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ORIGINAL ARTICLE

# Is an endometrial thickness of ≥4 mm on transvaginal ultrasound scan an appropriate threshold for investigation of postmenopausal bleeding?

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**Abstract** Uterine cancer is the fourth most common cancer in the UK. Transvaginal ultrasound (TVS) provides a reliable means of determining endometrial thickness. There is little consensus as to the optimum endometrial thickness threshold for investigation of endometrial cancer. The aim of our study was to ascertain an appropriate endometrial thickness (ET) while limiting unnecessary investigation. A prospective study of women with postmenopausal bleeding (PMB) referred to the rapid access clinic over a 2-year period was undertaken. The primary investigation was TVS and if the ET was ≥4 mm, an endometrial sampling (Pipelle®) or a hysteroscopy was undertaken. Endometrial cancers were identified from the pathology reporting system and a search of the Northern and Yorkshire Cancer Registry Information Service (NYCRIS). Pre-test/post-test risks of endometrial cancer and numbers needed to test were calculated to determine optimum ET threshold. There were 1045 referrals to the rapid access clinic with a history of PMB. Pre-test risk of endometrial cancer was 6.5 %. Post-test risk was stratified according to ET measurement. The probability of an endometrial cancer at an ET < 4 mm was 0.3 %. Binary logistic regression analysis confirmed a statistically significant linear correlation between ET and the risk of developing endometrial cancer ($p < 0.0001$). The numbers needed to test in order to diagnose one case of endometrial cancer at 3 mm is 11 when compared with 4 at 10 mm. The authors conclude a threshold of ET ≥ 4 mm ensures the majority of cancers are detected with minimal unnecessary invasive investigation.

**Keywords** Transvaginal ultrasound · Endometrial thickness and endometrial cancer

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## Background

Uterine cancer is the fourth most common cancer in women in the UK and the most common gynaecological cancer [1]. Since the late 1990s, mortality rates from uterine cancer have risen by one quarter. If diagnosed early, more than three quarters will live for at least 10 years. More than 90 % are diagnosed in the postmenopausal group >50 years [2]. Multiple risk factors for developing endometrial cancer have been identified: early onset menstruation, late menopause, nulliparity, obesity, unopposed estrogen exposure and tamoxifen. Lynch syndrome type II has a cumulative risk of 20 % [3].

Postmenopausal bleeding (PMB) is the most common reason for referral to the rapid access clinic (RAC) in our setting but <1 in 10 are diagnosed with endometrial cancer. Transvaginal ultrasound (TVS) is the primary investigation in combination with endometrial biopsy and hysteroscopy. There is little consensus as to the appropriate cutoff for endometrial thickness (ET) and further investigations [4–7].

## Methods

A prospective study of consecutive women referred to the RAC with PMB was undertaken over a 2-year period. Data was collected in an Excel spreadsheet for 1045 women over 45 years of age and reporting at least

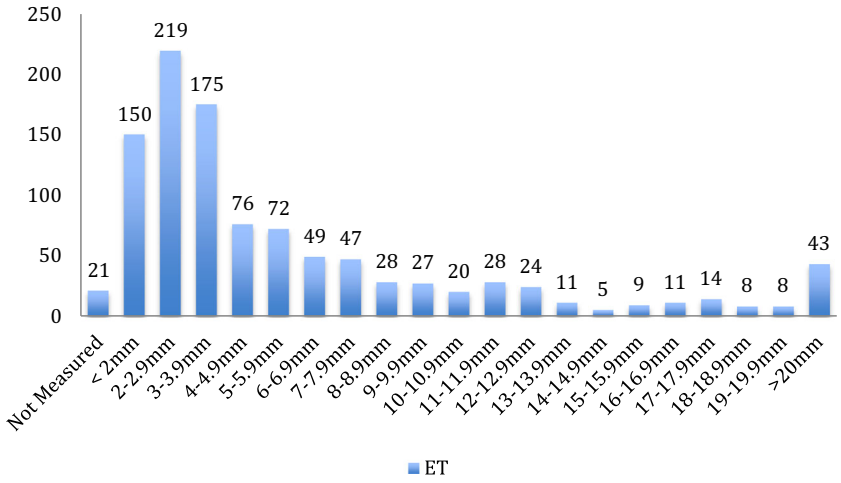


**Fig. 1** Endometrial thickness (ET) in 1045 women with PMB. X-axis denotes ET in millimetres and y-axis denotes the number of women (*n*)

12 months of menopause. The primary investigation was TVS. Endometrial sampling or hysteroscopy usually under a local anaesthetic was undertaken for an ET ≥ 4 mm. A diagnosis of endometrial cancer was identified from the hospital pathology reporting system in conjunction with a search of the Northern and Yorkshire Cancer Registry Information Service (NYCRIS). This was undertaken for a period of 12 months post initial investigation to identify any endometrial cancer that was not captured at the initial encounter. The population of the North East of England remains relatively static, and we were confident that the majority of the cancer diagnoses would be tracked through the above. Pre-test and post-test risks were calculated to determine the optimum threshold value of ET for endometrial sampling and cancer diagnosis. Statistical analysis was performed using binary logistic regression analysis on Minitab 17 statistical software package. A *p* value of <0.05 was considered statistically significant. The number needed to test (NNT) was calculated for different ET threshold using the formula (1/adjusted risk reduction).

## Findings

There were 1045 referrals from primary care to the RAC with a history of PMB during the study period. The mean age (±SD) of presentation was 62 years (±10.3). The weights of our cohort were included (mean weight (kg) ± SD 75.5 ± 19.4; median weight 71 kg) in analysis. The majority of the study group was classed as overweight (57.8 %) and a further 39.8 % classed as obese based on BMI (mean BMI ± SD 29.8 ± 7.9). A small proportion of the study group reported the use of hormone therapy (HT) currently (7 %) or within the previous 6 months (1.7 %). Continuous combined HT was the most common form (67.6 %), followed by cyclical combined (25 %) and tibolone (3.2 %). Fourteen women reported current use of tamoxifen, and a further 29 had used the drug in the past.

The primary investigation was TVS (*n* = 1035, 99 %) followed by transabdominal (*n* = 5, 0.5 %) and transrectal (*n* = 5, 0.5 %) ultrasound. The endometrial thickness was

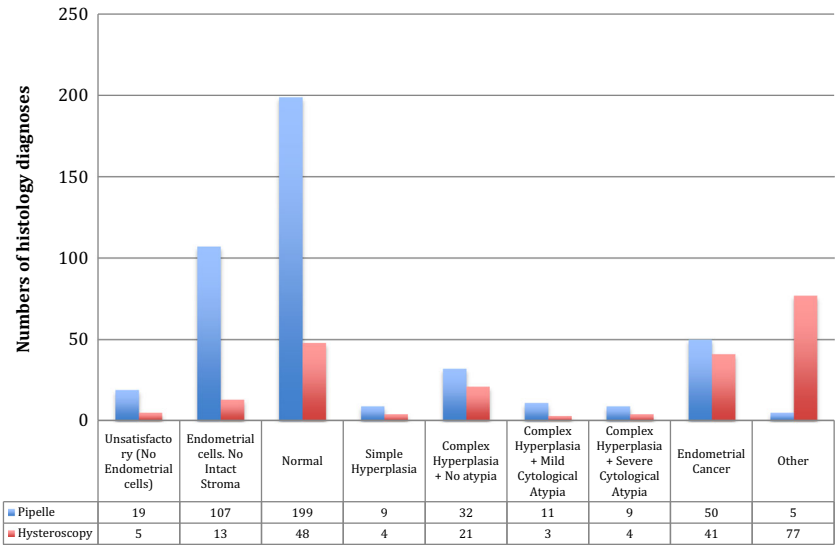


**Fig. 2** Histological diagnosis following initial Pipelle® endometrial biopsy (*n* = 441) and hysteroscopy (*n* = 222)

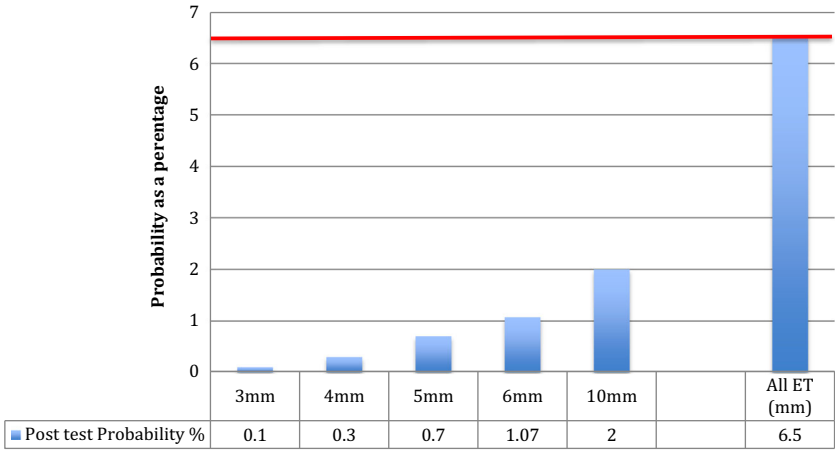


**Fig. 3** Post-test probability of developing endometrial cancer in percentage (based on 1024 patients with known ET values). The *red line* indicates the pre-test probability of 6.5 %

recorded in 98.1 %. There were difficulties in obtaining satisfactory views in 2 % ($n$ = 21) women. The reasons for this were axial uterus ($n$ = 4), fibroids ($n$ = 8), polyps ($n$ = 2), intrauterine devices ($n$ = 5), raised BMI of 57 ($n$ = 1) and no reason given ($n$ = 1). All women in this group underwent further investigation with a Pipelle® or hysteroscopy. All histology following these investigations was reported as normal, including two benign polyps removed at hysteroscopy. Endometrial polyps were diagnosed on TVS in 9.1 % ($n$ = 95) of the cohort prompting a hysteroscopy and polypectomy under a local anaesthetic. In this cohort of patients, 9.5 % ($n$ = 9) were diagnosed with endometrial cancer, 3.2 % ($n$ = 3) with atypical hyperplasia and 4.2 % with complex hyperplasia.

Figure 1 shows the distribution of recorded ET following TVS. An ET < 4 mm was recorded in 52.1 % ($n$ = 544). A failed attempt at biopsy was recorded in 3.8 % ($n$ = 19) of the 501 women that required biopsy; all but two went on to have a hysteroscopy, these two were not further investigated for other complex medical reasons. Two endometrial cancers were diagnosed following a hysteroscopy in this group. In the cohort below the ET threshold of 4 mm, 9.9 % ($n$ = 54) underwent a biopsy at initial presentation in view of fluid in the cavity/pyometra, recurrent symptoms or high index of suspicion (such as persistent bleeding in women remote from the menopause). One endometrial cancer and one severe atypical hyperplasia were diagnosed in this group.

Figure 2 shows the histological diagnosis following initial Pipelle® biopsy in patients with an ET ≥ 4 mm. Eighty-eight percent ($n$ = 441) of the eligible cohort had a Pipelle®; 3.8 % ($n$ = 19) had an unsuccessful attempt at Pipelle® with 8.2 % ($n$ = 41) being listed for hysteroscopy without attempting a biopsy; 11.3 % ($n$ = 50) of the cohort who underwent Pipelle® biopsy was diagnosed with endometrial cancer and 2 % ($n$ = 9) with complex hyperplasia with severe atypia. Within 1 month of initial appointment, a further 222 women underwent a biopsy at hysteroscopy largely in the outpatient setting. This was on the basis of suspicion of a polyp, insufficient or failed Pipelle®, an inability to measure ET on TVS or recurrent PMB. A percentage of 18.5 ($n$ = 41) were diagnosed or confirmed to have endometrial cancer; 66.7 % ($n$ = 6) of those with severe atypia on initial Pipelle® biopsy ($n$ = 9) were upgraded to cancer and 27.3 % ($n$ = 3) from mild atypia on initial Pipelle® biopsy ($n$ = 11) were upgraded to cancer with the directed biopsy taken at hysteroscopy. Two women who had unsuccessful attempts of a Pipelle® biopsy in RAC were confirmed to have cancer at hysteroscopy.

The NYCRIS cancer register identified a further nine endometrial cancers, within a year of the initial appointment in RAC, which were not captured by initial investigations. The clinical notes and ultrasound images were reviewed. Five had an ET ≥ 4 mm and had a normal biopsy at initial assessment. Two had unsatisfactory views during TVS due to raised BMI and an axial uterus. Three underwent secondary investigation with

**Table 1** All endometrial cancers diagnosed with an ET < 4 mm

| Number | BMI | ET(mm) | Good TVS view | Pipelle® | Hysteroscopy performed | Histology (FIGO) |
|---|---|---|---|---|---|---|
| 1 | 32 | 1.5 | Y | N | N | Grade 1 stage 1A endometrioid |
| 2 | 23 | 2 | Y | N | N | Grade 1 stage1A endometrioid |
| 3 | 30 | 2.7 | Y | N | Y | Grade 1 stage1A endometrioid |
| 4 | 40 | 3.6 | Y | Y | Y | Grade 1 stage1B endometrioid |

**Table 2** Odds ratio (OR) and 95 % confidence interval (CI) limits for ET thresholds of 3, 4 and 5 mm to detect endometrial cancer

| ET threshold | OR | Upper 95 % CI | Lower 95 % CI | *Z*-stat | *p* value |
|---|---|---|---|---|---|
| 3 mm | 11.86 | 38.1 | 3.68 | 4.147 | 0.0001 |
| 4 mm | 6.1413 | 12.27 | 3.07 | 5.135 | 0.0001 |
| 5 mm | 6.02 | 11.32 | 3.208 | 5.58 | 0.0001 |

hysteroscopy. Four had an ET < 4 mm and were not initially biopsied according to our protocol. All presented within a year with recurrent symptoms and underwent further investigation with ultrasound and biopsy or hysteroscopy and biopsy.

Pre-test risk of endometrial cancer was 6.5 % (68 out of 1045). Post-test risk can be stratified according to ET measurement (Fig. 3). Analysis was performed on 1024 patients (21 where excluded as they did not have a measurable ET on ultrasound). Of these, 67 were diagnosed with endometrial cancer. The probability of an endometrial cancer at an ET < 4 mm was 0.3 % which rises to a 6.5 % probability if the ET > 20 mm. In our cohort, there were four endometrial cancers diagnosed with ET < 4 mm. Table 1 details the endometrial cancers diagnosed and those identified from the NYCRIS database with an ET < 4 mm.

Binary logistic regression analysis confirmed a statistically significant linear correlation between ET and the risk of developing endometrial cancer ($p < 0.0001$) with odds ratio (OR) of 1.18 and 95 % confidence interval (CI) of 1.14–1.22. Table 2 shows the OR and 95 % CI for the three common ET thresholds to detect endometrial cancer.

Figure 4 explores the numbers needed to test in order to diagnose one case of endometrial cancer. If the threshold for investigation was lowered to ET ≥ 3 mm, a further 175 endometrial biopsies would be required to diagnose just one case of endometrial cancer. There would be a rise in insufficient samples and a requirement for more invasive testing with little yield.

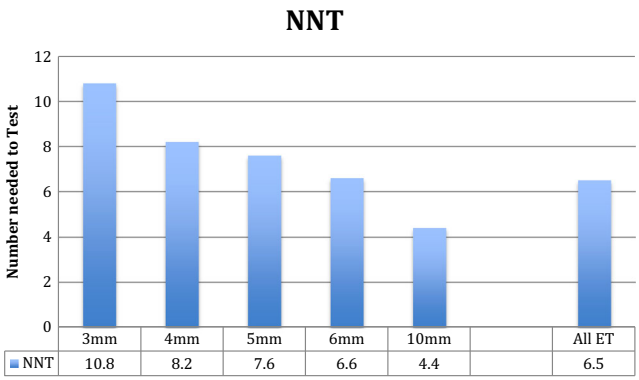


**Fig. 4** The numbers needed to test (NNT) to detect one case of endometrial cancer for the different ET thresholds for biopsy

## Conclusions

TVS is a consistently reliable way of assessing the ET and morphology in women presenting with PMB. It is invaluable in identifying a group of postmenopausal women that have a thin endometrium and at a low risk of disease, requiring no further investigation unless bleeding recurs. This is beneficial as it is non-invasive and more acceptable in the older population.

ET thresholds have long been debated and evidenced in the different values that are used throughout the UK. The meta-analysis in obstetrics and gynaecology by Timmermans et al. recommend a cutoff ET of 3 mm with a sensitivity of 98 % [7–9], but Mateos et al. in the *European Journal of Gynecological Oncology* suggest an endometrial thickness of over 6 mm will have a sensitivity of 88.6 %, specificity of 90.6 % and a positive predictive value of 92 % [4]. Similarly, Granberg et al. found an ET ≥ 5mm to have a positive predictive value of 87.3 % thus reducing the need for diagnostic curettage [10]. It is clear from the data available in our cohort and previous publications that the lower the threshold for ET and biopsy, the more cancers will be detected. However, this has to be balanced against the discomfort of the procedure and relatively low yields both in the diagnosis of cancer and the rise in insufficient samples prompting further action. This further action may increase anxiety in the patient and prompt costly hysteroscopy assessment in order to identify pathology.

Our cohort had a pre-test probability of 6.5 % of endometrial cancer. We were reassured that an ET cut-off ≥4 mm meant that 52.1 % could avoid an initial endometrial biopsy. Those with an ET < 4 mm could be reassured that their post-test risk of endometrial cancer was 0.3 %. Our data is comparable and in fact reveals a lower post-test probability when compared with the largest meta-analysis demonstrating an ET < 3 mm giving a post-test probability of 1.1 %; a 4-mm threshold of 1.8 % and 5-mm threshold of 2.1 % [10, 11].

Pipelle® is an effective device for evaluating patients suspected of having endometrial cancer [12, 13]. It has been shown to have high accuracy when combined with ultrasound. This accuracy relies on an adequate sample being obtained. Clark et al. have demonstrated that a post-test probability of endometrial cancer was 81.7 % (95 % CI 59.7–92.9 %) for a positive test and 0.9 % (95 % CI 0.4–2.4 %) for a negative test

result [14]. In our cohort, those Pipelle® biopsies reported as insufficient or failed underwent investigation with a hysteroscopy which resulted in a further two cancers identified in the failed group and none in the insufficient group. Farrell et al. would argue that an "insufficient" Pipelle® sample should prompt secondary investigation as they discovered a further two endometrial carcinomas in their cohort. [15]. However, this has not been demonstrated in our cohort that underwent hysteroscopy following an insufficient histology report. It is our practice to investigate the endometrium further with Pipelle® or hysteroscopy if we are unable to measure ET accurately during TVS. Van Doorn et al. support secondary investigation if ET cannot be determined by TVS [16]. This group could include women with a high BMI at higher risk of endometrial cancer. Our data has reported normal histology for 21 women that fell into this category. However, we would still exercise caution.

All women discharged from the RAC received an information leaflet instructing them to seek advice if the PMB was recurrent or persistent. If any patient returned with recurrent PMB, it would prompt further assessment with hysteroscopy. It is not clear from our data whether subsequent cancers that were diagnosed were missed by initial investigation (even in those with a biopsy) or new pathology. An example in our cohort was one woman with an initial ET of 2.7 mm who returned 6 months later as a result of the advice enabling us to perform a hysteroscopy, which identified an endometrial cancer. This emphasises that continued vigilance is a key part of the early diagnostic strategy for endometrial cancer.

The authors conclude that a threshold of ET ≥ 4 mm ensures the majority of cancers are detected with minimal invasive investigation. It is reassuring to note that even when endometrial cancer was subsequently diagnosed below the threshold, all were early cancers. Three were FIGO grade 1 stage 1A endometrioid adenocarcinoma, and one was FIGO grade 1 stage 1B endometrioid adenocarcinoma and treated with our standard management of total laparoscopic hysterectomy, bilateral salpingo-oophorectomy and peritoneal washings.

**Authors' contributions** Michelle Russell performed data analysis and manuscript writing. Meenakshi Choudhary performed data collection and analysis and manuscript editing. Mark Roberts contributed to project development, data collection and analysis and manuscript editing.

**Compliance with ethical standards** Appropriate ethical approval was obtained from the local ethics committee. Informed consent was obtained for all patients included in this study.

**Conflict of interest** The authors declare that they have no competing interests.

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