ORIGINAL PAPER

Correlation Between Early Diagnosis of Ovarian Neoplasm and Long-Term Prognosis

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Abstract

Ovarian cancer is the seventh most commonly diagnosed cancer in women, with the highest mortality rate among female genital cancers. Due to the nonspecific symptoms and the lack of effective screening strategies, ovarian cancer is often diagnosed in an advanced stage of the disease, with a 5-year survival rate of 25%. The efforts of specialists are aimed at identifying screening methods, with the lowest possible rates of false positive or false negative results in order to diagnose the disease at an early stage, when the 5-year survival rate is 92%. In this study we analyzed the incidence of ovarian cancer in the last five years in the Bucharest University Emergency Hospital, being registered 153 cases of ovarian cancer. The aim of this paper is to analyze the correlation between the early diagnosis of ovarian cancer and the long-term prognosis.

Keywords: ovarian cancer, survival rate, screening, early diagnosis.

Rezumat

Cancerul ovarian este al șaptelea cancer diagnosticat ca frecvență la femei, având cea mai mare rată de mortalitatea în rândul cancerelor feminine din sfera genitală. Din cauza simptomelor nespecifice și lipsa unor strategii eficiente de screening, de cele mai multe ori cancerul ovarian este diagnosticat într-un stadiu avansat de boală, cu o rată de supraviețuire la 5 ani de 25%. Eforturile specialiștilor sunt îndreptate către identificarea unor metode de screening, cu rate cât mai mici de rezultate fals pozitive sau fals negative pentru a diagnostica boala într-un stadiu incipient, când rata de supraviețuire la 5 ani este de 92%. În acest studiu am analizat incidența cancerului ovarian în ultimii cinci ani în Spitalul Universitar de Urgență București, în această perioadă fiind înregistrate 153 de cazuri de cancer ovarian. Scopul acestei lucrări este reprezentat de analiza corelației între diagnosticului precoce al neoplasmului ovarian și prognosticul pe termen lung.

Cuvinte cheie: cancer ovarian, rată de supraviețuire, screening, diagnostic precoce.

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INTRODUCTION

Ovarian cancer is the seventh most common cancer diagnosed in women around the world[1], occupying the fifth place among deathscaused by cancer in women, being the most lethal neoplasm of female genital organs[2]. In 2020, there were approximately 314.000 new cases of ovarian cancer and 207.000 deaths worldwide[2], with the highest incidences observed in Eastern and Central Europe (6-11.4:100,000 inhabitants/year). In the recent years, there has been only a minimal improvement in the survival rate, this being mainly due to the non-specific symptoms that occur when the cancer has reached already an advanced stage and the lack of effective screening strategies that could detect the abnormalities at an early stage of the disease. Only 15% of patients are diagnosed during the stage I of the disease, when the 5-year survival rate is 92%. In patients diagnosed at an advanced stage of the disease, when distant metastases apeared, the 5-year relative survival rate is 25%. The overall 5-yearrelative survival rate, across the globe, is 30-40%, since 1995 registering modest increases of 2-4%[1]. Genetic predisposition, for example mutations in the BRCA1/BRCA2 genes, Lynch syndrome, is known to be present in about 10% of patients with ovarian cancer. In one study, the risk of developing ovarian cancer among women with a BRCA1 mutation was 39%-65%, with a BRCA2 mutation it was 11-37%and for Lynch syndrome of 3-33%[3].

SCREENING

In recent years, no significant changes have occurred in the prognosis and survival rate of patientswith ovarian neoplasm, mostofthem being diagnosed at an advancedstage of thedisease. Thus, the identification of an ideal screening test would lead to an early detection of the ovarian cancer, reducing the associated mortality rate. No screening strategy has been shown to reduce mortality, being associated with a high rate of false positive tests leading to a series of invasive procedures with of surgical complications[4].

Transvaginalultrasound, CA-125 and bimanual pelvic examination have been used in various studies to assess their role as screening tests, but there is no clear evidence of their usefulness[5].

The UK CollaborativeStudy for Ovarian Cancer Screening (UKCTOCS) is a randomised clinical trial conducted on 202.638 women in postmenopausal women, which were not known at high risk of developing ovarian cancer, aged between 50 and 74 years. There has been formed a control group in which screening tests were not used, a group of women in which the examination was performed by transvaginal ulrasound and a group examined by determining the CA-125 values annually. After a median follow-up of 11.1 years, no significant differences in ovarian neoplasm mortality were revealed between the control group and the two intervention groups (0.35% in the control group, 0.32% in the transvaginal ultrasound group and 0.32% in the ROCA CA-125 group)[6,7].

In the PLCOstudy of the prostate, lung, colorectal and and ovarian cancer, with a median follow-up of 12.5 years, conducted in the USA, no significant difference was revealed in the mortality rate from ovarian neoplasm between the control group (0.29%) and the screening group (0.34%) (8.9). The American Cancer Society and the American College of Obstetricians and Gynecologists (ACOG) also do not recommend screening for ovarian cancer for women at medium risk. However, ACOG recommends that the evaluation of women at high-risk to include transvaginal ultrasoundand CA-125 testing in addition to the bimanual physical examination. Memorial SloanKetting (MSK) recommends that ovarian cancer screening in women with gene mutations (BRCA1/2, MMR: MLH1, MSH2, MSH6), by determining CA-125 values and transvaginal ultrasound to begin from the ages of 35-40 years. In women over 35 years of age with BRCA1/2 mutations, NCCN (the National Comprehensive Cancer Network) recommends risk-reducing bilateral salpingo-oophorectomy (rrBSO) [10]. Similarly, the USPSTF (the United States Preventive Services Task Force) does not recommend screening in asymptomatic women who are not at increased risk of developing ovarian neoplasm[9].

The CA-125 values can be increased in ovarian neoplasm, but those present a low sensitivity in the early stages of the disease, asserum marker levels can also be found in pregnancy, endometriosis, menses, pelvic inflammatory diseases[11]. Another biomarker overestimated in ovarian cancer is the human epididy malprotein 4 (HE4)[12]. The specificity of these biomarkers is maintainable, but with low sensitivity, this leading to the development of algorithms used in the diagnosis of pelvic tumor formations: ROMA score ((Risk of Ovarian MalignancyAlgorithm), RMI (Risk

of Malignancy Index),OVA1, OVERA test, DNAEX model[13].

Family history of ovarian, breast, colorectal, pancreatic, prostate cancer is essential in identifying patients at high-risk of developing ovarian neoplasm. From a patient's anemnesis are important aspects such as family history of cancer, Ashkenazi Jewish origin, the existence of gene BRCA1/2mutations, Lynch syndrome, these aspects placing the patient at high-risk of developing ovarian cancer, changing the conduct of screening and therapeutics[14]. These patients may benefit from specific risk reduction strategies, such as bilateral risk reduction salpingo-ooforectomy (rrBSO)[15]. In asymptomatic women at medium risk (with no genetic predisposition or family history of ovarian cancer), screening for ovarian cancer is not recommended[16].

STATISTIC REPORT

We analyzed the incidence of ovarian cancer during the last five years in the University Emergency Hospital of Bucharest, having the approval of the Unit's Ethics Committee.

We carried out a descriptive analysis of data, calculating indicators as mean, median, standard deviations, maximum and minimum values, percentages of variables and also presented results in graphical forms, by means of SPSS and Excel software.

The demographic characteristics were analyzed comparatively with other gynecologic cancers, respectively uterus, breast and uterine cervix.

From the histopathological point of view, the analyzed categories were: Brenner tumor (2.1), serous (2.2) and mucinous (2.3) ovarian carcinoma, granulosa cell tumor of the ovary (2.4), germinal ovarian tumor (2.5), Borderline ovarian tumor (2.6) and endometrioid carcinoma (2.7); each of them noted conventionally for statistical analysis.

In our unit, during the studied period, 153 cases of ovarian cancer were registered. The mean age in this studied group was 57 years, with a maximum of 87 and a minimum of 19.

Referring to the histopathological types, the incidence of each was as represented in Table 1. The most frequent encountered was serous ovarian carcinoma (57.4%) followed at a significant difference by the mucinous carcinoma (10.3%).

Table 1. Report of ovarian cancer histopathological types

21.00	2	100.0%	0	.0%	2	100.0%
22.00	88	98.9%	1	1.1%	89	100.0%
23.00	15	93.8%	1	6.3%	16	100.0%
24.00	9	100.0%	0	.0%	9	100.0%
25.00	12	100.0%	0	.0%	12	100.0%
26.00	13	100.0%	0	.0%	13	100.0%
27.00	14	100.0%	0	.0%	14	100.0%

Table 2 includes the descriptive data for each histopathological form analyzed, with no statistical significant difference between the analyzed types as regards the mean age, maximum and minimum.

21.00	**Mean**	**52.5000**
	Minimum	**49.00**
	Maximum	**56.00**
22.00	**Mean**	**60.0000**
	Minimum	**19.00**
	Maximum	**87.00**
23.00	**Mean**	**57.6667**
	Minimum	**38.00**
	Maximum	**76.00**
	Mean	**50.2222**
24.00	**Minimum**	**30.00**
	Maximum	**63.00**
25.00	**Mean**	**51.4167**
	Minimum	**33.00**
	Maximum	**78.00**
26.00	**Mean**	**50.9231**
	Minimum	**25.00**
	Maximum	**76.00**
27.00	**Mean**	**55.5000**
	Minimum	**30.00**
	Maximum	**76.00**

Descriptive data for each histopathological form. Brenner tumor (2.1), serous (2.2) and mucinous (2.3) ovarian carcinoma, granulosa cell tumor of the ovary (2.4), germinal ovarian tumor (2.5), Borderline ovarian tumor (2.6) and endometrioid carcinoma (2.7).

The incidence was significant higher in 2017, with a significant decrease for the next year and staying around the same values for years to come (Figure 1).

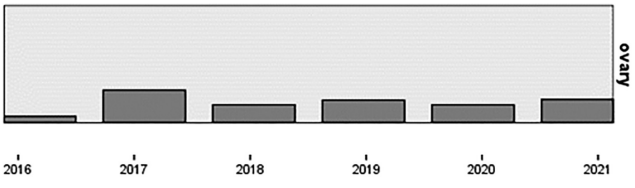

Figure 1. Incidence of ovarian cancer in the Emergency University Hospital for each year analyzed

Compared to other gynecological cancers, ovarian cancer has the lowest proportion among them (Figure 2).

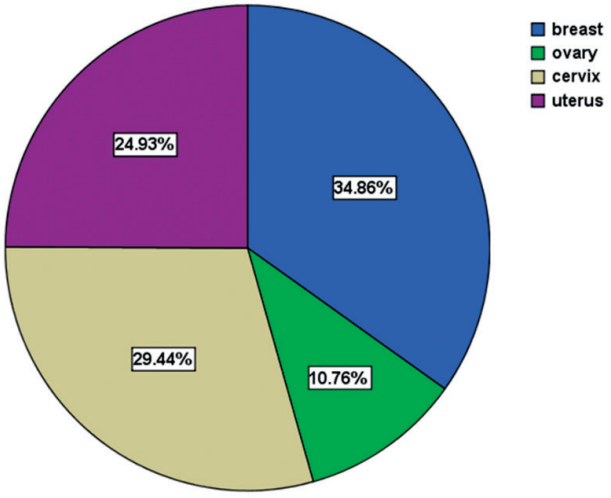

Figure 2. Percentages coresponding to each type of gynecological cancer from our unit during the studied period.

DIAGNOSIS

Approaching patients with suspected ovarian cancer

The diagnosis of ovarian cancer requires surgical exploration with the removal of bioptic samples and its histopathological evaluation. The main cause for this is due to the fact that women with early-stage disease (without malignant cells in the ascites fluid or peritoneal cytology) benefitfrom intact ablation of the tumor mass, since the incision or rupture of them asses results in a superior stage of the disease, negatively affecting the prognosis.

Thus, in general, imaging-guided ovarian biopsy is not performed, patients under going surgical procedures to identify malignant pathology. Patients who present signs of extensive malignant disease (liver or lung metastases, massive ascites) at imagingi nvestigations and a poor ECOG performance status are treated with neo-adjuvant chemotherapy and imagistically evaluated by paracentesis, thoracocentesis, not by surgery before treatment[17].

Women with suggestive characteristics of ovarian cancer are generally evaluated in two phases. Initially, an evaluation is carried out to determine the presence of an ovarian tumor mass or the presence of increased tumor markers, thus it is found, whether there is an increased clinical suspicion of malignancy, to resort to surgery. In the event that there is no indication of surgery, the clinician must follow other etiologies of the signs and symptoms of the patient. If an ovarian tumor mass is identified and on the basis of the initial evaluation there is a suspicion of ovarian cancer, it proceeds to surgical evaluation.

Preoperative evaluation has as objectives: exclusion of a primary synchronous cancer, exclusion of the presence of metastases, the possibility that the ovarian tumor mass is a secondary tumor of an extra ovarian primary cancer. This assessment may lead to the decision to start treatment with neo-adjuvant chemotherapy before surgery[17].

Women with symptoms and signs suggestive for ovarian cancer should be evaluated for the identification of an ovarian tumor mass bypelvic, clinical and imaging examination.

Clinical Diagnosis

The symptoms of ovarian cancer are most often vague and overlap with symptoms of much more common conditions, such as digestive pathology („loan symptomatology"), menstruation and menopause.

As the tumor spreads into the pelvis and to the upper abdomen, patients begin to complain of pain or discomfort in the pelvis or abdominal area, postprandial bloating, flatulence, eructations, nausea, diarrhea, constipation, feeling of early satiety. Patients may also experience postmenopausal vaginal bleeding and rectal bleeding. As the disease progresses, there may appear weight loss, anemia, inappetence, fatiguability, they may develop intestinal obstructions with the appearance of occlusions (these are surgical emergencies) or ureteral obstructions with the appearance of hydronephrosis of varying degrees (with the need for nephrostomy). In general, these symptoms have an increased specificity, but a modest sensitivity for ovarian cancer[17,18].

In patients with ovarian cancer, certain signs may appear at the pelvic, abdominal and lymphnodes clinical examination, such as: peripheral inguinal adenopathies, signs of peritoneal/ascitescarcinomatosis, the presence of pleural collections, palpation of pelvic formations at the vaginal/inguinal stroke or abdominal formations[17,18].

Sometimes women with epithelial ovarian cancer may experience a paraneoplastic syndrome or may develop a syndrome in the course of the disease. Paraneoplastic syndrome sassociated with ovarian epithelial

cancer are: polyneuritis, cerebellar degeneration, dermatomyositis, Zollinger Ellison syndrome, hyperamilazemia, hemolytic anemia, disseminated intravascular coagulation, migratory thrombophlebitis, hypoglycemia, acanthosis, Cushing's syndrome or nephrotic syndrome[19,20].

Very rarely, patients with EOC may initially present with venous thromboembolism[21]. In a studyi nvolving 668 people who had cancer at the time of an episode of venous thromboembolism, 5.2% occurred in patients with ovarian cancer[22].

Screening in asymptomatic women for ovarian cancer is not effective, but these symptoms can helpi dentify patients at an early stage of the disease. Among the symptoms suggestive for ovarian cancer, therefore, are pelvic and abdominal pains, urinary imperiosity, increased frequency of urination (polakiuria), bloating and early satiety, being even more suggestive if the symptomatology is a new one, occurring for less than 1 year and frequent (more than 12 days a month).

The appearance of any symptom 12 times a month, in less than a year, had a sensitivity of about 56.7% for the disease in the early stage and 79.5% for the disease in the advanced stage. Specificity was 90% for patients older than 50 years of age and 86.7% for patients up to 50 years of age. An important aspect of anamnesis is the family history of ovarian or breast cancer and the presence or not of risk factors and protective factors[18,23].

Paraclinical diagnosis

Transabdominal ultrasound is used in the diagnosis of ovarian cancer, being an investigation easily tolerated by patients, having as an advantage the visualization of abdominal processes (ascites, extension of the neoplastic disease at the abdominal level) [24]. Transvaginal ultrasound has a higher resolution than transabdominal ultrasound. The characteristics that suggest the malignant character of an ovarian formation are: the presence of the solid component, often nodular or papillary but not hyperecogenic, the presence of thick septa (>2-3 mm), the presence of intense vascularization in the solid component viewed with the color Doppler and Power Doppler,the presence of ascites (any intraperitoneal fluid in postmenopausal women is abnormal), the presence of peritoneal masses, enlarged lymph nodes, intestinal volvulus (they are difficult to visualize by ultrasound) [25]. As regards to the tumour mass, studies have not found any significant difference in size between malignant and benign masses[26,27]. This is due to the fact that the total size of a tumour mass also includes the cystic component, in addition to the solid one, the last one being a risk factor for malignancy.

An approach to preoperatively determining the likelihood of malignancy of an ovarian tumor, was described by the study group IOTA (The International Ovarian Tumor Analysis). It is based on the presence of five features seen on ultrasonography: B-characteristics for benign tumors and M-characteristics.for malignant tumors.

The B-characteristics are: unilocular tumor (of any size), the presence of a solid component less than 7 mm in diameter, the presence of shadow cones, multil ocular tumors with a diameter of less than 10 cm and the absence of bloodf low with Doppler examining.

The M characteristics are: solid and irregular tumor, the presence of ascites, the presence of at least 4 papillary structures, irregular solid-multilocular tumor with the largest diameter ≥ 10 cm and the presence of intense blood flow with Doppler examining.

When using ‚Simple rules', tumors are classified as benign if only B-characteristics are present and as malignant if only M-characteristics are present. If these characteristics are not present or if conflicting characteristics are observed, the ‚Simple rules' are considered to be incapable of classifying the tumor as benign or malignant, the result being inconclusive[29].

Computed tomography (CT), pelvic and abdominal magnetic resonance imaging (MRI) help to assess the presence of ascites, assess the degree of extensionand invasion of the disease. CT is more used in practice due to lower costs. When the patient is allergic to the contrast substance, MRI isused. Some data reveal that compared to CT alone or MRI, positron emission tomography alone or combined with CT increases the detection of metastases. Chest CT canal so be performed to evaluate metastases[17,30].

Chest X-ray is done in the vast majority of patients to assess the presence of pleurisy, pulmonary metastases and mediastinal lymphadenopathy[17].

Abdominal radiography on the hollow, irrigography, is performed to evaluate the extension of ovarian cancer and to evaluate metastases[20].

Urography, cystoscopy are used to evaluate the extension of ovarian cancer[20].

Bone and brain scans are not necessary unless signs and symptoms reveal metastatic brain and bone determinations[17].

Paracentesis can be performed in patients with ascites, with the analysis of the puncture fluid, being useful also for tracking the treated patients[17].

Thoracentesis is performed in patients with pleural overflow ({Citation}).

Other investigations: Rectoscopy, Hepatic Scintigraphy, Lymphography, Angiography[17,20].

Tumor markers: CA-125, HE4, CEA, CA 19-9, AFP, hCG, LDH, etc. are used in the initial evaluation of malignancy in a patient with ovarian tumor mass.

CONCLUSIONS

Ovarian cancer is distinguished by the increased rate of associatedmortality, thistype of cancer beingresponsible for themajority of deathsfromcancers in thegynecologicalsphere. It istheduty of every doctor tofight for theimprovement of diagnostic strategies, preventionandtreatment of thispathology.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. 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.

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