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Research Article

# Ovarian cancer experience from a Romanian regional center: preliminary results

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**Abstract.** Objective: Epithelial ovarian cancer represents the most frequent cause of death among women with gynecological malignancies, primarily due to the fact that symptoms generally occur when an advanced stage of disease has been reached, but also due to misunderstanding of the general standard of care and therapeutic approach. The aim of this study was to present the demographic, pathological, clinical features (symptoms and diagnosis method) and treatment protocol and outcome of patients with ovarian cancer. Material and Methods: From January 2007 to December 2007, 251 patients had been diagnosed and treated for ovarian cancer within the Oncology Institute "Prof. Dr. Ion Chiricuta" Cluj-Napoca. Of these, 89 patients with written consent for research studies were included. A retrospective study was performed with the data collected from patient files. Results: The median age at diagnosis was 52 years, with approximately 80% of patients having a good performance status. Of the paraclinical methods used for initial diagnosis, a clinical pelvic examination by a gynecologist and a pelvic ultrasound were most commonly used. After treatment follow-up included ultrasound examinations in more than 90% of patients, CA 125 in 70% of cases, and CT scans in 60%. Only 4,5% of patients did not report for follow-up in our center. The majority of cases (more than 85%) were epithelial ovarian tumors, with a total of approximately 70% grade 2 and 3. More than 50% of patients were diagnosed in stages III and IV of disease. Conclusion: This report provides a great deal of information about basic patient characteristics, diagnosis and follow-up tools, surgical conduct and treatment results and points out areas where standardization and improvement of care is required..

**Key Words:** Ovarian cancer, retrospective, epidemiology, diagnosis.



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## Introduction

Epithelial ovarian cancer represents the most frequent cause of death among women with gynecological malignancies, primarily due to the fact that symptoms generally occur when an advanced stage of disease has been reached, but also due to misunderstanding of the general standard of care and therapeutic approach. Worldwide, approximately 200.000 women are diagnosed with this pathology and more than half will die in spite of new surgical and chemotherapeutic protocols available (Schorge *et al* 2008). More than 90% of cases are epithelial tumors, including borderline masses. Epithelial ovarian cancer is unique compared to other solid malignant tumors, in that it originates at the surface epithelium rather than the parenchimatous area of the organ. The rest of the 10% originate either in the germinative ovarian cells or are stromal tumors (Dutta *et al* 2010). The clinical onset of the disease is non-specific and allows for confusion with many benign diseases, especially digestive and urological. Optimal debulking surgery remains the only effective treatment with which long-term disease free intervals and cure can be achieved and remains the most important survival prognostic factor for ovarian cancer. While at some point a residual disease less than 1 cm, even 2 cm was accepted as optimal surgical treatment, currently, the standard of care requires that no microscopic disease is present after cytoreductive surgical treatment. No gross residual disease is associated with improved overall survival, and radical surgery is effective for achieving this (Chang *et al* 2012).

Several epidemiological studies on ovarian cancer exist, generally showing similar results, while retrospective reports have almost consistently demonstrated that age, performance status, histological grade and subtype, clinical stage and size of residual disease are independent prognostic factors (Skírnisdóttir *et al* 2007). Furthermore, prospective randomized phase III trials have showed that platinum-based chemotherapy, especially when combined with paclitaxel, was associated with a higher response rate and median survival compared with other regimens (Piccart *et al* 2000).

The global risk for a patient to develop ovarian cancer throughout their lifetime is 1,8% (Dutta *et al* 2010). There is no effective screening method and the clinical presentation is scarce and non-specific. Consequently, more than 75% of cases are diagnosed in an advanced stage (FIGO III/IV). Despite some improvement of median survival due to the development of primary surgical procedures and chemotherapy protocols, the percentage is relatively constant around 30%. Alternatively, women diagnosed in the first stages of disease will not only undergo much less aggressive surgery, but will also have a 90% 5-year survival rate and better quality of life. Unfortunately, the high percentage of patients diagnosed in advanced stages

underlines the lack of efficiency of pelvic examination (which is notably inaccurate in detecting subtle changes in ovarian size and morphology, particularly in postmenopausal women) and imaging techniques in confirming incipient disease. This calls for a standardization not only of treatment but also diagnostic protocols used, especially in patients at high risk for developing this disease. Biochemical diagnostic tools (CA-125 and the ROMA/ROCA score) have emerged as the investigations with the highest sensitivity and specificity used to refer patients at high risk to further investigation. The diagnostic protocol requires using an imaging technique to complete pelvic examination and characterization of pelvic masses (Transvaginal ultrasound, gray-scale or contrast enhanced, CT/MRI).

More recently, focus is shifting on the importance of treatment center and surgical team in the outcome of ovarian cancer care, with some countries developing referral guidelines that recommend that ovarian cancer patients be treated in specialized centers because treatment in such hospitals has been shown to result in better survival. Furthermore, general gynecologists with a special interest in gynecologic oncology, who operate on all patients with ovarian cancer in their clinic and work with gynecologic oncologists from regional specialized centers, might also provide adequate care to ovarian cancer patients (Vernooij *et al* 2008).

Epithelial ovarian cancer in Romania has not been adequately studied (except for prospective clinical trials) probably because of the lack of electronic medical records and a central regsitry of patient data, making them practically inaccessible to researchers. The Oncology Institute "Prof. Dr. Ion Chiricuta" holds a consistent archive of patient data, cases that have been referred to, diagnosed or treated in this hospital, representing an invaluable source of information.

The aim of this study was to present the demographic, pathological, clinical features (symptoms and diagnosis method) and treatment protocol and outcome of patients with ovarian cancer.

## Materials and method

From January 2007 to December 2007, 251 patients had been diagnosed and treated for ovarian cancer within the Oncology Institute "Prof. Dr. Ion Chiricuta" Cluj-Napoca. The cancer diagnosis was histologically documented by expert pathologists and cytopathologists from referral centers with experience in gynecological malignancies. From the patient base, only those files with written consent for participation in research studies were analyzed, thus remaining 89 eligible cases for statistical analisys. These files were analyzed within the archive of the Oncology Institute "Prof. Dr. Ion Chiricuta".

Demographic data consisted of: source environment, age, parity, menarche and menopause onset age, performance index at diagnosis and associated pathology. For every patient studied, we documented the diagnosis protocol used (clinical and/or imagistical methods) for initial diagnosis and also for follow up of patients that were continuously referred to our center after therapy. We made a record of main clinical symptoms upon referral for all patients included in our study. Tumor characterization included histological subtype, tumour grading and stage at diagnosis. Surgical reports were collected for all the patients and the type of operation and extent of residual disease were recorded, as well as the chemotherapy protocol administered and response obtained.

This patient base is part of an extensive 5-year retrospective study underway at our center, with prognostic correlations to be published with our final results.

The statistical processing of data was performed using Medcalc Software version 12.7. Quantitative variables were tested for normality of distribution using Kolmogorov-Smirnov test. Non-normally distributed variables were described using the median and range. Nominal and ordinal variables were characterized by frequency and percentage.

## Results

The basic patient characteristics are illustrated in Table 1. The median age at diagnosis was 52 years, with approximately 80% of patients having a good performance status. Of the most common associated pathologies found, obesity and hypertension were among the most frequent ones (found in 12% and 32% of patients respectively).

Table 1. Basic patient characteristics

| | Median | Range |
|---|---|---|
| **Age** | 52.4 | 22-77 |
| **Age at menarche** | 13.7 | |
| **Age at menopause** | 46.4 | |
| | **N** | **%** |
| **Source environment** | | |
| **Urban** | 46 | 51.7 |
| **Rural** | 43 | 48.3 |
| **Parity** | | |
| **Nuliparous** | 10 | 11.3 |
| **Multiparous** | 78 | 88.7 |
| **PS (performance status)** | | |
| **0** | 36 | 40.4 |
| **1** | 38 | 42.6 |
| **2** | 14 | 15.7 |
| **3** | 1 | 1.1 |
| **Associated pathology** | | |
| **Obesity** | 11 | 12.3 |
| **Hypertension** | 29 | 32.6 |
| **Diabetes mellitus** | 8 | 8.9 |
| **Hyperlipidemia** | 6 | 6.7 |

Of the paraclinical methods used for initial diagnosis, a clinical pelvic examination by a gynecologist and a pelvic ultrasound were most commonly used, with over 50% of patients undergoing these examinations. However, biochemical evaluation (CA 125) was only used in 27% of patients and in approximately one third of patients diagnosis was unexpected, during surgery for another pathology (suspected benign gynecologic tumors or acute surgical pathology).

After treatment follow-up included ultrasound examinations in more than 90% of patients, CA 125 in 70% of cases, and CT

scans in 60%. Only 4,5% of patients did not report for follow-up in our center.

Tabel 2. Initial and follow-up diagnosis methods

| | N | % |
|---|---|---|
| **Initial diagnosis method** | | |
| **Pelvic exam** | 50 | 56.1 |
| **Ultrasound** | 51 | 57.3 |
| **CA 125** | 24 | 26.9 |
| **Incidental** | 24 | 26.9 |
| **Follow-up** | | |
| **Ultrasound** | 82 | 92.1 |
| **CT scan** | 56 | 62.9 |
| **CA 125** | 64 | 71.9 |
| **Basic lab work-up** | 38 | 42.6 |
| **No follow-up** | 4 | 4.5 |

Clinical onset was scarce and non-specific, abdominal pain and discomfort being the reason for seeking medical help in almost 70% of patients. Gynecologic symptoms (vaginal bleeding) were only found in 12% of cases, the rest presenting with digestive or urinary symptomatology, or for weight loss and fatigue.

Table 3. Clinical characteristics of patients

| | N | % |
|---|---|---|
| **Main clinical symptoms** | | |
| **Pain and abdominal discomfort** | 60 | 67.4 |
| **Digestive symptoms (nausea, vomiting, loss of appetite)** | 16 | 18 |
| **Weight loss** | 8 | 9 |
| **Fatigue** | 9 | 10 |
| **Urinary symptoms** | 8 | 9 |
| **Vaginal bleeding** | 11 | 12.3 |
| **Number of symptoms** | | |
| **0** | 24 | 26.9 |
| **1** | 32 | 35.9 |
| **2** | 19 | 21.3 |
| **3** | 14 | 15.7 |

The majority of cases (more than 85%) were epithelial ovarian tumors, with a total of approximately 70% grade 2 and 3. More than 50% of patients were diagnosed in stages II and IV of disease.

Of the patients that underwent surgery in our center, more than 70% were left with no macroscopic residual disease, and approximately 13% with residual disease of 2 cm or more. Complete response after adjuvant therapy was obtained in more than 65% of cases, and no response after therapy in 11%.

## Discussions

The mainly descriptive nature of this study points out certain important characteristics of the case population. Ovarian cancer patients in our region are most often inappropriately investigated

Table 4. Tumor characterization

| | N | % |
|---|---|---|
| **Histology** | | |
| **Epithelial tumors** | 76 | 85.3 |
| **Sex-cord stromal tumors** | 4 | 4.5 |
| **Germinative-cell tumors** | 3 | 3.3 |
| **Borderline tumors** | 6 | 6.7 |
| **Metastatic tumors** | 1 | 1.1 |
| **Grading** | | |
| **G1** | 15 | 16.8 |
| **G2** | 37 | 41.5 |
| **G3** | 28 | 31.4 |
| **Stage at diagnosis** | | |
| **I** | 36 | 40.4 |
| **II** | 5 | 5.6 |
| **III** | 43 | 48.3 |
| **IV** | 5 | 5.6 |

Table 5. Treatment completion and response

| | N | % |
|---|---|---|
| **Residual disease** | | |
| **R0** | 64 | 71.9 |
| **R1** | 10 | 11.2 |
| **R2** | 12 | 13.4 |
| **Response after adjuvant therapy** | | |
| **RC** | 59 | 66.2 |
| **RP** | 10 | 11.2 |
| **BEV** | 10 | 11.2 |

prior to a surgical intervention and methods with a screening utility such as transvaginal ultrasound and CA-125 are only used in approximately one third to one half of patients suspect of pelvic masses. Standardization of pre-treatment care could lead to a better and earlier diagnosis of patients with malignant ovarian tumors, and patients with suggestive symptoms (non-specific as they may be, in context of a menopausal woman with risk factors for ovarian cancer can be suggestive) should be referred to centers where diagnostic methods are more widely available.

The importance of treatment center is obviously pointed out when analyzing the large statistical difference between pre-treatment and follow-up investigations. Initial diagnosis is still made in more than 50% of patients in an advanced stage (III or IV). On the other hand, after patients have been referred to a cancer-specialized center, the use of standard-of-care methods is increased (up to 90% of patients underwent recommended investigations for treatment monitoring).

The standard treatment of epithelial ovarian cancer at all clinical stages is currently debulking surgery (Akahira *et al* 2001, Oksefjell *et al* 2007, Winter *et al* 2007, 2008). Patients subjected to total abdominal hysterectomy + bilateral salpingo-oophorectomy + omentectomy + retroperitoneal lymph node sampling have a survival benefit compared to those not treated according to the standard surgical procedure. Optimal debulking results

in our study were quite high (over 70%), concordant to current literature results, showing a proper affiliation to current treatment standards with good results. The goal of every cytoreductive procedure should be to debulk the cancer to no visible disease. In addition, several studies suggest that lymphadenectomy, especially in those who have all disease resected, may improve outcomes (du Bois *et al* 2010). Additionally, surgical specialization has been associated with higher rates of optimal cytoreduction, appropriate surgical care and survival (Goff *et al* 2007, Engelen *et al* 2007, Vergote *et al* 2010). Whenever possible, a gynecologic oncologist should be involved in the surgical management of all women with ovarian cancer. In general, with gynecologic oncology involvement approximately 60-70% of patients will be able to be optimally cytoreduced using the new definition of no visible residual disease.

While the finding that most cases were epithelial ovarian tumors is not surprising, as this is the case in most populations studied, however we found an increased number of patients (over 70%) with a poor histological grading (G2 or G3) that more often correlates with a poor response to chemotherapy and short disease-free interval.

Clinical onset, while scarce and misleading, can still be suggestive, and any female patient (especially after menopause) presenting with abdominal discomfort, change in appetite or other digestive symptoms should be referred to a gynecologist for examination to exclude the presence of a pelvic mass.

Upon completion of our study series, we hope to analyze the correlation between prognostic factors and disease free intervals and also focus on the impact proper diagnosis and follow-up have on patient evolution after treatment and on disease stage upon diagnosis, and also have a proper characterization of population at risk in our region.

## Conclusions

In conclusion, this report provides a great deal of information about basic patient characteristics, diagnosis and follow-up tools, surgical conduct and treatment results and points out areas where standardisation and improvement of care is required.

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