

ORIGINAL PAPER

HIGH-GRADE VERSUS LOW-GRADE SEROUS CARCINOMA OF THE OVARY – CURRENT DIFFERENTIAL DIAGNOSIS AND PERSPECTIVES

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ABSTRACT

Introduction. Serous carcinoma is responsible for 47% of all ovarian cancers, and from these cases, only 5% are represented by low-grade serous carcinoma, the rest of them accounting for high-grade serous carcinoma.

Objective. The aim of this study is an observational approach of the differences and similarities of the two types of serous carcinoma of the ovary, that must be seen as different forms of cancer and rendered with care.

Methods. We performed a retrospective study using three cases of ovarian high-grade serous carcinoma and three cases of ovarian low-grade serous carcinoma, diagnosed at the University Emergency Hospital Bucharest. We analyzed patients' age, clinical symptoms, macroscopic and microscopic features together with immunohistochemistry tests.

Results. Mean age for HG carcinoma was 71.3 years old and for LG carcinoma 47.6 years old. Average tumor diameter was with 5.67 cm higher for LG carcinoma. The most encountered stage for HG tumors was pT2a and for LG tumors was pT1a. Mean value

RÉSUMÉ

Comparaison entre les deux types de carcinome séreux de l'ovaire, à haut et à bas degré-diagnostic différentiel courant et perspectives

Introduction. Le carcinome séreux est responsable de 47% de tous les cancers de l'ovaire. Parmi ces cas, 5% seulement sont représentés par un carcinome séreux à bas degré, le reste d'entre eux représentant un carcinome séreux à haut degré.

Objectifs. Le but de cette étude est une approche observationnelle des différences et des similitudes entre les deux types de carcinome séreux de l'ovaire, qui doivent être considérés comme des formes différentes de cancer et traités avec précaution.

Méthodes. Nous avons réalisé une étude rétrospective utilisant trois cas de carcinome séreux ovarien à haut degré et trois cas de carcinome séreux à bas degré ovarien, diagnostiqués à l'Hôpital Universitaire d'Urgence de Bucarest. Nous avons analysé l'âge des patients, les symptômes cliniques, les caractéristiques

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for Ki67 was with 36.33% higher for HG carcinoma. AR expressed diffuse positivity in two cases of LG and only focal positivity in two cases of HG. CD44 expressed focal positivity in all cases of LG and had different patterns in HG.

Conclusions. We found considerable differences between patients' mean age, macroscopic and microscopic features, together with immunohistochemistry expression for Ki67, AR, CD44.

Keywords: high-grade serous carcinoma, low-grade serous carcinoma, AR, CD44.

Abbreviation list

AR = androgen receptor
BRAF = human gene that encodes a protein called B-Raf
CD44 = cluster of differentiation 44
ER = estrogen receptor
HER2 = human epidermal growth factor receptor 2
HG = high-grade
Ki67 = Anti-human Ki-67 Antibody = proliferation index
KRAS = a gene that acts as an on/off switch in cell signaling, first identified as an oncogene in Kirsten RAt Sarcoma virus
LG = low-grade
MAPK= mitogen-activated protein kinase
p53 = tumor protein p53, encoded by tumor suppression gene TP53
Pi3K/mTOR = intracellular signaling pathway Phosphatidylinositol-4,5-bisphosphate 3-kinase/mammalian target of rapamycin
Rb1 = retinoblastoma protein
WHO = World Health Organization
WT1 = Wilms tumor protein, encoded by WT1 gene

INTRODUCTION

Ovarian cancer represents the 5th cause of cancer and the 5th cause of death due to cancer in females in the European Union¹. Serous carcinoma is responsible for 47% of all ovarian cancers, and from these cases, only 5% are represented by low-grade serous carcinoma, the rest of them accounting for high-grade serous carcinoma^{2,3}. The separation of these two entities has started even from 2004, but was officially stated as different reporting system worldwide when 2014 edition of WHO Classification of Tumors of the Female Reproductive Organs appeared^{2,4,5}. They are considered two forms of cancer with different biological behavior and outcome⁶. Because the low-grade tumors are rare, their differences in origin and development are not fully understood^{2,6}.

macroscopiques et microscopiques ainsi que les tests d'immunohistochimie.

Résultats. L'âge moyen du carcinome à HG était de 71,3 ans et celui du carcinome à LG à 47,6 ans. Le diamètre moyen de la tumeur était supérieur de 5,67 cm pour le carcinome LG. Le stade le plus rencontré pour les tumeurs HG était le pT2a et pour les tumeurs LG était le pT1a. La valeur moyenne pour Ki67 était de 36,33% plus élevée pour le carcinome HG. AR a exprimé une positivité diffuse dans deux cas de LG et une positivité focale dans deux cas de HG. La CD44 exprimait une positivité focale dans tous les cas de LG et présentait des profils différents de HG.

Conclusions. Nous avons trouvé des différences considérables entre l'âge moyen des patients, leurs caractéristiques macroscopiques et microscopiques, ainsi que l'expression immunohistochimique de Ki67, AR, CD44.

Mots-clés: carcinome séreux à haut degré, carcinome séreux à bas degré, AR, CD44.

THE OBJECTIVE OF THE STUDY

We performed an observational study on the differential diagnosis between the two types of serous carcinoma of the ovary with current and new perspectives on the approach of these malignancies.

MATERIAL AND METHODS

We performed a retrospective study using three cases of high-grade (HG) serous carcinoma and three cases of ovarian low-grade (LG) serous carcinoma, diagnosed at the University Emergency Hospital Bucharest, Romania. We used hospital's data base and pathology department records for clinical information and macroscopic features such as: tumor diameter, solid/cystic component, tumor extension, lymph node status; using hematoxylin-eosin stains we analyzed the microscopic

features: solid area growth, papillary formation, mitotic count, presence of necrosis. We performed immunohistochemistry tests on archived paraffin-embedded tissue blocks: WT1, p53, Ki67, ER, AR, CD44.

RESULTS AND DISCUSSIONS

The mean age of patients with high-grade serous carcinoma was 71.3 years old and of patients with low-grade serous carcinoma 47.6 years old (Figure 1). In the literature, we found a lower mean age, of 57-63 years old for HG carcinoma and 42 years old for LG

carcinoma⁷ (Figure 1). All patients, except one case of high-grade carcinoma, had urban home environment.

The average tumor diameter was of 8.83 cm for HG tumors and of 14.5 cm for LG tumors, with 5.67 cm higher for LG carcinoma. The most encountered stage for HG carcinomas was pT2a (66.6%) and for LG carcinomas was pT1a (66.6%).

On macroscopic examination, high-grade carcinomas have a predominant solid growth (Figure 2), with evident hemorrhage and necrosis and smaller quantities of serous fluid than low-grade carcinomas, which are predominantly cystic tumors, with small to medium vegetations that correspond to papillary growth with invasive areas (Figure 3).

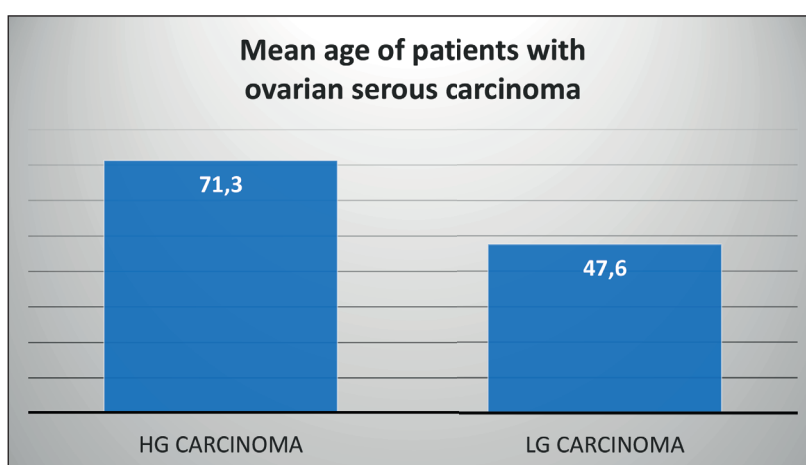


Figure 1. Mean age of patients with ovarian serous carcinoma

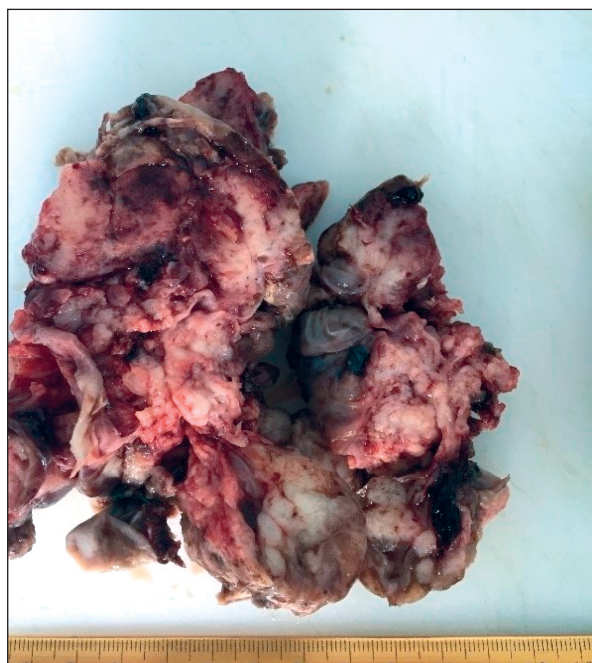


Figure 2. Macroscopic appearance of ovarian high-grade serous carcinoma

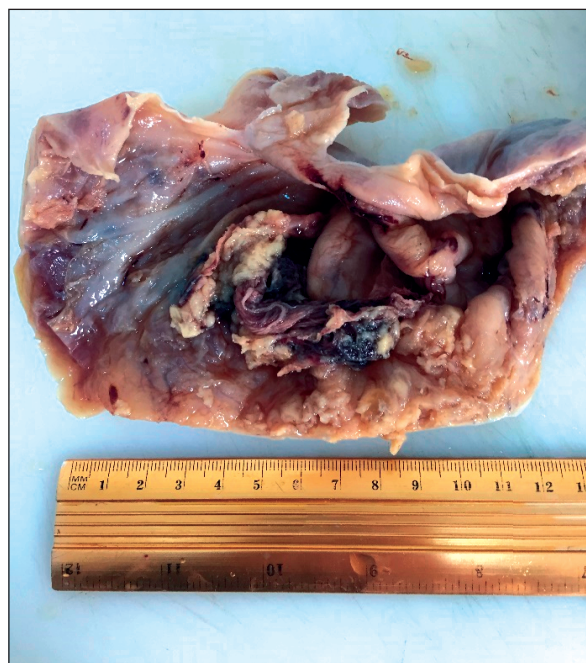


Figure 3. Macroscopic appearance of ovarian low-grade serous carcinoma

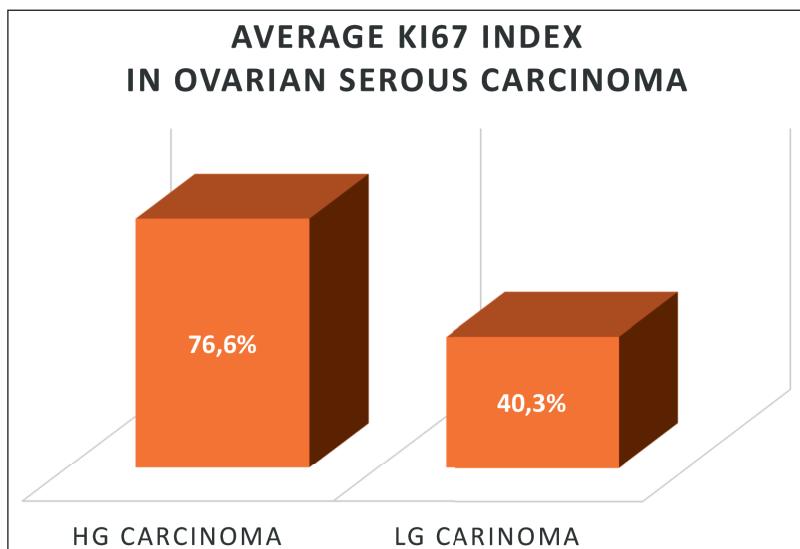


Figure 4. Average Ki67 index in ovarian serous carcinoma

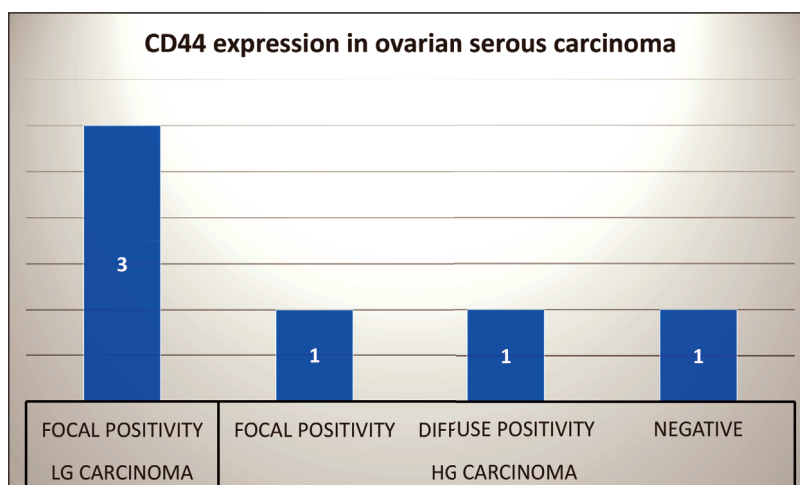


Figure 5. CD44 expression in ovarian serous carcinoma

On histopathological examination, high-grade tumors have predominantly solid areas of severe atypical cells, mitotic count over 30 mitosis/10HPF (high power field) and large areas of necrosis, whereas low-grade tumors have papillary and micropapillary architecture, mitotic count under 15 mitosis/10HPF and rare focal areas of necrosis.

Lymph node status could be evaluated in two cases of high-grade serous carcinoma (one case with lymph node metastasis and the other free of invasion) and in only one case of low-grade serous carcinoma (free of invasion). Lymph node sampling and taking blind peritoneal biopsies are important in surgical staging of early ovarian cancer and involvement of only para-aortic lymph nodes in advanced stage results in a better chance of survival than involvement of pelvic lymph nodes only or

both pelvic and para-aortic lymph nodes simultaneously^{8,9}.

The mean value for Ki67 index was 76.6% for HG carcinoma and 40.3% for LG carcinoma, with 36.33% higher for HG group (Figure 4). However, we found one study in the literature where expressions of p53 and Ki67 were found to have little correlation with overall survival and disease-free survival¹⁰.

WT1 (Wilms Tumor protein 1), p53 were positive for both categories, and ER (estrogen receptor) was positive over 80% for 66.6% of each group. WT1 and p53 showed previous success for use in small biopsy specimens from extraovarian sites due to little variability between ovarian and omental sites¹¹. In their study of sex steroid hormone receptors expressed in ovarian carcinomas, Gomora MJ

et al found a high frequency of ER negative HG carcinoma¹². However, other studies confirmed ER positivity in these tumors, associated with recurrent disease and peritoneal metastasis¹³. Also, other studies stated that LG tumors have higher ER and PR expression compared to HG tumors and that estrogen receptor expression was associated with increased risk of lympho-vascular space invasion^{14,15}.

Mutation of TP53 gene is the most frequent genomic alteration of high-grade carcinomas, while KRAS and BRAF mutations are more likely encountered in low-grade ones^{2,16,17}. In one study DNA derived from tumor was detected in the vaginas of 60% of patients with ovarian cancer with intact fallopian tubes and harbored the exact same TP53 mutation¹⁸. Other frequent mutations but poorly understood are RB1 (retinoblastoma) deletions in high-grade serous carcinoma¹⁹. Compared to other localizations, alteration in PI3K/mTOR, MAPK pathways and HER2 expression/amplification is more frequent in uterine serous carcinoma than in ovarian serous carcinoma²⁰.

AR expressed diffuse positivity in two cases of LG and only focal positivity in two cases of HG. In the literature, reported cases expressed androgen receptor in 47.5% of serous carcinomas, but with lower value compared with benign and borderline disease and suggested that AR signaling capacity may be reduced with the development but not metastatic progression of serous ovarian cancer^{21,22}.

CD44 is a glycoprotein receptor activated by hyaluronic acid, with role in cell to cell adhesion and recently described as a stem cell marker, reported positive in the majority of epithelial ovarian cancer and correlated with advance stage disease and unfavorable 5-year prognosis^{23,24}. CD44 expressed focal positivity in all cases of LG carcinoma (100%) and had different patterns in HG carcinoma (Figure 5).

Prognosis of low-grade serous ovarian carcinoma shows favorable overall survival, compared to general ovarian cancer population, but is suspicious of resistance to conventional treatments²⁵. Some studies suggest that mitogen-activated protein kinase (MAPK) inhibitor and MAPK mutations might eventually be useful in guiding treatment²⁶.

While most high-grade ovarian serous carcinomas are highly sensitive and can benefit of cytoreductive surgery and platinum and taxane-based chemotherapy, the majority of patients experience recurrence of treatment-resistant tumors²⁷. Bohm S et al developed a chemotherapy response score system and applied it to an independent validation cohort of HG patients²⁸. That is why further characterization of immunomodulatory factors are required in developing immune checkpoint therapies. The tumor

microenvironment of HG tumors was stated to have other important elements that may influence treatment response, including fibroblasts, endothelial cells and the extracellular matrix²⁹.

Although a dual pathway of ovarian serous carcinogenesis has been proposed, cases of coexistence of low-grade and high-grade carcinoma in the same patient have been reported, and even accompanied by undifferentiated carcinoma, regarded as a possible form of dedifferentiation³⁰. That is why ovarian serous carcinoma is a very complex spectrum of disease and it should be rendered with care by medical staff.

CONCLUSIONS

We found considerable differences between patients' mean age, macroscopic and microscopic features, together with immunohistochemistry expression for Ki67, AR and CD 44 markers of the two groups represented by high-grade and low-grade carcinoma, respectively. The differential diagnosis is important because tumor's biological characteristics and behavior are different, and with the help of new perspective markers we can further study possible correlations and take into consideration novel therapeutic targets.

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All the authors contributed equally to the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Compliance with Ethics Requirements:

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study“

„The authors declare no conflict of interest regarding this article“

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