Summary
Introduction. Ovarian cancer is an intra-abdominal, chemosensitive, chronic disease and according to current protocols, it is primarily treated with surgery followed by adjuvant chemotherapy. In Serbia, 820 cases of ovarian cancer are newly diagnosed annually. The aim of the study is to present the results of surgical treatment in 304 patients with ovarian cancer, treated during a 15-year period (2003 – 2017) at the Clinic of Gynecology and Obstetrics, Clinical Center of Vojvodina in Novi Sad. Material and Methods. Before the operation, clinical, gynecological, ultrasonography examination and analysis of cancer antigen 125 blood concentrations were performed in all patients. Based on basic diagnostics, additional pelvic, abdominal and thoracic computed tomography or magnetic resonance imaging studies, together with colonoscopy if needed, were performed. The selection of the type and extent of surgical procedure was based on intraoperative assessment of the stage of disease, intraoperative histopathological confirmation of ovarian cancer, wish for fertility preservation and general patient’s condition. Exclusion criteria were histopathologically confirmed benign or borderline ovarian tumors, i.e. absence of cancer in the final microscopic specimen. Results. The patients’ age ranged from 19 – 88 years, with a median of 53.4 years. According to the International Federation of Gynecology and Obstetrics staging, most patients had stage III – 98 (33.1%) and epithelial ovarian cancer – 240 (84.2%). The most common surgical procedures were hysterectomy with bilateral adnexectomy and omentectomy, whereas cytological analysis was performed in 138 (45.4%) treated patients. Complications were recorded in 13 (4.3%) operated patients with inflammation and wound seroma being the most common (4 patients – 1.3% of cases). Conclusion. Ovarian cancer treatment is planned individually, depending on the stage of the disease, histological tumor type, patient’s general condition, wish for fertility-sparing treatment and technical capacity of the institution where the treatment is performed. Key words: Ovarian Neoplasms; Diagnostic Imaging; CA-125 Antigen; Biomarkers; Tumor; Morphological and Microscopic Findings; Neoplasm Staging; Surgical Procedures; Operative; Postoperative Complications; Prognosis

Sažetak
Uvod. Karcinom jajnika je intraabdominalno, hemiosenzitivno, hronično oboljenje koje se primarno leci hirurški, nakon čega sledi dopunska hemoterapija prema važećim protokolima. U Srbiji se godišnje otkriva oko 820 novih slučajeva karcinoma jajnika. Cilj istraživanja je prikaz rezultata lečenja kod 304 operisane pacijentkinje od karcinoma jajnika u 15-godišnjem periodu (2003–2017) na Kliničkom centru Vojvodine u Novom Sadu. Materijal i metode. Kod svih pacijentkinja pre operacije izvršen je klinički, ginekološki, ultrazvučni pregled i određivanje koncentracije tumorskih markera CA 125 iz krvi. Na osnovu ove osnovne dijagnostike izvršeni su dopunska pregledi skenerom ili magnetnom rezonancom karlike, abdomena i grudnog koša a prema potrebi i kolonoskopija. Izbor vrste i obima hirurškog postupka izvršen je na osnovu intraoperativne procene stadijuma bolesti, histopatološke potvrde da se radi o karcinomu jajnika u toku operacije, želje za rađanjem i opštem stanja pacijentkinje. Kriterijum za isključenje iz istraživanja je patohistološki potvrđen benigni ili graničnomaligni (borderline) tumor jajnika odnosno odsustvo karcinoma na definitivnom mikroskopskom preparatu. Rezultati. Uzrast pacijentkinja kretao se između 19 i 88 godina, u prosеку 53,4 godine. Najviše pacijentkinja bilo je prema kriterijumima Internationale Federation of Gynecology and Obstetrics u III stadijumu bolesti 98 (33,1%) i grupi epitelijalnih karcinoma jajnika 240 (84,2%). Najčešće sprovedena operacija bila je histerektomija sa obostranom adneksektomijom, omentektomijom i citologološkom analizom koja je izvršena kod 138 (45,4%) operisanih pacijentkinja. Komplikacije su zabeležene kod 13 (4,3%) operisanih pacijentkinja a najčešće su bili zastupljeni inflamacija i serom rane u četiri slučaja (1,3%). Zaključak. Lečenje karcinoma jajnika planira se individualno u zavisnosti od stadijuma bolesti, histološke vrste tumor, opšteg stanja pacijentkinje, želje za očuvanjem fertilne sposobnosti i tehničkih mogućnosti ustanove u kojoj se sprovodi lečenje. Ključne reči: ovarijalne neoplazme; dijagnostički imidžing; CA-125 antigen; tumorski biomarkeri; morfološki i mikroskopski nalazi; klasifikacija karcinoma; operativne hirurške procedure; postoperativne komplikacije; prognozinski nalazi; klasifikacija karcinoma; operativne hirurške procedure; postoperativne komplikacije; prognoza

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Ovarian cancer is an intra-abdominal, chemosensitive chronic disease and according to current protocols, it is primarily treated with surgery followed by adjuvant chemotherapy [1]. The incidence of newly diagnosed ovarian cancer worldwide is 4% of all malignant tumors in female population, and it is twice higher in economically developed countries. In Serbia, 820 cases of ovarian cancers are newly diagnosed every year, and it is the leading cause of death among all malignant gynecological tumors [2]. It affects the elderly population, and in more than 80% of cases it is diagnosed after the age of 60 years [3]. The first symptoms are nonspecific, including the sensation of abdominal pressure and pain, bloating, loss of appetite, nausea, increased abdominal circumference, defecation problems etc. [4]. There are no successfully organized screening programs for ovarian cancer yet. The diagnosis is based on imaging, which comprises ultrasonography (US) and color Doppler, computed tomography (CT) and magnetic resonance imaging (MRI) [5]. Preoperative analysis of specific tumor marker concentrations (cancer antigen (CA) 125, human epidymis protein (HE) 4, CA 19.9, alpha fetoprotein (AFP), beta human chorionic gonadotropin (hCG) etc.) can aid the diagnosis [6, 7]. Definite diagnosis is based on histopathological analysis of tissue specimen following laparoscopy or laparotomy [1–3]. Nowadays, distinction between two different entities: low-grade serous carcinoma (LGSC) and high-grade serous carcinoma (HGSC), which have different precursors, biological behavior and molecular diversity, is of significant importance. Most low-grade cancers have a mutation of Kirsten rat sarcoma viral oncogene homolog (KRAS) and v-Raf murine sarcoma viral oncogene homolog (BRAF) genes, with the assumption that serous borderline tumors are precursors of this disease. High-grade tumors have a tumor protein (TP) 5 mutation, about 50% have breast cancer gene (BRCA) 1 and BRCA2 abnormalities and are not related to borderline tumors [8, 9]. Two most important prognostic factors are tumor dissemination at the moment of diagnosis and volume of residual tumor after surgical treatment [10]. Assessment of ovarian cancer dissemination or stage of the disease is performed intraoperatively by detailed examination of all intra-abdominal organs and obtaining biopsy specimens for histopathological examination from all suspicious sites and serous surfaces of pelvic and abdominal cavity (peritoneum, diaphragm domes, liver, spleen, small and large intestine etc.) according to up to date International Federation of Gynecology and Obstetrics (FIGO) classification [1–5]. The aim of the study is to present the results of surgical treatment in 304 patients with ovarian cancer treated during a 15-year period (2003 – 2017) at the Clinic of Gynecology and Obstetrics (CGO), Clinical Center of Vojvodina in Novi Sad.

### Material and Methods

The study included 304 patients operated for ovarian cancer. Before the surgery, clinical, gynecologic, ultrasonography examination and analysis of tumor marker CA 125 blood concentrations were performed in all patients. Based on the test results, additional diagnostic tests, including pelvic, abdominal and thoracic computed tomography (CT) or magnetic resonance imaging (MRI), additional blood levels of tumor markers tests (CA19.9, AFP, beta hCG etc.), as well as colonoscopy, gastroscopy etc., were performed. Indications for surgical treatment with intraoperative ex tempore diagnostics included patients with: suspicion of ovarian cancer based on imaging tests (US, CT, MRI); presence of papillary proliferations on the inner tumor capsule larger than 3 mm, honeycomb and solid portions within the cystic tumors, predominantly solid tumors, presence of ascites, increased number of separations larger than 3 mm, etc. In all patients, bowel preparation was performed 24 – 48 hours prior the surgery. Two hours before the surgery, lower extremities were bandaged, and anticoagulant therapy with Fraxiparin and one dose of antibiotics (Cephalosporin 1 – 2 g) were administered. Apart from standard blood and urine laboratory tests, preoperative preparation included chest X–ray, electrocardiography (ECG), examination by internal medicine specialist and anesthesiologist, as well as reservation of decanted erythrocytes if hemoglobin levels were below 100 g/l and organization of intraoperative histopathological ex tempore analysis. The selection of type and extent of surgical procedure was based on intraoperative assessment of FIGO stage of the disease, intraoperative histopathological confirmation of ovarian cancer, wish for fertility preservation, and general patient’s condition. In all cases where different intra-abdominal organs were involved (small and large intestines, liver, spleen, peritoneum, diaphragm), an abdominal surgeon joined the surgery. Assessment of ovarian cancer dissemination to surrounding tissues (stage of the disease) was performed based on intraoperative and histopathological findings of biopsies of different pelvic and abdominal organs according to FIGO classification for ovarian cancer from 2009. Histopathological confirmation of cancer was based

### Abbreviations

- CGO – Clinic of Gynecology and Obstetrics
- US – ultrasound
- CT – computed tomography
- MRI – magnetic resonance imaging
- FIGO – International Federation of Gynecology and Obstetrics
- CA – cancer antigen
- AFP – alpha fetoprotein
- hCG – human chorionic gonadotropin
- BRCA – breast cancer gene

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**Introduction**

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on intraoperative ex tempore findings and definite histopathological examination of all obtained tumor tissue specimens. Inclusion criterion was a confirmed ovarian cancer on definite histopathological specimen, while exclusion criteria were histopathologically confirmed benign or borderline tumors. In all patients with advanced stages of the disease (FIGO III and IV) with involvement of intra-abdominal organs (colon, liver, spleen, peritoneum, diaphragm domes, urinary bladder, or kidney), an abdominal surgeon and urologist joined the surgery. After the surgery and final histopathological reports, all patients were presented at the Gynecologic-Oncologic Committee at our Clinic, and then at the Institute of Oncology in Sremska Kamenica. The decision on adjuvant chemotherapy was considered according to current protocols and recommendations in all cases where FIGO stage was IB or higher. After completion of therapy, follow ups were performed at the Outpatient Department of CGO of the Clinical Center of Vojvodina and Institute of Oncology in Sremska Kamenica.

Results

In the period from 2003 – 2017, 304 ovarian cancer patients underwent surgery at the CGO of the Clinical Center of Vojvodina in Novi Sad. The age distribution of operated patients is shown in Graph 1. Most surgical procedures were performed in 2017, a total of 34. The age of patients ranged from 19 to 88 years (mean age 53.4 years). According to the FIGO classification, there were 92 (30.6%) patients with FIGO I stage, 53 (16.5%) with stage II, 98 (33.1%) with stage III, and 61 (19.8%) patients with stage IV. Based on histopathological type, ovarian cancers were classified into the following groups: epithelial 240 (84.2%), germ cell 21 (5.4%), stromal sex cord tumors 22 (5.6%), sarcomas 2 (0.4%) and metastatic tumors 19 (4.4%). Table 1 shows the types of performed surgical procedures. The most frequent surgical procedure was total abdominal hysterectomy with bilateral adnexectomy, and total omentectomy in 138 (45.4%) patients. Table 2 shows the distribution of complications in the operated patients and the most frequent was wound inflammation in 4 (1.3%) patients. In 109 (35.8%) patients, besides hysterectomy, adnexectomy, and omentectomy, radical surgical procedures also included lymphadenectomy and surgical excision of involved organs (colon, liver, spleen, urinary bladder, kidney, and peritoneum). Only explorative laparotomy with biopsy followed by histopathology and adjuvant chemotherapy was done in 15 (4.9%) operated patients with advanced stage (FIGO III and IV) of ovarian cancer. Figure 1 and Figure 2 show different intraoperative findings and surgical procedures in advanced FIGO III and IV stages of ovarian cancer.

Table 1. Types of surgical procedures according to FIGO staging

| Type of surgery | FIGO Stage of the disease | Percentage | | |
|---|---|---|---|---|
| | I | II | III | IV |
| Unilateral adnexectomy Biopsy + Citology | | | | |
| | 15 | 4 | 0 | 0 | 6.3 |
| Hysterectomy + Bilateral adnexectomy | | | | |
| Histerektomija + obostrana adneksektomija | 19 | 0 | 4 | 0 | 7.6 |
| Hysterectomy + Bilateral adnexectomy + Omentectomy | | | | |
| Histerektomija + obostrana adneksektomija + omentektomija | 53 | 24 | 38 | 23 | 45.4 |
| Hysterectomy + Bilateral adnexectomy + Omentectomy + Hemicolec- tomy + Splenectomy/Histerektomija + obostrana adneksektomija + hemikolektomija + splenektomija | 0 | 5 | 32 | 14 | 16.7 |
| Hysterectomy + Bilateral adnexectomy + Omentectomy + Lymphadenectomy + Nephrectomy + Urinary bladder resection | | | | |
| Histerektomija + obostrana adneksektomija + omentektomija + limadenektomija + nefrektomija + resekcija mokraćne bešike | 1 | | | 0.3 |
| Hysterectomy + Bilateral adnexectomy + Omentectomy + Hemicolec- tomy + Splenectomy + Liver resection/Histerektomija + obostrana adneksektomija + omentektomija + hemikolektomija + splenektomija | 3 | | | 1 |
| Hysterectomy + Bilateral adnexectomy + Omentectomy + Peritoneectomy/Histerektomija + obostrana adneksektomija + omentektomija + peritonektomija | 6 | 19 | 22 | 7 | 17.8 |
| Exploratory laparotomy + Biopsy | | | | |
| Eksplorativna laparotomija + biopsija | 0 | 0 | 5 | 10 | 4.9 |
| Total/Ukupno | 93 | 52 | 102 | 57 | 100 |

Legend: FIGO - International Federation of Gynecology and Obstetrics
Discussion

The aim of surgical treatment of ovarian cancer is complete tumor reduction, with residual microscopic cancer cells in the abdominal cavity. It has been proven that patients with complete cytoreduction have better prognosis compared to those with minimal residual tumors [11]. According to different studies, optimal cytoreductive surgery is performed in about 20 - 30% of all ovarian cancers. Definition of “optimal” and “maximal” cytoreductive surgery is still controversial. Nowadays, it is considered that optimal surgical cytoreduction can be defined only if there are no macroscopically visible remains. The aim of cytoreductive surgery is to enhance the effects of cytostatics on possible residual tumor cells [12, 13]. When planning the treatment of ovarian cancers, special circumstances and situations must be considered: sparing surgery which preserves woman’s fertility, surgery of ovarian cancer with low malignant potential (borderline tumors), surgical treatment of epithelial and germ cell ovarian cancer adjusted to different FIGO stages, use of laparoscopic technique and surgical treatment of ovarian cancer in pregnancy [2]. Considering the fact that ovarian cancer is an intra-abdominal disease which may disseminate to all serous surfaces, organs and topographic parts of the pelvic and abdominal cavity, the attitude - surgeon as a prognostic factor is being often mentioned in the literature [14]. The success of surgical treatment strongly depends on the experience, knowledge and treatment conditions in the referent institution, as well as general patient’s condition. Only a well trained surgical team can perform all necessary interventions on different abdominal organs, including large and small bowel, liver, spleen, lymph nodes, diaphragm etc. and be a reliable “prognostic factor” in ovarian cancer surgical treatment [11–14].

The study presents results of surgical treatment in 304 patients of average age of 53.4 years. Most patients had FIGO III stage of the disease 98 (33.1%) and epithelial ovarian cancer 240 (84.2%). According to up to date references, about 70% of ovarian cancer cases are diagnosed in advanced stages (FIGO III and IV) [1–3, 14, 15]. This was not the case in our study, where 52.3% of cases were diagnosed at FIGO stage III and IV, while 47.4% at early FIGO stage I and II. This can be explained by

| Type of complication | Number/Broj | %/Procent |
|----------------------|-------------|-----------|
| Bleeding + relaparotomy | 3           | 1.1       |
| Wound dehiscence | 3           | 1.1       |
| Seroma + wound inflammation | 4          | 1.3       |
| Sepsis + pleural empyema | 1          | 0.4       |
| Injury of ureter and bladder | 2         | 0.8       |
| Total/ukupno | 13          | 4.3       |

Graph 1. Age distribution of 304 patients operated for ovarian cancer at the CGO, Clinical Center of Vojvodina, Novi Sad, from 2003 to 2017

Graphikon 1. Distribucija 304 operisane pacijentkinje od karcinoma jajnika prema godinama na Klinici za ginekologiju i akušerstvo Kliničkog centra Vojvodine u Novom Sadu, u periodu 2003–2017.

Table 2. Types of complications after ovarian cancer surgery

| Type of complication | Number/Broj | %/Procent |
|----------------------|-------------|-----------|
| Bleeding + relaparotomy | 3           | 1.1       |
| Wound dehiscence | 3           | 1.1       |
| Seroma + wound inflammation | 4          | 1.3       |
| Sepsis + pleural empyema | 1          | 0.4       |
| Injury of ureter and bladder | 2         | 0.8       |
| Total/ukupno | 13          | 4.3       |

Figure 1. A and B – characteristic ultrasonography images of ovarian cancer with intracystic proliferations and solid portions; C – serous cystadenocarcinoma FIGO stage IB (low grade); D – intraoperative finding of pelvic organs infiltration FIGO stage IIIC

Slika 1. A i B – ultrazvučne karakteristike karcinoma jajnika sa intracističnim proliferacijama i solidnim delovima; C – serozni tip cistadenokarcinoma jajnika stadijuma I B (nizak stepen malignosti); D – intraoperatorivni nalaz infiltracije organa male karlice kod stadijuma III C karcinoma jajnika
The fact that more patients with cystic ovarian tumors, over 60 mm in the longest diameter, are relatively early operated by laparoscopy with intraoperative biopsy, is true for patients with fast-growing tumors. The age of patients was 53.4 years, and most patients had International Federation of Gynecology and Obstetrics stage III and IV: A – peritoneectomy of diaphragmatic domes above the liver; B – peritoneectomy of vesicouterine peritoneum; C – complete colectomy with peritoneectomy; D – complete pelvic peritoneectomy.

**Figure 2.** Surgical procedures in advanced ovarian cancer stages III and IV: A – peritoneectomy of diaphragmatic domes above the liver; B – peritoneectomy of vesicouterine peritoneum; C – complete colectomy with peritoneectomy; D – complete pelvic peritoneectomy.

These results are in accordance with current trends in surgical treatment of ovarian cancer with the aim of achieving maximal surgical tumor reduction, including interventions (resections) of affected organs of the upper abdomen. In developed countries, such extensive operations are performed in centers specialized for this type of surgery involving a multidisciplinary team [15–18]. Complications were recorded in a total of 13 (4.3%) patients. Most common were minor complications such as inflammation and wound seroma in 4 (1.3%) cases. Relaparotomy was performed in 3 (1.1%) patients due to bleeding caused by fall of vascular ligatures. In 1 (0.4%) patient with germ cell ovarian cancer, infection of abdominal organs occurred after the surgery, accompanied by sepsis and pleural empyema, which was successfully treated by reoperation, abdominal and thoracic cavity drainage and administration of antibiotics based on an antibiogram from the obtained microbiology samples.

**Conclusion**

During the 15-year period (2003 – 2017), 304 patients underwent surgery for ovarian cancer at the Clinic of Gynecology and Obstetrics. The average age of patients was 53.4 years, and most patients had International Federation of Gynecology and Obstetrics stage III and IV: A – peritoneectomy of diaphragmatic domes above the liver; B – peritoneectomy of vesicouterine peritoneum; C – complete colectomy with peritoneectomy; D – complete pelvic peritoneectomy.

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