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Review

Low-grade serous carcinoma: New concepts and emerging therapies ☆

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HIGHLIGHTS

- Low-grade serous carcinoma is characterized by relative chemoresistance and prolonged survival.
- The MAP kinase signaling pathway is an important target for low-grade serous carcinoma.

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ABSTRACT

For the past several years, all women with epithelial ovarian cancer have been treated identically, whether in a clinical trial or off protocol. Over the past decade, we have come to appreciate the magnitude of the heterogeneity of ovarian cancer. The development of the binary grading system for serous carcinoma was a major advance leading to separate clinical trials for patients with this subtype originating from the Gynecologic Oncology Group's Rare Tumor Committee. The mitogen-activated protein kinase (MAPK) pathway appears to play a prominent role in the pathogenesis of this subtype. Approximately 20–40% of low-grade serous carcinomas have a KRAS mutation, while BRAF mutations are rare — about 5%. Primary treatment of low-grade serous carcinoma includes surgery + platinum-based chemotherapy (either adjuvant or neoadjuvant). Clinical behavior is characterized by young age at diagnosis, relative chemoresistance, and prolonged overall survival. Current options for treatment of relapsed disease include secondary cytoreduction in selected patients, salvage chemotherapy, or hormonal therapy. A recently completed trial of a MEK inhibitor for women with recurrent disease demonstrated promising activity. Future directions will include further investigations of the molecular biology and biomarker-driven clinical trials with targeted agent monotherapy and combinations.

Contents

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Introduction

Cytoreductive surgery and combination chemotherapy have improved outcomes in ovarian cancer over the last three decades. However, attempts to improve survival by adding additional cytotoxic drugs to carboplatin and paclitaxel have not succeeded [1]. Within the past few years, substantial hope has been placed in therapy that targets specific abnormalities in ovarian cancer cells. To personalize care by matching targeted therapy to specific abnormalities, an in depth analysis of different subtypes of ovarian cancer will be required. More than 300 high-grade serous epithelial ovarian cancers have been characterized — copy number abnormalities, RNA expression, microRNA expression and promoter methylation [2]. A similar study has not yet been performed for the less common low-grade serous carcinomas (LGSC). The Gynecologic Cancer InterGroup (GCIG) Consensus Conference has, however, recently affirmed the need to develop specific treatment options/trials for the histological subtype of LGSC [3].

In order to provide a more detailed view of this unique entity [4], we have reviewed the currently available literature regarding the pathology, epidemiology, molecular abnormalities, clinical course, and treatment of LGSC. Based on this review, we have suggested some priorities for future clinical studies that may lead to a personalized approach to treating patients with LGSC.

Defining low-grade serous carcinomas

Epithelial ovarian cancer (EOC) is a heterogenous disease which includes five main histologic subtypes — serous, mucinous, endometrioid, clear cell, and transitional cell carcinomas [5–9]. Epithelial ovarian cancers can also be classified with regard to invasiveness and degree of differentiation. Tumors of low malignant potential (LMP) generally lack stromal invasion. Invasive carcinomas have been considered low- or high-grade [10].

Systems for grading serous carcinomas have not been universally accepted and have used inconsistent criteria and categories, creating confusion regarding the optimal definitions [12–15]. As we approached the 21st century, clearer pathologic criteria for low- and high-grade lesions were warranted for planning therapy for individual patients and in performing clinical trials.

Traditionally, serous carcinomas have been classified as high-, intermediate, or low-grade [11]. After over a decade of experience, a two-tier system with clear morphologic criteria was reported and subsequently validated, and inter- and intra-observer reproducibility was demonstrated (Table 1) [16,17].

Another classification, the Shimizu–Silverberg three-tiered grading system, scores pleomorphism, mitotic activity, and architectural features for all EOC histologies aside from clear cell carcinomas [18]. Malpica et al. compared the two-tiered grading system developed at MD Anderson Cancer Center (MDACC) to the Shimizu–Silverberg system in the same subset of ovarian serous carcinomas [16]. Most grade 2 tumors in the three-tier system were considered high-grade in the two-tiered MDACC classification. When the MDACC two-tiered system was compared to the three-tiered FIGO grading system (Table 2) [11], 71% of FIGO grade 2 tumors were also considered high-grade using the MDACC system [16]. Consequently, the Shimizu/Silverberg and FIGO grade 1 tumors fall into the MDACC low-grade serous carcinoma category, whereas most of the Shimizu/Silverberg and FIGO grade 2 and 3 tumors are classified as the MDACC high-grade serous carcinomas.

Additional reports have strengthened the concept that the MD Anderson binary grading system for serous carcinomas is superior to other proposed two-tier systems and preferable to a three-tier system. Seidman and colleagues compared the MD Anderson grading system to another binary grading system developed at the Washington Hospital Center and found the former to be more promising [19]. Vang et al. described 111 high-grade serous carcinomas of the ovary or peritoneum that were further subclassifed as either moderately or poorly differentiated using the FIGO grading system [20]. Based on p53 mutational analysis and in vitro extreme drug resistance assays, the investigators concluded that the subclassification into moderately and poorly differentiated serous carcinomas is not relevant. More recently, Bodurka and colleagues, using the binary grading system to reclassify 241 cases of serous carcinoma originally graded using the FIGO system in Gynecologic Oncology Group (GOG) 158, validated that the MD Anderson two-tier grading system is more predictive of outcome than the standard FIGO grading system in women with advanced ovarian cancer [21]. Using the 2-tier system, patients with LGSC versus high-grade serous carcinoma had significantly longer progression-free survival (45.0 vs 19.8 months, respectively; $P = .01$). Using the 3-tier system, there was no difference in clinical outcome in patients with grade 2 or 3 tumors.

A different pattern of molecular alterations in low- and high-grade serous cancers also supports a two-tier grading system [22]. Low-grade cancers may exhibit mutations of KRAS or BRAF, but rarely p53, whereas high-grade lesions contain mutations of p53, but not KRAS or BRAF. Further information on the molecular biology of LGSC is provided below.

Evidence to date indicates that there is a close relationship between LGSC and serous LMP tumor. Some 60% of LGSC are associated with serous LMP tumors [16], but the LGSC component has prognostic significance, and it is essential that LGSC be distinguished from LMP tumors. In addition, when stage II–IV serous LMP tumors recur, the vast majority is LGSC. In one study, when relapses were observed following an initial diagnosis of an LMP tumor, 73% contained LGSC elements [23]. Different histologic patterns of LGSC have recently been stressed considering the difficulty of the diagnosis [24].

The classic distinction between serous LMP tumors and LGSC focuses on the degree of infiltrative growth. The World Health Organization (WHO) definition distinguishes both entities by the presence or absence of obvious destructive stromal invasion [25]. The presence of microinvasion in serous LMP tumors with a maximal invasive focus size of 10 mm^2 does not affect prognosis in most studies [26,27], but it has in others [28,29]. Critics of this view suggest that there is compelling evidence that microinvasion could represent an early stage in the pathogenesis of LGSC [30].

The presence of micropapillae defined by at least 1 continuous area of micropapillary growth measuring at least 5.0 mm in dimension without stromal invasion can be found in 10–20% of serous LMP tumors. Stage I serous LMP tumors with micropapillary features have a

Table 1
MD Anderson two-tiered grading system: features defining low- and high-grade serous ovarian carcinoma (Malpica et al. [16]).

Feature	Low-grade	High-grade
Nuclear atypia in the worst area of the tumor	Uniformity	Pleomorphism
Form	Oval/round	Variation
Size and shape	Uniform	Variation (≥3:1) size
Nucleoli	May exist	Present
Mitotic index (secondary feature)/10 HPF	≤12	>12

HPF: High power field.

Table 2
FIGO three-tiered grading system compared to the MD Anderson two-tier grading system (Malpica et al. [16]).

MDACC grading	FIGO grading			Total
	1	2	3	
Low-grade	35	15	0	50
High-grade	1	38	11	50

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