

## ROLE OF THE PATHOLOGIST IN DIAGNOSIS OF THE OVARIAN CANCER

BOŽENA ŠARČEVIĆ

Department of Clinical Pathology, University Hospital for Tumors,  
University Hospital Center Sestre milosrdnice, Zagreb, Croatia

### Summary

Ovarian cancer is the eighth most commonly diagnosed cancer among women in the world, accounting for nearly 4% of all female cancers, also represent the third leading gynecologic cancer, and mortality is high because women typically present with late stage disease. Cases of suspected and confirmed advanced stage ovarian cancer should be discussed by multidisciplinary team within which the pathologist is a key member.

KEY WORDS: *ovarian cancer, histopathological diagnosis, prognostic factors*

### ULOGA PATOLOGA U DIJAGNOSTICI KARCINOMA JAJNIKA

#### Sažetak

Karcinoma jajnika je na osmom mjestu po učestalosti u žena u svijetu, čini gotovo 4% svih karcinoma u žena, također je na trećem mjestu unutar ginekoloških karcinoma a smrtnost je velika jer žene tipično dolaze u kasnom stadiju bolesti. Slučajevi sa suspektnim ili dokazanim uznapredovalim stadijem karcinoma jajnika moraju se raspraviti na multidisciplinarnom timu gdje je patolog ključan član tima.

KLJUČNE RIJEČI: *karcinom jajnika, patohistološka dijagnostika, prognostički čimbenici*

### INTRODUCTION

Ovarian cancer (OC) is the eighth most commonly diagnosed cancer among women in the world, accounting for nearly 4% of all female cancers (1). OC also represent the third leading gynecologic cancer, and mortality is high because women typically present with late stage disease when the overall 5-year relative survival rate is 44% (2). Despite the high incidence and mortality rates, the etiology of this lethal disease is not completely understood. Research to identify the causes of OC sorely needed; such knowledge could inform strategies for risk assessment, prevention, surveillance, early detection and treatment. Ovarian cancer patients interact with many doctors during the course of their treatment, but rarely do they meet the specialist who plays a critical role in

the outcome: the pathologist who diagnoses their cancer by analyzing samples of tissue. Precise diagnosis is what drives patient decisions and therapy. If pathology is wrong, everything that follows will likely be incorrect as well. Cases of suspected and confirmed advanced stage ovarian cancer should be discussed by multidisciplinary team and pathologist is one the key person within the team. Never before in history have pathologist been so critically important.

### CORE HISTOLOGICAL DATA

#### 1. Tumor type

The tumor should be designated according to the World Health Organization (WHO) classification (3). Epithelial ovarian tumors are heteroge-

neous neoplasms which are primarily classified according to cell type into serous, mucinous, endometrioid, clear-cell, transitional and squamous cell tumors. More importantly, these tumors are further subdivided into benign, borderline (intermediate), and malignant (carcinoma) depending on the degree of cell proliferation and nuclear atypia, and the presence or absence of stromal invasion (4).

Borderline tumors show epithelial proliferation greater than that seen in their benign counterparts and variable nuclear atypia; however, in contrast to carcinomas, there is absence of stromal invasion, and their prognosis is much better than that of carcinomas. Despite the lack of stromal invasion, serous borderline tumors, particularly those with exophytic growth, can implant on peritoneal surfaces and, rarely progress to low-grade serous carcinoma (LGSC), and invade the underlying tissue. Mucinous borderline tumors should be subclassified as intestinal (more common) or endocervical (Mullerian) type.

Currently, based on histopathology, immunohistochemistry, and molecular genetic analysis, at least five main types of ovarian carcinomas are identified: high-grade serous carcinomas (HGSC), endometrioid carcinoma (EC), clear cell carcinomas (CCC), mucinous carcinomas (MC) and low-grade serous carcinomas (LGSC) (5).

## 2. Tumor grade

According to recent study serous carcinoma is low (LGSC) or high grade (HGSC). They are fundamentally different tumor types, and consequently different diseases. LGSCs are associated in most cases with a serous borderline component, carry KRAS and BRAF mutations, and are unrelated to p53 mutations and BRCA abnormalities. In contrast, HGSCs are not associated with serous borderline tumors and typically exhibit p53 mutations and BRCA abnormalities (6).

Mucinous carcinoma are graded in a similar manner to endometrioid carcinoma, as is done in the uterus. Recently, mucinous carcinomas have been divided into two categories: an expansile type without obvious stromal invasion, but exhibiting back-to-back or malignant glands with minimal or no intervening stroma, and exceeding 10 mm<sup>2</sup> in area and an infiltrative type showing evident stromal invasion. The expansile pattern of

growth is associated with a more favorable prognosis than the infiltrative pattern (7).

Endometrioid carcinomas are graded as I, II or III using the FIGO grading system which is used for the grading of uterine endometrioid adenocarcinomas (8).

Ovarian clear cell carcinomas and transitional cell carcinomas are regarded as automatically high grade or grade III.

## 3. Microinvasion

Microinvasion may occur within an otherwise typical borderline tumor, usually of serous or mucinous type. Microinvasion has been found to have no adverse effect on prognosis and may be multifocal. If the foci of microinvasion are clearly separate, these can be regarded as multiple distinct foci of microinvasion and the size of separate foci need not be added together (9).

## 4. Lymph nodes

The total number of lymph nodes examined from each anatomical site and the number involved by tumor should be recorded.

## 5. Peritoneal biopsies

The presence or absence of tumor involvement in biopsies from each anatomical site should be recorded. Peritoneal involvement in association with an ovarian borderline tumor, especially of serous type, may take form of invasive or non-invasive implants which may coexist. The lesions were confined to the surface of organs are non-invasive implants or infiltrated the underlying tissue are invasive. This is a difficult area and may require specialist internal or external review.

## 6. Omentum

The size of the largest omental metastatic deposit should be documented. Omental involvement in association with a borderline tumor, especially of serous type, may take the form of invasive or non-invasive implants. Since invasive and non-invasive implants may, on occasions, coexist and since invasive implants are associated with an adverse prognosis are an indicator for adjuvant chemotherapy, extensive omental sampling should be undertaken when non-invasive implants are identified in the original sections.

## 7. Fallopian tubes

The presence or absence of tubal involvement should be documented as well as site of tubal involvement, for example mucosal or serosal. Tubal involvement in ovarian carcinoma is not uncommon and the fimbria is the most common site. It has, in fact been suggested that the tubal fimbria is the site of origin of many pelvic serous carcinoma. It is now accepted that a number of what have been thought to be primary ovarian cancer are originated in other pelvic organs and involve the ovary secondarily (10).

## 8. Staging

Tumors should be staged according to the FIGO staging systems (11). Although it is useful to record the provisional stage on the histopathology report, the final stage should be determined at the multidisciplinary team meeting (MDTM) where the results of all clinical, radiological and pathological parameters can be correlated.

Some others parameters as the weight of the ovaries, the presence or absence of lymphovascular invasion, the results of any immunohistochemical studies may be included as part of a complete report but their are of uncertain prognostic relevance.

The pathologist also needs key clinical information, and the specimen request form should include full patient details and the results of any previous biopsy or cytology specimens.

Most ovarian carcinomas are removed without a preoperative histological diagnosis, the diagnosis being made on the basis of a combination of clinical, serological and radiological features in an MDTM setting. Sometimes radiologically guided **core biopsies** are performed to confirm the diagnosis preoperatively or prior to chemotherapy or in patients who are too ill to undergo a laparotomy. The number of core biopsies should be stated and the length of each core documented. Tissue may need to be preserved so that a range of immunohistochemical markers can be performed. Materials received with core biopsies are small biopsy specimens and pathologists need to be highly qualified and experienced in gynecological pathology.

### Intraoperative pathological consultation

The frozen section is of value in cases where clinical management decisions may be altered depending on the histological type and grade of tu-

mor, e.g. young women for whom continuing fertility is crucial.

Situations where frozen section examination might be performed include:

- intraoperative assessment of a neoplasm confined to the ovary to assess whether this is benign, borderline or malignant; this may direct whether lymphadenectomy or other staging procedures are undertaken
- for confirmation of an epithelial neoplasm, for subtyping of an epithelial malignancy and, in cases of obvious malignancy to distinguish between a primary ovarian and a metastatic neoplasm.

Clinicians should be aware that a single sample may be not provide adequate material for the histopathologist whereas, further sampling for paraffin sections may result in upgrading of a frozen section diagnosis of benign to borderline tumor or of high grade borderline tumor to invasive carcinoma. If any doubt is expressed by the pathologist in frozen section, the more conservative diagnosis must be the 'working' diagnosis for immediate patient management (12).

The removed ovary with tumor mass should be ink because it is useful in easy identification of capsular blocks and capsular integrity. Prior slicing of the neoplasm may be undertaken to allow adequate fixation. For suspected borderline tumors the accepted standard is one block to tumor per centimetre of maximum diameter of the 'solid' ovarian mass. This is to detect small areas of high-grade invasive carcinomas, which might otherwise be missed, and is particularly important in mucinous tumors. Mucinous neoplasms may be extremely heterogeneous with close proximity of benign, borderline and malignant areas and more generous sampling may need to be undertaken, especially from grossly solid or suspicious areas, depending on the histological findings in the original sections (13). For cystic lesions with papillary processes on the internal or external surface, the papillary areas should be extensively blocked. If one of the ovaries is grossly normal, one or two blocks will suffice. In patient with BRCA 1 or 2 mutations the entire 'normal' ovary should be submitted for histological examination.

### Immunohistochemistry

With many applications in the field of ovarian neoplasia, the use of immunohistochemistry

has significantly increased in recent years (14). The results of any immunohistochemical stains should always be carefully interpreted in conjunction with the clinical, gross and microscopic features. However, areas where immunohistochemistry may contribute significantly include the following:

- distinction between a primary ovarian adenocarcinoma and metastatic adenocarcinoma from various sites ( potentially useful markers include cytokeratin 7 and 20, CA 125, CEA, CA 19.9, WT 1, TTF-1, oestrogen receptor and CDX 2)
- typing of an ovarian adenocarcinoma, most ovarian serous carcinoma exhibit nuclear positivity with WT 1, while most of the other morphological subtypes are negative
- the distinction between an epithelial and a sex cord-stromal tumor ( potential useful markers include inhibin, calretinin positive in sex cord-stromal tumors and epithelial membrane antigen- EMA and cytokeratin 7 positive in epithelial neoplasms)

#### Molecular genetics

Many advances of molecular genetics of ovarian cancer have been made, but these are not yet affecting clinical practice except BRCA 1 and BRCA 2 genes. Ovarian cancer mostly arises sporadically, but a fraction of cases are associated with mutation in BRCA 1 and BRCA 2 genes. The presence of BRCA mutations in ovarian cancer patients, especially in patients with HGSC has been suggested as a prognostic and predictive factor. Tumor pathological data are very important for the molecular analysis and should be included in the results of molecular testing (15).

#### CONCLUSION

Numerous studies in recent years have changed the classification of epithelial ovarian tumors especially due to the results of changes at the molecular level. Determination of prognostic and predictive factors, and interpretation of results of molecular testing requires highly experienced pathologist in the field of gynecological pathology. In addition, the pathologist has become a key person in a multidisciplinary team and the person very responsible for the implementation of specific individual therapy.

#### REFERENCES

1. Ferlay J, Shin H, Bray F, Forman D et al. GLOBOCAN 2008; [http:// globocan.iarc.fr](http://globocan.iarc.fr) Accessed on 12/18/11. 2008.
2. Howlader NNA, Krapcho M, Neyman N, Aminou R et al. SEER cancer statistics review, SEER website, 2011.
3. Kurman RJ, Carcangiu ML, Herrington CS, Young RH. World Health Organization classification of Tumors of Female Reproductive Organs. Lyon: IARC Press; 2014. str. 15-40.
4. Prat J. Pathology of the Ovary. Philadelphia: Saunders; 2004.
5. Prat J. New insight into ovarian cancer pathology. *Ann Oncol.* 2012;23(Suppl 10):111-17.
6. Malpica A, Deavers MT, Lu K et al. Grading ovarian serous carcinoma using a two-tier system. *Am J Surg Pathol.* 2004; 28: 496-504.
7. Provenza C, Young RH, Prat J. Anaplastic carcinoma in mucinous ovarian tumors: a clinicopathologic study of 34 cases emphasizing the crucial impact of stage on prognosis, their histologic spectrum, and overlap with sarcomalike mural nodules. *Am J Surg Pathol.* 2008; 32:383-9.
8. Tothill RW, Tinker AV, George J et al. Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. *Clin Cancer Res.* 2008; 14: 5198-208.
9. Khunamornpong S, Russell P, Dalrymple JC. Proliferating (LMP) mucinous tumours of the ovaries with microinvasion: morphologic assessment of 13 cases. *Int J Gynecol Pathol.* 1999;18:238-46.
10. Jarboe E, Folkins A, Nucci MR et al. Serous carcinogenesis in the fallopian tube a descriptive classification. *Int J Gynecol Pathol.* 2008;109:168-73.
11. Prat J. FIGO Committee on Gynecologic Oncology. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. *Int J Gynecol Obstet.* 2014;124 (1):1-5.
12. Lechago J. The frozen section. *Pathology in the trenches.* *Arch Pathol Lab Med.* 2005;129(12):1529-318.
13. Ronnett BM, Kajdacsy-Balla A, Gilks CB et al. Mucinous borderline ovarian tumors: points of general agreement and persistent controversies regarding nomenclature, diagnostic criteria, and behaviour. *Hum Pathol.* 2004;35:949-60.
14. Kriplani D, Mandakini MP. Immunohistochemistry: A diagnostic aid in differentiating primary epithelial ovarian tumors and tumors metastatic to the ovary. *South Asian J Cancer.* 2013;2(4):254-8.
15. Kohn EC, Romano S, Lee JM. Clinical implication of using molecular diagnostics of ovarian cancer. *Ann Oncol.* 2013 Dec;24(Suppl 10):22-6.

*Authors address: Božena Šarčević, Department of Clinical Pathology, University Hospital Center Sestre milosrdnice, Ilica 197, 10000 Zagreb, Croatia. e-mail: bozena.sarcevic@kbcs.m.hr*