

Patterns of Recurrence in Low-Risk Endometrial Cancer

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Abstract

Objective: Endometrial cancer is the most common gynaecological cancer in high-income countries and has a good prognosis, particularly when diagnosed early. Early stage, low-grade endometrial cancer has a low risk of recurrence, and is detectable on routine follow up. This study aims to identify rates and patterns of recurrence in low-risk endometrial cancer patients and provide evidence for transitioning to community-based follow-up care. **Methods:** Retrospective study of patients with early-stage, low-grade endometrioid endometrial adenocarcinoma treated with surgery from January 1981 to December 2018. The rate and patterns of recurrence were identified and analysed. **Results:** Of 1215 eligible patients, 24 developed recurrent disease (1.98%). The majority of recurrences were pelvic (70%), and confined to the vaginal vault (41.7%). The median duration of follow up was 44.4 months, and time from primary surgery to diagnosis of recurrent disease was 30.5 months. No significant differences were found between the group of patients who recurred and the group of patients who did not. Twelve (50%) patients with recurrences were asymptomatic, but of these, 10 (83%) had obvious findings during routine surveillance physical examination. The remaining 12 patients (50%) presented with symptoms that prompted investigation that led to the recurrence diagnosis. 78% of recurrences were treated with combination therapy (surgical excision, chemotherapy, radiotherapy and hormonal). Ten patients (42%) had salvageable disease. For the non-salvageable cases, there was a mean of 2.1 years from recurrence diagnosis to death. **Conclusions:** The low recurrence rate of low-risk endometrial cancer following primary surgical management, and the feasibility of detection of recurrent disease, support transitioning surveillance to community-based settings.

Keywords

Endometrial Cancer, Recurrence, Surveillance, Survivorship, Vaginal Vault

1. Introduction

Endometrial cancer is the most common gynaecological cancer in high-income countries, and the second most common in low-income countries, following cervical cancer [1]. Approximately 3000 new cases of uterine cancer are diagnosed every year in Australia, the majority of which are endometrial cancer, affecting one in 40 Australian women by the age of 85 [2]. The incidence of endometrial cancer is increasing, in parallel with known risk factors such as obesity, with projected increases until at least 2029 [3] [4]. The prognosis of endometrial cancer is good, primarily due to diagnosis at an early stage of disease. In Australia, the five-year survival from uterine cancer is 83.3% and has increased over the last 25 years [2]. Given projected increases in incidence and survival, uterine cancer can be expected to constitute a large part of Gynaecology-Oncology service provision in the future.

Stratifying patients as having either a low or high-risk disease in terms of survival informs the need for adjuvant treatment and appropriate models of care for follow-up of patients after initial disease treatment. Low-risk disease is defined as endometrioid histological type, grade 1 or 2 and tumour limited to the endometrium or invading up to halfway into the myometrium, 2009 FIGO Stage IA [5] [6]. The primary treatment for early-stage endometrial cancer involves total hysterectomy and bilateral salpingo-oophorectomy as a minimum, with lymph node assessment based on uterine factors and/or intraoperative frozen section as well as clinical discretion [7] [8] [9]. The surgical FIGO staging has been found to be highly prognostic [10], and the risk of recurrence for low-risk disease has been found to be less than five percent in previous studies [11] [12]. Therefore observation rather than adjuvant treatment is routinely recommended [7] [13].

Historically the goals of post-operative surveillance include early detection of recurrences, especially local pelvic (salvageable) disease. However, in recent times, a more holistic approach is recommended, including assessing patients' evolving comorbidities, psychosocial and sexual well-being, referral to further genetic counselling when appropriate, and promoting a healthy lifestyle. Significantly, cardiovascular disease is the leading cause of death amongst endometrial cancer survivors, rather than recurrent cancer [14]. Follow-up consultations involve taking a thorough history, performing physical and gynaecological examinations, and educating cancer survivors regarding healthy lifestyle and symptoms suggestive of recurrence [13]. Investigations such as vault cytology, blood tests and imaging are no longer recommended, as they have not been shown to be cost-effective [13]. One study showed that the use of vaginal cytology at each visit resulted in an estimated cost of 27,000 USD per case of recurrent disease detected [15]. Clinical surveillance using a combination of gynaecological and general physical examination, with review of symptoms, has resulted in detection rates of recurrence, exceeding 80% in some studies [16] [17].

Post-operative surveillance models vary between countries and health services. Frequent follow-up in the first 2 - 3 years by a gynaecology oncology special-

ist has been the norm as 70% to 100% of recurrences occur within three years of primary treatment [18] [19]. However, evidence is emerging that surveillance with generalist gynaecologists, primary care practitioners or nurse practitioners is reasonable without changing the detection rate of recurrence or worsening prognosis [13] [20] [21] [22].

This paper describes the incidence of recurrent disease in a large cohort of low-risk endometrial cancer patients, how it was detected, modes of treatment, and subsequent outcomes. These findings can serve as a basis for integrating future models of care for low-risk endometrial cancer survivors.

2. Materials and Methods

All patients with low-risk endometrial cancer, defined as grade 1 - 2 endometrioid adenocarcinoma, 2009 FIGO classification Stage 1A treated in a gynaecology-oncology unit in Melbourne, Victoria, Australia between years 1981 and 2018 were included. Patients whose primary treatment was non-surgical were excluded. Information was obtained from the purpose-built gynaecological oncology database, Gemma, into which data has been prospectively entered since 1981. Patients with stage I disease that were treated prior to the implementation of the FIGO 2009 revised staging system were re-staged as per their myometrial depth of invasion. After eligible patients were identified using this low risk stage and grade classification, information regarding their demographics, site of recurrence, presentation of recurrence, salvage treatment and long-term outcomes were collected and analysed. Clinical histories were reviewed when necessary for further information.

Data collection and analysis took place over eight months during 2018 and 2019. Local ethics approval was obtained from the Royal Women's Hospital Research Committee and RWH Human Research Ethics Committee (AQA19/13).

Initial analyses were undertaken with univariate logistic regression. All variables of interest were binary except for age which was treated as continuous. Odds ratios (with 95% confidence intervals) and p-values were calculated with a p-value below 0.05 defined as statistically significant. A multivariate analysis was planned using variables from the initial analysis with a p-value of 0.2 or less, however this was not performed as only two variables met this criteria. Data was analysed using Stata version 15 (Statacorp, Texas, USA).

3. Results

3.1. Recurrence Rate

Between January 1981 until December 2018, 1635 patients were treated for endometrial cancer at our institution. One thousand five hundred and fifty-seven (95.23%) patients were treated primarily with surgery. The remaining 78 (4.77%) patients were excluded as they were treated non-surgically (hormonal treatment, radiotherapy or chemotherapy). Of those treated with primary surgery, 78.03% (n = 1215) patients were identified as having low-risk endometrioid adenocar-

cinoma (FIGO 2009 stage IA, grade I/2) and constituted the study population. The remaining 21.97% (n = 342) had either a different histological type of endometrial cancer or a high-risk stage/grade and therefore received adjuvant treatment. Twenty-four of the low-risk patients had recurrent disease, giving a recurrence rate of 1.98% (n = 1215) (Figure 1).

3.2. Recurrence Location

Seventeen of twenty-four recurrences were pelvic (70.8%). In 58.8% (n = 10) of the pelvic recurrence patients the recurrence was confined to the vaginal vault, while in 41.2% (n = 7) disease involved other parts, but was confined to the pelvis. In 25% (n = 6) of the recurrence patients' distant disease was also found at the time of pelvic recurrence. In one patient (4.17%), the recurrent disease was distant but isolated to the anterior abdominal wall (Table 1).

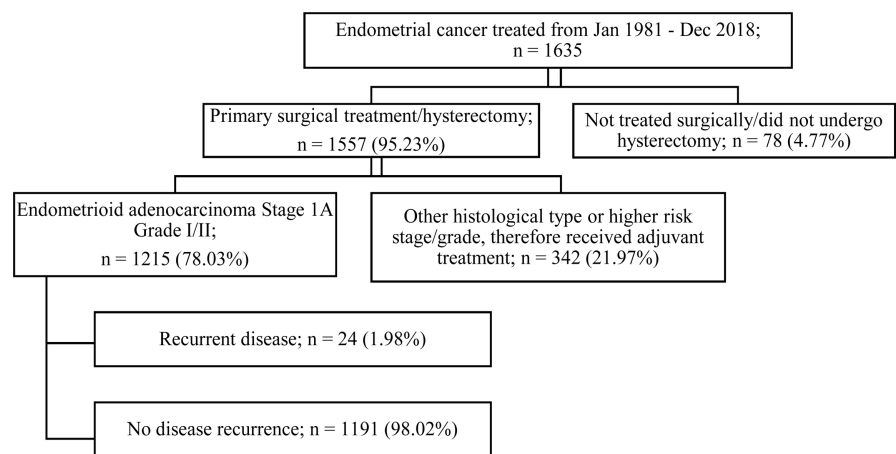


Figure 1. Recurrence rate in low-risk endometrial adenocarcinoma.

Table 1. Recurrence rate in low-risk endometrial adenocarcinoma.

Recurrence region	n = 24	Percentage	Locations
Local	10	41.67	Vaginal vault
Loco-regional	7	29.17	Ovary
			Pelvic lymph nodes
			Rectum
Distant	1	4.17	Vaginal vault
			Abdominal wall
Loco-regional and distant	6	25	Abdomen
			Ascites
			Omentum
			Abdominal lymph nodes
			Vaginal vault

3.3. Diagnosis of Recurrence

The median time to diagnosis of recurrence was 30.5 months (range of 8 - 91 months). 67.7% (n = 16) of the recurrences were diagnosed by gynaecology-oncology specialists. Other recurrences were diagnosed by either the primary care practitioner (n = 6, 25%) or a general gynaecologist (n = 2, 8.3%). Symptomatic patients presented to either their gynaecology-oncology specialist or their other practitioner based on their individual surveillance recommendations.

3.4. Patient Characteristics and Follow-Up

Overall, there were no statistically significant differences between the patients who developed recurrent disease were similar to those who did not (**Table 2**). The majority of patients completed follow-up at our institution (n = 992, 81.6%). The remaining 18.4% of patients had follow up either with their primary care practitioner or general gynaecologist. The median follow-up period was 44.4 months, and the median number of follow-up visits from surgery was six.

3.5. Recurrence Presenting Symptoms

50% (n = 12) of the patients who had a recurrence were asymptomatic. Ten of these patients had physical examination findings on routine follow-up that lead to the diagnosis of recurrence—vaginal or vault nodules or masses. The remaining two patients were diagnosed after incidental findings on imaging done for other indications. Patients who had symptomatic recurrence often presented

Table 2. Characteristics of patient with low-risk endometrial adenocarcinoma recurrence compared to those without recurrence.

		Patients without recurrence	Patients with recurrence	OR (95% confidence interval)	P value
Age at diagnosis (n = 1215)		59.6 (23 - 92)	64.1 (34 - 87)	1.04 (0.99, 1.07)	0.05
Menopausal status (n = 888*)	Post	689 (79%)	10 (77%)	0.89 (0.24, 3.30)	0.87
	Pre	186 (21%)	3 (23%)		
Histological grade at diagnosis (n = 1215)	Grade 1	886 (74%)	14 (58%)	2.07 (0.91, 4.71)	0.08
	Grade 2	305 (26%)	10 (42%)		
LVSI at initial surgical treatment (n = 1055*)	Negative	950 (92%)	18 (90%)	1.24 (0.28, 5.44)	0.77
	Positive	85 (8%)	2 (10%)		
Mode of hysterectomy (n = 761*)	Abdominal	287 (38%)	5 (45%)	0.80 (0.24, 2.65)	0.72
	Laparoscopic	430 (57%)	6 (55%)		
	Vaginal	33 (4%)	0		
Lymphadenectomy performed (n = 929*)	Yes	336 (37%)	8 (50%)	1.71 (0.64, 4.62)	0.28
	No	577 (63%)	8 (50%)		
Peritoneal washings (n = 1061*)	Positive	40 (4%)	1 (6%)	1.48 (0.19, 11.36)	0.71
	Negative	1003 (96%)	17 (94%)		

*For every variable, data calculated for number of patients with available data.

with a constellation of symptoms that prompted further investigation given their history of endometrial cancer, such as vaginal bleeding, abdominal pain and gastrointestinal changes. In two patients with distant recurrence, the symptoms were non-specific constitutional symptoms such as weakness, fatigue and loss of weight.

3.6. Recurrence Treatment

79.2% (n = 19) of patients with recurrent disease were treated with different therapy combinations, including surgical resection, radiotherapy, chemotherapy and hormonal treatment. 8.3% (n = 2) underwent surgical resection alone; two were treated with radiotherapy (8.3%) alone; one patient had chemotherapy only.

3.7. Patient Outcomes

42% (n = 10) of patients with a recurrence had salvageable disease. Six of these patients were still alive at the conclusion of this study, and the other four were deceased from unrelated causes. Of the patients who had salvageable recurrences, eight patients had disease confined to the vaginal vault. Interestingly two patients with distant recurrences were also salvaged. Ten patients had disease recurrence which was not salvageable with equal numbers of loco-regional and distant recurrence locations. 16.7% (n = 4) were lost to follow-up from following treatment of their recurrence (**Figure 2**). 58.3% (n = 14) of patients with recurrent disease were deceased when completing this study. In ten of these patients, this was as a result of recurrent disease. The mean time from diagnosis of recurrence to subsequent death was 2.1 years (range of 1 - 5 years).

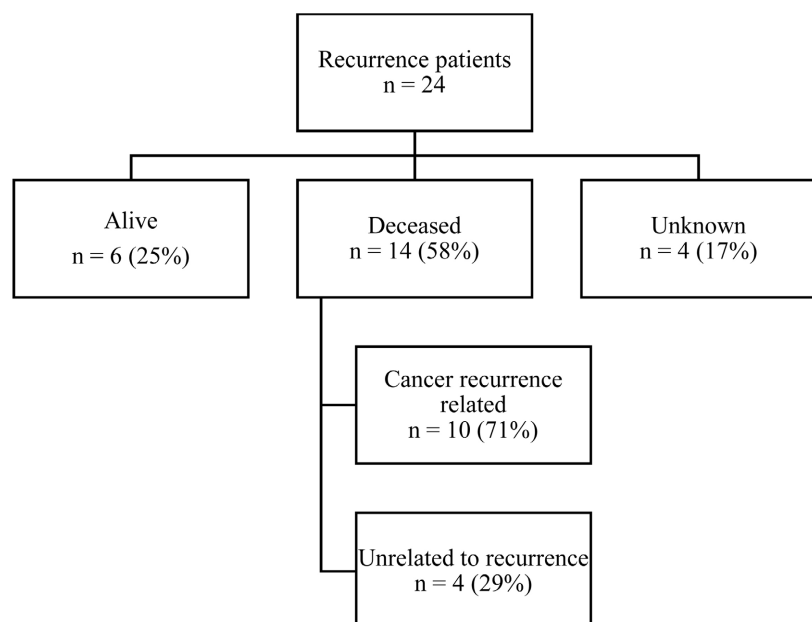


Figure 2. Patient outcomes following treatment of recurrent low-risk endometrial adenocarcinoma at time of audit.

4. Discussion

Endometrial cancer is the most common gynaecological cancer diagnosed in Australia, and its incidence is rising with an increasing prevalence of known risk factors such as obesity. Gynaecology oncology service provision needs to adapt accordingly, as there will be an increasing number of people surviving low-risk endometrial cancer, with very few recurrences. In order to address holistic health needs and maintain tertiary service capacity, primary care practitioners will be required to provide more follow-up care. In this study, we present the long-term disease-related follow-up outcomes for a large cohort of patients with low-risk endometrial cancer after primary surgery, resulting in a recurrence rate of less than 2%. Over nearly 30 years, the comorbidities and risk factors for endometrial cancer have increased, and despite this, our overall recurrence rate for low-risk endometrial cancer remained exceptionally low at 1.98%. This recurrence rate is even lower than the rate of 2.9% recently published by Stasenکو *et al.* [23]. Clinicians should be mindful that in our study the median time to recurrence prolongs to 30 months of follow up. None of the demographic or histopathological risk factors we analysed were significantly linked to recurrence (Table 2).

Overall, we believe that our findings support transitioning to a community-based model of care for patients treated surgically for low-risk endometrial cancer. Firstly, the ultra-low risk of incidence of recurrence makes the cost-effectiveness of tertiary specialised gynaecology-oncology follow-up questionable [15]. Secondly, this analysis shows that patients with recurrent disease, especially patients with confined loco-regional disease who are potentially salvageable, usually present with very distinct symptoms that lead to their diagnosis. Half of the patients with recurrent cancer presented with symptoms that warranted investigation, and the majority of the other asymptomatic patients had obvious findings on physical examination. The leading cause of death in endometrial cancer survivors is cardiovascular disease, not recurrent disease, mainly due to these patients' comorbidities. The diagnosis of endometrial cancer can serve as a "window of opportunity" for patients to adopt a healthier lifestyle. A strong and continuous relationship with their primary care practitioner can support and promote this. Community-based follow-up has the advantage of delivering post-treatment care closer to home, particularly for patients treated initially in gynaecology oncology centres with a broad geographic reach [24]. Furthermore, the transfer of care from a "cancer-focused" setting to a more holistic primary care or nurse-led setting would significantly reduce anxiety associated with fear of cancer recurrence [25].

In recent times, community-based follow-up of low-risk endometrial cancer patients has become evidence-based and is increasingly supported by different cancer societies worldwide, although is not yet standardised [13] [20] [21] [22]. Most countries have a more intensive follow-up for the first few years as 70% - 100% of recurrences occur within three years of primary treatment [18] [19]. In the United States, the Society of Gynaecologic Oncology (SGO) recommends the

first two years of follow-up for low-risk disease to be performed six monthly exclusively by gynaecologic oncology specialists [13]. Following this, either a generalist (including general practitioners) or a gynaecology oncology specialist can continue the surveillance yearly. Surveillance is recommended to continue yearly beyond five years [13]. The British Gynaecological Cancer Society (BGCS) has broader guidelines, with multiple follow-up options to be decided upon in a multidisciplinary setting for low-risk disease [20]. Patients can have a limited number of infrequent visits with a gynaecology oncology specialist for the first years. In some instances, they can be discharged immediately following initial treatment. There is also a choice to opt for traditional clinic-based follow-up, led by either general gynaecology doctors or gynaecology nurses. Primary care reviews or nurse-led telephone calls can also be alternatively instituted [7] [20].

If transitioning low-risk endometrial cancer patients to nurse-led and/or community-based surveillance with their primary care practitioners, then important systems would need to be implemented to ensure adequate education of patients and care providers. Adequate systems for communication are essential, with fast-track processes in place for patients to be referred urgently for gynaecology oncology specialist review. We have previously published a pilot study to assess the feasibility of community-based follow-up for low-risk endometrial cancer patients. Patients had a post-operative review with a gynaecology oncology specialist and a one-hour meeting with a senior clinical nurse before being discharged to ongoing follow-up with their primary care practitioner [24]. Both patients and primary care practitioners were educated regarding their care plan by the gynaecology oncology unit. The results showed that most patients and primary care practitioners found this program useful, reassuring and effective. An outstanding question regarding primary care practitioner follow-up care will be regarding the need for physical examination at surveillance visits. Half of the recurrences in our cohort (0.99% of all low-risk endometrial cancer patients) were detected on physical examination. Hypothetically, if these patients were not examined, they might eventually become symptomatic; however, their disease may be detected at a later stage. It is unclear whether this would alter their overall prognosis, and it is also unclear if all patients in this low-risk cohort should undergo routine pelvic exams or examination only based on symptoms. Further testing between community and hospital based follow up outcomes is underway to ensure the feasibility of community based follow up.

To our knowledge, this is the longest study analysing a cohort of low-risk endometrial adenocarcinoma and the features of their recurrences, reflective of decades of treatment, and this is our analysis' strength. However, our study has a few limitations; given the retrospective nature of our study over such an extended time frame, inherently data may be missing or inaccurate. Some patients were lost to follow-up or potentially referred to other centres upon recurrence, so our reported recurrence rate may actually be higher. Also, due to the long period of this study, we could witness several changes of practice in management

of these patients as standards of care developed, which may have affected follow-up data. An additional factor to consider is that the triaging of endometrial cancer into low- and high-risk disease is changing from a purely grade and stage based methodology, to one that includes molecular testing [23]. Given that this study spans back 40 years, it is not possible to retrospectively perform molecular analysis on our cohort of patients. However, in the future this practice will impact how we can identify those at a high risk of recurrence, and will have implications for which patients will be suitable for community led follow up.

5. Conclusion

Given low-risk endometrial cancer has a low recurrence rate and that recurrences are easily detectable, we suggest that hospitals can safely transition to community-based follow-up. Given the burden this disease and patients' comorbidities will progressively pose in the years to come, supporting the development of primary care-based surveillance and referral pathways for specialist centres will be critical.

Conflicts of Interest

No conflicts of interest to disclose.

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