



## Short communication

## Can a symptom checklist improve the triage of patients following successful endometrial cancer treatment?

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## ABSTRACT

Endometrial cancer (EC) is the fifth most common cancer in women in developed countries. Clinical practice guidelines recommend patients should be followed-up every 3–6 months after primary treatment of EC. Evidence suggests that 40% to 80% of patients develop symptoms prior to being diagnosed with EC recurrence, however which symptoms are key remains unclear. We previously conducted a comprehensive literature review and developed a questionnaire on patient-reported symptoms associated with EC recurrence.

This is a brief communication on a pilot prospective cohort study among 120 Australian patients who completed primary treatment for EC in the past three years. The study showed 47 of the 120 patients (39.2%) self-reported at least one symptom, four of whom (3.3%) were diagnosed with a recurrence. Back or lumbar pain ( $P = 0.012$ ), vaginal bleeding ( $P < 0.001$ ), and lethargy, fatigue, exhaustion or tiredness ( $P = 0.002$ ) were significantly associated with the development of EC recurrence.

The checklist will be further validated as part of a randomized controlled clinical trial to confirm the observed relationship between symptoms and the development of EC recurrence.

## 1. Introduction

Endometrial cancer (EC) is the fifth most common cancer in women in developed countries, such as North America, Europe and Australia with an estimated worldwide incidence of 382,069 new cases per year (Bray et al., 2018). In Australia, age-standardised incidence rates increased from 14/100,000 in 1982 to an estimated 20/100,000 in 2019 (Australian Government and Cancer Australia, 2019). The current standard treatment for EC includes a hysterectomy, bilateral salpingo-oophorectomy with or without surgical staging (Chi et al., 2017). Selected patients are offered postoperative radiation treatment, chemotherapy or a combination of both (Chi et al., 2017).

Despite the lack of prospective data on the effectiveness of surveillance following primary treatment of EC, some evidence and current clinical practice guidelines suggest patients should be seen every 3–6 months for follow-up (Bristow et al., 2006; Morice et al., 2001). During these visits a history is taken and a physical examination is performed. Descriptive studies suggest that 75% of all patients who develop recurrence are diagnosed at the vaginal vault within 3 years from primary treatment (Tjalma et al., 2004). Follow-up aims to detect

small, isolated recurrences at the vaginal vault that are amenable for curative treatment. It has also been shown that 40–80% of patients develop symptoms prior to being diagnosed with EC recurrence (Salani et al., 2017).

However, the type of symptoms associated with EC recurrence is unclear. Therefore, and following a review of the literature (Witt et al., 2015), we developed and prospectively piloted a patient-reported symptoms checklist associated with EC recurrence in an Australian cohort.

## 2. Methods

Our study is a single-centre, prospective cohort study. Our pilot study was conducted at an Australian tertiary gynaecological cancer centre, the Royal Brisbane and Women's Hospital, which is part of Queensland Centre for Gynaecological Cancer in Brisbane, Australia. In our institution, patients are seen every 3–6 months for the initial 2 years after surgery and then 6-monthly until 5 years after completion of primary treatment. To be included into the study, the patients should (a) have completed primary treatment for EC in the past three years; (b)

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be presumed recurrence-free; (c) be able to read and understand English; (d) have access to a telephone and adequate hearing and (e) be willing to complete questionnaire on satisfaction with the telephone and clinic follow-up. The participants were excluded if they presented (a) with assumed or diagnosed EC recurrence or relapse; (b) with metastatic disease presentation; (c) more than 3 years post EC treatment; (d) unable to read or understand English; (e) unable to access to a telephone or (f) with hearing difficulties.

To develop the EC symptom checklist, we performed a comprehensive literature review of studies on signs and symptoms indicating EC recurrence published between 1982 and 2012 (Witt et al., 2015). The study identified available symptom checklists (National Comprehensive Cancer, 2013; Reddoch et al., 1995; Salani et al., 2011), determined their comprehensiveness and generated an updated list of symptoms potentially associated with a recurrence of EC.

During January 2012 to April 2014, a total of 150 eligible patients were contacted by a gynaecologic oncology staff member and invited to participate in the study. A total of 120 patients (80.0%), who fulfilled the eligibility criteria, agreed to be enrolled. All participants provided written informed consent. The study was approved by Human Research Ethics Committee of Royal Brisbane & Women's Hospital (approval number HREC/12/QRBW/98).

Interviews were conducted face-to-face or by telephone 2–5 days prior to a scheduled follow-up appointment that included a physical examination. All participants were asked whether they are currently experiencing any one or multiple of the following symptoms, including unusual pain (pelvis, abdomen, hip, neck, shoulder, arms, legs, chest, back/lumbar, bone, pain during intercourse), unusual bleeding (vaginal, rectal, urethral), skin lesion/masses/lumps or any skin abnormalities (groin, inner thighs, vagina, rectum area), frequent urination or voiding, difficulty or painful urination, diarrhea, constipation, bloated abdomen, coughing, shortness of breath, irregular heartbeat, headache, loss of sensation, decreased appetite, nausea, vomiting, weight loss, lethargy/fatigue/exhaustion/tiredness, swelling of the legs, depression, fever, dizziness/blackout, and enlarged lymph node/glands. Subsequent to the interviews, patients were seen by medical staff for a physical examination, including an external examination to examine the abdomen, both groins and the neck, to exclude clinical lymphadenopathy. We also conducted an examination of the external genitalia, a vaginal speculum examination, a bimanual vaginal examination as well as a rectal digital examination. Medical imaging or vaginal vault cytology was only performed when clinically indicated. All recurrences were confirmed through tissue biopsy and histopathology. All recurrences that developed within 12 months of the conversation preceding the follow up consultation were considered.

Fisher's exact test was used to examine the association between post-treatment symptoms and EC recurrence. A two-sided *P* value of 0.05 was indicative of statistical significance. Stata 16.0 was used to conduct the analysis.

### 3. Results

The median (range) age of the 120 participants was 65 years (39–87 years). A total of 89 (74.2%) patients had a diagnosis of International Federation of Gynecology and Obstetrics (FIGO) stage I EC, followed by stage II (13, 10.8%), stage III (8, 6.7%), unknown (6, 5.0%) and stage IV (4, 3.3%). According to cancer grade, 51 (42.5%) were grade 1, 48 (40.0%) were grade 2, 14 (11.7%) were grade 3, and 7 (5.8%) were with unknown grade. Patient characteristics are given in Table 1.

The median (range) time from surgery to questionnaire was 1.04 years (0.03–4.3 years) in patients without recurrence and 0.81 years (0.1–3.0 years) in patients with recurrence.

Forty-seven of the 120 patients (39.2%) self-reported at least one symptom during the nurse-led follow-up conversation. The frequencies of reported symptoms are shown in Table 2. Four of the 120

**Table 1**  
Basic characteristics of the included participants.

Variables	Overall (n = 120)	Recurrence (n = 4)	Non-Recurrence (n = 116)
Age (years), median (range)	65 (39–87)	61 (58–72)	66 (39–87)
Tumour cell type, n (%)			
Endometrioid	94 (78.3)	4 (100.0)	90 (77.6)
Others	26 (21.7)	0 (0.0)	26 (22.4)
Stage			
1	89 (74.2)	2 (50.0)	87 (75.0)
2	13 (10.8)	2 (50.0)	11 (9.5)
3	8 (6.7)	0 (0.0)	8 (6.9)
4	4 (3.3)	0 (0.0)	4 (3.5)
Unknown	6 (5.0)	0 (0.0)	6 (5.2)
Grade			
1	51 (42.5)	0 (0.0)	51 (44.0)
2	48 (40.0)	4 (100.0)	44 (37.9)
3	14 (11.7)	0 (0.0)	14 (12.1)
Unknown	7 (5.8)	0 (0.0)	7 (6.0)

**Table 2**  
The frequency of symptoms among the participants, stratified by recurrence.

Symptoms	Overall (n = 120)	Recurrent (n = 4)	Non-recurrent (n = 116)	<i>P</i> value
Any symptom	47 (39.2)	4 (100.0)	43 (37.1)	0.022
Unusual pain	22 (18.3)	2 (50.0)	20 (17.2)	0.153
Pelvis	2 (1.7)	0 (0.0)	2 (1.7)	1.000
Abdomen	9 (7.5)	0 (0.0)	9 (7.8)	1.000
Hip	3 (2.5)	0 (0.0)	3 (2.6)	1.000
Neck	3 (2.5)	0 (0.0)	3 (2.6)	1.000
Shoulder	3 (2.5)	1 (25.0)	2 (1.7)	0.097
Arms	2 (1.7)	1 (25.0)	1 (0.9)	0.066
Legs	4 (3.3)	0 (0.0)	4 (3.4)	1.000
Chest	3 (2.5)	1 (25.0)	2 (1.7)	0.097
Back/Lumbar	6 (5.0)	2 (50.0)	4 (3.4)	0.012
Bone	1 (0.8)	0 (0.0)	1 (0.9)	1.000
Intercourse	1 (0.8)	0 (0.0)	1 (0.9)	1.000
Unusual bleeding	5 (4.2)	3 (75.0)	2 (1.7)	< 0.001
Vaginal	5 (4.2)	3 (75.0)	2 (1.7)	< 0.001
Rectal	0 (0.0)	0 (0.0)	0 (0.0)	NA
Urethral	0 (0.0)	0 (0.0)	0 (0.0)	NA
Skin abnormalities	0 (0.0)	0 (0.0)	0 (0.0)	NA
Groin	0 (0.0)	0 (0.0)	0 (0.0)	NA
Inner thighs	0 (0.0)	0 (0.0)	0 (0.0)	NA
Vagina	0 (0.0)	0 (0.0)	0 (0.0)	NA
Vulva	0 (0.0)	0 (0.0)	0 (0.0)	NA
Rectum area	0 (0.0)	0 (0.0)	0 (0.0)	NA
Frequent urination or voiding	6 (5.0)	1 (25.0)	5 (4.3)	0.188
Difficulty/painful urination	3 (2.5)	0 (0.0)	3 (2.6)	1.000
Diarrhea	4 (3.3)	1 (25.0)	3 (2.6)	0.128
Constipation	3 (2.5)	0 (0.0)	3 (2.6)	1.000
Bloated abdomen	1 (0.8)	0 (0.0)	1 (0.9)	1.000
Coughing	2 (1.7)	0 (0.0)	2 (1.7)	1.000
Shortness of breath	1 (0.8)	0 (0.0)	1 (0.9)	1.000
Irregular heartbeat	1 (0.8)	0 (0.0)	1 (0.9)	1.000
Headache	5 (4.2)	0 (0.0)	5 (4.3)	1.000
Loss of sensation	3 (2.5)	0 (0.0)	3 (2.6)	1.000
Decreased appetite	5 (4.2)	1 (25.0)	4 (3.4)	0.158
Nausea	4 (3.3)	1 (25.0)	3 (2.6)	0.128
Vomiting	2 (1.7)	1 (25.0)	1 (0.9)	0.066
Weight loss	0 (0.0)	0 (0.0)	0 (0.0)	NA
Fatigue	11 (9.2)	3 (75.0)	8 (6.9)	0.002
Swelling of legs	3 (2.5)	1 (25.0)	2 (1.7)	0.097
Depression	2 (1.7)	0 (0.0)	2 (1.7)	1.000
Fever	0 (0.0)	0 (0.0)	0 (0.0)	NA
Dizziness/blackout	4 (3.3)	1 (25.0)	3 (2.6)	0.128
Enlarged lymph node/glands	2 (1.7)	1 (25.0)	1 (0.9)	0.066

NA, not applicable.

participants (3.3%) were diagnosed with recurrence within one year after starting the telephone follow-up (3 vagina, 1 pelvis).

The first patient had surgical cytoreduction, adjuvant chemotherapy and radiation treatment for a stage 4 mixed serous/clear cell endometrial carcinoma. She developed her first vaginal vault recurrence within 18 months and a further vaginal vault recurrence after another 10 months. The second patient had treatment for a stage 2 endometrioid adenocarcinoma of the endometrium and developed multi-site recurrence in vagina, liver, lung and adrenals 16 months post initial treatment. The third patient had surgery plus adjuvant radiation treatment for a stage 2 uterine serous carcinoma and developed a large vaginal recurrence causing right hydronephrosis. This patient also developed hepatic and retroperitoneal node metastases at the same time. The fourth patient had surgery, chemotherapy and radiation treatment for a stage 3A endometrioid endometrial carcinoma. She developed pelvic and aortic node recurrence, and lung metastases 25 months after surgery. All four patients indicated symptoms consistent with recurrence, which was diagnosed not later than 3 months from the onset of symptoms.

All four patients who developed recurrence reported symptoms, whereas only 43 of 116 patients who remained recurrence-free within 12 months reported symptoms ( $P = 0.022$ ). Back or lumbar pain ( $P = 0.012$ ), vaginal bleeding ( $P < 0.001$ ), and lethargy, fatigue, exhaustion or tiredness ( $P = 0.002$ ) were significantly associated with the development of EC recurrence. None of the other symptoms were associated with the subsequent development of recurrence (Table 2).

#### 4. Discussion

In this prospective cohort study of 120 EC patients, the absence of symptoms was associated with a negative physical examination to detect EC recurrence.

Numerous studies focus on the predictive ability of clinical and sociodemographic factors, such as FIGO stage, histology, age at diagnosis, smoking, and education, on the risk of recurrence of EC (Han et al., 2017; Jeppesen et al., 2016). To date, few and only retrospective studies compared EC survival probabilities of women with and those without symptoms (Carrara et al., 2012; Jeppesen et al., 2017). In a study including 282 patients from 8 Italian institutions the presence of symptoms at the time of recurrence was associated with a more than two-fold risk of death (Carrara et al., 2012). In another retrospective cohort study, the three-year survival rate of women with asymptomatic recurrence was 80.3% compared to 54.3% in the symptomatic group ( $P < 0.01$ ) (Jeppesen et al., 2017). In both studies, the type of symptoms were not specified and symptoms were abstracted retrospectively from charts (Carrara et al., 2012; Jeppesen et al., 2017), but both studies suggested impaired survival outcomes in symptomatic compared to asymptomatic patients. Therefore, one might cautiously speculate that the earlier detection of recurrence might positively impact on survival outcomes subsequent to the detection of recurrence.

Of particular interest was the fact that three of four patients developed vaginal bleeding and all three patients were diagnosed with vaginal recurrence subsequently. This is consistent with the evidence from the current literature suggesting that vaginal bleeding is commonly associated with endometrial cancer recurrence (Salani et al., 2017).

The most significant limitation to our study is the small sample size, including heterogeneity of patients and the single-centered study design. Only 4 (3.3%) patients developed recurrence during the one year follow-up.

Our prospective pilot study has shown that more than 60% of patients presenting for EC follow-up consultations are symptom free and that the rigorous assessment of being symptom-free after EC treatment was reassuringly associated with a negligible risk of recurrence within 12 months.

We plan to validate the EC symptom checklist as part of a large,

phase 3 randomized controlled clinical trial to increase our understanding of the relationship between symptoms and the development of EC recurrence.

#### 5. Conclusions

In our study, 4 of 120 EC patients developed recurrence within one year of telephone follow-up. Forty-seven (39.2%) patients self-reported at least one symptom, four of whom were diagnosed with a recurrence. Reporting back or lumbar pain, vaginal bleeding, or lethargy, fatigue, exhaustion, or tiredness were all associated with a recurrence within 12 months.

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#### Declaration of Competing Interest

AO is the founder and managing director of SurgicalPerformance Pty. Ltd. AO also receives travel grants from The OR Company and personal fees from consultant for Covidien. YP and MJ declare no conflict of interest.

#### Author's contribution

AO and MJ designed the study and supervised staff. YP completed the statistical analysis. All authors reviewed the final draft of the manuscript.

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