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Current Update on Borderline Ovarian Neoplasms

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OBJECTIVE. Borderline ovarian tumors comprise a unique group of noninvasive ovarian neoplasms with characteristic histology and variable tumor biology that typically manifest as low-stage disease in younger women with resultant excellent prognosis.

CONCLUSION. Borderline tumors are considered to be precursors of low-grade ovarian cancers. Accurate diagnosis and staging facilitate optimal patient management particularly in patients desiring to preserve fertility.

Keywords: borderline ovarian tumors, imaging neoplasms, ovarian cancer, ovarian tumors of low malignant potential

DOI:10.2214/AJR.09.3936

Received November 9, 2009; accepted after revision November 13, 2009.

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AJR 2010; 194:330–336

0361–803X/10/1942–330

Borderline ovarian tumors comprise up to 15–20% of ovarian epithelial neoplasms [1]. Borderline ovarian tumors are histologically characterized as epithelial tumors with a stratified growth pattern but without destructive stromal invasion. Serous and mucinous neoplasms constitute the majority of borderline tumors and occur mostly in women of reproductive age [1]. Howard C. Taylor, Jr., [2] is credited with the first use of the term "semimalignant tumors" in 1929 for a subset of large ovarian tumors that had an indolent clinical course with relatively favorable patient outcome despite the presence of peritoneal disease. However, borderline ovarian tumors were not considered a distinct entity until 1971 when the International Federation of Obstetric Gynecology (FIGO) established a separate borderline category of tumors. Since then, considerable controversy has surrounded the definition and management of borderline ovarian tumors because of their enigmatic pathogenesis and perplexing biologic behavior [3]. Synonyms of borderline ovarian tumors include tumors of borderline malignancy, tumors of low malignant potential, and atypical proliferative tumors.

Several studies have described the characteristic cytogenetics, epidemiology, natural history, and biologic behavior of specific subtypes of borderline ovarian tumors. Researchers have postulated that specific genetic changes contribute to their pathogenesis and stepwise progression to low-grade invasive ovarian carcinomas. Although the majority of serous and mucinous borderline ovarian tumors are characterized by *KRAS* mutations, β-*catenin* and *PTEN* mutations are commonly seen with endometrioid borderline ovarian tumors [4]. In addition, endometriosis is an important precursor of endometrioid and clear cell borderline ovarian tumors.

Serous borderline ovarian tumors are unique neoplasms that may behave in an aggressive fashion with associated peritoneal "implants" and regional lymphadenopathy. Because women with extraovarian spread of disease have a very good prognosis, the peritoneal lesions are classified as implants instead of metastases. Although conservative management suffices in women with early-stage borderline ovarian tumors wanting to preserve fertility, radical surgery is warranted in patients with late-stage disease. In contradistinction to high-grade serous carcinomas (the most common ovarian malignancy), borderline ovarian tumors are notoriously resistant to platinum-based chemotherapy [5]. Prognosis is generally excellent. Although the imaging features of borderline ovarian tumors significantly overlap with those of invasive epithelial cancers, cross-sectional imaging studies play a major role in the diagnosis, management, and surveillance of patients with borderline ovarian tumors [6].

Epidemiology and Taxonomy

Borderline ovarian tumors are relatively uncommon with an incidence of 1.5–2.5 per 100,000 people per year. Approximately, 3,000 cases of borderline ovarian tumors are annually diagnosed in the United States [7]. Borderline ovarian tumors most commonly

affect white women of reproductive age typically during the fourth decade. Up to 27% of patients with borderline ovarian tumors are younger than 40 years [8]. The mean age of presentation of borderline ovarian tumors is approximately 20 years earlier than that of invasive ovarian carcinomas [9]. Most patients with borderline tumors present with nonspecific symptoms such as abdominopelvic pain or mass. Approximately 16% of patients are asymptomatic at the time of diagnosis [10]. According to the 2003 World Health Organization classification schemata [11], borderline ovarian tumors are classified on the basis of histopathology and histogenesis into serous, mucinous, endometrioid, clear cell, and transitional (Brenner) subtypes. Salient features, including precursor lesions and cytogenetics, of borderline ovarian tumors are summarized in Table 1.

Serous Borderline Ovarian Tumors

Serous borderline ovarian tumors comprise the most common histologic subtype of borderline ovarian tumors, accounting for approximately 65% of all borderline ovarian tumors [12]. The mean age range of presentation is 34–40 years. Serous borderline ovarian tumors are slow-growing neoplasms that may be associated with aggressive biologic behavior in the form of peritoneal implants and regional lymphadenopathy in approximately 35% and 27% of patients, respectively. Histologically, serous borderline ovarian tumors are divided into typical, 90% of serous borderline ovarian tumors, and micropapillary, 10% of serous borderline ovarian tumors, types [11]. Most low-grade serous carcinomas are thought to arise from micropapillary borderline ovarian tumors. Serous surface borderline tumor is another variant that shows polypoid excrescences that occupy the outer surface of the ovary.

Recent advances in cytogenetics have yielded unique insights into the pathogenesis and biologic behavior of serous borderline ovarian tumors. In several studies, investigators have found that only a small subset of serous cystadenomas progress to serous borderline ovarian tumors and that activating mutations of *BRAF* and *KRAS* genes are early events in tumorigenesis of borderline ovarian tumors. In contradistinction to high-grade serous carcinomas, the most common subtype of ovarian cancer, that are characterized by *p53* mutations in more than 50% tumors, serous borderline ovarian tumors are characterized by *KRAS* and *BRAF* mutations in two thirds of tumors (Fig. 1). Up to 50% of serous borderline ovarian tumors are characterized by *BRAF* mutations, and *KRAS* mutations are

TABLE 1: Summary of Borderline Ovarian Tumors

Type of Borderline Ovarian Tumor	Precursor	Progression to	Cytogenetics	Characteristic Features	Prognosis
Serous	Serous cystadenoma or adenofibroma	Invasive low-grade serous carcinoma	Mutations in *KRAS* or *BRAF* genes ≈ 67%	May follow dualistic oncogenic pathway; invasive or noninvasive implants may occur; presence of invasive implants is a poor prognostic factor; associated with regional lymphadenopathy Typical subtype (90%) Micropapillary subtype (10%) is closely associated with invasive implants	70% of cases are stage I; survival is almost 100% 30% of cases are advanced stages; survival is 95.3% if implants are noninvasive and 66% if implants are invasive
Mucinous	Intestinal subtype (90%): mucinous cystadenoma Müllerian subtype (10%): endometriotic cysts?	Intraepithelial carcinoma then to invasive mucinous carcinoma	Mutations in *KRAS* (> 60%)	Intestinal subtype (90%) is unilateral; is multicystic with smooth capsule; is associated with pseudomyxoma peritonei; has larger multilocular cystic lesions; shows fluids of different signal intensities on T1- or T2-weighted MR images Müllerian subtype (10%) is bilateral in 20–30%; is exophytic and paucilocular; mimics serous tumors hence termed "seromucinous"; implants may present	82% of cases are stage I; 5-year survival is up to 99–100% 18% of cases are advanced stages; mortality may reach up to 50% depending on stage
Endometrioid	Endometriosis, endometrioid adenofibroma	Intraepithelial carcinoma then to low-grade invasive endometrioid carcinoma	Gene mutations in β-*catenin* (> 50%); loss of heterozygosity or *PTEN* mutations (20%); microsatellite instability (13–50%)	None	Benign course with high survival rates
Clear cell	Endometriosis, clear cell adenofibroma	Intraepithelial carcinoma then to invasive clear cell carcinoma	*KRAS* mutations (5–16%); microsatellite instability (≈ 13%)	None	Benign course with high survival rates
Brenner	Benign Brenner	Malignant Brenner?	Not yet identified	None	Benign course with high survival rates

seen in more than a third of serous borderline ovarian tumors.

A dual oncogenic pathway has been described in which serous borderline ovarian tumors undergo stepwise transformation to low-grade serous carcinomas and high-grade serous carcinomas possibly arise de novo from surface epithelia due to *p53* and *BRCA* mutations [13–15]. Serous borderline ovarian tumors are characterized by activation of specific tumor suppressor genes (*SERPINA5* and dual specificity phosphatase 4 [*DUSP4*]) that inhibit degradation of the extracellular matrix, a key event in the pathogenesis of invasive growth [16]. Thus, serous borderline ovarian tumors charter an indolent course due to genetic events that promote tumor proliferation but not metastases. In addition, pharmacologic inhibitors of the *KRAS–BRAF* pathway are being considered to treat patients with advanced serous borderline ovarian tumors to improve patient survival.

The serous borderline ovarian tumors are unique among the borderline ovarian tumors in that invasive or noninvasive peritoneal implants may occur in 35% of cases. The nomenclature is dependent on whether the implants are simply "stuck on" the peritoneal surfaces (noninvasive) or have invaded the underlying tissue such as omentum and bowel wall [3]. Although noninvasive implants are associated with benign behavior, the presence of invasive implants portends a poor prognosis [11, 17]. A small subset of implants also may originate de novo from nodal endosalpingiosis (spectrum of secondary müllerian system involvement in the pelvis) [3]. Psammoma bodies may be associated with noninvasive implants.

Lymph node involvement may be seen in about 27% of serous borderline ovarian tumors [18]. Although lymph node involvement has no prognostic value, lymph nodes may serve as sites of recurrence and progression to carcinoma [18, 19]. It is hypothesized that these nodal metastases most likely exit the ovary through the peritoneal lymphatics rather than through the ovarian lymphatics. Commonly involved lymph nodes in advanced serous borderline ovarian tumors include the following in descending order of frequency: pelvic, omental and mesenteric, and paraaortic and supradiaphragmatic regions [19].

Serous borderline ovarian tumors manifest as complex cystic adnexal masses with thin septations and endocystic or exocystic vegetations [20] (Fig. 2). The solid components commonly show moderate enhancement during contrast-enhanced CT or dynamic MRI (Fig. 3). Approximately one third of serous borderline ovarian tumors are bilateral. Noninvasive peritoneal implants occur more frequently than invasive implants (78% vs 22%, respectively) [12]. A serous tumor with invasive implants macroscopically may have profuse papillary projections that actually consists of many vesicles perforating and extending beyond the ovarian capsule without a solid component. The lesion may have high signal intensity on contrast-enhanced T1-weighted imaging and water signal intensity on the T2-weighted imaging, suggesting the absence of solid elements [21]. Barring the presence of extraovarian disease (Fig. 4), the imaging findings of serous borderline ovarian tumors are indistinguishable from other borderline ovarian tumors and advanced borderline ovarian tumors masquerade as invasive ovarian carcinomas.

At the time of presentation, 70% of serous borderline ovarian tumors are confined to the ovary (stage I). Survival for women with stage I tumors is virtually 100%. The overall prognosis is dependent on the presence of peritoneal implants. After 7.4 years (mean) of follow-up, the survival for advanced stage serous

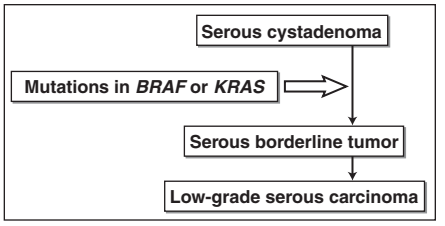

Fig. 1—Schematic representation shows progression of serous borderline tumor to low-grade serous carcinoma.

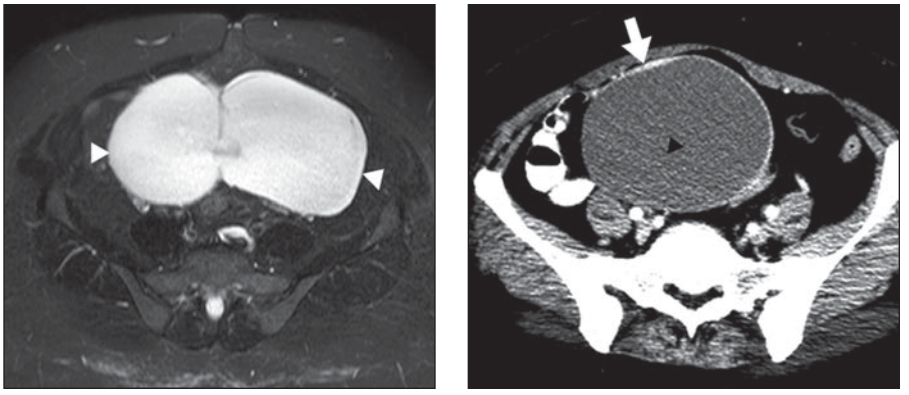

Fig. 2—Benign serous cystadenoma versus serous borderline tumor: imaging findings.
A, 46-year-old woman with benign serous cystadenoma. Axial T2-weighted MR image shows well-defined hyperintense cystic lesion (*arrowheads*) in pelvis without mural nodules or solid components. Surgical excision confirmed diagnosis of left ovarian serous cystadenoma.
B, 45-year-old woman with serous borderline tumor. Axial contrast-enhanced CT image through pelvis shows well-defined cystic lesion with thin internal septations (*arrowhead*) and eccentric wall thickening along right anterolateral wall (*arrow*).

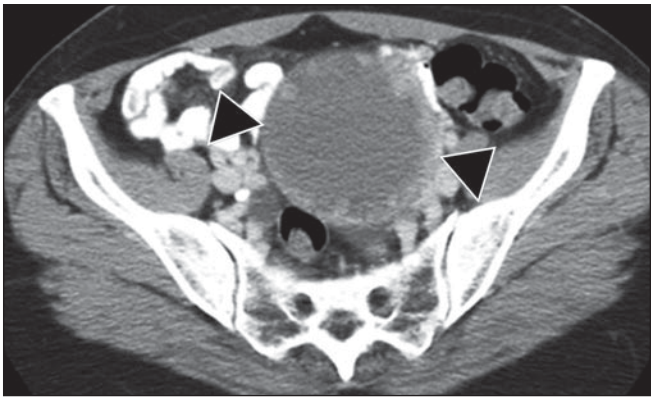

Fig. 3—52-year-old woman with serous carcinoma with background serous borderline tumor. Axial contrast-enhanced CT scan through pelvis shows left ovarian cystic lesion (*arrowheads*) with multiple enhancing intracystic solid papillary excrescences. Surgical excision confirmed diagnosis of serous carcinoma with background serous borderline tumor.

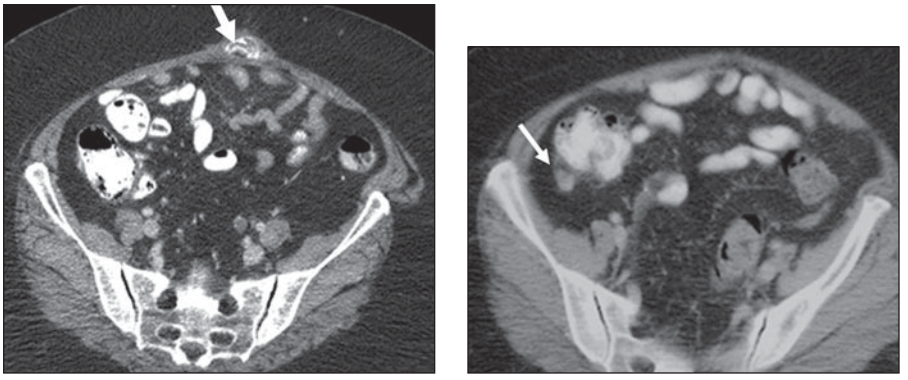

Fig. 4—Serous implants.
A, 48-year-old woman with noninvasive implants showing psammomatous calcifications. Axial CT image through pelvis shows midline paraumbilical calcified implant (*arrow*) in anterior abdominal wall.
B, 37-year-old woman with right paracolic invasive implants (*arrow*).

borderline ovarian tumors with noninvasive implants is 95.3%, whereas survival for patients with tumors with invasive implants is 66% [19]. Micropapillary architecture in the primary ovarian tumor is closely associated with the presence of invasive implants [10]. Serous borderline ovarian tumors with invasive and noninvasive implants may have 45% and 11% recurrence rates, respectively, over a period of 15 years [20]. The tumors usually recur as invasive carcinomas in up to 77% of patients, with a high rate of resultant mortality (up to 74%) [22].

Mucinous Borderline Ovarian Tumors

Mucinous borderline ovarian tumors comprise about 32% of all borderline ovarian tumors [12]. The mean age of presentation is 45 years. Mucinous borderline ovarian tumors consist of two distinct histologic subtypes: the intestinal (90%) and the müllerian (endocervicallike, 10%) histotypes [11]. The intestinal subtype is usually unilateral and may coexist with pseudomyxoma peritonei in up to 17% of cases [1]. The müllerian subtype is bilateral in up to 40% cases and coexists with ipsilateral ovarian or pelvic endometriosis in 20–30% of cases [1, 11]. The müllerian mucinous borderline ovarian tumors mimic serous borderline ovarian tumors to an extent and hence are also termed "seromucinous borderline ovarian tumors." Like serous borderline ovarian tumors, these tumors may be associated with abdominal or pelvic implants, which may be invasive in some cases.

Before the diagnosis of mucinous borderline ovarian tumor is made, it is important to exclude a metastatic adenocarcinoma, most commonly from the gastrointestinal tract, usually an appendiceal or colonic primary. Immunohistochemistry using a cytokeratin panel is useful in differentiating metastatic versus primary ovarian tumors [3].

There is strong evidence that the mucinous borderline ovarian tumors associated with pseudomyxoma peritonei (i.e., ascites with abundant mucoid or gelatinous material) are actually metastatic rather than an ovarian primary [3, 11]. Mucinous borderline ovarian tumors are thought to represent an intermediate stage in the orderly, stepwise progression to invasive carcinoma akin to the adenoma–carcinoma sequence in colorectal carcinomas. Mucinous borderline ovarian tumors are associated with *KRAS* mutations in more than 60% of cases. The increasing frequency of *KRAS* mutations (33–86%) has been described in mucinous cystadenomas, borderline ovarian tumors, and carcinomas [4, 13].

On imaging, mucinous borderline ovarian tumors may be twice the size of serous borderline ovarian tumors and may manifest as multilocular or unilocular cystic masses (Figs. 5 and 6). Mucinous borderline ovarian tumors commonly appear as multilocular cystic masses with numerous septa and contain fluids of different signal intensities on T1- or T2-weighted MR images [20]. The endocystic vegetations of mucinous borderline ovarian tumors show delayed uptake of contrast medium. On T1-weighted images, the mucinous component may impart a high signal intensity.

The imaging features of müllerian mucinous borderline ovarian tumors arising from endometriotic cysts are distinctive. The mül-

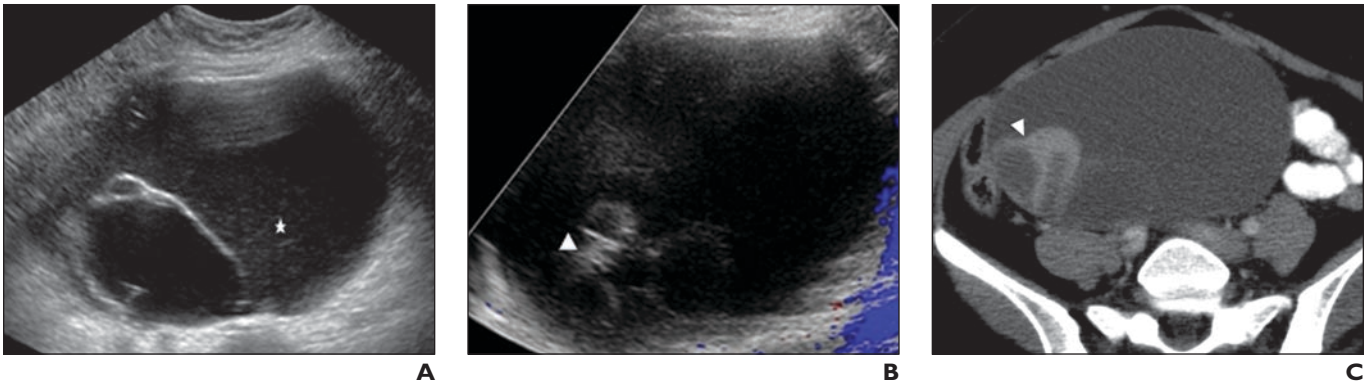

Fig. 5—44-year-old woman with mucinous borderline tumor.
A and **B,** Transvaginal ultrasound images show large multiloculated cystic mass with thick internal septations and small solid components (*arrowhead*, **B**). Larger loculation (*star*, **A**) on left anterolateral aspect shows fine internal echoes.
C, Axial contrast-enhanced CT image through pelvis shows large cystic mass (*arrowhead*) with thick septations and mural nodules along periphery.

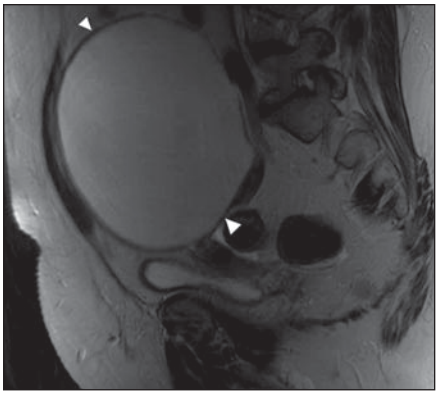

Fig. 6—48-year-old woman with unilocular mucinous borderline tumor. Sagittal T2-weighted MR image through pelvis shows large unilocular cystic mass (*arrowheads*) without internal septations or mural nodules.

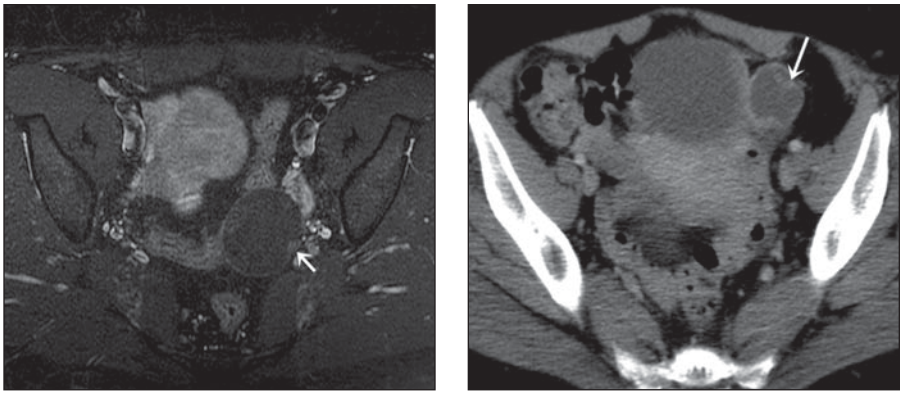

Fig. 7—Müllerian borderline tumors.
A, 46-year-old woman with müllerian borderline tumor. Axial fat-suppressed T2-weighted image through pelvis shows unilocular cystic lesion with small eccentric hyperintense mural nodule (*arrow*).
B, 52-year-old woman with mucinous (müllerian subtype) borderline tumor with background endometriotic cyst. Axial CT image through pelvis shows small unilocular lesion with enhancing mural nodules (*arrow*).

lerian mucinous borderline ovarian tumors are typically uni- or paucilocular cystic masses with mural nodules (Figs. 7 and 8). The fluid component shows high intensity on both T1- and T2-weighted images. The mural nodule shows high intensity on T2-weighted images as well as contrast enhancement [23].

At the time of diagnosis, approximately 82% mucinous borderline ovarian tumors are confined to the ovary and clinically behave similarly to serous borderline ovarian tumors with 5-year survival rates of up to 99–100% [24]. Patients with these tumors rarely have a recurrence or die of the disease. Advanced-stage (18%) mucinous borderline ovarian tumors, however, may have a mortality up to 50% that is stage dependent [13].

Miscellaneous Borderline Tumors

Uncommon subtypes of borderline ovarian tumors encompass 3–4% all borderline ovarian tumors and include endometrioid, clear cell, and transitional cell (Brenner variety) tumors. Endometrioid borderline ovarian tumors resemble analogous endometrioid tumors arising from the uterine corpus and arise either from the surface ovarian epithelium or from endometriosis. Clear cell borderline ovarian tumors are ovarian tumors of low malignant potential characterized by the presence of clear or hobnail cells set in a dense fibrous stroma with absence of stromal invasion. Borderline Brenner tumors are ovarian transitional cell tumors with atypical or malignant features of the epithelium but lacking stromal invasion. The mean age for miscellaneous borderline ovarian tumors ranges between 45 and 65 years.

Endometriosis and endometrioid adenofibromas serve as precursors of endometrioid borderline ovarian tumors. In contrast to serous and mucinous borderline ovarian tumors, endometrioid borderline ovarian tumors are characterized by mutations involving the β-*catenin* gene (50%), *PTEN* gene (20%), and microsatellite instability (up to 50%) [11]. Endometrioid borderline ovarian tumors have the potential to progress to low-grade invasive carcinoma. Although clear cell borderline ovarian tumors have been associated with endometriosis and adenofibromas, a stepwise molecular pathway for the progression of endometriosis or adenofibroma to clear carcinoma has not yet been elucidated. Clear cell borderline ovarian tumors are characterized by *KRAS* mutations (5–16%) and microsatellite instability (13%) [15]. Molecular and genetic changes in Brenner tumors have not yet been described [4, 13].

Nonserous, nonmucinous borderline ovarian tumors do not show characteristic imaging features and may resemble other borderline ovarian tumors as well as early-stage ovarian carcinomas (Fig. 9). The miscella-

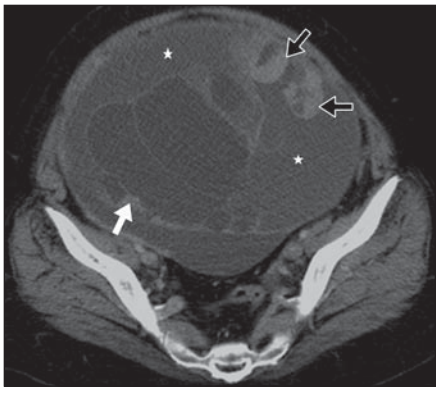

Fig. 8—49-year-old woman with mucinous adenocarcinoma in background of mucinous borderline tumor. Axial contrast-enhanced CT image through pelvis shows large multiloculated cystic lesion with irregular and thick internal septations (*white arrow*). There is noceable variation in densities of various loculi; some loculi (*stars*) appear hyperdense in comparison with others. Intracystic enhancing mural nodules and solid components (*black arrows*) are visualized along left anterior wall.

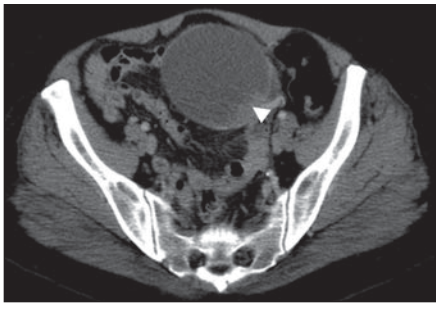

Fig. 9—41-year-old woman with endometrioid borderline ovarian tumor. Axial contrast-enhanced CT image through pelvis shows unilocular cystic lesion with mural nodule along left posterolateral wall (*arrowhead*) mimicking low-grade carcinoma.

neous borderline ovarian tumors chart a benign course after tumor removal with exceptionally rare recurrences or metastasis. The survival rate is up to 100%.

Imaging Algorithm for the Diagnosis of Borderline Ovarian Tumors

Borderline ovarian tumors commonly present as adnexal masses. Accurate diagnosis and distinction from advanced ovarian malignancy facilitate management including fertility-preserving surgery. Transvaginal sonography is the primary screening imaging technique in the evaluation of any suspected adnexal mass [25, 26]. Borderline ovarian tumors manifest usually as complex cystic masses with septations and occasionally as mural nodules.

The use of color and spectral Doppler ultrasound may provide additional information about tumoral angioarchitecture. However, gray-scale and color Doppler sonograms have been shown to be of limited value in characterizing borderline ovarian tumors. Adnexal lesions may, at best, be categorized as benign or aggressive on sonography. MRI and MDCT can characterize adnexal masses into benign and malignant in up to 93% [27, 28] and 89% [29] of the cases, respectively. Sonographically indeterminate lesions thus require MRI for further characterization (Fig. 10).

MRI, on account of its superior soft-tissue distinction and multiplanar capabilities, allows better characterization of complex cystic masses particularly with regard to the depiction of septations and mural nodules. Dynamic MRI characteristics of ovarian tumors have recently been studied [30–32], first during the arterial phase (30-second delay) and on delayed contrast-enhanced MR images (> 4 minutes). The time–intensity curves of borderline ovarian tumors were compared with those of normal outer myometrium. Although the tumors that showed a gradual increase in enhancement without a well-defined peak were correlated to benign ovarian tumors, borderline ovarian tumors showed moderate initial enhancement followed by a plateau.

Both MRI and MDCT can be used to map peritoneal disease and provide information for preoperative planning and staging. Borderline ovarian tumors are not PET-avid and hence are interpreted as "benign" tumors on FDG PET [33, 34]. Ovarian masses that show complex features on MRI that are concerning for malignancy but appear as "benign" on PET are said to be characteristic of borderline ovarian tumors [33]. However, final diagnosis and staging of borderline ovarian tumors require pathologic evaluation after surgical excision [5].

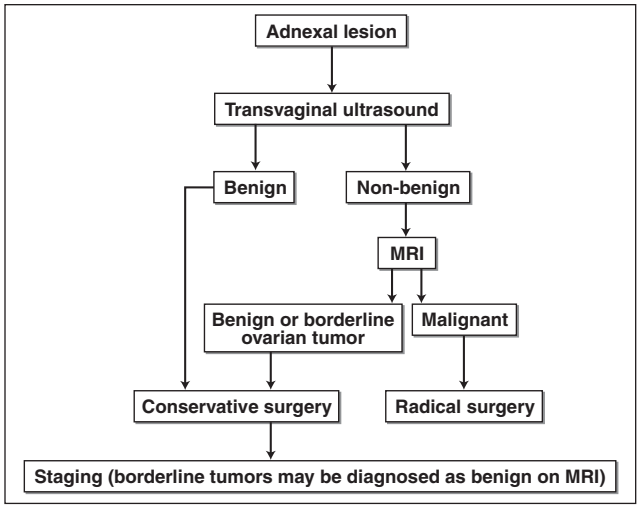

Fig. 10—Imaging algorithm for diagnosis of borderline tumors.

Staging, Management, and Surveillance Algorithm

Borderline ovarian tumors follow a staging system similar to that used for staging ovarian epithelial carcinomas. The staging is surgical and the suggested guidelines include taking specimens from the omentum; intestinal serosa and mesentery; pelvic peritoneum including the cul-de-sac, bladder peritoneum, and pelvic wall; and abdominal peritoneum including paracolic gutters, diaphragmatic surface, and retroperitoneal nodes [1, 5]. The FIGO staging for borderline ovarian tumors is summarized in Table 2.

When postoperative surgical staging ascertains borderline ovarian tumors without invasion, peritoneal seeding, or distant metastasis, no further treatment is required. However, advanced-stage disease requires cytoreduction surgery with or without platinum-based chemotherapy. Patients with a suspected borderline ovarian tumor and desiring fertility preservation may opt for a conservative approach such as cystectomy or salpingo-oophorectomy instead of radical surgery. An outline of optimized patient management is depicted in Figure 11.

Follow-up is usually a combination of clinical examination, transvaginal ultrasound, and CA-125 levels. During the initial 2 years, follow-up evaluation is performed every 3 months. Patients are then evaluated biannual-

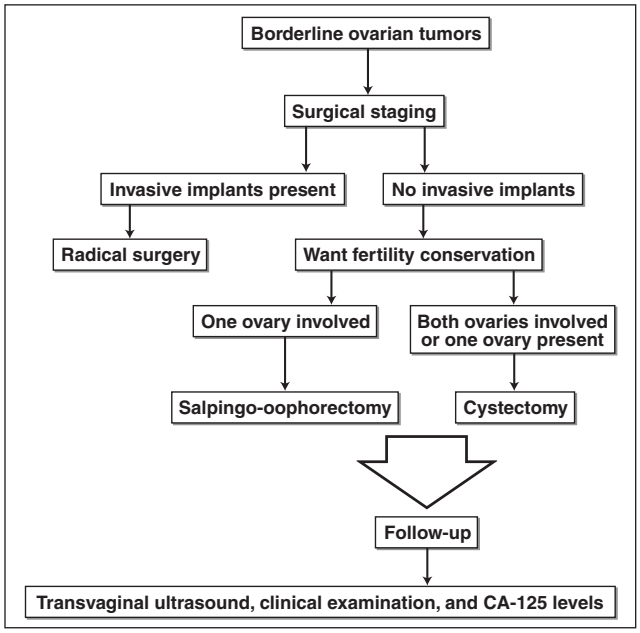

Fig. 11—Schematic representation of management and surveillance algorithm for borderline ovarian neoplasms. Information from [5] was incorporated in this algorithm.

TABLE 2: Summary of International Federation of Obstetric Gynecology (FIGO) Staging

FIGO Stage	Definition
I	Tumor confined to ovary
II	Peritoneal implants within the pelvis
III	Peritoneal implants beyond the pelvis, positive lymph nodes, or both
IV	Liver parenchyma involvement or tumor beyond the peritoneal cavity

ly for 3–5 years after surgery and then annually thereafter [5]. Transvaginal sonography or pelvic MRI may be performed for the detection of local recurrence. MDCT is better suited for the detection of peritoneal disease or extrapelvic spread of disease.

Conclusion

Borderline ovarian tumors are an interesting subset of epithelial neoplasms that affect younger women in the reproductive age group, chart an indolent course, and show excellent prognosis. Borderline tumors typically manifest as complex cystic masses with mural nodularity and septations. The imaging findings may be indistinguishable from those of invasive ovarian carcinomas. Fertility-sparing surgery may suffice in patients with tumors that are confined to the ovary. Radical surgery is recommended in patients with advanced disease. Long-term surveillance is recommended to document and treat late recurrences.

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