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Advancements in Low Grade Serous Carcinoma of the Ovary and Peritoneum

Rachel N. Grisham, MD[1], **Michael Herman Chui, MD, FRCPC**[2]

[1:]Gynecologic Medical Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, NY, New York, USA

[2:]Department of Pathology, Memorial Sloan Kettering Cancer Center, NY, New York, USA

Abstract

Purpose of Review: Low grade serous ovarian cancer (LGSOC) is a rare form of epithelial ovarian cancer that generally exhibits a protracted course and is less sensitive to chemotherapy than high grade serous ovarian cancer. Over the past decade it has become clear that patients with LGSOC have a clinically distinct course and are molecularly and histologically unique from patients with high grade serous ovarian cancer.

Recent Findings: Endocrine therapy is frequently used for treatment of patients with recurrent LGSOC and is now also part of the standard upfront treatment of this disease, with an ongoing Phase III clinical trial seeking to determine if chemotherapy can be eliminated altogether from the initial treatment of LGSOC. Tumors are frequently found to exhibit alterations affecting the Mitogen Activated Protein Kinase (MAPK) pathway, recently leading to developments in the use of targeted treatments for those patients with recurrent disease.

Summary: LGSOC is a clinically, histologically, and molecularly unique form of epithelial ovarian cancer. Recent advances in the understanding of endocrine and molecular drivers of this disease have led to changes in both the treatment of newly diagnosed and recurrent disease, with ongoing studies focused on refining upfront therapy and seeking novel targeted combinations for those patients with recurrent disease.

Keywords

Low grade serous; ovarian cancer; serous borderline; MAPK; KRAS; BRAF; MEK; MEK inhibitor

Corresponding author: Rachel N. Grisham, Mailing Address: Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, Phone:646-888-4653, Fax: 646-888-4267, grishamr@mskcc.org.

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Conflicts of Interest:

Dr. Grisham reports personal fees from Clovis, personal fees from Mateon, personal fees from Regeneron, unpaid consulting for Verastem, personal fees from Amgen, personal fees from Medscape, personal fees from Aptitude Health, personal fees from PER, personal fees from Signatera, personal fees from GSK, personal fees from Corcept, personal fees from Springworks, outside the submitted work. Dr. Chui reports personal fees from Roche, outside the submitted work.

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Introduction:

Serous carcinoma of the ovary accounts for up to 80% of epithelial ovarian, tubal, and peritoneal cancers. It is subclassified into high grade serous ovarian cancer (90–95% of serous tumors) and low grade serous ovarian cancer (LGSOC; 5–10% of serous tumors) based on morphologic, immunohistochemical, and molecular features [1, 2]. High grade serous carcinoma (HGSOC) is characterized by high levels of chromosomal instability, recurrent *TP53* mutations, and germline alterations in homologous recombination repair-related genes including BRCA1/2, leading to homologous recombination deficiency (HRD) in ~50% of patients [3–6]. Clinically, HGSOC presents at a median age of 63 years, is highly platinum responsive, and often has an aggressive disease course [7]. Meanwhile, LGSOC is characterized by low mutational burden, low frequency of *TP53* mutations, and an unclear germline association [8–10]. LGSOC is typically less responsive to chemotherapy than HGSOC, and more likely to display an indolent behavior [7, 11, 12]. Recent research has focused on defining the stepwise progression of LGSOC from its premalignant precursor, serous borderline tumor (SBT), and optimizing endocrine and targeted strategies for treatment of patients with advanced disease.

Etiology:

There is no known hereditary or environmental predisposition for development of LGSOC and the incidence of *BRCA* mutations in patients with LGSOC approaches that of the general population. The primary risk factor for LGSOC is a personal history of its non-invasive precursor, SBT.

LGSOC is thought to arise via a stepwise progression, from benign serous cystadenoma to SBT, which progresses to micropapillary SBT, and ultimately invasive LGSOC (Figure 1A–C). LGSOCfrequently presents with a co-existing SBT. Another scenario is the finding of extra-ovarian invasive disease despite the presence of only SBT in the ovary. Previously termed “invasive implants” (more commonly associated with micropapillary SBT), the WHO Classification 5th edition now recommends classifying these lesions as low-grade serous carcinoma, with the term “implant” being reserved for non-invasive tumor deposits. Patients with previously resected ovarian SBT can also develop recurrences as invasive low-grade serous carcinoma, sometimes decades later [13]. Rare cases of “primary peritoneal” low-grade serous carcinoma, in the absence of any ovarian neoplasm, have also been described, which may originate from endosalpingiosis[14, 15].

A comprehensive population study performed by Vang et al included all patients in Denmark diagnosed with a SBT between 1978–2002. Of 1,042 cases of SBT, subsequent development of carcinoma occurred in 4% of patients, of which 93% were low-grade and 7% were high-grade serous carcinoma. Median time to development of subsequent invasive cancer was 10 years, with a range up to 25 years[16].

Immunohistochemical and Molecular Profile:

SBT and LGSOC show immunohistochemical expression (nuclear staining) for PAX8, WT1, ER and PR. In contrast to HGSOC, which exhibits aberrant expression of p53 (either strong,

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diffuse staining in tumor cells or complete absence of staining), LGSOC almost universally exhibit a wildtype p53 expression pattern (heterogeneous staining of tumor cells). Hence, p53 immunohistochemistry is often a useful adjunct to distinguish between LGSOC and HGSOC (Figure 1C, D).

Germline mutation testing to evaluate for presence of mutations in the *BRCA* gene is recommend by the National Comprehensive Cancer Network (NCCN) and ASCO for all patients with ovarian cancer[17]. While *BRCA* mutations are rare in this population, patients should still be offered germline testing.

Somatic tumor testing can also be helpful to determine prognosis and likelihood of response to certain therapies. The presence of a somatic *BRAF V600E* mutation in patients with SBT may predict for decreased likelihood of progression and improved prognosis [18, 19]. In a retrospective study by Grisham et al of 75 tumors of serous borderline or low grade serous ovarian cancer histology, 57 tumors harbored either a *KRAS* (n=17) or *BRAF V600E* (n=26) mutation[9]. The presence of *BRAF V600E* mutation was associated significantly with early disease stage (stage I/II; $p< 0.001$) and serous borderline histology (p=0.002). A study performed by Wong and colleagues analyzed 30 serous borderline tumors and found that 9 (30%) harbored *BRAF* mutations. In contrast when they examined LGSOC tumor samples from 43 patients with advanced disease they found that only 1 (2%) harbored a *BRAF* mutation, leading them to conclude that advanced stage, aggressive, LGSOCs are more likely derived from serous borderline tumors without a *BRAF* mutation[19].

In a study by Chui et al, mutational analysis of the *KRAS* and *BRAF* genes was performed on 201 SBTs following centralized pathology review. *BRAFV600E*mutated SBTs were less likely to exhibit micropapillary features ($p< 0.0001$) and were more frequently stage I ($p = 0.0023$). After adjusting for age and stage, the risk of subsequent serous carcinoma was significantly lower among women with *BRAF*-mutated SBTs [HR 0.27 (0.08 – 0.93), $p = 0.038$], but not with *KRAS*-mutated SBTs [HR 1.00 (0.45 – 2.23), $p = 0.99$], compared to SBTs lacking mutations in either gene [20]. In a study of 79 cases of LGSOC with tumor tissue available for Sanger sequencing analysis, the 21 patients with presence of *KRAS* or *BRAF* mutation had a significantly better overall survival than those with wild-type *KRAS* or *BRAF* (n=58) [106.7 months (95% CI, 50.6, 162.9) vs 66.8 months (95% CI, 43.6, 90)], respectively (p=0.018)[21].

Recently, somatic tumor testing has become a standard of care at many institutions to aid in identification of potentially targetable alterations for patients with recurrent LGSOC. Somatic *KRAS* mutations are found in approximately a third of patients with LGSOC and may help to predict response to targeted therapy (Table 1) [8, 22–25]. The MILO/ENGOT-ov11 study was the largest prospective therapeutic clinical trial performed to date in women with recurrent LGSOC. It enrolled women with recurrent LGSOC who had progressive disease following 1–3 prior lines of therapy and randomized them 2 to 1 to treatment with the oral MEK inhibitor, binimetinib, or physicians choice of chemotherapy. Archival tissue was submitted at time of study registration and molecular testing (Foundation Medicine) was performed on the tumor samples from the 215 patients with adequate archival tissue available. *KRAS* mutation was found in 33% of tumor samples and was evenly distributed

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between those patients receiving binimetinib (32%) and those receiving physicians' choice of chemotherapy (34%). Unbiased univariate analyses evaluating best response rate to therapy as a binary response showed *KRAS* mutation was significantly associated with response to treatment with binimetinib (odds ratio [OR], 3.4; 95% CI, 1.53 to 7.66; unadjusted P = 0.003) but not PCC (OR, 2.13; 95% CI, 0.67 to 6.81; P = 0.2). Among those patients treated with binimetinib the rate of complete or partial response to therapy was 44% in those with a *KRAS* mutation, versus 19% in those without a *KRAS* mutation[26] [21]. A post-hoc analysis performed by Grisham et al on archival tumor tissues submitted at time of study entry to the MILO/ENGOT-ov11 Phase III study showed that those patients harboring a *KRAS* mutation in their tumor had 3.4 times the odds of responding to treatment with the MEK inhibitor binimetinib vs those without a KRAS mutation (95% CI 1.57, 7.67; p-value 0.002)[25].

GOG 0281 also examined the use of single agent MEK inhibitor vs physician's choice of therapy in patients with recurrent LGSOC. This phase II/III study of the MEK inhibitor trametinib vs physician's choice of chemotherapy or endocrine therapy in patients with recurrent disease and unlimited prior lines of chemotherapy found a significant difference in median PFS with trametinib (13 months) vs. physician's choice of chemotherapy (7.2 months; HR=0.48; p<0.001). The overall response rate (ORR) was 26% for trametinib and 6.2% for physician's choice of treatment ($p < 0.0001$)[27].

Treatment of Newly Diagnosed Disease:

For those patients with SBT, complete surgical resection of disease is the primary treatment. In those patients who desire future fertility and/or preservation of ovarian function, fertility sparing surgery is the preferred approach. Patients with a history of SBT require continued monitoring for risk of recurrence or progression to LGSOC. The frequency and modality of follow-up depends on the specific case, but is routinely performed through pelvic exams and transvaginal U/S to avoid excessive radiation and contrast exposure. Chemotherapy and endocrine therapy have not shown benefit in the treatment of SBT with non-invasive implants and should generally be reserved for those cases of confirmed LGSOC.

Patients with advanced LGSOC should undergo complete surgical staging with total hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), omentectomy, lymph node dissection, washings, and attempted removal of all gross disease via either an open or minimally invasive approach, with fertility sparing surgery reserved for select cases.

For patients with Stage Ia or Ib disease, following completion of surgical staging observation alone is recommended; while for those patients with Stage Ic disease either observation or 3 cycles of adjuvant chemotherapy or endocrine therapy can be considered. For those patients receiving adjuvant chemotherapy the standard regimen is chemotherapy with carboplatin (at an AUC of 5–6) administered in conjunction with paclitaxel 175mg/m2 in a 3-week cycle.

For those patients with stage II-IV LGSOC 6 cycles of adjuvant carboplatin/paclitaxel chemotherapy are recommended with consideration for endocrine therapy following completion of chemotherapy. Endocrine therapy is usually given in the form of an aromatase

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inhibitor, primarily letrozole. There is not currently a standard of care as to how long aromatase inhibitor therapy should continue following completion of upfront chemotherapy, however, if well tolerated and there is no evidence of disease progression, the AI is generally continued for at least 5–10 years after completion of chemotherapy.

The recommendation for use of endocrine maintenance therapy following completion of adjuvant chemotherapy is based upon a retrospective study performed by Gershenson and colleagues examining patients with stage II-IV low grade serous ovarian cancer treated at MD Anderson Cancer Center between 1981 and 2013. All patients examined were treated with primary cytoreductive surgery followed by platinum-based chemotherapy. At completion of chemotherapy patients were either followed with observation or endocrine maintenance therapy, as per their physician's discretion. Median PFS for patients followed with observation following chemotherapy was 26.4 months compared with 64.9 months for those receiving endocrine maintenance therapy after completion of chemotherapy ($P<0.001$), however there was not a statistically significant difference observed in overall survival between the two groups (102.7 vs 115.7 months, respectively)[28].

Multiple retrospective studies have shown that response rates to cytotoxic chemotherapy in the frontline setting are lower in LGSOC then in HGSOC. Grabowski and colleagues examined 5114 patients with advanced epithelial ovarian cancer treated on 4 randomized phase III trials with first-line platinum-based chemotherapy. Response rates to chemotherapy in those patients with suboptimal debulking were reported, and found a response rate of 23.1% in the patients with LGSOC vs 90.1% in those with high grade serous ovarian cancer[11]. In select patients, particularly those at higher risk of chemotherapy associated complications, or those who decline chemotherapy, hormonal maintenance therapy alone (without adjuvant chemotherapy) is acceptable. At some institutions it has become a standard of care to treat with adjuvant endocrine therapy alone for all stages of newly diagnosed LGSOC following completion of initial staging surgery. An ongoing international Phase III study (NRG-GY019; NCT04095364) seeks to determine if letrozole maintenance therapy alone is non-inferior to IV carboplatin/paclitaxel chemotherapy followed by maintenance letrozole, with respect to PFS, in women with newly diagnosed LGSOC following primary debulking surgery. NRG-GYO19 is enrolling women with stage II-IV LGSOC following completion of initial debulking surgery and randomizing these patients 1:1 to treatment either with 6 cycles of carboplatin and paclitaxel chemotherapy followed by letrozole maintenance therapy or letrozole maintenance therapy alone.

For those patients receiving adjuvant chemotherapy as a standard of care option, the addition of bevacizumab 15mg/kg in combination with upfront carboplatin/paclitaxel chemotherapy, followed by 15 months of bevacizumab maintenance at completion of chemotherapy, may also be considered for select patients with advanced disease, particularly those with high risk features of suboptimal debulking or stage IV disease.

There is a paucity of data regarding the use of PARP inhibitors in LGSOC. However, given that LGSOC is less sensitive to platinum-based chemotherapy in the upfront and recurrent setting, and rarely associated with BRCA mutations, we generally favor the use of

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endocrine maintenance or bevacizumab maintenance therapy over the use of PARP inhibitor maintenance therapy for these patients.

Treatment of Recurrent Disease:

The majority of women with LGSOC will initially present with advanced stage disease and ultimately develop recurrent disease. Given the less chemo-sensitive nature of LGSOC, it is important that patients continue to follow with a gynecologic oncologist for consideration of surgical resection at time of recurrence. Patients may have multiple resections of recurrent disease over the course of their life, as clinically appropriate. In a retrospective study of 41 women with recurrent LGSOC, those who achieved a complete gross resection of disease had a significantly better PFS (60.3 months vs 10.7 months) and OS (93.6 months vs 45.8months) from the time of secondary surgery when compared with those patients who had gross residual disease following surgery[29].

At time of recurrence, patients are classified as platinum sensitive or platinum resistant. For those patients with platinum sensitive disease (>6 months since completion of last platinum-based chemotherapy) it is appropriate to treat with a platinum-based doublet again, either alone or in combination with bevacizumab followed by bevacizumab maintenance. For those patients with platinum resistant disease (recurrence < 6 months since completion of last platinum-based therapy) pegylated liposomal doxorubicin or weekly paclitaxel, alone or in combination with bevacizumab are early-line options. Bevacizumab has been observed to have activity in patients with recurrent LGSOC either alone or in combination with chemotherapy in multiple retrospective studies[30, 31].

In addition to chemotherapy, endocrine therapy is frequently used in the treatment of recurrent LGSOC, especially for those patients with low volume or indolent disease where disease stability is clinically meaningful. The majority of LGSOC cases are hormone receptor positive (87% ER positive; 58% PR positive)[32]. In a single-institution study of 64 patients with recurrent LGSOC treated with 89 endocrine regimens, the objective response rate to endocrine therapy was 9% and 61.8% of patients experienced stable disease[33]. The most common hormonal agents used for treatment in this study were anastrozole, fulvestrant, letrozole, leuprolide and megestrol acetate. In GOG 0281, a phase II/III study of trametinib vs physicians' choice of therapy in patients with recurrent LGSOC, patients treated in the control arm were allowed to receive chemotherapy, letrozole or tamoxifen. While 0/27 patients treated with tamoxifen achieved an objective response, the response rate to letrozole was 13.6% (6/44). Therefore, letrozole is generally the preferred regimen for endocrine therapy of this disease[34]. Ongoing studies are currently examining the addition of CDK 4/6 inhibitors to endocrine therapy in an attempt to enhance efficacy of this well tolerated option. The phase II study GOG-3026 (NCT03673124) is currently examining the combination of ribociclib with letrozole in patients with recurrent, measurable LGSOC; while a pilot study of neoadjuvant fulvestrant in combination with abemaciclib is studying the activity of this combination in women with advanced newly diagnosed LGSOC that is not appropriate for primary debulking surgery (NCT03531645).

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The first prospective clinical trial to examine the use of single agent MEK inhibitors for recurrent LGSOC was a single arm study (GOG 0239) that treated women with recurrent measurable LGSC with selumetinib (AZD6244) until time of progression or intolerable toxicity. The study showed what was considered at that time to be a promising objective response rate of 15%. No correlation was found between presence of *KRAS* or *BRAF* mutation and response to therapy; however, sufficient DNA was available for analysis in only 34 (65%) of the 52 of evaluable patients[35].

Since completion of GOG 0239 two randomized phase 3 studies, MILO and GOG 0281 have both shown promising response rates for use of singe agents MEK inhibitors for patients with recurrent disease. Trametinib is now NCCN compendium listed for treatment of patients with recurrent LGSOC. The next generation of clinical trials in LGSOC will seek to build upon these findings by combining MEK inhibitors with other potentially active agents. The ongoing FRAME study treated patients with selected recurrent cancers with the dual MEK/RAF inhibitor VS-6766 in combination with the FAK inhibitor defactinib. Interim results presented at AACR in 2020 showed the response rate was 67% (4/6) amongst LGSOC patients with a KRAS mutation and 50% (4/8) in all LGSOC patients, regardless of mutation status. Of the 4 patients with LGSOC who responded to treatment, 3 had previously received a MEK inhibitor [36]. Based on these promising results, the phase II RAMP201 Trial (GOG-3052/ENGOT-ov60; NCT04625270) randomizes patients with recurrent, measurable, LGSOC to treatment with either VS-6766 alone or in combination with defactinib and is currently accruing patients in the United States and Europe [37].

Conclusions:

LGSOC has demonstrated lower response rates to chemotherapy, but patients often display a more protracted course with opportunities present for endocrine and targeted therapy. Recent advances in the understanding of endocrine and molecular drivers of this disease have led to changes in both the treatment of newly diagnosed and recurrent LGSOC. Ongoing studies in the upfront setting aim to determine if chemotherapy can safely be eliminated from the initial adjuvant therapy of advanced LGSOC and replaced by endocrine maintenance therapy alone, or even used in the neoadjuvant setting. Currently enrolling studies in the recurrent setting are focused on capitalizing on the MAP Kinase alterations that have been identified within this disease and utilizing novel targeted and combination therapy approaches.

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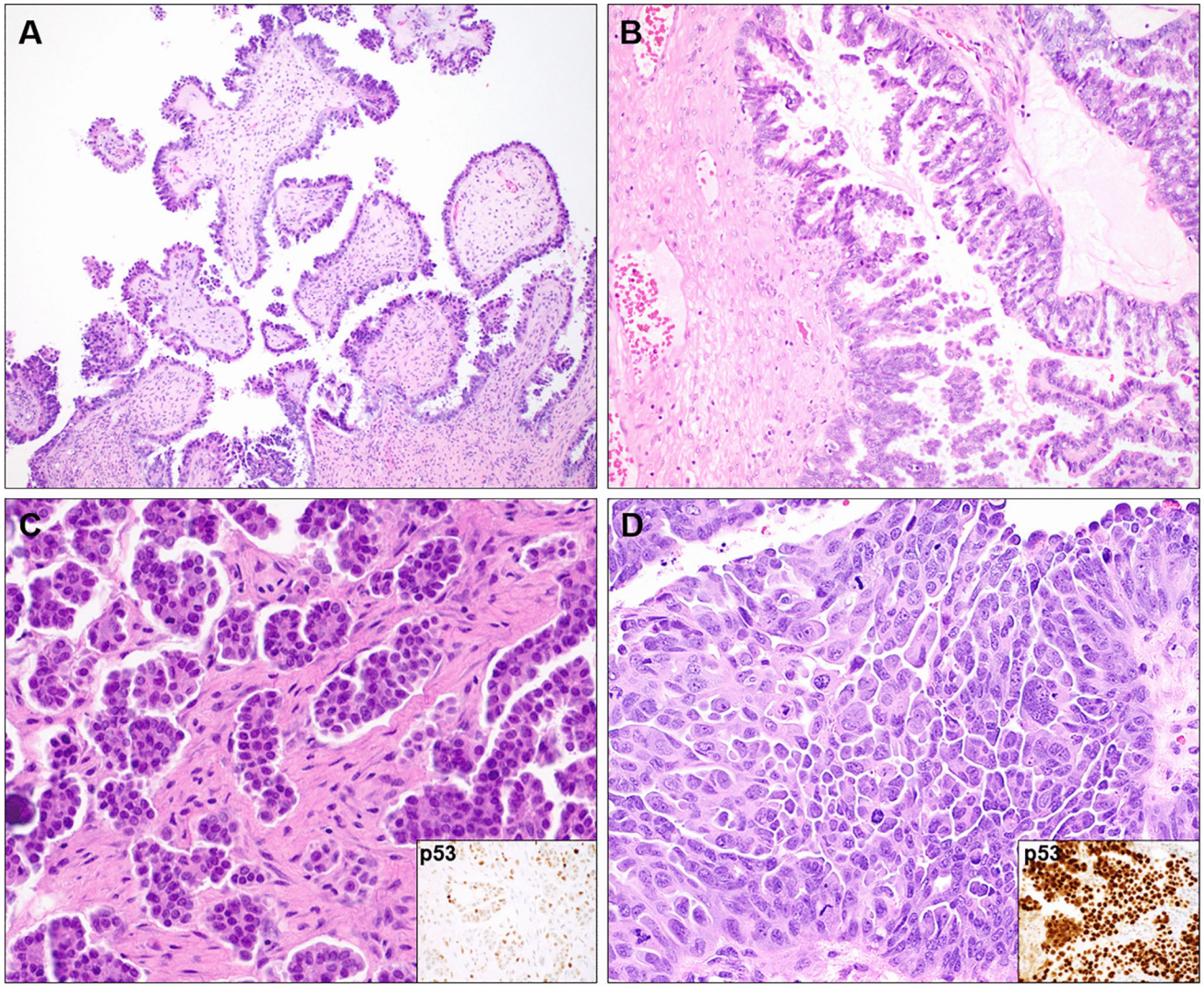

Figure 1:

Histopathologic spectrum of ovarian serous tumors. (A) Serous borderline tumor, showing ciliated and non-ciliated tubal-type epithelium, with stratification and tufting, lining hierarchically-branching papillae containing cores of fibrous stroma. (B) Micropapillary serous borderline tumor, characterized by tumor cells forming long, thin micropapillae, imparting a “Medusa head” appearance. (C) Low-grade serous carcinoma is distinguished from serous borderline tumor by the presence of invasion, represented here as small nests of tumor cells within clefted spaces infiltrating through stroma. The nuclei are round and monotonous and mitotic activity is low. Immunohistochemistry for p53 shows a heterogeneous (wildtype) expression pattern (*inset*). (D) In contrast, high-grade serous carcinoma exhibits marked nuclear atypia and pleomorphism (≥ 3:1 variability in nuclear size and shape) and frequent mitotic figures. Immunohistochemistry shows aberrant p53 expression, either as diffuse over-expression, as in this case (*inset*), or complete absence of staining.

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Table 1:

Somatic Molecular Alterations Frequently Found in LGSOC

Gene	Percentage of Patients With Mutation
KRAS	33%
NRAS	8%
BRAF	6%
NF1	5%
RAF1	2%