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Original Research Article

Stratified follow up for endometrial cancer according to the characteristics of a tumour

Gemma K S Cass[1,*], Amit Patel[1], Jo Bailey[2], Katy Horton Fawkes[1], Vivek Nama[3]

[1]*Dept. of Obstetrics and Gynaecology, St Michaels Hospital, Bristol, England*
[2]*St Michaels Hospital, Bristol, BS2 8EG*
[3]*Dept. of Obstetrics and Gynaecology, Croydon University Hospital, Croydon, London, England*

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ABSTRACT

We explore cost effectiveness and the role of tumour characteristics to stratify women for follow up with endometrial cancer, A risk stratified pathway of post treatment management for women with endometrial cancer is necessary. Grade 3 disease and presence of LVSI may be risk factors for death and recurrence of endometrial cancer that can help to stratify women for follow up.

1. Introduction

Endometrial cancer is the fourth commonest cancer in Europe and rates are continuing to rise. The majority are in an early stage where the disease is confined to the uterus (Stage 1 FIGO 2009) and overall survival across all stages at five years is 70%.[1] Most recurrences from early endometrial cancer occur in the first two years after diagnosis.][2–8] Various prognostic factors such as grade, stage, the presence of lymphovascular space invasion, and tumour free distance from the serosa have been stipulated to affect recurrence risk[2,3,6–14] and currently, these are used to tailor adjuvant treatment. However, while planning follow- up these risk factors are not considered.

Follow up for women with endometrial cancer is often conducted in a clinic setting with a focus on identifying a recurrence. Regular follow may also offer reassurance[15] to some women and provides an opportunity to address side effects of the treatment. However, there is a lack of evidence to support the use of routine follow up to improve prognosis through early detection of recurrence. In fact, the majority of endometrial cancer recurrences occur in the interval between scheduled follow-up visits and are symptomatic.[2,16–20] Additionally, there is no demonstrable benefit in the overall survival for those who had a screen detected recurrence compared to those who were symptomatic.[16,18–21] It is arguable that there may be no clinical justification for routine follow up in these women. However many clinicians are reluctant to discharge women as lack of evidence does not directly relate to lack of benefit.

The National Cancer Survivorship Initiative (NCSI) aims to improve care after treatment by advocating self-management as a form of follow up for low-risk patients.[22] As part of survivorship work, the NCSI have developed a recovery package to run alongside patients who will self-manage the side effects of treatment. The package involves a Holistic Needs Assessment (HNA), treatment summary, cancer care review in primary care and access to wellbeing clinics.[23,24] Currently, these recovery packages are not set up uniformly through out the U K, and there is a compelling argument to fund these recovery packages in favour of 'routine' follow up.

* *Corresponding author.*
E-mail address: gem_cass@hotmail.com (G. K S Cass).

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Stratified follow up consisting of either individualised follow up or supported self-management is now being delivered by multidisciplinary teams for breast and prostate cancer survivors.[25] The pathways are delivered in conjunction with the recovery package and replace routine review appointments with either more bespoke appointments with clinicians, or a self-directed aftercare (SDA) pathway including nurse led follow up. Evaluation of risk stratified pathways have demonstrated that over half of women with newly diagnosed breast cancer are suitable for the SDA pathway and joint surgery and oncology follow up appointments have fallen by 39%.[26]

As the number of endometrial cancers is on the rise, so too are the women who survive and live with cancer beyond treatment. With this uncertain evidence, we wanted to explore the economic costs of follow up and the role of stratified follow up in patients with stage I and II Endometrial cancer. We hypothesize that tumour characteristics used to tailor adjuvant treatment can be used to individualise patient follow up as part of stratified post cancer treatment care.

2. Materials and Methods

We retrospectively studied all women diagnosed with endometrial carcinoma from 2005 to 2015 at St Michaels Hospital, Bristol (n=459). Patients with stage 3 or 4 disease, synchronous tumours, who had incomplete surgical staging, were either unfit or had palliative treatment were excluded. Clinical data was collected fr om electronic patient records, multidisciplinary tumour board database and pathology database (Ultra). Data were collected on age, date of diagnosis, grade, histological subtype, depth of myometrial invasion, lymphovascular space invasion, the distance of a tumour to the serosa and adjuvant treatment. Tumours were staged according to the Figo 2009 staging system.[27] Follow up data was also gathered including details of recurrence events and survival. Recurrences were classified as pelvic or distant and multiple or solitary. Vaginal and distant solitary recurrence were diagnosed by tissue biopsy. Recurrence, with a disease free interval of more than five years were always diagnosed by a tissue biopsy. Data was analysed using JMP statistical software program version 12.2.0 and IBM SPSS Statistics version 24.

Descriptive data was described using mean and standard error. Kaplan–Meier curves were generated to examine the overall and disease free survival. Disease free survival was defined as the time from diagnosis to the date of recurrence. Timescale used was months and the follow-up time was censored at death (from disease or other causes) and last date of follow up. The Cox regression model was used to identify and simultaneously evaluate any independent prognostic factors associated with relative survival and recurrence. A p value of < 0.5 was considered as statistically significant.

There is heterogeneity in practice across the UK regarding lymph node management. In our Centre, we do not offer systematic lymphadenectomy for endometrial cancers. Only Grade 3 endometrioid cancers or type II endometrial cancers have a pre-operative computed tomography (CT) scan to rule out an extra uterine disease. All patients with good performance status have a hysterectomy with bilateral salpingo-oophorectomy, performed laparoscopically in 97% of cases (unpublished data). If the lymph nodes are suspicious on CT, then selective lymphadenectomy is performed. The administration of adjuvant treatment is upon established risk factors for pelvic lymph node involvement on the uterine histology.[4–6,8,11] We believe that this is the least invasive means of treating endometrial cancers without compromising oncological outcomes.

3. Follow up

Current practice in our Centre is to follow up women every third month for the first year, every fourth month for the second year, every sixth month for a further three years. At each appointment, a targeted history is taken and an examination performed. Imaging is arranged if there is a clinical suspicion of recurrence. Women with stage 1 grade 1 endometrioid endometrial cancers par take in one Holistic Needs Assessment (HNA) by a Specialist nurse at three months after surgery. According to the Service Level Agreement for our Trust, the cost of a routine follow up is £104.

4. Results

459 women were diagnosed with stage 1 and 2 endometrial cancer between 2005 and 2015 at the Bristol Gyn Oncology Centre. There was insufficient follow- up data available on 8 (1.7%) women, and 21 (4.6%) women had a synchronous tumour diagnosed at presentation. A further 19 (4.1%) women were excluded from analysis due to unreliable follow-up data for reasons outlined in figure 1. We included 411 of Stage I and II Endometrial cancers. 67.2% were Stage Ia, 19.5% were Stage Ib, and 13.3% were Stage II at diagnosis. 45.7%, 33.1% and 21.2 % were Grade 1, 2 and 3 respectively. 76.2% had no LVSI, and 23.8 % had LVSI. Depth of myometrial invasion was $< 50\%$ in 54% and $> 50\%$ in 24.3. 21.7% had no myometrial invasion. The distance from the serosa was divided into a binomial variable as $> 1.75\%$ and < 1.75 % based on previous ly published data.[14] The details of demographics, treatments received, stage of the disease, histology and follow- up are presented in Tables 1 and 2.

Overall survival was 79% at five years across all women with stage 1 and 2 diseases. Mean overall survival for women with stage 1 and 2 endometrial cancer was 70.4 months. Mean disease free survival was 68.7 months. 54

(13.1%) women had died by the end of the study period, and 21 (38.9%) deaths were related to endometrial cancer.

5. Recurrences

Of the 411 women, 30 (7.3%) women had a recurrence during the study period. Of the 30 recurrences, 13 were diagnosed in the first year, 10 in the second year. 90% were diagnosed within three years, and only three women presented after this time. Recurrences occurred between 2 and 96 months (mean 23.6 SD 18.1). The interval between recurrence and follow up was 0.7 to 134 months. (mean 39.8 SD 28.5). Pelvic recurrent disease was diagnosed in 11 women while the remaining 19 had distant disease. 22 (73%) women presented in between appointments and of those that were detected at routine follow up only five were asymptomatic. Eight women with recurrence had a salvageable disease which was amenable to surgery or radiotherapy. 15 of these women had stage Ia disease, 4 stage 1b and 11 stage 2 disease. The rate of recurrence of women with stage 1 endometrial cancer was 5.9% which is comparable to other studies.[2,3,6,9]

According to our follow up protocol 2545 appointments were carried out for women with stage 1 and 2 disease during the study period. Only 5 (16.7%) asymptomatic recurrences were detected at these appointments. Of the se five asymptomatic recurrences, two were low risk according to PORTEC criteria[2,3,6,9] and recurred at the vault and were salvage able. The remaining 3 had adjuvant pelvic radiotherapy and brachytherapy and recurred with distant disease. Mean overall survival in women with recurrent disease was 58.5 months (SD 8.9). 21 women with recurrence subsequently died from the disease. 12 of these women died within a year of the recurrence event.

Logression analyses showed that the risk of death and recurrence was increased by two and four fold respectively in high-grade cancers (OR 2.58 (1.34-4.97) p=0.005), (OR 4.37 (1.72-11.13) p=0.002). (Table 3). The absence of LVSI was associated with a statistically significant reduction in the risk of recurrence (OR 0.26 (0.07-0.95) p=0.042). High-grade disease was also associated with a six fold increase in death in women who had recurrence although this failed to reach statistical significance probably due to the small subgroup of patients (OR 6.88 (0.50-94.95) p=0.15) (Table 3).

6. Cost calculations

We found that symptoms at the time of diagnosis of a recurrence or whether recurrence is detected as part of routine examination does not appear to have a significant impact on survival corroborated by other studies.[16,18–21] Routine follow up detected one woman with asymptomatic recurrence for every 509 appointments. Each follow- up appointment is tariffed at £104 meaning a total of £52,936 was spent to pick up one asymptomatic recurrence. The additional 509 appointments.

If all Stage 1 cancers were not followed up for 5 years, we would have missed 25 recurrences (6 solitary and 9 metastatic) with a saving of 14,094 appointments and a cost saving of £1,465,776. If no follow up was restricted to Stage 1a, grade 1 tumours we would have missed 2 recurrences (1 pelvic, 1 metastatic) with a saving of 7830 appointments and £814,320. Both these protocols would save £561,600 and 5400 appointmenes for every 100 patients treated in each group.

7. Discussion

The number of cancer survivors is increasing by 3% a year due to the increased incidence and improving survival rates.[28] We have demonstrated a 79%, five- year survival in women with stage 1 and 2 endometrial cancer with a low risk of recurrence. A UK survey has shown that 98% of respondents undertake regular hospital follow up appointments for gynecology cancers[29] despite evidence that intense surveillance of women with endometrial cancer does not improve long term outcomes.[2,16,20] Recently the ENDCAT trial has validated the use of telephone follow up by Specialist Nurses for women with stage 1 endometrial cancer.[30] There were no detrimental psychological, or physical consequences and women were highly satisfied with nurse led telephone consultations. Furthermore, there was no delay in diagnosis of recurrence in women who had telephone led follow-up and therefore it is reasonable to suggest that this can replace or complement traditional hospital led follow up in stage 1 endometrial cancer.[31]

Considering the cost to the health care system, irrespective of its funding models, there is undoubted need to readdress follow up strategies for endometrial cancer to ensure resources are appropriately utilized without compromising oncological outcomes.

We have demonstrated a cost benefit to stratified follow up but the amount of clinical time saved needs to also be considered. As each clinic appointment is scheduled for 15 minutes, an extra 32 clinics of 4 hours each could be more efficiently used for other clinical needs according to our results.

We suggest that those women with Stage 1 and 2 diseases enter such a stratified pathway of follow up dependant on characteristics of a tumour and risk of disease recurrence. Those with no risk factors can be empowered to self-manage disease with educational support packages that detail signs and symptoms that need to alert these women to seek medical advice. Women at higher risk of recurrence can enter individually tailored follow up which could be nurse led via the telephone. From our study, we suggest that those women with Grade 3 disease or LVSI may be at higher risk of recurrence and may benefit the most from individually tailored follow up.

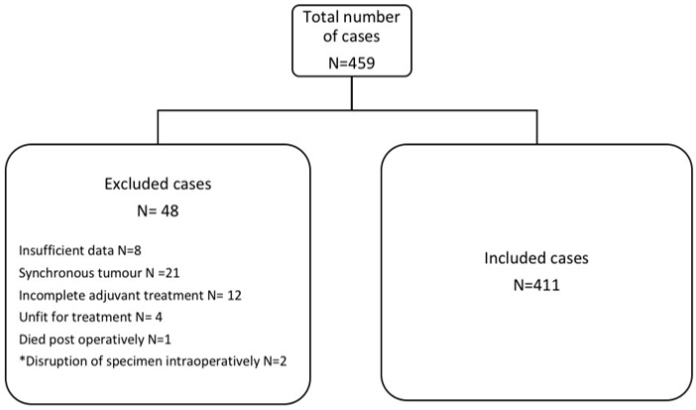

Fig. 1: Reasons for excluded cases. Values given as N (% of 459 patients) *Intraoperative disruption of uterine cavity during primary surgery so women were upstaged and managed with adjuvant radiotherapy and chemotherapy

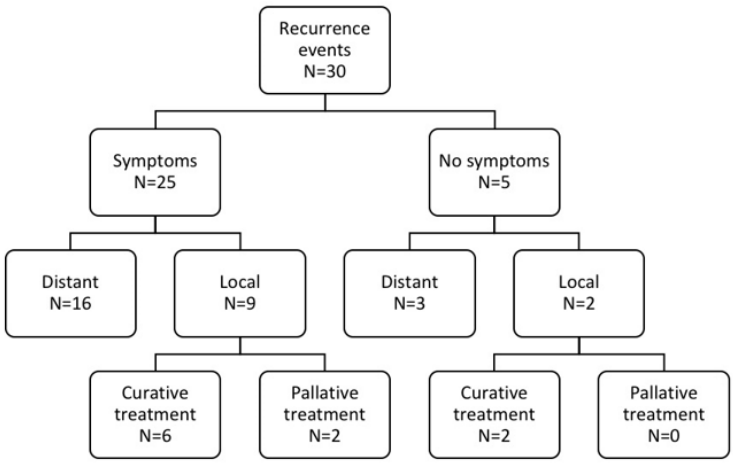

Fig. 2: Site of recurrence, presence of symptoms and salvageble *disease for women with recurrence of endometrial cancer. Values given as N

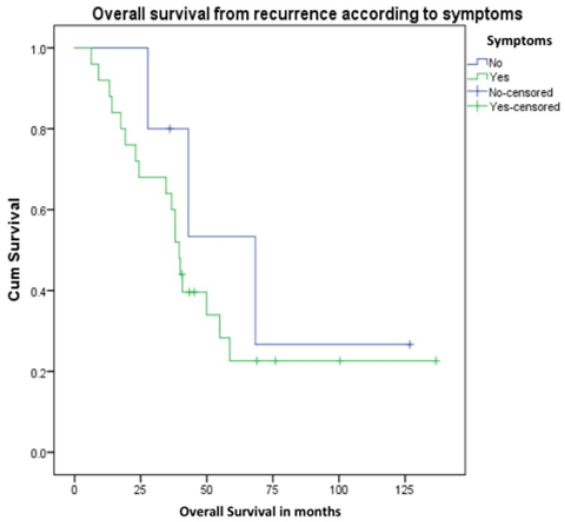

Fig. 3: Overall survival in women with recurrence according to the presence of symptoms (p=0.451)

Table 1: Characteristics of all cases diagnosed with endometrial cancer, cases of recurrent disease and cases of death from disease Values are given as N (% of N patients)

Characteristics		**All included cases** (N=411)		**Recurrent disease** (N=30)		**Death due to disease** (N=21)	
			%		%		%
Figo stage	Ia	276	67.2	15	50	10	47.6
	Ib	80	19.5	4	13.3	3	14.3
	II	55	13.3	11	36.7	8	38.1
Grade	1	188	45.7	3	10	1	4.8
	2	136	33.1	11	36.7	7	33.3
	3	87	21.2	16	53.3	13	61.9
LVSI	Yes	98	23.8	17	56.7	14	66.7
	No	313	76.2	13	43.3	7	33.3
Depth of myometrial invasion	<50%	222	54	12	40	8	38.1
	>50%	100	24.3	13	43.3	10	47.6
	None	89	21.7	5	16.7	3	14.3
Cervical invasion	Both	21	5.1	1	3.3	7	33.3
	Epithelium	7	1.7	0	0	0	0
	Stroma	34	8.3	10	33.3	1	4.8
	None	349	84.9	19	63.4	13	61.9
Distance from the serosa*	<1.75	28	6.8	3	10	2	9.5
	>1.75	191	46.5	13	43.3	8	38.1

*192 cases missing as not reported as part of pathology. Cut off of 1.75mm used as demonstrated to be prognostic indicator for recurrence14

Table 2: Adjuvant treatment according to stage of disease. Values are given as N (% of 411 patients)

	External beam radiotherapy	**Brachytherapy**	**Chemotherapy**
	N (%)	N (%)	N (%)
Ia	3 (0.7) *	62 (15.1)	0 (0)
Ib	35 (8.5)	74 (18.0)	0 (0)
II	47 (11.4)	54 (13.1)	11 (2.7)

*Decision for EBRT as MMMT on histology, serosal clearance <3mm and grade 3.

Table 3: Logistic regression. Risk of death and recurrence according to characteristics of the tumour

	Risk of death		**Risk of recurrence**		**Risk of death from recurrence**	
	OR (CI)	p value	OR (CI)	p value	OR (CI)	p value
Grade 3	2.58 (1.34-4.97)	0.005	4.37 (1.72-11.13)	0.002	6.88 (0.50-94.95)	0.15
Stage 1b *	0.66 (0.19-2.37)	0.53	0.092 (0.016-0.54)	0.008	1.23 (0.01-132.54)	0.93
Absence of LVSI	0.54 (0.19-1.53)	0.25	0.26 (0.07-0.95)	0.042	0.08 (0.004-2.24)	0.14
Distance from serosa	0.99 (0.89-1.13)	0.93	1.05 (0.91-1.20)	0.52	0.93 (0.67-1.28)	0.64

* Odd ratio refers to stage 1b and 1a compared to stage II

The decision for women to undergo self-management depends on the level of risk associated with cancer, effects of treatment co-morbidities and the patient's knowledge and confidence to manage their condition. NHS Improvement Cancer has clear and helpful documentation for units to implement stratified pathways to ensure they are safe and effective.[32,33] A key component of self- management is the ability to re-access specialist services. Undoubtedly a fast track re-access system must be in place for women who have self-management follow-up.[26,28,31]

It is also important that before stratified follow-up implementation, the recovery package for cancer survivors must be fully embedded into post treatment management to ensure there is adequate support for women.[23–25] In our hospital, the recovery package is fully accessible.

Finally, there is no clear recommendation on the duration of follow up. Currently, most patients are being followed up for five years. In our study, 90% of recurrences occurred

within three years of the diagnosis, so we suggest those women who undertake a surveillance pathway for follow up only to do so for three years. Alongside implemention for a new follow up pathway, there must also be stringent audit and monitoring to ensure the highest and safest standard of care.

8. Conclusion

A risk stratified pathway of post treatment management for women with endometrial cancer is necessary to improve women's experience of surviving with cancer and release resources in diagnosing more new patients and supporting those with a metastatic and complex disease. Grade 3 disease and the presence of lymphovascular space invasion may be risk factors for death and recurrence of endometrial cancer that can help to stratify women for follow-up. Women with stage 1 or 2 endometrial cancer and these characteristics may benefit from follow up whilst others would be suitable for self-management. This predictive model of stratified follow up for early stage endometrial cancer now needs to be developed and implemented nationally.

9. Author contributions

All authors were involved in the design, planning and conduct of the manuscript. G Cass, V Nama and A Patel were involved in data analysis and all authors contributed to manuscript writing.

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11. Conflict of interest

No authors have a declaration of interest to declare.

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Author biography

Gemma K S Cass Consultant

Amit Patel Consultant

Jo Bailey Consultant

Katy Horton Fawkes Consultant

Vivek Nama Consultant

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