

Research Article

A Simple Ultrasound Examination as Diagnostic Tool for Malignant Ovarian Tumor

Pemeriksaan Ultrasonografi Sederhana sebagai Alat Diagnostik Tumor Ovarium Ganas

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Abstract

Objective: To know the diagnostic value of simple ultrasound examination to detect malignant ovarian tumor.

Method: This study used cross-sectional design in gynecology outpatient clinic at Dr. Cipto Mangunkusumo Hospital. We recruited the patients with ovarian tumor undergoing surgery between March and July 2015. Samples were taken using consecutive sampling. Analysis was done using Chi-square test and logistic regression to find the relationship between ultrasound morphologic patterns with histopathologic findings, where the significant relationship was p value less than 0.05. Furthermore, a model derived from logistic regression was made to calculate the probability having ovarian malignancy.

Result: There were 80 subjects which 58 subjects (72.5%) had benign tumor and 22 subjects (27.5%) had malignant tumor. Ultrasound examination result using ≥ 2 morphologic patterns gave malignant result in 53.8% subjects with the sensitivity of 100%, specificity of 82.8%, positive predictive value of 68.8%, and negative predictive value of 100%. The most important patterns were irregular internal cyst wall, multilocular, presence of papillary projection, and presence of solid component. The probability of subject having ovarian malignancy with ≥ 3 morphologic patterns was more than 88.9%.

Conclusion: Simple ultrasound examination can be used to detect malignant ovarian tumor.

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Keywords: diagnostic, histopathology, morphology pattern; ovarian tumor; ultrasonography

Abstrak

Tujuan: Mengetahui nilai diagnostik pemeriksaan ultrasonografi sederhana dalam menilai keganasan tumor ovarium dibandingkan hasil histopatologi pascaoperasi.

Metode: Penelitian ini merupakan studi potong lintang pada pasien tumor ovarium di poliklinik Ginekologi RSCM Jakarta yang dilakukan operasi pada bulan Maret-Juli 2015. Sampel penelitian diambil dengan metode consecutive sampling. Analisis menggunakan uji Chi-square dan regresi logistik untuk mencari hubungan antara pola morfologi ultrasonografi dengan hasil histopatologi di mana terdapat hubungan bermakna apabila nilai $p < 0,05$. Selain itu, dibuat model persamaan dari regresi logistik untuk menghitung probabilitas.

Hasil: Terdapat 80 subjek penelitian di mana 58 subjek (72,5%) dengan tumor jinak dan 22 subjek (27,5%) dengan tumor ganas. Hasil ultrasonografi dengan pola morfologi ≥ 2 menunjukkan hasil ganas pada 53,8% subjek dengan nilai diagnostik sensitivitas 100%, spesifisitas 82,8%, nilai duga positif 68,8%, dan nilai duga negatif 100%. Pola morfologi yang paling berpengaruh terhadap keganasan tumor ovarium adalah permukaan dalam dinding kista reguler, multilokular, terdapat penonjolan papiler, dan ada bagian padat dalam tumor. Probabilitas subjek mendapat tumor ganas apabila memiliki pola morfologi ≥ 3 adalah lebih dari 88,9%.

Kesimpulan: Pemeriksaan ultrasonografi sederhana dapat digunakan untuk mendeteksi keganasan tumor ovarium.

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Kata kunci: diagnostik, histopatologi, pola morfologi, tumor ovarium, ultrasonografi

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INTRODUCTION

Ovarian cancer is the fourth rank of cancer among women in developed country.¹ In Indonesia, ovarian cancer is the third most often malignancy in women after cervical and breast cancer.² Based on the recent world's estimation, there are 204,449 new cases annually, in which it contributes to 124,860 deaths associated with ovarian cancer.³ Ovarian cancer is considered as a silent killer. Five-year-survival rate depends on the stage of can-

cer.^{4,5} Among all gynecology cancers in Indonesia, the death rate of ovarian cancer is around 22.6%. Approximately 42.5% of ovarian cancer patients seek treatment when already in stage II-IV. About 70-80% of advanced stage ovarian cancer has spread widely and goes through metastasis. Five-year-survival rate of ovarian cancer is 72.8% in stage I, 46.3% in stage II, 17.2% in stage III, and only 4.8% in stage IV.⁵

A high mortality rate is due to the difficulty to detect the early-stage of ovarian cancer. Therefore, holistic approach need to be done to reduce mortality. The ovarian cancer can be diagnosed from comprehensive history taking by exploring the symptoms, potential risk factors, and family history.⁶ According to Olson et al. in 2001,⁷ the ovarian malignancies does not present specific complaint and they often misleading with dyspepsia syndrome in primary health care. Furthermore, we should do the physical examination; however, it has poor sensitivity in diagnosing the ovarian cancer around 15-51%.⁶

Ultrasound is the best tool to predict ovarian malignancy with the sensitivity of 80-100%.⁸ Galvan, et al. concluded that ultrasound examination (sensitivity 98.6%; specificity 94.9%) was better than history taking (sensitivity 79.5%; specificity 96.2%) and pelvic physical examination (sensitivity 97.3%; specificity 85.9%).⁹ In order to screen ovarian malignancy, morphological evaluation was performed in accordance to study by Galvan, et al.⁹, Sassone, et al.¹⁰, Ferrazzi, et al.¹¹ International Ovarium Tumor Analysis (IOTA)¹² stated that the criteria to detect the malignant ovarian tumor should be seen from several aspects, such as bilateral symmetry, wall thickness (thin \geq 3mm, thick $>$ 3mm), wall surface (regular/irregular), septation (thin \geq 3mm, thick $>$ 3mm), papillary projection, solid area (not present, present \leq 1x1 cm in internal wall surface), ascites, echogenicity (cystic/solid), acoustic shadow (present/not present), if Doppler examination is available, neovascularization can be examined with resistance index ($<$ 0.41).

Unfortunately, in Indonesia, ultrasound examination has not become a standard procedure in primary health care. In primary health care, ultrasound examination is usually performed to screen obstetric problem not in gynecologic problem. In order to reduce mortality rate of ovarian cancer, screening is necessary in primary health care. This study aims to evaluate the use of simple ultrasound examination in assessing ovarian tumor in Indonesia. In the future, it is expected that ultrasound examination can be a routine diagnostic tool for ovarian cancer screening in primary health care.

METHODS

This study was descriptive analytic with cross sectional design using secondary data from medical

records in Dr. Cipto Mangunkusumo hospital. Samples were taken using consecutive sampling. The inclusion criteria were patients suspected ovarian neoplasm in Dr. Cipto Mangunkusumo Hospital that undergone operative procedure from March to July 2015 and those patients had a complete medical record to be further investigated. Simple ultrasound morphologic patterns analyzed were bilateral symmetry, wall surface, unilocular/multilocular cyst, presence of solid area, and ascites. These simple ultrasound morphologic patterns were compared with the histopathology results post surgery. We excluded the patients if the history data from histopathology and ultrasound examination were not complete, post chemotherapy in advanced stage of ovarian cancer, solid ovarian neoplasm, and dermoid cyst.

The collected data were statistically analyzed with SPSS version 21.0. Analysis was done using Chi-square test and logistic regression to find the relationship between ultrasound morphologic patterns and histopathologic findings. We considered the significant relationship when p value was less than 0.05. We searched for the specificity, sensitivity, positive and negative predictive value, positive and negative likelihood ratio, and the accuracy. Furthermore, a model derived from logistic regression was made to calculate the probability having ovarian malignancy. This study has been approved by the Committee Ethic of RSCM on No. 711/ UN2.F1/ETIK/2015.

RESULTS

There were 101 patients diagnosed with ovarian neoplasm and we excluded 21 patients; therefore, the number of subjects analysed in this study were 80 subjects. The mean age of the subjects was 39.1 (SD 12.4) years old. The age of malignant group was older than benign group (44 vs 36 years old). Forty-five percent of the subjects were nullipara. The commonest symptom felt by subjects was abdominal enlargement (76.3%). The median level of CA-125 was higher in malignant group compared with benign one (247 U/ml vs 127 U/ml).

The histopathology results showed that 27.5% was malignant with mucinous cystadenocarcinoma (10%) at most. While, of the benign group, endometriosis cyst (35%) was the highest prevalence. There was significant relationship between morphologic patterns from ultrasound and histopathology results ($p < 0,001$). If we used ≥ 2 ma-

lignant morphologic patterns found, the sensitivity 100%, specificity 82.8%, positive predictive value (PPV) 68.8% and negative predictive value (NPV) 100%. Whereas, if we used ≥ 3 malignant morphologic patterns, the sensitivity, specificity, PPV, NPV were 77.3%, 89.7%, 73.9%, 91.2%; consecutively.

There was significant relationship between histopathology results and morphologic patterns of ultrasound, such as wall irregularity ($p < 0.001$), multilocular ($p = 0.002$), papillary projection ($p = 0.004$), presence of solid part ($p < 0.001$), and ascites ($p = 0.008$). There was no significant relationship between histopathology result and bilateral symmetry ($p = 0.137$) (shown on Table 1). After all the data had been collected, all variables with p value < 0.25 in the bivariate analysis was inserted to multivariate analysis (shown on Table 2). The result explained that morphologic patterns that influenced the malignancy together were wall irregularity, multilocular, papillary projection, and presence of solid part.

Table 1. Diagnostic Value of Ultrasound Morphologic Pattern.

Morphologic pattern	Diagnostic value							
	P	Sens	Spec	PPV	NPV	LR+	LR-	Accuracy
Uni/bilateral	0.137	54.5%	63.8%	36.4%	78.7%	1.51	0.71	61.3%
Wall surface	<0.001	54.5%	94.8%	80.0%	84.6%	10.55	0.48	83.8%
Locus	0.002	63.6%	74.1%	48.3%	84.3%	2.46	0.49	71.3%
Papillary projection	0.004	31.8%	94.8%	70.0%	78.6%	6.15	0.72	77.5%
Solid area	<0.001	90.9%	77.6%	60.6%	95.7%	4.06	0.12	81.3%
Ascites	31.8%	31.8%	93.1%	63.6%	78.3%	4.61	0.73	76.3%

*Sens = sensitivity

*Spec = specificity

*PPV = positive predictive value

*NPV = negative predictive value

*LR (+) = likelihood ratio (+)

*LR (-) = likelihood ratio (-)

Table 2. Multivariate Analysis of Ultrasound Morphologic Pattern and Histopathology Result

Variable	p value	OR	95% CI
Wall surface	0.010	18.42	2.02 - 167.93
Locus	0.019	10.73	1.47 - 78.37
Papillary projection	0.011	28.37	2.14 - 375.43
Solid area	0.009	23.64	2.19 - 254.73

We got the equation model that obtained from multivariate analysis with
 $y = -6,366 + 2,914* (\text{Irregular of the wall}) + 2,373* (\text{multilocular}) + 3,345* (\text{presence of papillary projection}) + 3,163* (\text{solid area})$

with the probability of each subject having the outcome of ovarian malignancy was calculated by:

$$p = 1/(1 + e(-y))$$

Table 3. Probability of the Subjects to Become Ovarian Neoplasm Correlated with Type and Number of Morphologic pattern

Variable	y	P
(A) Wall irregularity	-3.452	3.1%
(B) Multilocular	-3.993	1.8%
(C) Papillary projection	-3.021	4.6%
(D) Solid area	-3.203	3.9%
A + B	-1.079	2.4%
A + C	-0.107	47.3%
A + D	-0.289	42.8%
B + C	-0.648	34.3%
B + D	-0.830	30.4%
C + D	0.142	53.5%
A + B + C	2.266	90.6%
A + B + D	2.084	88.9%
A + C + D	3.056	95.5%
B + C + D	2.515	92.5%
A + B + C + D	5.429	99.6%

Table 3 showed that the greatest probability of the morphologic pattern leading to malignancy; while, if it appeared alone, the highest chance of being ovarian neoplasm was papillary projection (4.6%) followed by solid area (3.9%). If there were 2 morphologic patterns, the probability of malignancy was ranged from 25.4% to 53.3%. If there were 3 morphologic patterns, the probability of malignancy was increased between 88.9% and 95.5%. If the subjects had 4 morphologic patterns, the probability was almost perfect (99.6%).

DISCUSSION

The mean age of the subjects was 39.2 (SD 12.4) years old with the age of malignant group was older than benign group (44 vs 36 years old). The result was similar to study conducted by Yazbek, et al. in King's College Hospital, London. The mean of patient's age with malignancy was 52 years old and the mean of patient's age with benign adnexa tumor was 39 years old.¹³ As in literature, the risk of malignancy in ovarian neoplasm was higher as the increasing of age.

The median of labor history was once (0-5 times) with 45% of them were nullipara. Similar to Goff, et al. study, there were 1,709 subjects; whereas, 48% of them were nullipara.¹⁴ Continuous ovulation associated with nulliparity increases the risk of ovarian malignancy because every ovulation cycle will induce invagination and damage to the surface of epithelial cell.

The commonest symptom was abdominal enlargement (76.3%) in malignant group (95.5%) and benign group (69.0%). This result was similar to Goff, et al. study from 128 women (84 benign tumor and 44 malignant tumor), the most often complaint was bloating (70%) followed by abdominal enlargement (64%).¹⁴ Symptom of ovarian neoplasm was not specific; thus, ovarian malignancy was difficult to detect in early stage.

Level of tumor marker CA-125 in malignant tumor had a median of 247 U/ml; while, the benign tumor was 127 U/ml. Similar result obtained in a retrospective study by Bouzari Z, et al. on 182 women that the level of CA-125 as the tumor marker was higher in cases with malignant ovarian tumor than benign. Bouzari, et al. found that the cut-off point of CA-125 (88 U/ml) would offer the sensitivity of 88%, specificity of 97%, positive predictive value of 84% and negative predictive value of 99%.¹⁵

The histopathology results described that 27.5% was malignant with mucinous cystadenocarcinoma (10%) at most. While from the benign group, endometriosis cyst (35%) was the most often. This result was not much different from Timmerman D, et al. study on 1,066 subjects; 27% of them were malignant.¹²

There was significant relationship ($p < 0.001$) between morphologic patterns from ultrasound and histopathology results. If using ≥ 2 malignant morphologic patterns found that sensitivity, specificity,

positive predictive value (PPV), and negative predictive value (NPV) were 100%, 82.8, 68.8%, 100%; respectively. While finding ≥ 3 malignant morphologic patterns, the sensitivity, specificity, PPV, NPV were 77.3%, 89.7%, 73.9%, 91.2%; respectively. Similar result was obtained in the study by Hafeez S, et al., the sensitivity of ultrasound in detecting ovarian malignancy was 93%, specificity 89%, positive predictive value 91%, negative predictive value 89% and the accuracy reached 91%.⁸

From bivariate analysis, there was significant relationship between histopathology results and morphologic patterns of ultrasound, such as wall irregularity ($p < 0.001$), multilocular ($p = 0.002$), papillary projection ($p = 0.004$), presence of solid part ($p < 0.001$), and ascites ($p = 0.008$). There was no significant relationship between histopathology results and bilateral symmetry ($p = 0.137$). All variables with p value < 0.25 in the bivariate analysis was inserted into multivariate analysis, in which the morphologic pattern that influenced the malignancy were wall irregularity, multilocular, papillary projection, and presence of solid part. Similar result was shown by the study of Timmerman, D et al. which found a significant relationship between morphology patterns from ultrasound in ovarian neoplasm, such as ascites, irregularity of wall, papillary projections, bilateral symmetry, septum, and acoustic shadow and the results of histopathology ($p < 0.01$). A significant relationship was also found in multilocular with solid parts ($p < 0.01$), unilocular with solid parts ($p = 0.02$), multilocular and unilocular without solid part ($p < 0.01$), and the presence of the solid part ($p < 0.01$).¹² This study found that no significant relationship in bilateral symmetry pattern, this was due to many benign tumors in this study had bilateral pattern (63.6%).

In this study, the presence of solid part had the highest sensitivity (90.9%), while the highest specificity was wall irregularity and papillary projection (94.8%). The best positive predictive value was wall irregularity (80%) and the best negative predictive value was presence of solid part (95.7%). The highest accuracy rate was wall irregularity (83.8%). The greatest probability of the morphologic pattern leading to malignancy while appearing alone was papillary projection 4.6% followed by presence of solid part 3.9%. If there were 2 morphologic patterns, the probability of malignancy was ranged from 25.4% to 53.3%. If there were 3 morphologic patterns, the probability

of malignancy was increased between 88.9% and 95.5%. If the subjects had 4 morphologic patterns, the probability was 99.6%. The diagnostic value of morphologic pattern in Timmerman D, et al. study (1,066 subjects with adnexal tumor), found the highest sensitivity was the presence of solid part (91.8%), while the highest specificity was ascites (96.1%).¹² Factors in Timmerman study correlating to ovarian malignancy using logistic regression were age, history of ovarian tumor in family (OR 4.95), diameter of tumor, diameter of solid part, presence of ascites (OR 4.72), presence of blood flow in papillary projection (OR 3.23), presence of solid part (OR 2.53), wall irregularity of the cyst (OR 3.13).^{12,16} In study by Timmerman, et al., they included demographic characteristics and ultrasound result as the malignancy predictor in ovarian neoplasm; meanwhile, in this study, we only recruited the ultrasound patterns. Based on that, we found similar result where the presence of solid components and irregular internal wall surface of the cyst tended to malignancy.¹⁶

CONCLUSION

In order to reduce mortality rate of ovarian cancer, screening is necessary in primary health care. Simple ultrasound examination is a great diagnostic tool which has high sensitivity and specificity in diagnosing ovarian malignancy

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