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The Role of Ultrasound in Endometrial Cancer

Review Article

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Abstract

Endometrial cancer is the most common gynecologic malignancy in developed countries. The vast majority of cases occur after menopause, with postmenopausal bleeding being the presenting symptom in 95% of the cases.

The use of transvaginal ultrasonography (TVS) is the sin e qua non in the assessment of these women. The finding of endometrial thickness of 5 mm or more is associated with increased likelihood for endometrial cancer, and should prompt further investigations. In cases with confirmed endometrial cancer, MRI and ultrasound are used to assess the depth of invasion to the myometrium and the cervical stroma. Recent studies have shown that – in experienced hands - a combination of gray-scale ultrasound with color and/or power Doppler examination has comparable results to that of MRI in the estimation of cancer invasion ≥ 50% in the myometrium or in the cervical stroma. Lack of uniformity in objective measurements is the main problem that hampers our ability to correctly predict myometrial or cervical stroma invasion with ultrasound. However, ultrasound is cheap, easy to perform and more readily available than any other imaging modality. The present article examines the use of gray-scale and Doppler ultrasound imaging in estimating the risk of endometrial cancer.

Keywords: Endometrial Cancer; Myometrial Invasion; Cervical Stromal Invasion; Transvaginal Sonography; Ultrasound

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Introduction

Endometrial carcinoma is the most common malignancy of the female reproductive tract in developed countries,with the vast majority of cases occurring after menopause [1]. Postmenopausal bleeding is the presenting symptom in 95% of the cases [2].

The use of transvaginal ultrasonography (TVS) is the sin e qua non in the assessment of these women. There is worldwide consensus that the finding of endometrial thickness of 5 mmor more is associated with increased likelihood for endometrial cancer, and should prompt further investigations [3]. In contrast, with values below that threshold, the presence of endometrial carcinoma is reported to be less than 1% [4].

Endometrial sampling is the first choice invasive procedure when dealing with increased endometrium, since it is easy to perform, cheap, and with very few contra-indications. Nonetheless, because of its high failure rates, many authors considered an alternative approach. The use of hysteroscopy although more effective, [5] has not reached a consensus yet [6]. On the other hand, various models incorporating clinical and/or ultrasonographic parameters have been proposed [7,8].

Time is of essence when dealing with patients that have an increased risk for cancer. Moreover any investigation that could further stratify the risk, i.e. patients with increased endometrial thickness, but with overall low risk for endometrial cancer, could be beneficial both to the patients and the health systems. It could decrease the number of invasive procedures, and reduce costs allowing more resources to be allocated elsewhere. To that matter ultrasound can play an important role. The present articleexamines the use of gray-scale and Doppler ultrasound imaging in estimating the risk of endometrial cancer.

Modus Operandi

Whenexaminingtheuterinecavityandtheendometrium,transvaginal is the preferred route. A transabdominal (TAS) approach should be used when a TVS is considered unsuitable e.g. large fibroids, a much enlarged uterus, Virgo. If TAS is unsatisfying, a transrectal ultrasound examination may be considered. In postmenopausal women on HRT (Hormonal Replacement Therapy) the examina-

tion should be performed 5-10 days after the last progestin tablet. Before menopause, it is better to schedule the examination in the early proliferative phase (cycle day 4–6) [9,10].

The assessment of the uterus begins with identification of the bladder and the cervix. Following that, an overview of the uterus is recognized by acquiring both sagittal (from horn to horn) and transverse planes (from cervix to fundus), with verification of its position. Magnification should always be used up to the point that the image contains only the uterine corpus.

Variations in uterine position either natural or due to previous surgeries may pose difficulties in the examination. Abdominal pressure, emptying and filling of the bladder can be used at the examiner's discretion. Ideally, the angle of insonation between the endometrium and the ultrasound beam should be 90° to optimize image quality. If any difficulties arise, tracing the endometrium from the endocervical canal may be of help. Saline or gel instillation, if needed, can further enhance image quality and provide valuable information.

Quantitative Assessment

The measurement should beperpendicular to the endometrial midline, include both layers (double thickness), and should be measured at its thickest point. If fluid is present the thickness of bothsingle layers is measured and added. The amount of fluid is defined by itslargest measurement in the sagittal plane. In about 10% of the cases there is failure to visualize the entire endometrium, and if so it should be reported as 'non-measurable' and no attempt should be made to measure it.When a lesion is present, the total endometrial thickness including the lesion is measured. However, in cases of fibroids that can be clearly identified, they should not be included in the measurement of endometrial thickness. Any lesion should be measured in three perpendicular diameters. The volume of the lesion may be calculated using the formula for an ellipsoid ($d1 \times d2 \times d3 \times 0.523$).

Qualitative Assessment

This should include assessment of endometrial echogenicity, the endometrial midline and the endometrial–myometrial junction.

The echogenicity is defined as hyper-, iso - or hypo-echogenic by comparing it to that of the myometrium. If homogenous at its entire length, the echogenicity is further reported as uniform or non-uniform (i.e. when appears as heterogeneous, asymmetrical orcystic)accordingly.

The endometrial line is defined as linear (straight), non-linear if a wave-like appearance is seen, and as irregular inthe absence of a distinct line.

The endometrial–myometrial junction is described as regular, irregular, interrupted or not defined. Synechiae are defined as strands of tissue crossing the endometrium.

The IETA (International Endometrial Tumor Analysisgroup) has issued a consensus statement on terms, definitions and measurements that may be used to describe the sonographic features of the endometrium and uterinecavity on gray-scale sonography, color flow imaging and sonohysterography [11].

The qualitative assessment of the uterine cavity can be further enhanced with the instillation of fluid into theuterine cavity to act as a negativecontrast agent (sonohysterography).Saline instillation or gel instillation sonohysterography can be used [14]. The same definitions as in unenhanced TVS examination apply. By using sonohysterography, the endometrial outline facing the endometrial cavity can be further examined. It is defined as regular if a smooth line is found or irregular when folds or deep indentations are recognized [11].

Color and Power Doppler Assessment

The color and power Doppler box should include the endometrium with the surrounding myometrium. Magnification and settings should be adjusted to ensure maximal sensitivity for blood flow (ultrasound frequencyat least 5.0 MHz, pulse repetition frequency 0.3–0.9 kHz, wall filter 30–50 Hz, color power Doppler gain reduced until all color artifacts disappear). The color score is a more or less subjective assessment; nevertheless, it may be scored using the International Ovarian Tumor Analysis (IOTA) color score applied previously to ovarian masses [12].

The report on the vascular arrangements of the endometrium should include the presence or absence of main (dominant) vessels. As such, are considered one or more distinct vessels (arterialand/or venous) crossing the endo-myometrial junction. Further branching within the endometrium, must be described as either orderly or non-orderly. When multiple vessels are recognized, their origin (focal or multi-focal) should be noted. Other patterns, such as dispersed vessels without clear origin and circular flow should be reported as well.

Risk Estimation

The constructing of a scoring system that estimates the individual risk for endometrial cancer is not a new idea, with clinical parameters and endometrial thickness being the basis of such models. Several reports are already published in the literature, with some models based on large populations [7,14-15]. However, there is a clear tendency towards the use of more sophisticated ultrasound techniques that can provide more accurate estimates and can further stratify the risk [16-21].

Increased endometrial thickness i.e. ≥ 5 mm remains the golden standard for risk estimation. The thicker the endometrium, the higher the risk is. In cases with endometrium ≥ 10-12 mm the positive likelihood ratio (LR+) is 3.5, and when ≥ 15 mm is 5.5 [21].

Irregular echogenicity of the endometrium or the endo-myometrial border further increases the risk. The findings of an interrupted border or a not intact junctional zone are bad prognostic factors as well.

The presence of increased vascularity and/or distorted blood vessels at power Doppler examination increases the risk of malignancy. The same applies for high color content at the color Doppler examination [8,22]. In specific, multiple endometrial vessels, especially large or with irregular branching, as well as the discovery of areas with densely packed or color splash vessels increase very much the risk for malignancy [21].

Sonohysterography can add to the risk estimation since it can help better distinguish between regular and non-irregular endometrial surface outline. Furthermore intra-cavity lesions such endometrial or localized ones can be better defined.

Preoperative Assessment

The prognosis of endometrial cancer depends on the histological type and grade, the tumor size, the depth of invasion in the myometrium and/or the cervical stromal, and the presence of lymph node metastases [23]. Malignancies of the uterine corpusinfiltrating≥50% into the myometrium, cancers infiltrating the cervical stroma and cancers with lymph node metastases are high-risk endometrial cancers. These women need extensive surgery with pelvic and para-aortal lymphadenectomy, while infiltration of the cervical stromais an indication of radical hysterectomy.

Undoubtedly, imaging technology is essential when planning the treatment of womenwith endometrial cancer. It is used to estimate the degree of invasion in the myometrium and the cervical stroma, with Magnetic Resonance Imaging (MRI) and ultrasound being the current modalities used. Several studies have assessed subjective assessment of myometrial invasion using transvaginal ultrasound, with reported sensitivities of 68–93% and specificities of 82–83% [24]. Nevertheless, very few of them compare MRI with ultrasound regarding their ability to correctly identify the degree ofmyometrial and cervical stromal invasion [25-31]. In all of them, TVS was found to have the same capability as the MRI to recognize myometrial cancer invasion ≥ 50%, as well as the presence of cervical stroma invasion. The use of 3D ultrasound did not confer much, since it had lower sensitivity than MRI but a better specificity. In one study, positron emission tomography (PET) combined with computed tomography (PET-CT) was found superior to both MRI and TVS in the identification of cervical stromal [25].

The main problem when assessing the invasion of the myometrium with TVS is the lack of uniform objective measurements. Subjective assessment is widely used [25,26], but is prone to biases. A recent study showed these "errors" are not related to body mass index (BMI), to the position of the uterus in the pelvis or to imagequality. Conversely, tumor size, density of tumor vascularization, and tumor vessel architecture has a significant impact on this evaluation [31]. It appears that there is a tendency to underestimate the invasion in well-differentiated endometrial cancers that are smaller in size, with thick minimum tumor-free myometrium and lower perfusion. In contrast there is more often overestimation in moderately and poorly differentiated cancers that are larger in size, with thin minimum tumor-free myometrium and richer perfusion. Nevertheless, our inability to develop objective signs hampers our ability to correctly predict myometrial or cervical stroma invasion, and is a major setback.

Conclusion

The preoperative evaluation of myometrial and cervical stroma invasion in women with endometrial cancer is a useful tool in planning the appropriate type of surgery. MRI and PET-CT can be used to assess the involvement of pelvic tissues. However, recent studies have shown that a combination of gray-scale ultrasound with color and/or power Doppler examination demonstrates precision equal to that of MRI in the estimation of cancer invasion ≥ 50% in the myometrium or in the cervical stroma. It is true that there is a lack of uniformity in objective measurements as well as a shortage in prospective studies, validating any findings already reported. Still ultrasound assessment can be accomplished as part of the gynecological examination, is easier and faster to perform, and with substantially less cost. Therefore we believe that ultrasound deserves to play an important role in the diagnosis and management of endometrial cancer [32].

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