# Well differentiated endometrioid adenocarcinoma of the uterus: a cancer unit or centre case?

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**Summary**

*Objective*: The purpose of this study was to investigate what proportion of cases showing a well differentiated endometrioid endometrial adenocarcinoma in the hysterectomy specimen removed at two UK cancer centres had adverse pathological features or advanced stage disease at the time of presentation. *Study Design:* Ninety-eight patients who were operated on at either the South East London Cancer Centre, London or the Kent Oncology Centre, Maidstone had a histological diagnosis of well differentiated (grade 1) endometrioid adenocarcinoma in their hysterectomy specimen. These were identified using the multidisciplinary meeting database as well as the respective pathology department databases. The histology reports for these patients were examined and analysed for the purpose of this study. *Results:* Of the initial 98 cases, 65 patients (66.3%) were referred with a preoperative curettage showing a well differentiated endometrioid adenocarcinoma, 25 cases (25.5%) were referred with atypical endometrial hyperplasia, seven patients (7.1%) were referred with a moderately differentiated endometrioid adenocarcinoma, and one case (1.0%) was referred with a possible malignant mixed Mullerian tumour. Subsequent histological examination of the hysterectomy specimens revealed that all of these cases had a well differentiated endometrioid adenocarcinoma. In 20 of the 98 cases (20.4%) there was no myometrial invasion, 56 cases (57.1%) showed invasion of the inner half of the myometrium and 22 cases (22.4%) showed outer half involvement. There was no cervical involvement in 78 cases (79.6%), endocervical gland involvement in eight patients (8.2%) and cervical stromal involvement in 12 patients (12.2%). The total percentage of cases with cervical involvement was 20.4%. Thirty-eight cases (out of the 98) underwent a bilateral pelvic lymphadenectomy. Of these 38 cases, four cases had locoregional nodal metastases (10.5% of the patients who underwent lymphadenectomy). There were ovarian metastases in one case and metastasis to one fallopian tube in another. From our study, 33.6% of cases with a well differentiated endometrioid adenocarcinoma of the uterus were Stage Ic or more at the time of presentation; 12.2% were at least FIGO Stage Ic, eight patients (8.2%) were FIGO Stage IIa, seven patients (7.1%) were Stage IIb and six patients (6.1%) were Stage III. In these patients a full surgical staging operation with a pelvic lymphadenectomy was indicated according to FIGO recommendation. *Conclusion:* A significant proportion (33.6%) of well differentiated tumours in a hysterectomy were found to have Stage Ic disease or more at the time of presentation, and thus full surgical staging including a lymphadenectomy should have been carried out in these cases. Cases with a preoperative biopsy showing atypical hyperplasia or well differentiated adenocarcinoma should have a preoperative MRI scan or preferably an intraoperative frozen section examination to identify those cases with adverse pathological features which need to be fully staged with pelvic and paraaortic lymphadenectomy.

*Key words:* Well differentiated endometrial adenocarcinoma; Staging; Prognostic factors.

## Introduction

Endometrial cancer is the most common malignancy of the female genital tract in the United States with over 40,000 new cases and 7,000 deaths in 2004 [1]. In the United Kingdom and Ireland uterine cancer accounted for around one in 30 cancer cases and one in 50 cancer deaths in the 1990s and is the fifth most common cancer in women with over 90% occurring in women over the age of 50 years [2]. The main risk factors for endometrial carcinoma are associated with prolonged or increased exposure of the uterus to oestrogen and include early age at menarche, low parity, late age at menopause, anovulatory cycles and obesity as well as unopposed administered oestrogens [2]. There is also a 2-3 fold increased risk of endometrial cancer in women treated with tamoxifen for breast cancer [3, 4].

The cornerstone of treatment for well differentiated endometrial cancer is a total abdominal or laparoscopic assisted vaginal hysterectomy and bilateral salpingo-oophorectomy. Some pathological characteristics are associated with a higher risk of nodal involvement. These factors include depth of myometrial invasion > 50%, cervical or adnexal involvement. Many gynaecological cancer centres (including our own) consider the presence of these factors an indication for surgical staging by pelvic lymphadenectomy. In addition these patients may also require postoperative adjuvant radiotherapy.

Since the publication of the Calman Hine report in 1995 [5] and the subsequent development of cancer centres and cancer units in the UK, the majority of patients with grade 1 endometrioid adenocarcinoma of the endometrium are treated in cancer units. This decision is usually taken after the endometrial biopsy has been reviewed by an experienced gynaecological pathologist and the case is discussed at a multidisciplinary team meeting.

In addition, the majority of patients with endometrial hyperplasia are also treated in the local unit hospitals. Endometrial hyperplasia is characterised by an increased endometrial thickness with glandular crowding. In the presence of cytologic atypia the potential for malignancy

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may be as high as 30% [6-9]. Kurman *et al.* demonstrated a 1.6% risk of progression to cancer in the absence of cytological atypia, with the risk increasing to 23% in the presence of atypia [6], while Ferenczy and Gelfand found a progression rate of 25% [10]. A common diagnostic problem arises when atypical hyperplasia is diagnosed in preoperative biopsy histology as it may be difficult to distinguish between atypical hyperplasia and a well differentiated adenocarcinoma, especially in small biopsy specimens. Several morphological features have been described which when seen in a biopsy are predictive of myometrial invasion in the uterus [11]. However, under-diagnosis of adenocarcinoma and limitations of sampling probably account for the fact that adenocarcinoma is found in 17-43% of hysterectomy specimens performed for a preoperative diagnosis of atypical hyperplasia [9, 12].

The aim of this study was to examine how many cases, operated on in two UK cancer centres, with a histologically proven grade 1 tumour in the hysterectomy specimen showed adverse pathological features or advanced stage disease at the time of presentation.

## Materials and Methods

Ninety-eight patients who were operated on at the Kent Oncology Centre in Maidstone, Kent, UK between December 2002 and December 2005, and the South East London Cancer Centre, London, UK during 2006, had a histological diagnosis of a well differentiated endometrioid adenocarcinoma of the endometrium on the final histology of the hysterectomy specimens. In both cancer centres all hysterectomy specimens were examined and reported by a specialist gynaecological pathologist.

These cases of grade 1 tumours of the endometrium were identified using the respective multidisciplinary team meeting databases as well as the pathological departmental databases. The histology reports for these patients were then examined and analysed for the purpose of this study.

## Results

Ninety-eight patients had a hysterectomy for endometrioid adenocarcinoma of the uterus or atypical endometrial hyperplasia and had a well differentiated endometrioid adenocarcinoma of the endometrium on the histology of the hysterectomy specimen.

Sixty-five patients (66.3%) were referred with a preoperative biopsy showing a well differentiated endometrioid adenocarcinoma, 25 patients (25.5%) were referred with atypical hyperplasia, seven patients (7.1%) were referred with a moderately differentiated tumour and one patient (1.0%) was referred with a preoperative biopsy of a possible malignant mixed Mullerian tumour; all of these had a final hysterectomy histology of a well differentiated endometrioid adenocarcinoma.

### *Depth of myometrial invasion*

Twenty cases out of the 98 patients (20.4%) had tumour confined to the endometrium, 56 patients (57.1%) had invasion into the inner half of the myometrium and in 22 patients (22.4%) the tumour invaded the outer half of the myometrium (Table 1).

Table 1. — *Degree of myometrial invasion in 98 cases of well differentiated endometrioid adenocarcinoma.*

| Myometrial invasion | Number (n = 98) | Percentage of total (98 cases) |
|---|---|---|
| No myometrial invasion | 20 | 20.4% |
| Inner 1/2 | 56 | 57.1% |
| Outer 1/2 | 22 | 22.4% |

In the 22 patients with outer half myometrial invasion, four had a preoperative biopsy showing atypical hyperplasia. Ten of these 22 patients had concomitant cervical involvement (nine had stromal involvement and in one patient, endocervical gland involvement) while the other 12 patients had a normal cervix on histology. In 17 of these 22 cases a bilateral pelvic lymphadenectomy was performed and in two patients there was metastatic tumour in the lymph nodes. In the remaining five cases a lymphadenectomy was not performed.

### *Cervical involvement*

Seventy-eight patients (79.6%) had a benign cervix, 12 had cervical stromal invasion (12.2%) while eight (8.2%) had endocervical gland involvement on the histological examination of the hysterectomy specimen (Table 2). In our study population of 98 patients with grade 1 endometrioid adenocarcinoma of the endometrium, 20 patients had some degree of cervical involvement (20.4%).

Table 2. — *Cervical involvement in 98 cases of well differentiated endometrioid adenocarcinoma.*

| Cervical assessment | Number (n = 98) | Percentage of total (98 cases) |
|---|---|---|
| Negative cervix | 78 | 79.6% |
| Endocervical gland involvement | 8 | 8.2% |
| Cervical stromal invasion | 12 | 12.2% |

### *Nodal involvement*

A bilateral pelvic lymphadenectomy was performed in 38 out of the 98 patients with a grade 1 endometrioid adenocarcinoma. External iliac, internal iliac and obturator nodes were removed. Lymphadectomy was performed in these well differentiated tumours since it is the practice at the Kent Oncology Centre to perform an intra-operative frozen section of the hysterectomy specimen in those patients referred with atypical hyperplasia or endometrial carcinoma to identify poor prognostic factors. These factors included outer half myometrial invasion (17 patients) and 14 patients with cervical involvement (5 cases with tumour in endocervical glands and 9 with cervical stromal invasion). Three patients had a referral preoperative endometrial biopsy of moderately differentiated adenocarcinoma and one with a possible malignant mixed Mullerian tumour, and therefore underwent a full pelvic lymphadenectomy as part of the surgical staging.

One patient had an endometrioid tumour in the fallopian tube and another had ovarian metastatic deposits. The mean node harvest was 20 lymph nodes (range 4 to 48 nodes) in these cases.

Four out of the 38 patients with a well differentiated carcinoma for whom a pelvic lymphadenectomy was performed had positive nodes (10.5%). Two patients had involvement of the inner half of the myometrium but one of these also had ovarian deposits, while the other two had deep myometrial invasion. Interestingly all the four cases had cervical stromal invasion and extensive lymphovascular space invasion (LVSI). Two of the cases had positive peritoneal washings.

*Patient age*

The mean age for the study group of 98 patients with well differentiated endometrioid adenocarcinoma was 62 years (range 30 to 87 years). For the group of 65 patients with early-stage disease (FIGO Stage 1a/1b) the mean was 61.45, while in the group of 33 patients with more advanced stage disease (FIGO Stage 1c-3) the mean was 62.97. There was no statistical significance between these two groups with a p value of 0.5003 (95% CI: 6.000 to 2.953).

## Discussion

The main prognostic risk factors in endometrial cancer include tumour grade, histological subtypes (serous papillary adenocarcinoma, clear cell adenocarcinoma, malignant mixed mullerian tumour), depth of myometrial invasion, cervical involvement, LVSI and positive peritoneal cytology [13].

*FIGO recommendations for management of endometrial cancer*

FIGO divided endometrial cancers into two risk groups. Low-risk cases include well and moderately differentiated endometrioid adenocarcinomas limited to the endometrium or invading less than one half of the myometrium. High-risk cases include all poorly differentiated endometrioid tumours irrespective of the stage, high risk histological subtypes (serous papillary adenocarcinoma, clear cell adenocarcinoma, malignant mixed mullerian tumour), tumours invading the outer half of the myometrium, or those cases with a suspicion of nodal metastasis on preoperative magnetic resonance imaging (MRI) or computed tomography (CT) scan [13, 14].

For low-risk cases, FIGO recommend a hysterectomy and bilateral salpingo-oophorectomy with peritoneal washings for cytology and palpation of the lymph nodes plus sampling if any suspicious nodes. Lymphadenectomy is not carried out routinely, as in these cases less than 5% will have positive nodes. If high-risk features are found postoperatively on histopathology, adjuvant radiotherapy should be considered [13].

In patients with macroscopic cervical involvement, a radical hysterectomy with bilateral pelvic lymphadenectomy and selective aortic node dissection is recommended. Recent studies indicate no benefit from the addition of radiotherapy for patients with negative nodes [13, 15-17].

Grade of the disease and histological subtype from a preoperative biopsy is generally used to decide the surgical management and in the UK suitability for surgery to be performed in the units as opposed to the cancer centres. It is not unusual for more advanced stage disease to be treated without full surgical staging, as staging in endometrial cancer is histopathological. FIGO guidelines, however, do not include the postoperative management for Stage II disease with grade 1 histology that were treated without lymphadenectomy.

FIGO recommends complete lymphadenectomy for cases with high-risk features. However, only some of these high-risk features are known preoperatively, namely tumour grade and type. The majority of these high-risk features are usually known only after or during surgery (deep myometrial invasion, cervical involvement, LVSI and positive peritoneal cytology). MRI scanning is not a routine practice in the preoperative assessment for women with endometrial cancer. If intraoperative frozen section is available, then most of these high-risk features can be identified at the time of the operation.

The FIGO recommendation for the management of low-risk tumours includes palpation of lymph nodes and sampling if suspicious. In addition the recommendations state that if cervical involvement is noted then the most appropriate action is a modified radical hysterectomy in experienced hands [13]. However, most of these tumours are not operated in a cancer centre by gynaecological oncologists trained in performing lymphadenectomies or more radical surgery. As a result, many patients will receive less than adequate staging and hence treatment.

*Patient age*

Older patients have a worse prognosis and may be better treated in a gynaecology oncology centre rather than in a non specialised unit as they are more likely to receive more appropriate initial surgery.

A review of three randomised controlled trials in 2002 investigated the role of surgery and adjuvant radiation in Stage I-II endometrial adenocarcinoma [18]. All three RCTs have shown a higher risk of disease recurrence in older patients. They suggested a survival benefit of adjuvant radiotherapy but there is no prospective data that demonstrates improvement in overall survival with adjuvant radiotherapy for older patients.

A retrospective review of 243 patients with endometrial adenocarcinoma was performed to assess the effect of age on the long-term outcome [19]. In this study, older women (> 63 years old) were found to have a greater risk of recurrence following postoperative radiotherapy independent of other prognostic factors and/or treatment technique. In addition they have a significantly decreased overall survival and cause-specific survival. The impact of the treatment-related variable did not alter the age-related outcome.

However, another retrospective study included 74 women aged 75 years or more who had Stage I-II

endometrial adenocarcinoma [20]. This demonstrated that 58% of these women had high-risk disease (Stage 1b G3, 1c and 2b). Some patients did not receive postoperative radiotherapy because of concern over toxicity. Treated women had a better cause-specific survival than untreated (p = 0.003).

In our series of 98 patients with a well differentiated endometrioid adenocarcinoma at hysterectomy, the mean age for the two groups, Stage 1a/b and Stages 1c-3, was 61.45 and 62.97 years, respectively, and was not statistically significant p = 0.5003 (95% CI: 6.000 to 2.953). In this study, age alone was not a good preoperative predictor for advanced stage disease at the time of presentation.

*Predictive value of tumour grading on preoperative biopsy*

Well differentiated (grade 1) adenocarcinomas account for 33.7% of all endometrioid endometrial adenocarcinomas [21]. The histological grade of the endometrioid adenocarcinoma, diagnosed on the preoperative biopsy, is an important guide to the depth of myometrial invasion and involvement of the pelvic lymph nodes [14]. This helps in planning the surgical treatment and whether full surgical staging with a pelvic lymphadenectomy is indicated. In addition tumour grade is used in the UK to determine where the surgery is carried out (unit vs cancer centre). However many studies show a low correlation between the tumour grade on preoperative biopsy and the final grade from the hysterectomy specimen.

A retrospective study by Eltabbakh *et al.* in 2005 included 182 patients referred with well differentiated endometrial adenocarcinoma on biopsy [22]. All women were treated with a total abdominal hysterectomy and bilateral salpingo-oophorectomy and lymphadenectomy. Postoperatively, 30% of women were found to have moderately or poorly differentiated cancer on the hysterectomy specimen. Only 116 patients (63.7%) were FIGO Stage 1b or less and 36.3% of patients were Stage 1c or more. This data demonstrated that in the management of endometrial cancer, grade 1 on endometrial biopsy on its own is not a reliable predictor of the true extent of the disease.

Other studies have also found a large discrepancy in grading between the preoperative endometrial biopsy and the final histology of the hysterectomy specimen. The discrepancy was greatest in those cases reported as well differentiated carcinomas on preoperative biopsy (40-55%) when compared to moderately and poorly differentiated carcinomas (29-36.7% and 16-25.6%, respectively) [23-28].

If decisions about patient management continue to rely on the preoperative biopsy for histological grading of these tumours, some patients will be inadequately treated while others may experience unnecessary morbidity.

Preoperative investigation with a MRI and CT scan may help in selecting those patients with a well differentiated carcinoma who may have advanced stage disease. The accuracy of MRI for predicting depth of myometrial invasion is 81-95%, cervical involvement of 80-95% [29-32]. A CT scan will help identify those patients with nodal involvement and distant metastasis.

In the Kent Oncology Centre, patients with a referral preoperative biopsy histology showing atypical hyperplasia or well differentiated endometrioid adenocarcinoma have an intraoperative frozen section at the time of hysterectomy. If the frozen section examination shows a carcinoma with poor prognostic factors, then a full pelvic lymphadenectomy is carried out. These include patients with poor histological subtypes (serous papillary, clear cell, malignant mixed Mullerian tumour), grade 2 and 3 carcinomas, outer one-half myometrial invasion and cervical or adnexal involvement. Our data have shown an accuracy of 84.3% for accurate grading, 94.3% for depth of myometrial invasion, and 86.7% for cervical involvement. This is comparable with the published literature reporting accuracies of assessment of 60-98% for grade, 80-96.6% for depth of myometrial invasion and 60-94% for cervical involvement [33-43]. Intraoperative frozen section is superior to preoperative MRI in that apart from detecting deep myometrial and cervical invasion, it can accurately diagnose the histological subtype and grade of the cancer. Microscopic deposits present on the cervix or adnexa can also be detected during frozen section; these are usually too small to be detected by preoperative MRI.

Our study has shown that a significant number of patients (33.6%) with a well differentiated cancer are FIGO Stage 1c or more at the time of presentation. The outer half of myometrial invasion was found in 22.4% and cervical involvement in 20.6%. Of the 38 patients who had a lymphadenectomy, four had positive nodes and in all these cases there was cervical involvement which was picked up by intraoperative frozen section.

## Conclusion

Tumour grading on preoperative endometrial biopsy is unreliable and decisions regarding patient management should not rely solely on this. A preoperative MRI may help to identify patients with advanced stage disease who could be operated on in a centre by surgeons experienced in performing lymphadenectomy. Intraoperative frozen section can also identify those high-risk patients who require a full surgical staging operation and spare those low-risk patients from unnecessary morbidity.

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