THE JOURNAL OF
Obstetrics and Gynaecology Research

doi:10.1111/j.1447-0756.2012.02060.x J. Obstet. Gynaecol. Res. 2012

Grave outcome of granulocyte colony-stimulating factor-producing endometrial cancer: A case report and literature review

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Abstract

Granulocyte colony-stimulating factor (G-CSF)-producing nonhematopoietic malignancies have been reported in various organs, and most of them have been associated with poor clinical outcome. However, because of the rarity of reported cases, information regarding G-CSF-producing gynecological malignancies, especially uterine corpus cancer, is limited. We report a case of G-CSF-producing endometrial cancer, which exhibited a grave clinical outcome. Our case strongly indicates the aggressive nature of G-CSF-producing endometrial cancer.

Keywords: endometrial cancer, granulocyte colony-stimulating factor leukocytosis, neutrophil, survival.

Introduction

The first case of granulocyte colony-stimulating factor (G-CSF)-producing malignant tumor was reported in 1977, which was a patient with lung cancer.[1] Since then, an increasing number of G-CSF-producing nonhematopoietic malignancies have been reported in the liver, bladder, uterine cervix, and many other sites.[2-4] Most reports suggested the very aggressive nature of G-CSF-producing tumors with an extremely poor patient prognosis. However, because of the rarity of reported cases, information regarding G-CSF-producing gynecological malignancies, especially uterine corpus cancer, is limited (Table 1).

We herein describe our experience of a case of G-CSF-producing endometrial cancer, which exhibited a grave clinical outcome.

Case Report

A 68-year-old Japanese woman (gravida 3, para 2) presented with 3 days of abdominal pain. Her past medical and surgical history was unremarkable. Pelvic examinations revealed a pelvic tumor. No rebound tenderness was noted. Transvaginal ultrasonography showed an 8 × 7-cm spherical pelvic tumor, which was suspected for pyometra or hematometra. A computed tomography (CT) scan of the abdomen and pelvis revealed a 14 × 12 × 10-cm enlarged uterus (Fig. 1a). A diagnosis of pyometra or hematometra accompanied by left ovarian tumor was suspected. Laboratory tests revealed an elevated white blood cell (WBC) count (22 400/mm^3) and elevated C-reactive protein (22.8 mg/dL). As the patient's abdominal pain progressed, we offered her abdominal hysterectomy plus bilateral salpingo-oophorectomy on the same day.

Received: August 7 2012.
Accepted: September 18 2012.
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Exploratory laparotomy revealed an enlarged uterus, normal-sized ovaries, and disseminated peritoneal tumors, which were suspected of being advanced-stage endometrial cancer or primary peritoneal carcinoma. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, and biopsies from peritoneal tumors were performed. Lymphadenectomy could not be performed owing to unresectable peritoneal disseminations. Intraoperative frozen pathological examination of the surgical specimen indicated carcinoma of the uterine corpus accompanied by peritoneal disseminations. The uterine cavity was markedly distended and filled with degenerated tumor cells. Pyometra or hematometra was not noted. The final pathology was undifferentiated carcinoma of the uterine corpus, with marked infiltration of neutrophils (Fig. 1b). Tumor cell infiltration into the outer one-third of the myometrium and cervical stroma with marked lymphovascular space invasion was noted. Disseminations to resected peritoneum and both ovaries were also noted. A diagnosis of FIGO stage IVb endometrial cancer was confirmed.

Table 1 Summary of the reported cases of G-CSF-producing endometrial cancer

Article	Age	FIGO Stage	Histology	G-CSF (pg/mL)†	WBC/Neutrophil counts (/μL)‡	Treatment	CT regimen	Survival
Hada *et al.*, 2004[8]	57	IVb	Undifferentiated adenocarcinoma	284	23 000/20 240	CT followed by surgery	CAP	12 months (at least)
Present case 2012	68	IVb	Undifferentiated adenocarcinoma	305	109 900/102 207	Surgery followed by CT	TC	4 weeks

†Serum G-CSF concentration at the time of diagnosis of G-CSF-producing endometrial cancer; ‡White blood cell or neutrophil counts at the time of diagnosis of G-CSF-producing endometrial cancer. CAP, cisplatin, cyclophosphamide and adriamycin; CT, chemotherapy; FIGO, International Federation of Gynecology and Obstetrics; G-CSF, granulocyte colony-stimulating factor; TC, paclitaxel and carboplatin.

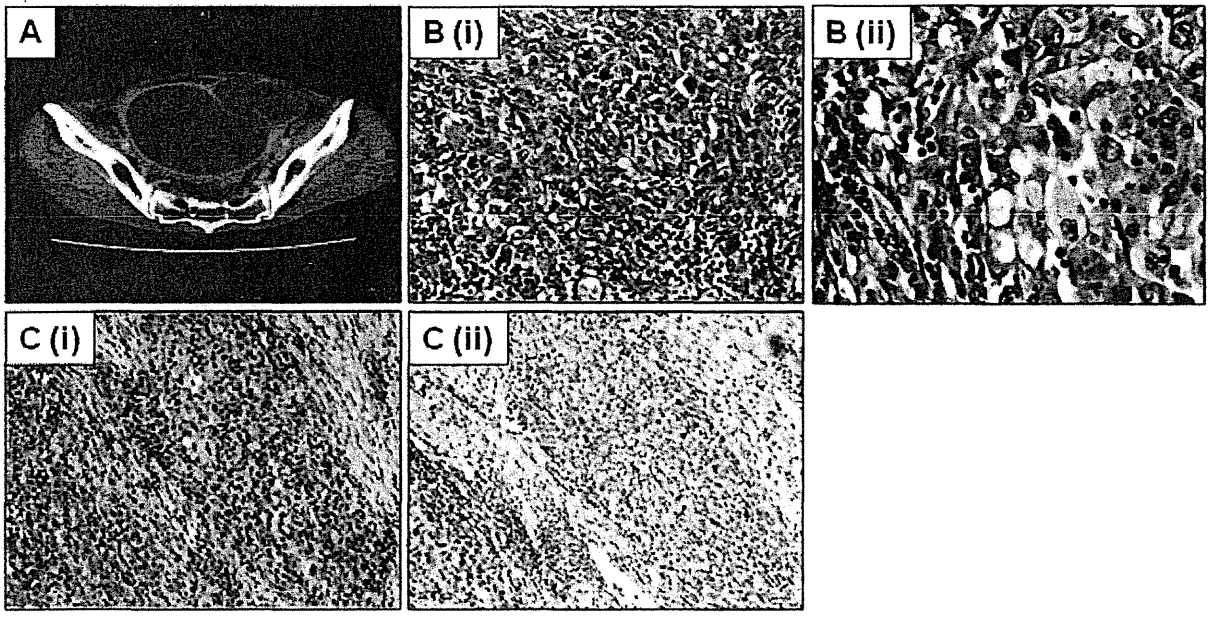

Figure 1 (a) Computed tomography (CT) scan of the abdomen and pelvis revealed an enlarged uterus measuring 14 × 12 × 10 cm. (b) Undifferentiated carcinoma of the uterine corpus with marked infiltration of neutrophils on the hysterectomy specimen (hematoxylin-eosin staining, original magnification × 400); magnification, ×100 (i) and ×400 (ii). (c) Immunohistochemical findings of the same specimen stained with anti-granulocyte colony-stimulating factor (G-CSF) monoclonal antibody; (i) the tumor cell cytoplasm was diffusely positive for G-CSF, but very weak in the surrounding non-cancerous lesions (original magnification × 400); (ii) no positive signal was observed for nonimmune sera.

Two weeks after surgery, the patient's WBC count increased to 109 900/mm^3 with 93.0% neutrophils. In contrast to her raised WBC count, her C-reactive protein level remained stable (19.7 mg/dL). Blood and urine culture tests conducted just before surgery and 2 weeks after were negative, and she showed no obvious sign of infection. A G-CSF-producing tumor was suspected because of the raised WBC count in the absence of infection and marked infiltration of neutrophils into the tumor, leading to a blood test for the serum level of G-CSF. As the serum concentration of G-CSF was abnormally elevated to 305 pg/mL (normal range: <18.1 pg/mL), using surgical specimens, immunohistochemical staining with a specific antibody against human G-CSF was performed. The tumor cell cytoplasm was diffusely positive for G-CSF, but very weak in the surrounding non-cancerous lesions (Fig. 1c). From these results, we concluded that this tumor was a G-CSF-producing endometrial cancer. To investigate whether systemic metastasis was present, FDG PET/CT was performed, which showed abnormal FDG uptake in the whole abdominal cavity, compatible with widespread peritoneal dissemination of endometrial cancer, suggestive of very rapid tumor progression in this case (Fig. 2). Moreover, the FDG PET/CT showed diffusely intense bone marrow FDG uptake (Fig. 2), which could be explained by the increased bone marrow metabolism in response to the G-CSF produced by tumor cells as reported previously.[5] Salvage chemotherapy consisting of carboplatin and paclitaxel was initiated on the 14th postoperative day. However, her serum G-CSF concentration increased to 120 000 pg/mL on the 25th postoperative day, and she died from rapid disease progression 28 days after the surgery.

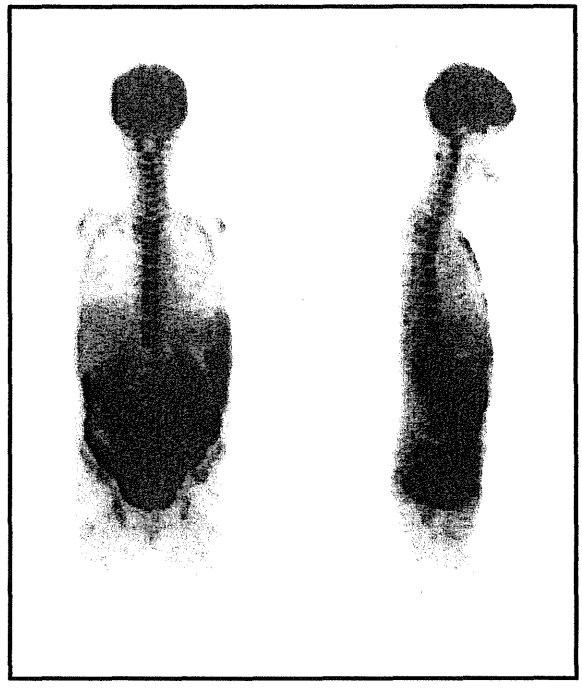

Figure 2 Coronal and sagittal positron emission tomography (PET) images.

Discussion

G-CSF-producing tumors are generally associated with poor prognosis in various types of cancer.[1–4] Among patients with uterine cervical cancer, G-CSF expression and the resulting leukocytosis have been associated with short survival.[6] However, it seems that the same cannot be said for ovarian cancer.[7] According to a previous report, although strong G-CSF expression was observed in 13.1% of tumor specimens, it was not associated with poor prognosis in patients with epithelial ovarian cancer. With regard to endometrial cancer, to our knowledge, only one case of G-CSF-producing tumor has been reported in the English literature.[8] In this article, the author reported a case of G-CSF-expressing endometrial carcinoma that displayed elevated WBC count and markedly increased serum G-CSF concentration (Table 1). However, information regarding the survival outcome of the patients was not described in detail.[8] Thus, the prevalence as well as the clinicopathological characteristics of G-CSF-producing endometrial cancer remains unknown.

The clinical stage of our case was already advanced at the time of initial diagnosis. Although surgery was performed, WBC count and the serum G-CSF concentration continued to increase up to 109 900/mm^3 and 120 000 pg/mL, respectively. This may be explained by the G-CSF produced by the rapidly growing peritoneal tumors (Fig. 2), which resulted in the increased WBC/neutrophil counts. Despite the intensive treatments consisting of surgery plus chemotherapy, the patient died of rapid disease progression four weeks after the initial treatment. This case, in agreement with previously reported cases,[1–4] may suggest the aggressiveness of this type of tumor.

Mainly due to the rarity of reported cases, the optimal treatment for G-CSF-producing endometrial cancer has not been established. In the present case, chemotherapy consisting of paclitaxel and carboplatin

was employed in accordance with our institutional treatment guidelines for endometrial cancer. However, a previous case report showed a response of this type of tumor to high-dose cisplatin, cyclophosphamide, and adriamycin (Table 1). Thus, the clinical activity of high-dose cisplatin, cyclophosphamide, and adriamycin in patients with G-CSF-producing endometrial cancer should be evaluated in future clinical studies.

G-CSF plays a crucial role in granulopoiesis. By stimulating the proliferation, survival, and neutrophilic differentiation of hematopoietic progenitor cells, G-CSF increases the neutrophil count, which is the most abundant cell type among circulating white blood cells. However, the precise mechanism responsible for the aggressiveness of G-CSF-producing tumor remains unclear. It has been reported that G-CSF may serve as an autocrine growth factor.[9,10] Previous studies demonstrated that treatment with exogenous G-CSF enhanced the growth of bladder cancer cells *in vitro*.[9,10] More recently, a paracrine effect of G-CSF has also been reported. Treatment with G-CSF stimulated tumor-associated $CD11b^{+}Gr1^{+}$ myeloid cells and facilitated tumor angiogenesis in vivo.[11] To understand the mechanism responsible for the aggressiveness as well as to establish an optimal treatment for this type of tumor, further investigations are needed.

In summary, we present a case of G-CSF-producing endometrial cancer. Because of its rarity, little is known about G-CSF-producing endometrial cancer. We believe that the reporting of even individual cases is important in order for optimal treatment to be established.

Disclosure

The authors declare that they have no conflicts of interest.

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adrenocorticotropin	ACTH
angiotensin converting enzyme	ACE

antidiuretic hormone	ADH
arginine vasopressin	AVP
atrial natriuretic peptide	ANP
bovine serum albumin	BSA
brain natriuretic peptide	BNP
corticotropin-releasing hormone	CRH
cytidine 5'-mono-, di-, and triphosphates	CMP, CDP, CTP
dehydroepiandrosterone	DHEA
dehydroepiandrosterone sulfate	DHEAS
deoxyribonucleic acid	DNA
ethylenediamine tetra-acetate	EDTA
follicle-stimulating hormone	FSH
growth hormone-releasing hormone	GHRH
gonadotropin-releasing hormone	GnRH (LHRH)
growth hormone (somatotropin)	GH
guanosine 5'-mono-, di-, and triphosphates	GMP, GDP, GTP
high density lipoprotein	HDL
human chorionic gonadotropin	hCG
immunoglobulin	Ig
insulin-like growth factor	IGF
international unit	IU
intramuscular(-ly)	im
intraperitoneal(-ly)	ip
intravenous(-ly)	iv
low density lipoprotein	LDL
luteinizing hormone	LH
melanocyte-stimulating hormone	MSH
messenger RNA	mRNA
nicotinamide adenine dinucleotide phosphate	NADP
its reduced form	NADPH
nicotinamide adenine dinucleotide	NAD
its reduced form	NADH
not significant	ns
oral(-ly)	po
parathyroid hormone	PTH
polymerase chain reaction	PCR
probability	p
prolactin	PRL
reverse transcription-polymerase chain reaction	RT-PCR
ribonucleic acid	RNA
sex hormone-binding globulin	SHBG
somatostatin	SRIF or SS
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standard error	SE
standard error of the mean	SEM
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thyrotropin	TSH
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Comparison of the Prognoses of FIGO Stage I to Stage II Adenosquamous Carcinoma and Adenocarcinoma of the Uterine Cervix Treated With Radical Hysterectomy

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Objectives: To evaluate the significance of adenosquamous carcinoma (ASC) compared with adenocarcinoma (AC) in the survival of surgically treated early-stage cervical cancer.
Methods: We retrospectively reviewed the medical records of 163 patients with International Federation of Gynecology and Obstetrics stage IA2 to stage IIB cervical cancer who had been treated with radical hysterectomy with or without adjuvant radiotherapy between January 1998 and December 2008. The patients were classified according to the following: (1) histological subtype (ASC group or AC group) and (2) pathological risk factors (low-risk or intermediate/high-risk group). Survival was evaluated using the Kaplan-Meier method and compared using the log-rank test. Multivariate analysis of progression-free survival (PFS) was performed using the Cox proportional hazards regression model to investigate the prognostic significance of histological subtype.
Results: Clinicopathological characteristics were similar between the ASC and AC histology groups. Patients with the ASC histology displayed a PFS rate similar to that of the patients with the AC histology in both the low-risk and intermediate/high-risk groups. Neither the recurrence rate nor the pattern of recurrence differed between the ASC group and the AC group. Univariate analysis revealed that patients with pelvic lymph node metastasis and parametrial invasion achieved significantly shorter PFS than those without these risk factors.
Conclusions: Characteristics of the patients and the tumors as well as survival outcomes of ASC were comparable to adenocarcinoma of early-stage uterine cervix treated with radical hysterectomy. Our results in part support that the management of ASC could be the same as the one of AC of the uterine cervix.

Key Words: Cervical cancer, Radical hysterectomy, Adenocarcinoma, Adenosquamous carcinoma, Survival

Received March 24, 2012, and in revised form July 22, 2012.
Accepted for publication July 24, 2012.

(*Int J Gynecol Cancer* 2012;22: 1389–1397)

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ISSN: 1048-891X
DOI: 10.1097/IGC.0b013e31826b5d9b

This work was supported in part by a grant-in-aid for General Scientific Research No 23592446 from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.
The authors declare no conflicts of interest.
Mabuchi, Okazawa, and Morii contributed equally to this study.

Adenocarcinoma (AC) and adenosquamous carcinoma (ASC) of the uterine cervix are relatively uncommon histological subtypes of cervical cancer. The incidence of cervical cancer has decreased by more than 40% during the past 40 years owing to the wider implementation of cytological screening. In contrast to the marked decrease in the incidence of squamous cell carcinoma, the absolute incidence of AC/ASC and its relative frequency compared with squamous cell carcinoma have increased.[1] As a result, AC/ASC of the cervix currently accounts for approximately 20% of all cervical cancers, which is significantly higher than the incidence of 5% to 10% observed in the 1970s.[1]

Early-stage cervical cancer (International Federation of Gynecology and Obstetrics [FIGO] stages IB1-IIA) can be effectively treated with radical hysterectomy or definitive radiotherapy (RT) with similar survival outcomes.[2] Several risk factors have been identified that compromise the treatment outcome in patients with early-stage cervical cancer who are primarily treated with radical surgery.[3–5] Generally, patients with risk factors such as positive pelvic nodes, parametrial invasion, and a positive vaginal margin are regarded to be at "high risk" of recurrence. Moreover, patients with a tumor confined to the cervix that display risk factors such as large tumor size, lymphatic vascular space invasion, and deep stromal invasion are considered to be at "intermediate risk" of recurrence.[3–5] Postoperative RT is usually recommended for patients with these pathological risk factors.[4,5] To date, histological subtype has not been demonstrated to be an independent prognostic factor for survival.

Adenosquamous carcinoma, a variant of adenocarcinoma, is composed of malignant glandular and squamous invasive elements.[6] Although ASC can exhibit unique biological behavior and a different response to treatment compared with AC, currently, patients with ASC receive the same frontline treatments as those with AC.[4,5] The prognostic significance of the ASC histology has been investigated since the 1980s.[7–19] However, mainly owing to the rarity of this condition, it remains uncertain whether patients with ASC have a worse prognosis than those with AC and whether they should follow the same treatment strategy.

The purpose of the current study was to investigate the significance of ASC compared with AC in patients with early-stage cervical cancer treated with radical hysterectomy.

MATERIALS AND METHODS

Patients

Permission to proceed with the data acquisition and analysis was obtained from the Institutional Review Board of Osaka University Hospital and Osaka Medical Center for Cancer and Cardiovascular Diseases. A list of patients who had undergone radical hysterectomy and pelvic lymphadenectomy for FIGO stage IA2 to stage IIB cervical cancer from January 1998 to December 2008 was generated from our institutional tumor registries. Then, through a chart review, patients with ASC or AC were identified. Patients with squamous cell carcinoma, adenoid basal carcinoma, adenoid cystic carcinoma, glassy cell carcinoma, undifferentiated carcinoma, or small cell carcinoma were excluded. Finally, a total of 163 patients (20 patients with ASC and 143 patients with AC) were selected for the statistical analysis. The histological classification of cancers was performed by 2 independent gynecological pathologists based on the World Health Organization (WHO) staging system for tumors of the uterine cervix.[20]

The patients were clinically staged according to the FIGO staging criteria. The pretreatment workup consisted of a complete medical history; a physical examination; a complete blood cell count; biochemistry panels; chest x-rays; computed tomography (CT) of the abdomen and pelvis; pelvic magnetic resonance imaging; and optional intravenous pyelogram, cystoscopy, and rectosigmoidoscopy. For all patients, a preoperative evaluation of the para-aortic lymph nodes (PALN) was performed with a CT scan of the abdomen as part of the routine initial evaluation. Of a total of 163 patients, 76 patients were treated within the context of previous clinical studies.[21–24]

Treatments

Surgery

All patients were treated with radical hysterectomy (type III) and pelvic lymphadenectomy, as reported previously.[21–23] The lymphadenectomy procedure included complete bilateral pelvic lymphadenectomy with the aim of removing all of the external iliac, internal iliac, common iliac, obturator, suprainguinal, and presacral lymph nodes. Intraoperative assessment of the PALN was routinely performed by manual palpation. When PALN metastasis was suspected in a preoperative CT scan or by intraoperative palpation, a nodal resection was performed for histological confirmation. All histological specimens were examined by at least 2 independent pathologists that specialized in gynecological oncology. Patients who had histologic examination–confirmed PALN metastasis were excluded from the study.

Postoperative Radiotherapy

Postoperative RT was indicated when a patient's pathological report displayed any one of the following prognostic factors (intermediate/high-risk group): parametrial invasion, pelvic lymph node metastasis, a positive surgical margin, deep stromal invasion, lymphovascular space invasion, or a large tumor (>4 cm in diameter).

A group of patients with early-stage cervical cancer without any of the above-mentioned adverse risk factors did not undergo postoperative adjuvant therapy (low-risk group).

Basically, the patients were treated with external beam pelvic RT plus concurrent chemotherapy (CCRT), as reported previously.[21–23,25] Patients who refused CCRT or who had cervical cancer before January 1999 were treated with pelvic RT alone. Postoperative pelvic RT was performed using 10-megavolt (MV) x-rays delivered from a linear accelerator using the anteroposterior parallel opposing technique. The superior margin of the external radiation field was located at the top of the fifth lumber vertebra, and the inferior border of the obturator foramen was used as the inferior margin.

TABLE 1. Patients' characteristics and treatment outcomes (ASC vs AC)

	ASC Group (n = 20)		AC Group (n = 143)		
	n	(%)	n	(%)	*P*
Patients' characteristics					
Age					
Median	48		48		0.77
Range	30–67		19–84		
FIGO stage					0.35
IA	0	0	2	1.4	
IB1	12	60.0	99	69.2	
IB2	4	20.0	13	9.1	
IIA	3	15.0	11	7.7	
IIB	1	5.0	18	12.6	
Pelvic node metastasis					0.36
Negative	15	75.0	119	83.2	
Positive	5	25.0	24	16.8	
Parametrial invasion					1.0
Negative	17	85.0	122	85.3	
Positive	3	15.0	21	14.7	
Margin status					0.49
Negative	19	95.0	139	97.2	
Positive	1	5.0	4	2.8	
Stromal invasion					0.15
Less than half	9	45.0	90	62.9	
More than half	11	55.0	53	37.1	
LVSI					0.06
Negative	6	30.0	76	53.1	
Positive	14	70.0	67	46.9	
Maximal tumor diameter,* median, mm	30		25		0.22
Postoperative treatments					0.44
No	8	40.0	79	55.2	
RT	5	25.0	27	18.9	
CCRT	7	35.0	37	25.9	
Treatment outcome					
Patients with recurrence	5	25.0	36	25.2	1.0
Site of recurrence					0.007
Pelvis	2	10.0	14	9.8	
Pelvis and distant	3	15.0	4	2.8	
Distant	0	0	18	12.6	
5-year survival rate, PFS (%)	79.2		74.1		0.97

*The maximal tumor diameter was measured 3-dimensionally based on T2-weighted images.
LVSI, lymphovascular space involvement; No, no adjuvant treatment.

Laterally, the field extended 2 cm beyond the lateral margin of the bony pelvic wall. We used multileaf collimators to block the upper and lower corners of the radiation field. The external irradiation was delivered to the whole pelvis at 2 Gy per fraction in 5 fractions per week for a total of 25 fractions (50 Gy).

Nine patients whose pathological reports revealed multiple pelvic node metastases were treated with extended-field RT (EFRT) without concurrent chemotherapy, as reported previously.[22] Postoperative EFRT was also administered to the patients via 10-MV x-rays delivered from a linear accelerator using the anteroposterior parallel opposing technique. The

radiation field encompassed the pelvic and PALN drainage area. The superior margin of the PALN area was located at the bottom of the T12 vertebral body, and the inferior margin was located at the inferior border of the obturator foramen. The lateral margin was located 1.5 to 2 cm lateral to the widest point of the bony pelvis. The external irradiation was delivered to the EFRT fields for a total of 45 Gy in 25 fractions and to the whole pelvis at 1.8 Gy per fraction for a total of 28 fractions (50.4 Gy).

Follow-Up

The patients were followed up regularly by both gynecological oncologists and radiation oncologists, as reported previously.[26,27] When recurrence was suspected, a biopsy was taken for confirmation whenever possible. The median follow-up duration was 61 months (range, 6–146 months) and 62 months (range, 11–183 months) in the ASC and AC groups, respectively.

Statistical Analysis

The differences between the 2 groups with respect to categorical variables such as clinical stage, histological type, parametrial involvement, deep stromal invasion, surgical margin status, and the recurrence rate were assessed with the Fisher exact test, and odds ratios with 95% confidence intervals were determined. Continuous variables such as age, maximum tumor diameter, and the pretreatment hemoglobin level were analyzed with the Student t test or the Mann-Whitney U test. Survival curves were computed with the Kaplan-Meier method, and the significance of each survival difference was determined with the log-rank test. Significance of survival outcomes was evaluated in univariate (log-rank test). Among the variables that demonstrated statistical significance in the univariate analysis, the multivariate analysis with Cox hazard regression test was performed. All statistical analyses were 2-tailed, and $P < 0.05$ were considered statistically significant. All analyses were performed using MedCalc (MedCalc Software, Mariakerke, Belgium) or Statistical Package for Social Scientists software (SPSS version 12.0, IL).

RESULTS

Patients' Characteristics

One hundred and sixty-three patients were included in this retrospective study. Twenty patients (12.3%) had ASC and 143 patients (87.7%) had AC. The patients' characteristics are shown in Table 1. The median age of the patients with ASC and AC was 48 years. Of the patients with ASC, 12 patients (60%) displayed pathological risk factors such as positive pelvic lymph nodes, parametrial involvement, a positive surgical margin, deep stromal invasion, lymphovascular space involvement, or a large tumor diameter categorized as intermediate/high-risk group. Among the patients with AC, 64 patients (44.8%) displayed pathological risk factors (intermediate/high-risk group). The patients in the intermediate/high-risk groups received postoperative adjuvant RT or CCRT. Eight patients (40%) in the ASC group and 79 patients (55.2%) in the AC group displayed no risk factors (low-risk group), and therefore received no adjuvant therapy after surgery. When the ASC group was compared with the AC group, there were no significant differences in age, clinical stage, pathological risk factors (pelvic node status, parametrial invasion, margin status, stromal invasion, lymphovascular space involvement, and tumor diameter), or postoperative treatment types.

Survival Outcomes

As shown in Table 1, at the time of the data analysis, 5 patients (25.0%) and 36 patients (25.2%) had recurrence in the ASC and AC groups, respectively. There was no significant difference between the recurrence rates of the 2 groups. In the ASC group, 2 patients (10%) developed pelvic recurrence, 3 patients (15%) developed recurrence at both pelvic and distant sites. In the AC group, 14 patients (9.8%) developed pelvic recurrence, 18 patients (12.6%) developed distant

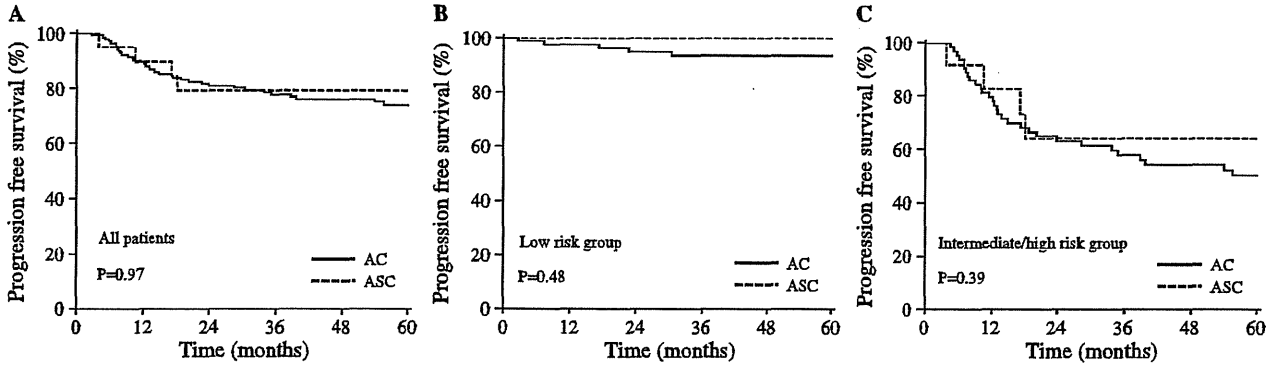

FIGURE 1. Progression-free survival (PFS) of patients with ASC versus those with AC. A, All patients. The PFS rate in the ASC group was equivalent to that in the AC group (log-rank, $P = 0.97$). B, Low-risk patients. The PFS rate in the ASC group was equivalent to that in the AC group (log-rank, $P = 0.48$). C, Intermediate/high-risk patients. The PFS rate in the ASC group was equivalent to that in the AC group (log-rank, $P = 0.39$).

TABLE 2. Patients' characteristics and treatment outcomes (low-risk and intermediate/high-risk groups)

	Low-Risk Group					Intermediate/High-Risk Group				
	ASC Group (n = 8)		AC Group (n = 79)			ASC Group (n = 12)		AC Group (n = 64)		
	n	(%)	n	(%)	*P*	n	(%)	n	(%)	*P*
Patients' characteristics										
Age										0.91
Median	44		45		0.30	52		51		
Range	32–50		29–75			30–67		19–84		
FIGO stage										0.50
IA	0	0	2	2.5	0.10	0	0	0	0	
IB1	7	87.5	76	97.5		5	41.7	23	35.9	
IB2	1	12.5	1	0		3	25.0	12	18.8	
IIA	0	0	0	100		3	25.0	11	17.2	
IIB	0	0	0	0		1	8.3	18	28.1	
Pelvic node metastasis										1.0
Negative	8	100	79	100	1.0	7	58.3	40	62.5	
Positive	0	0	0	0		5	41.7	24	37.5	
Parametrial invasion										0.74
Negative	8	100	79	100	1.0	9	75.0	43	67.2	
Positive	0	0	0	0		3	25.0	21	32.8	
Margin status										1.0
Negative	8	100	79	100	1.0	11	91.7	60	93.8	
Positive	0	0	0	0		1	8.3	4	6.3	
Stromal invasion										0.68
Less than half	8	100	79	100	1.0	1	8.3	11	17.2	
More than half	0	0	0	0		11	91.7	53	82.8	
LVSI										1.0
Negative	4	50.0	66	83.5	0.044	2	16.7	10	15.6	
Positive	4	50.0	13	16.5		10	75.0	54	84.4	
Maximal tumor diameter,* median, mm	25		20		0.15	40		20		0.94
Postoperative treatments										1.0
No	8	100	79	100	1.0	0	0	0	0	
RT	0	0	0	0		5	41.7	27	42.2	
CCRT	0	0	0	0		7	58.3	37	57.8	
Treatment outcome										
Patients with recurrence	1	12.5	5	6.3	0.46	4	33.3	31	48.4	0.37
Site of recurrence										1.0
Pelvis	1	12.5	2	2.5	1.0	1	8.3	12	18.8	
Pelvis and distant	0	0	2	2.5		0	0	2	3.1	
Distant	0	0	1	1.3		3	25.0	17	26.6	
5-year survival rate, PFS (%)	100		93.5		0.63	64.2		50.2		0.32

*The maximal tumor diameter was measured 3-dimensionally based on T2-weighted images.

recurrence, and 4 patients (2.8%) developed recurrence at both pelvic and distant sites. The median time from surgery to recurrence was 17 months (range, 4–64 months) in the ASC group and 13 months (range, 3-107 months) in the AC group. The estimated 5-year progression-free survival (PFS) rates of the ASC and AC groups were 79.2% and 74.1%, respectively

(Table 1). The PFS rate of the ASC group was not significantly different from that of the AC group, as shown in Figure 1A.

We next investigated the prognostic significance of the ASC histology based on pathological risk factors (Table 2; Fig. 1B–C). In the low-risk group, recurrence was observed in 1 patient (12.5%) in the ASC group and 5 patients (6.3%) in the AC group. The estimated that 5-year PFS rates of the ASC and AC groups were 100% and 93.5%, respectively, that is, the patients with ASC displayed a recurrence rate ($P = 0.46$) and PFS rate ($P = 0.48$) similar to those of the patients with AC (Table 2; Fig. 1B).

In the intermediate/high-risk group, recurrence was observed in 4 patients (33.3%) in the ASC group and 31 patients (48.4%) in the AC group. The estimated 5-year PFS rates of the ASC and AC groups were 64.2% and 50.2%, respectively, that is, the patients with ASC displayed a recurrence rate ($P = 0.37$) and a PFS rate ($P = 0.39$) similar to those of the patients with AC (Table 2; Fig. 1C).

Taken together, our results indicate that the ASC histology was associated with comparable survival outcomes compared with the AC histology in patients with early-stage cervical cancer treated with radical hysterectomy (Fig. 1A–C).

To identify prognostic factors, we next investigated the PFS of the patients with ASC according to clinicopathological variables. As shown in Table 3, our univariate analysis identified 2 factors that were associated with shorter PFS: positive pelvic nodes and parametrial invasion. In the multivariate analysis, pelvic nodal metastasis was identified as an independent variable associated with shorter PFS (Table 3; Fig. 2).

DISCUSSION

Based on a positive result from a prospective randomized clinical trial (Gynecologic Oncology Group [GOG] 109/Southwest Oncology Group 87–97), concurrent chemotherapy

TABLE 3. Survival analysis in early-stage adenosquamous carcinoma patients

		PFS	Univariate Analysis		Stepwise Multivariate Analysis†	
Covariate	**No. Patients**	**Median (Months)**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, yrs						
≤50	14	39.8	5.22 (0.58–47.0)	0.14		
>50	6	82.7				
FIGO stage						
≤IB1	12	52.7	2.30 (0.38–13.8)	0.36		
≥IB2	8	58.7				
Pelvic node metastasis						
Negative	15	64.9	21.0 (2.28–193.6)	0.007	25.6 (2.04–330)	0.012
Positive	5	17.2				
Parametrial invasion						
Negative	17	64.0	6.54 (1.06–40.4)	0.043	0.70 (0.08–5.98)	0.74
Positive	3	10.6				
Margin status						
Negative	19	64.0	1.0	1.0		
Positive	1	3.9				
Deep stromal invasion						
Negative	9	38.2	3.11 (0.34–28.1)	0.31		
Positive	11	78.7				
LVSI						
Negative	6	53.2	38.6 (0.02–94227)	0.36		
Positive	14	51.1				
Maximum tumor diameter,* mm						
≤40	17	41.4	1.40 (0.16–12.6)	0.77		
>40	3	78.7				

*The maximal tumor diameter was measured 3-dimensionally based on T2-weighted images.
Conditional backward method was used for stepwise multivariate analysis and only statistically significant variables are shown in the table.
95% CI, 95% confidence interval.

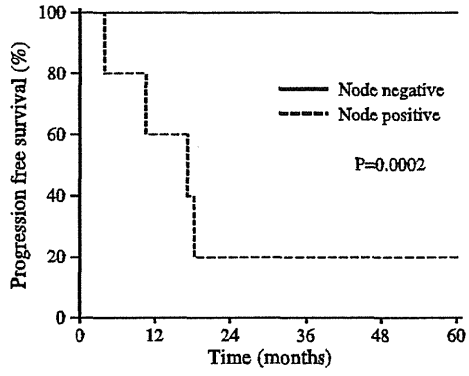

FIGURE 2. Progression-free survival in patients with ASC according to pelvic node status. Node-negative patients with ASC displayed significantly longer PFS than the node-positive patients (log-rank, $P = 0.0002$).

with pelvic RT has become the standard adjuvant treatment after radical hysterectomy for early-stage cervical cancer irrespective of the histological difference.[4] However, because of the lack of a prospective study investigating the survival difference according to histologic type, it remains unclear whether patients with ASC have a poorer prognosis than those with AC.

Adenosquamous carcinoma of the uterine cervix, which was described in 1933 as a "secretory type of epidermoid carcinoma of the cervix", is considered to be a variant of adenocarcinoma.[28] In patients with early-stage cervical cancer treated with radical surgery, some previous retrospective studies showed that patients with AC have a poorer prognosis than patients with squamous cell carcinoma.[13,18,29] The prognosis of ASC was first reported in 1956.[6] In this article, the authors indicated that the ASC histology was associated with a poorer prognosis than pure AC histology.[6] Since then, an increasing number of authors have investigated the prognostic significance of the ASC histology in early-stage cervical cancer.[7–19] We have summarized the articles investigating the prognostic significance of ASC in patients with cervical cancer published after 1980 in Table 4. As shown, to the best of our knowledge, 14 studies, including our study, have been reported. Except for one study,[14] all of these studies were retrospective investigations.[7–13,15–19] Of these, 7 studies included only surgically treated patients, but the others included patients who were treated with surgery or definitive RT. Four of the 14 studies reported a worse prognosis in patients with ASC than in patients with AC. However, including our results, 10 studies have reported equivalent survival outcomes

TABLE 4. Summary of articles investigating the prognostic significance of ASC histology in patients with cervical cancer

Article			No. ASCs			No. ACs			Survival Analysis			
			FIGO Stage			FIGO Stage			5-Year Survival Rate (%)			ASC vs AC
Author (Ref)	Year	Primary Treatment	I	II	III–IV	I	II	III–IV		ASC	AC	*P*
Gallup et al[7]	1985	S+R	15	3	2	7	2	1	Stages I–IV	20	80	<0.01
Hopkins et al[8]	1988	S+R	37	0	0	87	0	0		53	62	NS
Kilgore et al[9]	1988	S+R	37		10	93		22	Stage I	82	71	NS
									Stages II–IV	28	37	NS
Goodman et al[10]	1989	S+R	14	0	0	35	0	0		86	79	NS
Yazigi et al[11]	1990	S+R	28	0	0					88		
Harrison et al[12]	1993	S	45		0	25		0	Stages I–II	78	78	NS
Shingleton et al[13]	1995	S+R	185	67	0	667	175	0	Stage I	77	84	NS
									Stage II	54	57	NS
Look et al[14]	1996	S	64	0	0	104	0	0		72	88	0.007
Lea et al[15]	2003	S	39	0	0	139	0	0	Low-risk	88	99	<0.01
									High-risk	63	79	<0.01
Farley et al[16]	2003	S+R	60	19	9	148	16	21	Stage I	86	89	NS
									Stages II–IV	22	63	<0.01
Alfsen et al[17]	2001	S	20	0	0	253	0	0		55	80	NS
Yasuda et al[18]	2006	S	28	0	0	81	0	0		82	92	NS
Reis et al[19]	2007	S	29	0	0	97	0	0		82	92	NS
Current study	2012	S	16	4	0	114	29	0		79.2	74.1	NS

NS, not significant; R, radiotherapy; Ref, reference number; S, surgery; SCC, squamous cell carcinoma.

between patients with ASC and AC.[8–13,17–19] Moreover, when we examined the articles that included only surgically treated patients, 5 of the 7 studies have reported equivalent survival outcomes among the 2 histological subtypes.[12,17–19] The results from these studies indicate that the ASC histology is not associated with a worse prognosis than pure AC histology in patients with early-stage cervical cancer.

In the current study, although the patients with ASC in the low-risk group were effectively treated with radical surgery, a significant number of patients with ASC in the intermediate/high-risk group had recurrence and died of their disease (Fig. 1B-C). Our multivariate analysis revealed that pelvic nodal metastasis was an independent predictor of shorter PFS in patients with ASC. This finding is consistent with those of a previous report that showed that patients with ASC with positive pelvic nodes display worse survival than those without this finding.[13] The prognostic factors in patients with ASC need to be investigated further in larger clinical studies.

To improve the prognosis of patients with ASC with pelvic node metastasis, novel treatment strategies need to be developed. One strategy that might improve patient outcomes is the addition of consolidation chemotherapy after postoperative CCRT. Based on the results of a recent investigation demonstrating the survival benefit of adding consolidation chemotherapy to definitive chemoradiotherapy,[30] the Gynecologic GOG is currently conducting a phase 3 clinical trial (GOG0724) comparing postoperative cisplatin-based CCRT with or without consolidation chemotherapy using carboplatin-paclitaxel.[31] As 60% (3/5) of recurrences developed at distant sites in the current study, the clinical benefit of adding consolidation chemotherapy after postoperative CCRT should be investigated in future clinical trials with the aim of controlling occult distant metastases and prolonging survival.

The limitations of our study need to be addressed. One is the small sample size. Because only 20 patients with ASC were included in the current study, we could not investigate the survival difference between AC and ASC according to the adjuvant treatment used, that is, postoperative RT alone or concurrent chemoradiotherapy. Moreover, owing to its retrospective nature, potential confounding biases might have been missed in the analysis.

In conclusion, we showed that patients with early-stage cervical ASC have an equivalent prognosis to those with AC. In the multivariate analysis, pelvic nodal metastasis was identified as an independent variable associated with shorter PFS in patients with ASC. To draw a definitive conclusion regarding the prognostic significance of the ASC histology, further investigations should be performed in the setting of a large-scale, prospective, randomized controlled study.

ACKNOWLEDGMENTS

The authors thank the colleagues Drs Takayuki Enomoto, Masami Fujita, Kiyoshi Yoshino, Tateki Tsutsui, Fumiaki Isohashi, Yasuo Yoshioka, Shintaro Maruoka, Takashi Miyatake, and Yukinobu Ota for participating in this study. The authors also thank Remina Emoto for her secretarial assistance.

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Contemporary management of endometrial cancer

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The treatment of endometrial cancer has changed substantially in the past decade with the introduction of a new staging system and surgical approaches accompanied by novel adjuvant therapies. Primary surgical treatment is the mainstay of therapy but the effectiveness and extent of lymphadenectomy has been challenged, and its acceptance as a routine procedure varies by country. The role of radiation has evolved and chemotherapy has been incorporated, either alone or combined with radiation, to treat the many patients in whom cancer recurs because of a tumour outside the originally radiated pelvic and lower abdominal area. Use of traditional adjuvant chemotherapeutics has been challenged in clinical trials of new agents with improved side-effect profiles. Novel agents and targeted therapies are being investigated. Research into genetic susceptibility to endometrial cancer and the potential genetic aberrations that might translate into therapeutic interventions continues to increase. Substantial global variability in the treatment of endometrial cancer has led to examination of long-accepted norms, which has resulted in rapidly changing standards. International cooperation in clinical trials will hasten progress in treatment of this ubiquitous cancer.

Published Online
March 22, 2012
DOI:10.1016/S0140-6736(12)60442-5

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Introduction

Endometrial cancer is a major cause of morbidity and mortality for women worldwide, with nearly 200 000 cases diagnosed every year; it is the seventh most common malignancy.[1] Incidence differs between regions: it is the most common cancer of the female genital tract and the fourth most common cancer after breast, lung, and colorectal cancers in North America and Europe.[2,3]

Most women with endometrial cancer are diagnosed at an early stage with uterine-confined tumours, often after having vaginal bleeding. Despite the overall favourable prognosis of endometrial cancer, some women have aggressive neoplasms such as high-grade or deeply invasive lesions, or tumours consisting of non-endometrioid cells such as papillary serous or clear cells, and are at substantial risk of recurrence and death. Prognostic factors include age, race, stage, grade, ploidy, depth of invasion, tumour size, receptor status, and cell type.[4] The most common pattern of presentation is postmenopausal bleeding, and diagnosis is generally via endometrial biopsy or dilatation and curettage (figures 1, 2).

Endometrial cancer occurs most frequently in postmenopausal women. The most important risk factor for endometrial cancer is exposure to unopposed oestrogen. Case-control studies[5,6] have suggested that the risk for women who use unopposed oestrogen is two-times to ten-times higher than for non-users. As a result of the production of oestrone by adipose tissue, obesity is also an important risk factor for endometrial cancer.[7] Results of a meta-analysis[8] showed that endometrial cancer was one of the cancers most strongly associated with obesity. Similarly, tamoxifen is associated with a slightly increased risk of endometrial cancer. In women with breast cancer using tamoxifen, the relative risk for the development of endometrial cancer compared with controls was 7·5 (1·6/1000 *vs* 0·2/1000).[9]

Although most endometrial cancers are thought to be sporadic, some women have a genetic predisposition for the disease. The most common genetic syndrome associated with endometrial cancer is hereditary non-polyposis colorectal cancer syndrome (HNPCC) or Lynch syndrome,[10] which is an autosomal dominant cancer-susceptibility syndrome. It is most often due to an inherited mutation in one of the DNA mismatch repair genes *MLH1, MSH2, MSH6,* or *PMS2*.[10,11] Endometrial cancer associated with HNPCC occurs in young women.[11] The lifetime risk of endometrial cancer in women with HNPCC has been estimated at 40–60%.[12,13]

Endometrial cancers have been broadly classified into two types.[14] Type I neoplasms, which are most common, include endometrioid adenocarcinomas. Type I neoplasms generally arise from atypical endometrial hyperplasia and are oestrogen dependent. Type II neoplasms include more aggressive histological variants such as clear-cell and serous carcinomas and uterine carcinosarcomas. Non-endometrioid tumours are less common than endometrioid tumours but are associated with disproportionately high mortality. Our Review focuses on type I endometrial tumours. Treatment frameworks for endometrial cancer have changed substantially in the past decade because traditional modes of management have been challenged, and novel approaches have emerged. Several initiatives designed to improve outcomes are being assessed. We discuss unresolved issues about the route and extent of surgical staging, use of adjuvant therapy for patients at intermediate and high risk, and treatment of recurrent disease.

Search strategy and selection criteria

We searched Medline, Current Contents, and PubMed, between Jan 1, 1980 and Jan 31, 2011 with the search terms "uterine cancer" and "endometrial cancer". We included select references from articles identified by this strategy. We included only papers published in English between 1980 and 2010, plus abstracts converted to final publications up to Nov 15, 2011.

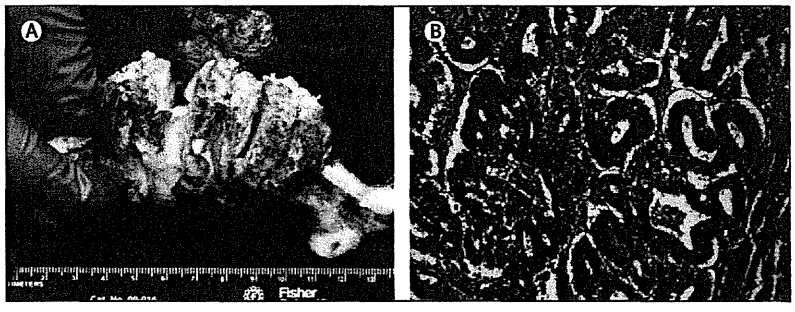

Figure 1: **Endometrial adenocarcinoma**
(A) Tumour invading 60% into the uterus wall. (B) Micrograph of well differentiated endometrioid type adenocarcinoma. The tumour has endometrial glands and stroma. Magnification ×40.

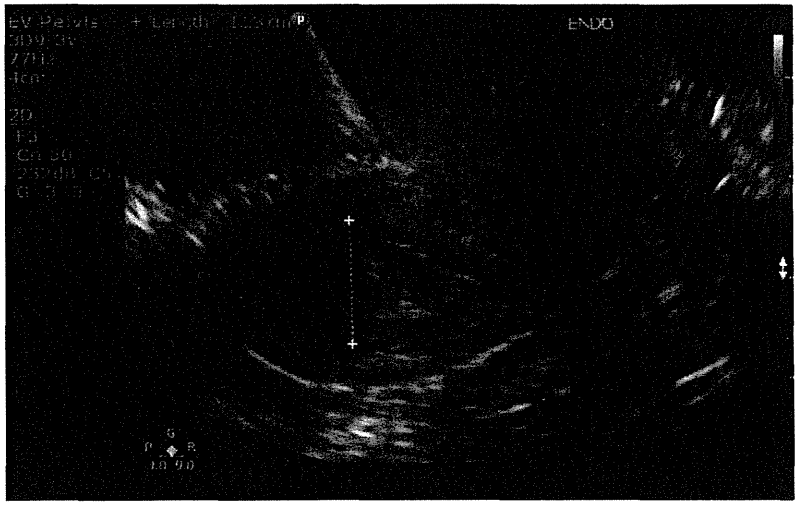

Figure 2: **Transvaginal ultrasound of the uterus**
Cross-sectional image of the uterus shows a thickened endometrial lining (12·3 mm) characteristic of endometrial cancer.

	Description
Stage I	Tumour confined to the corpus uteri
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
Stage II	Tumour invades cervical stroma, but does not extend beyond the uterus*
Stage III	Local or regional spread of tumour, or both
IIIA	Tumour invades the serosa of the corpus uteri or adnexae, or both†
IIIB	Vaginal or parametrial involvement, or both†
IIIC	Metastases to pelvic or para-aortic lymph nodes, or both†
IIIC1	Positive pelvic nodes
IIIC2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV	Tumour invades bladder, or bowel mucosa, or distant metastases, or all three
IVA	Tumour invasion of bladder or bowel mucosa, or both
IVB	Distant metastases, including intra-abdominal metastases or inguinal lymph nodes, or both

At all stages, tumour grade can be 1, 2, or 3. *Endocervical glandular involvement should be considered only as stage I and no longer as stage II. †Positive cytology has to be reported separately without changing the stage.

Table 1: **International Federation of Gynecology and Obstetrics staging system for endometrial cancer, 2009[21]**

Pathological factors and staging

Spread to the regional lymph nodes is the most important prognostic factor for women with endometrial cancer.[15–18] A series of surgicopathology studies associated several uterine risk factors including tumour grade, myometrial invasion, lymphvascular space involvement, and cervical stromal invasion with an increased risk of nodal metastasis and decreased survival.[4,19,20] For example, the risk of lymph-node metastasis is five-times greater in women with deeply myoinvasive tumours than in those with superficially invasive neoplasms. Poorly differentiated cancers are six-times more likely to spread to the regional lymphatics than are well differentiated lesions.[4] The presence or absence of nodal disease and uterine risk factors affect the choice of adjuvant treatment for women with endometrial cancer. The importance of uterine risk factors and nodal metastasis was recognised in 1988, when the staging criterion for endometrial cancer was changed from a clinical to a surgical staging system. In 2009, the International Federation of Gynecology and Obstetrics further modified this classification system (table 1).[21]

Primary surgical treatment

Historically, hysterectomy was often preceded by intracavitary radiation but this approach has been replaced by initiatives to stage patients surgically to avoid unnecessary use of radiotherapy. Furthermore, traditionally almost all investigations were done via laparotomy whereas many operations worldwide are now done by minimally invasive techniques, where availability of technology allows. Vaginal hysterectomy is another option, but this approach restricts exploration of the abdominal cavity, peritoneal washing procurement, lymph-node dissection, and omentectomy as indicated. Issues of contention are the route and role of comprehensive staging, specifically whether and to what extent lymph-node dissection is necessary, and whether ovaries should be preserved in some patients. Many women with endometrial cancer are elderly and have several medical comorbidities. Therefore, both the primary surgical treatment and adjuvant therapy must be tailored accordingly.

Although the main route of spread for endometrial cancer is through lymphatic dissemination, the role of lymphadenectomy for women with early stage endometrial tumours is controversial. Some gynaecological oncologists advocate selective lymph-node sampling in women at high risk for nodal metastases (with high-grade or deeply invasive tumours) whereas others recommend routine systematic lymphadenectomy in all patients. Strategies using selective nodal assessment are potentially limited by the difficulty in prediction of the depth of tumour invasion and final tumour grade intraoperatively.[22,23] In a report of 181 patients with a preoperative diagnosis of grade 1 endometrial tumours, 19% of the tumours were upgraded and 18% of patients were upstaged on final pathology.[24] Proponents of

www.thelancet.com Published online March 22, 2012 DOI:10.1016/S0140-6736(12)60442-5

lymphadenectomy have argued that the procedure provides important diagnostic information that best selects optimum delivery of adjuvant therapy.[25]

Several studies have investigated the therapeutic potential of lymphadenectomy and its effect on survival. The necessary extent of nodal dissection is debated. Fotopoulou and colleagues[26] recorded high rates of metastasis in para-aortic nodes even above the level of the inferior mesenteric artery. Although results of retrospective reports suggest that survival is improved in women who undergo extensive nodal dissection,[27–29] results of two randomised trials[30,31] did not show a survival benefit for the procedure.[27–31] The multinational ASTEC (A Study in the Treatment of Endometrial Cancer) trial randomly assigned more than 1400 women to hysterectomy and salpingo-oophorectomy with or without lymphadenectomy. After surgery patients underwent a second randomisation into a radiotherapy trial. The investigators recorded no benefit for lymphadenectomy in either overall or recurrence-free survival.[31] Another study of more than 500 women reached similar conclusions.[30] Although critics have pointed out several methodological flaws of the studies such as the absence of quality control for the lymphadenectomy, findings from these studies have raised questions about the therapeutic role of lymphadenectomy in endometrial cancer.[32] Both trials reported small but statistically significant increases in the rates of perioperative complications and operative times with lymphadenectomy.[30,31] To decrease the morbidity of lymphadenectomy several studies have examined sentinel lymph-node dissection. Estimates of sensitivity and specificity for the detection of metastatic disease have varied widely and the technique is considered experimental.[33]

Hysterectomy and bilateral salpingo-oophorectomy are the foundation of treatment of endometrial cancer. The method by which this operation is done has changed substantially during the past decade in most parts of the world as both laparoscopic and robotic approaches have been shown to be feasible. In 1993, Childers and colleagues[34] reported the feasibility and safety of laparoscopic or laparoscopic-assisted approaches including lymphadenectomy. The results have been confirmed in other studies.[35–37] Prominent among these studies was the Gynecologic Oncology Group LAP-2 trial,[37] a randomised comparison of conventional abdominal hysterectomy plus lymphadenectomy with laparoscopic assisted vaginal hysterectomy plus lymphadenectomy in more than 2600 patients with clinical stage I or IIA endometrial cancer. The laparoscopic approach was associated with longer operating times but a shorter hospital stay than laparotomy. Laparoscopy was initiated in 1682 patients and completed without conversion in 1248 (74·2%). The main advantage of these minimally invasive approaches compared with laparotomy has been faster recovery, shorter hospital stay, and lower morbidity overall in patients with endometrial cancer, many of whom have significant comorbid disorders. The median number of lymph nodes removed was 24 (IQR 16–34) for laparoscopy and 25 (16–33) for open surgery.[37] However, laparoscopy was associated with only small improvements in quality of life.[38] Follow-up to establish the effect of laparoscopy on recurrence and survival is continuing.

Robotic-assisted surgical staging and treatment of endometrial carcinoma has been suggested as a useful alternative to open or laparoscopic surgery.[39] Reported advantages of robotic hysterectomy over conventional laparoscopy include three-dimensional imaging, greater range of motion, a shorter time to learn the technique, and possibly improved feasibility of lymphadenectomy in obese patients.[40] In one retrospective cohort study[39] comparing robotic, laparoscopic, and open hysterectomy, the robotic approach was associated with the highest lymph-node yield, shortest hospital stay, and lowest blood loss. Despite the potential advantages of robotic hysterectomy, the substantial resources needed and cost of use are greater than with laparoscopic surgery.[41]

Although most women with endometrial cancer are postmenopausal, about 20% of endometrial cancers occur in premenopausal women. For young women, ovarian preservation has been advocated in carefully selected patients who undergo surgery.[42–44] Although ovarian preservation prevents surgical menopause, patients are at risk of synchronous and metasynchronous ovarian neoplasms. For women who have not completed childbearing, uterine preservation by medical treatment with a progestational agent can be considered. Results of several small observational studies[45] have suggested that as many as three-quarters of women with well differentiated endometrial cancer will respond to progestagen-based therapy. Careful follow-up is mandatory in these patients because recurrences are common.[45] The ideal progestational agent and duration of therapy are unknown.

	Grade 1	Grade 2	Grade 3
Stage IA			
Adverse risk factors not present	Observe	Observe or vaginal brachytherapy	Observe or vaginal brachytherapy
Adverse risk factors present	Observe or vaginal brachytherapy	Observe or vaginal brachytherapy with or without pelvic radiotherapy	Observe or vaginal brachytherapy with or without pelvic radiotherapy
Stage IB			
Adverse risk factors not present	Observe or vaginal brachytherapy	Observe or vaginal brachytherapy	Observe or vaginal brachytherapy with or without pelvic radiotherapy
Adverse risk factors present	Observe or vaginal brachytherapy with or without pelvic radiotherapy	Observe or vaginal brachytherapy with or without pelvic radiotherapy	Observe or pelvic radiotherapy with or without vaginal brachytherapy with or without chemotherapy

Potential adverse risk factors include age older than 60 years, lymphovascular space invasion, tumour size, and lower uterine (cervical or glandular) involvement.

Table 2: **National Comprehensive Cancer Network recommendations for the adjuvant treatment of endometrial cancer, 2011[46]**

Adjuvant treatment for low-risk and intermediate-risk endometrial cancer

The adjuvant treatment of women with low-risk and intermediate-risk endometrial cancer is one of the most controversial topics in gynaecological oncology. Table 2 shows the US National Comprehensive Cancer Network treatment recommendations for stage I and II endometrial cancer.[46] Women with grade 1 and 2 tumours confined to the endometrium have an excellent prognosis and are considered low risk. In one analysis[47] the 10-year recurrence risk for this subset of patients was only 3%. In view of this favourable prognosis, adjuvant therapy is usually withheld.[48–51]

Although definitions vary in individual studies, the remainder of women with stage I and II tumours are considered intermediate risk. So far, no study of adjuvant treatment has convincingly shown survival benefit in this subgroup of women. In patients who have undergone comprehensive staging, survival is favourable even without further therapy.[52] Radiation has been the most frequently prescribed treatment; however, two studies[53,54] have examined the use of chemotherapy either alone or in combination with radiation for intermediate-risk patients. Radiation reduces the risk of local, pelvic recurrence but does not improve survival in women with stage I or II endometrial cancer (table 3).[55–59] Investigators for the Postoperative Radiation Therapy for Endometrial Carcinoma (PORTEC)-1 trial randomly assigned 715 patients with stage IB grade 2–3 tumours or stage IC grade 1–2 tumours to either observation or whole pelvic radiotherapy. After 10 years of follow-up survival did not differ between groups but pelvic radiation reduced the risk of vaginal recurrence from 15% to 4%.[55] A Gynecologic Oncology Group trial[56] done in the USA in women with early-stage disease who had undergone lymphadenectomy as part of their treatment had similar findings.

The inability of adjuvant pelvic radiotherapy to improve survival stems partly from the fact that many recurrences occur at the vaginal cuff and can be salvaged with radiotherapy at the time of recurrence. However, the results from these trials must be interpreted with caution because many patients included in the studies were at low risk of death from endometrial cancer.[55–58] These trials might therefore not have the power to identify a survival advantage for early-stage patients at greatest risk.

In view of these limitations, investigators have attempted to identify subgroups of patients with early-stage endometrial cancer who might benefit from radiotherapy. An analysis of more than 21000 patients in the US National Cancer Institute's Surveillance, Epidemiology, and End Results database showed that radiation improved survival for women with stage IC tumours.[60] Results of two meta-analyses[61,62] have suggested that radiation is associated with improved survival for patients with stage IC, grade 3 neoplasms.

Pelvic radiotherapy, especially after lymphadenectomy, can be associated with pronounced adverse effects.[55,56] 25% of 354 patients in the radiotherapy group of PORTEC-1 had late complications.[55] To decrease the morbidity associated with pelvic radiotherapy while attempting to preserve the benefits of decreasing locoregional recurrences, vaginal brachytherapy is now widely used for intermediate-risk endometrial cancer.[62] Vaginal brachytherapy is administered in the outpatient setting with a vaginal cylinder. With high-dose rate schedules, three fractions of 7 Gy each are delivered at 1 week intervals. A randomised trial comparing[59] whole pelvic radiotherapy and vaginal brachytherapy for intermediate-risk endometrial cancer (PORTEC-2) showed no difference in survival between the two methods. The investigators noted that although the vaginal recurrence rate was 1·8% for brachytherapy compared with 1·6% for external beam radiation, pelvic recurrences were more frequent with brachytherapy (3·8% *vs* 0·5%).[59]

Endometrial cancer was previously thought to spread predominantly through lymphatic dissemination, but clinicians now recognise that even women with tumours

	Sample size	Inclusion criteria	Surgery	Treatment	Locoregional recurrence	Overall survival
Norwegian Radium Hospital[57]	540	Stage I (all)	TAH or BSO	Brachytherapy *vs* brachytherapy and pelvic radiotherapy	7% *vs* 2% (5 year) p<0·01	89% *vs* 91% (5 year) p=NS
PORTEC-1[55]	715	Stage IB (grade 2, 3), stage IC (grade 1, 2)	TAH or BSO (LNS allowed)	Observation *vs* pelvic radiation	14% *vs* 4% (5 year), p<0·0001	85% *vs* 81% (5 year), p=0·31
GOG 99[56]	392	Stage IB, stage IC, stage II occult	TAH or BSO or LNS	Observation *vs* pelvic radiation	12% *vs* 3% (2 year), p=0·007	86% *vs* 92% (4 year), p=0·55
ASTEC[58]	905	Stage IA or IB (grade 3), IC, IIA	TAH or BSO with or without LNS	Observation *vs* pelvic radiation	6·1% *vs* 3·2% (5 year), p=0·02	84% *vs* 84% (5 year), p=0·31
PORTEC-2[59]	427	Stage IC (grade 2, 3, age >60 years), IB (grade 3, age >60 years), IIA	TAH or BSO with or without LNS	Brachytherapy *vs* pelvic radiation	5·1% *vs* 2·1% (5 year), p=0·42	86% *vs* 82% (5 year), p=0·66

TAH=total abdominal hysterectomy. BSO=bilateral salpingo-oophorectomy. LNS=lymph node surgery. NS=not significant.

Table 3: **Randomised controlled trials of adjuvant therapy for intermediate-risk endometrial cancer**