Assessing myometrial infiltration by measuring the tumor free distance and depth of invasion through 2D transvaginal ultrasound among patients with endometrial cancer*

By Harry C. Navarete, Jr., MD, FPOGS and Lara Marie David-Bustamante, MD, FPOGS, FPSUOG
Department of Obstetrics and Gynecology, Philippine General Hospital, University of the Philippines-Manila

ABSTRACT

Background: Myometrial invasion is one of the most important prognostic factors in the preoperative evaluation of patients with endometrial cancer. Several techniques have been used for the preoperative evaluation such as transvaginal ultrasound (TVS), magnetic resonance imaging (MRI) and computed tomography (CT). Transvaginal ultrasound has been shown to have comparable accuracy with MRI, cost effective and is widely available.

Main Objective: To determine the diagnostic accuracy of 2D transvaginal ultrasound in assessing myometrial infiltration by measuring the tumor free distance (TFD) and depth of invasion (DOI) among patients with endometrial cancer admitted for elective gynecologic surgery at Philippine General Hospital Department of Obstetrics and Gynecology.

Methods: This prospective validation study involved 49 patients with endometrial cancer admitted for elective surgery at the Department of Obstetrics and Gynecology of the Philippine General Hospital from October 1, 2016 to February 28, 2017. All patients had 2D transvaginal ultrasound at least within 1 week prior to schedule of surgery. The tumor free distance (TFD) and the depth of invasion (DOI) were prospectively measured and compared with the histopathologic result. Diagnostic accuracy in assessing myometrial infiltration by measuring the tumor free distance and depth of invasion through 2D transvaginal ultrasound were computed and test of association was done using 2x2 Fischer Exact test at 0.05α while AUC-ROC was plotted.

Results: The association between transvaginal ultrasound and final histopathology in assessing the myometrial infiltration was statistically significant (p=0.004). Moreover, the transvaginal ultrasound for assessing myometrial infiltration demonstrated 94.4% sensitivity and 43.8% specificity in detecting >50% infiltration wherein a likelihood would likely to occur by 1.68 times higher than those with <50% based on the final histopathology. Moreover, the accuracy values of TVS reflected in the AUC index were as follows, a TFD cut off value of ≤0.82cm showed a higher sensitivity (46.88%) and specificity (100%) in predicting >50% myometrial infiltration while a DOI ratio of 0.50 is the cut off value which initiated a sensitivity (16.7%) and a higher specificity (75%) in predicting >50% infiltration. Finally, TFD (AUC = 0.749) yielded a higher accuracy as compared with DOI (AUC = 0.388) in predicting myometrial infiltration.

Conclusion: Assessment of myometrial infiltration by measuring the tumor free distance and depth of invasion through 2D transvaginal ultrasound among patients with endometrial cancer demonstrated clinically acceptable accuracy with higher sensitivity in detecting >50% myometrial infiltration. TFD (cut off value of ≤0.82cm) has a higher accuracy compared with DOI in predicting >50% myometrial infiltration.

Keywords: Endometrial Cancer, Tumor Free Distance (TFD) Depth of Invitation (DOI)

INTRODUCTION

Cancer of the corpus uteri specifically endometrial cancer, is one of the most frequent gynecologic malignancy involving the female genital tract.[1] It is the fifth most common malignancy affecting women comprising about 4.8% of female cancers following breast (25.2%), colorectal (9.2%), lung (8.8%), cervix uteri (7.9%), corpus uteri and stomach cancers both with 4.8%.[2] In the Philippines, endometrial cancer ranks 3rd following cervical and ovarian cancer among malignancies involving the female reproductive tract and majority affecting postmenopausal women with a median age in their 60s,[3,4] but up to a quarter of cases (25%) maybe premenopausal. The lifetime risk of developing endometrial cancer is 2.6%. Based on the Surveillance Epidemiology and End Results (SEER) data on endometrial cancer, the age adjusted incidence rate is 23.0 per 100,000 women per year, and age-adjusted death rate is 4.2 per 100,000 per year.[5] These rising incidence of endometrial cancer

**First Place, Philippine Society of Ultrasound in Obstetrics and Gynecology (PSUOG) Research Paper Contest, October 27, 2018, 3rd Floor Function Room, Dr. Jose Fabella Memorial Hospital, Philippine Blood Center Compound, Diliman, Quezon City.

can be brought about by the increasing number of older women and the increasing number of with obesity.

The risk factors for developing endometrial cancer are: 1. Obesity; 2. Early age at menarche; never been pregnant; late menopause; 3. History of infertility and irregular menses; 4. History diabetes mellitus type 2, hypertension, gall bladder disease and thyroid disease; 5. Prolonged unopposed estrogen exposure; 6. Tamoxifen for hormonal therapy in breast cancer and 7. Women with Lynch II syndrome or (HNPCC) hereditary non-polyposis colorectal cancer which is a form of an inherited colon cancer syndrome. (estimated relative risk of 6-20%).[6] Women taking combined oral contraceptive pills, DepoProvera (medroxyprogesterone acetate) and Levonorgestrel containing IUD (LNG-IUS) have shown to have a favorable effect against developing endometrial cancer.[7]

Abnormal uterine bleeding drives a patient to seek medical and clinical evaluation. Despite being one of the most common malignancies, it is not the primary cause of cancer deaths because a greater number of patients are diagnosed most often at an early stage. Stage I disease represents 75-80% of cases.[8] Other frequent presenting symptoms involves pain in the pelvis, pain associated with voiding and during intercourse, abnormal vaginal discharge and loss of weight.

Apart from the history, physical examination and endometrial biopsy, for preoperative assessment, a complete blood count, liver and renal function test and chest x-ray should be done. The current FIGO staging uses both the surgical and histopathological evaluation which consists of the: 1. Depth of myometrial invasion; 2. Cervical glandular and stromal extension; 3. Tumor size and location; 4. Tumor involving the tubes and ovaries; tumor grade and histologic type; lymphovascular space invasion and lymph node status.[9] Assessment of the myometrial invasion is an integral part of the preoperative evaluation in patients with endometrial cancer because it is one of the most important prognostic factor for lymph node metastases, tumor recurrence and survival.[10] The deeper the myometrial invasion, the more dismal is the outcome. It is usually associated with an increase lymph node involvement.

The current International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial cancer are as follows:

Endometrial cancer has 2 histologic types: Type 1, the endometrioid adenocarcinoma which is related to estrogen exposure and is the most common type presenting majority of cases. Generally the prognosis is good and usually presents as a stage I disease. It is of 3 subtypes; (Grade 1) well differentiated, (Grade 2) moderately differentiated, (Grade 3) poorly differentiated tumors. Type 1 endometrial cancer commonly presents with vaginal bleeding and associated with endometrial hyperplasia and majority is encountered among the perimenopause and in patients who are obese.[12] Type 2 disease which comprises about 20% of cases usually involves a thin, older woman with atrophic endometrium and is independent of estrogen. Majority of type 2 disease are poorly differentiated tumors and with dismal outcome. About half of relapses occur in type 2. The type 2 tumors include adenocarcinoma with squamous differentiation, adenoacanthoma (benign squamous component), adenosquamous (malignant squamous component), papillary serous or clear cell, carcinosarcoma (malignant mixed Mullerian tumors), uterine sarcoma, mucinous and undifferentiated subtypes and are more likely to suffer recurrent disease.[13]

About 10% of all endometrial cancers, involve a familial type known as the Lynch II syndrome, also known as hereditary non - polyposis colorectal cancer (HNPCC).[6]

Table 1. FIGO 2009[11] Staging of Endometrial Carcinoma

Description Stage	2009
Tumor confined to the uterus	**I**
No myometrial invasion	IA
Myometrial invasion < 50%	
Myometrial invasion ≥ 50%	IB
Cervical involvement	**II**
Endocervical glandular involvement only*	
Tumor extends to the cervical stroma	
Tumor extends to the uterine serosa, adnexae, lymph nodes or vagina	**III**
Serosal or adnexal involvement or positive peritoneal cytology†	IIIA
Vaginal and/or parametrial involvement‡	IIIB
Metastases in pelvic lymph nodes	IIIC1
Metastases in para-aortic lymph nodes	IIIC2
Tumor extends to the abdominal organs and/or has distant metastases	**IV**
Tumor extends to the bladder or rectum	IVA
Metastases in abdominal organ parenchyma or extra-abdominal metastases, including inguinal lymph nodes	IVB

*According to the FIGO 2009 staging, an isolated endocervical glandular involvement is considered as Stage I.†In the FIGO 2009 staging, a positive peritoneal cytology is reported separately without changing the stage.

Classically, dilatation and curettage (D and C) is the procedure undertaken to diagnose endometrial cancer. However, outpatient endometrial sampling can also be done using disposable devices (Pipelle endometrial biopsy) with equivalent accuracy. A meta-analysis on the efficacy of the numerous devices used for endometrial sampling showed a specificity rate of 98%.[14] Hysteroscopic guided D and C, although not required, can capture discreet and focal endometrial lesions with higher accuracy and superior positive yield.[1]

Routine screening in the general population is currently not recommended. However, in patients with LYNCH II syndrome, the American Cancer Society recommends annual endometrial sampling with or without transvaginal ultrasound screening starting at the age of 35 years old until childbearing is completed.[15]

Surgery is the keystone for the management of endometrial cancer. It includes Extrafascial hysterectomy (EH) and bilateral salpingo - oophorectomy (BSO). This can be either an open or a laparoscopic procedure with or without pelvic and para - aortic lymphadenectomy. The abdominal organs like the liver, intestines, omentum and the rest of the peritoneal cavity should be inspected and palpated for the presence of disease. A consultation with a gynecologic oncologist in the preoperative evaluation and intraoperative decision making is imperative to modify treatment especially in patients who needs comprehensive staging and debulking.[1,12]

The Society of Gynecologic Oncologists of the Philippines (SGOP) Clinical Practice Guidelines 2015 recommends initial surgery in the form of extrafascial hysterectomy (EH) with bilateral salpingo - oophorectomy (BSO), pelvic and para - aortic lymph node dissection and peritoneal fluid cytology (PFC). When there is extension into the cervical stroma or stage II disease, a radical hysterectomy (RH) with BSO is advocated with pelvic and para - aortic lymphadenectomy.[3]

Endometrial cancer surgical staging can also be undertaken via laparoscopy. In the GOG LAP2 (2009), a randomized controlled trial involving 2616 patients, the conversion rate from laparoscopy to laparotomy is 25.8% mainly due to bad and poor exposure and is dependent on BMI. (57.1% are morbidly obese patients with a BMI ≥ 40).[16] In the LACE study (2010) the quality of life is being compared after laparoscopy versus laparotomy. Laparoscopy is associated with longer operative time but with earlier recovery phase and improved quality of life in the first 6 month following the procedure. Laparotomy was associated with more postoperative complications than with laparoscopy.[17]

These are the group of patients that are good candidates for laparoscopic - assisted vaginal hysterectomy and laparoscopic hysterectomy: 1. Endometrioid type; 2. BMI <60 kg/m^2; 3. Uterine size <10 cm and non-adherent; 5. No severe cardiorespiratory disease; 6. No previous abdominal and pelvic irradiation; 7. Clinical stage I and II with non - bulky lymphadenopathy seen on imaging.[3]

About 9% of women diagnosed with endometrial cancer are younger than 44 years old, who have not completed the family size and are highly desirous for pregnancy, a fertility - sparing treatment can be advised. In these group of patients, the tumor grade and the depth of myometrial invasion is imperative because the higher the tumor grade and the deeper the myometrial involvement, the higher the risk for extrauterine disease and lymphovascular invasion. For patients who will consider conservative management, the following criteria should be observed: 1. An informed consent; 2. Grade 1 endometrioid type cancer; 3. No myometrial and extrauterine invasion; 4. Strong desire for future pregnancy and with no contraindication for medical treatment.[18] In 2011, Chao AS et al presented a case series and literature review of the pregnancy outcomes among 50 women who underwent conservative therapy of endometrial cancer. There were documented 65 deliveries with 77 live births with 1 maternal death due to recurrent disease following assisted reproductive technology and spontaneous pregnancy.[19]

For low risk patients belonging stage IA, grade 1 and grade 2 diseases with a tumor diameter ≤ 2 cm and confined to the corpus, adjuvant treatment is not needed. For those with intermediate risk, stage IA with grade 1 and grade 2 with tumor size >2 cm; stage IA, grade 3; stage II, grade 1 and grade 2; stage IB, grade 1 and grade 2, adjuvant vaginal brachytherapy should be instituted. For high risk patients with stage IB, grade 3; stage II, grade 3, adjuvant treatment with pelvic EBRT (external beam radiotherapy) should be initiated.[3]

REVIEW OF RELATED LITERATURE

The use of a high resolution transvaginal ultrasound (TVS) is often the first imaging technique employed in a patient who presents with vaginal bleeding. Apart from the endometrial thickness, presence of intrauterine fluid, depth of invasion, some other sonographic features associated with endometrial cancer are the heterogeneity and the presence focal or isolated endomyometrial lesions.[20] To exclude the potentiality of endometrial cancer in the post-menopausal age group, the endometrial thickness cut-off of <4 mm is acceptable. Endometrial thickness of more than 4 mm and/or with the presence of any focal lesions need to be investigated by sampling and biopsy.[21] Savelli et al, in 2008, the accuracy of the preoperative performance for the staging of endometrial cancer using transvaginal ultrasound and magnetic

imaging resonance has been evaluated and concluded that both are comparable with no obvious statistical difference. The sensitivity, specificity, positive and negative predictive values, and overall diagnostic accuracy for TVS in the evaluation of myometrial infiltration were 84%, 83%, 79%, 88% and 84%, respectively. Respective values for MRI were 84%, 81%, 77%, 87% and 82%.[22] Myometrial infiltration assessment using transvaginal ultrasound is superior to CT scan. The accuracy of TVS is up to 84%, MRI about 82% and CT scan has been reported at 61-76%.[22,23] A meta-analysis by Luomaranta A et al (2015) denotes that the overall diagnostic performance of transvaginal ultrasound for the determination of the depth of myometrial invasion has a pooled sensitivity of 82% and a pooled specificity of 81%. For MRI it ranges from 81-90% and 82-89% respectively.[24] However, MRI is not readily available and costly, thus it should be offered only when TVS produces images of poor quality.

Transvaginal ultrasound when compared to MRI and CT scan is less expensive and is widely available even in the less advantage areas. It is non-invasive, easy to perform, can be reproduced and is well tolerated by patients. However, to achieve high accuracy, the operator's knowledge and experience is needed.[25]

These modern imaging techniques can also check for cervical invasion, lymph node involvement and distant metastases. Nodal involvement prediction prior to surgery is helpful in patients with endometrial cancer. This would identify who among these patients will undergo a more radical surgery and thus avoiding over treatment of an early stage disease.[26] Lymph node metastases can be predicted by measuring the depth of myometrial infiltration and as well as with cervical extension. Superficial invasion of the myometrium has a risk of 3% for nodal metastases and this will increase to up to 40% with deeper invasion.[9] Their role in the preoperative evaluation of endometrial cancer patients is of utmost importance and may serve as a guide for planning the extent of surgery and therefore to achieve optimum treatment.[27] However, ACOG agreed that routine preoperative imaging in patients with endometrial cancer to test for metastatic lesions is not imperative.[1] (Level A)

For more than 2 decades now, Cacciatore et al (1989), who first introduced the use of transvaginal ultrasound in assessing myometrial invasion by comparing

Table 2. International Studies Comparing the Method Used, Sensitivity, Specificity, PPV, NPV, Accuracy, Objectives and Conclusion of TVS for Myometrial Assessment.

Study	Method used	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)	Objectives	Conclusion
Savelli, Testa, Mabrouk, Zannoni Ludovisi, Seracchioli, Scambia and De Laco (2012)	(pros)	75	89	86	79	81	To compare the accuracy of preoperative sonography and intraoperative frozen section in the assessment of myometrial invasion of endometrial cancer	Intraoperative frozen section performed better than preoperative TVS in the assessment of myometrial invasion. The diagnostic performance of FS is higher than that of TVS.
Ortoft, Dueholm, and Mathiesen et al (2012)		77	72	69	79	74	To evaluate the accuracy of different preoperative modalities for the staging of endometrial cancer to restrict extensive surgery to patients at high risk of metastatic disease.	Preoperative staging with MRI and hysteroscopic directed biopsy can identify 8 of 10 women with high risk of lymph node metastases and spare eight of 10 low risk women for extended surgery.
Karat-Pektas, Gungor Mollamahmutoglu (2008)	DOI (pros)	66	72	60	75	69	To investigate the relation between uterine histologic alterations and sonographic findings in women diagnosed with endometrial cancer.	TVS has moderate sensitivity and moderate - high specificity which limits its use. However, endometrial thickness, myometrial invasion and resistance index values determined by Doppler can indicate the tumor grade allowing individualized treatment to be planned.
Berretta, Merisio and Piantelli (2008)	GOR-DON (retro)	62	79	54	82	73	To evaluate the concordance between myometrial infiltration detected by ultra-sound and gross inspection with respect to the histologic examination	Ultrasonography and macroscopic gross examination appear to be simple, fast and reliable methods to predict the myometrial invasion in low risk for lymph node metastasis
Savelli, Ceccarini, Ludovisi, Fruscella, De Iaco, Salizzoni, Mabrouk, Manfredi, Testa, Ferrandina, (2008)	TFD (pros)	84	83	79	88	84	To compare the accuracy of Transvaginal Ultrasound (TVS) and Magnetic Resonance imaging (MRI) in preoperative staging of endometrial cancer.	TVS performed by specialist can be considered a feasible, economic imaging modality with diagnostic accuracy comparable to that of MRI
Ruangvutilert, Sutantawibul, Sunsaneevithayakul, Boriboonhirunsam, Chuenchom (2004)	DOI	69.4	70.6	53.2	82.8	70.3	To evaluate the accuracy of transvaginal ultrasound for the evaluation of myometrial invasion in endometrial cancer in comparison with standard paraffin section.	TVS for assessment of depth of myometrial invasion in endometrial cancer provided acceptable accuracy compared with standard paraffin section.
Arko and Takac (2000)	TFD and DOI (pros)	79	69	63	83	73	The aim of the study is to assess the depth of myometrial invasion by endometrial cancer using TVS.	The role of the high frequency transvaginal ultrasonography in preoperative assessment of the depth of myometrial invasion is limited.
Alcázar, Jurado and López-García (1999) 46	DOI	87	94	87	94	92	To compare the ability of transvaginal sonography and serum CA 125 levels to predict myometrial invasion in patients with endometrial cancer	TVS is more sensitive than CA 125 in predicting myometrial invasion in endometrial cancer.
Karlsson , Norstrom , Granberg and Wikland (1992)	Karls-son	79	100	100	73	87	To correlate the ultrasound data with macroscopic findings of uterine specimen and to histopathology.	Endovaginal ultrasound seems to be a reliable method of assessing tumor invasion and engagement of the cervix.

the accuracy of transvaginal versus transabdominal scan. Transvaginal ultrasound has an accuracy rate of 87% (20/23) while that of transabdominal route being 78% (18/23).[28] There are several other ways to measure myometrial involvement which include the Gordon's, Karlsson's, depth of myometrial invasion, the tumor free distance and the subjective evaluation which include 1. Tumor size and proportion; 2. Regularity of the endometrial-myometrial borders and 3. Vascular patterns.

In 2015, a systematic review and meta - analysis by Alcazar et al., on the preoperative evaluation of myometrial involvement in patients with endometrial cancer, concluded that the diagnostic efficiency of the transvaginal ultrasound is moderate. Most of the studies involved in the review are both the subjective and objective measurements.[29] Among the objective measurements employed were the Gordon's[30] approach (Figure 21) which is the ratio of the distance between the maximum tumor depth (B) and the entire myometrial thickness (A), with B/A >50% signifies deep myometrial invasion and the Karlsson's[31] approach (Figure 22) which uses the ratio between the maximum anteroposterior (AP) diameter of the endometrial lesion (B) and the uterine AP diameter (A), with B/A >50% denoting profound involvement. In this study of Karlsson, the sensitivity was 79%, specificity of 100%, PPV of 100%, NPV of 73% and accuracy rate of 87%.

To maximize the balance between sensitivity and specificity in predicting recurrence, the tumor free distance (TFD) defined as the distance from the deepest myometrial invasion to the serosa, Lindauer et al (2003)[32] and Schwab et al (2009)[4] used a cut off value of 10 mm. With these, the negative predictive value of TFD is 95%. This would put the tumor free distance (TFD) as a reasonable unit to measure endometrial adenocarcinoma.[32]

Arko and Takac (2000)33 and Berretta et al (2008)34 have similar results in their accuracy rates for the preoperative assessment of myometrial invasion by transvaginal ultrasound at 73% when correlated

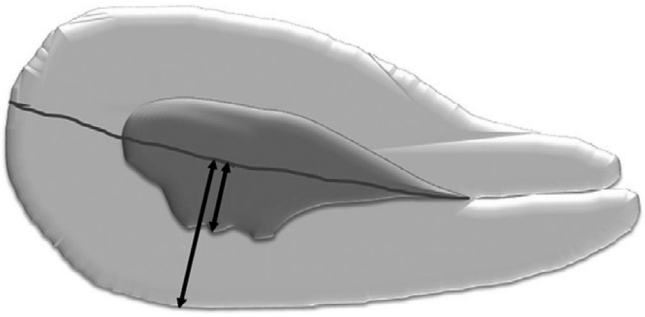

Figure 21. Schematic illustration of the uterus in the sagittal plane, showing Gordon's approach. Depth of infiltration was measured as the ratio of the distance between the maximum tumor depth (B) and the total myometrial thickness (A), with B/A >50% indicating deep myometrial infiltration.

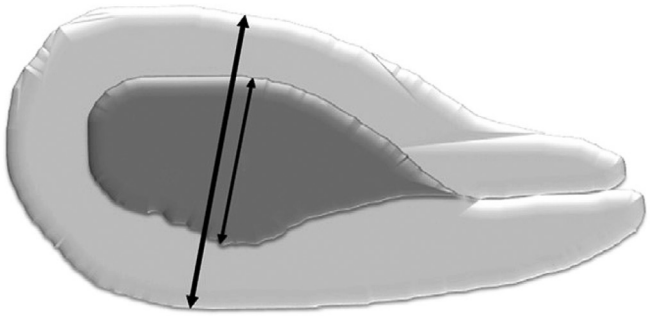

Figure 22. Schematic illustration of the uterus in the sagittal plane, showing Karlsson's approach. Depth of infiltration was measured as the ratio between the maximum anteroposterior (AP) diameter of the endometrial lesion (B) and the uterine AP diameter (A), with B/A >50% indicating deep myometrial infiltration.

with the histopathologic results. Karat - Pekyas et al (2008) has a lower sensitivity of 62%, specificity of 75%, PPV of 66%, NPV of 71% and accuracy rate of 69%.[35] Schwab et al (2009) in a prospective study to evaluate the prognostic significance of the tumor free distance of 99 patients and showed that TFD significantly predicts lymph node involvement, lymphovascular space invasion (LVSI), and tumor grade.[4]

Alcazar et al. (2009) conducted a study by uterine virtual navigation using 3D ultrasound and have showed that the best cut off for ultrasound measured TFD is 9.0 mm, with a sensitivity of 100%; specificity 61%; NPV, 100%; PPV, 50% as compared to the subjective evaluation with s sensitivity of 92.6%; specificity of 82.3%; NPV 96.6%, PPV 67.7%.[36]

Mascilini et al., (2013)[37], conducted a multicenter, prospective study involving 144 patients with endometrial cancer. In predicting deep myometrial infiltration, the study results showed that the tumor/uterine AP diameter ratio cut off was 0.53, while the minimal tumor free distance cut off was 0.71cm, with a sensitivity of 72% and 85% and specificity of 76% and 50% respectively. Another study conducted by Savelli et al. (2012), myometrial invasion was correctly predicted by sonography in 81% of the cases in contrast to an earlier study (2008) with 84%.[22,38] Of the same year Orloft et al has an accuracy rate of 74%.[39]

Ozbilen et al (2015) in a retrospectively study concluded that the depth of myometrial invasion is more important than the tumor free distance from uterine serosa for the prediction of lymph node metastasis. Likewise, the tumor free distance is a better predictor for adnexal tumor spread.[40]

A local study conducted by San Juan, et al. (Table 3) and Benavides, Luna and Bustamante showed an accuracy rate of 79.4% and 78.6 % respectively.[41,42] In 2011, Espinosa and Comia made a 5 year retrospective review of the accuracy of TVS in determining the depth of myometrial invasion and cervical infiltration among patients preoperatively

Table 3. Local Studies Comparing the Method Used, Sensitivity, Specificity, PPV, NPV, Accuracy, Objectives and Conclusion of TVS for Myometrial Assessment.

Study	Method used	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)	Objectives	Conclusion
Datu and Bustamante (2014)	DOI TFD	65.1 59.7	32.4 36	64.1 72.9	33.3 23.7	53.6 53.6	To compare the diagnostic accuracy of the 3 different methods of measuring the depth of myometrial invasion using transvaginal ultrasound in preoperative assessment of endometrial cancer.	Depth of invasion was still the best technique to use in the preoperative assessment of myometrial invasion. The tumor-free distance (TFD) from the serosa was as good or better as depth of invasion in terms of accuracy.
Espinosa and Comia (2011)	DOI	86	76	86	76	80.7	To evaluate the diagnostic accuracy of transvaginal ultrasound (TVS) in preoperative assessment of the depth of myometrial invasion and the presence of cervical infiltration in endometrial carcinoma	TVS can be considered as a feasible, economical and simple imaging modality with high accuracy for the prediction of cervical infiltration. However, it is a less reliable method in estimating the depth of myometrial invasion.
San Juan, Manabat, Limson and Manalo (1994)	DOI	76.5	82.4	91.3	77.8	79.4	To correlate the findings of the preoperative pelvic sonographic studies in determining tumor myometrial invasion ans cervical involvement with the histologic findings.	The use of ultrasound in the diagnostic paraphernalia of the gynecologist has opened the doors to improvement in the clinical preoperative evaluation of the disease in gynecologic malignancies.

diagnosed with endometrial cancer with a sensitivity 86%, specificity of 76%, positive predictive value of 86%, negative predictive value of 76% and overall diagnostic accuracy of 80.7%.[43] The depth of invasion (DOI) was the method used to measure myometrial infiltration on all these studies.

Another local retrospective study done by Datu and Bustamante in August 2013 - August 2014 with a total of 97 patients, DOI and TFD had comparable diagnostic accuracy. DOI had sensitivity of 65.1%, specificity of 32.4%, positive predictive value of 64.1%, negative predictive value of 33.3% and accuracy of 53.6%. TFD had sensitivity of 59.7%, specificity of 36%, 72.9% positive predictive value, 23.7% negative predictive value and accuracy of 53.6%.[44]

In this study, we will compare 2 methods of ultrasound measurements in assessing myometrial invasion, TFD and DOI as measurement techniques and correlate sonographic results with histopathology. Local prospective studies have not yet been published.

RESEARCH OBJECTIVES

General

To determine the diagnostic accuracy of the Tumor Free Distance (TFD) compared with the Depth Of Invasion (DOI) utilizing 2D transvaginal ultrasound in determining myometrial invasion among patients with endometrial cancer admitted for elective gynecologic surgery at Philippine General Hospital Department of Obstetrics and Gynecology.

Specific

1. To determine the sensitivity, specificity, positive predictive value and negative predictive value and overall accuracy of transvaginal ultrasound in assessing the myometrial infiltration of patients with endometrial cancer by measuring the tumor free distance and the depth of invasion;
2. To correlate the 2D transvaginal ultrasound tumor free distance and depth of invasion measurements with the final histopathology results used as the gold standard;
3. To determine and construct the area under curve index of accuracy of 2D transvaginal ultrasound tumor free distance and depth of invasion measurements with the final histopathology results used as the gold standard;
4. To describe the clinical profiles of patients diagnosed with endometrial cancer in terms of a) age, b) gravidity, c) parity, d) BMI, e) FIGO Stage,

Table 4. Methods, Techniques Employed (Based from the Original Paper of Y.P. Geels et al. Gynecologic Oncology 129 (2013) 285-291, 4, 11, 34 (For the Diagram, see Figure 24)

Methods	Technique
Myometrial thickness	Measured from the endomyometrial junction to the serosa, the section where the tumor demonstrated the deepest invasion,
Endomyometrial junction	If with irregular endomyometrial junction, the measurement is done where the deepest invasion is seen.
Depth of invasion	Measured from the endomyometrial junction to the deepest point of the myometrial invasion. In the presence of myoma uteri, the myometrial thickness in the area next to the myoma is measured. In cases of exophytic growth, the DOI cannot be measured.
Tumor free distance	Measured from the deepest point of myometrial invasion to the serosa.

f) Grade, g) personal history of other cancer and h) family history of cancer

Significance

Determining the accuracy of the TFD and DOI methods by preoperative transvaginal ultrasound evaluation of myometrial involvement can help identify and prepare patients prior to surgical operation. Preoperative planning, preparation for a more extensive surgery which often involves bilateral lymph node dissection and proper counseling of the patient is undertaken ahead of surgery. On the part of the sonologists, this study will help provide the best option for the measurement of the extent of tumor involvement especially in the low resource areas where MRI is not readily available.

MATERIALS AND METHODS

Design

This is a prospective cross sectional study (diagnostic validity) comparing the accuracy of tumor free distance and the depth of myometrial invasion in assessing myometrial infiltration among endometrial cancer patients using histopathology result as the gold standard.

Setting

This study was conducted at the Ultrasound Section, Department of Obstetrics and Gynecology, Philippine General Hospital.

Subjects

All patients with the diagnoses of endometrial cancer through biopsy and admitted for elective surgery and surgical staging at the Philippine General Hospital from October 1, 2016 to February 28, 2017 were included in the study using the following criteria;

Inclusion

1. All patients with endometrial cancer underwent a 2D transvaginal ultrasound measuring the tumor free distance and the depth of myometrial invasion done by 1 ObGyne sonologist within at least one week prior to the elective surgery at Philippine General Hospital from October 1, 2016 to February 28, 2017.
2. With surgicopathologic staging / histopathology results as gold standard

Exclusion

1. Patients without informed consent.
2. Time interval between ultrasound and surgery was more than 1 week.
3. Patients without histopathology results.
4. Patients histologically diagnosed with endometrial cancer but not operated.
5. Patients diagnosed with other primary carcinoma aside from endometrial cancer.

Sample size computation

Reference: For the sample size calculation, the prevalence in Datu (2014)[44] retrospective study suggesting Stage I rate of 47%.

- Philippine setting which are Stage I – 47%, Stage II – 19%, Stage III – 23% and Stage IV – 11% (note: since most of the prevalent endometrial cancer is at stage 1, we will used stage 1 rate – 47%
- Sample size equation;
  Detailed explanation:

By equation:

Explanation on the calculation of sample size in Sensitivity & Specificity Studies:

		Disease +	Disease -	
Test	+	a	b	
	-	c	d	
		$(a+c)$	$(b+d)$	N

The sample size that we want to calculate is "total sample size" N.

What the study would like to determine are "Sensitivity" which is $a/(a+c)$, and "Specificity" which is $d/(b+d)$.
Therefore, we need to calculate the sample size to acquire an appropriate precision for estimating "Sensitivity" and "Specificity".

By using usual single proportion sample size formula (1), we can calculate the sample size for $(a+c)$, if we use 'Sensitivity' as P. (Δ is precision).
After we get $(a+c)$, the total sample size can be obtained by using Prevalence of the disease (using the formula 2).
Similary, we can calculate the sample size for $(b+d)$, if we use specificy as P in formula (1). After getting $(b+d)$, the total sample size can be calculated by formula (3).

FORMULA

$$n = \frac{Z^2 * P(1-P)}{\Delta^2} \qquad (1)$$

n will be $(a+c)$ if we use Sensitivity as P, and n will be $(b+d)$ if we use Specificity as P in formula (1).

$$N = \frac{(a+c)}{\text{Prevalence}} \qquad (2)$$

$$N = \frac{(b+d)}{(1-\text{Prevalence})} \qquad (3)$$

In order to compute for sample size appropriate for testing validity or accuracy of diagnostic tool, we used appropriate equation. Above mentioned was the appropriate equation.

1. We anchored our computation based on the reported statistics from previous studies.
2. In our case, we assumed that the tumor free distance and the depth of myometrial invasion measurements yielded an accuracy of 85% (sensitivity and specificity) in assessing Myometrial Infiltration (according to literature and standards, a sensitivity of 85% and specificity of 85% were clinically acceptable values so that the diagnostic tool which was being evaluated

was valid and can be recommended to be used as assessment tool to predict a certain outcome.
Some literature would consider 70% and above, however, just to be strict 85% is the safest.

3. Also, according to literature, the rate of myometrial infiltration would occur at a rate of 47% , then the rate estimate is considered using +/-14% margin of error at CI 95%.

Thus, we used the 47% and precision +/- 14% as part of the equation (above)

Thus, the sample size was computed using the 85%, 85%, 47%, 10%, and CI 95% or z=1.96 to arrive with the computed sample size of 54.

FORMULA

$$n = \frac{Z^2 * P(1-P)}{\Delta^2} \quad (1)$$

n will be $(a+c)$ if we use Sensitivity as P, and n will be $(b+d)$ if we use Specificity as P in formula (1).

$$N = \frac{(a+c)}{\text{Prevalence}} \quad (2)$$

$$N = \frac{(b+d)}{(1-\text{Prevalence})} \quad (3)$$

Sample size calculation for Sensitity & Specificity Studies

Expected Sensitivity	0.85	◄ From literature or pilot study
Expected Specificity	0.85	◄ From literature or pilot study
Expected Prevalence	0.47	◄ From literature or pilot study
Desired Precision	0.14	◄ Researcher's judgment
Confidence level	95%	◄ 95% is recommended.

To achieve the precision of 0.14 for 'Sensitivity', we need 'the total sample size' of = 54
With this sample size, the precision for 'Specificity' will be = 0.131

- Assuming that the tumor free distance and the depth of myometrial invasion measurements would yield accuracy of 85% (sensitivity and specificity) in assessing Myometrial Infiltration among 47% +/-14% affected patients with endometrial cancer, then, the sample size needed is 54 estimated at CI 95%.

Data collection procedure

All study participants had an informed consent. The clinical profile of patients were described as to her age, gravidity, parity, BMI, FIGO stage, and tumor grade, personal history of other cancer and family history of cancer.

All patients had a histologic diagnosis of endometrial cancer by biopsy or hysteroscopy and were admitted for elective surgery.

Transvaginal scan using Samsung machine model UGEO WS80A with a wide vaginal probe which offered field of view up to 210 degrees or with Mindray Model:DC-7. The transvaginal ultrasound probe frequencies ranges from 5 to 10 MHz while the transabdominal ultrasound probe used frequencies between 3 and 5 MHz. The transvaginal ultrasound was done at least within one week prior to the scheduled surgery.

The procedure lasted approximately 30 minutes. All patients were examined in the dorsal lithotomy position with an empty urinary bladder. The assessment of the uterus started with the identification of the urinary bladder and the cervix. The uterus, uterine cavity and the endometrium were examined and scanned in a sagittal plane transvaginal route. The image was then magnified in such a way that only the uterus occupied about 70% of the screen. In patients with large fibroids, virgin and who didn't consent for transvaginal scan, a transabdominal or transrectal approach was done. The transvaginal probe was moved from one uterine lateral border to the other. Each protrusion of the endometrium into the myometrium were evaluated.

The endometrium was evaluated using echogenicity and the characteristics of the endometrial - myometrial junction using the International Endometrial Tumor Analysis (IETA) group terms and descriptions. The endometrial echogenicity were compared with the sonographic appearance of the myometrium and were described as uniform (three layer pattern), hyperechogenic, isoechogenic or hypoechogenic. (Figure 25), heterogeneous, asymmetrical or cystic. (Figure 27). The endometrial - myometrial junction was described according to its appearance as regular, irregular, interrupted or not defined. (Figure 26).[45]

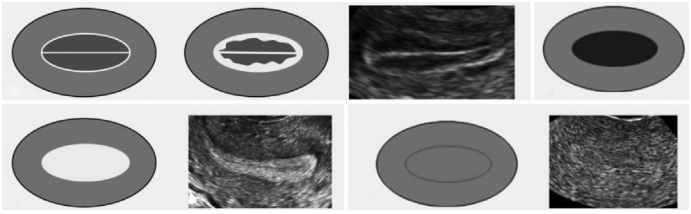

Figure 25. Uniform' endometrial echogenicity: three-layer pattern (a), hypoechogenic (b), hyperechogenic (c) and isoechogenic (d).

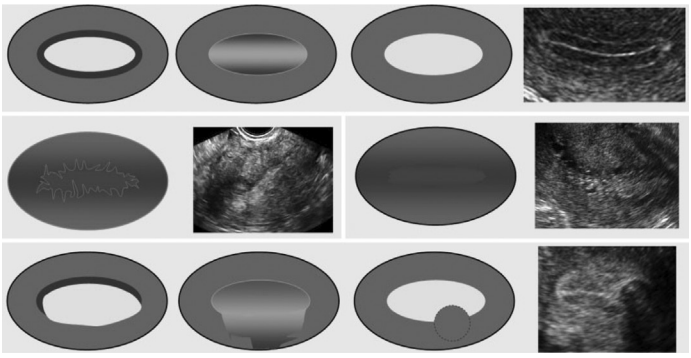

Figure 26. Endometrial–myometrial junction: 'regular' (a), 'irregular' (b), 'interrupted' (c) (dark gray area denotes the endometrial–myometrial halo; in this case the halo is interrupted) and 'not defined' (d).

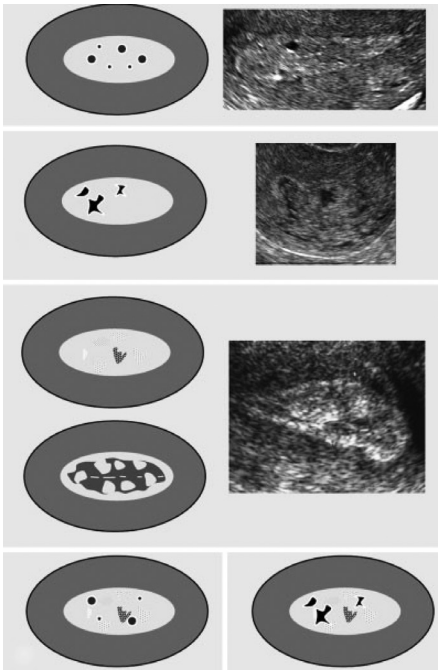

Figure 27. 'Non-uniform' endometrial echogenicity: homogeneous background with regular cystic areas (a), homogeneous background with irregular cystic areas (b), heterogeneous background without cystic areas (c), heterogeneous background with regular cystic areas (d) and heterogeneous background with irregular cystic areas (e); black color denotes cystic spaces.

The endometrial tumor was then measured in 3 dimensions at its deepest myometrial invasion.

Technique A (Figure 22). The tumor free distance (TFD) is defined as the distance from deepest myometrial invasion to the serosal surface. It measured the shortest myometrial tumor free distance (TFD) to the serosa. This parameter was assessed and assigned <50% myometrial invasion if >1.0 cm and >50% if < 1.0 cm.

Technique B (Figure 23). The conventional method, DOI was defined as the distance between the endomyometrial junction and deepest myometrial invasion and was measured from the endometrial - myometrial interface to the deepest edge of the tumor extension into the myometrium and were related to the width of the normal myometrium.

All measurements were done in the same site where the deepest tumor invasion was found. In case of a leiomyoma on the same site of the section, the myometrial thickness in the area directly next to the leiomyoma were measured. Each of the patients had at least 3 slides (ranging 1 - 5 slides) with tumor and adjacent myometrium with serosa for evaluation of the depth of myometrial invasion. Figure 24 showed examples of how measurements were performed.

The ultrasound result gave information as well as the descriptions of the tumor according to location, size (3 diameters) and sonomorphology (echogenicity,

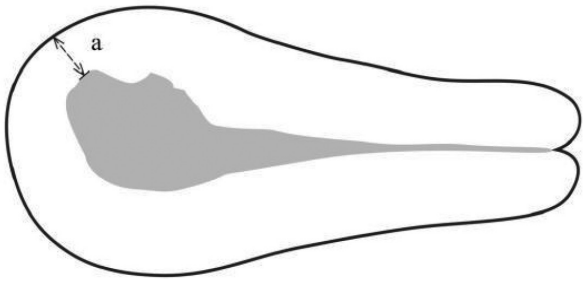

Figure 22. The shortest myometrial tumor-free distance (TFD) to the serosa, which is a measure of the distance between maximal myometrial invasion and the uterine serosa.

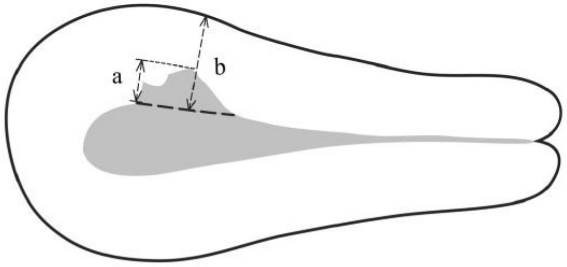

Figure 23. The depth of myometrial invasion (DOI) was measured from the endometrial-myometrial interface to the deepest edge of the tumor extension into the myometrium (a) and will be related to the width of the normal myometrium (b).

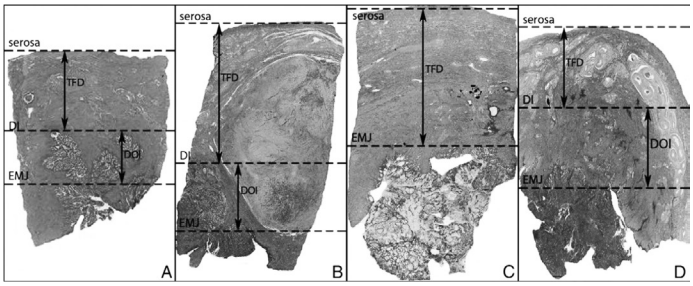

Figure 24. Depth Of myometrial Invasion DOI, tumor free distance to the serosa (TFD), endomyometrial junction (EMJ), Deepest Invasion (DI). A: Example of assessment of DOI and TFD.B: Example of assessment of DOI and TFD in a patient with leiomyoma. C: Example of assessment of DOI and TFD in a patient with exophytic tumor growth, there is no DOI in this case. D: Example of assessment of DOI and TFD in a patient with deep myometrial invasion.
[Based and copied from the original paper of Y.P. Geels et al. Gynecologic Oncology 129 (2013) 285-291]

homogeneity, endometrial - myometrial junction), and evaluation of the extent of tumor infiltration into the myometrium and towards the cervix. The digital copies of the ultrasound images and results were stored at the Ultrasound Section official computers and storage were retrieved. Back - up was done by storing digital files in disks. Furthermore, the filled - up data collection forms were kept and carefully handled by the primary investigator.

All patients with primary endometrial cancer at the University of the Philippines - Philippine General

Hospital from October 1, 2016 until February 28, 2017 were included in the study underwent complete surgical staging with Exploratory laparotomy, either by Extrafascial hysterectomy with bilateral salpingo - oophorectomy or Radical hysterectomy with bilateral salpingo - oophorectomy, cytology and lymph node dissection. The surgicopathologic data were reviewed from the postoperative reports. Histopathology results were followed - up from the UP - PGH Department of Pathology. The reference standard was the final surgicopathological diagnosis based on the criteria recommended by the International Federation of Gynecology and Obstetrics.

Data Management Plan and Statistical Tools

DOI and TFD were expressed as continuous variables and being evaluated for their ability to predict the myometrial infiltration using final histopathology as gold standard. Univariate and multivariable analysis were used to examine the data.

The data gathered were encoded in MSEXCEL spreadsheets in preparation for data processing and analysis.

The patients' age, gravidity, parity and BMI were described using mean and standard deviation while FIGO Stage, Grade and histologic type were categorized and presented using frequency and percentage distribution. The ultrasound measurement techniques, the depth of invasion (DOI), and tumor free distance (TFD) from the serosa categories were expressed in frequency and percentage distributions.

In testing the association among depth of invasion and tumor free distance from the serosa using the measurement <50% and >50% and myometrial invasion, a 2 x 2 Fischer Exact test was used. Moreover, the average and standard deviation of the actual values for each measurement technique such as depth of invasion, percentage myometrial invasion, and tumor free distance from the serosa as stratified by the presence of <50% and >50% myometrial invasion were compared using Unpaired t-test. The sensitivity, specificity, negative and positive predictive values, and overall accuracy of the cut-off values of the two (2) measurement techniques such as depth of invasion and tumor free distance from the serosa were computed. Also, diagnostic accuracy performance of TFD and DOI were determined using an Area Under Curve estimate with ROC figure wherein an AUC of 0.70 and above is considered a clinically acceptable diagnostic tool.

Any associated p-values lesser than 0.05α were considered statistically significant. IBM SPSS version 20 and SAS program were used in the processing of data.

RESULTS

There were a total of 49 patients who met the inclusion criteria and were included in the study. The age ranges from 31-80 years old, with a mean age of 53 years old. There were 23 postmenopausal patients, with a mean age of menopause at 48.78 years old. Majority of the patients were of the endometrioid type comprising about 89.8% of cases and more than half (54%), with an age above 50 years old.

Table 5, showed data with regards to the tumor Grade and FIGO Staging and LVSI, majority of Grade 1 tumor (12/44), 91.7% (11) were FIGO Stage I-A and 8.3% (1) was Stage I-B. Grades 2 and 3 tumors were higher in patients >50 years old, comprising 65.6% (21/32) and they too have a higher stage tumors (Stage III and IV, n =16), 81.3% (13/16) versus 18.7% (3/16) of those younger than 50 years old. For lymphovascular space invasion (LVSI), 59.1% (26/44) among patients with endometrioid type adenocarcinoma showed absent LVSI while 4 of 5 patients with non - endoemtrioid type have positive results. The non - endometrioid type tumors (n=5) seen were, Serous carcinoma (2), Mullerian adenosarcoma (1), Carcinosarcoma with mixed endoemetrioid and clear cell (1) and Adenosquamous carcinoma (1).

Table 6, showed that those 44 cases with endometrioid type cancer, their profiles are as follows, average age of 52.14 years old, 70% were multigravidas as well as multiparities (70%), with average BMI of 25.69, 48% were overweight, 50% with cancer Grade 2, average age at menarche of 13.21 years old, average menopause age of 49.26 years old, and comorbidities such as hypertension (30.2%), with family history of cancer (18.6%), and with diabetes (9.3%).

Further analysis showed that all patients' characteristics were not significantly associated with presence of endometrial cancer.

As noted in Table 7, among 14 cases with <50% myometrial infiltration assessed in TVS, 13/14 (92.9%) were also <50% in the final histopathology while among those 35 cases with >50% infiltration, 51.4% (18/35) were also >50% infiltration in the final histopathology. The association between transvaginal ultrasound and final histopathology in assessing the myometrial infiltration was statistically significant (p=0.004). Overestimation of myometrial invasion was seen in almost half of cases (17/35), and was underestimated in 1 out of 14 cases.

In Table 8, the transvaginal ultrasound for myometrial infiltration demonstrated 94.4% sensitivity and 43.8% specificity in detecting <50% and >50% infiltration wherein a likelihood of >50% assessment in TVS would likely to occur by 1.68 times higher than those with <50% based on

Table 5. Demographic Profiles, FIGO Stage, Tumor Grade and Lymphovascular Space Invasion (LVSI) Between Patients with Endometrioid and Non - Endometrioid Type Cancers

Patients' Characteristics	Non - Endometrioid	Endometrioid	p-value
No. of cases	n = 5 (10%)	n = 44 (90%)	
Age distribution (years)			
31- 40	1 (20%)	4 (9%)	<0.001
41- 50	0 (0%)	17 (39%)	
51- 60	0 (0%)	14 (32%)	
61 - 70	2 (40%)	9 (20%)	
71 - 80	2 (40%)	0 (0%)	
Tumor Grade			
Grade 1	-	12 (27%)	-
Grade 2	-	22 (50%)	
Grade 3	-	10 (23%)	
FIGO Stage			
I-A	0 (0%)	22 (50%)	0.14
I-B	0 (0%)	6 (13.6%)	
II	1 (20%)	4 (9.1%)	
III-A	1 (20%)	2 (4.5%)	
III-B	1 (20%)	2 (4.5%)	
III-C1	0 (0%)	2 (4.5%)	
III-C2	0 (0%)	1 (2.3%)	
IV-A	0 (0%)	0 (0%)	
IV-B	2 (40%)	5 (11.4%)	
Lymphovascular space invasion (LVSI)			
YES	4 (80%)	18 (41%)	0.087
NO	1 (20%)	26 (59%)	

Table 6. Age, Gravidity, Parity, BMI, Grade, Personal History of Other Cancer and Family History of Cancer Between Patients with Endometrioid and Non-Endometrioid Type Cancers

Patients' Characteristics	Non - Endometrioid	Endometrioid	p-value
	n = 5	n = 44	
Age, years			
mean±SD	59.40±20.26	52.14±9.35	0.158
Gravidity			
mean±SD	3.02±12.52	3.05±2.52	0.368
Nulli	3 (60%)	10 (23%)	0.143
Primi	0 (0%)	3 (7%)	
Multi (2 above)	2 (40%)	31 (70%)	
Parity			
mean±SD	2.67±2.28	2.66±2.26	0.359
Nulli	3 (60%)	10 (23%)	0.143
Primi	0 (0%)	3 (7%)	
Multi (2 above)	2 (40%)	31 (70%)	
BMI			
mean	25.79	25.69	0.788
std.deviation	±4.82	±4.73	
BMI categories			
normal	2 (40%)	17 (39%)	0.338
underweight	1 (20%)	2 (5%)	0.301
overweight	1 (20%)	21 (48%)	
obese	1 (20%)	3 (7%)	
extreme obese	0 (0%)	1 (2%)	
menarche (age)			
mean	13.31	13.21	0.310
std.deviation	±1.72	±1.7	
menopause (age)			
mean	45.5	49.26	0.432
std.deviation	±4.81	±4.71	
Co-morbidities			
hypertension	2 (40%)	13 (30%)	0.451
diabetes	2 (40%)	4 (9%)	0.113
Family History of cancer	0 (0%)	8 (18%)	0.404
History of other cancer	0 (0%)	0 (0%)	-

the final histopathology results. Moreover, the predictive values of TVS were as follows, namely, 48.6% positive and 93.3% negative predictive values.

In Table 9, showed that there is a significant difference in the tumor free distance as measurement by TVS (0.87 vs 0.40) when grouped by <50% and >50% in final histopathology (p=0.001) while the depth of invasion ratio were not statistically significant in both groups (0.65 vs 0.74, p=0.176).

In Table 10, a TFD cut off value of 0.82cm and below generated higher sensitivity (46.88%) and specificity (100%) in predicting myometrial infiltration of >50% while a DOI ratio of 0.50 is the cut off value which initiated increase sensitivity (16.7%) and higher specificity (75%) in predicting >50% infiltration.

In Table 11, which describes the endometrial mass as well as the endomyometrial junction. Majority of the endometrial masses have had heterogeneous background without cystic areas comprising 81.6% (40/49) of combined endometrioid and non - endometrioid types. With regards to the endometrial - myometrial (EMM) junction, irregular and not defined EMM junction comprises 81.6% (40/49) as opposed to regular EMM junction which is 18.4% (9 cases, all of which are in stage I-A).

Table 12, Showed the number of patients with concurrent adenomyosis and leiomyoma according to age group and whether endometrioid or non - endometrioid types. There were 6 cases with concurrent adenomyosis, all were of the endometrioid type, with which 83.3% (5/6) were of the 41-50 year old age group and

Table 7. Association of Transvaginal Ultrasound and Final Histopathology in Assessing the Myometrial Infiltration

Transvaginal ultrasound	Final histopathology		Total	2x2
				Fischer Exact test,
Myometrial infiltration	<50%	>50%		p-value
<50%	13	1	14	0.004
>50%	17	18	35	
Total	30	19	49	

Table 8. Accuracy of Myometrial infiltration (<50% and >50%) As Measured by Transvaginal Ultrasound in Predicting Final Histopathology in Assessment of Myometrial Infiltration

Accuracy	Accuracy		
Transvaginal ultrasound	Estimate	Confidence Interval at 95%	
Myometrial infiltration		Lower	Upper
Sensitivity	94.4%	83.9%	105.0%
Specificity	43.8%	26.6%	60.9%
Likelihood Ratio +	1.68	1.21	2.32
Predictive value positive	48.6%	32.0%	65.1%
Predictive value negative	93.3%	80.7%	106.0%
Overall accuracy	62.0%	48.5%	75.5%

Table 9. Comparisons of 2D Transvaginal Ultrasound Measurement: TFD and DOI Ratio of Myometrial Infiltration as Grouped by Final Histopathology Findings

2D transvaginal ultrasound measurement	Final Histopathology				p-value
	<50%		>50%		
	Mean	Std. Deviation	Mean	Std. Deviation	
tumor free distance (cm)	0.87	0.57	0.40	0.19	0.001(sig)
depth of invasion ratio	0.65	0.20	0.74	0.25	0.176 (not sig)
depth of invasion ratio	*Range 0.23-0.94*		*Range 0.01-0.99*		

Table 10. Accuracy 2D Transvaginal Ultrasound Measurement of Myometrial Infiltration in Terms of TFD and DOI Ratio Cut off Values in Predicting Final Histopathology Findings

TVU Measurement	Sensitivity	Specificity	Likelihood + Ratio	PPV	NPV
TFD Cut off values					
0.1	100.00%	5.56%	1.06	65.31%	100.00%
***0.82**	***46.88%**	***100.00%**	**-**	***100.00%**	***51.43%**
1.55	9.38%	100.00%	-	100.00%	38.30%
2.27	0.00%	100.00%	-	0.00%	36.00%
2.99	0.00%	100.00%	-	0.00%	36.00%
DOI Ratio					
0.01	5.60%	100.00%	-	100.00%	65.30%
0.25	5.60%	96.90%	1.78	50.00%	64.60%
***0.50**	***16.70%**	***75.00%**	***0.67**	***27.30%**	***61.50%**
0.74	27.80%	46.90%	0.52	22.70%	53.60%
0.99	100.00%	0.00%	1	36.00%	100.00%

(*) the recommended cut off value

Table 11. Endometrial Mass Description According to Echogenicity Between Endometrioid and Non-Endometrioid Type Cancers

Echogenicity	Non - endometrioid	Endometrioid
Uniform (Three layer pattern)	**(n =5)**	**(n=44)**
Hypoechogenic	0 (0%)	0 (0%)
Hyperechogenic	0 (0%)	0 (0%)
Isoechogenic	0 (0%)	0 (0%)
Non - Uniform		
Homogeneous background with regular cystic areas	0 (0%)	0 (0%)
Homogeneous background with irregular cystic areas	0 (0%)	0 (0%)
Heterogeneous background without cystic areas	3 (60%)	37 (84.1%)
Heterogeneous background with cystic areas	0 (0%)	0 (0%)
Heterogeneous background with irregular cystic areas	2 (40%)	7 (15.9%)
Endometrial - Myometrial Junction		
Regular	0 (0%)	9 (20.4%)
Irregular	2 (40%)	26 (59.1%)
Interrupted	0 (0%)	0 (0%)
Not defined	3 (60%)	9 (20.4%)

Table 12. Age Distribution of Patients with Concurrent Myoma Uteri and Adenomyosis

Age Distribution (years)	Myoma uteri (n=10)		Adenomyosis (n=6)	
	Non-endometrioid	Endometrioid	Non- endometrioid	Endometrioid
31 - 40	0 (0%)	0 (0%)	0 (0%)	0 (0%)
41 - 50	0 (0%)	1 (11.1%)	0 (0%)	5 (83.3%)
51 - 60	0 (0%)	5 (55.6%)	0 (0%)	1 (16.7%)
61 - 70	0 (0%)	3 (33.3%)	0 (0%)	0 (0%)
71 - 80	1 (100%)	0 (0%)	0 (0%)	0 (0%)

all were Stage I-A except 1 with a Stage IV-B. There were 10 patients seen with concurrent leiomyoma of which 90% (9/10) were of the endometrioid type. The presence of myoma and adenomyosis didn't affect much of the measurements since majority of the myomas were small and of subserous and cervical location.

As illustrated in Figure 1, only TFD measurement generated a clinically acceptable accuracy in predicting >50% myometrial infiltration while DOI ratio yielded poor accuracy in predicting >50% infiltration. Based on standardized index, an AUC of 0.70 is considered a clinically acceptable diagnostic tool.

DISCUSSION

The use of a high resolution transvaginal ultrasound (TVS) is often the first imaging technique employed in a patient who presents with vaginal bleeding. Apart from the endometrial thickness, the presence of intrauterine fluid and depth of invasion, some other sonographic features

Infiltration using Final Histopathology As Gold Standard

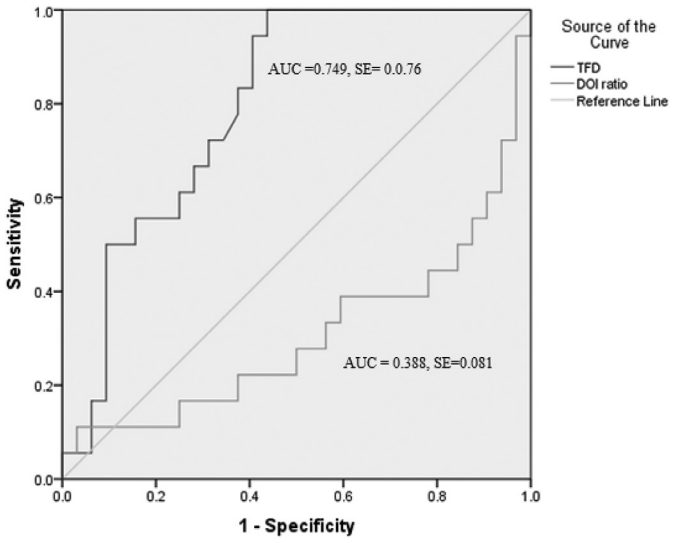

Figure 1. Receiver's Operating Curve Generated by TFD and DOI Ratio Accuracy in Predicting >50% Myometrial

associated with endometrial cancer are the heterogeneity and the presence focal or isolated endomyometrial lesions. Lymph node metastases can be predicted by measuring the depth of myometrial infiltration and as well as with cervical extension. Superficial invasion of the myometrium has a risk of 3% for nodal metastases and this will increase to up to 40% with deeper invasion.[9] Among the 49 patients with endometrial cancer in this study, there were only 3 who have had nodal involvement {stage IIIC-1(2), III-C2 (1)}, 2 with >50% myometrial invasion and 1 with <50%.

This prospective validation study aimed to test the validity of 2D transvaginal ultrasound measuring the tumor free distance and the depth of myometrial invasion using histopathology result as the gold standard. The study involved 49 patients with the diagnoses of endometrial cancer through biopsy and admitted for elective surgery and surgical staging at the Philippine General Hospital from October 1, 2016 to February 28, 2017.

Based on the findings of this study, the 2D transvaginal ultrasound for myometrial infiltration demonstrated 94.4% sensitivity and 43.8% specificity in detecting <50% and >50% infiltration wherein a likelihood of >50% assessment in TVS would likely to occur by 1.68 times time higher than those with <50% based on the final histopathology results. Moreover, the predictive values of TVS were as follows, namely, 48.6% positive and 93.3% negative predictive values, with an overall accuracy of 62%. Two of the previous studies by Arko et al (2000)[33] and Berretta et al (2008)[34] have a sensitivity of 79% and 62%, specificity 69% and 79%, positive predictive value of 63% and 54%, negative predictive value of 83% and 82%, accuracy of 73% and 73%, respectively. This study had a higher sensitivity and negative predictive values, but with much more lower specificity, positive predictive value and accuracy. (Table 13)

A more recent similar study by Fischerova D et al, (2014)47 (n=210) showed a sensitivity of 79.3 (69.3 - 87.3), specificity 73.2 (64.4 - 80.8), PPV 67.6 (57.7 - 76.6), NPV 83.3 (74.9 - 89.8) and accuracy 75.7 (69.3 - 81.4).

Another local retrospective study comparing the accuracy of the DOI, % MI (myometrial invasion) and TFD by Datu and Bustamante (2014)44 (n=97), the DOI sensitivity of 65.1%, specificity of 32.4%, PPV of 64.1%, NPV of 33.3% and accuracy of 53.6%, while for the TFD the sensitivity was 59.7%, specificity of 36%, PPV of 72.9, NPV of 23.7 and accuracy of 53.6%. Comparing with the previous studies, there is no concordance with our results, this might be brought about by the lower number of patients included in this paper.

To maximize the balance between sensitivity and specificity in predicting disease recurrence, Lindauer et al (2003)32 and Schwab et al (2009)[4] used a TFD cut off value of 10 mm. Both of these studies measured TFD in gross specimen with a median follow up of 2.4 and 2.7 years respectively. With these, the negative predictive value of TFD is 95%. This would put the tumor free distance (TFD) as a reasonable unit to measure tumor invasion in endometrial adenocarcinoma.[32] Mascilini et al. (2013)[37], compared the diagnostic accuracy between subjective and objective ultrasound measurements and reported a minimal tumor free margin cut off of 7.1mm, with a sensitivity of 85% and specificity of 50%. This study showed a bit higher cut off value of 8.2mm for which the tumor free distance (TFD), will give a sensitivity of 100%, specificity of 46.9%, positive predictive value of 51.4% and a negative predictive value of 100%. The depth of invasion (DOI) ratio of 0.50 cut off value which initiated increase sensitivity of 16.7% and a specificity of 75% in predicting >50% infiltration. (Table 14)

Further results of this study revealed that the common profiles of patients with endometrial cancer were as follows, average age of 52.14 years old, 70% were multigravidas as well as multiparities (70%), with average BMI of 25.69, 48% were overweight, 50% with cancer Grade 2, average menarche of 13.21 years old, average menopause age of 49.26 years old, and co-morbidities such as hypertension (30.2%), with family history of cancer (18.6%), and with diabetes (9.3%).

In the Geels YP et al (2012)10 study, involving 335 patients with endometrioid type endometrial cancer, the median age was 64 years old (ranging 24 - 93 years old) and with a mean BMI of 28.1 kg/m2 (ranging from 18.4 - 65 kg/m2). As to the cancer Grade, Grade 1 (42.2%), Grade 2 (40.6%) and Grade 3 (17%). For FIGO Staging, majority of patients were of the Stage I-A and I-B comprising 85.6% (287/335) as opposed to this study with Stages I-A and I-B comprises 59.2% (29/49), we have a much lower BMI with a mean of 25.73 kg/m^2. This data also showed that majority of the patients about 73.5% (36/49) were less than 60 years old with a mean age of 52.14 years old.

Fischerova et al (2014)[47], have pointed out that the BMI, position of the uterus and the quality of images does not significantly affect the errors incurred during the evaluation of myometrial involvement. Myometrial invasion was overestimated by ultrasound (false positive estimation of deep invasion ≥50%) in 15.7% (33/210 of cases) and found out that the factors responsible for overestimation were: increase in tumor volume, more thickened endometrium, thinned - out normal myometrium, high vascularity of the tumor and a tumor Grade ≥ 2 postoperative histopath result. Compared with this study, overestimation of myometrial invasion >50% was 34.7% (17/49 of cases) and majority 82.4% (14/17) were of Grade ≥ 2, that is congruent with the study of Fischerova et al.[47]

Table 13. Showing the comparison of Current study with Previous Studies, According to the Method, Sensitivity, Specificity, PPV, NPV and Accuracy

Study	Method used	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)
Current study (2017) (n=49)	TFD DOI (0.50) <50%and >50% myometrial infiltration	94.4 16.7	43.8 75.0	48.6 27.3	93.3 61.5	62
Fischerova et al. (2014) (n=210)	Subjective assessment of myometriaal invasion using ultrasound (pros)	79.3	73.2	67.6	83.3	75.7
Datu and Busta-mante (2014) (n=97)	DOI TFD (retro)	65.1 59.7	32.4 36	64.1 72.9	33.3 23.7	53.6 53.6
Berretta, Merisio and Piantelli (2008) (n=75)	GORDON (retro)	62	79	54	82	73
Arko and Takac (2000) (n=120)	TFD and DOI (pros)	79	69	63	83	73

Table 14. Comparison of TFD Cut off Values Accuracy Performance using ROC Curve Index between the Current Study vs Jaina Lindauer et al (2003), Katherine Schwab et al (2009) and F. Mascilini Findings

Study	Population	TFD Cut off value (cm)	ROC Curve value	Remarks
Jaina Lindauer et al (2003)	(n=153)	≤ 1.0	0.760	Clinically acceptable accuracy
Katherine Schwab et al (2009)	(n=99)	≤ 1.0	0.649	Clinically acceptable accuracy
F Mascilini et al (2013)	(n=144)	0.71	0.780	Clinically acceptable accuracy
Currrent Study (2017)	(n=49)	0.82	0.760	Clinically acceptable accuracy

In the Philippines, endometrial cancer is the third most common cause of malignancy affecting the female reproductive tract, following cervical and ovarian cancers. Most cases involved in the study were younger and seen in a more advance state of disease. This could be attributed to poverty, lack of facilities that provide earlier diagnosis and intervention as well as the lack of knowledge regarding the disease entity.

CONCLUSION

Transvaginal ultrasound is a useful diagnostic tool that is safe, easy to use and with reproducible results, affordable and readily available even in the less fortunate areas.

Assessment of myometrial infiltration by measuring the tumor free distance (TFD) and depth of invasion (DOI) through 2D transvaginal ultrasound among patients with endometrial cancer demonstrated clinically acceptable accuracy wherein its sensitivity is higher or detecting >50% myometrial infiltration. TFD is easier to perform and can be ideal measurement technique in low resource areas where advancement in ultrasound technology may be remote.

Furthermore, a TFD cut off value of 0.82cm and below generated higher sensitivity (46.88%) and specificity (100%) in predicting myometrial infiltration of >50% while a DOI ratio of 0.50 is the cut off value which initiated increase sensitivity (16.7%) and higher specificity (75%) in predicting >50% infiltration.

Only TFD measurement generated a clinically acceptable accuracy in predicting >50% myometrial infiltration while DOI ratio yielded poor accuracy in predicting >50% infiltration. Based on standardized index, an AUC of 0.70 is considered a clinically acceptable diagnostic tool.

The limitation of the study is the lack of the number of patients seen and operated during the study period.

This study features the validity of ultrasound preoperative evaluation of myometrial involvement using histopathology findings as gold standard. This will help in the preoperative evaluation of endometrial cancer patients and for a more planned intervention.

RECOMMENDATION

Since the 2D transvaginal ultrasound can predict >50% myometrial infiltration among patients with endometrial cancer, the researcher would like to recommend the following:

- For the sonologist, the tumor free distance can be used as an alternative measurement tool

- A larger prospective study is warranted to test for the validity of the tumor free distance (TFD) as an alternative measurement to determine its value in clinical practice

- As a health care provider, impart to patients, Filipino women as a whole the increase awareness of the symptomatology of endometrial cancer and provide an easy access of health care facilities to help reduce the occurrence of advance stage disease when first diagnosed.

REFERENCES

1. ACOG Practice Bulletin No. 149. Endometrial Cancer. American College of Obstetricians and Gynecologists. *Obstet Gynecol*. April 2015: Vol. 125, NO. 4. 1006-1026.

2. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: GLOBOCAN 2012.

3. SGOP Clinical Practice Guidelines for the Obstetrician-Gynecologist. 2nd ed. Nov 2015.

4. Schwab KV, O'Malley DM, Fowler JM, Copeland LJ and Cohn DE (2009). Prospective evaluation of prognostic significance of the tumor-free distance from uterine serosa in surgically staged endometrial adenocarcinoma. *Gynecol Oncol*. 112:146-149.

5. "SEER Cancer Statistics Review 1975-2008," National Cancer Institute, 2011.

6. Bonadona V, Bonaiti B, Olschwang S, Grandjouan S, Huiart L, Longy M, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. French Cancer Genetics Network. *JAMA*. 2011; 305:2304-10.

7. Gierisch JM, Coeytaux RR, Urrutia RP, Havrilesky LJ, Moorman PG, Lowery WJ, et al. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. *Cancer Epidemiol Biomarkers Prev.* 2013; 22:1931-43.

8. Boronow RC, Morrow CP, Creasman WT, et al. Surgical staging in endometrial cancer: clinical-pathologic findings of a prospective study. *Obstet Gynecol*. 1984; 63:825-32

9. Plataniotis G, Castiglione M (2010). Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 21 (Supplement 5): v41-v45, 2010doi:10.1093/annonc/mdq245.

10 Geels YP, Pijnenborg JM, van den Berg-van Erp SH, Snijders MP, Bulten J, Massuger LF. Absolute depth of myometrial invasion in endometrial cancer is superior to the currently used cut-off value of 50%. *Gynecologic Oncology.* 2013; 129:285-91.

11. Creasman W. Revised FIGO staging for carcinoma of the endometrium. *Int J Gynaecol Obstet*. 2009; 105:109.

12. Sorosky JI (2008). Endometrial cancer. *Obstet Gynecol*. 111:436-447.

13. Geels YP, Pijnenborg JM, van den Berg- van Erp SH, Bulten J, Visscher DW, Dowdy SC,et al. Endometrioid endometrial carcinoma with atrophic endometrium and poor prognosis. *Obstet Gynecol*. 2012; 120(5):1124-31 [Epub 2012/10/24].

14. Dijkhuizen FP, Mol BW, Brolmann HA and Heintz AP (2000). The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis. *Cancer.* 89:1765-1772.

15. American Cancer Society. Cancer Facts and Figures, American Cancer Society , New York, NY, USA, 2012.

16. Walker JL, Piedmonte MR, Spirtos NM, Eisenkop SM, Schlaert JB, Mannel RS, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. *J Clin Oncol*. 2009; 27:5331-6.

17. Janda M, Gebski V, Brand A, Hogg R, Jobling TW, Land R, et al. Quality of life after total laparoscopic hysterectomy versus total abdominal hysterectomy for stage I endometrial cancer. (LACE): A randomised trial. *Lancet Oncol* .2010; 11:772-80.

18. Erkanli S, Ayhan A. Fertility - sparing therapy in young women with endometrial cancer: 2010. *Int J Gynechol Cancer*. 2010; 20:1170-87.

19. Chao AS, Chao A, Wang CJ, Lai CH, Wang HS. Obstetric outcome of pregnancy after conservative treatment of endometrial cancer: case series and literature review. Taiwan *J Obstet Gynecol*. 2011; 50:62-6.

20. Barwicka TD, Rockalla AG, Bartonb DP, Sohaibc SA. Imaging of endometrial adenocarcinoma. *Clinical Radiology*. 2006; 61:545-555.

21. O'Connell LP, Fries MH, Zeringue E, Brehm W. Triage of abnormal postmenopausal bleeding: a comparison of endometrial biopsy and transvaginal sonohysterography versus fractional curettage with hysteroscopy. *Am J Obstet Gynecol*. 1998; 178:956-61.

22. Gull B, Karlsson B, Milsom I, Granberg S. Can ultrasound replace dilatation and curettage? A longitudinal evaluation of postmenopausal bleeding and transvaginal sonographic measurement of the endometrium as predictors of endometrial cancer. *Am J Obstet Gynecol*. 2003; 188:401-8.

23. Savelli L, Ceccarini M, Ludovisi M, Fruscella E, De Iaco PA, Salizzoni E, Mabrouk M, Manfredi R, Testa AC, Ferrandina G, Preoperative local staging of endometrial cancer: transvaginal sonography vs. magnetic resonance imaging. *Ultrasound Obstet Gynecol*. 2008; 31:560-566.

24. Luomaranta A, Leminen A, Luokovaara M, Magnetic resonance imaging in the assessment of high risk features of endometrial cancinoma. A meta-analysis. *Int J Gynecol Cancer.* 2015; 25:837-842.

25. Lubusky M, et al. Preoperative assessment of myometrial invasion in Endometrial Cancer patients by Ultrasonography and MRI. *Ceska Gynekol*. 2006 Sept; 71(5):394-8.

26. Creutzberg CL. Lymphadenectomy in apparent early-stage endometrial carcinoma: do numbers count? *J Clin Oncol*. 2005; 23:3653-5.

27. Kinkel K, Kaji Y, Yu KK, et al. Radiologic staging in patients with endometrial cancer: a meta-analysis. *Radiology*. 1999; 212:711-8.

28. Cacciatore B, Lehtoverta P, Wahlstrom T, Ylanen K, Ylostalo P. Contribution of vaginal scanning to sonographic evaluation of endometrial cancer invasion. *Acta Oncol*. 1989; 28:585-588.

29. Alcazar JL, Orozco R, Martinez-Astorquiza Corral T, Juez L, Utrilla-Layna J, Minguez JA and JJurado M. Transvaginal ultrasound for preoperative assessment of myometrial invasion in patients with endometrial cancer: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2015; 46:405-413.

30 Gordon AN, Fleischer AC, Reed GW. Depth of myometrial invasion in endometrial cancer: preoperative assessment by transvaginal ultrasonography. *Gynecol Oncol*. 1990; 39:321-327.

31. Karlsson, A Norstrom, S Granberg, Wikland M. The use of endovaginal ultrasound to diagnose invasion of endometrial carcinoma. *Ultrasound Obstet Gynecol*. 1992; 35-39.

32. Lindauer J, Fowler JM, Manolitsas TP, Copeland LJ, Eaton LA, Ramirez NC, et al. Is there a prognostic difference between depth of myometrial invasion and the tumor-free distance from the uterine serosa in endometrial cancer? *Gynecol Oncol*. 2003; 91:547-51.

33. Arko D and Takac I (2000). High frequency transvaginal ultrasonography in Preoperative assessment of myometrial invasion in endometrial cancer. *J Ultrasound Med*. 19:639-643.

34. Berretta R, Merisio C, Piantelli G, Rolla M, Giordano G, Melpignano M and Nardelli GB (2008). Preoperative transvaginal ultrasonography and intraoperative gross examination for assessing myometrial invasion by endometrial cancer. *J Ultrasound Med.* 27:349-355.

35. Karat-Pektas M, Gungor T and Mollamahmutoglu L (2008). The evaluation of endometrial tumors by transvaginal and Doppler ultrasonography. *Arch Gynecol Obstet*. 277:495-499.

36. Alcazar JL, Galvan R, Albela S, Martinez S, Pahisa J, Jurado M, Lopez-Garcia G. Assessing Myometrial Infiltration by Endometrial Cancer: Uterine Virtual Navigation with Three-dimensional US. Radiology. 2009 March; 250:3.

37. F Mascilini, AC Testa, C Van Holsbeke, L Ameye, D Timmerman and E Epstein. Evaluating myometrial and cervical invasion in women with endometrial cancer: comparing subjective assessment with objective measurement techniques. *Ultrasound Obstet Gynecol.* 2013; 353-358.

38. Savelli L, Testa AC, Mabrouk M, Zannoni L, Ludovisi M, Seracchioli R, Scambia G and De Iaco P (2012). A prospective blinded comparison of the accuracy of transvaginal sonography and frozen section in the assessment of myometrial invasion in endometrial cancer. *Gynecol Oncol*. 124:549-552.

39. Ortoft G, Dueholm M, Mathiesen O, Hansen ES, Lundorf E, Møller C, Marinovskij E and Petersen LK (2013). Preoperative staging of endometrial cancer using TVS, MRI, and hysteroscopy. *Acta Obstet Gynecol Scand*. 92:536-545.

40. Ozlem Ozbilen, Derya Kilic Sakarya, Incim Bezircioglu, Burcu Kasap, Hakan Yetimalar, Seyran Yigit. Comparison of Myometrial Invasion and Tumor Free Distance from the Uterine Serosa in Endometrial Cancer. *Asian Pac J Cancer Prev.* 2015; 16(2)519-522.

41. San Juan F, Manabat M, Limson G and Manalo A. A preoperative ultrasound determination of depth of myometrial invasion and cervical involvement in endometrial carcinoma - A preliminary report. *Acta Medica Philippina.*

42. Benavides D, Luna JT and Bustamante LM. The accuracy of ultrasound in preoperative assessment of poor prognostic factors in endometrial carcinoma: a Preliminary report. *The Philippine Journal of Gynecologic Oncology*. 2005; 2:1-10.

43. Espinosa J and Comia L. The accuracy of Transvaginal Ultrasound in Determining Depth of Myometrial Invasion and Cervical Infiltration among Patient preoperatively diagnosed with Endometrial Cancer: A 5-year Retrospective Review 2011.

44. Datu MM, David-Bustamante LM, Preoperative Sonographic Evaluation of Myometrial Invasion in Endometrial Cancer: A Comparative Study on the Diagnostic Accuracies of Various Measurement Techniques (unpublished).

45. F. P. G. Leone, D. Timmerman, T. Bourne, L. Valentin, E. Epstein, S. R. Goldstein, H.Marret, A. K. Parsons, B. Gull, O. Istre,W. Sepulveda, E. Ferrazzi and T. Van Den Bosch. Terms, definitions and measurements to describe the sonographic features of the endometrium and intrauterine lesions: a consensus opinion from the International Endometrial Tumor Analysis (IETA) group. *Ultrasound Obstet Gynecol*. 2010; 35:103-112.

46. Alcázar JL, Jurado M and López-García G (1999). Comparative study of transvaginal ultrasonography and CA 125 in the preoperative evaluation of myometrial invasion in endometrial carcinoma. *Ultrasound Obstet Gynecol*. 14:210-214.

47. D Fischerova, F Fruhauf, M Zikan, I Pinkavova, R Kocian, P Dundr, K Nemejcova, L Dusek and D Cibula. Factors affecting sonographic preoperative local staging of Endometrial cancer. *Ultrasound Obstet Gynecol*. 2014; 43:575-585