Published in final edited form as:

AJR Am J Roentgenol. 2018 April ; 210(4): 918–926. doi:10.2214/AJR.17.18254.

CT Features of Ovarian Tumors: Defining Key Differences Between Serous Borderline Tumors and Low-Grade Serous Carcinomas

Stephanie Nougaret^{#1,2,3}, Yulia Lakhman^{#2}, Nicolas Molinari⁴, Diana Feier^{2,5}, Chiara Scelzo^{2,6}, Hebert A. Vargas², Ramon E. Sosa², Hedvig Hricak², Robert A. Soslow⁷, Rachel N. Grisham⁸, Evis Sala²

¹Service de Radiologie, Institut Régional du Cancer de Montpellier, 208 Avenue des Apothicaires, Montpellier, Herault 34298, France.

²Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY.

³Institut de Recherche en Cancérologie de Montpellier, University of Montpellier, Montpellier, France.

⁴Department of Statistics, Centre Hospitalier Universitaire de Montpellier, University of Montpellier, Montpellier, France.

⁵Department of Radiology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania.

⁶Department of Surgery, Gynecology and Obstetrics Section, Tor Vergata University, Rome, Italy.

⁷Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY.

⁸Department of Medicine, Gynecologic Medical Oncology Service, Weill Cornell Medical College, New York, NY.

[#] These authors contributed equally to this work.

Abstract

OBJECTIVE—The objective of our study was to investigate whether the CT features of serous borderline tumors (SBTs) differ from those of low-grade serous carcinomas (LGSCs) and to evaluate if mutation status is associated with distinct CT phenotypes.

MATERIALS AND METHODS—This retrospective study included 59 women, 37 with SBT and 22 with LGSC, who underwent CT before primary surgical resection. Thirty of 59 patients were genetically profiled. Two radiologists (readers 1 and 2) independently and retrospectively reviewed CT examinations for qualitative features and quantified total tumor volumes (TTVs), solid tumor volumes (STVs), and solid proportion of ovarian masses. Univariate and multivariate associations

Address correspondence to S. Nougaret (stephanienougaret@free.fr).

Supplemental Data

Available online at www.ajronline.org.

FOR YOUR INFORMATION

A data supplement for this article can be viewed in the online version of the article at: www.ajronline.org.

of the CT features with histopathologic diagnoses and mutations were evaluated, and interreader agreement was determined.

RESULTS—At multivariate analysis, the presence of bilateral ovarian masses ($p = 0.03$), the presence of peritoneal disease (PD) ($p = 0.002$), and higher STV of ovarian masses ($p = 0.002$) were associated with LGSC. The presence of nodular PD pattern ($p < 0.001$ each reader) and the presence of PD calcifications (reader 1, $p = 0.02$; reader 2, $p = 0.003$) were associated with invasive peritoneal lesions (i.e., LGSC). The presence of bilateral ovarian masses ($p = 0.04$ each reader), PD (reader 1, $p = 0.01$; reader 2, $p = 0.004$), and higher STV ($p = 0.03$ for each reader) were associated with the absence of *BRAF* mutation (i.e., wild type [wt]–*BRAF*).

CONCLUSION—The CT features of LGSCs were distinct from those of SBTs. The CT manifestations of LGSC and the wt-*BRAF* phenotype were similar.

Keywords

BRAF mutation; CT; low-grade serous ovarian carcinoma; radiogenomics; serous borderline tumor

Borderline ovarian tumors are relatively uncommon, accounting for 15–20% of epithelial ovarian neoplasms [1]. Serous borderline tumors (SBTs) are the most common histologic subtype of borderline ovarian tumors. They account for two-thirds to three-quarters of all borderline ovarian tumors.

The pathogenesis and molecular profiles of SBTs and low-grade serous carcinomas (LGSCs) are distinct from those of more common high-grade serous carcinomas (HGSCs). Whereas HGSCs arise de novo from the fallopian tube lining, LGSCs develop via a stepwise process from benign serous cystadenofibromas, to SBTs, and eventually to LGSCs [2]. In fact, approximately 44% of patients who are initially diagnosed with stage II or higher SBT eventually recur, and disease in 83% of those patients progresses to LGSC [3]. These differences in pathogenesis between HGSC versus SBT and LGSC are underpinned by distinct gene mutations. Whereas *p53* mutations are ubiquitous in HGSC, they are rare in SBT and LGSC. In contrast, although *BRAF* *V600E* (hereafter abbreviated as “*BRAF*”) and *KRAS* mutations are rare in HGSC, *BRAF* mutations occur in up to 50% of SBTs and *KRAS* mutations are frequent in both SBTs and LGSCs [4–7]. Recently, *BRAF*-mutant status has been associated with SBT histology, early-stage disease at diagnosis, and improved outcomes [4, 6]. This information may potentially guide the identification of novel therapeutic targets and allow better prognostication.

Accurate distinction between SBT and LGSC is a challenging but clinically relevant task. First, SBTs commonly present in women of reproductive age who often desire fertility preservation. Given the overall favorable prognosis, fertility-sparing surgery (preservation of uterus and at least a part of one ovary) may be appropriate for young women with SBT. Conversely, total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal and nodal staging may be required for patients with LGSC [8]. Second, the differentiation of SBT from LGSC is also important in the setting of recurrence. Whereas tumor recurrence as an SBT can be followed, tumor recurrence as an LGSC requires prompt surgery [9].

At present, the distinction between SBT and LGSC is based on histopathologic specimen review, which is possible only during or after surgery or, occasionally, after biopsy; however, biopsy is prone to sampling error. The histologic features of both primary ovarian masses and peritoneal lesions (if present) must be examined to establish the correct diagnosis. Peritoneal lesions were originally classified into noninvasive and invasive implants [10]. Noninvasive implants (hereafter referred to as “implants”) lack infiltration of the underlying nonneoplastic connective tissue and may be observed with SBT [11, 12]. Peritoneal lesions that infiltrate into the underlying tissues (invasive implants) are now classified as LGSC—regardless of whether LGSC is also found in the ovary—because of the shared histology and similar clinical outcomes [11, 13, 14].

Currently, no standardized imaging approaches exist to differentiate SBT from LGSC and to assess the invasiveness of peritoneal lesions. Furthermore, there are no data to date on whether *BRAF* and *KRAS* mutations translate into distinct imaging phenotypes [4].

Preoperative imaging that could accurately differentiate SBT from LGSC, detect invasive peritoneal lesions, and identify imaging manifestations of prognostically relevant gene mutations would facilitate initial treatment design, especially if fertility preservation is being considered. It would also aid lesion selection for biopsy and the timing of surgery in the setting of recurrence. Thus, the aims of our study were to investigate whether the CT features of SBTs differ from those of LGSCs and if mutation status is associated with distinct CT phenotypes.

Materials and Methods

The institutional review board approved this retrospective HIPAA-compliant study and waived the requirement for informed consent.

Eligibility Criteria

The inclusion criteria for the study were as follows: first, diagnosis of SBT or LGSC based on the final surgical pathology from the primary surgical resection at a tertiary care cancer center (Memorial Sloan Kettering Cancer Center [MSKCC]) between February 1, 2002, and December 30, 2014; and, second, preoperative contrast-enhanced CT of the abdomen and pelvis. Fifty-nine consecutive patients satisfied these eligibility criteria. The mean number of days between preoperative CT and surgery was 35 days. Thirty of 59 patients had sufficient archival tissue available onsite to perform mutation analysis.

There are overlaps in the patient population of this study with those of two previously published studies. First, 14 patients in this study were in a study by Pannu [15], which did not test the association of the CT features with SBT versus LGSC diagnoses (including peritoneal lesions) and gene mutation status. Second, 30 patients in this study were in a study by Grisham et al. [4] that did not evaluate imaging.

Histopathologic Specimens

Clinical histopathologic reports that were rendered by fellowship-trained pathologists at the time of the original surgical specimen review served as our reference standard. The

histologic features of primary ovarian masses and peritoneal lesions (if present) described in the report were rereviewed, and the diagnosis of SBT or LGSC was rendered according to the 2014 World Health Organization (WHO) guidelines from the *WHO Classification of Tumours of Female Reproductive Organs* [13]. Briefly, SBT was diagnosed if the histologic features of SBT were present in the primary ovary mass alone or in combination with noninvasive implants. Tumors with micropapillary architecture but with neither ovarian invasion nor peritoneal invasion were classified as SBT (micropapillary subtype). LGSC was diagnosed if the histologic features of LGSC were observed in the primary ovarian mass or peritoneal lesions. When LGSC was present in association with SBT, it was designated as LGSC in accordance with the 2014 WHO classification [13].

CT Acquisition and Image Analysis

The CT examinations were performed on helical MDCT scanners with 4–64 detector rows at MSKCC ($n = 30$ patients) or outside institutions ($n = 29$). All CT images were acquired during breath-holding using the following acquisition parameters: 120 kVp; automatic milliamperage setting depending on patient size, with a range of 240–400 mA; mean section thickness and reconstruction interval of 4.7 mm (range, 0.625–7.5 mm); and mean pitch of 1.2 ± 0.5 . All patients who underwent scanning at MSKCC received 150 mL of nonionic IV contrast material (iohexol 300 [Omnipaque 300, GE Healthcare]) using a power injector at 2.5 mL/s. The time delay from contrast agent injection to scanning was approximately 70 seconds. All patients received oral contrast material, either 900 mL of 2% barium sulfate suspension (E-Z-EM, Bracco Diagnostics) or 100 mL of iohexol (Omnipaque) in 1000 mL of solution (Crystal Lite, Kraft Foods) approximately 30 minutes before CT. CT examinations that were performed at outside institutions either met or exceeded these technical standards. All CT scans were sent to a PACS (Centricity, GE Healthcare).

Qualitative CT features—Two radiologists (with 8 and 5 years of experience in gynecologic oncologic imaging, respectively) who were blinded to all clinical and mutation data independently and retrospectively evaluated all CT scans. Both readers recorded the presence and location of the ovarian mass (unilateral or bilateral), margins (smooth or irregular), texture characteristics (cystic or predominantly cystic [$\geq 50\%$ cystic] vs solid or predominantly solid [$< 50\%$ cystic]), calcifications (present or absent), papillary projections (present or absent), thick (> 3 mm) septa (present or absent), and thick (> 3 mm) wall (present or absent) (Fig. 1). Among patients with bilateral ovarian masses, a CT feature was considered present if it was observed in at least one ovarian mass. If texture characteristics differed between bilateral ovarian masses, more solid texture was selected. Readers also recorded the presence of ascites and peritoneal disease (PD). Among patients with PD on CT, PD calcifications (present or absent) and PD pattern (nodular or infiltrative) were noted. Nodular PD pattern was defined as single or multiple well-defined soft-tissue nodules; infiltrative PD was defined as poorly marginated lesions without discrete nodules (Figs. 2 and 3).

Quantitative volumetric data—Both readers independently quantified total tumor volumes (TTVs) and solid tumor volumes (STVs) using a semiautomated method (Aquarius, TeraRecon). Briefly, TTV was determined by manually outlining the outer borders of each

ovarian mass with a track ball; the same process was repeated for STV, but this time only the solid portion of each ovarian mass was included (Fig. 1). The software automatically calculated TTV and STV by summing all outlined areas and multiplying by the slice thickness. In cases of bilateral ovarian masses, the volumes of both ovarian masses were added together. The solid proportion of each ovarian mass was calculated as a ratio of STV to TTV.

Reader-determined diagnosis—Both readers independently formed an impression regarding the most likely diagnosis for each patient based on their conclusions about the qualitative CT features and their experience. They recorded their impression using the following 5-point confidence scale: 1, definitely SBT; 2, probably SBT; 3, indeterminate; 4, probably LGSC; or 5, definitely LGSC.

Gene Mutations and Tissue Analysis

Archival formalin-fixed, paraffin-embedded tissue samples were macrodissected to remove stromal contamination and to ensure tumor cellularity of 80%. Tumor DNA was extracted using a DNA extraction and purification kit according to the manufacturer's instructions (DNeasy, Qiagen).

Each specimen was analyzed using a custom assay (iPLEX, Sequenom) to detect *KRAS* and *BRAF* hot-spot mutations. Each variant detected was manually reviewed. Tumors that harbored a mutation and had sufficient DNA underwent confirmation of mutation status with an orthogonal method. All primer sequences are available on request.

Statistical Analysis

Patient characteristics, qualitative CT features, CT volumes, and histopathologic findings were summarized using descriptive statistics. Medians and interquartile ranges were used for continuous variables, whereas frequencies with corresponding percentages were used for categorical variables.

Interreader agreement for qualitative CT features and continuous volumetric data were evaluated using the Cohen kappa statistic and interclass correlation coefficient, respectively, with corresponding 95% CIs. The agreement was interpreted as follows: 0.00–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1.00, almost perfect.

Sensitivities, specificities, positive predictive values (PPVs), negative predictive values (NPVs), and overall accuracy for diagnosing LGSC, detecting PD, and identifying invasive peritoneal lesions were calculated separately for each reader. Five-point confidence scores for diagnosing SBT or LGSC were dichotomized as follows: Scores 1 and 2 indicated SBT, and scores 3, 4, and 5 indicated LGSC.

Univariate associations of qualitative CT features and CT volumes with histopathologic diagnoses and of qualitative CT features and CT volumes with the presence of a *BRAF* or *KRAS* mutation were analyzed separately for each reader using Fisher exact test or chi-square test for categorical data and Wilcoxon rank-sum test for continuous data; *p* values of <

0.05 were considered statistically significant, and CT features with $p < 0.05$ for both readers were included in a multivariate analysis.

Multivariate associations were evaluated using generalized estimating equations with independent working correlation matrices to account for both readers' assessments contained within the same model and were then selected in a stepwise-driven model.

Logarithmic transformation of nonnormally distributed variables (TTV, STV, solid proportion of ovarian masses) was performed before entering these variables into the model. All analyses were performed using R software (version 3.1.2, The R Foundation).

Results

Patient Characteristics and Histopathologic Findings

All patient characteristics, histopathologic diagnoses, and surgical procedures are summarized in Table 1. Fifty-nine women were included in our study (median age, 50 years; age range, 21–82 years). Of these women, 37 (63%) patients had SBT and 22 (37%) patients had LGSC. Twelve of 37 (32%) patients with SBT had noninvasive implants, and 21 of 22 (95%) patients with LGSC had invasive peritoneal lesions.

Among 30 patients (25 with SBT and five with LGSC) with mutation analysis, 12 patients had *BRAF*-mutant tumors (12/30, 40%) and all of these tumors were SBT. However, the trend toward predominance of *BRAF*-mutant tumor in patients with SBT did not reach statistical significance ($p = 0.07$). Six patients had *KRAS*-mutant tumors (6/30, 20%) (Table 1).

Interreader Agreement

Interreader agreement for qualitative CT features ranged from substantial to almost perfect ($\kappa = 0.65$ –1.00) and is summarized in Table S1. (Table S1 can be viewed in the *AJR* electronic supplement to this article, available at www.ajronline.org.)

Diagnostic Accuracy for Diagnosing Low-Grade Serous Carcinomas, Detecting Peritoneal Disease, and Identifying Invasive Peritoneal Lesions on CT

These results are summarized in Table 2.

Univariate Associations Between Qualitative CT Features and Low-Grade Serous Carcinomas at Histopathology

At univariate analysis, the presence of bilateral ovarian masses ($p = 0.001$ each reader), irregular ovarian mass margins ($p < 0.001$ each reader), solid or predominantly solid ovarian mass texture (reader 1, $p = 0.006$; reader 2, $p = 0.03$), ovarian mass calcifications ($p < 0.001$ each reader), presence of PD ($p < 0.001$ each reader), nodular PD pattern ($p < 0.001$ each reader), and PD calcifications (reader 1, $p = 0.02$; reader 2, $p = 0.003$) were significantly associated with the histopathologic diagnosis of LGSC for both readers (Table 3).

Univariate Associations Between Ovarian Mass Volumes and Low-Grade Serous Carcinomas at Histopathology

At univariate analysis, greater TTV (reader 1, $p = 0.047$; reader 2, $p = 0.04$), higher STV ($p < 0.001$ each reader), and larger solid proportion of ovarian masses ($p < 0.001$ each reader) were significantly associated with the histopathologic diagnosis of LGSC for both readers (Table 3).

Univariate Associations Between Qualitative CT Features and Invasive Peritoneal Lesions at Histopathology

Among 33 patients with PD, 21 (64%) had invasive peritoneal lesions. The presence of the nodular PD pattern ($p < 0.001$ each reader) and the presence of PD calcifications (reader 1, $p = 0.02$; reader 2, $p = 0.003$) were significantly associated with the presence of invasive peritoneal lesions for both readers (Table 4).

Multivariate Associations Between Qualitative CT Features, Ovarian Mass Volumes, and Low-Grade Serous Carcinomas at Histopathology

All variables with p values of < 0.05 for both readers were included in the multivariate analysis. The exceptions were PD pattern and PD calcifications because 26 of 59 patients lacked PD and, hence, could not be included in the multivariate model.

At multivariate analysis, the presence of bilateral ovarian masses ($p = 0.03$), the presence of PD ($p = 0.002$), and higher STV of ovarian masses ($p = 0.002$) remained significantly associated with the histopathologic diagnosis of LGSC.

Univariate Associations Between Qualitative CT Features, Ovarian Mass Volumes, and Mutation Status

At univariate analysis, the presence of bilateral ovarian masses ($p = 0.04$ each reader), the presence of PD (reader 1, $p = 0.01$; reader 2, $p = 0.004$), and higher STV ($p = 0.03$ each reader) were significantly associated with the absence of a *BRAF* mutation (i.e., wild type [wt]–*BRAF*) for both readers. Irregular ovarian mass margins were significantly associated with wt–*BRAF* for reader 1 only ($p = 0.02$) (Table S2, which can be viewed in the *AJR* electronic supplement to this article at www.ajronline.org). Qualitative CT features and ovarian mass volumes were not associated with *KRAS*-mutation status (Table S3, which can be viewed in the *AJR* electronic supplement to this article at www.ajronline.org).

Discussion

Our study results highlight key imaging differences between SBT and LGSC and underscore imaging characteristics of invasive peritoneal lesions on CT. This information may be important at the time of initial diagnosis to facilitate treatment planning and patient counseling and, in the setting of recurrence, to select the most suspicious lesion for biopsy and to optimally time surgical intervention. Furthermore, our results reveal the similarities in CT features between LGSC and wt–*BRAF* tumors, which may allow better prognostication.

Multiple imaging features and criteria have been proposed to help the differentiation of benign from malignant ovarian masses using various imaging modalities [16–22]. Furthermore, several risk prediction models have been put forth to discriminate between benign, borderline, and malignant ovarian masses [23, 24]. There are very few studies in the literature that describe the imaging features of SBTs [25–28], evaluate imaging differences between SBTs and LGSCs, or describe imaging signs of invasion within peritoneal lesions. Despite limited data, this information is of clinical importance. SBT is often diagnosed in patients who are young and frequently want to preserve their childbearing potential. At present, surgeons have limited diagnostic tools to determine the likelihood of invasion before operative staging. Given the fact that LGSCs often arise in a background of SBT, biopsies may provide disparate results depending on the lesion that is sampled.

We found that, at univariate analysis, the presence of bilateral ovarian masses, irregular ovarian mass margins, solid or predominantly solid ovarian mass texture, ovarian mass calcifications, higher TTV and STV, larger solid proportion of ovarian masses, presence of PD, nodular PD pattern, and PD calcifications were significantly associated with LGSC at histopathology for both readers. At multivariate analysis, the presence of bilateral ovarian masses, the presence of PD, and greater STV remained significantly associated with LGSC at histopathology.

In addition, we found the presence of the nodular PD pattern and PD calcifications to be significantly associated with invasive peritoneal lesions (LGSC) at histopathology. Our findings regarding the association between PD calcifications and invasive peritoneal lesions are concordant with those of Burkill et al. [29] who reported intratumoral calcifications to predominate in serous cystadenocarcinomas and proposed psammoma bodies to be the most likely source of these calcifications.

Our findings on CT regarding the morphologic difference in PD patterns between noninvasive implants and invasive peritoneal lesions are supported by the observations at histopathology. Thus, noninvasive implants may show hierarchically branching papillae or detached clusters of cells associated with nonfibrotic stroma (epithelial type of noninvasive implants), or they may be composed of clusters of cells that are “tacked on” to the peritoneal surface (desmoplastic type of noninvasive implants) that are akin to the infiltrative pattern of PD we observed on CT. In many cases, the tacked-on implants track along invaginations of peritoneum between lobules of omental adipose tissue, possibly accounting for the appearance of an infiltrative pattern of PD. On the other hand, invasive peritoneal lesions may display unequivocal invasion or may present as solid mass-forming nests of cells surrounded with micropapillae or cribriform growth that are akin to the nodular pattern of PD we noted on CT [10, 11, 13, 30].

Finally, we found associations between CT phenotypes and prognostically relevant *BRAF* mutation status. Recent studies in the literature have highlighted the potential role of gene mutations affecting the mitogen-activated protein kinase pathway in the development of SBT and LGSC [31]. Although both *BRAF* and *KRAS* mutations were observed in patients with these tumors, *BRAF*-mutant tumors were more frequent in patients with SBT or early-stage LGSC and were rare in patients with advanced-stage LGSC [4–6, 32]. Concordant with

these observations, we found *BRAF*-mutant status to be associated with early-stage disease on CT—that is, the presence of a unilateral ovarian mass and the absence of peritoneal implants. We also noted LGSC and wt-*BRAF* tumors to have similar CT features (bilateral ovarian involvement, presence of PD, and higher STV). This information may be of value to clinicians for initial medical decision-making, patient counseling, and prognostication.

Our study has several limitations. First, it is a retrospective review and has the limitations imposed by this study design. Second, our data were derived from a small cohort of patients, which is explained by the rarity of these tumors. Indeed, the combination of preoperative CT, genomics profiling, and surgery was available in only a subset of patients. Finally, we evaluated the CT features of only SBT and LGSC. However, this strategy is justified because CT is the most commonly used imaging modality for preoperative assessment of these patients, and therefore lesion characterization by this modality would be expected to be the most clinically useful method.

In conclusion, we identified distinct CT features associated with LGSC and invasive peritoneal lesions, and we observed important similarities between the CT features of LGSC and the wt-*BRAF* imaging phenotype. Although our study was limited by small numbers of patients and requires further validation, this information may provide improved prognostic information and may allow gynecologic oncologists to better determine if fertility-sparing surgery is likely to be an option for young women preparing for initial staging surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

We thank Joanne Chin for her editorial assistance with this manuscript.

This research was funded in part by a grant (P30 CA008748) from the National Institutes of Health/National Cancer Institute to Memorial Sloan Kettering Cancer Center and a grant from the L'Institut National du Cancer and Site de Recherche Intégrée sur le Cancer to S. Nougaret.

References

1. Morice P, Uzan C, Fauvet R, Gouy S, Duvillard P, Darai E. Borderline ovarian tumour: pathological diagnostic dilemma and risk factors for invasive or lethal recurrence. *Lancet Oncol* 2012; 13:e103–e115 [PubMed: 22381933]
2. Russell SE, McCluggage WG. A multistep model for ovarian tumorigenesis: the value of mutation analysis in the *KRAS* and *BRAF* genes. *J Pathol* 2004; 203:617–619 [PubMed: 15141374]
3. Silva EG, Gershenson DM, Malpica A, Deavers M. The recurrence and the overall survival rates of ovarian serous borderline neoplasms with noninvasive implants is time dependent. *Am J Surg Pathol* 2006; 30:1367–1371 [PubMed: 17063075]
4. Grisham RN, Iyer G, Garg K, et al. *BRAF* mutation is associated with early stage disease and improved outcome in patients with low-grade serous ovarian cancer. *Cancer* 2013; 119:548–554 [PubMed: 22930283]
5. Singer G, Oldt R 3rd, Cohen Y, et al. Mutations in *BRAF* and *KRAS* characterize the development of low-grade ovarian serous carcinoma. *J Natl Cancer Inst* 2003; 95:484–486 [PubMed: 12644542]
6. Wong KK, Tsang YT, Deavers MT, et al. *BRAF* mutation is rare in advanced-stage low-grade ovarian serous carcinomas. *Am J Pathol* 2010; 177:1611–1617 [PubMed: 20802181]

7. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature* 2011; 474:609–615 [PubMed: 21720365]
8. Morgan RJ Jr, Copeland L, Gershenson D, et al. NCCN ovarian cancer practice guidelines: the National Comprehensive Cancer Network. *Oncology (Williston Park)* 1996; 10(suppl 11):293–310 [PubMed: 8953610]
9. Crispens MA, Bodurka D, Deavers M, Lu K, Silva EG, Gershenson DM. Response and survival in patients with progressive or recurrent serous ovarian tumors of low malignant potential. *Obstet Gynecol* 2002; 99:3–10 [PubMed: 11777502]
10. Bell KA, Smith Sehdev AE, Kurman RJ. Refined diagnostic criteria for implants associated with ovarian atypical proliferative serous tumors (borderline) and micropapillary serous carcinomas. *Am J Surg Pathol* 2001; 25:419–432 [PubMed: 11257616]
11. Bell DA, Weinstock MA, Scully RE. Peritoneal implants of ovarian serous borderline tumors: histologic features and prognosis. *Cancer* 1988; 62:2212–2222 [PubMed: 3179935]
12. Seidman JD, Soslow RA, Vang R, et al. Borderline ovarian tumors: diverse contemporary viewpoints on terminology and diagnostic criteria with illustrative images. *Hum Pathol* 2004; 35:918–933 [PubMed: 15297960]
13. Kurman RJ, Carcangiu ML, Herrington CS, Young RH, eds. WHO classification of tumours of female reproductive organs, 4th ed., vol. 6 Geneva, Switzerland: WHO Press, 2014
14. Hart WR. Borderline epithelial tumors of the ovary. *Mod Pathol* 2005; 18(suppl 2):S33–S50 [PubMed: 15761465]
15. Pannu HK. CT features of low grade serous carcinoma of the ovary. *Eur J Radiol Open* 2015; 2:39–45 [PubMed: 26937434]
16. Brown DL, Doubilet PM, Miller FH, et al. Benign and malignant ovarian masses: selection of the most discriminating gray-scale and Doppler sonographic features. *Radiology* 1998; 208:103–110 [PubMed: 9646799]
17. Timmerman D, Testa AC, Bourne T, et al. Simple ultrasound-based rules for the diagnosis of ovarian cancer. *Ultrasound Obstet Gynecol* 2008; 31:681–690 [PubMed: 18504770]
18. Kinkel K, Hricak H, Lu Y, Tsuda K, Filly RA. US characterization of ovarian masses: a meta-analysis. *Radiology* 2000; 217:803–811 [PubMed: 11110947]
19. Hricak H, Chen M, Coakley FV, et al. Complex adnexal masses: detection and characterization with MR imaging—multivariate analysis. *Radiology* 2000; 214:39–46 [PubMed: 10644099]
20. Jacobs I, Oram D, Fairbanks J, Turner J, Frost C, Grudzinskas JG. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *Br J Obstet Gynaecol* 1990; 97:922–929 [PubMed: 2223684]
21. Sohaib SA, Mills TD, Sahdev A, et al. The role of magnetic resonance imaging and ultrasound in patients with adnexal masses. *Clin Radiol* 2005; 60:340–348 [PubMed: 15710137]
22. Kinkel K, Lu Y, Mehdizade A, Pelte MF, Hricak H. Indeterminate ovarian mass at US: incremental value of second imaging test for characterization—meta-analysis and Bayesian analysis. *Radiology* 2005; 236:85–94 [PubMed: 15955864]
23. Van Calster B, Van Hoorde K, Valentin L, et al.; International Ovarian Tumour Analysis Group. Evaluating the risk of ovarian cancer before surgery using the ADNEX model to differentiate between benign, borderline, early and advanced stage invasive, and secondary metastatic tumours: prospective multicentre diagnostic study. *BMJ* 2014; 349:g5920 [PubMed: 25320247]
24. Thomassin-Naggara I, Aubert E, Rockall A, et al. Adnexal masses: development and preliminary validation of an MR imaging scoring system. *Radiology* 2013; 267:432–443 [PubMed: 23468574]
25. Kim SH, Yang DM, Kim SH. Borderline serous surface papillary tumor of the ovary: MRI characteristics. *AJR* 2005; 184:1898–1900 [PubMed: 15908549]
26. Tanaka YO, Okada S, Satoh T, et al. Ovarian serous surface papillary borderline tumors form sea anemone-like masses. *J Magn Reson Imaging* 2011; 33:633–640 [PubMed: 21287653]
27. Zhao SH, Qiang JW, Zhang GF, et al. MRI appearances of ovarian serous borderline tumor: pathological correlation. *J Magn Reson Imaging* 2014; 40:151–156 [PubMed: 24923479]
28. Naqvi J, Nagaraju E, Ahmad S. MRI appearances of pure epithelial papillary serous borderline ovarian tumours. *Clin Radiol* 2015; 70:424–432 [PubMed: 25515794]

29. Burkill GJ, Allen SD, A'Hern RP, Gore ME, King DM. Significance of tumour calcification in ovarian carcinoma. *Br J Radiol* 2009; 82:640–644 [PubMed: 19332521]
30. Gershenson DM, Silva EG, Tortolero-Luna G, Levenback C, Morris M, Tornos C. Serous borderline tumors of the ovary with noninvasive peritoneal implants. *Cancer* 1998; 83:2157–2163 [PubMed: 9827720]
31. Grisham RN, Sylvester BE, Won H, et al. Extreme outlier analysis identifies occult mitogen-activated protein kinase pathway mutations in patients with low-grade serous ovarian cancer. *J Clin Oncol* 2015; 33:4099–4105 [PubMed: 26324360]
32. Koutsaki M, Zaravinos A, Spandidos DA. Modern trends into the epidemiology and screening of ovarian cancer: genetic substrate of the sporadic form. *Pathol Oncology Res* 2012; 18:135–148

Fig. 1—.

CT features of ovarian masses.

A, Drawing illustrates qualitative CT features of primary ovarian masses that were evaluated by each reader.

B, Reformatted coronal contrast-enhanced CT image of 45-year-old woman with low-grade serous carcinoma (LGSC) shows bilateral ovarian masses. Left ovarian mass has mixed predominantly cystic texture with thick wall (*black arrow*) and solid component with calcifications (*white arrow*). Right ovarian mass (*arrowhead*) is entirely solid.

C, Three-dimensional volume-rendered coronal CT image of same patient as in **B** shows solid proportion of bilateral ovarian masses.

Fig. 2—

CT features of peritoneal disease (PD) in patients with ovarian masses.

A, Drawing illustrates CT features of PD that were evaluated by both readers.

B, Axial contrast-enhanced CT image of 35-year-old woman with serous borderline tumor shows primary ovarian tumor (T) and ill-defined infiltration of peritoneal fat (*arrow*) consistent with infiltrative PD pattern.

C, Axial contrast-enhanced CT image of 68-year-old woman with low-grade serous carcinoma shows well-defined nodular peritoneal lesions (*arrows*) corresponding to nodular PD pattern.

Fig. 3—. Schematic representation (*upper image*) shows step-wise progression from serous borderline tumor (SBT) to low-grade serous carcinoma (LGSC). Axial contrast-enhanced CT image of 51-year-old woman with SBT (*lower left image*) and noninvasive implants shows ill-defined infiltration of omentum (*arrow*, lower left image). Axial contrast-enhanced CT image of 47-year-old woman with LGSC (*lower right image*) shows nodular peritoneal lesions with calcifications (*arrows*, lower right image) that corresponded to invasive lesions at histopathology.

TABLE 1:

Patient Characteristics, Histopathologic Diagnoses, and Surgical Procedures

Patient Characteristics	Entire Cohort (n = 59 Patients)	SBT (n = 37 Patients)	LGSC (n = 22 Patients)	p
Age at diagnosis (y), median (range)	50 (21–82)	47 (21–80)	53 (22–82)	0.13
FIGO stage				< 0.001
I or II	26 (44)	25	1	
III or IV	33 (56)	12	21	
Histology				
SBT		37 (63)		
LGSC			22 (37)	
Mutation status evaluation				
No. of patients with mutation status data available	30	25	5	
<i>BRCA</i> -mutant tumors	12 (40)	12 (48)	0 (0)	0.07
<i>KRAS</i> -mutant tumors	6 (20)	6 (24)	0 (0)	0.55
Surgery				
Total hysterectomy and bilateral salpingo-oophorectomy	43 (73)	22 (59.5)	21 (95)	
Bilateral salpingo-oophorectomy	2 (3)	2 (5.5)	0 (0)	
Unilateral salpingo-oophorectomy	11 (19)	10 (27)	1 (5)	
Ovarian cystectomy	3 (5)	3 (8)	0 (0)	
Peritoneal staging procedures				
Omental biopsy	16 (27)	16 (43)	0 (0)	
Omentectomy	5 (8.5)	4 (11)	1 (5)	
Omentectomy and debulking	38 (64.5)	17 (46)	21 (95)	
Peritoneal disease present	33 (56)	12 (32)	21 (95)	< 0.001

Note—Unless indicated otherwise, data are number (%) of patients. **Boldface** indicates the *p* value is statistically significant (*p* < 0.05). SBT = serous borderline tumor, LGSC = low-grade serous carcinoma, FIGO = International Federation of Gynecology and Obstetrics.

TABLE 2:

Diagnostic Accuracy for Each Reader for Diagnosing Low-Grade Serous Carcinoma (LGSC), Detecting Peritoneal Disease (PD), and Identifying Invasive Peritoneal Lesions

Diagnostic Accuracy	Performance Value				
	Sensitivity	Specificity	PPV	NPV	Accuracy
Diagnostic accuracy for diagnosing LGSC					
Reader 1	18/22, 82% (66–98%)	34/37, 92% (83–100%)	18/21, 86% (71–100%)	34/38, 89% (80–99%)	52/59, 88% (80–96%)
Reader 2	21/22, 95% (87–100%)	33/37, 89% (79–99%)	21/25, 84% (70–98%)	33/34, 97% (91–100%)	54/59, 91% (84–99%)
Diagnostic accuracy for detecting PD					
Reader 1	31/33, 94% (86–100%)	25/26, 96% (89–100%)	31/32, 97% (91–100%)	25/27, 93% (83–100%)	56/59, 95% (89–100%)
Reader 2	32/33, 97% (91–100%)	26/26, 100% (84–100%)	32/32, 100% (87–100%)	26/27, 96% (89–100%)	58/59, 98% (95–100%)
Diagnostic accuracy for identifying invasive peritoneal lesions ^a					
Reader 1	17/21, 81% (58–95%)	11/12, 92% (61–100%)	17/18, 94% (84–100%)	11/15, 73% (47–99%)	28/33, 85% (68–95%)
Reader 2	18/21, 86% (64–97%)	12/12, 100% (70–100%)	18/18, 100% (78–100%)	12/15, 80% (57–100%)	30/33, 91% (76–98%)

Note—Data are presented as number of tumors / total number of tumors, performance value (95% CI). PPV = positive predictive value, NPV = negative predictive value.

^a Among 33 patients with peritoneal disease, 21 (64%) had invasive peritoneal lesions.

TABLE 3:

Univariate Analysis of the Associations Between Qualitative CT Features, Ovarian Mass Volumes, and Low-Grade Serous Carcinoma (LGSC) at Histopathology

Characteristics	Reader 1			Reader 2		
	LGSC (n = 22)	SBT (n = 35)	p	LGSC (n = 22)	SBT (n = 35)	p
Ovarian mass						
Location						
Unilateral (reference)	2 (9)	24 (65)	0.001	2 (9)	24 (65)	0.001
Bilateral	20 (91)	11 (30)		20 (91)	11 (30)	
No mass	0 (0)	2 (5)		0 (0)	2 (5)	
Margins						
Smooth (reference)	6 (27)	30 (86)	<0.001	5 (23)	27 (77)	<0.001
Irregular	16 (73)	5 (14)		17 (77)	8 (23)	
Texture						
Cystic or predominantly cystic (reference)	9 (41)	27 (77)	0.006	11 (50)	27 (77)	0.03
Solid or predominantly solid	13 (59)	8 (23)		11 (50)	8 (23)	
Calcifications						
Absent (reference)	3 (14)	24 (69)	<0.001	2 (9)	22 (63)	<0.001
Present	19 (86)	11 (31)		20 (91)	13 (37)	
Papillary projections						
Absent (reference)	10 (45)	7 (20)	0.04	9 (41)	8 (23)	0.15
Present	12 (55)	28 (80)		13 (59)	27 (77)	
Thick ^a wall						
Absent (reference)	5 (23)	14 (40)	0.18	3 (14)	14 (40)	0.04
Present	17 (77)	21 (60)		19 (86)	21 (60)	
Thick ^a septa						
Absent (reference)	8 (36)	20 (57)	0.13	7 (32)	15 (43)	0.18
Present	14 (64)	15 (43)		15 (68)	20 (57)	
Total ovarian mass volume (cm ³)	397 [19–3305]	110 [1.3–1205]	0.047	403 [20–3210]	112 [1–1281]	0.04
Solid ovarian mass volume (cm ³)	148 [2–1700]	4.8 [0–396]	<0.001	122 [2–1756]	4.5 [0–396]	<0.001

Characteristics	Reader 1			Reader 2		
	LGSC (n = 22)	SBT (n = 35)	p	LGSC (n = 22)	SBT (n = 35)	p
Solid proportion of ovarian mass (%)	65 [0.72–100]	2.11 [0–100]	< 0.001	61 [0.62–100]	2.6 [0–100]	< 0.001
Peritoneum						
Ascites			0.28			0.47
Absent (reference)	7 (32)	17 (46)		8 (36)	17 (46)	
Present	15 (68)	20 (54)		14 (64)	20 (54)	
PD			< 0.001			< 0.001
Absent (reference)	1 (5)	26 (70)		2 (9)	25 (68)	
Present	21 (95)	11 (30)		20 (91)	12 (32)	
PD pattern			< 0.001			< 0.001
Infiltrative (reference)	3 (14)	11 (100)		2 (10)	12 (100)	
Nodular	18 (86)	0 (0)		18 (90)	0 (0)	
PD calcifications			0.02			0.003
Absent (reference)	7 (33)	9 (82)		7 (35)	11 (92)	
Present	14 (67)	2 (18)		13 (65)	1 (8)	

Note—For continuous variables, data are medians with ranges in brackets. For categoric variables, data are frequencies with percentages in parentheses. **Boldface** indicates the *p* value is statistically significant (*p* < 0.05). SBT = serous borderline tumor, PD = peritoneal disease.

^aDefined as > 3 mm.

TABLE 4:
Univariate Analysis of the Associations Between Qualitative CT Features and Invasive Peritoneal Lesions at Histopathology

CT Features	Reader 1		Reader 2		<i>p</i>
	Invasive Lesion (<i>n</i> = 21)	Noninvasive Implants (<i>n</i> = 12)	Invasive Lesions (<i>n</i> = 21)	Noninvasive Implants (<i>n</i> = 12)	
Ascites					
Present	15 (71)	11 (92)	14 (67)	10 (83)	0.43
PD pattern					< 0.001
Infiltrative (reference)	3 (14)	11 (92)	2 (9)	12 (100)	
Nodular	17 (81)	0 (0)	18 (86)	0 (0)	
No PD	1 (5)	1 (8)	1 (5)	0	
PD calcifications					
Present	13 (65)	2 (18)	13 (65)	1 (8)	0.003

Note—Data are frequencies with percentages in parentheses. **Boldface** indicates the *p* value is statistically significant (*p* < 0.05). PD = peritoneal disease.