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Ultrasonographic detection of asymptomatic endometrial cancer in postmenopausal patients offers no prognostic advantage over symptomatic disease discovered by uterine bleeding

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Abstract

The aim of this study was to investigate whether endometrial carcinoma (EC) screening by transvaginal sonography (TVS) has a prognostic advantage over symptomatic EC. In a retrospective study, 190 postmenopausal patients with symptomatic EC and 123 asymptomatic patients with suspicious endometrium detected by TVS were analysed regarding clinical, socio-economic and histopathological findings. Total bleeding time and the International Federation of Gynecology and Obstetrics (FIGO) tumour stage were evaluated with respect to their effect on survival. In 123 asymptomatic patients with suspicious endometrium, 16 (13%) EC, 61 (50%) polyps, 21 (17%) hyperplasias, 23 (19%) atrophias, 1 (0.8%) myoma and 1 (0.8%) metastasis were found. TVS findings in asymptomatic patients resulted in unnecessary operations, which were associated with considerable costs totalling at least €116 256. Compared with screened asymptomatic patients, symptomatic patients were significantly ($P < 0.05$) older, more frequently obese, and hypertensive, had a larger proportion of cases living in rural areas and visited their gynaecologists rarely. The bleeding time of symptomatic patients strongly correlated with the tumour stage ($P < 0.0001$). Depending on the bleeding time, the 5-year disease-free survival and overall survival rates were 77% and 86% (no bleeding), 83% and 98% (< 8 weeks), 74% and 90% (8–16 weeks), and 62% and 69% (> 16 weeks), respectively. The corresponding tumour stage-related data for disease-free and overall survival were 100% (Ia; both rates), 87% and 95% (Ib), 66% and 93% (Ic), 63% and 78% (II) and 36% (III/IV; both rates), respectively. Postmenopausal vaginal bleeding represents an early symptom of EC, but it is not always perceived as problematic by the patients. There is no prognostic advantage for screened compared with symptomatic patients, who had bleeding of shorter than 8 weeks. Moreover, patients who are at a high risk for EC tend to avoid TVS screening. Finally, endometrial screening often results in unnecessary operations, which are associated with increased morbidity and costs.

Keywords: Postmenopausal bleedings; Endometrial carcinoma; Transvaginal sonography; Bleeding time

1. Introduction

Due to an increased life expectancy generally observed worldwide, there will be a substantial increase in the number of postmenopausal and older women in the future and a subsequent increase in the number of patients with endometrial carcinoma (EC). The incidence of EC in Germany was reported to be approximately 10 000 new cases in 1997, most of which occurred in postmenopausal women [1]. The prognosis for patients with EC is good, if the disease is detected at an early stage [2–4]. Screening for endometrial carcinoma by transvaginal ultrasound (TVS) [5–7] or Vabra [8] presumably results in an earlier detection of asymptomatic disease and is, therefore, recommended. However, as the incidence of EC is low and the screening costs are high, false-negative ultrasound findings cause an increase in the rate of unnecessary invasive procedures.

A major concern with regard to screening is that many of the patients who are at high risk for the development of EC are elderly, obese women with substantial

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health problems, who tend to avoid endometrial screening. Furthermore, the rate of iatrogenic morbidity may increase with screening [9]. Thus, if postmenopausal bleeding is a symptom of early EC, TVS screening is not justified. However, there is no study confirming a prognostic advantage of TVS screening for asymptomatic EC with respect to disease-free survival and overall survival over symptomatically detected EC.

Thus, the aim of this study was to investigate whether vaginal bleeding in postmenopausal patients is an early symptom of EC and to compare these symptomatic patients with those in whom EC was detected by TVS screening thereby investigating any potential prognostic advantage of screening versus symptomatic detection of EC as well as assessing the costs involved.

2. Patients and methods

2.1. Study design and patients

Between June 1991 and June 1997, a histological examination was performed in 1150 postmenopausal patients, who presented to our clinic with vaginal bleeding from the uterus. 214 EC cases (19%) were confirmed histologically. 24 Patients (11%) with no follow-up data were excluded from the study. Finally, 190 patients with histologically confirmed EC were suitable for study. During the same period, 123 postmenopausal patients with sonographically suspicious endometrium, but without any bleeding were admitted to our clinic for histological examination. Since these patients reported no symptoms, the evaluation of the endometrium was based on TVS. The diagnosis of EC was confirmed in 16 (13%) of these asymptomatic patients. This retrospective study was designed to compare the 190 symptomatic EC patients with the 123 asymptomatic patients with sonographically suspicious endometrium with respect to patient characteristics, treatment and prognosis.

2.2. Analysed data

In symptomatic patients, the bleeding time was defined as the time between the first episode of postmenopausal vaginal bleeding and the definitive, histological diagnosis. The bleeding times were divided as follows: <8, 8–16 and >16 weeks. Age, body mass index (BMI), hypertension or diabetes, frequency of regular gynaecological examinations before symptoms were reported, place of residence, tumour grading, sonometry-derived endometrial thickness, and sonomorphological data were recorded. A low socioeconomic status was assigned to the patients when the yearly income was low enough to exempt them from any financial contribution to therapy costs. The median follow-up time was 55 months (range: 24–97). According to Ferrazzi and colleagues [10], body mass index (BMI) (weight in kilograms divided by the square of the height in metres) was subdivided as follows: $\leqslant 25$ $\mu g/m^2$ (normal weight), 26–29 (moderate overweight) and >29 (obesity). Maximum endometrial thickness was measured along the longitudinal plane of the uterus and sonographically imaged with a transvaginal probe of 5.0 MHz. Suspicious endometrium was characterised by a sonographically determined endometrial thickness equal to or thicker than 10 mm, and/or by an endometrial morphology showing at least one irregularity, such as inhomogeneity, lack of a clear border to the myometrium (loss of the hypoechogenic peripheral halo), or cystic areas.

2.3. Treatment

Hysteroscopy followed by dilatation and curettage (D&C) were recommended [11] and performed in 132 (69.5%) symptomatic and in 102 (82.9%) asymptomatic patients. The remaining 58 symptomatic women (30.5%) and 21 asymptomatic women (17.1%) underwent D&C only. Surgical therapy was tumour stage-dependent (hysterectomy with bilateral oophorosalpingectomy and proximal vaginal cuff resection for the International Federation of Gynecology and Obstetrics (FIGO) stage I EC [12], radical hysterectomy for FIGO stage II EC according to Wertheim-Meigs, and two exenterations for stage III EC were performed in 174 (84.5 %) of all EC patients. Due to advanced EC stages or severe contra-indications, 32 patients (15.5%) of the 206 EC cases were treated with primary radiotherapy. Since 1994, the removal of the pelvic lymph nodes has gradually become part of the surgical procedure in FIGO stage I patients. Thus, in many patients the lymph node status was not known and could, therefore, not be evaluated. Transcutaneous radiation therapy following surgery was performed in patients with FIGO stage Ic EC or higher disease stages. The current staging system, as described by the FIGO [12], was used for tumour classification. In 32 patients without surgically confirmed FIGO stage (e.g. in patients with primary radiotherapy), the tumour stage was classified clinically.

2.4. Cost–benefit analysis

Cost analysis was based on the charge per hospital day billed by the respective hospital as from January 2000 (€420 per day). For hysteroscopy and D&C, the hospital was reimbursed on the basis of two hospital days, i.e. €840 per patient. The hospital stay after hysterectomy with bilateral oophorosalpingectomy averaged 9.1 (6–21) days and depended on the mobilisation and reconvalescence of the older patients more than on the specifics of the surgical procedure.

2.5. Statistical analysis

The Mann–Whitney U-test, Chi-square test, and Spearman correlation coefficient were used for statistical analysis of the data. Differences in the survival of symptomatic and asymptomatic patients were evaluated by the log-rank test. Multivariate Cox analysis was used for disease-free survival. In all tests, the significance level was set at $P < 0.05$, and all tests were two-tailed.

3. Results

3.1. Patient characteristics

The clinical characteristics of the asymptomatic patients with suspicious endometrium and of the symptomatic patients with confirmed endometrial carcinoma (EC) are shown in Table 1. The mean age (±standard deviation; S.D.), of the asymptomatic patients (61.1±6.7 years) and symptomatic patients (68.8±5.5) differed significantly ($P < 0.0001$). Other conditions such as moderate or severe overweight ($P = 0.014$), hypertension ($P < 0.0001$), and diabetes mellitus ($P = 0.06$) were more frequently observed in the symptomatic EC group. While 68% of the symptomatic patients had not undergone a gynaecological examination during the year before symptoms were noticed by the patient, only 17% of the asymptomatic patients had not visited their gynaecologists ($P < 0.0001$) during this 1-year period. Patients with symptomatic endometrial carcinoma lived much more frequently ($P = 0.026$) in rural areas (29%) than asymptomatic patients (18%). No significant differences were seen regarding the socio-economic status and postoperative complications.

3.2. Histological findings

Endometrial carcinomas ($n = 16$, 13%), polyps ($n = 61$, 50%), hyperplasias ($n = 21$, 17%), unsuspicious cases of atrophic endometrium ($n = 23$, 19%), myoma ($n = 1$; 0.8%), and breast cancer metastasis ($n = 1$; 0.8%) were confirmed histologically in 123 asymptomatic patients with suspicious endometrium (Fig. 1). Hyperplasia was non-atypical (simple or complex) in 16 cases and atypical (simple or complex) in 5 cases. Due to hyperplasia,

Table 1
Patient characteristics

	Symptomatic patients with EC ($n = 190$) n (%)	Asymptomatic patients with thickened endometrium ($n = 123$) n (%)	P value
Age (years)			
Mean±S.D.	68.8±5.5	61.1±6.7	< 0.0001
Range	49–91	48–87	
Body Mass Index (BMI) (kg/m^2)			
⩽25	61 (32)	57 (46)	
26–29	78 (41)	47 (38)	0.014
> 30	51 (27)	19 (15)	
Hypertension			
Yes	98 (52)	37 (30)	< 0.0001
No	92 (48)	86 (70)	
Diabetes mellitus			
Yes	62 (33)	28 (23)	0.06
No	128 (67)	95 (77)	
Frequency of gynaecological examinations per year[a]			
0	129 (68)	21 (17)	
1–2	40 (21)	76 (62)	< 0.0001
⩾3	3 (2)	24 (20)	
No data	18 (9)	2 (2)	
Place of residence			
Urban	135 (71)	101 (82)	0.026
Rural	55 (29)	22 (18)	
Socioeconomic status			
Low	46 (24)	24 (20)	0.33
High	144 (76)	99 (80)	
Complications due to hysteroscopy or D&C	3 (2)	3 (2)	0.59

EC, endometrial carcinoma; S.D., standard deviation; D&C, dilation and curettage.
[a] Before symptoms were reported.

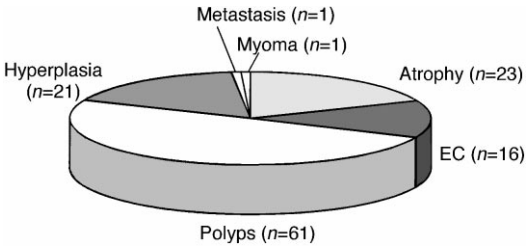

Fig. 1. Histopathological findings in asymptomatic patients with sonographically suspicious endometrium. EC, endometrial carcinoma.

10 patients underwent immediate hysterectomy, which did not reveal EC. In 6 patients with non-atypical hyperplasia, hysteroscopy and D&C were repeated after progestagen treatment. Hyperplasia persisted histologically in 2 of these 6 patients, but was not identified in the remaining 4 cases. However, 3 out of the 6 patients underwent a hysterectomy. All 16 patients with asymptomatic endometrial carcinoma underwent abdominal hysterectomy with bilateral oophorosalpingectomy and vaginal cuff. The final FIGO tumour stages were 3 patients with stage Ia (19%), 11 (69%) with stage Ib and two (13%) with stage Ic. These cases did not differ significantly ($P=0.10$) from the distribution in the 57 symptomatic patients with a bleeding time shorter than 8 weeks and FIGO stage I: 14% Ia, 65% Ib and 21% Ic (Table 2). Of the 16 asymptomatic patients with EC, both patients with stage Ic and 1 patient with stage Ib had disease recurrence. However, no recurrence was observed in the stage Ia patients.

3.3. Bleeding times

Using the Chi-square test, it was observed that the bleeding times were longer in patients with advanced tumour stages than in patients with earlier tumour stages. In 40% (57/141) of all stage I cases, bleeding lasted less than 8 weeks. In contrast, in only 10% (3/31) of the patients with stage III/IV, was the bleeding time shorter than 8 weeks. In 77% (24/31; $P=0.0001$) the bleeding lasted longer than 16 weeks. The mean age (±S.D.) of the patients in the asymptomatic group was 63.5±4.9 years. In the symptomatic patient group, a correlation was noticed between longer bleeding times

Table 2
Clinical and sonometric data correlated with bleeding times

Parameter	Bleeding time (in weeks)				Total ($n=206$) n (%)	P value
	0 ($n=16$) n (%)	<8 ($n=67$) n (%)	8–16 ($n=51$) n (%)	>16 ($n=72$) n (%)		
Age (years, mean + S.D.)	63.5±4.9	66.3±4.0	68.4±5.1	72.2±6.2		<0.05[a]
Body Mass Index						
<25	6 (38)	25 (37)	16 (31)	21 (29)	68 (33)	0.359
25–30	6 (38)	30 (45)	16 (31)	28 (39)	80 (39)	
>30	4 (25)	12 (18)	19 (37)	23 (32)	58 (28)	
FIGO stage[b]						
I	16 (100)	57 (85)	37 (73)	31 (43)	141 (68)	<0.0001
Ia	3 (19)	8 (14)	4 (11)	0	15 (11)	
Ib	11 (69)	37 (65)	27 (73)	19 (61)	94 (67)	
Ic	2 (13)	12 (21)	6 (16)	12 (39)	32 (23)	
II	0	7 (10)	10 (20)	17 (24)	34 (17)	
III/IV	0	3 (4)	4 (8)	24 (33)	31 (15)	
Grading						
I	5 (31)	24 (36)	16 (31)	27 (38)	72 (35)	0.51
II	9 (56)	24 (36)	20 (39)	21 (29)	74 (36)	
III	2 (13)	19 (28)	15 (29)	24 (33)	60 (29)	
Sonometry (mm)[c]						
<5	0	5 (7)	1 (2)	0	6 (3)	0.713
5–9	3 (19)	13 (19)	11 (22)	14 (19)	41 (20)	
⩾10	13 (81)	46 (69)	37 (73)	55 (76)	151 (73)	
not done	–	3 (4)	2 (4)	3 (4)	8 (4)	
Suspicious endometrial morphology[d]	14 (88)	58 (91)	41 (84)	51 (74)	164 (83)	0.37
Hypertension	8 (50)	41 (61)	30 (59)	38 (53)	117 (57)	0.54
Diabetes	3 (19)	23 (34)	15 (29)	26 (36)	67 (33)	0.55

[a] Mann–Whitney U-test; 0 versus <8 weeks: $P=0.018$; 0 versus 8–16 weeks: $P=0.001$; 0 versus >16 weeks: $P<0.001$.
[b] For statistical analysis, comparison of stage I with grouped together stages II–IV.
[c] For statistical analysis, cases with an endometrial thickness ⩽9 mm were grouped together and compared with cases with a thickness ⩾10 mm.
[d] Ultrasound was performed in 198 of the 206 patients with EC.

Table 3
Multivariate analysis with regard to disease-free survival

	P-value	Relative risk (95% confidence interval (CI))
FIGO stage	0.0001	2.2042 (1.6418–2.9592)
Age	0.0250	0.9629 (0.9315–0.9953)
Bleeding time	0.1139	0.9873 (0.9717–1.0031)
Sonometry	0.4582	1.0093 (0.9849–1.0343)

and increasing age, i.e. 66.3±4.0 years in patients with bleeding times shorter than 8 weeks, 68.4±5.1 (in patients with bleeding times of 8–16 weeks), and 72.2±6.2 (in patients with bleeding times of >16 weeks), respectively ($P<0.001$). No significant correlation could be detected between bleeding times and body mass index, histological grading, endometrial thickness, endometrial morphology, hypertension or diabetes, respectively (Table 2). In cases with an endometrium thinner than 5 mm, suspicious endometrial sonomorphology was only seen in 6 (3%) of the 190 patients with EC and vaginal bleeding.

The median bleeding times increased with advanced tumour stages (Fig. 2). Patients with stage Ia/b EC showed a median bleeding time of 12 (25th–75th percentile: 6–16) weeks. The corresponding data for stage Ic EC were 16 weeks (6–20; $P=0.11$), 16 weeks for stage II (12–28; $P=0.0001$), and 28 weeks for stages III/IV (16–78; $P=0.0001$). Twenty-five per cent of the patients with stage III/IV EC reported a bleeding time of more than 78 weeks. One women (aged 81 years) reported an atypical vaginal bleeding period of 5 years.

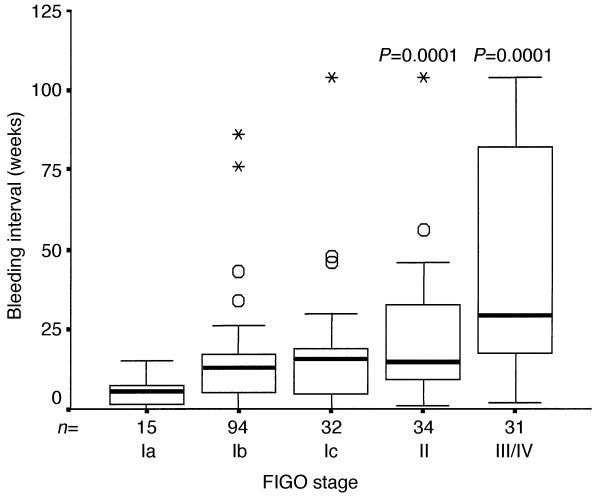

Fig. 2. Correlation of International Federation of Gynecology and Obstetrics (FIGO) stages in endometrial carcinoma (EC) with bleeding times. Significance levels of differences in bleeding times in comparison with Ia/b tumour stages. The boxes represent the range between the 25th and 75th percentiles with a horizontal line at the median. The bars delineate the 5th and 95th percentiles. The circles = more than 1.5 box lengths from the 75th percentile and asterisks = more than 3 box lengths from the 75th percentile indicate extreme values.

Using the Spearman test, a significant positive correlation could be confirmed between bleeding time and age (Rho = 0.1493, $P=0.032$), increased endometrial thickness (Rho = 0.3240, $P=0.001$), and advanced tumour stage (Rho = 0.4756, $P=0.0001$), respectively. No correlation was found between BMI and bleeding time or tumour stage (Rho = 0.0146, $P=0.289$).

3.4. Disease-free and overall survival

The recurrence-free survival and overall survival rates were estimated with respect to tumour stage and bleeding time using the Kaplan–Meier analysis (Figs. 3–6). Advanced tumour stage and longer bleeding time were generally associated with a poorer prognosis. Within a mean observation period of 55 months, there were no recurrences or deaths in patients with stage Ia EC. Patients with asymptomatic EC and patients with bleeding times of up to 8 weeks showed no significant differences in disease-free and overall survival.

Depending on the bleeding time, the 5-year disease-free survival and overall survival rates were 77% and 86% (no bleeding), 83% and 98% (<8 weeks), 74% and 90% (8–16 weeks), and 62% and 69% (>16 weeks), respectively. The corresponding tumour stage-related data for disease-free and overall survival were 100% (Ia; both rates), 87% and 95% (Ib), 66% and 93% (Ic), 63% and 78% (II) and 36% (III/IV; both rates), respectively.

To assess whether bleeding time is an independent early symptom of EC, multivariate analyses were done including age, sonometry, bleeding time and tumour stage (Table 3). Only the FIGO tumour stage ($P=0.0001$) and age ($P=0.025$) — but not the bleeding time — could be confirmed to be independent prognostic factors. With each more advanced tumour stage,

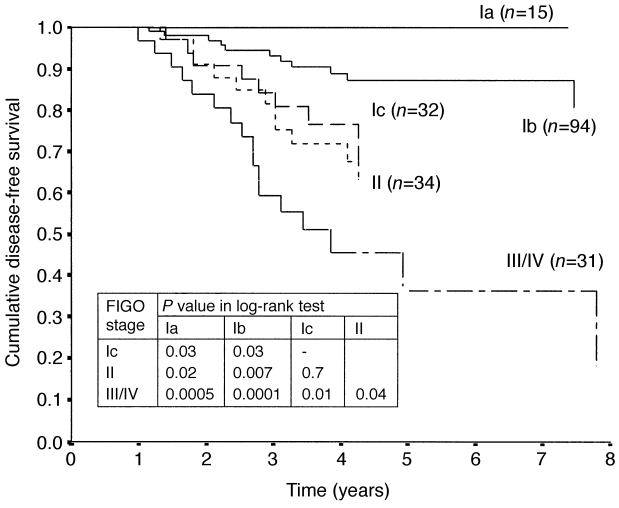

Fig. 3. Correlation between disease-free survival and FIGO tumour stage. Analysis of statistical significance between different bleeding times.

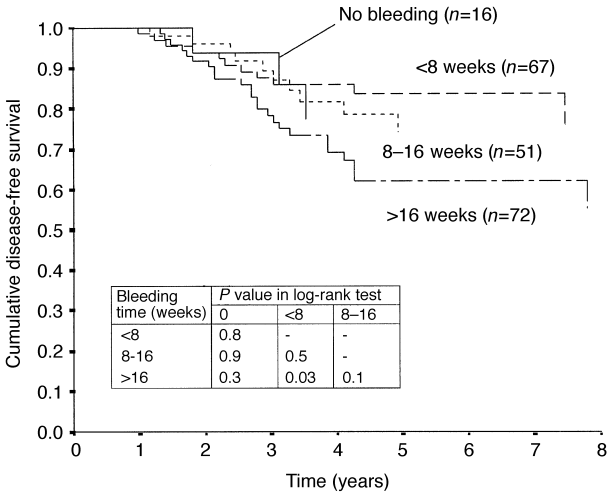

Fig. 4. Correlation between disease-free survival and bleeding time. Analysis of statistical significance between different bleeding times.

the risk of recurrence increased 2.2-fold compared with the lower stage tumours. However, with increasing age, the risk of recurrence decreased by 3.7% per year.

3.5. Cost–benefit analysis

Taken together, hysterectomy was strictly indicated in 5 cases with precancerous lesions (atypical hyperplasias) and 16 patients with EC. However, 29 patients underwent a hysterectomy, resulting in additional costs of approximately €30 576 (8 patients×9.1 days×€420) due to sonographical endometrial screening. Moreover, 102 patients with suspicious endometrium were subjected to hysteroscopy and D&C. The costs of these invasive diagnostic procedures amounted to €85 680 (102 patients×€840). In summary, TVS screening of the endometrium led to additional costs of at least €116 256.

4. Discussion

Screening for any type of carcinoma is aimed primarily at the detection of early-stage disease before symptoms occur and should result in a significantly improved overall survival. Moreover, screening tests should offer sufficient sensitivity, specificity and predictive values, preferably at low costs. In addition, it is necessary to achieve wide acceptance among patients and to include in particular, high-risk patients (for EC these include those of increased age with obesity, diabetes and/or hypertension). However, as shown in this study, many younger patients without such risk factors for EC development were frequently screened, whereas the high-risk patients would not regularly undergo gynaecological examinations including TVS. Thus, it seems that asymptomatic women give more attention to their body and health.

Nevertheless, the hypothesis that vaginal bleeding is a late symptom and does not occur before advanced stages have developed provides support for endometrial screening. In a prospective study of 18 patients, Shipley and Nelson [13] did not detect differences with regard to bleeding time in mild EC tumour stages (myometrial invasion $<50\%$, G1) compared with advanced disease (myometrial invasion $>50\%$, G3). In contrast, we and others [14,15] have found a significant correlation between increased bleeding time and advanced tumour stage. This confirms vaginal bleeding as an early symptom of EC in postmenopausal patients. Suspicious endometrium thinner than 5 mm was seen in only 3.0% of the EC patients with bleeding, but has never been found in asymptomatic patients. Independent of bleeding times, no statistically significant differences were detected in endometrial thickness and morphology between the asymptomatic and symptomatic patients. Thus, although TVS is a valuable tool for the evaluation

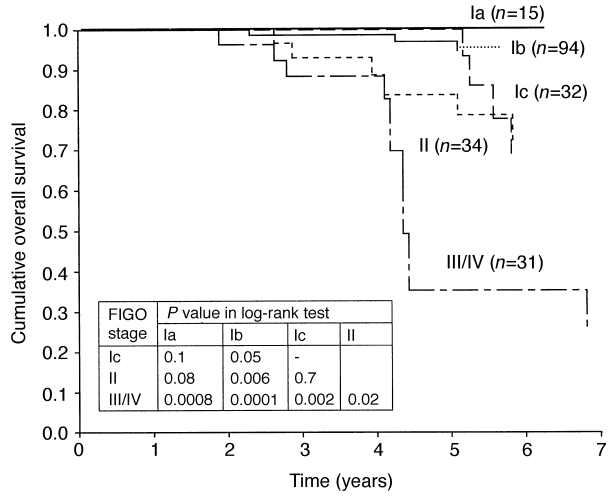

Fig. 5. Correlation between overall survival and FIGO tumour stage. Analysis of statistical significance between different bleeding times.

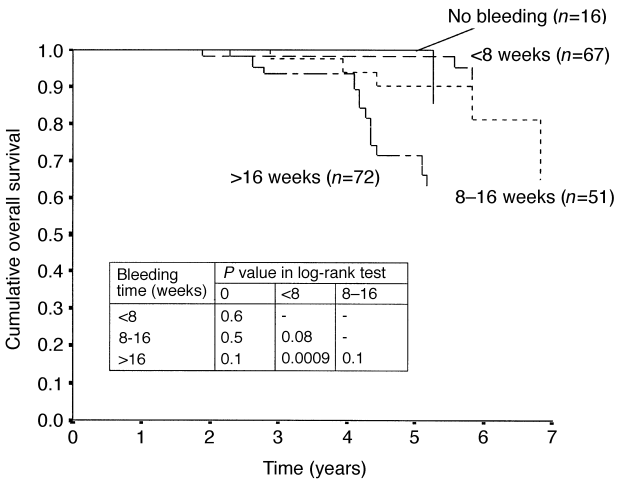

Fig. 6. Overall survival depending on the bleeding time. Analysis of statistical significance between different bleeding times.

of postmenopausal bleeding in addition to gynaecological examination, almost half of all postmenopausal bleedings are caused by functional conditions and do not necessitate invasive diagnostic procedures [10,16–19]. Moreover, colour Doppler sonography revealed no superiority over conventional ultrasound in the detection of premalignant and malignant lesions [20].

Obermair and associates [14] and Menczer and coworkers [21] demonstrated a possible correlation between longer bleeding times and age, histological grade, lymph-node status, vessel invasion, myometrial invasion and histological subtypes, but these values did not reach statistical significance. However, other studies [22,23] reported a significant correlation between longer bleeding time, increased myometrial invasion and histological grading. Garzetti and colleagues [15] found a significantly shorter mean diagnostic delay in patients with stage I disease versus stage III/IV cases. Diagnostic delay directly correlated with common prognostic variables, clinical stage, and depth of myometrial invasion. Anderson and colleagues [24] showed that morbid obesity positively affects survival in endometrial carcinoma. This effect is explained by the association of obesity with a less aggressive form of the disease. In the study presented here, we could not detect a significant correlation between BMI and bleeding time or tumour stage, but obesity was significantly more frequent in women with symptomatic EC than in women with asymptomatic EC.

Using a life table analysis, we found that tumour stage and duration of vaginal bleeding equally influence disease-free survival and overall survival of postmenopausal EC patients. Osmers and colleagues [6] showed that asymptomatic EC patients screened by transvaginal ultrasound are likely to have a better prognosis than those patients identified symptomatically. However, in our study, we did not find significant differences between symptomatically identified patients with bleedings shorter than 8 weeks and asymptomatic EC patients identified by screening with regard to the frequency of tumour stages and survival data. The prognosis of asymptomatic and symptomatic patients is mainly influenced by the FIGO tumour stage, but a correlation also exists between bleeding time and tumour stage. Multivariate analysis confirmed FIGO stage as the strongest factor for disease-free survival. FIGO stages indicate the degree of tumour aggressiveness (e.g. proliferation, grading, invasiveness, etc.) more clearly than bleeding alone. Advanced tumour stages increased the risk of recurrence 2.2-fold. Age could also be confirmed as a significant independent prognostic factor in that the risk of recurrence decreased with advancing age.

In addition to our finding that TVS screening of the endometrium does not have a prognostic advantage, the use of this method is also associated with iatrogenic morbidity, a decrease in the quality of life of mainly elderly women, and an increase in the costs of health insurance. We calculated the costs of unnecessary invasive procedures in asymptomatic patients to be €116 256, but these costs will increase considerably due to additional preoperative examinations (chest X-ray, eletrocardiogram (ECG), laboratory, spirometry, etc.).

In summary, our results show that asymptomatic EC patients identified by screening have no prognostic advantage over postmenopausal patients who visited their gynaecologists immediately after bleeding had occurred. Since TVS does not offer an advantage in the early detection of asymptomatic EC, a screening of the endometrium by TVS, in our opinion, is not justified. Moreover, this diagnostic procedure results in increased iatrogenic morbidity and unnecessary costs. As a consequence, patients who are at risk for the development of EC should be informed that vaginal bleeding is an early symptom of EC.

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