Research Article

Diagnostic Value of Transvaginal Ultrasonography to Determined Degree of Myometrium Invasion in Endometrial Cancer

Nilai Diagnostik Ultrasonografi Transvaginal dalam Menilai Kedalaman Invasi ke Miometrium pada Kanker Endometrium

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Abstract

Objective : : To show transvaginal ultrasound accuracy in determining the degree of myometrial invasion of endometrial cancer within five years in RSCM. Also, to know histopathology characteristics of endometrial cancer according to cell type, degree of invasion, and degree of differentiation of endometrial cancer, within the last five years in RSCM.

Methods : This study is a cross-sectional study with a sample of 82 subjects in January 2011 – December 2016 at RSCM. The data were collected by total sampling from cancer registry Oncology and Gynaecology Division of Obstetrics and Gynecology FKUI-RSCM.

Results : Transvaginal USG diagnostic test in detection invasion has sensitivity, specificity, PPV, and NPV as 78.79%, 50%, 86.67%, 36.36% respectively. For determine degree of myometrial invasion it has sensitivity, specificity, PPV, and NPV as 81.40%, 76.92%, 79.55%, and 78.90% respectively.

Conclusions : Transvaginal ultrasound has better accuracy in determining the degree of invasion compared to detecting myometrial invasion in endometrial cancer. In determining the degree of invasion, its sensitivity and specificity are 81.4% and 76.92%. For detecting any invasion its sensitivity and specificity was only 79.41% and 57.14%. Our study showed that transvaginal ultrasound was an efficient diagnostic tool fo determine further treatment and prognosis in endometrial cancer.

Keywords : accuracy test, HPV DNA, liquid-based cytology, pre-cervical cancer lesion.

Abstrak

Tujuan : *Mengetahui akurasi USG transvaginal dalam menilai invasi miometrium pada kanker endometrium dalam 5 tahun terakhir di RSCM. Serta karakteristik histopatologi berdasarkan tipe, invasi, dan derajat diferensiasi kanker endometrium dalam 5 tahun terakhir di RSCM.*

Metode : *Penelitian potong lintang dengan jumlah sampel 82 subjek pada Jan 2011 – Des 2016 di RSCM. Data dikumpulkan secara total sampling dari registrasi kanker Divisi Onkologi Ginekologi FKUI RSCM dan dilakukan uji diagnostik.*

Hasil : *Uji diagnostik USG transvaginal menilai ada tidaknya invasi memiliki sensitivitas, spesifisitas, NPP, NPN sebesar 78,79%, 50%, 86,67%, 36,36%. Sedangkan hasil uji diagnostik usg transvaginal dalam menilai derajat invasi memiliki sensitivitas, spesifisitas, NPP, NPN sebesar 81,40%, 76,92%, 79,55%, dan 78,90%.*

Kesimpulan : *USG transvaginal dalam menilai derajat invasi lebih baik dibanding menentukan ada tidaknya invasi. Sensitivitas, spesifisitasnya 81,4% dan 76,92% dibanding 79,41% dan 57,14%. Dalam hal ini USG transvaginal dapat digunakan sebagai alat bantu diagnostik efisien dalam menentukan tata laksana dan prognosis kanker endometrium.*

Kata kunci : *kanker endometrium, kedalaman invasi, uji diagnostik, USG transvaginal.*

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INTRODUCTION

Endometrial cancer is mostly suffered by postmenopausal women and in fourth place after breast, lung, and colon cancer. Endometrial cancer is the third most found cancer in Indonesia after cervical and ovarian cancer.[1,2] Early detection is the determinant factor in endometrial cancer and can be done by taking endometrial samples (biopsy and curettage) and imaging examination.[3]

Endometrial cancer imaging has many modalities such as MRI, CT-Scan and Sonography. This imaging purpose is to evaluate the depth of invasion and to determine the prognosis of the disease. This can predict the lymphovascular metastases to determine the next operative management (surgical staging).[4] MRI is considered the best diagnostic tool yet expensive, which has 88-90% sensitivity, 84-88% specificity and 86-90% accuracy in determining the degree of myometrium invasion.[5-7]Another modality is ultrasonography (USG) which is used in Indonesia because it is more applicable (cheaper and easier to use).[2,8] In another study about USG, transvaginal USG (5-9MHz frequency) in determining endometrial cancer <50% and > 50% has 69% sensitivity and 79%, with 73% accuracy rate. Gordon, using 5 MHz probe USG with 25 samples showed 75% in specificity and sensitivity, 76% accuracy.[4] In developing countries like Indonesia, transvaginal USG is the main modality because it is cheaper and easier to use. Diagnostic value in USG to detect the degree of myometrial invasion is still little known.

To determine the transvaginal USG accuracy on assessing myometrium invasion in endometrial cancer cases at RSCM for the last five years. This research is also to assess the characteristics such as demographic factor, the degree of myometrial invasion, cell type (histopathology) and the degree of differentiation in endometrial cancer cases.

METHOD

This research is using diagnostic study with 2x2 table and cross-sectional study design. As an addition, descriptive research using cross-sectional study will be used to determine the proportion of the type of cell (histopathology), the degree of invasion staging, and the degree of differentiation. The subjects of this study were registered patient with endometrial cancer which diagnosed within 1st January 2011 until 31st December 2016. Oncology division had the data written in the medical record at RSCM. Patients with other gynecology malignancy which did not perform hysterectomy were excluded from this research. The researcher took and specifically picked all the data from the medical record using inclusion and exclusion criteria. All the subjects were re-registered in research report form, including menopause status, parity, marital history, contraception history, and the degree of myometrial invasion based in preoperative transvaginal USG and post-operation histopathology examination. The cell type and the stage of cancer differentiation will also be examined histopathologically after the operation. Patient with incomplete data will be tracked down.

All the histopathology data about myometrial invasion degree based on preoperative and postoperative transvaginal USG were input in the 2x2 table, using the diagnostic study. The data were inserted into Power and Sample Size Analysis (PASS) to determine the power and alpha value based on used samples. As an addition, proportion based on the degree of invasion, histopathology type and the degree of differentiation were calculated.

RESULT

There were 82 responders data obtained from the medical record based on cancer registry cases by RSCM Oncology Gynecology division from 2011-2015, which exceeds from the research proposal's sample with 70 samples. Samples were taken using total sampling method considering inclusion and criteria exclusion. The samples then examined for the degree of myometrial invasion based on medical record transvaginal USG data and compared it with the gold standard examination (histopathology).

Table 1. Demographic characteristics

Characteristics	n (%)
Age (mean ± SD)	53.37 ± 11.33
Menopausal age (mean ± SD)	50.14 ± 5.50
Parity status	
Nullipara	26 (31.7)
Primipara	14 (17)
Multipara	32 (39)
Grande multipara	10 (12.3)
Menopausal status	
Pre Menopause	36 (43.9)
Post Menopause	46 (56.1)
Contraception history	
Pill	7 (8.53)
Injection	3 (3.65)
IUD	8 (9.76)
Implant	0
Not using any contraceptive method	64 (78.06)

From 82 samples, endometrial cancer mostly found with myometrial invasion > 50% based on histopathology examination. There were 43 subjects (53,44%) with myometrial invasion > 50% and 23 (28,05%) with myometrial invasion < 50% and 16 (19,51%) with no myometrial invasion.

The most common type of endometrial cancer in the last 5 years in RSCM was endometrioid adenocarcinoma of 76 people (92.68%), the second most common type was clear cell carcinoma type which was found in 3 people (3.66%) and 3 other types with *Endometrial Stromal Sarcoma* (ESS) 2 people (2.45%), and 1 person squamous cell carcinoma (1.22%). In the endometrial type was found to be a type of mucinosa in 1 patient and, adenosquamous in 4 patients. Types of serous papillary carcinomas are not found in this study.

Based on the degree of differentiation of G1 as many as 31 people (37.8%), G2 as many as 33 people (40.24%), G3 as many as 13 people (15.85%) and five other respondents with an unknown degree of differentiation (6.1%).

Table 2. Histopathology Characteristic

Characteristics	n	(%)
Degree of Invasion		
Without Invasion	16	19.51
< 50%	23	28.05
>50%	43	52.44
Histopathology Type		
Endometrioid Adenocarcinoma	76	92.68
Papillary Serous Carcinoma	0	0
Clear Cell Carcinoma	3	3.66
Others		
Endometrial Stromal Sarcoma (ESS)	3	3.66
Squamous Cell Carcinoma	2	2.45
Degree of Differentiation	1	1.22
G1	31	37.80
G2	33	40.24
G3	13	15.85
Unknown (Gx)	5	6.10
Total	82	100

Based on table 2 the characteristics of histopathology examination results based on the depth of invasion in RSCM which found mostly was endometrial cancer with depth of invasion > 50% as much as 53.44% and patients with depth of invasion <50% as much as 28.05%, while there was without invasion as much as 19.51%. The type of endometrial cancer in the last 5 years at RSCM was the most 92.68% endometrioid adenocarcinoma type, the second type of clear cell type was 3.66% and the other 3 respondents were Endometrial Stromal Sarcoma (ESS) 2 people (2.45%), and 1 person squamous cell carcinoma (1.22%). Based on the degree of differentiation of G1 as many as 31 people (37.8%), G2 as many as 33 people (40.24%), G3 as many as 13 people (15.85%) and five other respondents unknown degree of differentiation (6.1%).

Table 3. Diagnostic Value of Transvaginal Ultrasound to determine the Presence of Myometrial Invasion in Endometrial Cancer cases

Ultrasound Degree of Invasion(pre-operative)	Histopathology Invasion (Postoperative)		
	Presence	Absence	Total
Presence	52	8	60
Absence	14	8	22
Total	66	16	82

Sensitivity	: 78.79 % (95% CI 66.98– 87.89%)
Specificity	: 50 % (95% CI 24.65 – 75.35 %)
Positive Predictive Value	: 86.67 % (95% CI 79.67– 91.51%)
Negative Predictive Value	: 36.36 % (95% CI 22.53 – 52.89 %)
Positive Possibility Ratio	: 1.58 (95% CI 0.95 – 2.61)
Negative Possibility Ratio	: 0.42 (95% CI 0.22 – 0.83)

Table 4. Diagnostic Value of Transvaginal Ultrasound in todetermine theDegree of Myometrial Invasion in Endometrial Cancer cases

The Degree of Invasion based on USG examination (Preoperative) (%)	Histopathology Invasion (Postoperative)		
	>50%	<50%	Total
>50	35	9	44
<50	8	30	38
Total	43	39	82

Sensitivity	: 81.40 % (95% CI 66.60– 91.61 %)
Specificity	: 76.92 % (95% CI 60.67 – 88.87 %)
Positive Predictive Value	: 79.55% (95% CI 68.30– 87.53%)
Negative Predictive Value	: 78.95 % (95% CI 66.23 – 87.76%)
Positive Possibility Ratio	: 3.53 (95%CI 1.95 – 6.37)
Negative Possibility Ratio	: 0.24 (95% CI 0.13 – 0.46)

DISCUSSION

This study managed to get a total of 82 subjects. Based on our medical records on patients who have radiation or chemotherapy outside, with other gynecological malignancies, or no hysterectomy before which was not included in this study because it may affect the result of examinations. For transvaginal ultrasound examinations used in this study is Voluson E8 with transvaginal probes EC4-9ES with 4-9 MHz frequency The result of ultrasound examinations in this study can be considered valid if the USG tools were calibrated every year and used by experts who are competent in their field.

Based on menopausal status, endometrial cancer more likely found in menopause age (56.1%) compared to premenopause (43.9%). Based on demographic data that we obtained in this study showed that the mean age of endometrial cancer diagnosis at RSCM was 53 years, and menopause means age was 50 years. When viewed based on menopausal status, endometrial cancer more common in menopausal age patient (56.1%) than pre-menopause (43.9%). We obtained menopausal age same as mean menopausal age based on BKKBN data in 2015 that is 50 years. This different from SOGC data in 2013, which only 10-15% cases of endometrial cancer are found at premenopause age. This difference may be due to we do not control the risk factor, such as BMI and lifestyle, history of patient illness that may be a risk factor for endometrial cancer such as PCOS.[3,4] Our data showed multiparous patient had more than nulliparas because we do not seek another risk factor in these multipara patients and for two to four parity grouped as multiparous.

Other demographic data on contraceptive use in accordance with studies that stated contraceptive use decreases estrogen exposure and increases progesterone levels in women and has a protection effect.[9,10]Most of endometrial cancer cases found in subjects without history of contraception used 78.06% and least in women with a family history of hormonal contraceptives (8.53% pill or injection 3.65%). This study did not seek further effects of these risk factors on the endometrial cancer incidence, but only provides an overview of the spread of risk factors.

Based on the cancer register study in the last five years at RSCM, most cases were invasive. There were 52.44% cases with the invasion to endometrium depth >50%, 28.04% cases with <50% endometrium invasion and 19.51% cases with no invasion. Although most cases are endometrioid types with slow progress than other types of endometrial cancers, most finding, in this case, involves more than 50% of invasion. Like wise, in the degree of differentiation, G1 is more commonly found with less than one third of invasion in the myometrium.10 This may be due to the late diagnosis of endometrial cancer, which may be influenced by factors that will not be discussed further.

Based on cancer type, the incidence of endometrial cancer type 1 or endometrioid estrogen dependent is in the first place (92.68%). The second most common type is the clear cell type of 3.66%. Based on this study, no serous papilosa type was found in endometrial cancer patients at RSCM in the last five years.

The data is slightly different from the study in Turkey who acquired the endometrioid type as much as 87%, while the other type that is found is papillary serosa carcinoma of 7% not found in the last five years study data at RSCM. In the previous study, the percentage of clear cell types was not much different from the data we got as much as 2%. Histopathological study data from 432 patients in the Netherlands in 2013 showed the highest non endometrioid type was 7.6% paposa serosa not found in RSCM, in which case the possibility of races affected the incidence of this cancer.[11] More than 85% of endometrial cancers are endometrioid types of estrogen dependent. Risk factors for this type are long-term estrogen exposures.[9] Long-term estrogen exposure is also consistent with the findings of most endometrial cancer at menopause as much as 56.10% compared with premenopause.[9]

Based on the data, the endometrioid type for G1, G2 and G3 are 26%, 28%, and 10% from all cases. There was no estrogen receptor with a high differentiated degree and advanced stage on clear cell type. This data was fit with this study,

which showed only G3 differentiation staging and undifferentiated cases. ESS incidence was 1% and based on the histopathogenesis, long exposure estrogen and PCOS can not be conclusive to define as a risk factor for ESS. Undifferentiated cases on this tumor were not based on mitosis phase but based on pleomorfism and core necrosis. This statement fits with ESS characteristics in another study which had 2 subjects with undifferentiated stage ESS (Gx). Most of the endometrioid cases were found with stage 1 and 2 differentiation which had a good prognosis.[12]

The main objective of this study is to obtain the diagnostic value of transvaginal ultrasonography and to obtain sensitivity, specificity, positive predictive value, the negative predictive value of transvaginal ultrasound are 78.79%, 50%, 86.67% and 36.36%. Most of the studies which we found, did not differentiate between invasive findings and less than half of myometrium because of the risk of lymph nodes involvement was considered to be the same and did not affect the staging and management.[13] However, in the case of no myometrial invasion there was no pelvic lymph node metastase, whereas in the case of myometrial invasion although less than one-third of myometrial thickness, there were 3-9% pelvic lymph node metastases.[9] In addition, it affects the incidence of distant metastases. In patients who did not undergo a myometrial invasion, only 4.3% whereas if the invasion was found <50% the depth of myometrium is 10-11%. In this case, invasion finding although <50% based on transvaginal ultrasound may be considered for screening for distant metastases and operator accuracy in assessing intraoperative lymph node spreading.

Transvaginal ultrasound in assessing the myometrial depth of invasion >50% has sensitivity, specificity, positive predictive value, negative predictive value, and accuracy 81.40%, 76.92%, 79.55%. moreover, 82.69%. Based on the meta-analysis in 2014, the sensitivity and specificity og transvaginal ultrasound in assessing the depth of invasion is 82% and 81%. The different diagnostic value may be due to fewer sample sizes or due to the differences of endometrial depth measurement techniques with transvaginal ultrasound in ultrasonogrpaher that is different from each other in this study and previous studies.[13]

Our study shows that ultrasound can be a screening tool to see the invasion, because of its good sensitivity, but insignificant in determining the stage and prognosis. Based on this result, the use of transvaginal ultrasound can not be the only option to select the extensive candidate of operative patients.

In using transvaginal ultrasound, it is necessary to note the risk factors, type, and stage of invasion to be a diagnostic tool in determining the next procedure and patient prognosis.

The use of transvaginal ultrasound in assessing the stage of invasion can be a good and efficient diagnostic tool in preoperative assessment. However, the assessment of depth of invasion can nto be sparated from the assessment of the type of cancer and degree of differentiation in determining stage and prognosis. The disadvantage of this study is the incompleteness of medical record that allows for exclusion criteria of circumstances that allow for the occurrence of a false negative number that will affect the sensitivity and false positive numbers that will affect the specificity number. The absence of control throughout the preoperative assessment of transvaginal ultrasound by operative hysterectomy became the weakness of this study. In addition, Kappa test control is not performed to see the equivalence of ultrasound operators, whereas ultrasound diagnostic tools are highly operator dependent.

CONCLUSION

The accuracy of transvaginal ultrasound obtained from this study is not much different from other studies conducted in other countries. However, in this study obtained ultrasound accuracy in assessing the depth of invasion of endometrial cancer is better than determining the presence or absence of invasion. In this case, transvaginal ultrasound can be used as an efficient diagnostic tool in determining the management and prognosis of endometrial cancer. Based on the invasion of the incidence of endometrial cancer with invasion>50% is the most found in RSCM in 2011-2016 as much as 52.44%. Based on the type of histopathology, the most incidence of endometrial cancer is endometrioid type as much as 92.68%. Based on the degree of differentiation of the incidence of endometrial cancer in RSCM is G2 of 40.24%.

This cross-sectional study with a limited sample needs to be considered for further research, especially by performing a transvaginal ultrasound equivalent examination in assessing invasion by the same expert to avoid any bias between examiners. Moreover, as a transvaginal ultrasound diagnostic tool in assessing the depth of invasion needs to be combined with findings of differentiation and cell type degrees to determine prognosis.

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