UNIVERSITY "OVIDIUS" CONSTANŢA

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DIAGNOSTIC AND THERAPEUTICAL NEWS IN OVARIAN CANCER

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INTRODUCTION

Ovarian cancer is a late-onset affection, with a non-specific symptomatology with a rapid natural evolution and frequent recurrence of a relapse after a radical treatment. Currently, ovarian cancer is the fourth cause of female cancer mortality. Therefore, new methods are being sought to detect this neoplasia as early as possible. Ovarian cancer most affects young and middle-aged women, but can occur at any age, including girls. At birth, each little girl has a 5-7% risk of developing ovarian cancer during life, and about 15% of these will be malignant.

GENERAL PART

CHAPTER I

In this chapter information about embryology, anatomy, histology and physiology of the ovaries

CHAPTER II

2.1. EPIDEMIOLOGY OF OVARIAN CANCER

Ovarian cancer is the fifth female neoplasia as a frequency (20). Cindy Quinton Gladstone et al. (Toronto, 1994) report ovarian cancer as the fifth cause of malignancy in women after breast, colon, lung and uterine cancer and estimates incidence in Canada in 1993 at ca. 2,100 new cases per year, approximately 4% of all new cases of female cancer (21,22).

2.2. OVARIAN CANCER ETIOPATOGENE

2.2.1. RISK FACTORS INVOLVED IN OVARIAN TUMOR PROLIFERATION

2.2.1.1. GENETICAL FACTORS

Hereditary breast and ovarian cancer syndrome (HBOC) originates in a genetic predisposition to develop malignancy and is characterized by:

● Having a family of many cases of ovarian cancer, breast cancer, or both;

● Associating the same person with both ovarian and breast cancers;

● Early onset breast cancer. Although most cases of ovarian and breast cancer are not inherited, about 10% of ovarian cancers and 3-5% of breast cancers are incurable in breast and ovarian cancer syndrome. Several studies have shown that BRCA1 and BRCA2 gene mutations that are of interest to the germline are common for most cancers of the ovary and breast (28,29).

2.2.1.2. NON-GENETIC FACTORS

2.2.1.2.1. FACTORI GENERALI

2.2.1.2.1.1. Age. Most ovarian cancers (80%) are diagnosed in postmenopausal women over 50 years of age. The maximum incidence is between 40 and 65 years (23).

2.2.1.2.1.2. Race

The white race is most affected by ovarian cancer while the black race has the lowest incidence reported.

Ovarian cancer is more common in the Caucasian (white) race and especially in the Ashkenazi Jews. Narod and collaborators, like other authors, reported that the BRCA1 or BRCA2 mutation was found in 40% of the Ashkenazi Jewish women. Today, in medical practice, genetic tests are performed on these women (16,22).

2.2.1.2.1.3. Socio-economic situation

Residency in industrialized urban centers is also associated with a greater chance of developing ovarian neoplasm (16,22).

2.2.1.2.2. REPRODUCTIVE FACTORS

Multipurpose women are at a lower risk than those with fewer pregnancies, which in turn have a lower risk than niggas. Also, early menarhas and late menopause seem to contribute to an increased risk of ovarian cancer. Ovarian cancer is less likely to develop in women who have fewer ovulations during their lives. Especially in pregnant women, the risk of ovarian cancer is almost two times lower than in women who have never been pregnant. The risk of developing ovarian cancer is lower in women who have had multiple pregnancies and who have suckled.

2.2.1.2.3. EXOGENE HORMONES

2.2.1.2.3.1. Oral contraceptives Modern research has shown that the use of oral contraceptives in young women reduces the risk of ovarian cancer.

2.2.1.2.3.2. Hormone replacement therapy. Female sex hormone medications given to menopausal women may increase the risk of developing ovarian cancer regardless of treatment duration, dose, or type of hormone components of the medication used.

2.2.1.2.3.3. Fertilizing medication. Patients who have received fertility medication are more likely to devel

2.2.1.2.4. ENVIRONMENTAL FACTORS

2.2.1.2.4.1. Factors related to lifestyle

2.2.2.4.1.1. Diet. Some studies suggest that a diet rich in lactose could increase the risk of developing ovarian cancer (38,39).

2.2.1.2.4.1.2. Alcohol consumption is associated with an increased risk of ovarian cancer (40).

2.2.1.2.4.1.3. Smoking increases the risk of ovarian cancer (40).

2.2.1.2.4.1.4. Physical activity. Active lifestyle without risk behaviors will not prevent the cancer itself, but it will stimulate the body to fight against the possible changes that occur. The competent cells of the immune system have the ability to monitor and destroy the cells that begin to anarchically divide and begin to alter their functional characteristics (38, 39, 40).

2.2.1.2.4.2. Occupational exposure

Exposure to asbestos increases the risk of developing ovarian cancer (41)

2.2.1.2.4.3. Environmental contaminants

Chronic exposure to talc (perineal applications) is associated with a higher percentage of ovarian neoplasia (40).

2.2.1.2.5. ANTROPOMETRIC FACTORS

2.2.1.2.5.1. Body Mass Index Studies that support obesity as a risk factor in the ovary neoplasm suggest that excessive androgenic stimulation of ovarian epithelial cells occurs. Obesity, which

characterizes 80% of people with type 2 diabetes, increases the rate of progression of cancer after initial treatment (17,19).

2.2.1.2.5.2. Height We have not found studies correlating height with a high risk of ovarian cancer.

2.2.1.2.6. GYNECOLOGICAL SURGERY. Certain gynecological surgeries may constitute protective agents against ovarian neoplasm: prophylactic ovariectomy, hysterectomy, tubal ligation.

2.2.1.2.7. OTHER FACTORS

2.2.1.2.7.1. Endometriosis. Some authors consider endometriosis as a factor that increases the risk of ovarian cancer (42,43,44).

2.2.1.2.7.2. Polycystic ovarian syndrome may be a risk factor due to the increased secretion of androgenic hormones that characterize this condition (42,43,44);

2.2.1.2.7.3. Pelvic inflammatory diseases as well as anti-inflammatory drugs may pose risks for the development of ovarian cancer (42,43,44,45).

2.2.1.2.7.4. Consumption of green tea is cited as a protective factor against ovarian neoplasm (40,46).

2.2.2. THE PATHOGENIC THEORY

1. Growth factors of ovarian epithelial cells (uninterrupted ovulation theory)

Several studies have shown that the frequency of ovulation is associated with an increased risk for developing ovarian cancer.

1. Hormonal Factors (Hormonal Theory)

Observations that ovarian cancer is a more common disease in the period following the climax and associated with nullity have led to the formulation of the hypothesis of hormone involvement in the onset of the disease. Thus, steroid hormones, peptide hormones and peptide growth factors have the potential to influence normal growth or neoplasia of ovarian epithelial cells.

3. Oncogenes

In ovarian cancer, aberrant expression of some oncogenes was reported: ras, myc, fms, HER-2 / neu, jun, myb

4. Antioncogenes

Another genetic lesion involved in the genesis and development of ovarian cancer is the loss of normal p53 gene function. This gene, located on the 17p chromosome, is a tumor suppressor gene.

5. Chromosomal abnormalities

In ovarian cancer, the most damaged chromosomes were 1 and 11 (explains the particular biological aggressiveness of these cancers), then bb b chromosomes 3 and 7 (50, 51).

2.3. OVAR CANCER MORPHOPATHOLOGY

In the primitive urogenital crest, the development of the ovary (which consists of: surface epithelium, germ cells and support cells) is closely related to the primordial Mulerian, mesonefrotic and adrenal structures, which gives cancerous tumors a complex origin and extreme histological diagnosis delicate.

2.3.1.PATHOLOGICAL ANATOMY

I. Epithelial Tumors. These tumors derive from the Mueller duct or the parametrosonephrotic duct. Malignant tumors originating in the epithelial surface of the ovary are the most common 85-90%: - serous chistheno-carcinoma 50% - mucosal

chisthenicarcinoma 15-20% - endometroid 15-20% - Clear Cells (mezonefroid) 5% - undifferentiated 10-15%

II. Tumors from germ cells. They are derived from primordial germ cells, either directly (disgerminoma) or indirectly by embryonic differentiation, involving one or three embryonic (teratoma) foci or extraembryonic differentiation (coriocarcinoma, endodermal sinus tumor). Malignant forms are rare, only 3% of ovarian cancers.

III. Special mesenchymal stromal gonads tumors. They have a complex histological structure of epithelial cells in beaches in a fibrous tree atmosphere. The malignant potential depends on the cell type.

CHAPTER III

ACTUAL STAGE OF DIAGNOSIS AND TREATMENT OF OVARIAN CANCER

3.1. CLINICAL DIAGNOSIS

3.1.1. Symptomatically. Ovarian cancer is often discovered by chance and very often in advanced stages. Early symptoms for ovarian cancer are rare, except hormone-secreting tumors. Symptoms are not acute, specific, and often start with symptoms due to complications (metastasis in the liver, lung, intestinal occlusion). With some exceptions, malignant tumors are in the asymptomatic initial phase or with a confusing, misleading symptomatology.

1) Digestive disorders: vague pains, especially postprandial, in the lower abdomen, feeling full, flatulence, dyspeptic disorders, constipation.
2) Abdominal volume increase: it is usually a late sign, although some benign tumors may be giant and some barely palpable carcinomas. Generally, the rapid increase of abdomen through the tumor or ascites, plus transit disorders, suggests to a known tumor the possibility of malignancy.
3) Menstrual cycle disorders: do not occur except for hormone-secreting tumors. Menstrual cycle disorders can be generated by stromal hormone secretion stimulated by tumor proximity. Otherwise, metrorrhagia can be caused by endometrial hyperplasia, associated endometrial adenocarcinoma or tumor invasion in the endometrium. Dyspareunia or dysmenorrhea may occur.
4) Urinary disorders: they may appear by compression or bladder tumor invasion, but these are late signs.
5) Progressive weakening until emulation. It is noticeable in the advanced stages, in which fat and muscle mass melting is characteristic, in contrast to the impressive distension of the abdomen.
6) Uniform or bilateral thrombophlebitis of lower limbs. It is a serious prognostic factor (4).

3.1.2. CLINICAL EXAM

General Objective Examination: Identifies in advanced stages the abdominal and ascites tumors, possibly a right pleural effusions (Demon Meigs) and superficial and inguinal adenopathies. Thrombophlebitis or increased unilateral volume of a inferior member is a serious prognostic factor.

Pelvic Examination: It includes both vaginal and rectal tact.

3.1.3. OTHER EXAMINATIONS
3.1.3.1. LAPAROSCOPIA is valuable in the case of small tumors and for obtaining peritoneal lavage for cytology. Certain ovarian cancer is contraindicated because it promotes dissemination. Laparoscopy is also valuable in evaluating some chemotherapy treatments. Biopsy of encapsulated ovarian cysts may cause tumor cells to be sent to the peritoneal cavity, so they should be avoided.
3.1.3.2. EXPLORATORY LAPAROTHOMY solves diagnostic uncertainties, allows for tumor inspection, extraction and extemporaneous examination of primary lesions and metastases, assessment of tumor extension, correct staging of the case as well as surgical resolution of tumors and metastases. Second-look laparotomies allow the dynamic evaluation of a therapy and confirm healing or progression of the disease.
3.1.3.3. PELVISCOPY - the endoscopic method required in ovarian tumors (especially in young women). It is useful for early detection of ovarian cancer, not indicated in advanced stages. It is indicated in benign tumors, in borderline tumors, in high-risk groups of women, or in young women.
3.1.3.4. HISTEROSCOPIA provides information about the uterine cavity, especially in the case of metrorrhagia or menorrhagia, in the adult or postmenopausal period. Biopsy through hysteroscopy and histopathological examination of the fragments can translate the diagnosis.
3.1.3.5. UTERIN CHURCH is useful for hysteroscopy, but it is a blind maneuver. In the absence of hysteroscopy it is necessary for diagnostic and hemostatic purposes.
3.1.3.6. CULDOCENTEZA
3.1.3.7. THE ECOGIED POINT can be performed in the abdominal or vaginal probe sonography. It is preferable to puncture pelvic formations with a diameter of more than 5 cm.
3.1.3.8. BIOPSY. LAPAROSCOPY BIOPSY OR ASPIRATIONAL PUNCTURE of an intact ovarian tumor may result in the suturing of malignant cells in the peritoneal cavity, and intracisternal fluid aspiration and cytological examination are not a diagnostic method in ovarian cancer. It can be argued that positive laparoscopy (positive biopsy) is relevant, and negative laparoscopy subsequently requires an exploratory laparatomy.
3.2. BIOLOGICAL DIAGNOSIS ....
3.2.1. HEMATOLOGICAL DETERMINATION
Routine lab exams are of little value. There is an increase in VSH and reactive C protein.
3.2.2. DETERMINATION OF TUMORAL MARKERS
3.2.2.1. trophoblast
- human placental alkaline phosphatase (PAP) - occurs in serum at high levels in ovarian cancer but also in other cancers.
- human ovarian gonadotropin (HCG) is present in embryonic cell carcinoma (coriocarcinoma, disgerminoma).
- Placental breast lactogen (HPL) is a polypeptide hormone present in coriocarcinoma.
- Specific pregnancy globulin (SPI)
- TPA (tissue polypeptide antigen) is a polypeptide with specific antigenic properties produced in human placenta, human malignant tumors and cancer patient fluids. It is used as a tumor marker especially for monitoring the progression of breast or ovarian cancer patients during therapy (58).
3.2.2.2. Embryo - Carcinoembryonic antigen (CEA) is a glycoprotein found in the serum of ovarian cancer patients and increases with disease status. CEA was found in the serum of patients with stage III-IV ovarian cancer in a proportion of 60-80%, with a higher frequency in

the types of mucin carcinoma (Di Saia). It can also have elevated values in both colon and gastric cancers.
- embryonic prealbum
- oncofetal antigen
- A fetoprotein (AFP) has been used with some success in monitoring the treatment and follow-up of patients. AFP is increased in ovary teratocarcinoma and endodermal sinus tumor (58).
3.2.2.3. enzyme
- urokinase
- glycosyltransferase
- glycosidases
3.2.2.4. Ovarian antigens These are either on the surface of the cell membrane, either inside the tumor cell or in body fluids (11,15). The antigenic tumor markers used in ovarian cancer are:
- ovarian cancer antigen (OCA-A)
- OCA-1 (associated ovarian chistinocarcinoma)
- ovarian cancer 1 (OVC-1)
- ovarian cancer 2 (OVC-2)
- CA 19-9, CA 15-3, TAG 72, CA 54/61, NB / 70 K
- CA 125.

3.2.3. THE ROMAN SCORES (RISK OF OVARIAN MALIGNANCY ALGORITHM)
Premenopausal women:
ROMA score ≥11.4% = increased risk of ovarian cancer epithelial
ROMA score <11.4% = low risk of epithelial ovarian cancer
Postmenopausal women:
ROMA score ≥29.9% = increased risk of epithelial ovarian cancer
ROMA score <29.9% = low risk of epithelial ovarian cancer.

3.2. IMAGISTIC DIAGNOSIS
3.3.1. RADIOLOGICAL EXAMINATIONS
3.3.1.1. Simple abdominal radiography: calcifications in fibroids, benign teratomas; can give indications about associated ascites or intestinal occlusion; opaque images in disgerminom.
3.3.1.2. Pulmonary X-ray: shows the presence of pleurisy or pulmonary metastases.
3.3.1.3. The baritone test, as well as cystoscopy and pelvicography, helps to establish the existence of external compressions or tumor invasion.
3.3.1.4. Limphangiography was proposed to detect lymph node invasion. However, the sensitivity of the method is too low to be used in the therapeutic plan.
3.3.2. ULTRASONOGRAPHY
Transvaginal Doppler ultrasound is used as the first method in the initial assessment of anexal masses. It has a sensitivity of 86% and a specificity of 91%. It has been extensively tested in screening studies with good performance characteristics, although it is risky to extrapolate from the screening population to the symptomatic population. Transvaginal ultrasound is superior to abdominal ultrasound for details of structure and size of the ovaries.
3.3.3 COMPUTERIZED TOMOGRAPHY Computed tomography is used in preoperative or post-operative assessment with 90% sensitivity and 75% specificity.
3.3.4. NUCLEAR MAGNETIC Examination Examination of MRI of the pelvis can provide information about the tumor's relationship with neighboring organs and about the nature of an ovarian mass, especially if echography could not reveal the benign or malignant appearance of

the tumor. It is useful in determining the stage of the disease and especially in following the progression of postoperative and post-chemotherapy disease.

3.4. CITOLOGICAL AND MORPHOPATOLOGICAL DIAGNOSIS Histopathological examination of biopsied tissue or resections is the cornerstone of oncology diagnosis. The microscopic examination of the tumor tissue determines the histological type and degree of tumor differentiation.
3.5. STAY DIAGNOSIS OF OVAR CANCER Staging is usually clinically established by preoperative examinations, but ultimately is established postoperatively. The international staging of ovarian cancer is established by FIGO in 1995 along with the staging of TNM.
3.6. OVAR CANCER ACTUAL TREATMENT
3.6.1. PROFILACTIC TREATMENT According to some authors, ovarian cancer prophylaxis is illusory. After all, access to information, health education, peridical genital counseling in tandem with ultrasound, real hormonal contraception would be safe prevention factors and a real possibility of high risk group selection.
3.6.2. CURATIVE TREATMENT It is complex, therefore requires collaboration between several specialties (surgeon, oncologist, radiotherapist, anesthetist-reanimator). The treatment is determined by clinical staging, malignancy, extravascular extension, histological type and may be associated with:
- surgery,
- chemotherapy
- radiotherapy,
- hormone therapy,
- immunotherapy,
- genetic therapy,
- other types of complementary or adjuvant treatment.

3.6.2.1. SURGICAL TREATMENT Surgical treatment remains, after Dargent D. (1992), Di Saia J. Ph. (1990), MacKay T. H. (1998), Chiricuta I. (1981), the fundamental technical means in the treatment of ovarian cancer. Surgical treatment depends on TNM / FIGO pre-therapeutic staging.
a) For stages I and II in developed countries, the approach pathway is more frequent through surgical / operative pelvic surgery / operative laparoscopy. In Stage IA there are authors indicating only unilateral annexectomy, but depending on certain conditions (86). Adjuvant chemotherapy is not necessary in all cases. The second-look laparotomy can be practiced for 6 months per pan-pelviscopy and addresses patients who appear to have completely responded to chemotherapy or surgery alone
b) For Stage III and IV, technical problems are all the more complex as far as hyperbaric interventions are concerned (hysterectomy + bilateral anexectomy + omentectomy adds large locoregional and visceral extensions) from where the need to study the risk / benefit ratio.
3.6.2.2. CHEMOTHERAPY It calls for a combination of individually active drugs on ovarian cancer: alkylating agents, antimetabolites, antibiotics, organo-metallic compounds, plant derivatives (alkaloids). These drugs can be administered systemically or intraperitoneally.

PERSONAL CONTRIBUTIONS
MOTIVATION

By the theme of "Diagnostic and Therapeutic News in Ovarian Cancer", I have proposed a multidisciplinary approach to this topical issue with the selection of optimal diagnostic and treatment pathways, which are also a major clinical and surgical challenge. Starting from the desire and the need to identify a possible solution to the problems raised by the complex aspect of the tumor of the ovary, the incidence of which is increased during the reproductive and postmenopausal period, we considered it necessary to deepen the clinical-therapeutical interrelation and the physiological, pathophysiological, histopathological, immunohistochemicals by carrying out the present work. The complexity and the great importance of the analyzed problems have led me to study a detailed study in this direction because the diagnostic over-evaluation is frequent and the impact of the nosological classification as well as the interrelationship with the quality of woman's life (post-surgical status and loss of reproductive potential) major concept to be taken into consideration. The aim was to specify the correlation of the early diagnosis of ovarian cancer, postoperatively, depending on the morphological and histopathological aspect, but also preoperatively with the malignancy scores by using tumor markers with high specificity and sensitivity.

OBJECTIVES

The present study has proposed the following objectives:

1. Epidemiological evaluation and evaluation of ovarian tumor pathology in Dobrudja, a region characterized by a particular geographic position and ethnic heterogeneity of the population.
2. Prospective-observative analysis of cases of ovarian cancers operated at the Surgery Clinic and Obstetrics and Gynecology Clinic of Constanta County Emergency Clinical Hospital in 2011-2015 in order to make a correlation between prognostic and survival factors.
3. Researching a correlation between clinical and paraclinical parameters and malignancy of an ovarian tumor
4. The Impact of Modern CT and MRI Imaging Technologies on the Accuracy of Ovarian Cancer Diagnosis
5. Correlation of tumor marker values with the histopathological appearance of the ovarian lesion.
6. Develop an algorithm for the diagnosis and management of ovarian tumors using modern means of investigation to increase ovarian cancer. Predictability of Ovarian Cancer to Be Malignant The Key to Impact of Modern CT and MRI Imaging Technologies on the Accuracy of Ovarian Cancer Diagnosis
7. Correlation of tumor marker values with histopathological appearance of ovarian lesion.
8. Elaborate an algorithm for diagnosis and management of ovarian tumors using modern means of investigation in order to increase the detection of ovarian cancer. The predictability of an ovarian tumor to be malignant is the keystone of this pathology, as the therapies of a benign tumor differ fundamentally from those of a malignant tumor, as well as prognosis.
9. Develop a questionnaire / protocol for assessing the factors that influence the risk of ovarian cancer.

CHAPTER IV.

MATERIAL AND METHOD

In my study on ovarian cancer we started from a thorough theoretical study, based on the Romanian and foreign bibliography, in which I consulted the specialized textbooks and journals on this subject.

The study is prospective and took place over a period of 5 years (1.01.2011-31.12.2015), at the Surgery Clinic and Gynecology Obstetrics Clinic of Constanta County Emergency Clinical Hospital.

The study group consisted of 985 patients with at least one genital spinal pelvic tumor formation that were operated at the Surgery Clinic and the Obstetrics and Gynecology Clinic of the Constanta County Clinical Hospital and come from several sources: patients sent out of the ambulatory specialty (remarkable excellent cooperation with the gynecologists in Constanta County following the expression of the desire to collaborate in the realization of this study); patients sent by family doctors (both urban and rural) and echographers following a collegiate letter recommending a more careful echographic assessment of the pelvis and selecting potential cases of ovarian tumor formations; patients presented on their own initiative in the clinic or in the emergency service.

The selection criterion for patients was the presence of at least one genital pelvic tumor at the clinical / echographic examination.

Data collection:

In order to better centralize the data, we compiled a personal follow-up file for each of the patients enrolled in the study, in which we noted the parameters considered important in the study (ANEXA 1).

Each case went into study once (at the initial evaluation), the results of subsequent evaluations being described in the "follow-up" chapter.

Age: Depending on the age of the patients at the time of recording, they were divided into three age groups: under 30, between 30 and 60, over 60 years of age. We calculated the average age of the various study subgroups that resulted from the analysis of a particular parameter.

Residence: I have marked the county and the home town, with the administrative / urban category.

The presence of heredo-collateral antecedents of ovarian and mammalian pathology was considered important in the overall study considering the possibility of familial aggregation of ovarian cancers.

We have noted the presence of personal physiological and pathological antecedents, mentioning possible contraceptive or hormone replacement medication.

Through the genital clinical examination, we appreciated the presence of an ovarian formation, mobility, sensitivity, consistency, locoregional adenopathy. At the same time, we noted the presence of signs from neighboring organs (dysuria, hematuria, constipation, rectangles) and compressive phenomena. In some cases, patients were also evaluated by cystoscopy and colonoscopy.

Tumor markers were dosed for monitoring ovarian cancer patients or for differential diagnosis purposes. Depending on the histopathological type of the neoplasm, there were dosed: CEA, CA19-9, CA 15-3, CA 125 and ROMA score.

The echocardiography was performed in all patients included in the study using a LOGIQ 500 marker echograph equipped with a transducer with a variable frequency of 7.5-10MHz. The echocardiographic examination was performed both at the study entry of each patient and later on periodic examinations in re-evaluated patients.

Computed tomography (CT) and magnetic resonance imaging (MRI) was performed for preoperative diagnosis in all patients and for postoperative re-evaluation in some patients with neoplastic relapses.

Intraoperative and paraffin histopathological examination was performed on the whole lot studied

Immunohistochemistry has been used to differentiate certain benign cellular changes from neoplastic atipes or to indicate a cell line within the same type of neoplasm.

The therapeutic decision was based on the data obtained at the clinical examination and the results of the clinical and paraclinical examinations. I have to mention that in some cases the decision was made taking into account the patients' wishes.

Patients were followed periodically, the number of re-evaluations depending on the year of study entry; so most re-evaluations were in the patients highlighted in 2011. On the occasion of reassessments, the treatment of some of the patients was reconsidered. It is worth mentioning that some of the patients were lost from observation during the follow-up period. We also considered it necessary to study the characteristics of the group of patients lost in the study (age, domicile, ethnicity) to see if there are differences in treatment compliance according to these characteristics.

All of these data have been entered into a work table in Excel, sorted and filtered according to different criteria; I have tried comparing different subsets of data to see if there are notable differences. We calculated the statistical significance of some differences observed across the study between the various parameters.

We have developed a diagnostic algorithm and a postoperative and follow-up algorithm that takes into account the outcome of the histopathological examination on paraffin, the degree of risk and the postoperative biological status.

The processing of information corresponded to the following steps: • Material collection - for each case, a type sheet (ANEXA 1) was made.

• Quantitative and qualitative valorisation of collected data was then carried out. The presentation of the information for the analysis was done as follows:

• The data were collected in a complex way, based on several grouping characteristics (data processed in datasheets), aiming at the correlation study of the object of the research. The research has shown the following characteristics:

• volume delineation of the surveyed community: 985 cases

• delimitation in space: people in the counties of Constanta and Tulcea.

• The selection criterion for individuals was the presence of at least one tumor formation in the anterior throat of the throat at the clinical / echographic examination.

• the research was integral, studying the entire volume of the researched collectivity.

• time delineation: research over the period 2011-2015. Mathematical processing of collected data The data were systematized as experimental tables (by batches). The presentation of the data was done through "column" and "sectoral" graphic representations according to the scientific requirements existing in the field

CHAPTER V. RESULTS

It includes the results of our research on ovarian neoplasms. These results were presented in the form of tables and graphs.

CHAPTER VI.

DISCUSSIONS

In this chapter we compared the results obtained in our study with the results of other studies in the literature concerning the epidemiological aspects of ovarian cancer, the risk factors and the protective factors for this disease, its diagnosis and treatment as well as factors influencing survival and prognosis.

I have shown how the patients under study were monitored.
Since one of the purposes of this paper was to develop an early ovarian cancer screening program, we also conducted a study of 840 women who each completed two questionnaires: the OSCI questionnaire and the questionnaire for finding risk factors for ovarian cancer . After completing the risk factor questionnaire, it was found that 263 women (31.30%) had 3 or more risk factors.
At the end of this chapter we have presented an evaluation algorithm for the prevention of ovarian cancer that we have developed from this paper.

CHAPTER VII.
CONCLUSIONS

1. Our study revealed a lower incidence of ovarian cancer compared to the incidence reported in the European Union, probably due to the lower addressability of women, amid a lower quality education coupled with lower levels of material resources. We noticed a gradual increase in the number of patients from year to year, explained by increasing the awareness of other specialists about ovarian tumors, as well as improving the technical evaluation possibilities.
2. The risk for ovarian cancer is clearly associated with: over 50 years of age, nuliparity, early menarrh, late menopause, use of fertility medication and hormone replacement, body mass index greater than 28. Ovarian cancer was more common urban women versus those from rural areas, women smokers with non-smokers and women with gynecological pathology associated with women in whom this pathology was non-existent but the differences were not statistically significant. Multiparty, prolonged breastfeeding, early menopause, and contraceptive use have been associated with a lower risk of ovarian cancer.
3. Personal or family history of colon cancer, ovarian cancer or breast cancer increase suspected malignancy in patients who are investigated for an ovarian tumor, BRCA-1 and BRCA-2 genes being those involved in the hereditary line.
4. Symptomology of ovarian cancer as evidenced by the studied group is often noisy but non-specific. The classic name of silent killer is not found in this context, but rather the name of the noisy killer can be attributed to this condition. In this study, only 34.17% of the patients had no symptoms, the rest had a nonspecific symptom that was reported to the family doctor.
5. Nonspecific symptom of ovarian neoplasm causes it to be diagnosed late, sometimes by chance, in various medical or surgical specialties. Therefore, our peer review recommendation is not to exclude the diagnosis of ovarian cancer in any specialty.
6. Vaginal bruising and palpation of the abdomen have proved to be the best maneuvers in the clinical examination for the detection of an ovarian tumor, which is why we recommend that they be done by all doctors who are in front of a patient with abdominal or pelvic symptomatology.
7. From the analysis of the tests of different tumor markers whose values change in ovarian cancer, we can conclude that in the presence of a clinically or ultrasound pelvic massage it is recommended to dose a tumor marker pack (CA 125, CEA, α Fetoproteina, CA 19 -9, CA 15-3) and not a single marker (CA 125) since CA has elevated levels especially in epithelial cancers and the pelvic mass may be a cancer of non-papillary origin (7.17% in our study) that may have expression in the growth of other markers (CEA, alphapetoprotein, CA19-9, CA 15-3).
8. We believe that the ROMA score today is the most useful tool in framing clinically diagnosed or pelvic ultrasound patients in a low risk or increased risk of ovarian cancer epithelial cancer surgery.

9. Without accurately establishing the etiology of the tumor, surgical punishment may not bring the expected benefits if it is not performed in a qualified center (extemporaneous examination, peritoneal biopsy, cytology, staging, or radical intervention).
10. Ultrasound is preferred for investigating ovarian pathology. It can be supplemented by other imaging methods (CT, MRI) and tumor markers (CA 125, ROMA score) in suspicious cases of malignancy. The sensitivity and specificity of ultrasound, but especially the benefits of the method justify its widespread use, even in a screening event. Transvaginal ultrasound is considered the method of choice for evaluating ovarian tumor formations as it can make ecomorphological correlations of benignity or malignancy. CT and MRI examinations are very useful in highlighting tumor metastasis and in establishing the preoperative stage of the neoplasm as well as in following the response to treatment or in the detection of tumor recurrences. These investigations have a small contribution to the initial discovery of ovarian tumors, the vast majority of these tumors being made by echographic examinations.
11. We consider the diagnostic value of cytology in peritoneal lavage to be low.
12. As for the biopsy puncture of an annexe mass, our opinion is that this puncture can only serve to delay the diagnosis and treatment of ovarian cancer. Instead we recommend that if a clinical suggestion of ovarian cancer is present, the patient should undergo a surgical assessment for diagnosis and staging. We believe that fine needle aspiration, percutaneous biopsy or diagnostic paracentesis should be performed in patients with diffuse or ascitic carcinomatosis without obvious ovarian mass and in patients who are to be treated with neoadjuvant chemotherapy.
13. The gold standard in the diagnosis of ovarian cancer remains the histopathological examination of paraffin supplemented with the immunohistochemical study.
14. Surgery plays an essential role in all stages of ovarian cancer when applied as a sequence of multimodal therapy, constituting the first (diagnosis / therapeutic) treatment schedule in any of the following: radical, conservative, cytoreductive first-order, cytoreductive interval, palliative or exclusively exploratory.
15. Cytoreductive surgery is an important prognostic factor (maximum residual disease diameter correlates with disease-free survival and overall survival).
16. We did not see any better results in the patients with the second look, and those with reintervention for exesize the percentages in which the complete excercise was successful (2 out of the 79 reinterventions).
17. By correlating the observed intraoperative appearance in second look operations as well as in reinterventions with the results of histopathological examination of ovarian malignancies, we noticed that serum adenocarcinoma responded best to surgical treatment combined with chemotherapy. The worst response was germinal tumors and undifferentiated adenocarcinoma.
18. Three prognostic variables correlate with longer survival after cytoreductive surgery for recurrent disease: good performance status of the patient, absence of ascites fluid, and complete cytoreduction during primary surgery.
19. I noticed that despite the response rates increased after chemotherapy, the number of patients with ovarian cancers receiving a full therapeutic response demonstrated by negative second-look interventions remained low (28.26%).
20. In the SCJU Surgery Clinic Constanta we had the possibility to administer cytostatic intraperitoneally, which is why 17 of the ovarian cancer patients benefited from this therapy. Intraperitoneal chimiohiperthermia applied in the Surgery clinic, using the patented ANTIMETA device, increased the survival rate of patients operated for ovarian cancer. 10 of the 17 cases to

which this therapy was applied survived at 3 years (58.8%), but our casuistry is low and we think it should be much better researched in later research.
21. Predictive factors for the unfavorable development of CO are: age> 50 years on diagnosis, impaired performance status (ECOG ≥ 2), IC stage of disease (with ovarian cancer rupture) or more advanced diagnosis, increased tumor volume before and after dulking surgery, presence of dense tumor adhesions, presence of large amounts of ascites, clear cell / mucous cell histology, tumors with G3-4 differentiation, mutations in genesBRCA1, elevated CA 125 (1,2,7).
22. Patients treated for ovarian cancer should be closely monitored clinically and paraclinically.
23. Survival at 5 years in early stages is good, but 75-80% of patients present with advanced disease, with a life expectancy of only 5 years of only 20%.
24. The best survival was in patients with two of the following three criteria: complete resection at first surgery, good performance score and absence of ascites.
25. The family doctor has a very important role in early detection of ovarian cancer because it can establish the target population for screening, evaluate persistent dyspeptic symptoms and perform abdominal-pelvic ultrasound. A good method of early detection is to fill in the annual questionnaire by women who present themselves to family medical care.
26. Combating ovarian cancer and increasing survival chances is only through early detection of high-risk groups at age 30 (women who have a heredo-collateral history of breast cancer or maternal breast cancer, women without pregnancy , with benign tumors in the past, with endocrine pathology or other neoplasias). In these groups, the annual clinical examination, high resolution ultrasound coupled with doppler color and power doppler, eco-guided puncture, dosing of tumor markers (CA 125, CA 19-9, CA 15-3, BRCA-1 oncogene) allows early detection, a decrease in morbidity and mortality through ovarian cancer.
CHAPTER VIII It includes several cases from personal case, with intraoperative images and histopathological examinations.

BIBLIOGRAPHY

1. Papilian V., Anatomia Omului. Vol. II: Splanhnologia (editia a XII-a), Editura ALL, 2001; 287-295.
2. Exarcu I.T., Fiziologia şi fiziopatologia reproducerii umane, Editura Medicală 1977; 56-97.
3. Ranga V., Exarcu I.T., Anatomia şi fiziologia omului, Editura Medicală 1969; 561-612.
4. Munteanu I., Tratat de Obstetrica volumul I, Editura Academiei Romane, editia a II-a, 2000; 14-20.
5. Frank H. Netter, Atlas de Anatomie Umana, Editura Callisto. Netter Editia 2005; 380 – 384.
6. Radulescu C., Ginecologie Vol I, Editura Medicală 1988; 12-45;
7. Williams P.L., Gray's Anatomy, Publisher: Churchill Livingstone; 38th Edition 1995; 646-698
8. Berek J.S., Berek & Novak's Gynecology; Publisher: Lippinkott, Williams & Wilkins, 15th Edition, 2011; 68-116 .
9. Sirbu P., Chiricuta I., Pandele A., Chirurgia ginecologică, Vol I, Editura Medicală 1981; 34-76.
10. Angelescu N.,Tratat de patologie chirurgicala, Vol. II Editura Medicală 2003; 3025-3037; 3099-3122.

11. Ancar V., Ionescu C., Obstetrică și Ginecologie, Vol.I Editura Național 2008; 16-24; 231-262.
12. Evans J.P., Florman H.M., The state of the union: the cell biology of fertilization. Nature Medicine. 2002- 8 Suppl S57-63.
13. Edwards RG., Studies on human conception. Am J Obstet Gynecol. 1993 Nov 1;117(5):587–601. [PubMed]
14. Croxatto HB, Díaz S, Fuentealba B, Croxatto HD, Carrillo D, Fabres C., Studies on the duration of egg transport in the human oviduct. I. The time interval between ovulation and egg recovery from the uterus in normal women. Fertil Steril. 1992 Jul;23(7):447–458. [PubMed]
15. Edwards RG, Steptoe PC., Control of human ovulation, fertilization and implantation. Proc R Soc Med. 1974 September; 67(9): 932–936.
16. Adami H.O., Hunter D., Trichopoulos D., Textbook of cancer epidemiology, Oxford University press, 2002
17. Berek J.S., Hacker N.F. Practical gynaecologic oncology.4Th edition. Lippincott Williams&Wilkins, Philadelphia, 2005
18. Boyle P., Levin B., World Cancer report 2008. IARC Press, Lyon, France, 2008
19. Chen T, Jansen L, Gondos A, Emrich K, Holleczek B, Katalinic A, Luttmann S, Meyer M, Brenner H, Survival of ovarian cancer patients in Germany in the early 21st century: a period analysis by age, histology, laterality, and stage, Eur J Cancer Prev, 2012.
20. Centrul de Calcul, Statistică Sanitară şi Documentare Medicală: Registrul Naţional de Cancer, MSP, Bucureşti, 2003.
21. Cindy Quinton Gladstone, Screening for ovarian cancer, Toronoto 1994; 870-877
22. National Cancer Institute of Canada: Canadian Cancer Statistics 1993, Toronto, Canada, 1993:14.
23. Suteu O. Epidemiologia cancerului. In Nagy Viorica(ed) Principii de cancerologie generală. Curs pentru studenți. Editura Medicală Universitară ”Iuliu Hațeganu” Cluj-Napoca 2007; 1-24.
24. Primic – Zakelj M. Cancer Epidemiology. In Scrijvers D., Senn H.J., Mellstedt H., Zakotnk B.(eds). European Society of Medical Oncology Handbook of Cancer Prevention. Informa Healthcare 2008; 1 – 28.
25. Miron L. Epidemiologia cancerelor umane. In Miron L.(ed). Oncologia general. Ed. Egal, Bacău 2000; 16 – 26.
26. Ferlay J., Autier P., Boniol M., Heanue M., Colombet M., Boyle P. Estimates of cancer incidence and mortality in Europe in 2006. Annals of Oncology 2007; 581-592.
27. Mioara Calipsoana Matei, Teză de doctorat UMF Iași 2011
28. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists. Hereditary Breast and Ovarian Cancer, No.103, April 2009.
29. Nancie Petrucelli, Mary B Daly, Julie O Bars Culver, Gerald L Feldman. BRCA1 and BRCA2 Hereditary Breast/Ovarian Cancer. Gene Reviews, 2007. www.ncbi.nlm.nih.gov. ReferenceType: Internet Communication.

30. BRCA1 Gene, BRCA2 Gene. Gene cards. www.genecards.org. Reference Type: Internet Communication.
31. Ewald IP, Ribeiro Izetti PL, Plamero EI, Cossio SL, Giuliani R, Ashton-Prolla P. Genomic rearrangements in BRCA1 and BRCA 2: a literature review. In Genetics and Molecular Biology, 2009, 32, 3: 437-446.
32. . OMIM (Online Mendelian Inheritance in Man). Breast Cancer 1 Gene (BRCA1), Breast cancer 2 Gene (BRCA2). http://www.ncbi.nlm.nih.gov. Reference Type: Internet Communication.
33. Lin HR, Ting NSY, Qin J, Lee WH. M-Phase- specific phosphorylation of BRCA2 by Polo-like kinase 1 correlates with the dissociation of the BRCA2-P/CAF complex. In The Journal of Biological Chemistry, 2003, 278,13: 35979- 35978.
34. Welcsh PL, King MC. BRCA1 and BRCA2 and the genetics of breast and ovarian cancer. In Human Molecular genetics, 2001, 10 (7): 705-713.
35. Purdie DM, Bain CJ, Siskind V, Webb PM, Green AC. Ovulation and risk of epithelial ovarian cancer. Int J Cancer. 2003; 104(2):228-32.
36. Risch HA. Hormonal etiology of epithelial ovarian cancer, with hypothesis concerning the role of androgens and progesterone. J Natl Cancer Inst. 1998; 90(23):1774-86.
37. Nagle C.M., Bain C.J., Green A.C., Webb P.M. The influence of reproductive and hormonal factors on ovarian cancer survival. Int.J. Gynecol. Cancer 2008; 18(3): 407 – 413
38. Wallin A., Orsini N., Wolk A., Red and processed meat consumption and risk of ovarian cancer: a dose-response meta-analysis of prospective studies, Br J Cancer, 2011, 104(7):1196-201.
39. Chandran U., Bandera E.V., Williams-King M.G., Paddock L.E., Rodriguez-Rodriguez L., Lu S.E., Faulkner S., Pulick K., Olson S.H., Healthy eating index and ovarian cancer risk, Epub, 2011, 22(4):563-71.
40. M, Hunt J., Wei M., Buys S., Gren L., Lee Y.C., Tobacco, alcohol, body mass index, physical activity, and the risk of head and neck cancer in the prostate, lung, colorectal, and ovarian (PLCO) cohort, Head Neck, 2012.
41. Reid A., de Klerk N., Musk A.W., Does exposure to asbestos cause ovarian cancer? A systematic literature review and meta-analysis, Cancer Epidemiol Biomarkers Prev, 2001, 20(7):1287-95.
42. David C. Actualităţi în diagnosticul şi tratamentul maselor anexiale. Teză de doctorat. UMF Iaşi, 2008.
43. Mok S.C., Kwong J., Welch W.R. et al. Etiology and pathogenesis of epithelial ovarian cancer. Dis. Markers 2007; 23: 367 – 376.
44. Kajihara H., Yamada Y., Shigetomi H., Higashiura Y., Kobayashi H., The Dichotomy in the Histogenesis of Endometriosis-associated Ovarian Cancer: Clear Cell-type Versus Endometrioid-type Adenocarcinoma, Int J Gynecol Pathol, 2012, 31(4):304-12.
45. Ness R.B., Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. J Natl Cancer Inst. 1999; 91(17):1459-67.
46. Braem M.G., Onland-Moret N.C., Schouten L.J., Tjønneland A., Hansen L., Dahm C.C., Overvad K., Coffee and tea consumption and the risk of ovarian cancer: a

prospective cohort study and updated meta-analysis, Am J Clin Nutr, 2012, 95(5):1172-81.
47. Fleming J.S., Beaugie C.R., Haviv I., Chenevix – Trench G., Tan O.L., Incessant ovulation, inflammation and epithelial ovarian carcinogenesis: revisiting old hypotheses. Mol. Cell. Endocrinol.2006; 247(1 – 2): 4 – 21.
48. Landen Jr. C.N., Birrer :J., Sood A.K. Early events in the pathogenesis of epithelial ovarian cancer. J. Clin. Oncol.2008; 26: 995 – 1005.
49. Kurman R.J., Shih Ie. M. Pathogenesis of ovarian cancer: lessons from morphology and molecular biology and their clinical implications. Int J Gynecol Pathol. 2008 Apr;27(2):151-60
50. Hogg T., Friedlander M., Biology of epithelial ovarian cancer: implications for screening women at high genetic risk. J. Clin. Oncol. 2004; 22(7): 1315 – 1327.
51. Holschneider C.H., Berek J.S., Ovarian cancer: epidemiology, biology and prognostic factors. Semin. Surg. Oncol.2009; 19: 3 – 10.
52. Jazaeri A.A., Molecular profiles of hereditary epithelial ovarian cancers and their implications for the biology of disease. Molec. Oncol. 2009; 2: 10.1016/j.molonc.2009.01.001.
53. UICC-TNM – World Health Organisation. Classification of Malignant Tumors, Geneva 1973
54. Kosary, Carol L., "Chapter 16: Cancers of the Ovary", in Ries, LAG; Young, JL; Keel, GE et al., SEER Survival Monograph: Cancer Survival Among Adults: US SEER Program, 1988-2001, Patient and Tumor Characteristics, SEER Program, NIH Pub. No. 07-6215, Bethesda, (2007) : National Cancer Institute, pp. 133–144.
55. Xiu Y, Molecular and Cellular Mechanisms of Antibody Activity, ISBN978 – 1 – 4614 – 7107 – 3(eBook), Springer New York Heidelberg Dordrecht London, 159 – 162
56. Goff B.A., Mandel L.S., Drescher C.W., et al. – Development of an ovarian cancer symptom index: possibilities for earlier detection. Cacer 2007; 109(2): 221-227
57. Bălăceanu Alice, Rolul medicului de familie în screening-ul cancerului ovarian, Practica Medicală – Vol. VI, Nr. 4(24), 2011
58. Dobreanu Minodora, Aspecte metabolice în proliferări maligne-markeri tumorali. Biochimie Clinică - Implicaţii practice 2006, 257-276.
59. Henry, John Bernard. Immunoassay and Related Techniques; Tumor markers. In Clinical Diagnosis and Management by Laboratory Methods, 1998, 283-297.
60. Lothar Thomas, Petra Stieber, Tumor markers. Malignant diseases, In Clinical Diagnostics-Use and Assessment of clinical Laboratory Results. Th-Books Verlagsgesellschaft mbH, Frankfurt/Main germany, 1Ed, 1998,936-940.
61. Scambia G., Benedetti Panici P., Baiocchi G., Perone L., Di Roberto P., Mancuso S.Ca 15-3 serum levels in ovarian cancer Oncology, 1988; 45(3):263-7.
62. Bouchard D, Morisset D, Bourbonnais Y, et al. Proteins With Whey Acidic-Protein Motifs and Cancer. *Lancet Oncol*, 2006, 7(2):167-74.
63. Hellström I, Raycraft J, Hayden-Ledbetter M, et al. The HE4 (WFDC2) Protein Is a Biomarker for Ovarian Carcinoma. *Cancer Res*, 2003, 63(13):3695-700.

64. Laboratory Corporation of America. Directory of Services and Interpretive Guide. Human Epididymis Protein 4. www.labcorp.com 2015. Ref Type: Internet Communication.

65. Drapkin R, von Horsten HH, Lin Y, et al. Human Endometrioid Ovarian Carcinomas. *Cancer Res*, 2005, 65(6):2162-9.
66. Huhtinen K, Suvitie P, Hiissa J, et al. Serum HE4 Concentrations Differentiates Malignant Ovarian Tumours From Ovarian Endometriotic Cysts. *Br J Cancer*, 2009, 21:100(8):1315-9.
67. Moore RG, McMeekin DS, Brown AK, et al. A Novel Multiple Marker Bioassay Utilizing HE4 and CA125 for the Prediction of Ovarian Cancer In Patients With a Pelvic Mass. In *Gynecol Oncol*, 2009, 112(1):40-6.
68. Moore RG, Jabre-Raughley M, Brown AK, Robison KM, et al. Comparison of a novel multiple marker assay vs the Risk of Malignancy Index for the prediction of epithelial ovarian cancer in patients with a pelvic mass. *Am J Obstet Gynecol*. 2010.
69. Ruggeri G, Bandiera E, Zanotti L, et al. HE4 and epithelial ovarian cancer: Comparison and clinical evaluation of two immunoassays and a combination algorithm. In *Clin Chim Acta*. 2011;412(15-16):1447-53. Epub 2011 Apr 30.
70. Jinping Li, Sean C Dowdy, Tracy Tipton, Karl C Podratz, Wei-Guo Lu, Xing Xie, Shi-Wen Jiang. HE4 as a Biomarker for Ovarian and Endometrial Cancer Management: HE4 Application for Endometrial Cancer. www.medscape.com.
71. Laborator Synevo. Referinţele specifice tehnologiei de lucru utilizate 2015. Ref Type: Catalog.
72. Ferraro S, Schiumarini D, Panteghini M. Human epididymis protein 4: factors of variation. *Clin Chim Acta*. 2015 Jan 1;438:171-7.
73. Kappelmayer J, Antal-Szalmás P, Nagy B Jr. Human epididymis protein 4 (HE4) in laboratory medicine and an algorithm in renal disorders. *Clin Chim Acta*. 2015 Jan 1;438:35-42.

74. Brătilă Elvira ,Coroleucă C.B., Coroleucă C.A. , Comandașu Diana-Elena , Mehedințu Claudia , Bohîlțea Roxana, Cîrstoiu Monica, Mitran M. , Berceanu C. – Rolul examinarii Doppler în evaluarea patologiei ovariene- Ginecologia Anul IV Nr.144/2016 pag.46-54)
75. Ameye L., Timmerman D., Valentin L., Paladini D., Zhang J., Van Holsbeke C., Lissoni A.A., Saveli L., Tesla A.C., Amant F., Van Huffel S., Bourne T., Clinically oriented three-step strategy to the assessment of adnexal pathology. Ultrasound Obstet Gynecol 2012;40:582-591.
76. Timmerman D., Ameye L., Fischerova D., Epstein E., Melis G.B., Guerriero S., Van Holsbeke C., Saveli L., Fruscio R., Lissoni A.A., Tesla A.C., Veldman J., Vergote I., Van Huffel S., Bourne T., Valentin L., Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group. BMJ 2010; 341: 6939.
77. Jacobs I., Oram D., Fairbanks J., Turner J., Frost C., Grudzinskas J.G., A risk of malignancy index incorporating CA-125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br. J. Obstet Gynaecol 1990; 97: 922-929.

78. Timmerman D., Tesla A.C., Bourne T., Ferrazzzi E., Ameye L., Konstantinovic M.L., Van Calsler B., Collins W.P., Vergote I., Van Huffel S., Valentin L., International Ovarian Tumor Analysis Group. Logistic regression model to distinguish between the benign and malignant adnexal mass before surgery: a multicenter study by the International ovarian Tumor Analysis Group. J. Clin. Oncol. 2005; 23: 8794-8801.

79. Kappelmayer J, Antal-Szalmás P, Nagy B Jr. Human epididymis protein 4 (HE4) in laboratory medicine and an algorithm in renal disorders. *Clin Chim Acta.* 2015 Jan 1;438:35-42.

80. Brătilă Elvira ,Coroleucă C.B., Coroleucă C.A. , Comandașu Diana-Elena , Mehedințu Claudia , Bohîlțea Roxana, Cîrstoiu Monica, Mitran M. , Berceanu C. – Rolul examinarii Doppler în evaluarea patologiei ovariene- Ginecologia Anul IV Nr.144/2016 pag.46-54)

81. Ameye L., Timmerman D., Valentin L., Paladini D., Zhang J., Van Holsbeke C., Lissoni A.A., Saveli L., Tesla A.C., Amant F., Van Huffel S., Bourne T., Clinically oriented three-step strategy to the assessment of adnexal pathology. Ultrasound Obstet Gynecol 2012;40:582-591.

82. Timmerman D., Ameye L., Fischerova D., Epstein E., Melis G.B., Guerriero S., Van Holsbeke C., Saveli L., Fruscio R., Lissoni A.A., Tesla A.C., Veldman J., Vergote I., Van Huffel S., Bourne T., Valentin L., Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group. BMJ 2010; 341: 6939.

83. Jacobs I., Oram D., Fairbanks J., Turner J., Frost C., Grudzinskas J.G., A risk of malignancy index incorporating CA-125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br. J. Obstet Gynaecol 1990; 97: 922-929.

84. Timmerman D., Tesla A.C., Bourne T., Ferrazzzi E., Ameye L., Konstantinovic M.L., Van Calsler B., Collins W.P., Vergote I., Van Huffel S., Valentin L., International Ovarian Tumor Analysis Group. Logistic regression model to distinguish between the benign and malignant adnexal mass before surgery: a multicenter study by the International ovarian Tumor Analysis Group. J. Clin. Oncol. 2005; 23: 8794-8801.

85. Kurjack A., Fleischer A.C., Doppler Ultrasound in Gynecology. Partenon Publishing Group, 1998, New York.

86. Joshi M., Ganesan K., Munshi H., Ganesan S., Lawande A., 2009. Ultrasound of adnexal masses. Seminars in ultrasound, CT and MRI, 29(2), pp 72-97.

87. Timor- Trilsch I.E., Lerner J.P., Monteagudo A. et. al: Transvaginal ultrasonographic characterization of ovarian masses by means of color flowdirected Doppler measurements and a morphologic scoring sistem. Am. J. Obstet Gynecol 169-909-913,1993.

88. Bhatt S., Dogra V., Doppler imagine of the uterus and anexae. Ultrasound. Clin. 1: 201-221, 2006.

89. Shah D., Shah S., Parikh J., Bhatt C., Vaishnav K., Balla D., (2012). Doppler Ultrasound: a good and reliable predictor of ovarian malignancy. J. Obstet. Gynecol. India, 63(3), pp.186-189.

90. Funt SA, Hann L.E. – Detection and characterization of adnexal masses. Radiol Clin North Am. 2002; 40(3): 591-608 15. Komatsu T., Konishi I., Madai M., et al. – Adnexal masses: transvaginal US and gadolinium-enhanced MR imaging assessment of intratumoral structure. Radiology 1996; 198(1): 109-115)
91. Piver M.S., Ovarian Malignancies: Diagnostic and therapeutic advances. Churchill Livingstone, Edinborough, 1987. ISBN:0443033684, pp 245-297
92. Dargent D., Principles and practice of gynecologic oncology. Lippincot Williams&Wilkins, 1992; 269-289; 381-463
93. Dorval T., Cytokines and Cytokine Receptors. Physiology and Pathological Disorders. Taylor&Francis e-Library, 2005 ISBN 0-203-30513-2.
94. Di SaiaJ.Ph., Creasman W.T., Clinical Gynecologic Oncology, 8th. Edition, Philadelphia, PA: Elsevier/Saunders, c2012, ISBN 9780323074193
95. Nygel Acheson, Luesley D., Gynaecological Oncology, MRCOG 1988, ISBN 978-1-906985-21-9
96. Hoskins W.J.,, Carlos A. Perez, C. A., Young R.C., Barakat R., Markman M., Randall M.,Gynecologic Oncology Lippincott Williams&Wilkins, 2005, ISBN 0-7817-4689-2.
97. Gershenson DM. Update on malignant ovarian germ cell tumors. Cancer 1993; 71: 1581–1590.
98. Rose P.G., Nerenstone S, Brady M.F. et al. Secondary surgical cytoreduction for advanced ovarian carcinoma. N Engl J Med 2004; 351: 2489–2497.
99. Armstrong DK, Bundy B, Wenzel L et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 2006; 354: 34–43. 2. Bell J,
100. Williams SD, Blessing JA, Hatch KHomesley HD. Chemotherapy of advanced ovarian dysgerminoma: trials of the Gynecologic Oncology Group. J Clin Oncol 1991; 9: 1950–1955. Annals of Oncology 20 (Supplement 4): iv24-iv26, 2009 doi:10.1093/annonc/mdp118
101. Rustin GJ, Bast RC, Jr., Kelloff GJ et al. Use of CA-125 in clinical trial evaluation of new therapeutic drugs for ovarian cancer. Clin Cancer Res 2004; 10:3919–3926.
102. Rustin GJS, Nelstrop AE, McClean P et al. Defining response of ovarian carcinoma to initial chemotherapy according to serum CA 125. J Clin Oncol 1996; 14: 1545–1551.
103. Trimbos JB, Parmar M, Vergote I et al. International Collaborative Ovarian Neoplasm trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant Cancerul ovarian 29 chemotherapy in patients with early-stage ovarian carcinoma. J Natl Cancer Inst 2003; 95: 105–112.
104. Markman M, Liu PY, Wilczynski S et al. Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy: a Southwest Oncology Group and Gynecologic Oncology Group trial. J Clin Oncol 2003; 21: 2460–2465. 13. McGuire WP, Hoskins

105. McGuire WP, Hoskins WJ, Brady ME et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IVovarian cancer. N Engl J Med 1996; 334: 1–6.
106. Ozols RF, Bundy BN, Greer BE et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: A Gynecologic Oncology Group Study. J Clin Oncol 2003; 21:3194–3200.
107. Van der Burg ME, van Lent M, Buyse M et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. N Engl J Med 1995; 332:629–634.
108. Vergote I, De Brabanter J, Fyles A et al. Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma. Lancet 2001; 357: 176–182.
109. Kavanagh JJ, Pecorelli S, Benedet JL et al. Cancer of the ovary. In Pecorelli S, Ngan HYS, Hacker NF (eds): Staging Classifications and Clinical Practice.Guidelines for Gynaecological Cancers, 3rd edition. International Federation of Gynecology and Obstetrics 2000; 95–121; http://www.figo.org/docs/ staging_booklet.pdf.
110. Guppy A.E., Nathan P.D., Rustin G.J.S. Epithelial ovarian cancer: a review of current management. *Clin. Oncol.* 2005; 17 : 399-411.
111. Roett M.A., Evans P. – Ovarian cancer: An overview. Am Fam Physician 2009; 80(6):609- 616).
112. Alsop K, Fereday S, Meldrum C et al. BRCA Mutation frequency and pattern treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol 2012; 30: 2654–2663.
113. Varlas A., Bălăceanu A., Varlas V. – Neoplasm ovarian stadium IV. Infecţie urinară joasă. Gastrită hiperemică. Infomedica 2001, 11: 45-47 5.
114. Hamilton W., Peters T.J., Bankhead C., Sharp D. – Risk of ovarian cancer in women with symptoms in primary care: population based case-control study. BMJ 2009; 339; b2719 doi:10.1136/bmj.b2719 6.
115. Dobreanu, Minodora. Aspecte metabolice în proliferări maligne-markeri tumorali. În Biochimie clinică-Implicaţii practice 2006, 257-276.
116. Henry, John Bernard. Immunoassay and Related Techniques; Tumor markers. In Clinical Diagnosis andVan der Burg ME, van Lent M, Buyse M et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. N Engl J Med 1995; 332:629–634.
117. Vergote I, De Brabanter J, Fyles A et al. Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma. Lancet 2001; 357: 176–182.
118. Kavanagh JJ, Pecorelli S, Benedet JL et al. Cancer of the ovary. In Pecorelli S, Ngan HYS, Hacker NF (eds): Staging Classifications and Clinical Practice.Guidelines for Gynaecological Cancers, 3rd edition. International

Federation of Gynecology and Obstetrics 2000; 95–121; http://www.figo.org/docs/staging_booklet.pdf.
119. Guppy A.E., Nathan P.D., Rustin G.J.S. Epithelial ovarian cancer: a review of current management. *Clin. Oncol.* 2005; 17 : 399-411.
120. Roett M.A., Evans P. – Ovarian cancer: An overview. Am Fam Physician 2009; 80(6):609- 616).
121. Alsop K, Fereday S, Meldrum C et al. BRCA Mutation frequency and pattern treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol 2012; 30: 2654–2663.
122. Varlas A., Bălăceanu A., Varlas V. – Neoplasm ovarian stadium IV. Infecţie urinară joasă. Gastrită hiperemică. Infomedica 2001, 11: 45-47 5.
123. Hamilton W., Peters T.J., Bankhead C., Sharp D. – Risk of ovarian cancer in women with symptoms in primary care: population based case-control study. BMJ 2009; 339; b2719 doi:10.1136/bmj.b2719 6.
124. Dobreanu, Minodora. Aspecte metabolice în proliferări maligne-markeri tumorali. În Biochimie clinică-Implicaţii practice 2006, 257-276.
125. Henry, John Bernard. Immunoassay and Related Techniques; Tumor markers. In Clinical Diagnosis and Management by Laboratory Methods, 1998, 283-297.
126. Laboratory Corporation of America. Directory of Services and Interpretive Guide. www.labcorp.com 2010. Ref Type: Internet Communication.
127. The National Academy of Clinical Biochemistry. Practice Guidelines and Recommendations for Use of Tumor Markers in the Clinic (Laboratory Medicine Practice Guidelines), vol. 15, 2002: 17-18.
128. Wallach Jaques. Markeri tumorali. în interpretarea testelor de diagnostic, 2001, 88-1203.
129. Parkinson CA, Hatcher HM, Ajithkumar TV. Management of malignant ovarian germ cell tumors. Obstet Gynecol Surv 2011; 66(8): 507–514.
130. Hye-yon Cho and Min Sun Kyung: Serum CA19-9 as a Predictor of Malignancy in Primary Ovarian Mucinous Tumors: A Matched Case-Control Study. e-mail rk.ro.myllah@leefsm published online 2014 Joule 30.doi:10.12659/MSM.890954
131. Scambia G., Benedetti Panici P., Baiocchi G., Perone L., Di Roberto P., Mancuso S. Ca 15-3 serum levels in ovarian cancer.Oncology1988;45(3):263-7
132. Colombo N., Peiretti M., Castiglione M. – Non-epithelial ovarian cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. Ann Oncol 2010, 21(Supp5): V31-V36
133. Clarke-Pearson D.L. – Screening for ovarian cancer. NEJM 2009; 361:170-177
134. Hamilton W. – Cancer diagnosis in primary care. Br J Gen Pract 2010; 60(571): 121-128
135. Menon U., Gentry-Maharaj A., Hallett R., et al. – Sensitivity and specifi city of multimodal and ultrasound screening for ovarian cancer, and stage distribution of trial detected cancer: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) Lancet Oncol 2009;10:327-340
136. Shimizu Y, Kamoi S, Amada S et al. Toward the development of a universal grading system for ovarian epithelial carcinoma: testing of a proposed system in a

series of 461 patients with uniform treatment and follow-up. Cancer 1998; 82: 893–901.
137. Bodurka DC, Deavers MT, Tian C et al. Reclassification of serous ovarian carcinoma by a 2-tier system: a Gynecologic Oncology Group Study. Cancer 2012; 118: 3087–3094.
138. Farias FR. Gynecologic cancers. În: Casciato DA, ed. *Manual of clinical oncology*. Philadelphia: Lippincott, Williams & Wilkins, 2000:238-265.
139. Robin LH, Wittekind Ch. Tumorile genitale feminine. În: UICC. *TNM – Clasificarea tumorilor maligne.* 6th ed. New-York: Wiley-Liss, 2002 Versiune română, Editura Ministerului Sănătăţii 2005:165-170.
140. Sonda Y, Springgs D. Ovarian cancer. În: Chang AE, ed. *Oncology - an evidence based approach*. New York: Springer, 2006:903- 927.
141. DuBois A, Harter P. The role of surgery in advanced and recurrent ovarian cancer. *Ann Oncol* 2006; 17(suppl.10):x235-x240.
142. Karlan BY, Markman MA, Eifel PJ. Ovarian cancer, fallopian tube carcinoma and peritoneal carcinoma. În: DeVita VT Jr., Hellman S, Rosenberg SA, eds. *Cancer: principles and practice of oncology*. 7th ed. Philadelphia: Lippincott, Williams & Wilkins, 2005:1364-1398.
143. Covens AL. Critique of surgical cytoreduction in advanced ovarian cancer. *Gynecol Oncol* 2000:269-274
144. Vermorken JB. Intraperitoneal chemotherapy in advanced ovarian cancer: recognition at last. *Ann Oncol* 2006;17(suppl.10):x241-x246.
145. Van der Burg ME, Van Lent M, Buyse M, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecologic Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med* 1995;332:629.
146. Stewart LA, for the Advanced Ovarian Cancer Trialists Group (AOCTG). Chemotherapy in advanced ovarian cancer: an overview of randomized clinical trials. *BMJ* 1991;303:884.
147. Harper P. Where are we now in ovarian cancer? În: *Proceeding Book of The 15th International Congress on Anti-Cancer Treatament*, Paris, Franţa, 2004:5157.
148. Neijt JP, Ten Bokkel Huinink WW, Van der Burg ME, et al. Long-term survival in ovarian cancer. *Eur J Cancer* 1991;27:1367.
149. Vermorken JB. The role of intraperitoneal chemotherapy in epithelial ovarian cancer. *Ann Oncol* 2000;10(suppl.1):26-32.
150. Sârbu V., Măciuceanu B., Mihaela Pârvu, Mateescu C. Chimiohipertermia intraperitoneală prin lavaj în circuit închis la bolnavii cu neoplazii intraabdominale. *International Conference of Society for Medical Inovation, Sinaia, 7 – 9 oct. 2009. Volum rezumate pag.65*
151. Unc O.D., Sârbu V., Iordache I. Preliminary results for intraperitoneal chemotherapy in ovarian cancer. *Zilele medicale bârlădene, Nr.108/109, 2007*

152. Markman M, Walker JL. Intraperitoneal chemotherapy of ovarian cancer: a review, with a focus on practical aspects of treatment. *J Clin. Oncol* 2006;24(6):988-994.
153. Gore M. Intraperitoneal chemotherapy in ovarian cancer remains experimental. *J Clin Oncol* 2006;24(18):4528-4530.
154. Chan, JK, Kapp, DS, Shin, JY, et al. Influence of the Gynecologic Oncologist on the Survival of Ovarian Cancer Patients. Obstet Gynecol 2007; 109:1342
155. Achimaș Cadariu P., Bacalbașa N., Blidaru A. Sub redacția Nicolae Suciu.Tratat de chirurgie extrapelvină a cancerului de ovar. *Editura Academiei Române, 2017, pag.151 – 171*

ANEXA1
PERSONAL OBSERVATION FILE
Date of study entry
Name surname
CNP
Home
Heredocolateral history
- Neoplastic pathology in the family
- Breast cancer in the family
- Gynecological Pathology in the Family
- Neoplastic gynecological pathology in the family
Personal physiological antecedents
- Menarche
- Number of tasks
- Breastfeeding (number and duration)
- Menopause
- Contraceptive medication
- Fertility medication
- Hormone replacement medication
Personal pathological history
- Infectious diseases
- Chronic diseases
- Breast Pathology
- Gynecological Pathology
General clinical examination
Clinical genital exam
Dosage of tumor markers Abdominal
- pelvic ultrasound
Transvaginal ultrasound
CT
MRI
Puncture tumor formation
Ex. intraoperatively histopathologically
Ex. histopathologically to paraffin
immunohistochemistry
Therapeutic decision
Surgery reinterventions chemotherapy
- Systemic
- Intraperitoneal Control
- Control date –
Ex. general and genital clinic
- Ex. ultrasound
- Dosage of tumor markers
- CT, MRI
- The therapeutic decision