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Stage IVB endometrial cancer: clinical course and survival of patients with single and multiple metastases

O. Kraemer[1], E. Rapiti[2], D. Huber[1], E. Lopes-Raimundo[3], M. Usel[2], C. Bouchardy[2], P. Petignat[1]

[1] Surgical Gynecologic Oncology Unit, Gynecologic Division, Geneva University Hospital, Geneva
[2] Geneva Cancer Registry, University of Geneva, Geneva [3] Faculty of Medicine, University of Geneva, Geneva (Switzerland)

Summary

Objective: Metastatic endometrial cancer (EC) at initial presentation is a rare disease. The present aim was to evaluate prognostic factors and overall survival in patients diagnosed with metastatic EC. *Study Design:* Using data from the Geneva Cancer Registry, the authors included all patients diagnosed with Stage IVB EC from 1980-2007. Estimates of survival were calculated using the Kaplan-Meier method and compared using the log-rank test. *Results:* A total of 38 patients were identified. The most frequent metastases were peritoneal or pleural carcinomatosis (66%, n=25) and hematogenous metastases (53%, n=20). Five-year survival rate was 5.7% (95% confidence interval: 0.0 - 13.3), and median survival was 7.6 months. Survival of patients with a single metastasis at the time of diagnosis was longer than for patients with multiple metastases (16 versus two months, respectively; $p < 0.001$). *Conclusion:* Metastatic EC is rare disease with very poor prognosis particularly for patients with multiple site metastases.

Key words: Advanced endometrial cancer; Metastatic endometrial cancer; Stage IVB endometrial cancer.

Introduction

Endometrial carcinoma (EC) is the most common gynecologic malignancy in Switzerland with an incidence of 24-25/100,000 women per year and a mortality rate of 3.4/100,000 per year [1].

In almost 90% of cases, EC presents with abnormal vaginal bleeding or discharge leading to an early diagnosis [2-4]. In approximately 75% of EC patients, the tumor is confined to the uterine body corresponding to FIGO Stage I and has a favorable prognosis. For these patients, primary therapy is surgery (total hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy) and the five-year overall survival (OS) rate exceeds 85% [5]. Nevertheless, 3-13% of newly diagnosed EC patients present with advanced stage disease and a five-year survival rate ranging from 0-20% [3, 6, 7]. Stage IV EC accounts for up to 25% of disease-specific mortality during the first year following diagnosis [8, 9].

Stage IVA corresponds to a loco-regional extension to the bladder and/or the rectum and Stage IVB includes EC with distant metastases [10]. Treatment options for Stage IV EC include radiotherapy, chemotherapy, surgery, and hormonal therapy. The low incidence, the heterogeneous clinical presentation, and the poor prognosis contribute to the lack of consensus with respect to optimal management of advanced stage EC patients. Therapeutic strategies for Stage IVB EC patients remain a complex problem for the clinician as these women usually have important comorbidities and are believed to have aggressive forms of the disease and a limited life expectancy. To better understand prognosis, day-to-day treatment practices and OS, the authors conducted a population-based analysis of women diagnosed with Stage IVB EC.

Materials and Methods

The Geneva Cancer Registry collects information from various sources. All hospitals, pathology laboratories, and private practitioners are requested to report every cancer case. Trained tumor registrars systematically extract data from medical and laboratory records and physicians regularly receive enquiry forms to complete missing data. In addition to passive follow-up (routine examination of death certificates and hospital records), the registry regularly assesses survival through an active follow-up performed routinely each year using the files of the Cantonal Population Office, which is in charge of the registration of the resident population. For all dead patients, the registry medical staff systematically consults medical files and/or writes to the practitioner to assess cause of death and code the cause according to the WHO classification. The registry is considered accurate, as witnessed by its very low percentage (<2%) of cases recorded only from death certificates [5]. Recorded data include socio-demographic characteristics, diagnostic circumstances, tumor characteristics, stage of disease at diagnosis, treatment during the first six months after diagnosis, survival, and cause of death.

Searching the data from the Geneva Cancer Registry recorded between January 1980 and December 2007, the authors identified 1,164 women with EC. Patients with uterine sarcomas and malignant mixed Müllerian tumors were not included. A total of 47 patients were diagnosed with Stage IVB EC. Nine cases were ex-

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Table 1. — *Stage IVB endometrial cancer: patients and tumor characteristics (n=38).*

Variable		No. patients (%)
Age (years) median (range)		75 (*53-97*)
Parity	Nulliparous	10 (26)
	Multiparous	17 (45)
	Unknown	11 (29)
Histologic Type	Endometrioid	34 (89)
	Seropapillary, clear cells	4 (11)
Grading	G1	9 (24)
	G2	10 (26)
	G3	7 (18)
	Unknown	12 (32)

Table 2. — *Stage IVB endometrial cancer: symptoms at diagnosis and localization of metastasis (n=38).*

Variable	No. patients (%)
Symptoms*	
Gynecologic	23 (61)
General	16 (42)
Abdominal, gastrointestinal	10 (26)
Pain (neither abdominal nor pelvic)	6 (16)
Unknown	2 (5)
Metastatic site**	
Hematogenous metastasis	20 (53)
Lung	10 (26)
Liver	9 (24)
Other***	18 (47)
Lymph node metastasis	8 (21)
Peritoneal and/or pleural carcinomatosis	25 (66)

* Some patients had more than one symptom.
** Some patients had metastasis to more than one site.
*** Other: bone, intestine, brain, adrenal gland, and spleen.

Table 3. — *Stage IVB endometrial cancer: treatment at the time of diagnosis (n=38).*

Treatments	No. patients (%)
Surgical treatment of the primary tumor*	15 (39)
Therapy without surgery on the primary tumor	9 (24)
No therapy	14 (37)

* Total hysterectomy and bilateral salpingo-oophorectomy.

cluded according to the following criteria: a) diagnosis of a second cancer within two months (n=6), b) identification of metastases more than three months after diagnosis (n=1), and c) missing patient documentation (n=2). Therefore, statistical analysis was based on the remaining 38 patients. Variables of interest were age, parity, diagnosis-related symptoms, FIGO stage, histological subtype and grade, metastasis localization, and treatment during the first six months (surgery, radiotherapy, chemotherapy and hormonal therapy).

All patients were followed for survival up to April 30, 2010. Five-year OS was estimated according to the Kaplan-Meier method. The log-rank test was used to compare survival curves according to other variables such as grade, symptoms, site of metastasis, and treatments. Differences were considered statistically significant when the associated *p*-value was less than 0.05. All statistical analyses were performed using the SPSS software (Version 15).

Results

A total of 38 patients were diagnosed with Stage IVB EC, representing 3.2% of all EC cases recorded during the period under study. Patient and tumor characteristics are summarized in Table 1. Median age at diagnosis was 75 years (range 53-97). All patients were postmenopausal and 26% were nulliparous. Endometrioid carcinoma was the most common histological type (89%, n=34).

Symptoms at diagnosis were classified as follows (Table 2): gynecological symptoms (metrorrhagia, spotting, leukorrhea, and vaginal discharge), general symptoms (weight loss, asthenia, fatigue, nocturnal sweating, and dyspnea), abdominal symptoms (abdominal distension, abdominal pain, constipation, diarrhea, nausea, vomiting, and melena) as well as other forms of pain (bone and articulation pain, inguinal pain or pain while walking). Gynecological symptoms were predominant in 61%, while general symptoms were reported in 42% of the cases.

Thirty-six of 38 patients (95%) were diagnosed following a consultation due to symptoms; one patient was diagnosed during an annual examination, and one patient was diagnosed during recovery from an abdominal trauma. Table 2 summarizes the metastatic sites. Hematogenous dissemination was observed in more than 50% of patients (n=20, 53%), including pulmonary (n=10, 26%) and hepatic metastasis (n=9, 24%). Other metastatic sites in the present cohort were: peritoneum, pleura, bones, intestines, lymph nodes, brain, adrenal glands, and spleen.

The authors classified patients into three groups. Group I included 15 patients (39%) who benefited from surgery on the primary tumor with or without other therapies (radiotherapy, chemotherapy, hormonal treatments). Surgery included total hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy. Radical hysterectomy with recto-sigmoid resection was performed on two patients. One patient with peritoneal carcinomatosis underwent cytoreductive surgery and another patient had a lung lobectomy. Group II included nine patients (24%) who received other treatments but no surgical intervention on the primary tumor (i.e. no hysterectomy). Two patients benefited from cerebral metastasis resection and adjuvant brain radiotherapy. Group III included 14 patients (37%) who did not receive any type of treatment (Table 3).

The median survival time was 7.8 months (0.7 - 79 months; mean 14.8 months). The survival curve is plotted in Figure 1. The five-year OS rate was 5.7% (95% confidence interval [CI]: 0 - 13.3). Two patients were five-year survivors, one of whom was alive at 77.9 months of follow-up. One patient was lost to follow-up, three patients died of un-

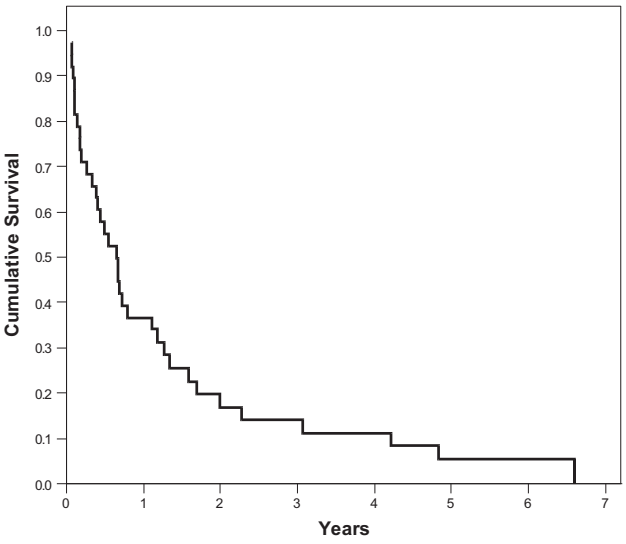

Figure 1. — Survival-curve of 38 patients with Stage IVB endometrial cancer.

Table 4. — *Stage IVB endometrial cancer: survival of women according to tumors characteristics, symptoms, metastatic site, and therapy (n=38).*

Variable	No. patients (%)	Median (months)	*p**
Grade			0.108
G1	9 (24)	3.2	
G2 + G3	17 (44)	14.0	
Unknown	12 (32)	4.6	
Symptoms			0.932
Gynecologic	23 (61)	8.0	
Others	15 (39)	5.1	
Site of metastasis			0.913
Peritoneal and/or pleural carcinomatosis	25 (66)	8.0	
Other	13 (34)	7.6	
Number of metastasis			0.000
Unique	22 (58)	14.0	
Multiple	16 (42)	2.0	
Treatment			0.000
Surgery on primary tumor	15 (39)	15.2	
Treatment without surgery on primary tumor	9 (24)	8.1	
No treatment	14 (37)	1.5	

* Survival estimates were compared using the log-rank test.

known causes, and four patients (11%) died from causes other than EC. Table 4 shows the median survival times according to histological grade, symptoms, metastatic site, and treatment. No significant difference in survival was observed between the histological subgroups ($p = 0.108$). The median survival time was eight months for the group with gynecological symptoms and 5.1 months for the group with other types of symptoms, but the difference was not statistically significant. Patients with peritoneal carcinomatosis (with or without other metastases) did not show any difference in median survival (eight months) from those without peritoneal carcinomatosis (7.6 months, $p > 0.05$). Survival inversely correlated with the number of metastatic sites (p log-rank test < 0.001). Twenty-two patients (58%) with a single metastasis had a median survival of 14 months (95% CI: 4.5 - 23.0), while 16 patients (42%) with multiple metastatic sites had a median survival of only two months (95% CI: 0.9 - 3.8). Five-year survival for a single metastasis was 9.9% versus 0% for multiple metastases (Figure 2). Statistical analysis revealed that the type of treatment was a significant prognostic factor. Median survival was 15.2 months (95% CI: 11.9 - 18.5) for patients in group I, 8.1 months (95% CI: 7.9 - 8.3) for those in group II, and 1.5 months (95% CI: 0 - 3.1) for those in group III ($p < 0.001$). Five-year OS estimates for the three groups were 7.5% (95% CI: 0 - 21.5), 11.1% (95% CI: 0 - 31.6), and 0%, respectively.

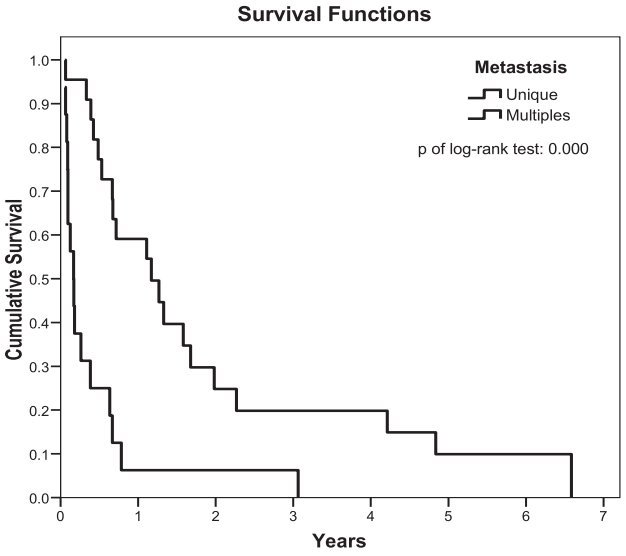

Figure 2. — Survival-curve of 38 patients with Stage IVB endometrial cancer by number of metastasis.

Discussion

In the present population, the incidence rate of metastatic EC was 3.2%, within the estimates of 1.3-9% reported in other studies [3, 10, 11]. Stage IVB EC encompasses a small and heterogeneous population with a wide diversity of clinical presentations and performance status, which impairs the identification of significant prognostic factors and explains the lack of standardized treatment protocols for these patients.

Classically, EC manifests by spontaneous and painless vaginal bleeding or discharge during the late reproductive years or in postmenopause. Ayhan *et al.* reported that up to

92% of Stage IVB patients presented with gynecologic symptoms [12]. In the presented series, only 23 patients (61%) exhibited gynecologic symptoms. Fifteen patients (39%) presented with symptoms related to the metastatic site. The most frequent metastatic sites were the peritoneum, the pleura, the lung, and the liver. The largest series published to date by Eto *et al*. included 248 Stage IVB EC patients having endometrioid, serous as well as carcinosarcoma, and reported that 77% had intra-abdominal metastases and in 44% of cases the peritoneum was involved [3]. In a series of 55 Stage IVB EC patients, Numazaki *et al.* reported a 65.5% rate of peritoneal carcinomatosis [13].

The most important prognostic factor in the present cohort was the number of metastatic sites at the time of diagnosis. Patients who had a single metastasis exhibited a better median survival than those who had multiple metastatic sites, 14 months versus two months, respectively ($p<0.001$). Bristow *et al.* [8] reported a similar observation.

Recent data in metastatic breast cancer suggest that removing the primary tumor could have a beneficial effect on survival [14-18]. To the present authors' knowledge, no data support an association between surgical removal of the primary tumor and improved long-term outcome in advanced stage EC patients. In the present series, patients in group I benefited from an advantage in survival compared with patients in groups II and III. Removal of the primary tumor might represent an attractive therapeutic option for a subset of patients unfit for optimal cytoreductive surgery and might offer a potential survival benefit. However, data about the general health status and complete comorbidities were lacking. It is probable that patients with a poor general status or with important comorbidities such as cardiopulmonary disease and morbid obesity were less likely to undergo surgery and constitute a selection bias accounting for the observed survival benefit of surgery.

Conclusions

The present study has several limitations including the small study group sample size, its retrospective nature, and incomplete data regarding patient comorbidities. The major strength was its population-based sampling over a period of 28 years. The present incidence rate may thus be one of the most accurate ever published for FIGO IVB EC. These data reflect the current management and treatment approaches proposed in everyday practice, including patients who did not receive treatment.

In conclusion, metastatic EC is a rare and heterogeneous disease with a great variety of clinical manifestations, ranging from a single metastasis to multiple organ involvement. This study supports the idea that total disease burden plays a central role in survival, as patients having multiple metastases have a poorer prognosis than those having a single one.

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Address reprint requests to:
D. HUBER, M.D.
Surgical Gynecologic Oncology Unit
Geneva University Hospital
30 Bd. de la Cluse, 1211 Geneva (Switzerland)
e-mail: danahuber1926@gmail.com