Original Paper

# Architectural Histopathological Changes in Ovarian Serous Carcinomas

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**ABSTRACT:** Ovarian serous carcinomas have a very large spectrum of growth patterns that contrast with the most primitive ovarian carcinomas, in which the morphology varies very much less. Serous carcinomas growth patterns include papillary and glandular aspects, but also cribriform, solid, microcystic and trabecular, some being common to the both high- and low-grade types of ovarian serous carcinomas, others being distinct. The study included 45 cases of ovarian serous carcinomas out of which five cases with low grade and 40 cases with high grade. High grade serous carcinomas were associated with mixed growth patterns, with large complex papillae, glands with irregular shape lined by stratified epithelia, often with areas of extended necrosis. In the case of low grade ovarian carcinomas we observed the association with more uniform growth patterns, micropapillary or glandular, the presence of optically empty slit-like spaces, psammoma bodies, the absence of necrosis and the association with a borderline or benign component. The recognition of the common histopathological aspects, allows a more accurate diagnosis of the ovarian serous carcinoma types and subtypes, which has a great importance in the actual era of personalized therapy.

***KEYWORDS:*** *Ovarian serous carcinoma, growth patterns*

## Introduction

Ovarian serous neoplasms are the most common group of surface epithelial ovarian tumors, representing around half of those.

Serous carcinomas represent 35% of all serous ovarian neoplasms and approximately 75% of the epithelial carcinomas with this localization [1].

Over 90% of the tumors are diagnosed in advanced stage of the disease (stage III or IV) [2,3], extending beyond the pelvis at the moment of diagnosis [4].

In time, ovarian serous carcinomas have been classified and reclassified using various systems, often descriptive. Recently, a more simple and reproducible system was proposed, based on biological arguments, according to which the tumors are subdivided in low grade serous carcinomas-type I and high-grade serous carcinomas-type II [5]. This approach indicates that these two types of serous carcinomas develop in different ways.

Serous carcinomas have a wide growth patterns spectra, especially the high grade ones, different from the most of the ovarian primitive epithelial carcinomas in which the morphology varies slightly. Therefore, the growth pattern of serous carcinomas include the papillary aspect, but also the glandular, cribriform, solid, microcystic and trabecular aspects [5-9].

Similarly, the tumors can associate in a variable proportion a series of changes which differentiate them from other ovarian carcinomas, as the presence of psammoma bodies and optically empty slit-like spaces that surround the papillary or glandular structures [5,8,9].

The study aim was the identification of the incidence of the various architectural changes for the two types of high and low grade of serous ovarian carcinomas.

## Material and methods

This study has been realized retrospectively on a number of 45 cases of ovarian serous carcinomas, diagnosed in a three years' time interval (2014-2016).

The biological material was represented by surgical specimens from patients hospitalized in the Gynecology and Surgery Clinics from the Emergency County Clinical Hospital Craiova and have been processed within the Pathology Department of the same hospital.

The surgically excised pieces have been fixated in 10% neutral buffered formalin, processed by the usual paraffin embedding technique and Hematoxylin and Eosin (HE) staining.

The lesions classification was done according to World Health Organization (WHO) recommendations [5].



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We follow the incidence of various architectural changes associated to ovarian serous carcinomas, like the growth pattern and tumoral stroma, the presence of necrosis areas, psammoma bodies, optically empty slit-like spaces and the association with borderline or benign tumor zones.

Image acquisition was realized with the Nikon Eclipse E600 microscope equipped with an image camera and Lucia 5 soft.

The statistical analysis used comparative tests ($\chi$2-chi square test) in the SPSS10 (Statistical Package for the Social Sciences) software.

The study was approved by the local ethical committee (no. 38/27.03.2018), and written informed consent was obtained from all the patients.

## Results

The study included a number of 45 ovarian serous carcinomas, out of which five (11.1%) corresponded to the low grade and 40 (88.9%) cases to the high grade. For each tumoral category we identified the architectural aspects of the neoplasia: growth pattern, presence of optically empty slit-like spaces, psammoma bodies, necrosis, tumoral stroma aspect and the association with borderline or benign areas (Table 1).

For low grade carcinomas, we observed they tend to have an uniform architecture, often characterized by a single growth pattern or rarely two such patterns. We identified the micropapillary, glandular and microcystic growth patterns.

The micropapillary growth pattern was observed in four cases (80%), being the most frequent architectural aspect of the tumors. We observed reduced in size micropapillae with the absence or very finely and delicate fibrovascular axis, englobed in stroma and surrounded by a very clear optical space (Fig.1A).

The surface of the micropapillae was smooth or irregular due to the hobnail cells.

The glandular growth pattern was observed in one case and was characterized by simple glandular structures with medium size comprised in fibrous stroma in association with a micropapillary component (Fig.1B).

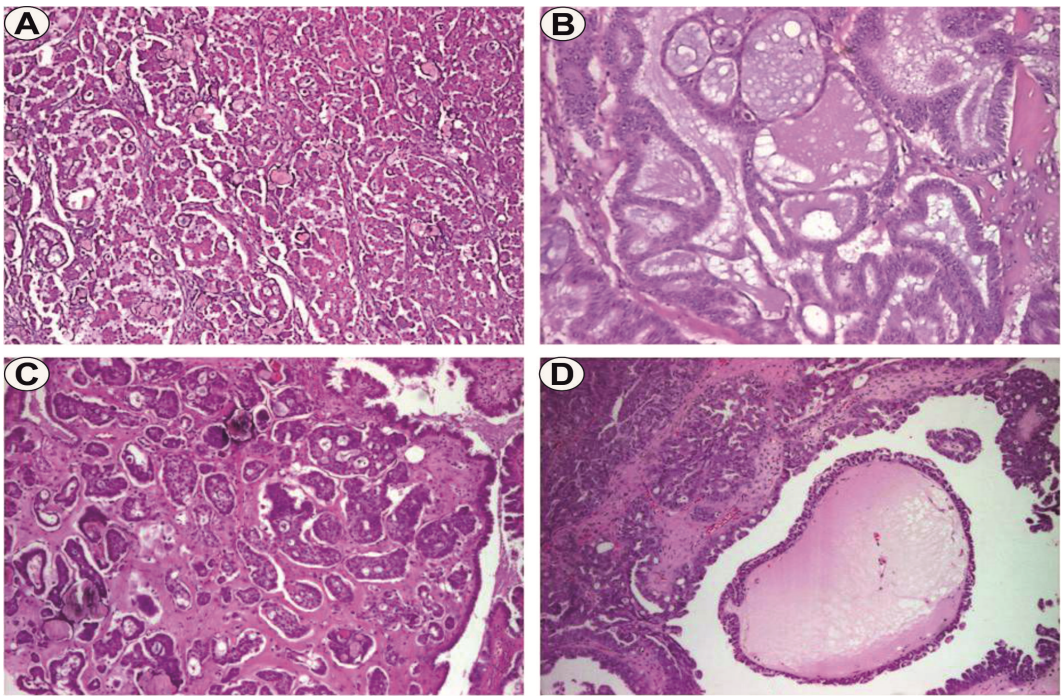


***Fig.1. Low grade serous carcinoma, HE staining. A. Micropapillary pattern and psammoma bodies, x100; B. Glandular pattern, x40; C. Cribriform pattern associated with benign and borderline zone, x100; D. Micropapillary and glandular patterns associated with borderline serous tumor area, x40***

In one case the glandular and micropapillary patterns were associated (Fig.1C). Also, in one case we observed the micropapillary component associated to the microcystic pattern (Fig.1D).

The tumoral stroma was fibrous, represented variably, the psammoma bodies being constantly observed and sometimes numerous, but without tumoral necrosis areas.

The association with a benign or borderline component has been identified in three cases of low-grade carcinomas (60%).

***Table 1. Case distribution according to the architectural characteristics of the ovarian serous carcinoma***

| Architectural Characteristics | | Low grade serous carcinoma | | High grade serous carcinoma | |
|---|---|---|---|---|---|
| | | No. cases | % | No. cases | % |
| Growth pattern | micropapillary | 4 | 80 | 3 | 7,5 |
| | macropapillary | 0 | 0 | 26 | 65 |
| | glandular | 1 | 20 | 15 | 37,5 |
| | insular | 0 | 0 | 3 | 7,5 |
| | microcystic | 1 | 20 | 2 | 5 |
| | diffuse | 0 | 0 | 29 | 72,5 |
| Optically empty slit-like spaces | - | 5 | 100 | | |
| Psammoma bodies | - | 5 | 100 | 10 | 25 |
| Necrosis | - | 0 | 0 | 40 | 100 |
| Stroma | fibrous | 5 | 100 | 38 | 95 |
| | myxoid | 0 | 0 | 4 | 10 |
| | edematous | 0 | 0 | 5 | 12,5 |
| | hyaline | 0 | 0 | 2 | 5 |
| Noninvazive component association | - | 3 | 60 | 2 | 5 |

For the high grade carcinomas we observed the fact that the tumors tend to have a heterogeneous architecture as a result of the mixture of two, three or even four different architectural patterns. Depending on the growth pattern we observed papillary aspects, frequently macropapillary, glandular, insular and diffused/solid, with the predominance of one or another component. The most frequent associations were represented by the macropapillary and diffuse growth pattern, glandular and diffuse growth patterns or macropapillary, glandular and diffuse growth patterns.

The papillary growth pattern presented often macropapillary aspects being characterized by the presence of large and complex papillae (Fig.2A), covered by frequently stratified epithelia, with irregular aspect and sometimes with the presence of optically empty slit-like spaces. The macropapillary aspect has been observed in 26 cases (65%). The macropapillay pattern was observed much less often, respectively in three cases (7,5%), in which we also observed the micropapillary growth model, but associated with the presence of high-grade nuclei.

The glandular growth pattern has been observed in 15 cases (37.5%). The glandular structures of high-grade serous carcinomas had an irregular shape, with a simple or complex aspect, sometimes associated with the presence of irregular spaces under the form of slit-like spaces (Fig.2B).

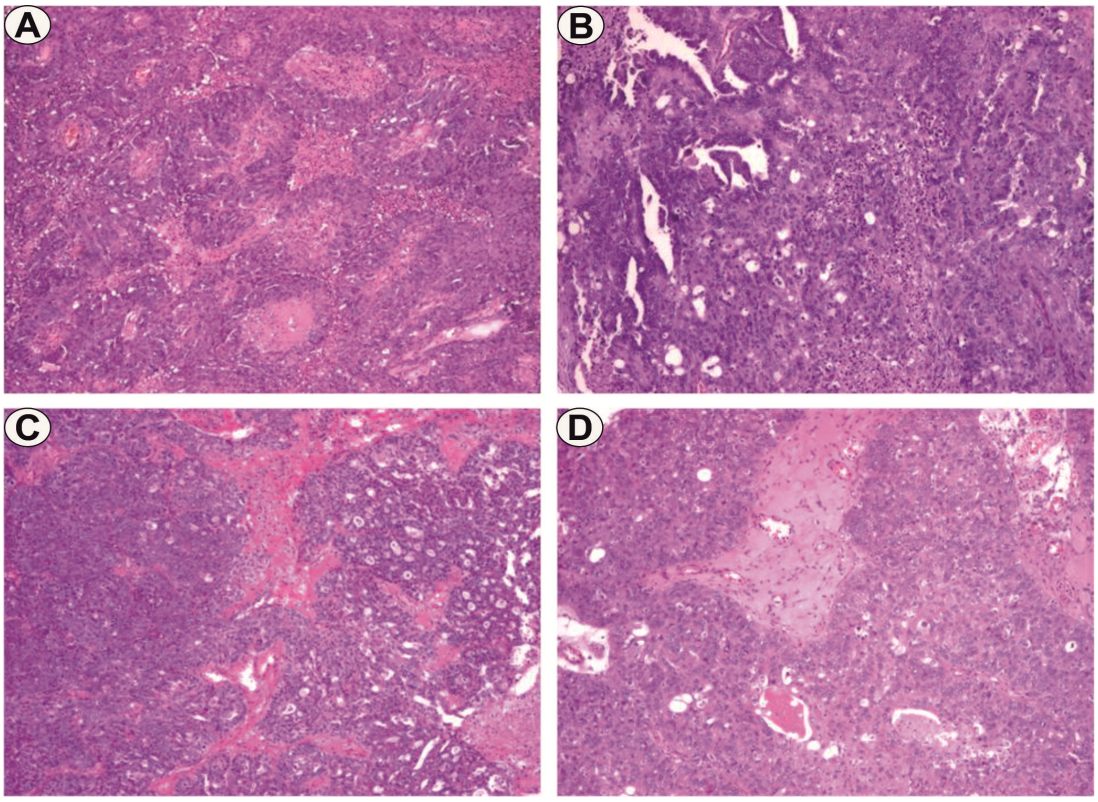


***Fig.2. High grade serous carcinoma, HE staining, x40. A. Macropapillary pattern; B. Cribriform and diffuse pattern; C. Glandular and diffuse pattern; D. Macropapillar and diffuse pattern, hyalinized stroma***


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Rarely, respectively in two cases (5%), we observed the microcystic growth pattern due to the presence of some small cystic structures disposed back-to-back, associated with the macropapillary pattern, or glandular with irregular lumens, as well as with the presence of psammoma bodies (Fig.2C).

The diffuse pattern has been identified in almost three-quarters of the cases (29 cases), and some tumors had a solid architecture so widely extended that an attentive search has been necessary for the identification of a glandular or papillary component in order to differentiate the high-grade serous carcinoma from the undifferentiated ovarian carcinoma (Fig.2D).

Tumoral stroma was fibrous, rarely associated with an edematous, myxoid, hyaline or desmoplastic type component. The necrosis has been constantly present in the high-grade serous carcinomas (100%), with a focal or extensive patterns. The psammoma bodies have been identified (25%), but less frequently than in the low-grade serous carcinomas.

The association with a benign or borderline component has been rarely identified, respectively in two high grade serous carcinomas (5%).

The statistical analysis indicated significant differences of the tumoral grade distribution in relation with the growth pattern (p=0.000, $\chi 2$ test), tumoral necrosis (p=0.000, $\chi 2$ test), the presence of psammoma bodies (p=0.002, $\chi 2$ test) and the presence of borderline/benign tumoral areas (p=0.007, $\chi 2$ test) (Fig.3A-D).

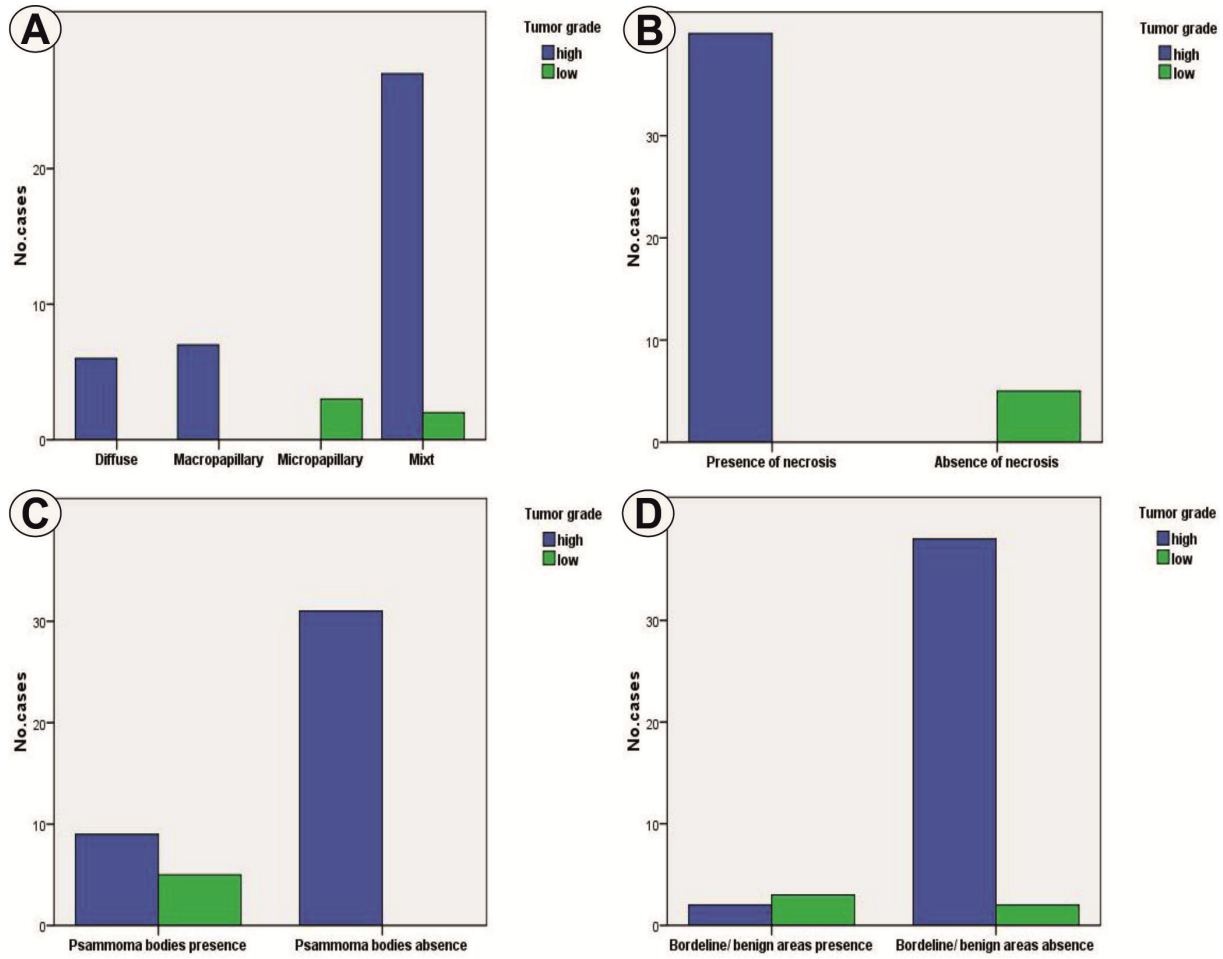


***Fig.3. Tumor grade distribution according with tumor growth pattern (A) and the presence of tumor necrosis (B), psammoma bodies (C) and borderline/benign tumor areas (D)***

The diffuse, macropapillary or mixed growth patterns were associated with the high grade of ovarian serous carcinomas, while the micropapillary pattern was specific to the low-grade lesions.

Tumoral necrosis was associated the high-grade carcinomas, and the presence of psammoma bodies and borderline/benign tumor areas were associated mainly to the low grade lesions.

## Discussions

The low- and high-grade serous carcinomas have some common morphological characteristic, but distinct others. In this study we have proposed to analyze the architectural characteristics present in variable proportion in both types of serous carcinomas.

The serous carcinomas growth pattern is extremely varied and partly common for the low- and high-grade serous carcinomas. The papillary pattern is frequently identified in serous carcinomas, but the micropapillary aspect is frequent in low grade forms, while the macropapillary aspect is more characteristic to the high-grade tumors [8,9]. In the high grade serous carcinomas the dominant frequent pattern is papillary growth, this aspect being present in almost all cases with at least focal character [10]. The genetic, morphological and molecular ascertainment indicates the fact that the macropapillae disposed in a random infiltrative model are the manifestation of the low-grade serous carcinomas invasion [11]. In this study, the micropapillary pattern has been associated in 80% to the low-grade serous carcinomas and only in 7.5% to the high grade carcinomas in contrast with the macropapillary pattern which was observed in 65% of the high grade serous carcinomas and in none of the low grade carcinomas. The carcinomas diffuse, macropapillary and mixed patterns were associated with the high grade, while the micropapillary pattern was specific to the low-grade lesions ($p=0.000$, $\chi 2$ test).

The optically empty slit-like spaces constitute an argument in favor of the serous carcinoma diagnosis, observed for both grades of the tumors. The presence of slit-like spaces or clefts optically empty which surround the papillary or glandular structures were reported as well in high grade carcinomas and in the low-grade carcinomas [5,8,9]. This aspect was identified in the performed study with an incidence of 100% for the low-grade tumors and 27.5% for the high grade tumors.

Similar to the data obtained by us, studies in the literature report that tumoral necrosis is absent in the low-grade serous carcinomas [8], in contrast to high grade serous carcinomas in which necrosis is often extended [9]. We identified the presence of necrosis areas in all the high-grade serous carcinomas, with focal or diffuse character ($p=0.000$, $\chi 2$ test).

Approximatively 30% of the serous carcinomas contain psammoma bodies [12]. They can be observed in high grade serous carcinomas, but the structures are much less frequent comparatively with the low-grade carcinomas [8,9]. In our study we observed the presence of psammoma bodies in all the low-grade serous carcinomas and in 25% of high grade serous carcinomas ($p=0.002$, $\chi 2$ test). The prognostic importance of the psammoma bodies is still very controversial. Some authors have suggested that tumors with psammoma bodies had a better prognostic compared to those in which they were not present [13] while other authors consider that the presence of psommomatous bodies have no prognostic significance [14]. In one study, in multi-varied analysis, the authors have appreciated that the presence of the psammomatous bodies is an indication of the long-term survival in the type I serous carcinomas, confirming a better significant prognostic for the serous carcinomas with a high number of psammomatous bodies and a better long-term survival [15].

The tumoral stroma in serous carcinomas is in general reduced, the fibrous type predominating. For the low grade serous carcinoma the stroma was fibrous in all cases. In the case of high grade serous carcinomas the stroma was present in all cases, but in five cases it was associated with edematous type changes, in three cases were observed the hyalinization areas and in other two cases myxoid areas.

In some reports, the low grade serous carcinomas have been associated with borderline serous tumors in 60% of the cases [16], a similar aspect with our study ($p=0.007$, $\chi 2$ test). Moreover, the association of high grade carcinoma with a borderline component, while unusual, has been identified in two of the analyzed cases. Boyd and McCluggage reporting seven cases of low-grade carcinomas which coexisted with the high-grade ones and they recommend an in-deep examination of the tumors, because the high grade zones can be focal or mixed with zones with similar aspect to the borderline serous tumors [17].

When in a high-grade ovarian carcinoma there is an identification of glands with irregular contours with lumens of slit shape, big complex papillae, covered by stratified epithelia, optically empty slit-like spaces around the papillary or glandular structures, necrosis zones and psammoma bodies, then the high-grade serous carcinoma is favored. In the case of a low-grade ovarian carcinoma in which the micropapillary and glandular aspect is observed along optically empty slit-like spaces, psammoma bodies and in the absence of necrosis, the low grade serous carcinoma diagnostic is favored.

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## Conclusions

Recognizing the specific microscopic aspects of the serous ovarian carcinomas types and subtypes allows a more exact diagnosis.

The necessity to do a histological standardization is particularly important in the actual era of personalized therapy, in which many patients who participate in clinical studies often have as selection criteria a certain histologic type and subtype.

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