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Differentiation of Serous and Non-serous Epithelial Ovarian Cancer by Radiological Imaging

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ABSTRACT

Background: Ovarian cancer has a high incidence and fatality rate, with the most prevalent type is epithelial origin. The serous subtype of epithelial cancer predominates. For therapy selection, it is important to differentiate this subtype by histopathological examination as a gold standard method. Since some patients are not eligible for a biopsy, radiological modalities such as Magnetic Resonance Imaging (MRI) are superior in discriminating tissue compared to computed tomography (CT) or ultrasound. The use of the T1 weighted imaging (T1WI) and T2WI sequences can best differentiate between a cystic and a solid lesion. The goal of this study was to use radiological examination to assist in the identification of ovarian cancer.

Methods: This cross-sectional study used secondary data from histopathology and MRI results from patients with ovarian cancer. Data was gathered utilizing electronic medical records in Dr. Sardjito Hospital between January 2017 and May 2022. The following MRI characteristics are evaluated including ascites, papillary projection, solid nodule, signal intensity of solid and cystic components, size, configuration, enhancement of contrast, and bilateral of the lesion.

Results: Thirty-eight subjects made up the study's sample, and 63% of them had serous subtypes. Bilateral lesion suggested a three times greater likelihood that it was serous ovarian cancer (p 0.02; binary logistic regression). Age >50 years old and strong enhancement on contrast was also relevant for separating the serous subtype from other subtypes (enhancement p 0.02; age p 0.044)

Conclusions: A bilateral lesion with a significantly enhanced pattern can be seen on the MRI of a serous subtype of epithelial ovarian cancer. The elderly are also more likely to develop this cancer.

INTRODUCTION

Ovarian cancer is the eighth most frequent cancer in women and the 18th most frequent cancer overall. In 2020, there were around 313,000 new cases of ovarian cancer [1]. After cervical cancer, ovarian cancer ranks as the second most frequent gynecological malignancy and has the highest fatality rate in the US [2]. There are different forms of ovarian cancer, with the epithelial type accounting for between 70 and 90 percent of cases [3,4]. There are many subtypes of the epithelial type that exist, including the endometrioid, serous, mucinous, clear cell, and Brenner's tumor. The management of cases in patients depends on determining the type of tumor. Some types of epithelial ovarian cancer are still sensitive to chemotherapy regimens, such as high-grade serous carcinoma and clear cell carcinoma. While low-grade serous, endometrioid, and mucinous carcinoma may become chemo-resistant [5]. Among other ovarian epithelial cancers, serous cystadenocarcinoma is the most prevalent (40%) type of malignancy [6]. This is what also drives how the samples in this study were grouped. Due to the asymptomatic nature of ovarian epithelial carcinoma, 75% of patients have advanced disease when they are finally detected. Although ovarian cancer can develop at any age, the majority of cases are detected in people over the age of 50 [7].

Each subtype shows characteristics. According to studies, the mucinous subtype typically manifests as big cystic lesions that are more likely to metastasize to the abdominal regions, whereas the serous subtype

frequently exhibits several tiny lesions [8]. Of course, this stage cannot be separated from the radiological imaging strategy. Imaging techniques like MRI, CT scans of the pelvis, and ultrasonography are frequently used to diagnose gynecological organ cancers. Unlike other imaging modalities, such as ultrasonography and CT, some physical characteristics of borderline lesions can be picked up by MRI. For depicting anatomical structures and tissue characteristics, T1WI and T2WI sequences work well. A malignant lesion is visible on the DWI sequence which shows a strong signal. Because the research samples employed in this study were all malignant tumors, it was obvious that it was not helpful [6].

Histopathological analysis remains to be the gold standard for ovarian cancer diagnosis. The preparation of the patient's condition must be of utmost importance in this regard because this examination necessitates an aggressive technique to retrieve the tissue. In patients who are elderly or have comorbidities such as heart disease, diabetes mellitus, kidney failure, and other illnesses, it may be challenging to identify the perfect patient condition. Meanwhile, radiological examinations often do not require invasive procedures, only in contrast to injection procedures, patients usually receive an intervention. The peripheral veins need to be accessed for this procedure. The components of each subtype of this epithelial type of cancer could be thoroughly described by MRI. Thus, this study is expected to be able to determine the characteristic differences in MRI images based on the type of ovarian epithelial malignancy.

METHODS

This study is cross-sectional and uses secondary data from ovarian cancer patients' electronic medical records in the form of imaging information and histological findings. Patients with a history of ovarian cancer who had at least one MRI of the pelvic region performed in Dr. Sardjito General Hospital comprised the study population. Ascites and an ovarian mass/tumor were discovered during the examination. Ascites, papillary projection, solid nodules, signal intensities of solid and cystic components, size, configuration, contrast enhancement, and side(s) of the lesion were the MRI parameters assessed in this study.

These patients' histopathological analyses revealed ovarian epithelial carcinoma with serous, mucinous, endometrioid, or clear cell subtypes. Thereafter, patients will be grouped into serous and non-serous due to the uneven number of samples. The MRI examination time frame was from January 2017 to May 2022. Without randomization, samples were collected one after the other until the required minimum sample size of 38 subjects was reached. These factors served as the study's inclusion criteria as well. Exclusion criteria for patients included histopathological diagnosis obtained by cytological examination, nodal metastatic examination, and histopathological examination other than large surgical excision of tissue and frozen sections of tissue, as well as histopathological examination results showing non-epithelial malignancy. Based on the inclusion and exclusion criteria, there were 25 patients with a total sample of 38 research subjects because a total of 15 patients showed bilateral lesions on both ovaries. Some of these bilateral lesions exhibit different subtypes in the same patient.

When interpreting MRI scans of samples, it is important to consider the age factor as well as the sides of the lesion, size, configuration, papillary projection, solid nodules, intensity of solid and cystic components, pattern of enhancement, and presence of ascites.

A radiologist served as an intraobserver for this study's re-reading of the MRI image interpretation to evaluate reliability. Chi-square tests and binary logistic regression were used as bivariate and multivariate analyses. A relationship between two or more dependent variables and the independent variables can be seen using the chi-square test. Nominal data is what was used.

RESULTS

The kappa score of 0.78 from the reliability test on ten of the 38 subjects in this study indicates that the instruments used in this investigation had good reliability in assessing research variables. By analyzing the tumor's properties based on the acquired MRI images, the fundamental characteristics of the study sample were ascertained. Following data collection and descriptive analysis, absolute and relative frequency distribution data (in percentage form) are produced, and **Table 1** shows these results.

A total of 24 (63.1%) subjects demonstrated the serous tumor type. Sixty-two point five percent of the serous type samples in the age category had an age more than 50. More than 50% of the tumor samples for both mucinous and clear cell types were under the age of 50. Between the age groups under 50 years and above 50 years, the endometrioid type exhibits the same number. The side(s) of the lesion variable showed that 91.7%, 66.7%, and 80% of serous, mucinous, and clear cell tumor types were bilateral lesions, respectively. The three different tumor types also demonstrated that 75%, 100%, and 80% of lesions were 6 cm or more.

Seventy-five percent of endometrioid types had solid cystic shape, while 66.7% had mucinous with solid cystic predominance. Serous tumors reveal that 45.8% of all tumor types are solid-cystic lesions, whereas the remaining 29.2% were solid-dominant lesions. Most serous, mucinous, and endometrioid cancers have papillary projections and solid nodules.

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Table 1. Baseline characteristics

Characteristics	Serous n(%)	Mucinous n(%)	Endometrioid n(%)	Clear Cell n(%)	Mix type n(%)
Number of subjects	24(63.1%)	3(7.9%)	4(10.5%)	5(13.2%)	2(5.3%)
Age (years old)					
≤ 50	9(37.5%)	2(66.7%)	2(50%)	4(80%)	2(100%)
> 50	15(62.5%)	1(33.3%)	2(50%)	1(20%)	0(0%)
Side(s) of lesion					
Bilateral	22(91.7%)	2(66.7%)	0(0%)	4(80%)	2(100%)
Unilateral	2(8.3%)	1(33.3%)	4(100%)	1(20%)	0(0%)
Tumor size					
< 6 cm	6(25%)	0(0%)	3(75%)	1(20%)	1(50%)
≥ 6 cm	18(75%)	3(100%)	1(25%)	4(80%)	1(50%)
Tumor configuration					
Solid	7(29.2%)	2(66.7%)	1(25%)	1(20%)	0(0%)
Solid-cystic	11(45.8%)	0(0%)	3(75%)	1(20%)	2(100%)
Uniloculated cyst	2(8.3%)	0(0%)	0(0%)	1(20%)	0(0%)
Multiloculated cyst	4(16.7)	1(33.3%)	0(0%)	2(40%)	0(0%)
Papillary projection					
Yes	15(62.5%)	3(100%)	3(75%)	2(40%)	2(100%)
No	9(37.5%)	0(0%)	1(25%)	3(60%)	0(0%)
Solid nodule					
Yes	18(75%)	2(66.7%)	4(100%)	2(40%)	2(100%)
No	6(25%)	1(33.3%)	0(0%)	3(60%)	0(0%)
Signal in solid component					
T1 hypo-T2 hyper	1(4.2%)	0(0%)	0(0%)	0(0%)	0(0%)
T1 iso-T2 hyper	19(79.2%)	2(66.7%)	3(75%)	2(40%)	2(100%)
T1 iso-T2 hypo	0(0%)	1(33.3%)	0(0%)	1(20%)	0(0%)
T1 hyper-T2 iso	0(0%)	0(0%)	0(0%)	1(20%)	0(0%)
Inhomogen	1(4.2%)	0(0%)	1(25%)	0(0%)	0(0%)
T1 & T2 iso	3(12.5%)	0(0%)	0(0%)	1(20%)	0(0%)
Signal in cystic component					
T1 hypo-T2 hyper	14(58.3%)	3(100%)	2(50%)	2(40%)	1(50%)
T1 iso-T2 hyper	6(25%)	0(0%)	0(0%)	0(0%)	0(0%)
T1 iso-T2 hypo	1(4.2%)	0(0%)	1(25%)	0(0%)	0(0%)
T1 hyper-T2 iso	1(4.2%)	0(0%)	1(25%	1(20%)	1(50%)
Inhomogen	1(4.2%)	0(0%)	0(0%)	1(20%)	0(0%)
T1 & T2 iso	1(4.2%)	0(0%)	0(0%)	1(20%)	0(0%)
Contrast enhancement					
Non-contrast	1(4.2%)	0(0%)	0(0%)	3(60%)	0(0%)
No enhancement	2(8.3%)	0(0%)	0(0%)	0(0%)	0(0%)
Mild	1(4.2%)	1(33.3%)	0(0%)	1(20%)	0(0%)
Moderate	0(0%)	0(0%)	3(75%)	0(0%)	0(0%)
Strong	20(83.3%)	2(66.7%)	1(25%)	1(20%)	2(5.3%)
Ascites					
Yes	11(45.8%)	0(0%)	1(25%)	2(40%)	2(100%)
No	13(54.2%)	3(100%)	3(75%)	3(60%)	0(0%)

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Table 2. Characteristics of MRI; serous vs non serous lesions

Number of subjects	Serous	Non Serous	*p*
Age (years old)			0.044***
≤ 50	9	10	
> 50	15	4	
Side(s) of lesion			0.034*
Bilateral	22	8	
Unilateral	2	6	
Tumor size			0.712*
< 6 cm	6	5	
≥ 6 cm	18	9	
Tumor configuration			0.986***
Solid	7	4	
Solid-cystic	11	6	
Uniloculated cyst	2	1	
Multiloculated cyst	4	3	
Papillary projection			0.728*
Yes	15	10	
No	9	4	
Solid nodule			1.000*
Yes	18	10	
No	6	4	
Signal in solid component			0.271***
T1 hypo-T2 hyper	1	0	
T1 iso-T2 hyper	19	9	
T1 iso-T2 hypo	0	2	
T1 hyper-T2 iso	0	1	
Inhomogen	1	1	
T1 & T2 iso	3	1	
Signal in cystic component			0.265***
T1 hypo-T2 hyper	14	8	
T1 iso-T2 hyper	6	0	
T1 iso-T2 hypo	1	1	
T1 hyper-T2 iso	1	3	
Inhomogen	1	1	
T1 & T2 iso	1	1	
Contrast enhancement			0.02**
Non-contrast	1	3	
No enhancement	2	0	
Mild	1	2	
Moderate	0	3	
Strong	20	6	
Ascites			
Yes	11	5	0.735*
No	13	9	

*Fisher Exact test, **Mann-Whitney test,
***Chi-square test with expected cells < 5 no more than 20%

Table 2 displays the results of the Chi-square test for each variable. The Fisher Exact's test was employed as an alternative for the variables for bilaterality, tumor size, papillary projection, solid nodules, and ascites. The bilaterality variable revealed, which was statistically significant at *p* 0.034. An ordinal variable of the pattern of contrast enhancement which used the Mann-Whitney test as an alternative Chi-square test showed *p* 0.02. And the age variable has *p* 0.044 by Chi-square, making both variables statistically significant. From this result, we chose these three variables need to be analysed using multivariate analysis which were binary logistic regression.

Test with binary logistic regression using a dichotomous Y response variable. In this study categorized into serous and non-serous. Meanwhile, the predictor variables X were defined as bilaterality, enhancement pattern and age. The first step in the binary logistic regression test is to perform a model fit test. This is useful to know a model without insignificant variables is the best model. This test uses the Hosmer and Lemeshow test to assess suitability, where *p* 0.666, indicating greater than α so that it is concluded that the model is hypothesized according to the observation data.

The next step is to determine the estimated parameters. After the parameter estimation results are obtained, the significance of the response variable is tested. Testing can be carried out simultaneously or partially/individually. The statistical test used to test the significance of the simultaneous regression parameters is the X2 test by looking at the Model Coefficient Omnibus table, where H0 is rejected if $p < \alpha$ (for $\alpha = 0.05$), which shows X2 = 14.159 and the *p* 0.003 means that there is one variable predictor (X) that statistically significant affects the response variable.

A Partial test of logistic regression parameters using Chi-square, H0 is rejected if $p < \alpha$. In this study there were only 2 significant parameters, these are the bilaterality of the lesions with *p* 0.02 and the age of subjects with *p* 0.036.

Table 3. Variable significance test in binary logistic regression

Variable	B	*p*
Age (A)	-2,398	0,036
Pattern of tumor enhancement (PE)	-0,167	0,565
Side(s) of the lesion (BL)	3,071	0,020
Constant	-0,379	0,822

Based on **Table 3** above, the regression equation can be formed as follows:

$Y = A + B1X1 + B2X2 + B3X3$

$JT = -0,379 - 2,398A - 0,167PE + 3,071BL$

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A constant of -0,379 means that if there is no difference in age, pattern of contrast enhancement, and bilaterality of the lesion, there will be no difference in the type of serous and non-serous malignancy. A negative constant means that the probability is considered 0 or there is no chance. The regression coefficient of the bilaterality variable is 3.0 which means that whenever there is bilaterality of the lesion, there is a possibility of a serous malignancy of more than 3 times.

At the end of the analysis using this regression method, it was also assessed to what extent the differences in the Y variable could be explained by the X predictor variable by looking at the Nagelkerke R-square. In this study, a value of 0.425 was obtained, which means that 42.5% of the differentiation of variable Y in the form of serous or non-serous epithelial malignancy subtypes can be explained by predictor variables.

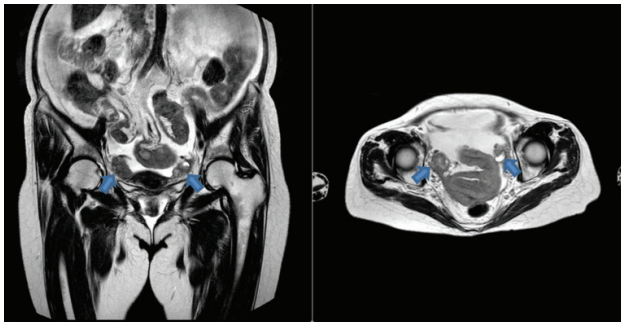

Figure 1. Bilateral lesion from 2 ovaries. Both showed histopathologically as serous ovarian cancer (arrow) mimicking normal ovaries. It also showed prominent ascites.

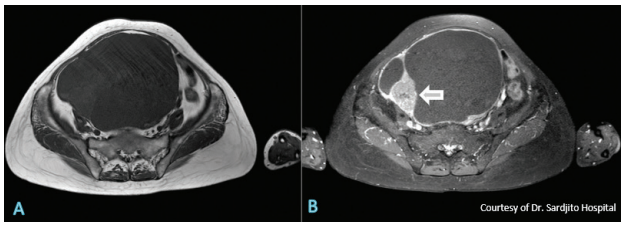

Figure 2. (A) There is a blurry nodule at the edge of the cystic wall (B) Lesion is clearly seen with strong enhancement in contrast addition (arrow)

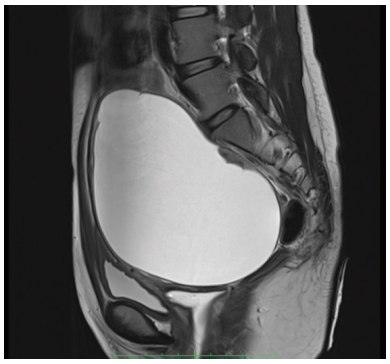

Figure 3. Big cystic lesion showed small part of solid lesion at its wall. Histologically showed high-grade serous carcinoma

DISCUSSION

Data from MRI image results dating back to 2017 up until May 2022, were used in this research. The results of exams conducted by the Department of Anatomical Pathology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, as well as results of examinations conducted outside the hospital, were used to acquire histopathological data. Serous subtypes made up the 24 subjects. This is in line with data on the incidence of epithelial tumors, the majority of which are high-grade serous epithelial tumors (high-grade serous carcinoma), accounting for up to 70% of cases, then endometrioid by 10%, clear cell 10%, mucinous 3% and low grade serous less than 5% [9].

The majority of the samples in the age group were discovered to be older than 50. This is also consistent with the findings of earlier studies [7], which found that while ovarian cancer can develop at any age, the majority of cases occur in people who are older than 50. Early age at menarche and late age at menopause increases risk by increasing the number of ovulatory cycles [9].

From the Chi-square analysis, the variables of side(s) of lesion, contrast enhancement, and age were considered statistically significant. Similarly, in the multivariate analysis, which bilateral tumor was a strong predictor that a lesion was a serous tumor, as shown in **Figure 1**. This is consistent with other studies showing that serous epithelial malignancies are bilateral lesions with relatively small lesions [10]. Different gene expression is seen during the developing phase in ovarian cancer with bilateral lesions, according to chromosomal analysis. While it is claimed that bilateral ovarian cancer has the same genesis based on the prior understanding. This further demonstrates the likelihood that the types of tumors on either side of the ovary can vary [11].

The variables of age and contrast enhancement pattern also have significant values in bivariate analysis. Lesions with bilateral tumor features that show strong enhancement, and occur in patients over 50 years of age suggest a serous epithelial malignancy.

Delivery and retention of the contrast by the lesion are necessary for ovarian mass enhancement, as you can see in **Figure 2**. The accumulation of contrast within the bulk and its increased amplification is caused by the vascular supply, capillary threads, and leakage of contrast into the interstitial (extravascular) area. Technical limitations like the procedure for contrast injection and delays in taking scan images might also have an impact on variations. It is well known that angiogenesis frequently occurs in cancer situations and aids in the growth of tumors. Vascular endothelial growth factor (VEGFR-2) regulates angiogenesis and vascular permeability, and invasive malignant lesions are thought to express more of it than benign lesions [12].

Few reports of ovarian malignancy's radiological characteristics exist. More frequently, the histopathological picture is examined by the anatomical pathology department after the surgery results are transmitted there to determine the morphological picture. Rarely is the macroscopic appearance of the complete lesion mentioned in histopathological reports. The specimen that was sent to pathology could, however, be a lesion that is incomplete or merely a small portion of the entire lesion, thus this report could simply be hypothetical. The position and specifics of the lesion can be seen clearly with an MRI scan, though.

Serous epithelial carcinoma is the most prevalent lesion of an ovarian malignancy, and other primary cancers of the ovarian epithelium include mucinous, endometrioid, and clear cell subtypes. Debulking surgery normally comes first in these patients' primary treatment plans, which are then followed by chemotherapy with cytotoxic drugs. Frequently, the findings indicate that the majority of patients will fare well. The terms low-grade serous carcinoma (LGSC) and high-grade serous carcinoma are widely used to describe these serous cancers (HGSC) [5]. A borderline lesion that frequently has papillary projections gives rise to several LGSCs. HGSC, however, is typically found as a solid nodule. Additionally, compared to the mucinous subtype, the serous epithelium malignancy is said to have a smaller look. This subtype often exhibits large multiloculated lesions [10].

Many have discovered that endometrioid and clear cell carcinomas are intimately associated to the malignant transformation of endometriosis in subsequent advances to date. Clear cell and mucinous cell subtypes are believed to be resistant to chemotherapy, although endometrioid malignancy itself is thought to be a susceptible subtype [5].

Research on ovarian cancer using radiological modalities, particularly MRI has not been done much in Indonesia. This study can certainly be a starting point to further test the validity of MRI's ability to determine ovarian epithelial cancer subtypes. So that later it can help in the approach to the diagnosis of ovarian cancer.

There are undoubtedly some shortcomings in this research. Researchers find it challenging to manage the homogeneity of the MRI modalities utilized, such as the type of MRI localization employed, pelvic, abdominal, or lumbar MRI which also displays intrapelvic organs, thanks to data obtained with secondary data. It is also challenging to distinguish between the 1.5 Tesla and 3 Tesla MRI devices that are employed. Even though the research sample exceeded the required minimum sample size, the findings were unbalanced since there were substantial numbers of differences across each subtype.

CONCLUSIONS

The typical bilaterality of the pelvic MRI data indicates that the lesion is three times more likely to be a serous ovarian epithelium cancer than a non-serous ovarian epithelium cancer. The pattern of significant contrast enhancement on the pelvic area MRI images and the patient's age of above 50 years can further help distinguish a serous epithelial ovarian cancer from a non-serous tumor.

DECLARATIONS

Competing interest

The authors declare no competing interest in this study.

Ethics Approval

This research approved by Medical and health Research Ethics Committee (MHREC), Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada – Dr. Sardjito General Hospital on April 28th 2022 with reference number KE/FK/0538/EC/2022

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