Low-grade serous ovarian cancer: expert consensus report on the state of the science

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ABSTRACT

Compared with high-grade serous carcinoma, low-grade serous carcinoma of the ovary or peritoneum is a less frequent epithelial ovarian cancer type that is poorly sensitive to chemotherapy and affects younger women, many of whom endure years of ineffective treatments and poor quality of life. The pathogenesis of this disease and its management remain incompletely understood. However, recent advances in the molecular characterization of the disease and identification of novel targeted therapies with activity in low-grade serous carcinoma offer the promise of improved outcomes. To update clinicians regarding recent scientific and clinical trial advancements and discuss unanswered questions related to low-grade serous carcinoma diagnosis and treatment, a panel of experts convened for a workshop in October 2022 to develop a consensus document addressing pathology, translational research, epidemiology and risk, clinical management, and ongoing research. In addition, the patient perspective was discussed. The recommendations developed by this expert panel—presented in this consensus document—will guide practitioners in all settings regarding the clinical management of women with low-grade serous carcinoma and discuss future opportunities to improve research and patient care.

INTRODUCTION

Low-grade serous carcinoma of the ovary or peritoneum is a relatively rare type of epithelial ovarian cancer, representing less than 10% of epithelial ovarian cancers.[1–3] Although low-grade serous carcinoma is associated with prolonged survival of patients compared with high-grade serous carcinoma, the disease is often diagnosed in younger women who may suffer for years from ineffective treatments and poor quality of life.[4] Recognizing that low-grade serous carcinoma is molecularly distinct from other ovarian cancers, a unique approach to clinical management is required to maximize survival. In 2019 we convened a panel of experts at a state-of-the-science conference to address the unique needs of low-grade serous carcinoma, which led to the publication of a consensus paper.[5]

Since that conference, research has progressed. However, this rare disease and its management remains incompletely understood. To update clinicians regarding recent scientific and clinical trial advancements and discuss unanswered questions related to low-grade serous carcinoma diagnosis and treatment, we convened a panel of experts to create an updated consensus document, which includes the areas of pathology, translational research, epidemiology and risk, clinical management, and ongoing research. In addition, the patient perspective, assembled from a social media-based survey, is included.

METHODS

In October 2022 we gathered experts for a one-day workshop in New York, USA. The panel consisted of investigators with expertise in basic, translational, and clinical science of low-grade serous carcinoma. A steering committee developed a series of questions before the workshop (authors BS, DG, and RG), according to categories that included pathology, translational research, epidemiology and risk, clinical management, clinical trials, and future research of low-grade serous carcinoma. Current evidence relating to each question was presented to the group at the workshop by a qualified investigator and discussed. Consensus statements were developed based on each question and the ensuing discussion.

PATHOLOGIC CONSIDERATIONS

Pathologic Definition of Low-Grade Serous Carcinoma

In 2020, the World Health Organization (WHO) defined low-grade serous carcinoma as 'an invasive serous neoplasm with low-grade malignant features'.[6] The WHO defined ovarian serous borderline tumor as 'a non-invasive, low-grade, proliferative serous epithelial neoplasm' and further stated that "Implants of serous borderline are, by definition, non-invasive; if there is invasion, a diagnosis of low-grade serous carcinoma should be made". The term 'non-invasive low-grade serous carcinoma', previously used synonymously with micropapillary serous borderline tumor, is no longer recommended. The micropapillary variant

of serous borderline tumor is not to be treated as cancer if the tumor is well sampled to rule out any apparent invasion. The diagnosis of 'microinvasive low-grade serous carcinoma' (<5 mm focus of ovarian stromal invasion) should only be made after careful pathologic examination, preferably with additional sampling of the specimen, to exclude overtly invasive low-grade serous carcinoma.[7] Ovarian serous borderline tumor with microinvasive low-grade serous carcinoma (or microinvasion) is not associated with an increased risk of recurrence in most studies,[8 9] and therefore should not be considered equivalent to overtly invasive low-grade serous carcinoma provided that extra-ovarian invasive implants are not present.

Consensus

The WHO 2020 definition of low-grade serous carcinoma, 'an invasive serous neoplasm with low-grade malignant features',[6] is accepted. The term 'non-invasive low-grade serous carcinoma' is not recommended. Ovarian serous borderline tumor with microinvasive low-grade serous carcinoma/microinvasion is not associated with a concerning prognosis and should be managed as borderline tumors.

Pathologic Definition of Serous Borderline Tumor with Invasive Implants

It is unclear whether ovarian serous borderline tumor with invasive peritoneal implants and advanced stage ovarian low-grade serous carcinoma are synonymous regarding clinical behavior. Whereas most stage III/IV ovarian low-grade serous carcinomas recur after primary therapy,[10] the risk of malignant recurrence is at least 30% for advanced stage ovarian serous borderline tumors with invasive implants.[8 11–13] The actual risk of recurrence varies across studies and should be interpreted with caution, as diagnostic criteria for the classification of implants have since become more standardized. The change in WHO nomenclature of invasive peritoneal implants to metastatic low-grade serous carcinoma in 2014[14] resulted in controversy, with the European Society of Gynecological Oncology (ESGO) retaining the former term. According to ESGO, serous borderline tumor with invasive implants should be considered separate from advanced low-grade serous carcinoma.[15] Further, ESGO recommended against adjuvant systemic therapy for the primary treatment of serous borderline tumors with extra-ovarian invasive or non-invasive implants.[15]

The current expert panel agreed that the extent of invasive disease as a prognostic factor has not been well studied and should be a focus of future research. For example, focal microscopic invasive implants associated with ovarian serous borderline tumor likely do not behave the same as ovarian low-grade serous carcinoma with widespread peritoneal carcinomatosis, although they are grouped in the same diagnostic category. Therefore, it may be premature to consider invasive implants equivalent to metastatic low-grade serous carcinoma. Further studies are necessary to characterize and predict which invasive implants are more likely to recur as low-grade serous carcinoma.

Further obscuring the issue is variable interpretation by pathologists. While the morphologic criteria for distinguishing between invasive and non-invasive implants are well defined,[6] some cases can be subjective. Consultation with a pathologist experienced in evaluating these lesions is recommended for accurate diagnostic classification. The current and historical literature has used various terms for low-grade serous neoplasms, leading to confusion among clinicians concerning appropriate treatment. Table 1 summarizes these terms and their appropriate management.

Clinical Behavior of Serous Borderline Tumor with Non-Invasive Implants

Across studies evaluating serous borderline tumor with non-invasive implants, an increased risk of low-grade serous carcinoma recurrence is observed and varies based on the study.[8 12 16–18] The highest risk of recurrence (overall 44%, malignant 34%) was observed by Silva et al among patients in a tertiary referral center, with a median progression-free survival of 7.1 years from the time of initial diagnosis (77% of recurrences occurred after 5 years).[17] A study by Vang et al of a population-based cohort in two Danish cancer registries showed that the risk of low-grade serous carcinoma recurrence with non-invasive implants is increased (16%), but not as high as with invasive implants (32%).[8] Differences in study populations, length of follow-up, and the pathologic definition of a non-invasive implant may have led to variability in estimating the magnitude of risk. Regardless, these patients require extended clinical follow-up, as malignant recurrences can occur over a decade after diagnosis. Survival of patients with serous borderline tumor and non-invasive implants has been reported to be >90% at 10 years.[8 12 17 18] Adjuvant chemotherapy is not recommended, as studies have reported a greater number of deaths from treatment complications than from the disease itself.[18 19]

Table 1 Pathologic terminology for low-grade serous tumors and treatment recommendations

Current term	Chemotherapy appropriate[43 120]	Former terminology[6 121]
Serous borderline tumor	No	Atypical proliferative serous tumor, serous tumor of low malignant potential
Micropapillary serous borderline tumor	No	Non-invasive low-grade serous carcinoma
Serous borderline tumor with microinvasive low-grade serous carcinoma	No	–
Serous borderline tumor with non-invasive implant(s)	No	–
Serous borderline tumor with invasive implant(s)/ metastatic low-grade serous carcinoma	May be considered	–
Ovarian low-grade serous carcinoma	May be considered	–

Consensus

Non-invasive implants appear to confer at least a 15–20% increased risk of subsequent low-grade serous carcinoma. These patients do not require adjuvant therapy if there is no residual disease but require extended clinical follow-up, as recurrences may occur 5 years or more after diagnosis.

Clinical Behavior of Low-Grade Serous Carcinoma Associated with High-Grade Serous Carcinoma

While low-grade serous carcinoma and high-grade serous carcinoma are considered distinct pathologic entities with different spectra of underlying molecular genetic alterations, rare cases of serous borderline tumor or low-grade serous carcinoma co-existing with or recurring as high-grade serous carcinoma or poorly-differentiated carcinoma have been reported in the literature.[20–24] Most of these reported cases were associated with a poor prognosis; however, given the small numbers, the data are insufficient for making conclusions regarding the clinical behavior of this rare group of patients and how they should be treated. Such cases should be excluded from low-grade serous carcinoma clinical trials, as they are not representative of the biology of most low-grade serous carcinomas.

Consensus

Low-grade serous carcinoma co-existing with or associated with subsequent high-grade serous carcinoma is rare. If high-grade serous carcinoma is substantial, the cancer should be managed as per high-grade serous carcinoma. Further studies are needed to understand the biology and clinical behavior of these tumors.

TRANSLATIONAL RESEARCH

Mechanisms of Low-Grade Serous Carcinoma Tumorigenesis

Current evidence indicates that low-grade serous carcinoma arises either de novo or after a diagnosis of serous borderline tumor.[25] The mechanisms of low-grade serous carcinoma tumorigenesis, particularly of those tumors that do not include a mitogen-activated protein kinase (MAPK) alteration, are not well defined and require further research. MAPK-pathway alterations are prominent in 50% of tumors.[26–29] In addition to *KRAS* and *BRAF*, other genetic alterations that are under investigation for their potential involvement in the pathogenesis of low-grade serous carcinoma include cyclin-dependent kinase inhibitor (*CDKN)2A/2B* deletion; *NRAS*, *ERBB2*, and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) alterations; and chromosome 1p36 deletion; however, it is unknown which genes are involved.[26 30–34] Other possible alterations include neurofibromin 1 (*NF1*) and erbb2 receptor tyrosine kinase 3 (*ERBB3*).[33 34] Whether low-grade serous carcinoma arises from fallopian tube epithelial progenitor cells remains controversial.[35–39] The presence of *AGR3*-positive ciliated cells in low-grade serous carcinoma and the observation that 60% of low-grade serous carcinoma are associated with ciliated serous borderline tumors might suggest an alternative cell origin other than the non-ciliated secretory fallopian tube epithelial cells.[38 39] No evidence is available to support opportunistic salpingectomy in the prevention of low-grade serous carcinoma.

Biomarker for Sensitivity to MEK Inhibitors

In patients with low-grade serous carcinoma, MAPK alteration status may be associated with a higher response to mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors; however, activity is also observed in patients without MAPK alterations.[40–42] Monk et al observed that, compared with *KRAS* wild type (WT) tumors, *KRAS* alteration was statistically significantly associated with a greater objective response rate to binimetinib (OR 3.4; 95% CI 1.53 to 7.66; unadjusted p=0.003) and prolonged progression-free survival (median progression-free survival 17.7 months *KRAS* mutant vs 10.8 months *KRAS* WT; p=0.006).[40] Gershenson et al observed *RAS* or *BRAF* alteration was associated with a greater objective response rate with trametinib than WT status (50% vs 8%); however, the test for interaction did not achieve statistical significance (p=0.11). In addition, alteration status was not a significant predictor of progression-free survival (p for interaction 0.72).[41] No clear consensus exists that MEK inhibitors should be limited to a single population based on a biomarker, as indicated in the National Comprehensive Cancer Network (NCCN) guidelines, which do not require biomarker positivity for MEK inhibitor use.[43]

Consensus

The optimal predictive biomarker for sensitivity of low-grade serous carcinoma to MEK inhibitors is unknown.

Biomarkers for Sensitivity to Endocrine Therapy

Panelists determined that whether immunohistochemistry testing for estrogen receptor (ER) or progesterone receptor (PR) positivity is performed in patients with low-grade serous carcinoma varies by institution. Most patients have ER- or PR-positive disease,[44] and whether resources should be used for testing ER or PR positivity is debatable.

Whether lack of ER or PR positivity should be used as a reason to exclude the use of hormonal therapy in the primary maintenance setting is controversial. Low-PR status (Allred score <2) has been associated with increased copy number changes compared with high-PR tumors.[45] In addition, high-ER and high-PR status have been associated with improved overall survival.[45] However, no study has reliably shown that immunohistochemistry levels are associated with endocrine therapy response. Identifying predictive biomarkers for endocrine therapy is challenging due to the inherently low response rates observed. While a benefit of endocrine therapy is observed with stable disease rates of 50–62%, objective response rates range from 9% to 14% in the recurrent setting.[41 46 47] Development of *ESR1* alterations would be expected to confer resistance to aromatase inhibitor therapy, based on evidence from other disease states such as breast and endometrial cancers.[48–54]

Consensus

The optimal biomarker for sensitivity of low-grade serous carcinoma to endocrine therapy is unknown. ER-positive disease does not correlate with efficacy of hormonal therapy.

EPIDEMIOLOGY AND RISK

Classification of Low-Grade Serous Carcinoma

The panel classifies low-grade serous carcinoma as a distinct rare disease. In the Orphan Drug Act, the US Food and Drug

Administration defines a rare disease as one affecting <200 000 people in the USA.[55] While current prevalence estimates for low-grade serous carcinoma are not available, it has been estimated that low-grade serous carcinoma represents <10% of new epithelial ovarian cancer cases.[1–3 56] Given that the prevalence of all ovarian cancer cases in the USA was estimated at 233 565 in 2019,[57] even with an approximate doubling in life expectancy,[4] the prevalence of low-grade serous carcinoma would not be expected to exceed 200 000 cases in the USA. Further, low-grade serous carcinoma is pathologically distinct from high-grade serous carcinoma, lacking *BRCA*-associated etiology.[58 59]

Consensus
It is appropriate to classify low-grade serous carcinoma as a distinct rare disease.

Risk Factors

Limited evidence from a Danish population-based case–control study identified factors affecting the risk for serous borderline tumor.[60] Parity, older age at first birth, and oral contraceptive use appear to be associated with a lower risk of serous borderline tumor. In contrast, infertility and hormone replacement therapy appear to be associated with a greater risk of serous borderline tumor.

Whether *BRCA* alteration is associated with low-grade serous carcinoma is an important consideration for patients and their families. Meager rates of *BRCA* mutation have been observed in low-grade serous carcinoma cohorts, generally ranging from 0% to 5%.[33 58 61 62] Vineyard et al evaluated personal and family histories of patients with ovarian cancer to elucidate factors suggestive of hereditary breast and ovarian cancer and found that women with low-grade serous carcinoma had a significantly lower risk estimate of hereditary breast and ovarian cancer than patients with high-grade serous carcinoma.[59] A lack of association between low-grade serous carcinoma and germline *BRCA* mutation is corroborated by a study that employed a secondary pathologic review and found no *BRCA* germline mutations among 79 patients with low-grade serous carcinoma who were treated at a comprehensive cancer center in a geographic region enriched with patients of Ashkenazi Jewish descent.[58] Overall, low-grade serous carcinoma is not considered to be *BRCA*-associated. However, as discussed below, it is recommended that all patients with epithelial ovarian cancer should undergo germline testing.

Consensus
Most participants agreed that the current evidence does not suggest that low-grade serous carcinoma is driven by *BRCA* mutation.

Germline Testing in Low-Grade Serous Carcinoma

Germline testing is recommended for all patients with newly diagnosed ovarian cancer in guidelines by the American Society of Clinical Oncology and the NCCN.[43 63] Panelists outlined reasons for testing, which include histologic uncertainty, a change in diagnosis over time, and risk for both patient and family by not identifying a *BRCA* alteration. In addition, routine testing will help provide additional knowledge about the true incidence of germline alteration in this population and whether any germline alterations are associated with low-grade serous carcinoma.

Consensus
All patients with low-grade serous carcinoma should undergo germline testing consistent with the overall population of patients with epithelial ovarian cancer.

Somatic Tumor Testing in Low-Grade Serous Carcinoma

The NCCN guidelines recommend a tumor molecular analysis panel in the up-front setting, including somatic tumor testing for both low-grade serous carcinoma and high-grade serous carcinoma.[43] The somatic tumor testing panel should test for a minimum of *KRAS*, *HRAS*, *NRAS*, *BRAF*, *NF1*, and *BRCA* alterations. Some studies demonstrate changes in somatic tumor alterations in patients over time; however, these were limited by small patient numbers and single-institution studies.[48 58 64] Reasons to repeat somatic tumor testing include aberrant clinical behavior, clinical trial eligibility, prolonged disease course, or cases of mixed low-grade serous carcinoma/high-grade serous carcinoma to identify which element is active.

Consensus
A somatic tumor testing panel should be conducted at diagnosis in patients with low-grade serous carcinoma consistent with current guidelines. Repeat somatic tumor testing may be justified in certain cases of low-grade serous carcinoma.

Prognostic Factors in Low-Grade Serous Carcinoma

Residual disease status at the end of primary therapy[10 65–67] and at age ≤35 years[65] are associated with worse outcomes for patients with newly diagnosed low-grade serous carcinoma. More recently, the prognostic implications of MAPK alterations have been evaluated. In the MILO/ENGOT-ov11 and GOG-0281/LOGS clinical trials, MAPK pathway alterations were associated with prolonged progression-free survival in the standard-of-care arms, although these differences were not statistically significant.[40 41] However, statistically significantly prolonged overall survival among patients with MAPK pathway alterations versus MAPK WT was observed by Gershenson et al (median 148 months and 78 months, respectively; p=0.001) and Manning-Geist et al (median 339 months and 125 months, respectively; p=0.02 in multivariate analysis).[58 68] Potential prognostic factors that require further evaluation include obesity,[67] CA-125 (pre-treatment or normalization),[66] lymph node ratio,[69] lymphovascular space invasion,[69] omental involvement,[69] and mRNA expression of Ki67 and polo-like kinase-1 (Plk1).[70 71]

Consensus
Residual disease at the end of primary therapy and younger age are associated with poor prognosis in patients with low-grade serous carcinoma. In general, MAPK alteration is associated with improved prognosis in patients with low-grade serous carcinoma.

Imaging Techniques in Low-Grade Serous Carcinoma

Whether a preferred imaging technique exists for low-grade serous carcinoma is unknown. Imaging techniques vary according to institution. The NCCN guidelines recommend computed tomography (CT), positron emission tomography (PET)-CT, PET head to thigh, or magnetic resonance imaging

(MRI).[43] Panelists agreed that clinicians should follow the NCCN guidelines to the extent possible and concurred that the chest, abdomen, and pelvis should all be included in CT imaging. A majority of panelists prefer CT to PET-CT. Panelists agreed that ultrasound should be used in patients with a retained ovary and can be considered in patients without ovaries to reduce cumulative radiation with repeat imaging. Novel imaging techniques requiring further study in low-grade serous carcinoma include PET/MR as reviewed by Virarkar et al,[72] dual-energy CT,[73 74] and F-18 16-alpha-fluoroestradiol (FES) PET.[75]

Consensus
There is not one optimal imaging technique for low-grade serous carcinoma; however, a majority of panelists prefer CT to PET-CT.

INITIAL MANAGEMENT

Primary Cytoreductive Surgery

Primary cytoreductive surgery represents the preferred initial treatment of low-grade serous carcinoma, with the goal of attaining complete gross resection.[43] Attainment of complete resection compared with gross residual disease is associated with prolonged progression-free survival and overall survival.[10 65 76 77] When compared with patients with complete gross resection, Fader et al demonstrated hazard ratios (HRs) for survival of 2.31 (95% CI 1.37 to 3.90; p=0.002) in patients with 0.1–1.0 cm of residual disease and 2.45 (95% CI 1.30 to 4.64; p=0.006) in patients with >1.0 cm of residual disease.[10] In a separate cohort, when compared with patients with residual disease of >1.0 cm, Grabowski et al reported HRs for survival of 0.51 (95% CI 0.26 to 1.02; p=0.06) in patients with 0.1–1.0 cm of residual disease and 0.14 (95% CI 0.07 to 0.29; p<0.001) in patients with no residual disease.[77] Based on available data, and unlike resection in high-grade serous carcinoma, optimal cytoreduction remains critical in low-grade serous carcinoma even if complete gross resection is considered unattainable.

Consensus
Generally, attainment of complete gross resection is ideal following primary cytoreductive surgery in low-grade serous carcinoma. However, given the lower sensitivity of this disease to chemotherapy, surgical resection should still be considered even if complete gross resection is unlikely to be achieved. All patients with newly diagnosed low-grade serous carcinoma should be evaluated by a gynecologic oncologist for consideration of surgical debulking; due to surgical complexity, additional surgical referrals (colorectal, urology) may be necessary as well to optimize surgical cytoreduction.

Fertility-Sparing Surgery

Without sufficient data,[78] panelists concurred that fertility-sparing surgery is an option in patients with stage IA–C1 low-grade serous carcinoma, following attempted comprehensive surgical staging. Whether fertility-sparing surgery is appropriate in later-stage disease was debated. No data are available to guide monitoring the remaining ovary in patients following fertility-sparing surgery. Signs that might prompt removal, such as a complex cyst or rising CA-125, are not agreed on. Some clinicians follow such patients with ultrasound every 3 months and retain the ovary as long as possible, whereas others remove the second ovary following childbearing.

Consensus
Fertility-sparing surgery is an option in stage IA–C1 low-grade serous carcinoma.

Oocyte Retrieval

The risks of hormone stimulation in patients with low-grade serous carcinoma are unknown.[79] The French national network dedicated to rare gynecological cancers concluded that controlled ovarian stimulation is contraindicated in patients with a history of low-grade serous carcinoma.[79] However, the recommendation was made in the absence of data and based on the hormone sensitivity of the tumor. During controlled ovarian stimulation, serum estradiol levels can increase 10-fold; however, peak estradiol levels can be reduced by administering an aromatase inhibitor (letrozole) with gonadotropins during ovarian stimulation without compromising oocyte and/or embryo yield.[80 81] The current expert panel concluded that oocyte retrieval from an unaffected ovary could be considered an option for patients with low-grade serous carcinoma, following discussion of uncertainties with the patient. Collaboration with a reproductive endocrinologist is essential.

Consensus
Oocyte retrieval from an unaffected ovary is an option for patients with low-grade serous carcinoma.

Neoadjuvant Chemotherapy

Primary surgery is preferred over neoadjuvant chemotherapy for treating low-grade serous carcinoma. Randomized trials demonstrating similar outcomes with neoadjuvant chemotherapy versus primary debulking surgery were conducted in populations consisting primarily of high-grade serous carcinoma rather than low-grade serous carcinoma.[82–84] Evidence regarding neoadjuvant chemotherapy in patients with low-grade serous carcinoma is limited to retrospective data.[85–87] Generally, low response rates to neoadjuvant chemotherapy in these studies (4–36%) indicate chemoresistance. Although Scott et al observed a 36% response rate to neoadjuvant chemotherapy, progression-free survival in the neoadjuvant chemotherapy cohort was significantly shortened compared with patients who had received primary surgery followed by chemotherapy (p=0.018).[87] This outcome may reflect that neoadjuvant chemotherapy delays effective cytoreductive surgery in favor of minimally effective treatment in low-grade serous carcinoma tumors. Whether neoadjuvant hormonal therapy combinations are beneficial in low-grade serous carcinoma remains unknown. Preliminary data from a pilot study of neoadjuvant fulvestrant plus abemaciclib in patients with low-grade serous carcinoma showed a promising response rate of 47%.[88] The expert panel concurred that, even if complete gross resection is considered unattainable, an attempt at surgical cytoreduction remains preferable to neoadjuvant

chemotherapy. Surgery may not be the optimal initial treatment in select advanced cases, and clinicians should consider enrollment in a clinical trial if available. A decision on initial treatment should be based on referral to or consultation with a gynecologic oncologist.[43 89]

Consensus
Neoadjuvant chemotherapy is not the preferred approach in patients with low-grade serous carcinoma. However, a small proportion of women may be candidates for neoadjuvant chemotherapy based on the presence of extensive tumor or comorbidities. There is no consensus regarding patient selection for neoadjuvant chemotherapy.

Primary Systemic Treatment

Low-grade serous carcinoma shows substantially lower sensitivity to chemotherapy compared with high-grade serous carcinoma.[77] The panelists concurred that the NCCN and European Society for Medical Oncology (ESMO)–ESGO guidelines represent the currently accepted standard of care for primary systemic treatment of low-grade serous carcinoma.[15 43] However, hormonal therapy is not well defined in the guidelines. Based on available evidence, aromatase inhibitors appear superior to tamoxifen as suggested by retrospective data and the response rates observed in the physician's choice arm of GOG-0281/LOGS (14% with letrozole (n=44) vs 0% with tamoxifen (n=27)).[41 46] The NRG-GY019 study will help clarify whether post-surgery hormonal therapy could be used alone versus chemotherapy plus hormonal therapy maintenance (NCT04095364).[90]

Consensus
The NCCN and ESMO–ESGO guidelines represent the currently accepted standard of care for primary systemic treatment of low-grade serous carcinoma.

Hyperthermic Intra-Peritoneal Chemotherapy

Current evidence demonstrating the benefit of hyperthermic intra-peritoneal chemotherapy arises from studies that primarily enrolled patients with high-grade serous carcinoma.[91 92] Although a prospective randomized trial demonstrated similar safety of surgery with or without hyperthermic intra-peritoneal chemotherapy,[91] a retrospective real-world study suggested that hyperthermic intra-peritoneal chemotherapy is associated with increased complication rates and longer hospital stays.[93] No available evidence demonstrates a benefit of treating low-grade serous carcinoma with hyperthermic intra-peritoneal chemotherapy, and potential complications justify caution. Use of hyperthermic intra-peritoneal chemotherapy in patients with low-grade serous carcinoma warrants further study.

Consensus
There is no role for hyperthermic intra-peritoneal chemotherapy outside of a clinical trial in the primary treatment of low-grade serous carcinoma.

Monitoring After New Diagnosis

The panelists concurred that the NCCN guidelines represent the currently accepted standard of care for monitoring patients with low-grade serous carcinoma following a new diagnosis.[43] Concerning imaging frequency, the NCCN guidelines recommend imaging be performed as clinically indicated. Panelists agree that imaging as clinically indicated is appropriate for earlier-stage disease. However, for patients with stage II–IV disease, the expert panel recommends routine imaging in conjunction with CA-125 be prioritized over CA-125 alone. CA-125 has primarily been studied in patients with high-grade serous histology; the utility of CA-125 as an independent marker of response and progression in low-grade serous carcinoma remains an area of active investigation. Imaging intervals of every 3 months in year 1, every 4 months in year 2, every 6 months in years 3–5, and then annually thereafter should be considered (in the absence of relapse). In addition, the panel recommends that bone mineral density be monitored in patients receiving an aromatase inhibitor. The panelists recommend routine imaging for patients with advanced serous borderline tumor and non-invasive peritoneal implants who had surgery; however, the optimal frequency is unknown.

Consensus
The NCCN guidelines generally represent the currently accepted standard of care for monitoring patients with low-grade serous carcinoma following a new diagnosis. However, imaging should be prioritized over following CA-125 alone, and bone mineral density should be monitored in patients receiving an aromatase inhibitor.

MANAGEMENT OF RECURRENT DISEASE

Secondary Cytoreductive Surgery

A retrospective analysis of 41 patients with recurrent low-grade serous carcinoma showed prolonged progression-free survival and a trend toward prolonged overall survival in patients who received secondary cytoreductive surgery before systemic therapy.[94 95] A median overall survival of 83 months was observed in patients who proceeded directly to secondary cytoreductive surgery compared with 33 months in patients who received systemic therapy (p=0.09).[94] An exploratory analysis of five randomized phase II/III trials comparing different chemotherapy regimens in patients with recurrent ovarian cancer found that 42 (4%) of the 1050 patients who were treated at first recurrence had low-grade histology with the other 1008 (96%) patients displaying high-grade disease. There were no significant differences in progression-free survival (p=0.91) or overall survival (p=0.25) between platinum-sensitive and platinum-resistant disease in patients with low-grade histology. A Cox regression analysis showed that ascites and residual disease after secondary cytoreductive surgery were independently associated with poor progression-free survival in patients with recurrent low-grade epithelial ovarian cancer.[56]

Complete gross resection should be the goal of secondary cytoreductive surgery.[96] Retrospective analyses demonstrate shorter progression-free survival and a trend toward shorter overall survival in patients with gross residual disease following secondary cytoreductive surgery.[56 94 96] Crane et al observed a median progression-free survival of 60 months

Table 2 Agents used for treatment of recurrent low-grade serous carcinoma with prospective data available

Agent	Study	Response rate
Liposomal doxorubicin	GOG-0281/LOGS and MILO/ENGOT-ov11	3% (1/40); 14% (9/66)
Topotecan	GOG-0281/LOGS and MILO/ENGOT-ov11	0% (0/8); 0% (0/9)
Weekly paclitaxel	GOG-0281/LOGS and MILO/ENGOT-ov11	9% (1/11); 15% (4/26)
Tamoxifen	GOG-0281/LOGS	0% (0/27)
Letrozole	GOG-0281/LOGS	14% (6/44)
Trametinib	GOG-0281/LOGS	26% (34/130)
Binimetinib	MILO/ENGOT-ov11	16% (32/198)

in patients with low-grade serous carcinoma with complete gross resection versus 11 months in patients with gross residual disease (p=0.0008).[94] Median overall survival times were 168 months and 89 months, respectively (p=0.10). In the exploratory analysis of randomized trials, multivariate analysis identified a HR for progression-free survival of 5.9 (95% CI 1.2 to 29.9; p=0.03) associated with the presence of gross residual disease.[56]

Patient selection criteria for secondary cytoreductive surgery in patients with low-grade serous carcinoma are not clearly defined. Prior criteria developed to aid in selecting patients for secondary cytoreductive surgery are based largely on the experience of patients with high-grade serous carcinoma.[97 98] However, these systems have limited relevance to low-grade serous carcinoma due to its lower sensitivity to chemotherapy. As such, selection criteria for secondary cytoreductive surgery in patients with low-grade serous carcinoma may be expanded beyond these established systems. The Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) identified factors associated with complete gross resection with secondary cytoreductive surgery in a population not limited to low-grade serous carcinoma.[97] However, due to the more indolent nature of low-grade serous carcinoma, complete gross resection may not be necessary to provide clinical benefit. Chi et al recommended disease-free interval and number of recurrent sites as deciding factors.[98] The current panel concluded that, while a solitary or limited number of masses is preferable to carcinomatosis, patients with low-grade serous carcinoma who have more extensive disease should not necessarily be excluded.

Consensus

Secondary cytoreductive surgery by a gynecologic oncologist should be considered in any patient with low-grade serous carcinoma. In carefully selected patients with low-grade serous carcinoma, tertiary surgery, quaternary surgery, and beyond may still provide clinical benefit. However, specific selection criteria for secondary cytoreductive surgery in patients with low-grade serous carcinoma remain unclear.

Systemic Therapy at Recurrence

Notably, the NCCN guidelines were recently updated to address low-grade serous carcinoma as a separate disease category.[43] Options for recurrent disease include a clinical trial, a MEK inhibitor, dabrafenib+trametinib for *BRAF V600E*-positive tumors, hormonal therapy, chemotherapy (including platinum-based chemotherapy for patients who have not received prior chemotherapy and either platinum-based or non-platinum chemotherapy in the recurrent setting, with or without bevacizumab), or bevacizumab as a single agent.[43] The best hormonal therapy is unknown. As noted previously, aromatase inhibitors appear superior to tamoxifen (Table 2).[41] Clinical trial enrollment should be considered for all patients with recurrent low-grade serous carcinoma. Ongoing phase II trials (Table 3) in recurrent low-grade serous carcinoma include GOG-3026, which is evaluating letrozole plus ribociclib (NCT03673124)[99]; BOUQUET, which is evaluating multiple biomarker-driven treatments (NCT04931342)[100]; and RAMP 201/ENGOT-ov60/GOG 3052, which is evaluating the novel dual RAF/MEK inhibitor, avutometinib, with or without the novel focal adhesion kinase (FAK) inhibitor, defactinib (NCT04625270).[101]

It remains unclear if there is a preferable sequencing strategy for treatment of patients with low-grade serous

Table 3 Ongoing studies in low-grade serous carcinoma

Study name	Phase	Setting	Intervention	Identifier
NRG-GY019	III	Adjuvant	Carboplatin/paclitaxel x6 followed by letrozole maintenance vs letrozole maintenance alone	NCT04095364
LEPRE trial	III	Adjuvant	Carboplatin/paclitaxel x6 vs letrozole	NCT05601700
MATAO	III	Adjuvant	Carboplatin/paclitaxel followed by letrozole vs placebo	NCT04111978
GOG-3026	II	Recurrent	Letrozole in combination with ribociclib	NCT03673124
WO42178/ENGOT-GYN2/ GOG-3051/BOUQUET	II	Recurrent	Multiple biomarker driven arms	NCT04931342
	II	Recurrent	Rogorafenib in combination with fulvestrant	NCT05113368
The FUCHSia Study	II	Recurrent	Fulvestrant	NCT03926936
PERCEPTION	II	Recurrent	Carboplatin-based chemotherapy in combination with pembrolizumab	NCT04575961
	II	Recurrent	Liposomal doxorubicin in combination with peposertib	NCT04092270
ENGOT-ov60/GOG-3052/ RAMP-201	II	Recurrent	Avutometinib (VS-6766) in combination with defactinib	NCT04625270

Table 4 Monitoring and treatment for select toxicities associated with MEK inhibitors

Toxicity	Management
Cutaneous skin reactions*[107 108 122]	Treatment options include oral or topical antibiotics and corticosteroids and isotretinoin[108] Preventative measures include emollients and use of high-SPF sunscreen[108]
Diarrhea[122]	Management consists of loperamide, diet modifications, fluid and electrolyte intake, and dose interruption (grade 2–3) or discontinuation (grade 4). Infection should be ruled out and antibiotics given for persistent grade 3–4 diarrhea or in the case of grade 3–4 neutropenia[106]
Peripheral edema[122]	Evaluate with standard cardiac work-up including ECG, echocardiogram, and referral to cardiologist if appropriate[106]
Cardiac toxicity†[122]	Assess LVEF by echocardiogram or MUGA scan before initiation of trametinib, 1 month after initiation, and then every 2–3 months during treatment.[123] Follow instructions in product labeling in the event of decreased LVEF
Ocular toxicity‡[109 122]	Ensure patient has ophthalmology follow-up with proactive monitoring for ocular toxicities.[107] Urgent ophthalmological evaluation should occur within 24 hours for loss of vision or other visual disturbances[123] Counsel patient about the possibility and timing of ocular toxicity, which most commonly occurs within 14 days after treatment initiation[124]
Interstitial lung disease or pneumonitis[106]	Patients who develop cough, shortness of breath, or abnormal chest signs should be evaluated for pneumonitis with plain chest X-ray or chest CT scan[106] Treatment consists of temporarily discontinuing MEK inhibitor treatment and initiating an oral steroid[125]

*Most frequently acneiform dermatitis, rash (maculo-papular, erythematous, or exfoliative), erythema, folliculitis, erysipelas.[108]
†Decreased ejection fraction, ventricular dysfunction.[122]
‡MEK inhibitor-associated toxicities: blurred vision, chorioretinopathy, retinal vein occlusion, retinal pigment epithelial detachment[122 123]; BRAF inhibitor-associated toxicities: retinal vein occlusion.[109]
CT, computed tomography; LVEF, left ventricular ejection fraction; MEK, mitogen-activated extracellular signal-regulated kinase; MUGA, multi-gated acquisition; SPF, sun protection factor.

carcinoma. Factors to consider when choosing treatment sequence include patient preference, prior therapy, prior progression history, and the adverse event profile of the drug. The panel members also discussed that it may be preferable to give bevacizumab earlier in the disease course, given the greater risk of obstruction and potential bowel perforation later in the course of the disease. Similarly, MEK inhibitors, currently only available as oral therapies, should be considered earlier in the disease course to avoid impairment of gastrointestinal absorption.

Consensus
Options consistent with the NCCN guidelines are recommended for the treatment of relapsed low-grade serous carcinoma, including the use of endocrine therapy, chemotherapy, anti-angiogenic and targeted therapies. No standard treatment sequencing exists in low-grade serous carcinoma, but the panel recommended consideration of the use of bevacizumab and MEK inhibitor therapy earlier in a patient's disease course, prior to development of bowel motility impairment.

Immunotherapy

The panel concurred that immunotherapy has no known role in treating low-grade serous carcinoma outside of a clinical trial. Ongoing clinical trials include phase II studies evaluating pembrolizumab plus chemotherapy in patients with platinum-sensitive recurrent low-grade serous carcinoma (PERCEPTION),[102 103] pembrolizumab in rare tumor types including rare ovarian tumors (AcSé),[104 105] and biomarker-driven therapies in rare ovarian tumors (BOUQUET).[100] Based on the tumor-agnostic indication, pembrolizumab or dostarlimab may be considered in very rare cases of documented mismatch repair deficiency.

Consensus
There is no known role for immunotherapy treatment of low-grade serous carcinoma outside of a clinical trial or confirmed cases of mismatch repair deficiency.

Treatment-Associated Toxicity Management

The panel concluded that proactive treatment of side effects is important in patients with low-grade serous carcinoma. Notably, it is important to monitor patients for MEK inhibitor-specific toxicities and address these side effects as they arise. An overview of treatments for MEK inhibitor-specific toxicities has been reviewed[106–109] and is summarized in Table 4. In GOG-0281/LOGS, grade 3 or 4 toxicities occurred in patients with low-grade serous carcinoma treated with trametinib as follows: skin rash occurred in 17 of 128 patients (13%), anemia in 13%, hypertension in 12%, diarrhea in 10%, nausea in 12%, and fatigue in 8%. Ten patients (8%) had a decrease in ejection fraction, three patients (2%) experienced pneumonitis, and two patients (2%) had a retinal vascular disorder.

Providers should refer to current guidelines and prior reviews regarding managing aromatase inhibitor toxicities, including musculoskeletal symptoms and osteoporosis.[110–114] Patients who are receiving aromatase inhibitors should be counseled regarding musculoskeletal side effects. Options for managing these side effects include exercise; acupuncture; application of heat or cold; use of a non-steroidal anti-inflammatory drug or other analgesics, a diuretic, duloxetine, or omega-3 fatty acids; conversion to an alternative aromatase inhibitor; and an aromatase inhibitor holiday.[110–113] Patients should be monitored for bone mineral density and treatment initiated for appropriate candidates.[110 111 114]

Consensus
Proactive treatment of side effects is important in patients with low-grade serous carcinoma.

CLINICAL TRIALS AND FUTURE RESEARCH IN LOW-GRADE SEROUS CARCINOMA

Entry Criteria in Recurrent Low-Grade Serous Carcinoma Clinical Trials

Platinum resistance in ovarian cancer has been historically defined as relapse within 6 months from prior platinum treatment.[15] However, the natural course of low-grade serous carcinoma differs from high-grade serous carcinoma, and a 6-month cut-off is unlikely to be applicable nor driven by susceptibility to platinum. In low-grade serous carcinoma, initial objective response rates to platinum therapy are substantially lower than in high-grade serous carcinoma.[77 115] An exploratory analysis of an AGO meta-database identified objective response rates to first-line platinum-taxane-based chemotherapy of 23% among patients with low-grade serous carcinoma and >1 cm measurable residual disease versus 90% among matched controls with high-grade serous carcinoma ($p<0.001$).[77] The panel concluded that response rates to platinum-based chemotherapy are not of sufficient magnitude to qualify patients with low-grade serous carcinoma as having platinum-sensitive disease. In a retrospective study, platinum-based chemotherapy followed by hormonal maintenance therapy was found to be superior to platinum-based chemotherapy followed by observation (median PFS, 64.9 months vs 26.4 months, respectively) ($p<0.001$).[116] Further, hormone therapy alone following primary cytoreductive surgery may represent a rational non-chemotherapy option; 3-year progression-free survival of 79% and overall survival of 93% were observed in one series.[117] As noted earlier, these approaches are being evaluated in NRG-GY019.[90] Based on these observations, prior platinum-based therapy should not be required in trials of recurrent low-grade serous carcinoma. Because systemic therapy varies across practices,[87 118 119] allowing any type of therapy for clinical trial inclusion is more appropriate than requiring specific therapy.

Consensus

Standard definitions of platinum sensitivity and platinum resistance are not applicable in low-grade serous carcinoma.

In trials of recurrent low-grade serous carcinoma, one prior line of systemic therapy should be required for entry, and a requirement for prior platinum-based therapy should be questioned.

Standard of Care in Future Recurrent Low-Grade Serous Carcinoma Trials

In the recent recurrent low-grade serous carcinoma clinical trials MILO/ENGOT-ov11 and GOG-0281/LOGS, the control standard-of-care arm consisted of treatment of physician's choice.[40 41] Permitted treatments were pegylated liposomal doxorubicin, paclitaxel, or topotecan in both trials; letrozole or tamoxifen were also permitted options in GOG-0281/LOGS. Platinum agents were not included as a standard-of-care option in either trial. Whether platinum should be included in a standard-of-care arm is unknown. At present, no defined standard-of-care treatment exists for recurrent low-grade serous carcinoma.

Consensus

There is no defined standard-of-care treatment for recurrent low-grade serous carcinoma.

Accelerating Progress in Low-Grade Serous Carcinoma Research

The panel concurred regarding the importance of accelerating research in low-grade serous carcinoma. An option for fostering research is developing registries. While registries require funding and intensive labor, these barriers might be mitigated by developing working groups and partnerships for thoughtful collaboration and employing real-world experience for regulatory purposes, thus acquiring funding. Additional options for fostering research include leveraging consortia, using electronic medical records and other real-world experience sources, and working toward creating a biorepository based on biospecimens collected from clinical trials.

Consensus

All options should be considered to accelerate research progress in low-grade serous carcinoma.

PATIENT PERSPECTIVES

Identifying the concerns and experiences of women with low-grade serous carcinoma will allow healthcare providers and researchers to better address their needs and improve their quality of life. A series of questions were posed to participants of the Facebook groups 'Low-Grade Serous Ovarian Cancer Peer Support', with over 250 patient members, and 'Low-Grade Ovarian Cancer Women/Caregivers', with over 1500 members. A total of 71 patients completed the survey. Each question and a summary of corresponding participant responses are detailed below.

What are the most important issues to women with newly diagnosed low-grade serous carcinoma?

Women with low-grade serous carcinoma identified the most critical issues as being treatment options; knowing where to find accurate information and resources; knowing where to find emotional and psychological support; fertility options; financial assistance; understanding this type of cancer and the difference between low-grade serous carcinoma versus high-grade serous carcinoma; risk of recurrence; proactive side effect management; and updated statistics and research.

Should prognosis be discussed with all newly diagnosed women with low-grade serous carcinoma?

Among 70 participants who responded to this question, 56 (79%) said yes, nine (13%) said no, and five (7%) said that they were unsure. Some proponents expressed a benefit on quality of life and life planning. Some who were unsure expressed fear of knowing the answer. Panelists recommend approaching the subject with patients sensitively and avoiding using population statistics to discuss prognosis with an individual patient.

What factors would influence your willingness to take part in clinical trials?

The greatest factor influencing patient participation is being asked to participate. Other factors identified by patients were availability of trials for their individual situation; time and cost associated with participation; impact on insurance coverage; location of the trial site and its accessibility; potential adverse effects associated with treatments; risk of disease recurrence; quality of life; a discussion of risks versus benefits of trial participation with their oncologist;

the patient's current stage of disease and prognosis; and whether receiving chemotherapy is required.

What do you see as the challenges or barriers associated with participating in a clinical trial?

Barriers to trial participation identified by patients were fear of the unknown (not fear of the trial); lack of communication with the trial coordinator; location of the trial site and required travel; the frequency of appointments; adverse effects associated with treatment; additional costs associated with participation (transportation, lodging); and lack of awareness about clinical trials.

Were you given the opportunity to have an appointment with an integrative medicine specialist? If yes, was it helpful? If no, is this something you wish your doctor had done?

Among 70 participants who responded to this question, 62 (89%) responded no and seven (10%) responded yes. Of those who responded no, 34 (55%) wished their doctor had provided the opportunity. Of those who responded yes, two (29%) found the appointment helpful. The expert panel identified challenges for physicians in providing access to integrative medicine for their patients. These challenges include lack of insurance coverage, lack of therapists, and an inability to group appointments for people who travel longer distances.

What are the best resources for low-grade serous carcinoma patients to connect with each other and to gain information about their disease?

Patients identified the following resources for information and connection: Cure Our Ovarian Cancer; STARR Ovarian Cancer; National Ovarian Cancer Coalition (NOCC); NCCN guidelines; Ovarian Cancer Research Alliance (OCRA); Facebook groups; and ovarian cancer charities and organizations.

Is there anything else you'd like to say to doctors?

Patients ask that their physicians take the time to listen to patients, have a good attitude, be honest with them, be compassionate and empathetic, be informative, and take the adverse effects of treatments seriously. Patients stated that discussing sexual health/vaginal dryness is important and requested better testing for recurrence and preferred ultrasound.

CONCLUSIONS

It is important to engage international experts in a rare disease such as low-grade serous carcinoma. This workshop addressed pressing outstanding issues in the diagnosis and treatment of low-grade serous carcinoma. The consensus statements developed by this expert panel will help practitioners in all settings to manage patients with low-grade serous carcinoma, while the discussion provides areas for future research and improved patient care.

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