ACTA ONCOLOGICA, 2017
VOL. 56, NO. 2, 262–269
http://dx.doi.org/10.1080/0284186X.2016.1267396

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Detection of recurrence in early stage endometrial cancer – the role of symptoms and routine follow-up

Mette Moustgaard Jeppesen[a], Ole Mogensen[b], Dorte Gilså Hansen[c], Maria Iachina[d], Malene Korsholm[a] and Pernille Tine Jensen[a]

[a]Department of Gynaecology and Obstetrics, Faculty of Health Sciences, Odense University Hospital, Clinical Institute, University of Southern Denmark, Odense, Denmark; [b]Department of Obstetrics and Gynaecology, Karolinska University Hospital, Sweden and Clinical Institute, University of Southern Denmark, Odense, Denmark; [c]The National Research Center of Cancer Rehabilitation, Research Unit of General Practice, University of Southern Denmark, Odense, Denmark; [d]The Research Unit of Clinical Epidemiology, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

ABSTRACT

Background: Considerable controversy remains as to the optimal organization of endometrial cancer follow-up.

Aim: To evaluate the relationship between the way recurrence was detected and survival after treatment for endometrial cancer. Further, to identify characteristics associated with a pre-scheduled examination in women with symptomatic recurrence.

Material and methods: All women with early stage endometrial cancer during 2005–2009 were included in a population-based historical cohort derived from the Danish Gynecological Cancer Database. Women diagnosed with recurrence within three years after primary surgery and the mode of recurrence detection were identified from hospital charts: asymptomatic recurrence detected at regular follow-up, symptomatic recurrence detected at regular follow-up or symptomatic recurrence detected in between follow-up. Survival of women with symptomatic and asymptomatic disease was compared. Furthermore, characteristics associated with self-referral as compared to presenting symptoms at regular follow-ups were identified using univariate analyses.

Results: In total, 183 cases of recurrence (7%) were identified in the cohort of 2612 women. Of these, 65.5% were symptomatic with vaginal bleeding as the most prevalent symptom. Asymptomatic women had a significantly better three-year survival rate compared to symptomatic women (80.3% vs. 54.3%, $p < 0.01$). A total of 2.3% of the entire population had an asymptomatic recurrence. Women diagnosed at a pre-scheduled visit due to symptoms had a higher educational level ($p = 0.03$) and more often high-risk disease ($p = 0.02$) than symptomatic women diagnosed at regular follow-up.

Conclusion: Early stage endometrial cancer carries a low risk of recurrence. Survival appears to be superior in asymptomatic patients, but length-time bias, i.e. the effect of aggressive tumor biology in symptomatic recurrences, may bias results in non-randomized controlled trials. Well educated patients with symptoms of recurrence more often sought medical attendance compared to less educated counterparts. This should be considered if patient-initiated follow-up is the standard care.

ARTICLE HISTORY
Received 15 August 2016
Accepted 21 November 2016

Follow-up of women with endometrial cancer is resource consuming and there is limited evidence to support that routine follow-up programs have a significant influence on morbidity and mortality [1]. Consequently, follow-up of this disease is controversial and evidence-based recommendations for post-treatment monitoring are to be developed [2].

Several studies have evaluated the efficacy of follow-up examinations by comparing the survival of women with symptomatic and asymptomatic recurrence [1,2]. However, lead- and length-time bias may invalidate conclusions drawn from these studies as both types of bias introduce an artificial survival advantage to recurrent cases detected at follow-up. Furthermore, the cited studies are challenged by their retrospective designs, unsystematic registration of symptoms and small study samples, leaving them exposed to selection and information bias. Most of the studies conclude that the majority [70% (95% CI 65–75)] of recurrences are symptomatic [2], and the survival rates of asymptomatic and symptomatic cases are similar thus challenging the current follow-up strategy [1,2]. However, a few studies demonstrated a better survival in asymptomatic cases [3,4] which may be interpreted as a need for regular follow-up.

Recurrent disease detected outside of the routine surveillance program is usually diagnosed in females requesting a pre-scheduled examination due to symptoms. Recognizing a symptom to be a sign of recurrence depends on several factors including the symptom itself, the woman's perception of the symptom, information given about the importance of the symptom, personal network, previous experiences with disease, and sociodemographic characteristics including age,

CONTACT Mette Moustgaard Jeppesen mmjepp1@gmail.com Department of Gynecology and Obstetrics, Odense University Hospital, Kløvervænget 10, 10., 5000 Odense C, Denmark

education and employment status [5,6]. Knowledge of the factors associated with a pre-scheduled examination in women with symptomatic recurrent disease is essential, as it enables more targeted counseling for a self-management follow-up approach.

The overall aim of the study was to evaluate the relationship between the way recurrence was detected and survival of women with early stage endometrial cancer. Sociodemographic and disease characteristics associated with a pre-scheduled examination in women with symptomatic recurrent disease were furthermore identified.

Methods

Population and design

All women diagnosed with stage I and II endometrial cancer in Denmark between January 2005 and December 2009 were included in a population-based, historical cohort.

Recurrence was defined as cases where the patient was without residual disease after primary treatment (surgery ± adjuvant therapy) and the recurrence was radiologically or histologically verified within three years follow-up. Radiologically verified recurrences were included if no concomitant cancer could explain the finding, and if it was treated as endometrial cancer recurrence by the physicians. The survival of the cohort was evaluated until death or the end of the study period (31 December 2014). In a previous study, we presented a comprehensive analysis of recurrence pattern of the same study population. Findings included the relationship between recurrence localization and overall survival as well as predictive factors of disease recurrence [7].

Staging and follow-up strategy during the study period

For patients diagnosed before 2009, staging was converted to the 2009 FIGO guidelines. Stage I disease was subdivided into three risk groups: low risk included grade 1 and 2 disease with $<$50% myometrial invasion; intermediate risk comprised grade 3 disease with $<$50% myometrial invasion or grade 1 and 2 with $>$50% myometrial invasion; and high risk comprised grade 3 disease with $>$50% myometrial invasion or more than 10% clear cell, serous, and undifferentiated carcinoma in the tumor tissue.

During the study period, Danish national guidelines recommended hospital-based follow-up examinations every 4–6 months for three years; a mean of eight scheduled visits during three years for each patient. The visits included a gynecologic medical history and a gynecologic examination including vaginal ultrasound that was further supplemented with biopsies in case of suspicious findings and imaging in case of a histologically verified recurrence or suspicion of distant metastases.

Data sources and variables

The population of endometrial cancer patients was identified using the Danish Gynecologic Cancer Database [8]. To identify patients with recurrent disease, additional searches were performed in the Danish National Pathology Registry [9] and the National Patient Registry [10]. The data construction and the external and internal validity of the databases have been described in detail previously [7]. Briefly, all women with a new histological diagnosis concerning a tumor, metastases or recurrence in the Danish National Pathology Registry or with a code for recurrence in the National Patient Registry were suspected of disease recurrence. The suspected recurrence was validated by review of hospital charts by two of the authors (MMJ, MK). In five cases of doubt (1.5%), consensus was reached by discussion.

Information collected from the charts included: date and localization of recurrence, symptoms at the time of recurrence diagnosis and whether recurrence was diagnosed at routine follow-up or at a pre-scheduled examination. Information on duration of symptoms was in the majority of cases not available.

Asymptomatic recurrences were defined as all cases where no symptoms were mentioned in the hospital charts at the time of diagnosis. Symptomatic recurrences included all women who experienced symptoms prior to the diagnosis of recurrence. A list of symptoms that were plausibly caused by recurrence was created prior to reading the hospital charts [5]. The list included: pelvic pain, vaginal bleeding, vaginal discharge, abdominal pain, changes in bowel habits, increased waist circumference, dysuria, increased frequency or urgency of urination, tiredness, involuntary weight loss, dyspnea and back pain. In case of other symptoms, these were discussed and added to the list of symptoms if an association with recurrence was considered likely, for instance deep venous thrombosis. It was further registered if the symptomatic women requested an extra pre-scheduled examination.

Localization of recurrence was grouped into four categories: vaginal vault, pelvic sidewall (including pelvic lymph nodes), paraaortic lymph nodes and distant metastasis. In case of several concomitant recurrence localizations, the patient was included in the group with the most advanced disease.

Information on socioeconomic status, for example highest educational level, labor market affiliation and net family income were obtained from population-based registries in Statistics Denmark [11]. Educational level was divided into three categories: basic school, high school or short cycle tertiary and higher education including bachelor, masters and doctoral levels. Labor market affiliation was divided into two categories: employment/unemployment and outside of work force. The latter included all cases of retirement, early retirement, sick leave, social security and rehabilitation. Net family income was presented as the €1000 median with interquartile range. Information on comorbidity were collected from the National Patient Registry and categorized into the Charlson Comorbidity Index (CCI) [10,12]. This index was developed to predict one-year mortality based on comorbidity data [13]. A total of 19 comorbid conditions were weighed according to their influence on mortality and validated in 685 breast cancer patients [13]. An overall comorbidity score was calculated for each patient by adding up the

indexes of their comorbid conditions. The score was divided into: none (CS =0), mild (CS =1), moderate (CS =2) or severe (CS >3).

Statistical analysis

Univariate analyses were performed to compare sociodemographic and disease characteristics in women with symptomatic versus asymptomatic recurrences. Kaplan-Meier plots with 95% CIs were used to compare the overall survival in women with symptomatic and asymptomatic recurrences. Furthermore, the overall survival of women with symptomatic versus asymptomatic recurrence confined to the vaginal vault was compared. Overall survival was defined as the time from hysterectomy to death from any cause or the end of the study period. Recurrence localization was related to symptoms (asymptomatic, vaginal or other symptoms) using Pearson's χ^2-test. To identify factors associated with self-referral as compared to presenting symptoms at regular follow-up a univariate comparison using Pearson's χ^2-test was performed. The factors included in these analyses were: age, body mass index, smoking status, CCI, employment status, family income, educational level, FIGO stage, histology risk group and symptoms (vaginal or other). A multivariate analysis of these factors was not performed due to the relatively small number of patients. A two-sided p-value below 0.05 was considered statistically significant.

Analyses were performed using Stata/IC 14.0 for Windows.

Ethical considerations

The study was approved by the National Committee on Health Research Ethics (S-20120223) and the Data Protection Agency (12/25796).

Results

A total of 2612 women were diagnosed with stage I and II endometrial cancer between January 2005 and December 2009 and 183 (7.0%) had recurrence within three years after hysterectomy. Hospital charts were available for 177 of the women (96.7%), six patients were lost to follow-up. Of the 177 patients with recurrent disease, 116 (65.5%) had a symptomatic recurrence, while 61 recurrences (34.5%) were classified as asymptomatic. There was no significant difference in time to recurrence between symptomatic and asymptomatic women (12.1 vs. 12.6 months after hysterectomy, p = 0.81) (Table 1). Women presenting with symptoms had a significantly higher family income (44.2 vs. 31.5 €1000) (Table 1). Otherwise no differences in sociodemographic and clinicopathological characteristics were observed between the two groups (Table 1).

Treatment of the recurrences was applied according to national guidelines [14], and consisted of: surgical resection (10%), radiation (34%), chemotherapy (26%), surgical resection + radiation and/or chemotherapy (16%), hormonal therapy (8%) or no treatment (5%).

Table 1. Sociodemographic and clinicopathological characteristics of the 177 women with symptomatic and asymptomatic relapse of endometrial cancer.

Variables	Asymptomatic n = 61 (%)	Symptomatic n = 116 (%)	p
Age at diagnosis (mean, SD)	71.0 (9.0)	69.6 (9.7)	0.37
Body mass index (median, interquartile range)	27 (24.0–31.1)	25.7 (22.8–30.9)	0.24
Smoking status			
Never	36 (68)	59 (61)	
Former	10 (19)	19 (20)	
Current	7 (13)	18 (19)	0.71
Charlson Comorbidity Index (CCI)			
0	41 (67)	70 (60)	
1	8 (13)	16 (14)	
2	6 (10)	9 (8)	
≥3	6 (10)	21 (18)	0.51
Employment status			
Employed/unemployed	11 (18)	21 (18)	
Outside of workforce	50 (82)	95 (82)	0.99
Family income (€1000, median, interquartile range)	31.5 (24.2–43.9)	44.2 (25.8–66.3)	**0.01**
Education			
Basic school	32 (53)	54 (49)	
High school or short cycle tertiary	21 (35)	30 (27)	
Higher education	7 (12)	26 (24)	0.15
Time to recurrence (median, interquartile range)	12.1 (8.2–19.3)	12.6 (6.7–21.8)	0.81
FIGO stage			
1a	25 (41)	42 (36)	
1b	19 (31)	34 (29)	
2	17 (28)	40 (34)	0.66
Histology			
Endometroid	47 (77)	89 (77)	
Non-endometrioid	14 (23)	27 (23)	0.96
Primary type of surgery			
RALH	1 (2)	2 (2)	
TAH	55 (90)	96 (83)	
Radical hysterectomy	3 (5)	14 (12)	
LAVH	1 (2)	2 (2)	
Other	1 (2)	2 (2)	–
Removal of pelvic lymph nodes	15 (25)	34 (29)	–
Removal of paraaortic lymph nodes	1 (2)	4 (3)	–
Adjuvant therapy			
None	25 (41)	55 (47)	
Radiotherapy	23 (38)	37 (32)	
Chemotherapy	9 (15)	11 (9)	
Radio- and chemotherapy	4 (7)	13 (11)	–
Risk group			
Low	21 (47)	33 (42)	
Intermediate	17 (38)	32 (41)	
High	7 (16)	14 (18)	0.87

Age: t-test, unequal, body mass index, family income: Mann-Whitney U-test; Categorical variables: Pearson's χ^2. Significant p-values are highlighted in bold. LAVH: laparascopically assisted vaginal hysterectomy; RALH: robotically assisted laparoscopic hysterectomy; TAH: total abdominal hysterectomy.

Survival analyses

The three-year survival rate of women with asymptomatic recurrence was 80.3% compared to 54.3% in the symptomatic group (p < 0.01, Figure 1(a)). The one-year survival of the asymptomatic group was 100%. Further sub-analyses were challenged by the comparatively small number of patients. Asymptomatic women with recurrences confined to the vaginal vault seemed to have a superior three-year survival compared to those with symptoms (99.9% vs. 69.6%, p = 0.16; Figure 1(b)) but the findings were statistically insignificant.

Symptoms at the time of recurrence

The 116 symptomatic women reported a median of one symptom (range 1–4) and the most prevalent symptom was

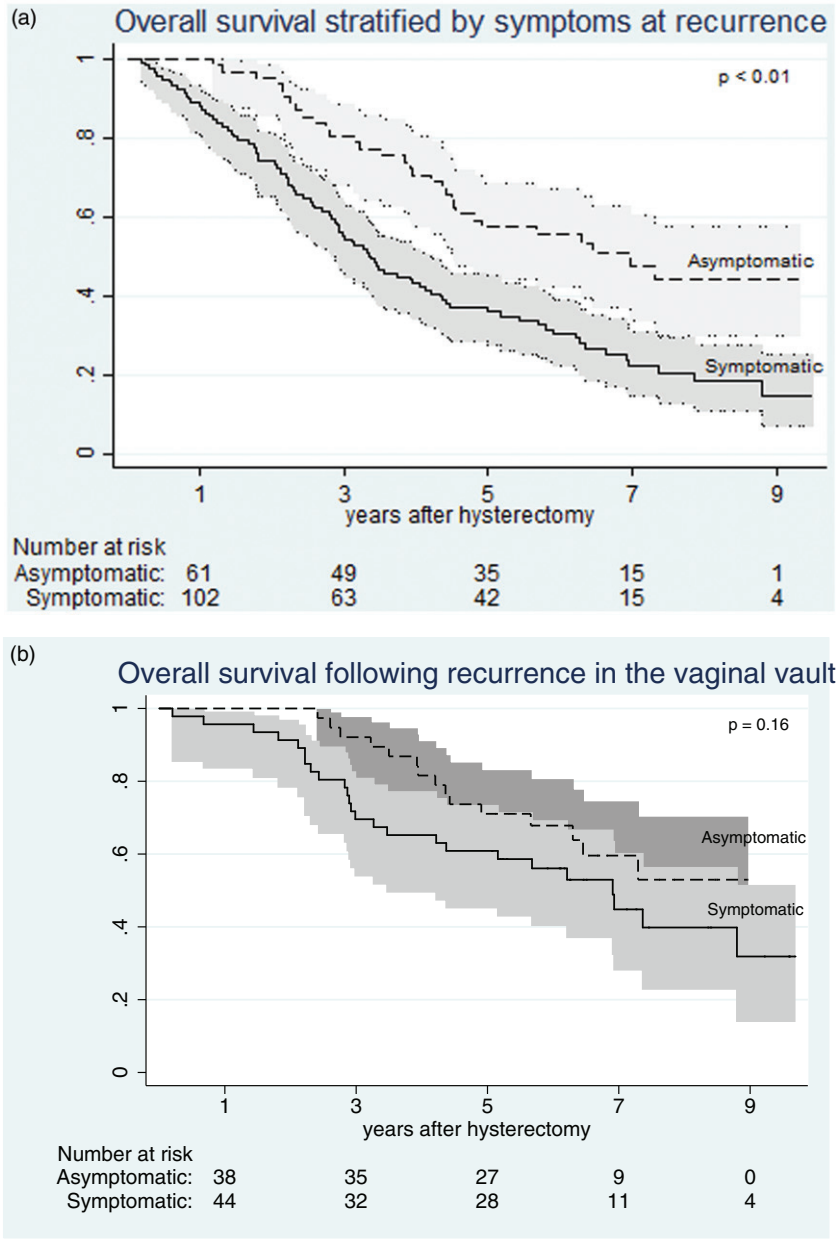

Figure 1 (a and b). Overall survival of women with symptomatic and asymptomatic endometrial cancer recurrence. Figure 1(a) depicts the overall survival of women with asymptomatic and symptomatic recurrence. In Figure 1(b) the survival of asymptomatic and symptomatic patients with recurrence confined to the vaginal vault. Gray areas represent 95% confidence intervals.

vaginal bleeding [47% (Figure 2)]. The type of symptom was associated with site of recurrence (Table 2), for instance women with vaginal symptoms more often had vaginal recurrence, whereas the women with other symptoms more often presented with a distant recurrence.

Symptomatic women diagnosed at a pre-scheduled visit had a higher educational level ($p = 0.03$) and more often high-risk disease ($p = 0.02$) compared to symptomatic women diagnosed at routine follow-up (Table 3). Women who responded to their symptoms by requesting an extra examination more often had vaginal symptoms compared to symptomatic women diagnosed at follow-up (55 vs. 40%) (Table 3), but this finding was statistically insignificant.

Discussion

In a national cohort of 2612 consecutive patients with early stage endometrial cancer, 183 (7%) were identified with recurrent disease within three years after primary treatment. Of these 65.5% had a symptomatic recurrence and vaginal bleeding was the most prevalent symptom. The recurrence was asymptomatic in 2.3% ($n = 61$) of the cohort and women with asymptomatic recurrence had a significantly better three-year survival compared to those with symptomatic recurrence (80.3% vs. 54.3%, $p < 0.01$). Women diagnosed at a pre-scheduled visit due to symptoms had a higher educational level and more often high-risk disease compared to symptomatic women diagnosed at regular follow-up.

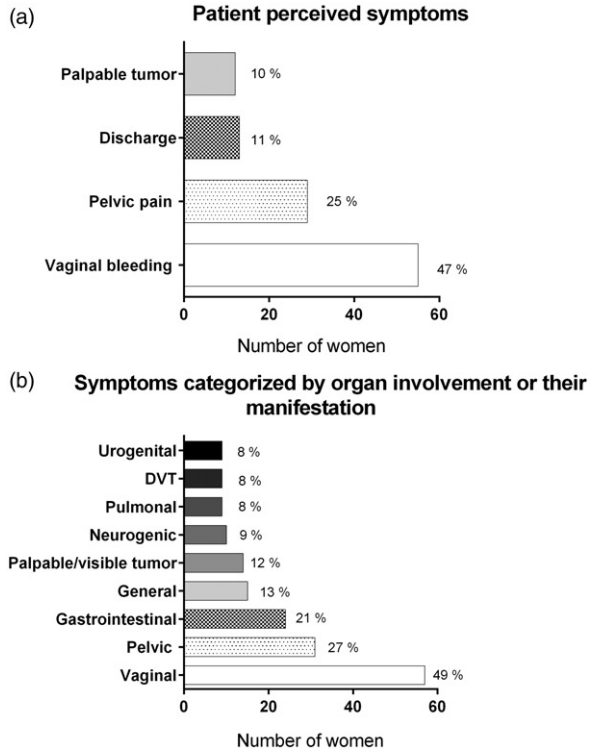

Figure 2 (a and b). Characterization and frequency of symptoms of recurrence as reported by the 116 symptomatic women. Figure 2(a) depicts the top four symptoms of recurrence as reported by the patient. In 11 of 13 patients with vaginal discharge, this symptom occurred in combination with vaginal bleeding. Figure 2(b) depicts the nature of the 178 symptoms reported by the 116 symptomatic patients. Rounded percentages represent the proportion of women reporting that symptom. The symptoms have been grouped into nine categories using the clinicians' perspective. DVT: deep vein thrombosis.

Table 2. Site of recurrence by symptoms at relapse, n = 177.

Site of recurrence	Asymptomatic n = 61 (%)	Vaginal symptoms n = 57 (%)	Other symptoms n = 59 (%)	p
Vaginal vault	38 (62)	31 (54)	15 (25)	**<0.01**
Pelvic sidewall	4 (7)	16 (28)	11 (19)	**<0.01**
Paraaortic lymph nodes	1 (2)	0 (0)	1 (2)	0.62
Distant[a]	18 (30)	10 (18)	32 (54)	**<0.01**

[a]Including 19 women, who had a combination of vaginal vault relapse and disseminated relapse.
Significant p-values are highlighted in bold.

Table 3. Univariate comparison of sociodemographic and disease characteristics of the 116 symptomatic women who initiated examination due to symptoms or were diagnosed at a regular follow-up visit.

Variables	Examination at symptoms n = 73 (%)	Examination at regular follow-up n = 43 (%)	p
Age at diagnosis (mean, SD)	70.0 (10.2)	69.0 (8.8)	0.59
Body mass index (median, interquartile range)	25.7 (22.8–30.0)	26.5 (23.4–31.1)	0.48
Smoking status			
Never	34 (61)	25 (63)	
Former	11 (20)	8 (20)	
Current	11 (20)	7 (18)	0.16
Comorbidities (CS)			
0	48 (66)	22 (51)	
1	7 (10)	9 (21)	
2	5 (7)	4 (9)	
≥3	13 (18)	8 (19)	0.30
Employment status			
Employed/unemployed	12 (16)	9 (21)	
Outside of workforce	61 (84)	34 (79)	0.54
Family income (€1000, median, interquartile range)	40.8 (24.3–67.7)	44.6 (30.6–62.3)	0.65
Education			
Basic school	35 (51)	19 (45)	
High school or short cycle tertiary	13 (19)	17 (40)	
Higher education	20 (29)	6 (14)	**0.03**
FIGO stage			
1a	31 (42)	11 (26)	
1b	17 (23)	17 (40)	
2	15 (35)	15 (35)	0.10
Histology			
Endometroid	52 (71)	37 (86)	
Non-endometrioid	21 (29)	6 (14)	0.07
Risk group			
Low	24 (47)	9 (32)	
Intermediate	15 (29)	17 (61)	
High	12 (24)	2 (7)	**0.02**
Symptoms			
Vaginal	40 (55)	17 (40)	
Other	33 (45)	26 (60)	0.11

Statistically significant p-values are highlighted in bold.

Previous studies have used retrospectively collected survival data to conclude on the efficacy and justification of follow-up visits [3,4,15–21]. In addition to the present study, a minority of the studies [3,4] found a better survival of women with asymptomatic recurrence and it seems tempting to conclude that follow-up visits improve survival. However, this conclusion is challenged by the use of non-randomized survival data in the evaluation of follow-up. Lead- and length-time bias may lead to an artificial prolongation of survival for asymptomatic recurrences (Figure 3). Lead-time bias occurs if a recurrent case is diagnosed early due to routine follow-up leading to a seemingly better survival than if the same case were diagnosed later due to symptoms [22]. In endometrial cancer lead-time bias may be influenced by biological, individual and organizational factors (e.g. the rate of tumor growth, the woman's attention to and perception of symptoms and the detection rate at follow-up). The present study aimed to eliminate the potential influence of lead-time bias by using the date of primary treatment instead of time of recurrence as the basis for the survival analyses (Figure 3(a)). Only two [4,15] of previously published studies have used this approach and lead-time bias can thus be expected to have influenced prior conclusions. Another challenge of survival analyses is length-time bias which occurs when fast-growing tumors give rise to symptoms sooner than slow-growing tumors. The fast-growing tumors are typically more aggressive with a worse prognosis [22]. Consequently, the symptomatic group may more often include fast-growing, non-curable recurrences. This will be reflected in a superior survival in the asymptomatic group which is not due to early diagnosis but merely a result of different tumor biology (Figure 3(b)). We suspect that length-time bias may have a substantial influence on the findings, even though this is an assumption that cannot be quantified. Finally, when information of symptoms is obtained through retrospective chart reviews, a risk of misclassification exists as some women forget to report their symptoms and doctors fail to ask or document symptoms in the chart. Based on the above considerations, non-randomized survival data should *not* be

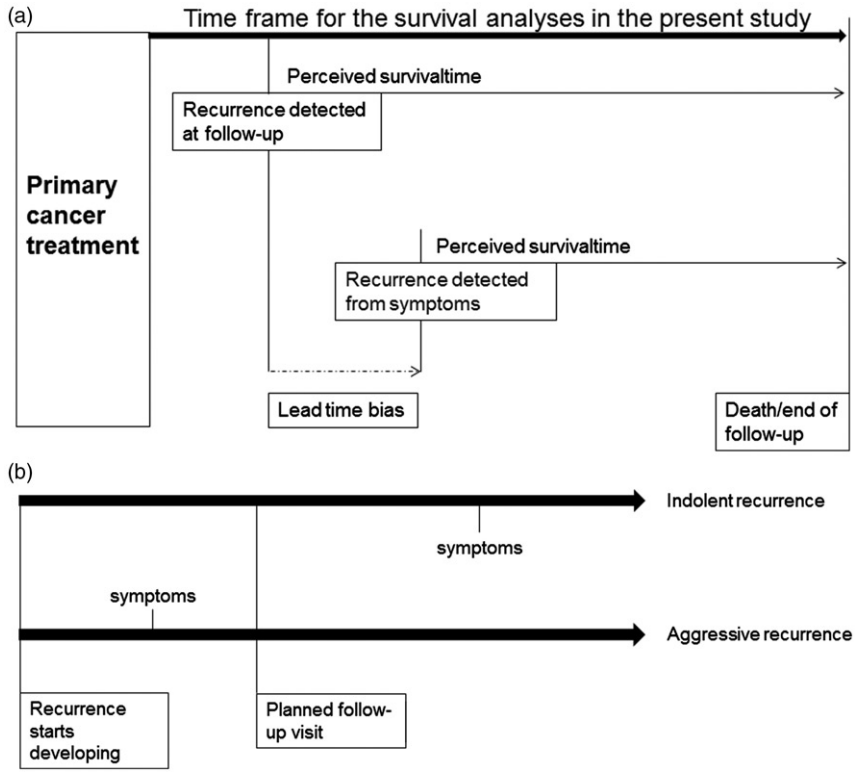

Figure 3 (a and b). Lead-time bias. Length-time bias. The figures illustrate lead- and length-time bias may occur. Furthermore, Figure 3(a) illustrates how the time frame of the present study was chosen to eliminate the risk of this type of bias.

used to conclude definitively on the rationale of routine follow-up. The present study adds to the knowledge gap regarding the association between mode of endometrial cancer recurrence detection, symptomatology, clinicopathological and sociodemographic characteristics. This is valuable information for future prospective studies in the field of post-treatment surveillance in endometrial cancer.

In the present study survival analyses focused on all-cause mortality rather than disease-specific mortality. The population under study is elderly with considerable comorbidity, and the impact of competing causes of death on the findings needs to be considered. However, women experiencing disease recurrence have a high risk of dying from endometrial cancer. The cause of death was not available for all women due to missing data but of the 122 registered deaths 84% could be directly linked to the recurrent disease. Consequently, disease-specific and overall survival would be expected to be very similar, and overall survival was considered to be the clinically most relevant and valid endpoint.

In the present cohort a total of 2.3% (61/2612) had an asymptomatic recurrence. The Danish national guidelines applied in the cohort recommended an average of eight follow-up visits per woman [14]. This would give rise to around 21 000 visits in the three-year follow-up period corresponding to 344 examinations per asymptomatic recurrence identified. In a previous study [7], we showed that recurrence localization significantly impacted on overall survival. The five-year survival rate was 64.8% in women with vaginal recurrence compared to 17.5% with distant recurrence. Among the 61 asymptomatic cases, 38 had a recurrence confined to the vaginal vault (1.5% of the population). Lately, the evidence regarding the cost-effectiveness of follow-up procedures in gynecologic malignancies have been reviewed [23]. It was concluded that the evidence in this area is poor due to low quality of available studies regarding study design and sample size [23]. The number of planned follow-up visits illustrates the intensity of post-treatment surveillance in a population of women at low risk of recurrence. Thus, future prospective economic evaluations on the cost-effectiveness of follow-up in early stage endometrial cancer are warranted.

This study is the first to identify factors associated with a pre-scheduled examination of women with recurrent endometrial cancer due to symptoms. The women with symptoms at the time of recurrence more often had high-risk disease compared to symptomatic women diagnosed at follow-up. Selective information to patients with a high risk of recurrence may induce a greater awareness of signs of recurrence. In addition, women diagnosed at a pre-scheduled visit had a higher educational level. Higher health literacy may improve these women's ability to communicate with health care professionals thus facilitating easier access to a pre-scheduled visit [24], whereas women with a lower educational level may be more reluctant in approaching the healthcare system outside of scheduled appointments [25]. This disparity in healthcare utilization is supported by several studies reporting on social inequality in cancer incidence and prognosis [26–28] and should be targeted in future interventions to ensure equal care for all endometrial cancer survivors.

The factors associated with a pre-scheduled visit due to symptoms are based on analyses of symptomatic patients with recurrent disease. No studies have examined the

presence of symptoms of recurrence in patients *without* recurrent disease. Thus, the health-seeking behavior in all endometrial cancer survivors is unknown and we cannot conclude on the predictive value of alarm symptoms of recurrence. We recommend the design of a prospective study of symptom prevalence in endometrial cancer survivors to estimate the predictive value of, for example vaginal bleeding.

This study has several strengths as it is based on national data from a large cohort where treatment was applied according to national guidelines. Recurrences were identified using highly valid registries and further validated by chart review. Efforts were made to eliminate the presence of lead-time bias in the survival analyses. Among limitations, hospital charts were missing for six of the patients (3.3%), due to lost paper files. These patients were treated at different centers. Consequently, we do not suspect that exclusion of these patients from the analyses introduced bias to the results.

Recurrences were detected using the Danish National Pathology Registry. In rare cases, for example older patients with signs of severe disseminated incurable recurrence, the physician may have refrained from biopsy and further diagnostics. Consequently, some of the women with the worst prognosis may not have been categorized as having recurrent disease, which could underestimate the recurrence rate.

We cannot rule out that some variations in treatment according to age, time and geography may have occurred. For example, in elderly women a more palliative approach may have been chosen which may have influenced the risk of recurrence and/or survival. Pelvic lymphadenectomy was only performed in 49 women, even though this procedure was recommended in intermediate, high-risk stage I disease and in stage II disease (127 women). These deviations from the guidelines occurred in women considered too fragile to undergo this procedure. Furthermore, some women with stage II disease were treated with external pelvic radiation, in which case lymphadenectomy was not performed. Such variations in treatment are a natural part of clinical decision making when dealing with an elderly comorbid patient group. The approach may lead to undetected staging errors and thus a misleading high risk of recurrence and mortality. However, the recurrence rate found in this study is comparable to the existing literature [7], and we suspect that staging errors have only had minimal impact on our findings.

Conclusion and perspectives

The majority of women with recurrence of early stage endometrial cancer were symptomatic at diagnosis. Only 2.3% of the entire study population had an asymptomatic recurrence. The overall survival was superior in women with asymptomatic recurrence compared to symptomatic recurrence but length-time bias and the risk of misclassification preclude any firm conclusion. The present study found that symptomatic women diagnosed at a pre-scheduled visit had a higher educational level than symptomatic women diagnosed at regular follow-up. Therefore, social inequality should be addressed in future follow-up programs.

In 2015, the Danish Board of Health published suggestions to evidence-based follow-up programs for gynecological cancer [29]. For endometrial cancer there was limited evidence regarding the cost-effectiveness of post-treatment surveillance programs. The working group behind the recommendations suggested individualized follow-up based on the patient's needs, that patients should be instructed in alarm symptoms, besides having easy access to outpatient wards in case of alarm symptoms. There has been paucity to implement the new national recommendations especially in patients at high risk of recurrence.

The present study provides knowledge of great value for the design of future randomized controlled trials that may result in more evidence-based allocation to differentiated surveillance programs. Additionally, a number of ongoing European randomized controlled trials may provide us with data on which future guidelines can be based. These studies aim to evaluate a variety of models for post-treatment surveillance; including patient-initiated follow-up (Trial number: NCT01853865), nurse-led follow-up (ISRCTN45565436), and less intensive follow-up (NCT02413606, NCT00916708).

Acknowledgments

We thank the Danish Gynaecological Cancer Group for providing us with clinical data from their database.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The research for this paper was financially supported by the Danish Cancer Society [grant no. R94-A5679 Rp7423], the University of Southern Denmark, the Region of Southern Denmark [grant no. 13/6697], and Odense University Hospital [grant no. 12/26914].The National Research Center of Cancer Rehabilitation at the Research Unit of General Practice, University of Southern Denmark, is partly funded by the Danish Cancer Society.

References

[1] Lajer H, Jensen MB, Kilsmark J, et al. The value of gynecologic cancer follow-up: evidence-based ignorance? Int J Gynecol Cancer. 2010;20:1307–1320.

[2] Fung-Kee-Fung M, Dodge J, Elit L, et al. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol. 2006;101:520–529.

[3] Ueda Y, Enomoto T, Egawa-Takata T, et al. Endometrial carcinoma: better prognosis for asymptomatic recurrences than for symptomatic cases found by routine follow-up. Int J Clin Oncol. 2010;15:406–412.

[4] Carrara L, Gadducci A, Landoni F, et al. Could different follow-up modalities play a role in the diagnosis of asymptomatic endometrial cancer relapses?: an Italian multicentric retrospective analysis. Int J Gynecol Cancer. 2012;22:1013–1019.

[5] Balasubramaniam K, Ravn P, Larsen PV, et al. Specific and unspecific gynecological alarm symptoms–prevalence estimates in different age groups: a population-based study. Acta Obstet Gynecol Scand. 2015;94:191–197.

[6] Whitaker KL, Macleod U, Winstanley K, et al. Help seeking for cancer 'alarm' symptoms: a qualitative interview study of primary care patients in the UK. Br J Gen Pract J R Coll Gen Pract. 2015; 65:e96–e105.

[7] Jeppesen MM, Jensen PT, Hansen DG, etet al. The nature of early-stage endometrial cancer recurrence: a national cohort study. Nat Early-Stage Endometrial Cancer Recurrence. 2016;69:51–60.
[8] Juhl CS, Hansen ES, Høgdall CK, et al. Valid and complete data on endometrial cancer in the Danish Gynaecological Cancer Database. Dan Med J. 2014;61:A4864.
[9] Erichsen R, Lash TL, Hamilton-Dutoit SJ, et al. Existing data sources for clinical epidemiology: the Danish National Pathology Registry and Data Bank. Clin Epidemiol. 2010;2:51–56.
[10] Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health. 2011;39:30–33.
[11] Thygesen LC, Daasnes C, Thaulow I, et al. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. Scand J Public Health. 2011;39:12–16.
[12] Thygesen SK, Christiansen CF, Christensen S, et al. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol. 2011;11:83.
[13] Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373–383.
[14] Danish guidelines for the management of endometrial cancer (translated) [Internet]. Denmark: Danish Gynecological Cancer Group; 2009 Dec 8 [cited 2016 Sep 27]. Available from: http://dgcg.dk/images/retningslinier/Corpuscancer/Endometriecancer_2010-jan.pdf.
[15] Agboola OO, Grunfeld E, Coyle D, et al. Costs and benefits of routine follow-up after curative treatment for endometrial cancer. CMAJ Can Med Assoc J. 1997;157:879–886.
[16] Berchuck A, Anspach C, Evans AC, et al. Postsurgical surveillance of patients with FIGO stage I/II endometrial adenocarcinoma. Gynecol Oncol. 1995;59:20–24.
[17] Gadducci A, Cosio S, Fanucchi A, et al. An intensive follow-up does not change survival of patients with clinical stage I endometrial cancer. Anticancer Res. 2000;20:1977–1984.
[18] Gordon AF, Owen P, Chien PF, et al. A critical evaluation of follow-up of women treated for endometrial adenocarcinoma. J Obstet Gynaecol/ J Inst Obstet Gynaecol. 1997;17:386–389.
[19] Sartori E, Pasinetti B, Carrara L, et al. Pattern of failure and value of follow-up procedures in endometrial and cervical cancer patients. Gynecol Oncol. 2007;107:S241–S247.
[20] Smith CJ, Heeren M, Nicklin JL, et al. Efficacy of routine follow-up in patients with recurrent uterine cancer. Gynecol Oncol. 2007;107:124–129.
[21] Shumsky AG, Stuart GCE, Brasher PM, et al. An evaluation of routine follow-up of patients treated for endometrial carcinoma. Gynecol Oncol. 1994;55:229–233.
[22] Duffy SW, Nagtegaal ID, Wallis M, et al. Correcting for lead time and length bias in estimating the effect of screen detection on cancer survival. Am J Epidemiol. 2008;168:98–104.
[23] Pagano E, Sobrero S, Cavallero C, et al. Economic considerations on the follow-up practice in gynecologic cancers: few lights and many shadows from a literature review. Int J Gynecol Cancer. 2015;25:1144–1150.
[24] Balasubramaniam K, Ravn P, dePont Christensen R, et al. Gynecological cancer alarm symptoms: is contact with specialist care associated with lifestyle and socioeconomic status? A population-based study. Acta Obstet Gynecol Scand. 2016;95:976–983.
[25] Robinson KM, Christensen KB, Ottesen B, et al. Socio-demographic factors, comorbidity and diagnostic delay among women diagnosed with cervical, endometrial or ovarian cancer. Eur J Cancer Care (Engl). 2011;20:653–661.
[26] Dalton SO, Steding-Jessen M, Gislum M, et al. Social inequality and incidence of and survival from cancer in a population-based study in Denmark, 1994-2003: background, aims, material and methods. Eur J Cancer. 2008;44:1938–1949.
[27] Woods LM, Rachet B, Coleman MP. Origins of socio-economic inequalities in cancer survival: a review. Ann Oncol. 2006;17:5–19.
[28] Booth CM, Li G, Zhang-Salomons J, et al. The impact of socioeconomic status on stage of cancer at diagnosis and survival: a population-based study in Ontario, Canada. Cancer. 2010;116:4160–4167.
[29] Danish Health and Medicines Authority. Follow-up for gynecologic cancer (translated). Denmark; 2015 Oct 26.