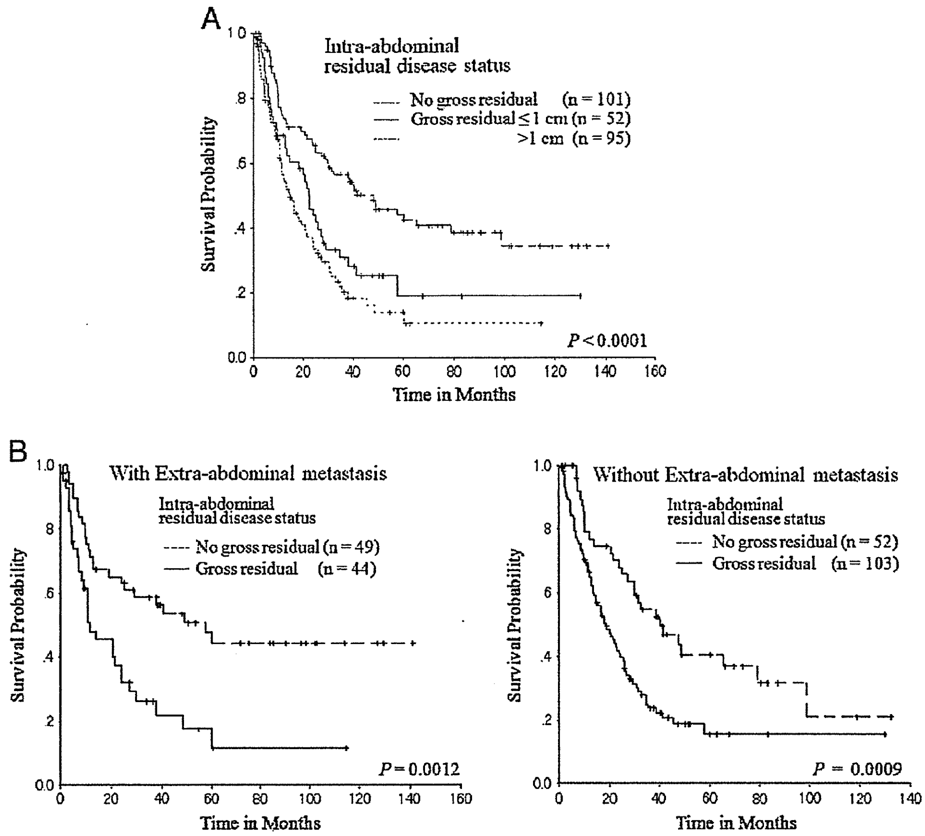

Fig. 2. Kaplan–Meier curves for OS. A: Median OS time according to intra-abdominal residual disease: no residual disease (dashed line), 48 months; ≤1 cm residual disease (solid line), 23 months; > 1 cm residual disease (dotted line), 14 months. B: Median OS time according to intra-abdominal residual disease in patients with (left) and without (right) extra-abdominal metastases. (left): no residual disease (dashed line), 58 months; gross residual disease (solid line), 11 months. (right): no residual disease (dashed line), 40 months; gross residual disease (solid line), 18 months.

The distribution of extra-abdominal disease in this cohort is not identical to that of all stage IVb patients because selection bias for surgery is expected. The majority of patients with extra-abdominal metastases in this cohort had metastases involving only one anatomical region, a good PS, and no symptoms. This group of patients may therefore have had less aggressive disease or a better response to adjuvant chemotherapy than patients with extra-abdominal metastases who did not undergo surgery. We were unable to definitively determine which characteristics were good prognostic factors in patients with extra-abdominal metastases. However, extra-abdominal disease was not associated with poor prognosis in this study. The OS was significantly longer in patients who underwent intra-abdominal cytoreduction than in patients with remaining gross intra-abdominal disease, even in patients with extra-abdominal metastases. We suggest that aggressive surgery should be undertaken to achieve complete macroscopic resection of all intra-abdominal disease if the patient's general condition is good.

The Gynecologic Oncology Group reported that systemic postoperative adjuvant chemotherapy with cisplatin + doxorubicin was associated with improved survival compared with postoperative whole abdominal irradiation [20]. Therapy with paclitaxel + doxorubicin + cisplatin was reported to be superior to doxorubicin + cisplatin [21]. In patients with advanced EMCA, platinum + anthracyclines and taxanes seem to be the most promising agents. Some prospective and retrospective studies of combination adjuvant chemotherapy and radiation for advanced or recurrent EMCA have been conducted [22–24]. However, no studies have focused on adjuvant treatment of stage IVb EMCA.

In the present study, adjuvant therapy was associated with longer OS. Most patients received chemotherapy alone as postoperative treatment, including taxanes + platinum or AP. There were no differences in OS between these two treatment groups. Although it is certain that chemotherapy is an ideal treatment for this systemic disease, we cannot comment on treatment outcomes according to the type of postoperative therapy due to the heterogeneity of treatment schedules in our cohort.

This study has several limitations. First, because it was a retrospective multicenter study, the quality of data may not be uniform. We made a considerable effort to collect uniform data using a case report form to standardize the information collected as much as possible. Second, there were heterogeneous treatment protocols in different institutions. In particular, there may have been a selection bias for the type of treatment initially chosen in patients with distant metastases. Third, the question of whether the improved outcome of patients who undergo optimal cytoreduction is due to the surgery or to the biology and aggressiveness of the tumor is unresolved.

In conclusion, our retrospective study showed that PS, histology/grade, postoperative treatment, and intra-abdominal residual disease were independent predictors of survival in patients with stage IVb EMCA who underwent primary cytoreductive surgery. Cytoreductive surgery and postoperative therapy may prolong survival time in some patients with stage IVb EMCA, particularly those with relatively favorable prognostic factors, even in the presence of extra-abdominal metastases.

Conflict of interest statement

The authors have no conflicts of interest.

Acknowledgments

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外陰癌・膣癌の治療

Treatment of vulvar and vaginal cancer

野河孝充　日浦昌道

Key words：外陰癌，膣癌，手術，放射線療法，化学療法

はじめに

外陰癌は婦人科腫瘍の5％，膣癌は約3％と更に低頻度のまれな疾患で[1,2]，閉経後および高齢者に好発するが，近年human papilloma virus(HPV)感染の拡がりから若年患者の増加がみられる[3]．外陰癌，膣癌ともにまれなため，大規模な無作為比較試験に基づくエビデンスレベルの高い推奨治療法が少なく，婦人科の一般的な癌である子宮頸癌に準じた治療計画が立てられている[4,5]．外陰部，膣はともに排泄，運動，性的機能など解剖学的に重要な部位であり，肛門・直腸や尿道・膀胱を合併切除する広汎手術は，手術侵襲が大きく，出血，感染，創部離開，排尿・排便障害，性的機能障害と精神的苦痛，リンパ嚢胞やリンパ浮腫などの手術合併症の問題がある．近年，術後のQOLと根治性向上を目的にリンパ節転移や再発危険因子の解析により，縮小手術やリンパ節郭清の省略，センチネルリンパ節の検索，放射線療法や化学療法の併用による治療の個別化が行われている．根治的手術時の直腸・肛門や膀胱・尿道などの合併切除では消化器外科や泌尿器科と，外陰再建術では自然な外観と機能再建が必要なため，再建術を熟知した形成外科との連携が重要である[6]．

1 外陰癌

1）新International Federation of Gynecology and Obstetrics(FIGO）進行期分類(2008)改訂

新FIGO進行期分類(2008)改訂の要点は，第一に間質浸潤がリンパ節転移の危険因子であること，第二に転移リンパ節の個数と大きさ，リンパ節被膜外浸潤が重要な予後因子である点に基づいて分類されている[7]．

本稿では新FIGO進行期分類(2008)に基づいて治療法を述べる．

2）診　断

外陰癌は，扁平上皮癌が大部分を占め，次にPaget病，悪性黒色腫および腺癌がある．

表1に示すように治療前診察では原発巣のサイズ，病巣部位が片側性か中心性か両側性か，特にHPV感染の関連する上皮内病変(vulva intraepithelial neoplasia: VIN)の有無を膣，子宮頸部，肛門で確認し，またMRI，CT，PETなどの画像検査で病巣の周囲への拡がり，所属リンパ節や遠隔転移を把握する．リンパ節転移は腫瘍サイズが2cm以上で高くなり，2cm以下でかつ間質浸潤が1mmまではリンパ節転移が極めてまれであり，間質浸潤が3mmを超えると対側リンパ節にも転移の危険が生じる[8]．術前の生検では，病巣中央部を深く生検して間質浸

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表1 外陰癌の治療前診察と検査

診 察	検 査
①視診・触診 ・片側性，中心性，両側性 ・単発性，多発性 ・大きさ：2cm以下か以上か ・浸潤性，浸潤の程度，上皮内病変 ・周囲臓器への進展(尿道・肛門) ・所属，遠隔リンパ節の腫大，可動性 ③内診：膣，子宮頸部・体部病変 ④直腸診：直腸進展	①コルポスコピー(外陰，膣，子宮頸部病巣確認) ②細胞診(リンパ節穿刺細胞診含む) ③組織診(病理組織型，マッピングバイオプシー) ④画像診断(胸部単純X線撮影，MRI，CT/PET-CT) ⑤直腸鏡，膀胱鏡 ⑥各種腫瘍マーカー(SCC，CEA，CA125) ⑦血液凝固能・線溶検査，末梢血，肝腎機能検査，検尿

表2 外陰癌治療法の選択

1. 外陰に限局

VIN3: レーザー蒸散/局所切除/単純(片側)外陰切除

Paget病: 外陰拡大局所切除術/単純(片側)外陰切除

IA期(腫瘍径≦2cm，浸潤≦1mm): 単純(片側)外陰切除術

IB期(腫瘍径＞2cm，浸潤＞1mm):

外陰拡大局所切除術±リンパ節生検/郭清
単純外陰切除術 ±リンパ節生検/郭清
広汎外陰切除術
(以上 ±術後放射線/化学療法)

放射線療法単独/同時化学放射線療法

2. 隣接臓器浸潤

尿道・膀胱，肛門・直腸浸潤(II，III，IV期)：放射線療法単独/同時化学放射線療法
広汎外陰切除術＋浸潤臓器切除/除臓術
±術後放射線/化学療法

FIGO進行期分類2008年に準じる.

潤の深さを確認し，リンパ節郭清の有無を判定する．外陰に限局する腫瘍では，辺縁からの健常部分の距離が8mm未満は局所再発の危険があり，少なくとも1cm以上十分に離れて切除する[9]．VINやPaget病などで境界が不明瞭なときはmapping biopsyで正確な切除範囲を決める[10]．

3) 治療法(表2)

a. 手 術

従来，外陰部から両側鼠径部まで連続皮膚切開して両側鼠径・大腿リンパ節をen blocに切除する広汎外陰切除術が標準治療法であったが，外陰部，鼠径部皮膚を3カ所に分割するthree separate incision法が創部の合併症が軽く，予後に差がないため，よく施行されている．近年，リンパ節転移の危険因子が解明され，術前に正確な腫瘍の広がり，深さを評価することにより，進行期に準じて手術方法が個別化されている．切除の深さはVINやPaget病などの上皮内病変では皮下脂肪組織を十分つけて，また浸潤癌では深さを確認して切除する．

手術術式に関しては，VINにはサイズや拡がりに応じてレーザー蒸散術や局所切除，外陰切除を行う．Paget病は腺癌合併の危険があり，拡大局所切除術を行うが，占拠部位や拡がりに応じて単純または片側外陰切除術を行う．

術前生検，術中迅速病理検査で浸潤が1mm以下と判明したIA期は拡大局所切除術を，多

発性・両側性には単純または片側外陰切除を行い，リンパ節郭清は不要である．IB期以上で尿道，肛門へ浸潤のないものには，腫瘍の拡がりと浸潤の程度に応じて，拡大局所切除術，単純または片側外陰切除に鼠径リンパ節生検/郭清，更に広汎外陰切除術などの手術の個別化を図る．明らかなリンパ節転移が存在または疑われるときは鼠径・大腿リンパ節郭清±骨盤リンパ節郭清を考慮する．なお，鼠径・大腿リンパ節転移が進行期決定と予後因子になることから，転移リンパ節の個数や形態の確認が必要であるが，術後リンパ浮腫などの発症の問題があり，局所所見を正確に把握してリンパ節郭清を行う．

尿道，肛門から直腸，膀胱へ進展するII-IV期は尿路変更や人工肛門，また骨盤除臓術の対象になるが，術後のQOL低下を考慮し同時化学放射線療法が適用される[5]．

b. センチネルリンパ節の同定

近年，外陰癌においてもセンチネルリンパ節を同定し，転移陰性であればリンパ節郭清を省略する研究が積極的に進められている[5]．Van der Zeeら[11]は4cm以下の外陰癌403例で，センチネルリンパ節陰性の259例中6例(2.3%)が2年後にリンパ節再発し，3年生存率は7%で，陽性のリンパ節郭清群に比べ創部離開やリンパ浮腫が有意に少なく，早期外陰癌手術の標準手技になると報告している．我が国では子宮頸癌，体癌に対し研究が始まった段階であり，外陰癌に対しても研究が望まれる．

c. 放射線療法

外陰癌の治療は手術が標準とされているが，根治手術は侵襲が大きく，合併症や後遺症の問題があり，高齢者の初期癌，尿道や肛門など隣接臓器に進展する局所進行癌，リンパ節転移例などに対する術後補助療法が対象となり，また進行癌で放射線療法単独よりも同時化学放射線療法が推奨されている[4,5]．

a) 術後補助放射線療法

術後補助放射線療法は，切除断端陽性や健常皮膚部分が8mm以下と不十分なものが適応となり[12]，また鼠径リンパ節転移群における骨盤リンパ節郭清に比し術後放射線療法の有効性が報告されている[13]．間質浸潤の深さや腫瘍サイズ，画像診断からリンパ節転移が疑われる症例には，術後放射線療法によるリンパ節郭清の手術侵襲の軽減や下肢リンパ浮腫などの後遺症を予防することも治療の選択肢である．

b) 同時化学放射線療法

同時化学放射線療法は，II-IV期の局所進行癌および手術不能例が対象となり，特に術前治療法は腫瘍の縮小による完全切除，手術侵襲の軽減，抗癌剤全身投与による遠隔再発の制御などを目的とする．T3，T4期の局所進行癌71例を対象にcisplatin(CDDP)と5-fluorouracil(5-FU)を併用したGynecologic Oncology GroupのPhase II研究では[14]，手術時に48%が肉眼的に腫瘍消失し，うち70%が病理学的CR，残存切除不能は2例のみであった．また切除不能リンパ節症例においても40例中38例がリンパ節切除可能となり[15]，今後期待される治療法である．

d. 化学療法

外陰癌の化学療法は，進行癌に対する腫瘍切除，縮小手術および抗癌剤による全身的治療を目的に術前同時化学放射線療法として施行されている．使用薬剤は5-FU，CDDP，mitomycin-C(MMC)などの多剤併用療法が多く，近年paclitaxel(TXL)併用も報告され，外陰癌の新規治療法として期待されている[15]．

2 腟 癌

原発性腟癌は極めてまれで婦人科癌の3%で，扁平上皮癌が80%以上を占め，前駆病変の腟上皮内新生物(vaginal intraepithelial neoplasia: VAIN)を高頻度に合併し，ハイリスクHPV(16型)が60%に検出される[16]．ほかの組織型では腺癌，悪性黒色腫，幼児に好発する葡萄状肉腫があるが，腟は転移性癌が少なくなく，子宮頸癌や外陰癌，更に他臓器からの転移癌との鑑別が必要である．発生部位は腟上部1/3，後壁が多く，また腟下方の小病変は腟鏡の前・後葉に隠れて見逃されやすく注意を要する．外陰癌と同様に治療法は，腫瘍の部位，サイズや進行期に応じて個別化されるが，特に隣接臓器(膀胱

・尿道，直腸)への手術や放射線による機能障害と治療後のQOLを考慮する必要がある．手術は腫瘍周囲を十分につけた切除が困難なため初期および限局性小病変が適応になる．VAIN3の表層性局在病変には病巣切除やレーザー蒸散術が，多発，広汎な病巣には腟内照射や腟全摘も選択肢となる．I期で腟上方に局在し，サイズが2cm以下の病巣には広汎子宮全摘術・上部腟切除・骨盤リンパ節郭清による根治術が施行される．また扁平上皮癌II期11例にTXLとCDDPの術前化学療法3コース後に根治術が施行され，10例が奏効し，再発は2例のみと化学療法併用の有用性を示した報告がある[17]．浸潤癌では放射線療法が標準的治療法となる．浸潤が軽度の表層性病変は腟内照射単独も可能であるが，サイズ2cm以上のI期，およびII-IV期の局所進行癌には骨盤外部照射と腟内照射が施行される．また病変が腟下部に及ぶときは鼠径・大腿リンパ節照射を加える．化学療法併用の放射線治療は増加傾向にあるが，SEER-medicare-linked databaseの解析では生存率改善は示されていない[18]．単独施設におけるCDDP併用の同時併用化学放射線療法では有効性の報告[19-21]があり，多施設共同臨床試験による新たな治療法の開発が課題である．

おわりに

外陰癌，腟癌ともに，まれかつ高齢者に頻度の高い癌であるが，HPV感染の関係より若年者の増加もある．治療に際しては，排尿，排便，性的機能温存を考慮し，またHPVワクチンによる予防も重要な課題である．

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Clinical Cancer Research

Imaging, Diagnosis, Prognosis

High-Risk Ovarian Cancer Based on 126-Gene Expression Signature Is Uniquely Characterized by Downregulation of Antigen Presentation Pathway

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Abstract

Purpose: High-grade serous ovarian cancers are heterogeneous not only in terms of clinical outcome but also at the molecular level. Our aim was to establish a novel risk classification system based on a gene expression signature for predicting overall survival, leading to suggesting novel therapeutic strategies for high-risk patients.

Experimental Design: In this large-scale cross-platform study of six microarray data sets consisting of 1,054 ovarian cancer patients, we developed a gene expression signature for predicting overall survival by applying elastic net and 10-fold cross-validation to a Japanese data set A ($n = 260$) and evaluated the signature in five other data sets. Subsequently, we investigated differences in the biological characteristics between high- and low-risk ovarian cancer groups.

Results: An elastic net analysis identified a 126-gene expression signature for predicting overall survival in patients with ovarian cancer using the Japanese data set A (multivariate analysis, $P = 4 \times 10^{-20}$). We validated its predictive ability with five other data sets using multivariate analysis (Tothill's data set, $P = 1 \times 10^{-5}$; Bonome's data set, $P = 0.0033$; Dressman's data set, $P = 0.0016$; TCGA data set, $P = 0.0027$; Japanese data set B, $P = 0.021$). Through gene ontology and pathway analyses, we identified a significant reduction in expression of immune-response–related genes, especially on the antigen presentation pathway, in high-risk ovarian cancer patients.

Conclusions: This risk classification based on the 126-gene expression signature is an accurate predictor of clinical outcome in patients with advanced stage high-grade serous ovarian cancer and has the potential to develop new therapeutic strategies for high-grade serous ovarian cancer patients. *Clin Cancer Res; 18(5); 1374–85. ©2012 AACR.*

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Translational Relevance

Using large-scale microarray expression data sets (n = 1,054) by applying an elastic net method, a novel risk classification system for predicting overall survival of patients with advanced stage high-grade serous ovarian cancer based on a 126-gene expression signature was developed and successfully validated. This study has profound significance in clarifying the downregulation of human leukocyte antigen class I antigen presentation machinery that characterizes high-risk ovarian cancer. These results from comprehensive gene expression analysis using large-scale microarray data suggest that our risk classification system might have the potential to optimize treatment of high-grade serous ovarian cancer patients.

Introduction

High-grade serous ovarian cancer comprises approximately 40% of epithelial ovarian cancer cases and is the most aggressive histologic type (1–4). This type of cancer usually presents as advanced stage disease at the time of diagnosis because there are no symptoms present at the early stage and no reliable screening test for early detection (1–4). Patients with advanced stage high-grade serous ovarian cancer generally undergo primary debulking surgery followed by platinum–taxane chemotherapy. However, 30% to 40% of patients recur within 12 months after the standard treatment, and the overall 5-year survival rate remains at approximately 30% (5, 6). Clinicopathologic characteristics, such as the International Federation of Gynecology and Obstetrics (FIGO) stage, histologic grade, and debulking status after primary surgery, are clinically considered important clinical prognostic indicators of ovarian cancer but are insufficient for predicting survival time.

The development of microarray technology has provided new insights into cancer diagnosis and treatment. Large-scale microarray studies in breast cancer have succeeded in clarifying 5 molecular subtypes based on gene expression profiles and in developing genomic biomarker for predicting recurrence in early breast cancer (MammaPrint; refs. 7, 8). Thus, breast cancer treatment strategies are being stratified according to molecular characteristics. In contrast, there are no gene expression signatures with high accuracy and reproducibility for clinical diagnosis and management in patients with ovarian cancer because there is a paucity of ovarian cancer samples available for microarray analysis compared with breast cancer. Although *TP53* somatic mutation is present in almost all high-grade serous ovarian cancer and plays an important role in the pathogenesis (9, 10), high-grade serous ovarian cancer exhibits much biological and molecular heterogeneity that should be considered when developing a novel therapeutic strategy for ovarian cancer (10, 11).

In this study, we aimed to establish a novel system for predicting the prognosis of patients with advanced stage high-grade serous ovarian cancer using large-scale microarray data sets (n = 1,054; refs. 10–13), leading to an optimal treatment based on molecular characteristics (14).

Materials and Methods

Clinical samples

Three hundred Japanese patients who were diagnosed with advanced stage high-grade serous ovarian cancer between July 1997 and June 2010 were included in this study. All patients provided written informed consent for the collection of samples and subsequent analysis. Fresh-frozen samples were obtained from primary tumor tissues during debulking surgery prior to chemotherapy. All patients with advanced stage high-grade serous ovarian cancer were treated with platinum–taxane standard chemotherapy after surgery. In principle, patients were seen every 1 to 3 months for the first 2 years. Thereafter, follow-up visits had an interval of 3 to 6 months in the third to fifth year, and 6 to 12 months in the sixth to tenth year. At every follow-up visit, general physical and gynecologic examinations were carried out. CA125 serum levels were routinely determined.

Staging of the disease was assessed according to the criteria of the FIGO (15). Optimal debulking surgery was defined as less than 1 cm of gross residual disease, and suboptimal debulking surgery was defined as more than 1 cm of residual disease. Progression-free survival time was calculated as the interval from primary surgery to disease progression or recurrence. Based on the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1; 16), disease progression was defined as at least a 20% increase in the sum of the diameters of target lesions, as unequivocal progression of existing nontarget lesions, or as the appearance of one or more new lesions. Overall survival time was calculated as the interval from primary surgery to the death due to ovarian cancer.

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