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The Presence of Ascites and Irregular Tumor Surface as Strong Predictors for Ovarian Malignancy

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Abstract

BACKGROUND: Ovarian cancer is the most dangerous gynecologic cancer and one of the top five causes of cancer death in women. One of the intraoperative strategies to diagnose and manage women with ovarian cancer is by doing intraoperative frozen section examination during surgery, but not all hospitals in Indonesia have this facilities, thus makes it difficult to achieve intraoperative diagnosis, which lead to substandard management of patients with ovarian cancer.

AIM: The purpose of this study is to investigate if one can determine whether an ovarian tumor is benign or not based on the gross appearance of the tumor.

METHODS: This study is a comparative, analytic, and cross-sectional study to compare the results of operator's assessment with the results of intraoperative frozen section examination in determining malignancy during surgery. After the tumor was removed, it was assessed by operator based on the gross appearance of the tumor whether the tumor was benign or not, then the tumor underwent frozen section examination, and based on the frozen section examination results, the patient was treated accordingly. Both of the results then compared to the histopathologic (paraffin block) results, as the gold standard of pathologic diagnosis.

RESULTS: This study shows that variables ascites, tumor seedings, tumor surface, tumor consistency, tumor lobes, and lymph node enlargement are statistically significant ($p < 0.05$). The combinations of highly significant variables ($p < 0.01$) show that a combination of ascites and irregular tumor surface give the suggestions that an ovarian is highly likely a non-benign tumor.

CONCLUSION: In the absence of intraoperative frozen section examination in a hospital, operator's assessment based on gross appearance of the tumor can be used as a substitute for intraoperative frozen section examination to determine the malignancy of an ovarian tumor during surgery.

Introduction

Ovarian cancer is the most dangerous type of gynecologic cancer and is one of the top five causes of cancer death in women. Ovarian cancer affects 1.3% of the female population of all ages, generally diagnosed at the age of 55–64 years when entering the menopause phase. Only about 45% of women with ovarian cancer survive 5 years or more after diagnosis. One of the good prognostic determinants is diagnosis as early as possible [1]. Diagnosis of ovarian cancer is quite difficult to establish at an early stage because there are no specific symptoms. Ovarian cancer is only detected at an advanced stage where the patient begins to complain of various symptoms such as ascites, indigestion, and abdominal pain [2]. To establish a diagnosis, a proper history, physical examination, and supporting examinations such as CT scan, ultrasound, tumor markers, and biopsy are required [3].

The definitive therapy for ovarian cancer is surgery [4]. In surgical procedures, gynecologists may find masses in the ovarian area unexpectedly, with suspicion of malignancy, frozen section examination can be a reliable guide so as to minimize the possibility of overtreatment or undertreatment that may require other operative procedures [5]. In diagnosing benign tumors, frozen section examination can reach 95% sensitivity and 100% specificity, as well as 90% sensitivity and 97% specificity in diagnosing malignant tumors. However, this examination only has a sensitivity value of 75% and specificity 94% in diagnosing borderline tumors [6].

Malignant tumors have different gross appearance from benign tumors. In tumors of the

epithelial type, benign tumors are generally unilocular/multilocular cystic gross appearance with regular and thin walls, sometimes transparent, while malignant tumors tend to give a macroscopic picture of a complex mass with solid and cystic sections, with irregular and thick septa [7]. Establishing a definite diagnosis still requires histopathological examination as the gold standard [8].

The problem that occurs in Indonesia is that there are limitations to high quality Histopathological examination access. This is due to inadequate examination facilities, which include: supporting facilities, preparation staff, and pathologists. This condition is exacerbated by the geography of Indonesia, which includes some remote areas, islands, and mountainous areas. Not all hospitals have frozen section facilities, so there is a difficulty in establishing an intraoperative diagnosis [9]. Under these limitations, an operator may only be able to rely on intraoperative clinical judgment in determining an ovarian malignancy and determining the appropriate operative procedure in treating a patient. Therefore, it is worth investigating if one can determine whether an ovarian tumor is benign or not based on the gross appearance of the tumor, which results can be used for optimalization of surgery in hospitals where intraoperative frozen section facilities are absent.

Methods

Design

This study is a comparative and analytical study with a cross-sectional approach to compare the accuracy of operator assessment in determining malignancy with the results obtained from intraoperative frozen section examination in surgical removal of ovarian tumors.

Subjects

The subjects of this study are women who had been diagnosed with ovarian tumor pre-operative and were planned to undergo surgery with intraoperative frozen section examination in Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. Patients that were found to have tumors from organs other than ovarian origins were excluded from the study.

This research was conducted after obtaining approval and recommendation from the Health Research Ethics Committee, Faculty of Medicine, Padjadjaran University, Dr. Hasan Sadikin General Hospital, Bandung, Indonesia.

Data collection

A total of 57 patients with ovarian tumors underwent mass removal surgery and intraoperative frozen sections at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, in the research period. Each subject's characteristic data were recorded from medical records. Intraoperatively, after the abdominal wall is open and the mass is visible, the operator observed the mass, and then based on the gross appearance of the tumor, the following data were recorded on each subject: ascites, adhesions, tumor seeding, tumor bilaterality, tumor surface, tumor consistency, tumor lobes, and enlarged lymph nodes. The surgeon then assessed whether the tumor was a benign or a non-benign tumor, and recorded the data in a form. After that, mass removal procedure (salpingooophorectomy) was conducted. The tumor then was sent for frozen section examination and assessed by the Department of Pathology. The results obtained were notified to the operator and were recorded in the same form as the surgeon's assessment. Tumors with borderline results were included in the non-benign group. Based on the results of the frozen section examination, the surgeon then decides whether to stop the operation or proceed with surgical staging/debulking. The final diagnosis of malignancy will be established from post-operative histopathological (paraffin block) examination as the gold standard for diagnosis.

Results

There were 57 patients eligible as this study subject. Table 1 describes patient characteristics by age, ultrasound results, tumor marker values, and histopathologic results. The average age of the patients was 43.81 ± 13,863 years with the most in the age group 20–49 years as many as 29 patients (50.9%), followed by the age group 50–69 years as many as 23 patients (40.4%), then the age group 11–19 years as many as 4 patients (7.0%), and there was only one patient (1.7%) who was more than 70 years old.

Table 1: Characteristics of the subjects

Variable	N = 57 (%)
Age (years)	
Mean ± SD	43.81 ± 13.863
Median	45.00
Range (min–max)	13.00–73.00
Age group	
11–19 years	4 (7.0)
20–49 years	29 (50.9)
50–69 years	23 (40.4)
≥70 years	1 (1.7)
Ultrasound results	
Malignant	23 (40.4)
Benign	10 (17.5)
Inconclusive	24 (42.1)
Histopathologic results	
Malignant	25 (43.9)
Non-benign	32 (56.1)

Pre-operative ultrasounds were conducted according to IOTA (International Ovarian Tumor Analysis) Simple Rules. For ultrasound results, the results of ultrasound were malignant in 23 patients (40.4%), benign in 10 patients (17.5%), and most of them were included in inconclusive results (42.1%). There were 25 patients (43.9%) with benign histopathologic results and 32 (56.1%) patients with non-benign histopathologic results.

Table 2 describes the variables of tumors gross appearance according to histopathological results. The mean tumor diameter was 23.60 ± 10,766 cm in benign tumors group, and 27.03 ± 10.215 cm in the non-benign group. Ascites was found in 5 patients (20%) of benign group and in 25 patients (78.1%) of the non-benign group. Adhesions occurred in 14 patients (56%) of benign group and in 19 patients (59.4%) of the non-benign group. Tumor seedings were found in 2 patients (8%) of benign group and in 15 patients (46.9%) of the non-benign group. Tumors were bilateral in 4 patients (16%) of benign group and in 8 patients (25%) of the non-benign group. Irregular tumor surfaces were found in 8 patients (32%) of benign group and in 25 patients (78.1%) of the non-benign group. The majority (72.0%) tumors in benign group were cystic tumors, the rest were partially solid cystic tumors (16.0%) and solid tumors (12.0%), while in the non-benign group, the majority of tumors were cystic tumors with solid parts (65.6%) and solid tumors (21.9%), and only 12.5% were cystic tumors. Tumors were multilocular in 13 patients (52%) of benign group and in 25 patients (78.1%) of non-benign group. None of the 25 patients in benign group had enlarged lymph nodes, while lymph node enlargement occurred in 9 patients (28.1%) of the non-benign group.

Table 2: Tumor gross appearance according to histopathologic results

Variable	Histopathologic result		p value
	Benign	Non-benign	
	N = 25 (%)	N = 32 (%)	
Tumor diameter			0.181
Mean ± SD	23.60 ± 10.766	27.03 ± 10.215	
Median	20.00	25.50	
Range (min-max)	8.00–50.00	10.00–60.00	
Ascites			0.0001**
Absence	20 (80.0)	7 (21.9)	
Presence	5 (20.0)	25 (78.1)	
Adhesion			0.798
Absence	11 (44.0)	13 (40.6)	
Presence	14 (56.0)	19 (59.4)	
Tumor seedings			0.0001**
Absence	23 (92.0)	17 (53.1)	
Presence	2 (8.0)	15 (46.9)	
Tumor bilaterality			0.408
Absence	21 (84.0)	24 (75.0)	
Presence	4 (16.0)	8 (25.0)	
Tumor surface			0.0001**
Absence	17 (68.0)	7 (21.9)	
Presence	8 (32.0)	25 (78.1)	
Tumor consistency			0.0001**
Cystic	18 (72.0)	4 (12.5)	
Cystic with solid part	4 (16.0)	21 (65.6)	
Solid	3 (12.0)	7 (21.9)	
Tumor lobes			0.038*
Unilocular	12 (48.0)	7 (21.9)	
Multilocular	13 (52.0)	25 (78.1)	
Lymph node enlargement			0.003*
Absence	25 (100.0)	23 (71.9)	
Presence	0 (0.0)	9 (28.1)	

*p < 0.05, **p < 0.01.

Results of statistical tests show that the variables ascites, tumor seedings, tumor surface, tumor consistency, tumor lobes, and lymph node enlargement are statistically significant (p < 0.05). Thus, it can be explained that an ovarian tumor with these variables is likely to be a non-benign ovarian tumor.

After bivariate analysis, we conducted a multivariate analysis to assess which combination of two variables from the tumor gross appearance that was the most significant in predicting whether an ovarian tumor is a benign or a non-benign tumor. The variables included were the variables that have high significancy (p < 0.001) in the bivariate analysis (ascites, tumor seedings, tumor surface, and tumor consistency). The results are shown in Table 3. Of the six combinations, the most significant combination was the ascites-tumor surface combination. Thus, it can be concluded that there is a strong suspicion that a tumor is a non-benign tumor if the tumor is found to have ascites and an irregular surface.

Table 3: Multivariate analysis combination of two variables gross appearance of tumor

Variables combination	Statistic test (Wald)	p value
Ascites	11.558	0.001*
Tumor seedings	3.677	0.055
Ascites	12.203	0.0001*
Tumor surface	6.274	0.012*
Ascites	11.219	0.001*
Tumor consistency	6.122	0.013*
Tumor seedings	4.282	0.039*
Tumor surface	6.165	0.013*
Tumor seedings	4.245	0.039*
Tumor consistency	6.921	0.009*
Tumor surface	5.813	0.010*
Tumor consistency	6.699	0.016*

*p < 0.05.

Discussions

Intraoperative frozen section examination is a method of histopathological examination of tissues and/or body fluids that acts as the gold standard in establishing a diagnosis. This method helps surgeons in the management of patients with malignancies, including ovarian tumor. Intraoperative frozen section has a fairly high level of sensitivity, specificity, and accuracy in diagnosing the malignancy of a tumor. Intraoperative frozen section assists the surgeon in making a diagnosis and in determining the right surgical procedure for the patient, as well as avoiding the occurrence of under-treatment or over-treatment [9].

The problem that occurs in Indonesia is that there are limitations to high quality Histopathological examination access. This is due to inadequate examination facilities, which include: supporting facilities, preparation staff, and pathologists. This condition is exacerbated by the geography of Indonesia, which includes some remote areas, islands, and mountainous areas. Not all hospitals have frozen

section facilities, so there is a difficulty in establishing an intraoperative diagnosis. Under these limitations, an operator may only be able to rely on intraoperative clinical judgment in determining an ovarian malignancy and determining the appropriate operative procedure in treating a patient [9].

The gross appearance of a tumor can give an idea of whether the tumor is a benign or malignant tumor. Granberg *et al*. in their study found that unilocular cystic tumors were very rarely a malignant tumor. However, the presence of papillae on the cyst wall is an appearance that must be watched out for malignancy, because in this study, it was found that 93% of tumors with papillae on the cyst wall were malignant tumors [7]. In multilocular tumors with a complex appearance, the risk of malignancy increases to 36%. The presence of a solid portion of a cystic ovarian tumor also suggests a malignancy. From the literature, it was found that in contrast to benign tumors, borderline or malignant tumors tend to have a dominant solid component, sometimes accompanied by areas of necrosis. The surface of the tumor also tends to be irregular or lumpy. Only 10–20% of benign tumors are found in both ovaries, while nearly two-thirds of malignant tumors are bilateral [5] (Figure 1).

Figure 1: Gross appearance of a malignant ovarian tumor. Notice the irregular surface and the solid part of the tumor. The postoperative histopathologic diagnosis was endometrioid carcinoma of ovary

A study in Turkey by Oge *et al*. found a mean tumor size of 25 (20–35) cm, borderline tumors of 20 (20–26) cm, and malignant tumors of 25 (20–30) cm, and these differences were not statistically significant in predicting ovarian malignancy [10]. However, Horvath's study found a significant difference between tumor size in early and advanced ovarian cancer, where the size of early-stage malignant ovarian tumors was more than twice as large as the tumor size in advanced stages [11].

Cell adhesion molecules play a significant role in cancer progression and metastasis. Cell-cell interactions of cancer cells with endothelium determine the metastatic spread. In addition, direct tumor cell interactions with platelets, leukocytes, and soluble components significantly contribute to cancer cell adhesion, extravasation, and the establishment of metastatic lesions. Therefore, tumor adhesions to adjacent organs could suggest metastatic tumor cells to those organs, although other benign conditions can also cause adhesions, such as inflammation or infection [12].

The presence of ascites is also a feature suggestive of malignancy. In a study in the United States, the positive predictive value (PPV) of ascites in detecting ovarian malignancy was 95%, and the negative predictive value (NPV) was 64%. The absence of ascites does not always indicate that the tumor is a benign tumor, because almost 50% of borderline tumors and 83% of early-stage malignant tumors do not have ascites. The study also observed the relationship between the presence of ascites and its volume with disease stage, where in early-stage diseases, there were only 17% of cases with ascites, and all of them were <0.5 L. Meanwhile, in 89% of advanced stages, ascites was found with the majority (66%) amounting to > 0.5 L [13].

Intraperitoneal dissemination is the most common mode of extension of varian cancers, with approximately 70% of patients having peritoneal metastases at staging laparotomy. The ovary is covered by a single layer of surface epithelium, which in the presence of epithelial ovarian cancer is frequently studded by macroscopic and microscopic excrescences. Since 90% of ovarian cancers originate from surface epithelial cells, the exfoliated tumor cells can enter the peritoneal circulation and spread as tumor seeding in different sites [14]. From the literature, it is said that tumor seeding is found in 50% of patients with epithelial ovarian tumors. In borderline tumors, it must be distinguished whether the seeding of this tumor is of the invasive or noninvasive type [5].

The presence of enlarged lymph nodes is also a marker of a predisposition to an ovarian malignancy. From a study conducted by Morice *et al*, it was found that the spread of the disease to the lymph nodes was 44%, of which 30% spread to the pelvic lymph nodes and 40% to the paraaortic lymph nodes. The frequency increases as the stage of the disease increases [15]. The same thing was also stated in a study conducted by Takeshima *et al*. in Japan [16].

This study results show that there were several variables that were statistically significant, namely multilocular tumors, the presence of solid parts, irregular tumor surfaces, the presence of ascites, the presence of tumor seeding, and enlarged lymph nodes. The combination of ascites and an irregular surface of the tumor was the most significant combination, so it can be said that if we find an ovarian tumor with ascites and an irregular surface, it is highly likely that the tumor is non-benign ovarian tumors. Very few studies have investigated the relationship between the gross appearance of tumors based on histopathological results. This study did not take account of the disease stage and did not differentiate between the origins of

tumor (epithelial, germ cell, or sex-cord stromal), and it can be a limitation for this study. Further research can be conducted to give more accurate results about tumor gross appearance variables suggestive of malignancy in ovarian tumor.

Conclusions

Intraoperative frozen section remains the choice for a Gynecologic-Oncologist to diagnose malignancy of an ovarian tumor. However, in the absence of an intraoperative frozen section examination facility, gross appearance of a tumor can give a suggestion for the surgeon whether the tumor is benign or not, and thus and determining the appropriate surgical procedure needed for a patient. The presence of ascites and an irregular surface in an ovarian tumor is a strong suggestion that the tumor is a non-benign tumor.

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