Vibrational Biospectroscopy for Endometrial Cancer Diagnosis and Screening

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Endometrial cancer (EC) is the sixth most common cancer and the fourth leading cause of death among women worldwide. Early detection and treatment are associated with a favourable prognosis and reduction in mortality. Unlike other common cancers, however, screening strategies lack the required sensitivity, specificity and accuracy to be successfully implemented in clinical practice and current diagnostic approaches are invasive, costly and time consuming. Such limitations highlight the unmet need to develop diagnostic and screening alternatives for EC, which should be accurate, rapid, minimally invasive and cost-effective. Vibrational spectroscopic techniques, Mid-Infrared Absorption Spectroscopy and Raman, exploit the atomic vibrational absorption induced by interaction of light and a biological sample, to generate a unique spectral response: a “biochemical fingerprint”. These are non-destructive techniques and, combined with multivariate statistical analysis, have been shown over the last decade to provide discrimination between cancerous and healthy samples, demonstrating a promising role in both cancer screening and diagnosis.

Keywords: endometrial cancer ; uterine neoplasm ; cancer of the endometrium ; spectroscopy ; Raman spectroscopy

1. Current Endometrial Cancer Diagnosis and Screening

Timely investigation of women presenting with symptoms, such as post-menopausal bleeding and persistent menstrual irregularities, allows most cases of EC to be identified in early stage.

Ultrasound imaging, hysteroscopy and endometrial biopsy, together with the histopathological tissue analysis, are the current mainstay of EC diagnosis. In addition, magnetic resonance imaging techniques (MRI) are useful in the assessment of depth of myometrium invasion, cervical stromal involvement and lymph node metastasis [1][2][3][4].

However, unnecessary procedure should be avoided, which may expose patients to complications, generate needless anxiety and take up financial resources. Indeed, hormonal imbalance, coagulopathies, benign endometrial lesions and the use of medications including hormone replacement therapy (HRT) are some of the factors associated with irregular and recurrent vaginal bleeding, which may occur in the absence of EC [5]. Consequently, the main challenge in early cancer diagnosis is the appropriate selection of those patients that require investigations and invasive procedures.

1.1. Ultrasound Imaging

Ultrasound imaging is a technique, which uses high frequency sound waves to provide information about tissue and organ characteristics. The procedure can be performed by the transabdominal and transvaginal access routes, does not require bowel preparation, is safe and is, overall, well tolerated by patients [6].

Ultrasonography is, however, highly operator dependent. Furthermore, excess adipose tissue interferes with sound wave signals, affecting image quality [6], thus women with high body habitus are at increased risk of suffering diagnostic delays [7].

Measurements of the endometrial thickness using ultrasound imaging are used as a surrogate marker to check for the presence of intrauterine abnormalities [8]. However, ultrasound imaging alone cannot discriminate whether an increased endometrial thickness is secondary to a benign lesion or to malignant disease [8].

Women with post-menopausal bleeding have a 8–11% risk of EC, which justifies the need for endometrial assessment in these patients [9]. The use of endometrial thickness cut-offs of 4 mm and 5 mm leads to the correct identification of 94.8% and 90.3% of EC cases, respectively [10]. However, the test specificity is poor, leading to a high risk of false positive results and, consequently, many unnecessary invasive investigations and biopsies [10][11].

In pre-menopausal women with abnormal uterine bleeding, the diagnostic role of endometrial thickness is controversial, as there can be overlap between physiological thickening caused by sex hormones and that caused by endometrial disease [12]. While it has been suggested that a thickness of <8 mm should be considered as non-hyperplastic [13], and only 1% of endometrial cancers occurs in women < 40 years of age [11], there is still no consensus on the ideal endometrial thickness cut-off in this group of patients [14], thus an alternative or complementary non-invasive triaging tool would facilitate the clinician's decision-making on when to refer for further invasive diagnostic procedures.

1.2. Hysteroscopy

The direct endoscopic visualisation of the endometrial cavity by hysteroscopy, using visible light at 4 to 5× magnification [15], is an invasive procedure that can be performed in order to evaluate the endometrial cavity, to remove lesions such as polyps or small fibroids and to obtain endometrial biopsies.

Hysteroscopy can be carried out both in the outpatient setting and in theatre, under regional or general anaesthetic [16]. Although, overall, the procedure has been shown to be well tolerated, safe, accurate and acceptable, regardless of the setting in which is performed [17][18][19], some patients do experience significant discomfort during outpatient hysteroscopy [19]. Unfortunately, it is difficult to identify this group of patients preoperatively, and for these women a routine hysteroscopic procedure may turn into a painful and traumatic experience. Furthermore, although uncommon, complications may arise, including bleeding, infection and uterine damage [20], and the failure rate of hysteroscopy, where the instrument cannot be successfully introduced into the uterine cavity, has been estimated at 4.2% [19][21].

Well-conducted systematic reviews and meta-analyses found that hysteroscopy is highly accurate for the diagnosis of EC in women with abnormal uterine bleeding [19][22][23] and it is useful at excluding endometrial disease [22][23], although the diagnostic accuracy for endometrial hyperplasia appears to be more modest [19].

Indeed, in its updated 2018 guidance, the UK National Institute for Health and Care Excellence (NICE) now recommends that hysteroscopy can be offered as a first-line investigation for heavy menstrual bleeding, in preference to pelvic ultrasound, if the woman's history suggests sub-mucosal fibroids, polyps or endometrial pathology [24].

The inevitable consequence of such a diagnostic strategy, however, is the need for a structural re-organisation of healthcare services, in order to absorb the estimated 10,000 extra procedures that would be performed in England each year [25] and their added financial costs. The availability of adequately sized and equipped facilities and investments in recruitment and training of skilled staff are some of the challenges to overcome, in order to implement the new guidance into clinical practice.

1.3. Endometrial Biopsy and Histological Analysis

Histological examination of an endometrial biopsy specimen is the current so-called: "Gold Standard" of EC diagnosis. The sample preparation and analyses, required to allow the visualisation of the internal architecture of cells and tissues and identify cancerous features [26] are, however, time-consuming, and can be subject to human error [27].

The condition or quality of an endometrial biopsy must be "adequate" in order to provide the histological diagnosis, but the lack of standard agreement on quality and quantity assessment criteria [28] leaves the decision regarding sample suitability to individual pathologists. This allows for a high inter-observer variability [29] and a risk of diagnostic delay and potentially detrimental consequences for patients. The reported rate of insufficient quality or quantity of endometrial tissue samples for histological diagnosis in post-menopausal women is 31% (range 7–76%) [30], while in pre-menopausal women it is lower, ranging between 2% and 10% [31]. The reasons for insufficient sampling appear unclear: the experience of the operator has not been confirmed to be a determining factor [32][33] and there is wide variance between insufficient sample rates reported in single versus multicentre studies, suggesting that study design may influence the results [19][32][33][34][35].

Importantly, obtaining an endometrial biopsy is not always a straightforward process. Indeed, endometrial sampling fails in approximately 11% of cases (range 1–53%), mostly as a consequence of cervical stenosis [30]. Factors such as the post-menopause, advanced age and nulliparity also appear to be associated with higher failure rates, likely as a consequence of variation in endometrial thickness and anatomical changes that occur in these patient groups [33].

Outpatient endometrial biopsy has mostly replaced traditional dilatation and curettage under general anaesthetic worldwide [36][37][38], as it has shown comparable performance, while being less invasive and more cost effective [39][40]. The diagnostic accuracy of these biopsies were investigated extensively and a number of meta-analyses were published,

reporting on sensitivity and specificity in relation to endometrial cancer, endometrial hyperplasia (with and without atypia) and benign endometrial disease [30][31][38][39][41]. Overall pipelle biopsy, with conventional histopathology, appears to be an effective tool to identify endometrial cancer when adequate samples are obtained; however, the test is not as reliable in the case of endometrial hyperplasia, where a negative result only decreases the hyperplasia risk by 2-fold [41].

The potential failure to diagnose or exclude disease after invasive procedures, such as hysteroscopy and endometrial biopsy, is concerning. Coupled with the highly subjective nature of histopathological assessments, it highlights the need for alternative approaches to complement current practice and provide pathologists with additional support in achieving a more objective tissue evaluation. Furthermore, in the context of EC research priorities [42], current diagnostic modalities, despite their established advantages, are insufficient to fully address the need for patient risk stratification and the demand for minimally invasive, individualised, screening, diagnostic and treatment monitoring pathways.

1.4. Screening for Endometrial Cancer

Screening is defined by the World Health Organisation (WHO) as “the presumptive identification of unrecognized disease in an apparently healthy, asymptomatic population by means of tests, examinations or other procedures that can be applied rapidly and easily to the target population” [43]. The researchers suggest that an ideal screening test should be accurate, well-tolerated, associated with minimal morbidity and cost-effective.

Women with known Lynch Syndrome already undergo a multimodal surveillance of the endometrium until hysterectomy is performed, due to their high lifetime risk of developing EC [44].

Unfortunately, there is no EC screening test which is accurate and reliable enough to be implemented for the general asymptomatic population [10][11][12][45][46]. Ultrasound imaging, despite its accessibility, safety and low cost, unfortunately lacks the required sensitivity and specificity, as demonstrated by the nested case-control study [45] within the 2016 United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) [47]. The study showed that if the general UK population were screened using an endometrial thickness cut-off of 5 mm, in order to diagnose 80.5% of cancers, for each endometrial cancer or atypical endometrial hyperplasia (AEH) case detected, 58 healthy women would have to undergo additional unnecessary investigation [45]. It is apparent that the modest test accuracy, potential patient risks and added costs, do not justify the implementation of such a screening strategy. There is, therefore, an unmet need to innovate current diagnostic and screening methods, to tackle the increasing endometrial cancer disease burden and allow early disease detection and timely treatment.

2. Biospectroscopy

The interaction between electromagnetic radiation and any particular matter results in the measurable linear and nonlinear physical phenomena of absorption, emission, reflection and scattering of the radiation by the matter; measurement of the radiation after its interaction with matter yields information on the makeup and arrangement of the matter and is known as spectroscopy. The measurement is displayed as a spectrum, which is a graphical representation of energy absorption, emission, reflection or scattering by the material as a function of the incoming radiation photon energy (plotted usually as frequency or wavelength). The application of spectroscopic techniques to biological materials is called biospectroscopy and the name was only coined in the 1960s [48].

Mid-infrared Absorption and Raman scattering spectroscopy, are sister-vibrational absorption techniques, being complementary as they are based on different quantum mechanical rules. They are label-free, non-destructive optical methods with the ability to investigate the vibration and rotation of atoms and molecules in biological materials, induced by irradiation by light.

The vibrational spectra that are generated depend on the specific biochemical structure of the sample tested; they provide information on the whole range of molecules within the sample simultaneously, which can, therefore, be interpreted as a unique “signature” or a “fingerprint” of that sample [49].

The alteration of molecular signatures in a cell or tissue, which has undergone disease transformation, can be objectively detected, gaining vibrational spectroscopic techniques a potential role in cancer diagnosis and screening [50][51][52].

2.1. Mid-Infrared Absorption Spectroscopy

Mid-infrared (MIR) light is a radiation region of the electromagnetic spectrum of 3–50 microns wavelength, as defined by ISO 20473:2007 [53]. When biological tissues are exposed to MIR light, part of the photon energy can be resonantly

absorbed, inducing vibrations; the quantum mechanical selection rules include that there must be a change in dipole moment during the vibration, hence heteropolar chemical bonds are vibrationally stimulated. The intensity and wavelength of each vibration depend on the nature of the chemical bonds and their specific molecular environment, that is its molecular structure [54]. The fraction of energy absorbed by the sample at different frequencies can be quantitatively measured by means of dispersive infrared (IR) spectroscopes [51].

The technology has been further refined and made faster since the 1970s by the introduction of Fourier transform (Ft) IR spectrometers, in which all broadband spectral information is collected simultaneously, and then many times, in order to average and then maximise the signal-to-noise ratio. The raw data obtained, called an interferogram, is then converted using the Fourier transform mathematical algorithm into wavelength intensity, from which the energy absorbed by the sample can be derived [54].

The majority of work reported to date used the technique of Fourier transform Infrared (FtIR) with Attenuated Total Reflectance (ATR) on excised tissue, or extracted body fluids, which overcomes the need for complex sample preparation [54]. Other image acquisition modes include transmission and transflection; these require the use of suitable substrates (e.g., calcium or barium fluoride slides) and longer machine and sample preparation compared with ATR [55]. Transflection was shown to introduce spectral artefacts and so has lost favour [56][57].

2.2. Raman Spectroscopy

Raman spectroscopy relies on the principle of inelastic scattering of photons, also known as Raman scattering, and was first discovered by Raman in 1928 [58]. When a monochromatic light source, such as a visible or near-infrared laser, interacts with a sample, most of the light which scatters off is unchanged in energy. However, a very small number of photons will exchange part of their energy with the molecules of the sample: the chemical bonds of the sample become temporarily excited to a virtual state, then relax to a different vibrational state, while the emitted photons shift to a lower (Stokes) or higher (Anti-Stokes) frequency [59]. The shift in frequency, measured by the Raman spectrometer, is indicative of specific vibrational modes of the sample molecules and, therefore, a unique “fingerprint” spectrum can be inferred [52]. The quantum mechanical selection rules of Raman include that the molecular bond should not undergo a change in dipole during vibration, thus favouring homopolar chemical bonds. Hence, Raman spectroscopy is unaffected by water, and is non-destructive and label-free [60]. These characteristics offer technology a high degree of flexibility, with potential applications to the study of fresh, fixed and live tissues and cells [61]. Spontaneous Raman scattering is a rare phenomenon, with a very low probability of occurrence (~1 in 10^8) [62]. In order to enhance the Raman-scattering signal level, several variations of Raman spectroscopy have been developed, including resonant Raman (RR), coherent anti-Stokes Raman scattering (CARS) and surface-enhanced Raman scattering (SERS) [50]; these are, however, expensive technologies, with a large footprint. Ultimately, the choice of instrument, desired wavelength and spatial resolution will vary depending on the required application.

2.3. Biospectroscopy for Endometrial Tissue Interrogation

The development of effective diagnostic, screening and treatment strategies for endometrial cancer finds its basis in a deep understanding of tissue physiological and pathological processes. In particular, to be clinically useful, a new diagnostic or screening tool should be able to accurately distinguish healthy patients from those with disease.

ATR-FtIR and Raman spectroscopy were used to categorise disease and identify cancer or intra-epithelial neoplasia in a number of excised tissues, such as prostate [63][64][65][66][67], gastrointestinal tract [68][69][70][71][72], brain [60][73][74], breast [75][76][77][78][79][80][81][82], lung [83][84] and skin [85][86][87]. Gynaecological applications include studies of cervical cytology and histopathology [88][89][90][91][92][93], ovarian cancer [94][95] and vulvar disease [96].

With regards to endometrial tissue, vibrational biospectroscopy was successfully applied in preliminary research to the study of its structural architecture [59][97], as well as the classification of cancerous lesions [98][99][100], specific cancer subtypes [99][100] and the identification of cell phenotypes with different drug sensitivity [101] . There is, however, a paucity of literature, and specifically of large studies, compared with other types of diseases.

2.4. Biospectroscopy of Biofluids: Screening and Cancer Diagnosis

With the endometrial cancer global disease burden expected to rise, disease screening, early detection and treatment monitoring will benefit from the development of more cost-effective, rapid, non-invasive and label-free techniques. Biological fluids, being readily accessible with low-cost procedures, represent the ideal sample target. Indeed, the study of biofluids with spectroscopy is becoming a rapidly emerging field and a number of pilot studies have now been published,

focusing on oncological applications, as well as on a broad range of acute and chronic medical conditions [52][95][102][103][104][105][106][107][108][109].

With regards to endometrial cancer, biospectroscopy was proposed as a novel approach to test blood, urine and saliva. The development of such techniques is particularly relevant as currently available methods, such as radiological imaging and blood biomarkers, lack the required sensitivity, specificity and accuracy to be used as effective screening tools. Interestingly, while Raman spectroscopy of blood serum was recently investigated for the first time as a non-invasive technique to diagnose endometriosis [110], no studies were found on the application of Raman spectroscopy to biofluids for EC diagnosis (**Table 1**).

Table 1. Spectroscopy of biofluids: endometrial cancer studies.

Author	Year	Sample	No of Patients	Preparation	Spectroscopy Method	Spectral Findings
Gajjar et al. [105]	2013	Endometrial cancer and healthy blood plasma and serum	60	Dried samples	ATR-FTIR	Plasma cancer vs. healthy: changes of stretching vibration in glycogen, RNA, fatty acids, amino acids and lower levels of lipids Serum cancer vs. healthy: changes of stretching vibration in DNA, RNA and lower levels of lipids
Paraskevaidi et al. [111]	2017	Endometrial cancer and healthy blood plasma and serum	89	Dried samples	ATR-FTIR	Discrimination between cancer subtypes for both plasma and serum due to protein and lipid alterations
Paraskevaidi et al. [112]	2018	Endometrial cancer and healthy blood plasma and serum	85 for plasma, 75 for serum	Dried samples	ATR-FTIR	Aluminium foil: - plasma cancer vs. healthy: changes in protein secondary structure and lipids - serum cancer vs. healthy: changes in glycogen, phosphate, fatty acid and amino acids Low-E slides: - plasma cancer vs. healthy: changes in protein secondary structure and lipids - serum cancer vs. healthy: changes in protein secondary structure and nucleic acids
Paraskevaidi et al. [108]	2018	Endometrial cancer and healthy urine	20	Dried samples	ATR-FTIR	Cancer vs. healthy: increased proteins and nucleic acids, decreased lipid content and alterations in protein secondary structure
Bel'skaya et al. [109]	2019	Endometrial cancer and controls saliva	55	Lipid extraction with Folch solution	FTIR	Cancer vs. controls: decreased lipid content

Author	Year	Sample	No of Patients	Preparation	Spectroscopy Method	Spectral Findings
Paraskevaidi et al. [113]	2020	Endometrial cancer, atypical hyperplasia, and healthy blood plasma	652	Dried samples	ATR-FTIR	Cancer vs. healthy: increased lipids and decreased content of carbohydrates and fatty acids Hyperplasia vs. healthy: higher nucleic acids, collagen and stretching vibration in DNA and RNA Type I vs. Type II cancers: changes in protein secondary structure
Mabwa et al. [114]	2021	Endometrial cancer and healthy blood plasma and serum	60	Dried samples	ATR-FTIR	- **Plasma and Serum (bio-fingerprint region 1430 cm^{-1} to 900 cm^{-1})—cancer vs. healthy: changes of stretching vibration in DNA, RNA, changes in fatty acid, amino acid and protein content**

Similar to experiments performed with endometrial tissue, the sample manipulations and chemometric analyses used to test biofluids vary between studies. The first pilot research, by Gajjar et al. [105], investigated the potential role of ATR-FtIR for cancer diagnosis using blood samples and, with the development of “machine classifiers”, reported classification rates of endometrial cancer versus controls up to 77.08% and 81.67% for serum and plasma, respectively. The same spectral data were more recently re-analysed by the research group [114], to evaluate the performance of alternative data-processing methods and classifier tools. Furthermore, the authors focused on the water-free sub-section of the spectrum (1430 cm^{-1} to 900 cm^{-1}), in contrast with the more extended bio-fingerprint region (1800 cm^{-1} to 900 cm^{-1}) used in the original paper. The researchers assessed four types of classifiers and reported high discrimination rates for both plasma (sensitivity of 0.865 ± 0.043 and specificity of 0.895 ± 0.023 with k-Nearest Neighbours algorithm) and serum (sensitivity 0.899 ± 0.023, specificity 0.763 ± 0.048 for LDA). This approach demonstrated for the first time the possibility of overcoming the dominant effect of water seen in the analysis of hydrated samples with MIR spectroscopy, which would support future applications of MIR spectroscopy in vivo to cancer diagnosis and screening [114].

Paraskevaidi et al. [111][112] used ATR-FtIR spectroscopy with PCA followed by support vector machine (PCA-SVM) to analyse blood plasma and serum from women with endometrial cancer and age-matched healthy controls. Test performance was described as high as 100% sensitivity and 85% specificity (98% accuracy) and changes in the bands associated with proteins and lipids were consistently responsible for the discrimination between blood plasma and serum from endometrial cancer and healthy samples. Traditionally, low-emissivity (low-E) slides have been used as ATR-FtIR substrates to support samples; however, their high cost may limit their use in large-scale studies and implementation in routine analysis. Aluminium foil substrate may represent an equivalent, cheaper, sample-support alternative for the detection of endometrial cancer with blood plasma and serum [112]. Indeed, Paraskevaidi et al. [112] showed that aluminium foil substrate was able to differentiate blood plasma and serum from patients with endometrial cancer and controls, with sensitivities and specificities comparable with the traditional low-E slides. The cost-effectiveness and ease of use, if validated in larger datasets, would greatly facilitate clinical application.

More recently, the same group, Paraskevaidi et al. [113], examined plasma from women with endometrial cancer, atypical hyperplasia and controls with ATR-FtIR in the largest diagnostic cross-sectional study to date (total n = 652). The study identified the six most discriminatory peaks for each subgroup analysis, suggesting these features could be developed in a panel of diagnostic spectral markers. Endometrial cancers and controls were differentiated with 87% sensitivity and 78% specificity (overall accuracy of 83%); further analysis of cancer subtypes achieved disease discrimination with sensitivities of 71–100% and specificities of 81–88%. In addition, the authors accounted for potential confounding factors, such as age, body mass index (BMI), diabetes, fasting status and blood pressure and found no impact on spectral classification after applying the MANOVA test (multivariate analysis of variance) to the spectral wavenumbers.

Discrimination between endometrial cancer and controls appears consistently superior for plasma over serum samples. It has been speculated that this might be due to the more complex and heterogeneous composition of the plasma; however,

the cause of superior diagnostic results, being a panel of biomolecules or the presence of higher concentration of cell-free DNA, still remains to be determined [105][112].

In addition to plasma and serum, pilot research has also applied biospectroscopy techniques for endometrial cancer diagnosis to urine and saliva analysis.

Urine spectra obtained by Paraskevaidi et al. [108] yielded high levels of diagnostic accuracy after the application of multivariate analysis and classification algorithms (95% sensitivity and 100% specificity, 95% accuracy). The classification methods used included: partial least squares discriminant analysis (PLS-DA), PCA-SVM and genetic algorithm with LDA (GA-LDA.) The majority of discriminating wavelengths were once more located in the lipid, protein and acid nucleic infrared regions.

Saliva spectral analysis by Bel'skaya et al. [109] showed interesting alterations in the lipid regions of patients with endometrial and ovarian cancer; in particular, the ratio of the intensity of the absorption bands 2923/2957 cm^{-1} appeared to consistently decrease in cancer samples compared with controls, leading the authors to propose its use as a new diagnostic criterion.

Spectral differences in lipid absorption bands of healthy and diseased samples, also documented in prostate [115] and breast cancer [116], may be explained by tumour-mediated changes of the lipid metabolism and may warrant further investigations in the context of non-invasive endometrial cancer biomarker development.

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