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Review

Ovarian low-grade serous carcinoma: A comprehensive update ☆,☆☆

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ABSTRACT

Ovarian low-grade serous ovarian carcinoma (OvLGSCa) comprises a minority within the heterogeneous group of ovarian carcinomas. Despite biological differences with their high-grade serous counterparts, current treatment guidelines do not distinguish between these two entities. OvLGSCas are characterized by an indolent clinical course. They usually develop from serous tumors of low malignant potential, although they can also arise *de novo*. When compared with patients with ovarian high grade serous carcinoma (OvHGSCa) patients with OvLGSCa are younger and have better survival outcomes. Current clinical and treatment data available for OvLGSCa come from retrospective studies, suggesting that optimal cytoreductive surgery remains the cornerstone in treatment, whereas chemotherapy has a limited role. Molecular studies have revealed the preponderance of the RAS–RAF–MAPK signaling pathway in the pathogenesis of OvLGSCa, thereby representing an attractive therapeutic target for patients affected by this disease. Improved clinical trial designs and international collaboration are required to optimally address the unmet medical treatment needs of patients affected by this disease.

Contents

Introduction

Ovarian cancer is the leading cause of death from gynecological cancer in the western world [1]. It comprises though a heterogeneous group of tumors with distinctly different histological characteristics, molecular features, and clinical behavior [2–5]. Among the epithelial ovarian cancers the most common subtype is serous carcinoma [6,7]. Histologic grade has been recognized as an important prognostic factor [8–10]. To that end, ovarian serous ovarian carcinoma

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(OvSCa) has been traditionally graded according to three major 3-tier grading systems:1) the FIGO (the International Federation of Gynecology and Obstetrics) system, which assesses the architectural features of the tumor [11]; 2) the World Health Organization (WHO) system, which is based on both architectural and cytologic features [12]; and 3) the Shimizu/Silverberg system, which analyzes three parameters: glandular architecture, degree of nuclear atypia, and mitotic index [13]. In 2004, Malpica et al. described a novel 2-tier system for grading OvSCa as either high-grade (usually former grades 2 and 3) or low-grade (usually former grade 1 tumors), based primarily on the degree of nuclear atypia, and using the mitotic rate as a secondary feature (Fig. 1) [14]. This 2-tier grading system was further validated allowing its universal use [15,16], with the subsequent benefits for standardizing the design and interpretation of clinical trials. In addition, this 2-tier grading system has allowed the meaningful segregation of cases of OvSCas as it has been found that the differences between the low and high grade cases are not limited to the pathology but also detected at the pathogenic and molecular levels, as well as in the epidemiologic and clinical features [17,18].

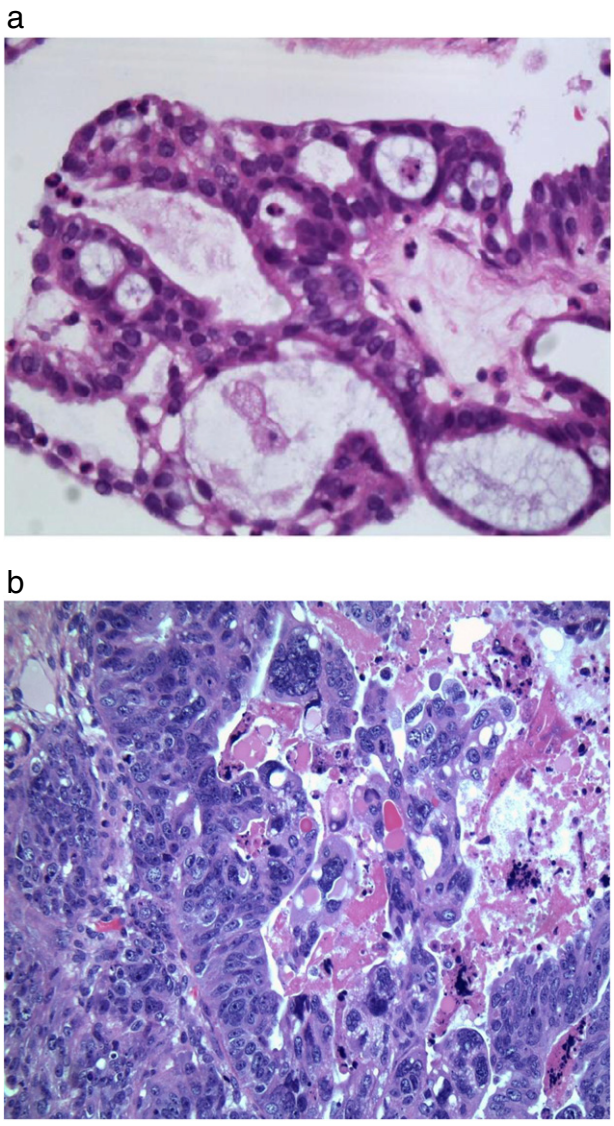

Fig. 1. Histopathology of serous ovarian cancer according to the two-tier grading system. a) Low-grade serous ovarian carcinoma: uniform nuclei and infrequent mitotic figures, in keeping with low nuclear atypia of well-differentiated tumors. b) High-grade serous ovarian carcinoma: nuclear pleomorphism and frequent mitotic figures. Nuclear atypia is characteristic of high-grade tumors.
Courtesy of Dr. Blaise A. Clarke, University of Toronto.

Despite the aforementioned differences, current treatment guidelines for ovarian carcinoma do not clearly distinguish between OvLGSCa and OvHGSCa thereby making uniform treatment recommendations for advanced disease (stages II–IV) [19,20]. Patients with OvLGSCa, usually have an indolent clinical course; however, they experience multiple recurrences and may ultimately die from disease [17]. The treatment of advanced-stage disease is a difficult and challenging situation for the clinician, whereby effective and high-quality evidence-based treatment options for this specific patient population are lacking. It is therefore relevant to improve our understanding of the singularities of OvLGSCa in order to offer better therapeutic options to these patients.

This review will provide an update regarding the distinctive epidemiologic, clinical, histological, and molecular features of OvLGSCa. It will also evaluate the current treatment options, focusing on advanced-stage disease, and the role of new targeted agents in OvLGSCa. We will also discuss methods in clinical study design that can potentially overcome the limitations of prior studies on this type of cases.

Clinical epidemiology

Data from representative population-based cancer registries (e.g. National Cancer Institute's Surveillance Epidemiology and End Results [SEER]) suggests that OvLGSCa represents a minority within the group of invasive serous tumors [21]. Plaxe et al. reported on a descriptive epidemiologic study that the median age at diagnosis for patients with OvLGSCa is 56 years, as opposed to 63 years for patients with OvHGSCa. The difference between these two groups was statistically significant (mean 7.2 years, confidence interval [CI] 6.0–8.2, $p = 0.0001$). Moreover, in the OvLGSCa population there was no significant difference between the age at diagnosis for patients with early or advanced-stage disease, whereas this difference did reach statistical significance for the OvHGSCa group (patients with advanced disease were an average of 2.5 years older than those diagnosed at early stage, CI 1.7–3–3, $p = 0.0001$). Over the period from 1992 to 2003, the annual incidence rate of OvLGSCa decreased by an average of 3.8% each year (CI −0.8% to −6.6%, $p = 0.02$), whereas this rate increased an average of 1.4% each year (CI 0.3–1.6%, $p = 0.02$) for OvHGSCa. No significant differences in the incidence of low-grade and high-grade tumors were seen among ethnicities. In this study, mean overall survival (OS) for OvLGSCa was significantly higher than that for OvHGSCa (99 versus 57 months, log-rank test $p = 0.001$). It is also worth noting that OvLGSCas were more likely to be confined to the ovary at the time of diagnosis. The rate ratio of advanced to early disease was 1.9 for OvLGSCa, whereas it was 10.2 for OvHGSCa. A major limitation of this study lies on its lack of central pathology review. Moreover, tumors were graded on a scale of 1 to 4, where grade 1 tumors were considered “well differentiated”, whereas grades 2, 3 and 4 were grouped as high-grade tumors. More recently, it has been suggested that the incidence of OvLGSCa might be slightly lower (3.4%) than previously reported. In their large retrospective series, Kobel et al. reported on the histopathology of a rigorously annotated database registry of ovarian cancer cases [22]. Major strengths of this study were, on the one hand, that all cases were centrally reviewed by experienced gynecological pathologists; on the other hand, the differentiation between low-grade and high-grade tumors of serous subtype applied the revised two-tier diagnostic criteria.

Population studies have also shown that different patterns of cancer incidence rate can unmask qualitative age interactions relevant to the pathogenesis or the outcome of a given tumor [23,24]. Grimley et al. analyzed the age-adjusted and age-specific incidence rate patterns of OvSCas using a comprehensive dataset from the SEER program [25]. The age-adjusted incidence rate ratio of high to low-grade