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Abbreviations:

RDOG = Radiology Diagnostic
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RI = resistive index

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Primary versus Secondary Ovarian Malignancy: Imaging Findings of Adnexal Masses in the Radiology Diagnostic Oncology Group Study¹

PURPOSE: To analyze ultrasonographic (US), computed tomographic (CT), and magnetic resonance (MR) imaging features of primary and secondary ovarian malignant neoplasms to determine if there is any significant difference in their appearance.

MATERIALS AND METHODS: Analysis of the multi-institutional Radiology Diagnostic Oncology Group data revealed 86 patients with primary ovarian carcinoma and 24 patients with a secondary ovarian neoplasm. Numerous imaging features that had been recorded for the adnexal masses with each imaging modality were reviewed and compared between primary and secondary malignant ovarian neoplasms.

RESULTS: Of the imaging features assessed with all three modalities, multilocularity as determined at US ($P = .02$) or MR imaging ($P = .01$) was the only significant feature. At US, 30 (37%) of 81 primary ovarian cancers were multilocular, whereas only three (12%) of 24 metastatic neoplasms were multilocular. At MR imaging, 40 (74%) of 54 primary ovarian cancers were multilocular, whereas only five (36%) of 14 metastatic neoplasms were multilocular. Neither a predominately solid appearance nor bilaterality was significantly different between primary and secondary neoplasms.

CONCLUSION: For malignant ovarian masses, multilocularity at MR imaging or US favors the diagnosis of primary ovarian malignancy rather than secondary neoplasm, but it is difficult to accurately distinguish between primary and secondary ovarian malignancies.

When an ovarian mass that is suspicious for malignancy is identified at an imaging examination, primary ovarian cancer is generally the main concern. However, it has been estimated that 5%–15% of malignant ovarian tumors are metastatic tumors to the ovary (1,2). These estimates are generally based on pathologic series, and the frequency of ovarian metastasis among all adnexal masses identified at imaging is likely lower. While metastases are an infrequent occurrence in daily practice, metastatic neoplasms of the ovary may be misdiagnosed as primary ovarian neoplasms (3,4), potentially leading to inappropriate management.

The imaging appearance of ovarian metastases has been described previously. Most investigators have described the computed tomographic (CT) findings (3–8), with a few reports of ultrasonographic (US) (9–11) or magnetic resonance (MR) imaging appearances (8,12,13). To our knowledge, no investigators have described the US, CT, and MR imaging findings of ovarian metastasis in the same patients. The data collected from the prospective multi-institutional Radiology Diagnostic Oncology Group (RDOG) study (14) sponsored by the National Cancer Institute of the National Institutes of Health provide an

opportunity to evaluate the appearance of ovarian malignancies with all three imaging modalities in the same patient cohort.

The purpose of this study was to compare the imaging features of secondary (ie, metastatic) ovarian neoplasms with those of primary malignant ovarian neoplasms to determine if there is any significant difference in their appearance. If there were a significant difference such that secondary neoplasms could be accurately predicted, patient care might be improved by directing a more thorough search for the primary neoplasm, and surgery might be avoided or more appropriately planned.

For purposes of this study, the term "secondary" neoplasm of the ovary is used synonymously with the term "metastatic" neoplasm of the ovary from a primary neoplasm of another organ. In this article, "metastatic" is not used to refer to metastasis from an ovarian primary neoplasm.

MATERIALS AND METHODS

Patient Population

Data for this study were obtained from the database of the RDOG ovarian cancer diagnosis and staging study. Details of the methods are available in the full report of that study (14). Briefly, women from five institutions were enrolled if they were suspected of having ovarian cancer on the basis of abnormal findings at preliminary gray-scale US or physical examination. The study was approved by the institutional review board at each institution, and patients provided written informed consent prior to participation. The abnormal mass detected at US had to be larger than 5 cm in premenopausal patients or any size in postmenopausal patients. It was intended that all patients undergo US, CT, and MR imaging, but they were to have completed at least two of the three imaging modalities within 4 weeks prior to surgical removal of the mass. Standardized protocols were used for each imaging modality at all the institutions. Basics of the pelvic portion of the imaging protocols are briefly reviewed next.

US Imaging Protocol

US of the pelvis was performed with 128XP or 128XP/10 scanners (Acuson, Mountain View, Calif) or UltraMark 9 or HDI 3000 scanners (Advanced Technology, Bothell, Wash). Transvaginal scanning (with 5–7-MHz transducers) was

used to evaluate the pelvis and with transabdominal scanning (with 2–5-MHz transducers) performed when transvaginal scanning was believed to be inadequate.

CT Imaging Protocol

Somatom Plus and Plus-S units (Siemens, Iselin, NJ) or 9800 Advantage and HiSpeed Advantage units (GE Medical Systems, Milwaukee, Wis) were used. The dynamic or spiral mode with 2-second scanning times in suspended respiration was used in each case. The gastrointestinal tract was opacified with orally administered contrast material. By using a power injector, 150 mL of 60% iodinated contrast material (ionic or nonionic) was injected at a rate of 2.5–3 mL/sec, and the pelvis was scanned during peak arterial enhancement. A collimation of 5 mm was used in the pelvis. Spiral CT was performed with a 5 mm/sec table speed and a 5-mm reconstruction thickness, and incremental CT was performed with contiguous scanning at a rate of 10 scans per minute.

MR Imaging Protocol

A 1.5-T Signa magnet (GE Medical Systems) with a 10 mT/m gradient system was used in all institutions. For the pelvis, a multicoil array was used whenever possible. A body coil was used when the mass was larger than 15 cm or when the patient was severely obese. Where possible, patients were asked to fast for at least 3 hours before the study, and each received 1 mg of glucagon intramuscularly before imaging.

Transverse images, followed by coronal and sagittal images, were obtained with fast spin-echo T2-weighted sequences (4,000–6,000/102–126 [repetition time msec/echo time msec]) with an echo train length of 16, a 5–10-mm section thickness, and a 0–2.5-mm intersection gap. Matrix size was 256 × 256, with two signals acquired. These were followed by transverse T1-weighted spin-echo sequences (600–800/11–20) with similar spatial resolution. After intravenous administration of 10–20 mL of a gadolinium chelate, the T1-weighted sequence was repeated with fat suppression.

Imaging Feature Analysis

Before surgery, a standardized data sheet for each imaging modality in each patient was completed by a radiologist blinded to the results of the other imaging studies. The following information

regarding the appearance of the ovarian mass was prospectively recorded for each of the three imaging modalities as follows: purely cystic and unilocular; multilocular; cystic with wall thickening greater than 3 mm; cystic, with septa of 3 mm or less; cystic, with septa greater than 3 mm; cystic, with nodules; cystic, with internal echoes; and solid. Each of these features was rated as one of three possible choices: present, absent, or indeterminate.

For solid masses, the percentage of solid component was subjectively rated as less than 25%, 25%–49%, 50%–75%, or greater than 75%. The measurements of the mass were recorded in centimeters, and mass volume was later estimated in cubic centimeters by using a simplified formula for volume of a prolate ellipsoid by multiplying the product of the three perpendicular diameters in centimeters by 0.52. Whether an ovarian mass was unilateral or bilateral was also recorded.

In addition, three pulsed Doppler parameters were evaluated for each mass: resistive index (RI), pulsatility index, and the presence of a diastolic notch. An attempt was made to record three pulsed Doppler waveforms from each of three areas (if present) in the mass: solid component of mass, wall of mass, and septa, if greater than 3 mm in thickness.

Two additional MR imaging features were compared: signal intensity and nature of the tissue. Signal intensity relative to normal skeletal muscle was recorded as homogeneously hyperintense, heterogeneously hyperintense, homogeneously isointense, heterogeneously hypointense, homogeneously hypointense, or not applicable (ie, sequence not done) for each of three sequences: T1-weighted before gadolinium enhancement, T2-weighted, and T1-weighted after gadolinium enhancement. The nature of the tissue was recorded as one of six choices: clear fluid, protein or bloody fluid, fat, necrotic debris, soft tissue, or unknown. This was based on assessment of the signal intensity characteristics, with and without gadolinium enhancement, for the largest component of the mass.

Surgical and Histopathologic Correlation

All patients underwent resection of their ovarian tumor. Pathologists from each institution evaluated the ovaries in a routine fashion using the revised World Health Organization histologic classification for ovarian neoplasms (15). The final diagnosis, that is, the standard, was determined by using

TABLE 1
Final Diagnoses

Type of Ovarian Malignancies	No. of Malignancies
Primary (<i>n</i> = 86)	
Serous adenocarcinoma	40
Serous cystadenoma of borderline malignancy	2
Mucinous adenocarcinoma	11
Mucinous cystadenoma of borderline malignancy	2
Endometrioid adenocarcinoma	8
Endometrioid, stromal or mixed mesodermal neoplasm	4
Clear cell adenocarcinoma	6
Undifferentiated adenocarcinoma	3
Sex-cord stromal tumors	4
Immature teratoma	1
Miscellaneous	5
Secondary (<i>n</i> = 24)	
Adenocarcinoma of undetermined site	4
Adenocarcinoma of peritoneum	3
Adenocarcinoma of pancreas	2
Carcinoma of the gallbladder	1
Carcinoma of gastrointestinal tract, with signet ring cells	1
Carcinoid	2*
Adenocarcinoma of colon	1
Endometrial carcinoma	1
Mixed mesodermal tumor of fallopian tube	1
Lymphoma	1
Adenocarcinoma of appendix	1
Mixed mullerian neoplasm, site unknown	1
Small cell carcinoma, site unknown	1
Mixoid liposarcoma	1
Unspecified	3

* One from appendix, one from unknown site.

TABLE 2
Age and Menopausal Status

Patient Information	Primary Neoplasm Group (<i>n</i> = 86)	Secondary Neoplasm Group (<i>n</i> = 24)
Age (y)*	56 ± 15	59 ± 13
Menopausal status†		
Premenopausal	27 (31)	6 (25)
Postmenopausal	59 (69)	18 (75)

* Data are the mean plus or minus the SD.

† Data are the number of patients. Data in parentheses are percentages.

the surgical and pathologic findings in each case. The histologic types of the primary and secondary ovarian neoplasms were obtained from the standardized pathology forms, and for this study, only data from patients with malignant neoplasms were analyzed.

Statistical Methods

The overall analyses of US, MR imaging, and CT features in the prediction of primary versus secondary ovarian malignancy were conducted by using the imaging feature data and the pathologic standard. Among the common features considered, only the measurements of the masses were continuous variables, with the rest being categorical variables.

For each imaging modality and feature, we conducted univariate analysis of the categorical data by constructing contingency tables of counts and proportions. If an imaging feature had been rated as indeterminate, it was considered not to be present. A two-sided Fisher exact test of independence was used to examine the relationship between each of the feature variables against the standard (16). For continuous data, a Student *t* test was used for testing the equality of underlying mean measurements between the primary and secondary ovarian cancers.

The minimum pulsatility index and RI obtained from each of the three areas in the mass was compared between primary and secondary neoplasms by using the

Student *t* test. The diastolic notch was considered present at each site if it was seen in any of three waveforms and was analyzed with the Fisher exact test. Similarly, the Fisher exact test was used for the two additional MR imaging features: nature of the tissue on an MR image and MR imaging signal intensity.

The analyses were performed in the group of unilateral masses and the largest mass when bilateral. The same analyses were repeated for the smaller mass in patients with bilateral masses. Patient age and menopausal status, as well as whether adnexal masses were unilateral or bilateral, were also compared between the two groups. Statistical software (S-PLUS; MathSoft, Seattle, Wash) was used for all analyses (17).

RESULTS

Of the 280 patients in whom had an ovarian mass was removed, there were 110 malignancies, of which 86 (78%) were primary ovarian neoplasms and 24 (22%) were secondary ovarian neoplasms (Table 1). Most of the primary ovarian malignancies were of the epithelial type, while the origin of the metastatic neoplasms was variable (Table 1). Age and menopausal status were not significantly different between patients with primary and those with secondary ovarian neoplasms (Table 2). In the 110 patients, US had been performed in 105 patients (81 with primary and 24 with secondary neoplasm); CT, in 86 patients (68 with primary and 18 with secondary neoplasm); and MR imaging, in 68 patients (54 with primary and 14 with secondary neoplasm).

Overall, the only imaging feature common to all three modalities that was significantly different between primary and secondary ovarian malignancies was multilocularity (Figure, Table 3), as determined at US (*P* = .02) or MR imaging (*P* = .01), which favored primary malignancy. CT did not yield a statistically significant difference between the two groups for multilocularity. At US, 30 (37%) of 81 primary ovarian cancers were multilocular, whereas only three (12%) of 24 metastatic neoplasms were multilocular. At MR imaging, 40 (74%) of 54 primary ovarian cancers were multilocular, whereas only five (36%) of 14 metastatic neoplasms were multilocular. (The positive predictive value of multilocularity for primary ovarian malignancy was 91% [30 of 33 findings] at US and 89% [40 of 45 findings] at MR imaging. Similarly, the

negative predictive value was 71% [51 of 72 findings] at US and 61% [14 of 23 findings] at MR imaging.) None of the other features, including predominately solid masses or bilaterality, were significantly different between primary and secondary ovarian malignancies.

No matter which modality was used, the presence of a solid component was not significantly different between primary ovarian cancers (69 [85%] of 81 cancers at US; 40 [59%] of 68 cancers at CT; 44 [81%] of 54 cancers at MR imaging) and metastatic neoplasms (17 [71%] of 24 neoplasms at US; 10 [56%] of 18 neoplasms at CT; 10 [71%] of 14 neoplasms at MR imaging). The percentage of solid component was also not significantly different. Bilateral adnexal masses were present in 30 (35%) of 86 of patients with primary ovarian neoplasms, compared with 12 (50%) of 24 with secondary ovarian neoplasms.

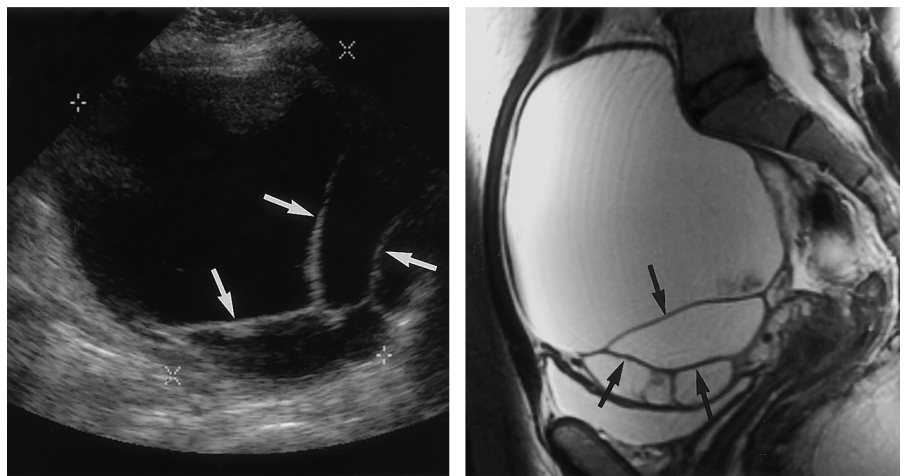
The only Doppler US feature that was significantly different between the two groups was the RI in the wall of the mass. The mean value of the minimum RI in the wall of the mass was 0.54 (SD, 0.19) for primary ovarian malignancy and 0.77 (SD, 0.19) for secondary ovarian malignancy ($P = .01$). This parameter was available in 36 primary ovarian neoplasms and six secondary ovarian neoplasms. Adequate pulsed Doppler waveforms were not obtainable in the other masses. The pulsatility index in the wall of the mass was not significantly different.

The nature of the tissue at MR imaging differed between the two groups, with primary ovarian malignancies more likely to be characterized as having protein or bloody fluid or clear fluid, whereas secondary neoplasms were more likely to be characterized as soft tissue. Of primary malignancies, 18 (33%) of 54 had protein or bloody fluid and 13 (24%) of 54 had clear fluid, whereas six (60%) of 10 secondary malignancies were characterized as soft tissue ($P = .02$). There were four cases of secondary malignancies for which data for this parameter were missing.

Additional analysis of the smaller mass, when bilateral, did not yield any significant findings, perhaps due to the relatively small number of such masses.

DISCUSSION

Breast cancer, colon cancer, gastric cancer, and lymphoma are the most frequent neoplasms to metastasize to the ovaries (1,18–20). Neoplasms from numerous other primary tumors, including endo-



a. Multilocular mass in a patient with primary ovarian carcinoma. (a) Sagittal transabdominal US image of a large adnexal mass (cursors) demonstrates septa (arrows) that divide the mass into multiple loculi. (b) Sagittal T2-weighted fast spin-echo image (4,000/102) of the same mass also demonstrates the multiple septa (arrows) that divide the mass into multiple loculi.

TABLE 3
Number of Multilocular and Unilocular Masses by Modality

Final Diagnosis	US ($n = 105$)*		MR Imaging ($n = 68$)†		CT ($n = 86$)‡	
	Multilocular	Unilocular	Multilocular	Unilocular	Multilocular	Unilocular
Primary neoplasm ($n = 86$)	30	51	40	14	35	33
Secondary neoplasm ($n = 24$)	3	21	5	9	9	9

* $P = .02$.

† $P = .01$.

‡ $P > .99$.

metrial carcinoma, melanoma, pancreatic carcinoma, and carcinoid tumor have also been reported to metastasize to the ovary. In many studies (3,7,10,18,21,22), the nonovarian primary neoplasm had often been diagnosed before an ovarian mass was found; however, in a substantial minority of patients, the metastatic ovarian neoplasm was recognized before the primary neoplasm was known.

It is unclear from the imaging literature whether there is a sufficiently characteristic appearance of an ovarian mass that allows one to make a confident distinction between primary and secondary ovarian malignancy. Features sometimes reported to be typical of metastases to the ovary were bilateral ovarian masses and a predominately solid appearance of the mass; however, it has also been reported (3,4,23) that the appearance of primary and secondary ovarian neoplasms are too similar to allow accurate distinction.

The frequency of bilateral ovarian in-

volvement with metastases has been reported in imaging and pathologic studies. In imaging studies (3,7,8,11,12) dealing with a mixture of primary tumors that have metastasized to the ovary, 59%–75% of metastatic neoplasms are bilateral. In pathologic studies (1,19,22) of ovarian metastases, bilateral ovarian lesions occurred in 33%–64% of those from breast cancer, in 58%–71% from colon cancer, in 67%–83% from gastric cancer, and in 80% from lymphoma. Ovarian metastases from endometrial cancer are more likely to be unilateral, however, with only 14%–21% reported (1,24) as bilateral.

In a pathologic series (18) dealing mainly with gastric cancer, both ovaries were involved in all 18 cases in which both ovaries were available for analysis, though the ovaries were often asymmetrically involved and, sometimes, the smaller ovarian involvement was only microscopic. While ovarian metastases from

breast cancer were bilateral in 64% of patients in one pathologic study (22), the ovaries were normal at gross pathologic inspection in 46% of the cases, and the metastases were smaller than 1 mm in 31% of cases, making an imaging diagnosis unlikely. Conversely, primary malignant neoplasms of the ovary are generally unilateral, but there is variability between the different subtypes of epithelial ovarian malignancies, with serous and undifferentiated cystadenocarcinoma more likely to be bilateral than mucinous or endometrioid cystadenocarcinoma (2). In our experience, secondary ovarian neoplasms tended to be bilateral more often than primary neoplasms, but the difference was not statistically significant. Thus, we cannot confirm that bilaterality is a reliable differentiating feature.

The imaging appearance of the ovarian metastases has been reported in a few series. In the majority of studies, the findings of only one imaging modality were described, and the study populations had a mixture of primary neoplasms. It is difficult to reach a reliable conclusion from reviewing these studies, as the capability of US, CT, and MR imaging to characterize masses may not be comparable. In addition, several of the studies were performed more than 15 years ago, when image quality was not as good, and the classification systems used in the studies were variable and were not always clearly defined.

As a whole, the previously reported imaging findings of these studies tend to suggest that most metastatic neoplasms are predominately solid or a mixture of cystic and solid areas. In comparison, primary epithelial ovarian neoplasms are more likely to be predominately cystic (8). Pathologic studies (1,19) have revealed that most ovarian metastases from gastric cancer, endometrial cancer, and breast cancer have a predominately solid component, while ovarian metastases from colon cancer tend to be either predominately cystic or have a mixture of cystic and solid areas.

In our series, multilocularity, as determined at US or MR imaging, was more typical of primary ovarian malignancy. This is likely a reflection that primary epithelial tumors are often predominately cystic (8). The finding that multilocularity was not a significant feature at CT suggests that septa may not be as readily identified with CT as they are with US or MR imaging. However, no comparison of imaging features with gross pathologic findings was made in this study. We did not find that a pre-

dominately solid appearance of the mass was predictive of metastasis.

Interestingly, however, the designation of the nature of the tissue at MR imaging did reveal that a soft-tissue designation was more likely with metastasis. This feature was probably a more specific assessment of the largest component of the mass, though this finding is based on a relatively small number of metastasis. Only one Doppler feature was significant, the RI in the wall of a mass. It is unclear to us why the pulsatility index in this same area was not significantly different, since the two indices tend to follow the same general pattern of high or low resistance, and why only the RI would be significant in that location in the mass. We suspect this is related to the small number of masses for which this parameter was available. Though the RI has been found to be unreliable for distinguishing benign from malignant ovarian masses, the RI does tend to be lower with malignant masses in general, and it is also unclear why metastases would have a relatively high RI (25).

Of the three imaging features that we found to be significant, we are skeptical of the reliability of the MR imaging nature of the tissue and the RI in the wall of the mass, because of the relatively small number of metastasis for which these two features were recorded. We suspect that these two parameters are not as reliable as multilocularity.

In patients who have an intraabdominal neoplasm that has metastasized to the ovary, the preoperative diagnosis of ovarian metastasis might be more reliable if imaging were able to consistently depict the primary intraabdominal tumor. We were unable to address this issue, as it was not a goal of the initial RDOG study. In one study (8), the primary neoplasm was not identified with CT or MR imaging in the majority of patients with ovarian metastases from colon or gastric cancer. It does seem, however, that patients with ovarian metastasis from gastric cancer are more likely to have other evidence of metastatic disease at CT than are patients with colon cancer (3). From a clinical perspective, ovarian metastasis from breast cancer is usually seen in patients with advanced disease, and it is generally known that the patient has breast cancer when the ovarian mass is identified (3,22,26). However, for patients with ovarian metastases from most other primary neoplasms, it is more variable as to whether the presence of a primary neoplasm is

already known when the ovarian mass is identified (3,7,10,18,21).

There are several limitations of our study. This was a secondary study of the RDOG data, and our purpose was not part of the original study. For this reason, not all data pertinent to our objective were available. In addition, we confined our analysis to proved malignant masses. We did not address benign ovarian masses, which are more common than malignant ovarian masses in clinical practice, and some benign masses may not be easily distinguished from malignant masses with imaging.

In addition, no assessment of interobserver variability for determining the various imaging features was made. Some of the parameters assessed were available for only a small number of patients, and this limited the comparison. The numbers are also too small to allow stratification by institution. Two features previously reported to favor metastasis, strong wall enhancement at CT or MR imaging (8) and hypointense solid areas on T2-weighted images at MR imaging (12), could not be evaluated, as these features were not directly recorded. The type of primary neoplasms metastatic to the ovary was variable in our study and was not typical of the most frequent primary neoplasms, such as colon, breast, and gastric cancers, reported in other studies. We are unable to evaluate the appearance of ovarian metastases from these more common primary tumors, since they were infrequent in our study.

In conclusion, we found three imaging features that favor the diagnosis of a primary or secondary ovarian malignant neoplasm. A multilocular cystic mass at US or MR imaging is more likely to be a primary ovarian neoplasm than a secondary ovarian neoplasm. The solid nature of the tissue at MR imaging and a relatively high RI in the wall of the mass at Doppler US seem to favor diagnosis of a secondary neoplasm; however, their reliability is less certain due to the relatively small number of patients with data available for these features.

Nevertheless, when ovarian metastases are considered as a general group, no imaging feature seems to be highly accurate in the distinction between primary and secondary ovarian malignancies. We speculate that if a significant difference in imaging appearance is to be found between primary and secondary malignant ovarian neoplasms, it will require separate analysis of specific primary neoplasms (such as breast, colon, and gastric cancer) that metastasize to the ovary.

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