Original article

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PROGNOSTIC DIFFERENCES IN TUBO-OVARIAN HIGH-GRADE SEROUS CARCINOMA STAGE IIIC

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Quantitative variations in peritoneal carcinomatosis and primary pelvic tumor size (TS) may reflect the diversity in high-grade serous carcinoma (HGSC) stage IIIC. The peritoneal cancer index (PCI) provides accurate evidence about the extent and distribution of tumor volume. The study aimed to investigate whether there is a difference among HGSCs in the International Federation of Gynecology and Obstetrics (FIGO) stage IIIC based on the principal disease burden and its impact on overall survival (OS). Medical records of primary tubo-ovarian HGSCs were reviewed from January 2019 to December 2022. Patients were separated into a group with PCI ≤ 10 and large TS (Group 1, n = 39) and a group with PCI > 10 and small TS (Group 2, n = 36). Group 2 was significantly more likely to have a larger volume of ascitic fluid (p = 0.017). Optimal cytoreduction (OC) was achieved in 53.9% of patients in Group 1 and only 11.1% of those in Group 2 (p < 0.001). *BRCA1/2* mutation was significantly more frequent in Group 1 (p = 0.012). OS was significantly better in Group 1 versus 2 (p < 0.001). Multivariate analysis identified group, ascitic volume, and cytoreduction completeness as independent prognostic survival factors. The FIGO stage IIIC of HGSC should evolve from a "one-size-fits-all" approach toward a more personalized treatment strategy that incorporates surgery, chemotherapy, and targeted therapy. The localization of the main tumor burden is a factor that makes a prognostic difference in stage IIIC HGSCs.

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Introduction

Epithelial ovarian cancer (EOC) is a heterogeneous disease comprising several histotypes with different modes of carcinogenesis, epidemiological, clinical, molecular, and microenvironmental features, all of which affect the tumor behavior (1). Among them, the most common histological type is high-grade serous carcinoma (HGSC), which originates from a noninvasive precursor called serous tubal intraepithelial carcinoma (STIC) in the distal end of the fallopian tube (2). Frequently, HGSC is diagnosed at the International Federation of Gynecology and Obstetrics (FIGO) stage III/IV. Therefore, the five-year cancer-specific survival for HGSC is much lower than for other common histological types despite the intense research efforts to improve treatment modalities and survival rates (3). Regardless of the same histotype and disease stage, HGSCs staged as FIGO IIIC represent a diverse group of patients with distinct prognoses (4). Consequently, there is a need to define more precise indicators that influence survival within the same stage.

Contrary to the conventional dissemination route for other carcinomas, HGSC does not require blood or lymph vasculature. HGSC characteristically metastasizes throughout the abdominal peritoneal cavity via cell detachment from the primary tumor. Secondary tumors bind the mesothelial cell layer and continue to grow in a completely altered setting. Some tubo-ovarian HGSCs favor abdominal peritoneal metastatic sites for future development rather than the original site of occurrence (5). This results in shifting the disease from the pelvis to the abdomen. Quantitative variations in peritoneal

carcinomatosis and primary pelvic tumor size (TS) may reflect the diversity in the stage IIIC of HGSCs.

There are many proposed systems for estimating abdominal and pelvic tumor load (6). One widely adopted score is the peritoneal cancer index (PCI) introduced by Jacquet and Sugarbaker initially used for metastatic colorectal and appendiceal cancers (7). In advanced ovarian cancer, PCI can be utilized as an efficient tool for evaluation of the peritoneal spread and provides accurate evidence about the extent and distribution of tumor volume (8).

The study aimed to investigate whether there is a difference among HGSCs currently grouped as FIGO stage IIIC based on the principal disease burden and its impact on overall survival (OS) in order to justify further stage subcategorization and distinctive therapeutic approach.

Materials and Methods

Patient Selection

Medical records of women diagnosed with primary tubo-ovarian HGSC FIGO stage IIIC were reviewed from January 2019 to December 2022. All patients underwent surgery at the Clinic of Gynecology and Obstetrics, University Clinical Center Niš, Niš, Serbia. Each surgery was performed via median laparotomy to remove as much of the visible tumor. Gynecologic pathologists reexamined hematoxylin and eosin-stained slides of operative tumor samples at the Center for Pathology, University Clinical Center Niš, Niš, Serbia. HGSC was classified as tubo-ovarian versus peritoneal primary based on criteria for primary site assignment in non-uterine HGSC proposed by Singh et al. (9).

Patients were excluded if they had prior surgery for tubo-ovarian cancer and if they received neoadjuvant chemotherapy. The following data were included: patients' age at diagnosis, PCI, TS, completeness of cytoreduction, ascitic volume (L), regional lymph node involvement, germline or somatic *BRCA1/2* mutation status, value of preoperative CA125 (U/ml), date of last follow-up, and cancer-specific death at last follow-up.

The PCI was calculated based on computed tomography (CT), magnetic resonance imaging (MRI), and operative and pathology reports, according to Jacquet and Sugarbaker's propositions (7). After calculation, PCI values were dichotomized at value 10 (8). A small TS indicates a primary tubo-ovarian tumor less than or equal to 5 cm and a large TS indicates a tubo-ovarian tumor greater than 5 cm in its largest diameter. Optimal cytoreduction (OC) is defined as complete removal or residual disease less than or equal to 1 cm, while suboptimal cytoreduction (SC) is defined as leaving tumor residues larger than 1 cm. The molecular evaluation of breast cancer genes *BRCA1/2* was performed at the Institute for Oncology and Radiology of Serbia, Belgrade, Serbia, to identify patients for poly-ADP-ribose polymerase (PARP) inhibitors treatment. OS was calculated from the date of surgery to the date of cancer-specific death. Surviving patients were censored at the date of the most recent follow-up.

All participating patients were well-informed and signed the consent form.

Statistical analysis

All statistical analyses were processed using the Statistical Package for Social Sciences (SPSS version 25.0; IBM, Armonk, NY, USA). The normality of the data was tested using the one-sample Kolmogorov–Smirnov test. The χ^2 test was used to compare differences between the categorical variables. The Student's t-test analyzed differences in the means of continuous measurements. The survival curves were obtained using the Kaplan–Meier method and the log-rank test was engaged to compare survival curves. Multivariate analyses were performed using the Cox proportional hazards regression model.

A two-tailed p-value of less than 0.05 was considered statistically significant for all tests.

Results

A total of 75 women with FIGO stage IIIC primary tubo-ovarian HGSC were included in this study after applying the above criteria. They were separated into two groups: patients with PCI ≤ 10 and large TS (Group 1, n = 39) and patients with PCI > 10 and small TS (Group 2, n = 36). Table 1 summarizes a comparison of baseline characteristics between the patients' groups. The mean age at the time of diagnosis was similar in both groups: 61.26 ± 12.23 years old for women in Group 1 and 60.58 ± 9.39 years old for Group 2 (p = 0.791). Patients in Group 2 were significantly more likely to have a larger volume of ascitic fluid than those in Group 1 (p = 0.017). Furthermore, OC was achieved in 23 (53.9%) patients in Group 1 and only 4 (11.1%) of those in Group 2, with a statistically significant difference (p < 0.001). Germline or somatic *BRCA1/2* mutation was observed significantly more frequently in women in Group 1 compared with Group 2 (p = 0.012). Although patients in Group 2 tended to have higher values of preoperative CA125 levels, the difference did not reach statistical significance (p = 0.087). We found no significant intergroup differences concerning lymph node involvement (p = 0.701).

Table 1. Comparison of groups according to baseline characteristics

	Group 1	**Group 2**	**p-value**
No. patients	39	36	
Age (yrs) Mean ± SD	61.26 ± 12.23	60.58 ± 9.39	0.791
Ascitic volume (L) Mean ± SD	2.47 ± 1.63	3.59 ± 2.27	**0.017**
Cytoreduction, n (%) OC SC	21 (53.9) 18 (46.1)	4 (11.1) 32 (88.9)	**< 0.001**
BRCA1/2 mutation, n (%) Present Absent	14 (39.9) 25 (64.1)	4 (11.1) 32 (88.9)	**0.012**
CA125 level (U/ml) Mean ± SD	823.00 ± 360.67	980.75 ± 425.68	0.087
Lymph node involvement, n (%) Present Absent	9 (23.1) 30 (76.9)	7 (19.4) 29 (80.6)	0.701

Bold values indicate that the difference reached statistical significance

Table 2. Results of multivariate analysis

Variable	**B**	**SE**	**HR**	**95% CI HR**		**p-value**
				Lower	Upper	
Group	-1.018	0.499	0.361	0.136	0.962	**0.042**
Age	0.023	0.018	1.023	0.987	1.061	0.211
Ascitic volume	0.220	0.095	1.246	1.033	1.502	**0.021**
Cytoreduction	-1.479	0.578	0.228	0.073	0.708	**0.011**
BRCA1/2 mutation	0.785	0.533	2.193	0.772	6.235	0.141
CA125 level	0.001	0.000	1.001	1.000	1.001	0.113
Lymph node involvement	-0.602	0.438	0.548	0.232	1.293	0.170

Bold values indicate variables with a significant impact on the OS

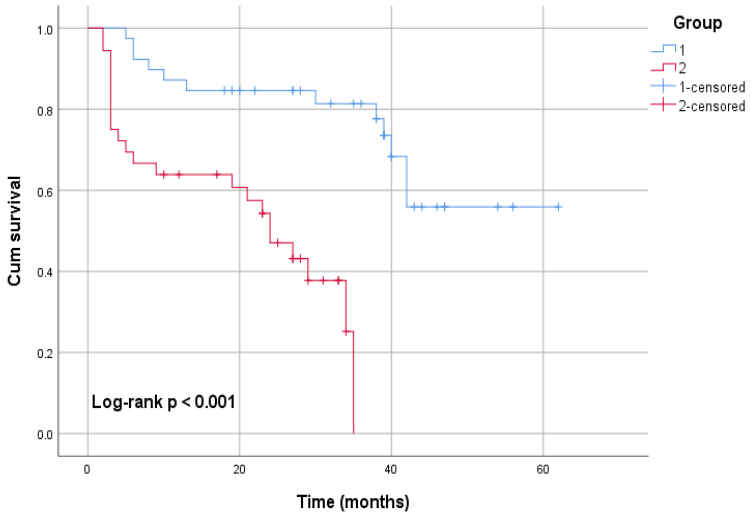

Figure 1. Comparison of OS by groups

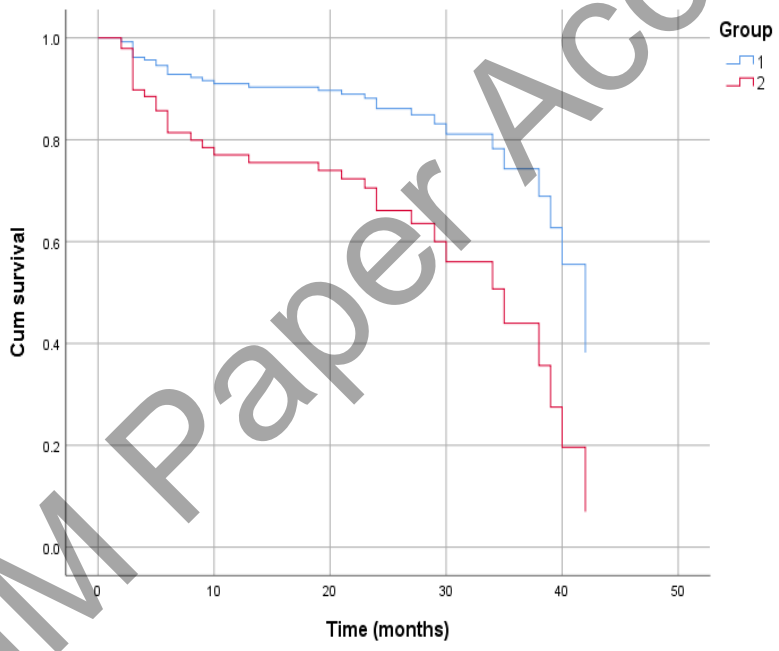

Figure 2. OS adjusted for prognostic variables and separated by groups

Survival analysis

The median OS for the entire population was 27 months (range 2–62). Separately, the median OS for patients in Group 1 was 38 months (range 5–62 months) while for patients in Group 2 was 22 months (range 2–35 months). As expected, Kaplan–Meier survival curves revealed a significantly better OS in Group 1 versus 2, as seen in Figure 1 ($p < 0.001$).

Multivariate analysis of the entire cohort with all data identified group, ascitic volume, and cytoreduction completeness as independent prognostic survival factors (Table 2). Group 1 was an independent predictive parameter for improved OS (HR = 0.361; p = 0.042). Another independent prognostic marker associated with a better outcome was OC (HR = 0.288; p = 0.011). The larger volume of ascitic fluid was significantly linked with worse OS (HR = 1.246; p = 0.021). Age, *BRCA1/2* mutation status, CA125 level, and lymph node involvement were not significant predictors of survival in the multivariate analysis. Figure 2 shows the different survival plots for patients in two groups after adjustment for prognostic variables.

Discussion

Extrapelvic peritoneal carcinomatosis is the most common presentation of HGSC. Peritoneal tumor spread depends on the unique and complex cooperation of the tumor microenvironment within the peritoneal cavity and ovarian cancer cells. Ascitic fluid, rich in cytokines, chemokines, growth factors, and proteinases additionally contributes to the growth and invasion of malignant cells. Although virtually every organ or structure in the peritoneal cavity may be involved, HGSC prefers the omentum (10).

Several reports have suggested a less favorable outcome for HGSC patients stage III/IV with large-volume extrapelvic disease especially for its upper abdominal distribution, even if complete cytoreduction was achieved (11, 12). There is an appreciable number of advanced HGSCs without definite adnexal enlargement and pelvic symptoms. Thus, some HGSCs can cause diffuse metastatic abdominal disease before reaching a detectable pelvic size by diagnostic procedures. After the splitting of advanced-stage HGSCs according to the presence of a normal-sized or enlarged adnexa, Paik et al. demonstrated a statistically significant poorer OS in patients with a normal-sized ovary than with an enlarged ovarian tumor. Moreover, a normal-sized ovary remained a significant factor for OS after multivariate analysis (13).

The patients are staged as FIGO IIIC if the minimal tumor size above the pelvic rim is more than 2 cm and/or if they have retroperitoneal lymph node involvement. This current classification does not give valuable information about disease extent since patients with stage IIIC may have an easily resectable tubo-ovarian tumor with localized, relatively small peritoneal carcinomatosis, but may also have widespread unresectable disease. We investigated whether some HGSCs stage FIGO IIIC are more aggressive than others according to the extensivity of pelvic and abdominal tumor burden. In this regard, we divided the FIGO IIIC HGSC patients based on dominant tumor load (pelvic versus abdominal), calculated using PCI. Comparing the two groups, we found a significant difference in OS. Women without notable tubo-ovarian tumor but with greater peritoneal carcinomatosis had a worse prognosis than women with large primary tumor, but smaller peritoneal disease. In multivariate analysis, the Group remained a significant prognostic marker for OS. These findings support the hypothesis that HGSCs behave differently, with some preferring the abdominal cavity for tumor growth more than their primary localization, causing an adverse end result.

The large volume of ascites has traditionally been accepted as an unfavorable prognostic sign in ovarian cancer patients. Szender et al. concluded that patients with more than 2 l ascites achieve fewer complete surgical resections. When they limited calculations to patients with FIGO stage IIIC/IV of disease, those with large volume ascites had significantly shorter OS when compared with patients with lower volume ascites (14). In the current analysis, Group 2 patients had a notably larger volume of ascites than Group 1. The amount of ascites was associated with cancer-specific death, which is in concordance with the previous study that recognized massive ascites as an independent poor prognostic factor in patients with advanced-stage EOC (15). It was even recommended that the presence of ascites should be included in a nomogram for the prediction of OS in patients with platinum-resistant EOC (16).

Cumulative data have shown that maximal-effort cytoreduction to microscopic residual disease is related to improved OS in HGSC patients. The operative possibilities are often challenged for patients with a high tumor burden, in which, not only the disease itself but also infrastructural resources and expertise may limit optimal treatment. Increasing tumor volume per number of involved abdominal fields negatively affects OS (17). We noticed that Group 1 patients had a significantly higher percentage of OC than Group 2. Multivariate analyses identified OC as an independent prognostic variable for better OS.

Petrillo et al. documented an inverse correlation between *BRCA* mutation status and extrapelvic tumor load in HGSC patients. *BRCA1/2* mutation carriers exhibited a higher rate of peritoneal and diaphragmatic carcinomatosis with greater intraperitoneal tumor size than those without the mutation. They also found a reduced incidence of ovarian masses in *BRCA1/2* mutated women (18). In contrast to previous conclusions, our results suggest that women with larger pelvic tumor, but with lesser abdominal carcinomatosis (Group 1) were significantly more frequently associated with *BRCA1/2* mutation than Group 2. The reason for this conflicting data could be that more BRCA1/2 mutated patients were included in previous investigation. We did not find in a multivariate analysis that *BRCA1/2* mutation status influenced OS. Other studies established that advanced-stage HGSC patients with *BRCA1/2* mutation have better prognosis with longer progression-free survival than those lacking BRCA mutations (19, 20). *BRCA1/2* mutation was more frequent in Group 1, an independent prognostic factor for improved OS.

Although CA125 has its limitations as a prognostic biomarker, it is the most used serum marker in diagnosing, following up, and validating the treatment response of patients with HGSC. In addition, CA125 has received attention in the role of oncogenesis, metastatic potential of EOC, and targeted therapy via interaction with mesothelin, β-catenin, and p120ctn translocation (21). Two CA125 glycoforms, CA125-STn and CA125-MGL, are recognized to have a high specificity to HGSC. Salminen et al. detected a significant difference in the serum levels of these glycoforms in patients with low tumor load and high tumor load while the serum levels of conventional CA125 did not differ significantly between groups (22). Women with higher abdominal tumor load (Group 2) showed a trend towards increased values of circulating

CA125, however, the difference was not statistically significant.

In one large prospective trial, patients with advanced EOC did not benefit from pelvic and paraaortic lymphadenectomy. In contrast, lymphadenectomy resulted in a higher incidence of postoperative complications (23). Significant risk factors for pelvic and paraaortic lymph node involvement in HGSC patients are tumor stage and CA125 level at diagnosis (24, 25). Both of our groups had a similar number of involved lymph nodes. Dominant tumor size did not have a significant influence on lymph node metastasis. Furthermore, lymph node involvement did not affect OS in the present research.

Various analyses speculated that the disease distribution and outcome may be determined by specific cell and molecular subtypes of HGSCs (26, 27). Opponents of extensive surgery advocate that despite the well-established importance of surgical treatment, it is the inherent tumor biology that regulates the resectability of the tumor, not surgical aggressiveness (11). Therefore, other reasons for the survival difference among HGSCs, such as tumor biology and genetic characteristics, need to be analyzed in the future. Heterogeneity within the tumor microenvironment and diverse interactions between tumor, immune, and stromal cells also contribute to the complexity of the HGSC (28).

A few limitations of the study must be taken into consideration. This study is retrospective with a moderate number of patients from a single institution and a relatively short length of follow-up. Detailed information such as dimensions of post-operative tumor residuals, amount of ascites, and a comprehensive description of the tumor spread should be part of every surgical report with translation into a standardized form of the digital bank.

Conclusion

The FIGO stage IIIC of HGSC should evolve from a "one-size-fits-all" approach toward a more personalized treatment strategy that incorporates surgery, chemotherapy, and targeted therapy. The study confirmed the difference in behavior and its impact on survival in the same stage of HGSC. The localization of the main tumor burden (pelvic versus abdominal) is a factor that makes a prognostic difference in FIGO stage IIIC HGSCs.

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PROGNOSTIČKE RAZLIKE TUBO-OVARIJALNOG SEROZNOG KARCINOMA VISOKOG GRADUSA U STADIJUMU IIIC

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Kvantitativne varijacije u peritonealnoj karcinomatozi i veličini primarnog pelvičnog tumora (engl. *tumor size* – TS) mogu odražavati raznolikost u seroznom karcinomu visokog gradusa (engl. *high-grade serous cacinoma* – HGSC) u stadijumu IIIC. Indeks peritonealnog kancera (engl. *the peritoneal cancer index* – PCI) daje precizan dokaz o proširenosti i lokalizaciji volumena tumora. Cilj ove studije bio je da se istraži postojanje razlika između HGSC-a u stadijumu IIIC FIGO klasifikacije (*International Federation of Gynecology and Obstetrics* – FIGO) na osnovu lokalizacije najvećeg volumena tumora i uticaja lokalizacije na ukupno preživljavanje (OS). Pregledana je medicinska dokumentacija primarnih tubo-ovarijalnih HGSC-a od januara 2019. do decembra 2022. godine. Bolesnice su podeljene u dve grupe: grupu sa PCI-jem ≤ 10 i velikim TS-om (Grupa 1, n = 39) i grupu sa PCI-jem > 10 i malim TS-om (Grupa 2, n = 36). Grupa 2 je imala značajno veću zapreminu ascitne tečnosti (p = 0,017). Optimalna citoredukcija (OC) postignuta je kod 53,9% bolesnica u Grupi 1 i samo kod 11,1% bolesnica u Grupi 2 (p < 0,001). *BRCA1/2* mutacija bila je značajno češća u Grupi 1 (p = 0,012). Ukupno preživljavanje bilo je značajno bolje u Grupi 1 nego u Grupi 2 (p < 0,001). Multivarijantna analiza identifikovala je grupu, volumen ascitesa i kompletnost citoredukcije kao nezavisne prognostičke faktore preživljavanja. FIGO stadijum IIIC HGSC-a trebalo bi da evoluira od univerzalnog pristupa do individualizovanog pristupa kada je reč o upotrebi hirurgije, hemioterapije i ciljane terapije. Lokalizacija najvećeg volumena tumora predstavlja faktor koji čini prognostičku razliku u stadijumu IIIC HGSC-a.

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***Ključne reči**: serozni karcinom visokog gradusa, FIGO stadijum, indeks peritonealnog kancera, razlika, prognoza*