Summary. Review of the literature is devoted to the possibilities of using cytological methods in the diagnosis of ovarian tumors. It is shown that cytological methods are informative and necessary at all stages of the examination of patients with this pathology. The principles of differential diagnosis of certain histological types of tumors are discussed. We discuss the use of additional criteria to determine the malignancy of tumors, the optimal design of the complex research to improve diagnosis and on this basis, more effective treatment of patients.

In Ukraine, as in other countries of the world, the rates of morbidity of malignant ovarian tumors are consistently high with tendency to increase [6, 45, 88]. According to the data of National cancer-register, in 2010 the level of morbidity constituted 15.1 per 100 thousands of female population. Ovarian cancer takes 3-rd place in structure of oncological morbidity of female reproductive system organs and 1-st – in structure of mortality [41]. Clinical symptoms of the disease are nonspecific and often manifest themselves only in later stages. It causes the complications in diagnosis, impossibility of radical treatment and low survival rates [37, 88].

The modern diagnosis of tumors and tumor-like ovarian neoplasms needs application of complex of diagnostic procedures for detection of neoplasms and determination of certain nosologic form. Morphological investigation is obligatory and key procedure in determination of diagnosis and choice of treatment of patients with ovarian tumors [7, 17, 20].

It should be mentioned that morphological diagnosis of ovarian tumors remains one of the hardest parts of oncogynecology. The complexity is conditioned with series of reasons, among which the many-component construction of ovary and combination of the various functional structures in it. The diversity of histological forms is connected with big amount of possible sources of rise of tumors [7, 20, 36, 38]. To them are referred normal components of ovary – the covering epithelium, tubal epithelial, ovary cell, granulose cells of theca-tissue, chyle cells and other components. Tumors also develop from embryonic rudiments: medullary cords, ovarian networks, epoophoron, paroophoron, mesonephric duct and additional tubules. Moreover, source of tumors can be postnatal parts of epithelium, exposed to the heterotopia, metaplasia and paraplasia, – excrescences of covering ovarian epithelium (mesothelium) out of multi-layer strata and cysts, islets, tubes and microcysts with ciliary epithelium, ovarianendometriosis (endometrioid heterotopia).

Histological WHO classification of ovarian tumors includes more than 150 subtypes of neoplasms [20, 83]. Among them are separated surface epithelial-stromal tumors, which form the biggest group; tumors of gonadal cord and ovarian stroma: germinomatous tumors; gonadoblastoma; mixed tumors from germinomatous cells and derivatives of gonadal cords or ovarian stroma of non-gonadoblastoma type; tumors of ovarian network; mesothelial tumors; tumors of unclear genesis and mixed tumors; gestational trophoblastic disease; soft tissue tumors, which are not typical for ovary; malignant lymphomas an leukosis; unclassified tumors; secondary (metastatic) tumors and tumor-like lesions.

Along with recognized histological method of diagnosis of ovarian tumors, the application of cytological methods of investigation, which are aimed to determine the features of neoplasm (benign or malignant), histological type and degree of diffusion of tumor process, becomes wider [3, 4]. Cytological method of diagnosis is widely used in the stage of examination of patients in conditions of polyclinic and hospital as well as during the surgical intervention. The objects of cytological investigation are ascetic and pleural liquid, materials of puncture of ovaries, Douglas cul-de-sac, lymph nodes, lavages of peritoneal cavity and rectal space, imprints of tumor [11].
The results of cytological investigation are often the only morphological substantiation of diagnosis before the beginning of the treatment [63, 66, 68]. Along with it, in available works there are contradictory views on the possibility of applying and value of cytological study in diagnosis of ovarian tumors. There are lots of researches devoted to the study of ovarian tumors at the histological level [20, 22, 25, 26, 29, 38, 80]. At the same time, issues of cytological specifying and differential diagnostics are not studied enough. Cytomorphological image of ovarian tumors are represented in single works, mostly of foreign authors, and concerns the particular histological types: granulose-cellular [21], dysgerminomas [5], subtypes of epithelial tumors [27, 34, 44, 52, 60, 63]. Till present time the international cytological classification of ovarian tumors has not been developed.

V.A.Ali-Zade, during the studying of cytomorphological signs of epithelial ovarian tumors, tried to create working cytological classification, which includes 6 types of epithelial tumors: serous, mucinous, endometrioid, renal cell, Brennertumor, undifferentiated carcinoma. Author aimed to specify differential-diagnostic criteria for recognition of different tumors at the cytological level [1]. He has determined the high effectiveness of cytological method in study of epithelial ovarian tumor. According to the author’s data, the coincidence of cytological and histological conclusions at study of material, obtained by different methods, achieves in determination of character and histological form of tumor 95.5 and 77.5% correspondently [1, 2].

The modern cytological diagnostics of ovarian tumors conventionally may be divided into pre-operational, which includes thin-needle aspirational biopsy of tumor, posterior fornix, study of ascetic and pleural liquid, and intraoperational – study of imprints and scrapes from removed tumor, peritoneal lavage.

Topographical-anatomic location of ovaries allows easy obtaining of material for cytological study under the control of ultrasound investigation, but the question of expediency of application of fine-needle aspiration puncture (APFN) till present time remains discussible. One group of researchers [67] states that at biopsy may take place the intraperitoneal implantation of tumor cells. Others are convinced that risk of such complications is not so high and is not documented [57].

Biopsy diagnostics of ovarian neoplasms is highly informative method. Many researchers have showed high diagnostic accuracy of APFN of ovarian tumors. In such way the sensitivity of APFN, according to the data of series of authors, achieves 100%, specificity and diagnostic efficacy constitute approximately 90% [51, 57–59, 61]. Mostly quite informative cytological material can be obtained with the help of punctate through the vaginal fornix [10–12, 42].

G. Mahdi and co-authors [47, 67] emphasize that use of APFN of ovarian tumors may be useful in young patients, who want to save reproductive function. In children and teenagers are mostly found tumor-like neoplasms (40-50%), which often imitate ovarian tumors, therefore it is quite complicated to identify them before surgery [17, 38]. Cytological diagnosis of obtained with the help of APFN material helps to avoid operative intervention in patients of given age group. APFN plays key role in estimation of material obtained from patients with suspicion of relapse of malignant ovarian tumor as well as in estimation of degree of diffusion of process. There are complications marked of cytological study through the APFN materials at differential diagnostics of tumors with low potential of malignancy (borderline) and highly-differentiated carcinomas [70]. One of the disadvantages of APFN of ovarian tumors are false-negative results, which are conditioned by not informative material (low cellularity of aspirate), in particular, at benign lesions [42, 57].

Malignant epithelial ovarian tumors are one of the most frequent factors, which cause the accumulation of exudative liquid in peritoneal, pleural and pericardial cavity. Carcinomatosal pleural exudates, connected with ovarian cancer, constitute approximately 10%. At the same time, among the causes of development of ascites in women, ovarian cancer takes the first place. Often patients first time appeal to the doctor with complaints on sharp enlargement of abdomen and decrease of diuresis.

Choice of treatment tactics needs the morphological verification of diagnosis [8, 15, 16, 24, 37]. Cytological study of content of peritoneal cavity allows to determine the presence of tumor cells in exudate and often to determine histological type of neoplasm.

It is important to emphasize that cytological evaluation of presence of tumor cells in ascitic and pleural liquid, lavage of peritoneal cavity is quite complicated. In the first stage of diagnostic process, cytologist needs to determine the presence of...
tumor cells in liquid and distinguish them from cells of reactive mesothelium. The complicity of differential diagnosis is conditioned, first of all, by origin of majority of epithelial ovarian tumors from cells of metaplasedmesothelium and, correspondently, their morphological similarity, as well as paradox changes of tumor ovariancells, such as increase of cell differentiation degree[40]. Such phenomenon does not correspond with general regularities of development of majority of tumors, which in process of neoplastic transformation become less differentiated than normal epithelium [28, 29].

In the classical cases in the presence of tumor exudate, which is conditioned by serous ovarian carcinoma, in specimens are detected ferro-like and papillary structures, often – cells with large vacuoles in cytoplasm. Sometimes single cells with signs of secretion – crown of thin mucus-like fibrils, which are reminding cilia, are noted. This feature is pathognomic for ovarian cancer. Presence of psammous bodies, which represent laminated calcareous masses, is regarded subsidiary diagnostic sign [14, 15, 24, 65].

If such cytomorphological criteria are absent, it is quite problematic to presume primary tumor focus in ovary by the cellular composition of exudate. The listed complications can be overcome with the help of additional methods of investigation. One of such methods is immuno cytochemical method (ICC). In diagnostic panel of ovarian tumors in serous liquids with the aim for differential diagnostics of tumor cells and reactive mesothelium are included monoclonal antibodies to antigen Ber-EP4 – calretinin. For specification of adenocarcinoma type, the determination of genes is conducted: CK 7, WT-1, CA-125, to estrogen receptors (ER), — typical for serous tumors; monoclonal antibodies to CA-19,9, cancer-embryonic antigen, cytokeratin 20, vimentin—for mucinous; to cytokeratins of type 7;8;20; ER and progesterone receptors (PR) – for endometrioid neoplasms. ICC-test plays important role in verification or elimination of tumor process, differential diagnostics of epithelial tumors, mesotheliomas and cells of reactive mesothelium as well as determination of organo-specific affiliation of tumor cells. ICC-test of exudates from serous cavities increases significance of cytological diagnostic, allows to increase number of observations with intraperitoneal dissemination and more precisely determine diffusion of tumor process[8, 9, 13, 16, 37, 49, 55, 62, 77, 89].

The important diagnostic task, which is required to solve during the study of exudates, is determination of degree of malignancy tumor cells. As known, diffusion of metastatic cells across the peritoneum already takes place in the stage of benign tumor. The presence of tumor implants at cyst-adenomas and borderline tumors have been observed in 8,4% and 52-81% of cases correspondently [36]. The use of proliferation markers – antigens Ki-67 and PCNAis effective in determination of features of tumor cells and stage of malignancy. M. Choudhury and co-authors [50] states that quantity of proliferative cells at malignant tumors of ovary is significantly higher (33,1 ± 16,7), than at benign tumors (3,2 ± 3,7). It is proved that content of Ki-67 positive cells is higher at the later stages of disease, in case of aggressive clinical course.

Morphometric parameters of cells (square of nucleus, nuclear-cytoplasmic correlation, “coefficient of form”) allow determine degree of histological differentiation of tumor that may be used as diagnostic and prognostic criteria, which give opportunity to prognosticate the presence of implantation and remote metastases with higher degree of probability [7, 22]. The independent prognostic value has determination of degree of ploidy of tumor cells at DNAinvestigation. The statistically significant differences in median lifespans of patients with tumors with diploid and aneuploidy set of chromosomes (47,6 and 13,9 months correspondently) has been determined [25–27, 30–32].

The analysis of nucleus organizing regions (AgNOR) of chromosomes is worth of special attention in complex study of ovarian neoplasms with the aim of determination of stage of tumordifferentiation [81, 86]. Detection of additional prognostically significant cytological, morphometric, biological features allows to improve diagnostics and differential approach to the treatment of patients. In accordance with recommendations of International Federation of Gynecology and Obstetrics, cytological study of ascitic liquid, free from peritoneal liquid and lavages of peritoneal cavity, is obligatory for performance of surgical staging of ovarian cancer. According to the staging criteria, the FIGO (FédérationInternationale de Gynécologieet d’Obstétrique) classification has been developed and implemented in practice [56]. At urgent intraoperational cytological study the imprints of ovarian tumor, parietal and visceral peritoneum, greater omentum, posterior and anterior vaginal fornix, place of tumor invasion in adjacent organs arestudied. The urgent intraoperational cytological study allows to
determine the features of pathological process and stage of diffusion, histological form of tumor and is key for determination of volume of operative intervention and prognosis of disease[3, 33–35, 48].

Majority of authors confirm high diagnostic accuracy, sensitivity and specificity of intraoperative cytological study at ovarian tumors [18, 19, 23, 33–35, 53, 54, 64]. It has been demonstrated that combination of cytological study of imprints, lavages from removed tumor with traditional macroscopic investigation and study of frozen sections improves results of intraoperative diagnostics. Series of researchers remarks that results of urgent intraoperative cytological study of ovarian tumors in some cases are more precise than results of study of frozen sections [72, 74, 76], and influence the tactics of operative intervention [33, 35]. The minimal diagnostic accuracy (66%) as well as at study of material, obtained with fine needle, has been remarked at borderline ovarian tumors [46, 54]. This fact is quite explainable, since the main morphological criterion of borderline tumors is the absence of invasive growth on the background of apparent proliferative changes of epithelium [39, 40, 70]. Cytological study of imprints and scrapes is important additional diagnostic method in conditions of intraoperative consultation, which allows to optimize tactics of treatment in every single case [33, 43, 44, 69, 82, 84, 87].

Summarizing stated above, it should be mentioned that cytological study is informative and relevant in all stages of examination of patients with ovarian tumors. The further study and improvement are required for issues of differential diagnostics of various types of tumors with detailed description of their cytomorphological signs, search of additional cytological criteria of malignancy. The attention shall also be concentrated on development of cytological classification of ovarian neoplasms, determination of optimal complex of additional tests for increase of efficacy of morphological diagnostics and therapy.

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