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Wedge liver resection as part of cytoreductive surgery in advanced ovarian cancer – a safe and feasible procedure for a gynecologic oncologist

Klinowa resekcja brzegu wątroby wykonywana przez ginekologa onkologa w trakcie operacji cytoredukcyjnej w zaawansowanym raku jajnika jest procedurą skuteczną oraz bezpieczną

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Abstract

Objective: In this study, we aimed to determine the learning curve for liver wedge resection performed as part of cytoreductive surgery in advanced ovarian malignant tumors. **Materials and methods:** This was a retrospective analysis of 120 women diagnosed with stage IIIC ovarian cancer according to the International Federation of Gynecology and Obstetrics (FIGO) classification: 22 underwent liver wedge resection as part of cytoreductive surgery (Group A), while 98 did not require liver surgery (Group B). In the study, the *t*-Student test was used for variables with normal distribution and the Mann–Whitney *U* test was utilized for increment and abnormally distributed variables. The variables categorized were shown as a number of cases (*n*) and a percentage (%), and compared using the chi-square test, with a p-value <0.05 considered significant. A cumulative sum control chart (CUSUM) method was used to investigate the learning curves in both groups and the entire cohort. **Results:** There were no significant differences in the operating time, intraoperative blood loss, postoperative hospitalization or minor and severe adverse effects between the Groups A and B. The operative time, total blood loss, and incidence of adverse effects showed a similar learning curve for Group B and the entire cohort. **Conclusion:** It is safe and feasible for gynecologic oncologists to perform wedge liver resections as part of cytoreductive surgery in women with advanced ovarian tumors.

Keywords: ovarian cancer, liver wedge resection, learning curve

Streszczenie

Cel: Celem pracy jest ocena krzywej uczenia się klinowej resekcji wątroby jako integralnej części operacji cytoredukcyjnej w zaawansowanym raku jajnika. **Materiał i metody:** Retrospektywna analiza objęła 120 kobiet z rozpoznaniem raka jajnika w stopniu zaawansowania IIIC według Międzynarodowej Federacji Ginekologów i Położników (International Federation of Gynecology and Obstetrics, FIGO) z roku 2018. Grupę A stanowiło 22 pacjentek, u których wykonano klinową resekcję wątroby; w grupie B 98 pacjentek nie wykonywano tej procedury. W analizie statystycznej wykorzystano test *t*-Studenta oraz test *U* Manna–Whitneya, jak również test chi^2 oraz metodę kontrolnego, skumulowanego wykresu sum (*cumulative sum control chart*, CSUM). Poziom istotności statystycznej ustalono jako $p < 0,05$. **Wyniki:** Nie stwierdzono istotnych różnic w medianach czasu zabiegu operacyjnego, śródoperacyjnej utraty krwi, czasu hospitalizacji po zabiegu, jak również w występowaniu zdarzeń niepożądanych pomiędzy grupą A i B. Krzywe uczenia analizujące czas zabiegu, śródoperacyjną utratę krwi oraz czas hospitalizacji po zabiegu były podobne w grupie B i w całej kohorcie badanych pacjentek. **Wnioski:** Klinowa resekcja przerzutów do wątroby wykonywana przez ginekologa onkologa w trakcie operacji cytoredukcyjnej u kobiet z zaawansowanym rakiem jajnika jest procedurą bezpieczną i nie zwiększa ryzyka zdarzeń niepożądanych.

Słowa kluczowe: rak jajnika, klinowa resekcja wątroby, krzywa uczenia

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INTRODUCTION

Ovarian malignancies include ovarian cancers, germ-cell tumors, sex-cord tumors and metastatic tumors. Ovarian cancer accounts for up to 90% of all ovarian malignancies and is the second most common gynecologic malignancy in the developed countries, following endometrial cancer[1–4]. Contrary to endometrial cancer, however, it presents a significantly poorer prognosis[1,2]. Ovarian cancer predominately affects women in perimenopausal age and, due to its non-pathognomonic symptoms, it has a rapid progression rate and there is no available screening for it. Up to 65% of ovarian cancers are stage III or IV per the International Federation of Gynecology and Obstetrics (Fédération Internationale de Gynécologie et d'Obstétrique; FIGO) classification at the time of diagnosis. Stage III ovarian cancer is subdivided into: (1) stage IIIA, defined as a presence of a primary gross tumor in the pelvis with cancerous cells spread in the abdominal cavity; (2) stage IIIB – in which gross cancerous tissue <2 cm is present above the pelvic brim; and (3) stage IIIC – in which gross cancerous tissue >2 cm is present above the pelvic brim and includes liver capsule involvement, but there are no parenchymal metastases[5]. Contrary to ovarian cancers, non-epithelial ovarian malignancies affect younger women and are smaller in diameter.

Debulking surgery is the core treatment for ovarian malignancy including ovarian cancer[3,5]. This can be performed as an initial treatment and is referred to as a primary debulking surgery (PDS) or – in cases when a PDS is not feasible – as an interval debulking surgery (IDS) done after the neoadjuvant chemotherapy. In both cases, the aim of the treatment is to achieve a complete resection of primary tumor and cancerous infiltration – R0. If this is not possible, it is accepted to remove all the macroscopic disease, but microscopic margins can be cancer-positive, which is known as R1 resection. Finally, the macroscopic residual tumor is classified as an R2 resection and significantly reduces the chance of complete recovery[6]. More than 40% of patients with stage IIIC/IV disease according to the previously-mentioned classification show widespread peritoneal carcinomatosis and require high-complexity surgery including extra-gynecologic procedures (e.g. rectosigmoid, large and small bowel, as well as diaphragmatic resection, splenectomy, and liver surgery including wedge resections to achieve R0 or R1 goals[7,8].

In this study, we aimed to evaluate the prevalence of liver involvement in women with ovarian cancer at the time of diagnosis, and to analyze the safety and feasibility of liver wedge resection as part of DS performed by a gynecologic oncologist.

MATERIALS AND METHODS

Identification of cases

We retrospectively identified 319 cases of ovarian cancer treated in our tertiary gynecologic oncology unit between the 1st of January 2010 to 31st of December 2019. The inclusion criteria for further analysis were following: (1) age 18+ years; (2) full histopathological report confirming ovarian cancer diagnosis; (3) FIGO stage IIIC disease; (4) PDS or IDS performed by a gynecologic oncologist. Patients with (1) incomplete medical records; (2) who had surgery co-performed by a colorectal, oncologic, hepatobiliary surgeon or a urologist; (3) with non-epithelioid ovarian malignancy were excluded from the study. Additionally, we identified 15 women with a history of a pelvic/abdominal surgery: 3 after laparoscopic cholecystectomy, 1 after laparoscopic appendectomy, 2 after laparoscopic supracervical hysterectomy, 1 after laparotomy and total hysterectomy and 8 after caesarean section. These patients were also included in the analysis to maintain the consecutiveness of cases as high as possible. Women classified for IDS were prescribed 3 courses of neoadjuvant standard chemotherapy based on taxanes and platinum derivatives.

The monodisciplinary surgical team consisted of two gynecologic oncologists who performed cytoreductive surgery during the whole study period. The third member of the surgical team was under training in obstetrics and gynecology and rotated according to their residency program[9]. Liver wedge resections were performed using monopolar coagulation, while argon plasma coagulation (APC) was used to maintain hemostasis if required.

The endpoints analyzed were as follows: (1) operating time measured from skin incision to skin closure; (2) intraoperative blood loss, defined as blood volume removed by suction; and (3) postoperative hospital stay length calculated from the first postoperative day to hospital discharge date. Women who had liver wedge resection performed as part of debulking surgery were enrolled to Group A, while Group B comprised patients who did not have this procedure.

Patients' safety evaluation

Patients' safety was evaluated based on the presence of adverse events, an inevitable aspect of the medical services provided, and these events were defined as minor Adverse Effects (mAEs) and severe Adverse Effects (sAEs). mAEs matched complications type I–IIIa according to the Clavien–Dindo classification[10] and included: (1) wound infection; (2) prolonged hospital stay (>10 days); and (3) hematoma managed nonsurgically. sAEs also corresponded with the Clavien–Dindo IIIb–V complications[10] and were as follows: (1) patient death; (2) admission to the intensive care unit; (3) reoperation due to intraperitoneal bleeding; (4) wound dehiscence requiring re-suturing under general anesthesia; (5) leakage of rectosigmoid colon anastomosis; (6) ureteral leakage; (7) vesico-vaginal and recto-vesical fistula.

Statistical analysis

Using the Kolmogorov–Smirnov test, the distribution of the continuous variables analyzed was checked. Data with

	Entire cohort (*N* = 120)	Group A (*n* = 22)	Group B (*n* = 98)	*p**
Mean age (±*SD*) [years]	57.60 (±13.03)	58.20 (±13.89)	56.31 (±11.03)	0.407
Mean BMI (±*SD*) [kg/m²]	26.88 (±4.57)	26.80 (±4.61)	27.08 (±4.52)	0.731
Mean age at menarche (±*SD*) [years]	12.71 (±2.59)	12,92 (±1.42)	12,71 (±2.02)	0.821
Parity: • **nulliparous** • **uniparous** • **multiparous**	 44 (36.66%) 12 (10.00%) 64 (53.34%)	 8 (36.36%) 3 (13.64%) 11 (50.00%)	 36 (36.73%) 9 (9.19%) 53 (54.08%)	0.756
Premenopausal (*n*; %) **Postmenopausal (*n*; %)**	40 (33.33%) 80 (66.67%)	8 (36.36%) 14 (63.64%)	32 (32.65%) 64 (67.35%)	0.425
Mean menopausal age (±*SD*) [years]	52.54 (±8.79)	52.98 (±6.42)	51.87 (±7.92)	0.721
Tumor histology: • **high-grade serous** • **low-grade serous** • **clear cell** • **endometroid** • **mucinous**	 72 (59.02%) 31 (27.68%) 5 (4.10%) 4 (2.46%) 8 (6.56%)	 13 (59.10%) 4 (18.17%) 2 (9.09%) 0 (0.00%) 3 (13.64%)	 59 (60.02%) 27 (27.74%) 3 (3.06%) 4 (4.08%) 5 (5.10%)	0.476
Timing of cytoreductive surgery: • **primary** • **interval**	 82 68.33%) 38 (31.67%)	 12 (54.55%) 10 (45.45%)	 70 (71.43%) 28 (28.57%)	0.088

SD – standard deviation; **BMI** – body mass index.
***** Compared between Group A and B.

Tab. 1. Baseline characteristics of patients

normal distribution were presented as medians and standard deviation (±*SD*), while variables with abnormal distribution, as well increment data, were shown as means and interquartile range (IQR). The *t*-Student test was utilized for variables with normal distribution and the Mann–Whitney *U* test was selected for increment and abnormally distributed variables. Categorized variables were shown as a number of cases (*n*) and a percentage (%) and compared using the chi-square test.

As described in our former study, we applied the cumulative sum control chart (CUSUM) analysis to investigate the learning curve in terms of operative time, intraoperative blood loss and the length of hospital stay as well as incidence of sAEs and mAEs in women treated surgically for stage IIIC ovarian cancer[10]. As one of the investigated groups had less than 30 cases, Yates correction was applied when appropriate.

A *p* value of 0.05 was considered statistically significant, and all the calculations were performed using the STATISTICA data analysis software (TIBCO Software Inc. 2017, version 13.0, Palo Alto, CA, USA).

RESULTS

Patients and procedures

From the total number of 323 identified patients with ovarian cancer, after applying the inclusion and exclusion criteria, 122 (48.61%) were identified as eligible for the study (Fig. 1). Baseline characteristics of the study cohort are shown in Tab. 1. Based on their medical records, we confirmed 22 cases of patients with liver wedge resection, who were included in Group A, while Group B comprised 98 women, who did not have this procedure performed during the debulking surgery (Fig. 1).

In the entire cohort, the median operating time was 345.00 min (IQR: 195.50), the median intraoperative blood loss was 2,120.00 mL (IQR: 1,422.50) and the median hospital stay was 11.00 days (IQR: 7.00). There were no significant differences between Groups A and B in the abovementioned variables analyzed (Tab. 2). When it comes to the incidence rate of mAEs and sAEs in the entire cohort, there were 62 (51.66%) and 42 (35.00%) cases, respectively.

	Entire cohort (*N* = 120)	Group A (*n* = 22)	Group B (*n* = 98)	*p**
Median operating time (IQR) [min.]	345.00 (IQR: 195.50)	360.00 (IQR: 205.00)	330.00 (IQR: 195.00)	0.287
Median postoperative hospital stay (IQR) [days]	11.00 (IQR: 7.00)	10.00 (IQR: 2.50)	11.00 (IQR: 8.00)	0.194
Median intraoperative blood loss (IQR) [mL]	2,120.00 (IQR: 1,422.50)	1,805.00 (IQR: 1,660.00)	2,135.00 (IQR: 1,275.00)	0.279
Number of minor adverse effects (%)	62 (51.66%)	9 (41.00%)	53 (54.08%)	0.777
Number of severe adverse effects (%)	42 (35.00%)	8 (36.36%)	34 (34.69%)	0.882

IQR – interquartile range.
***** Compared between Group A and B.

Tab. 2. Type of surgical procedures and outcomes

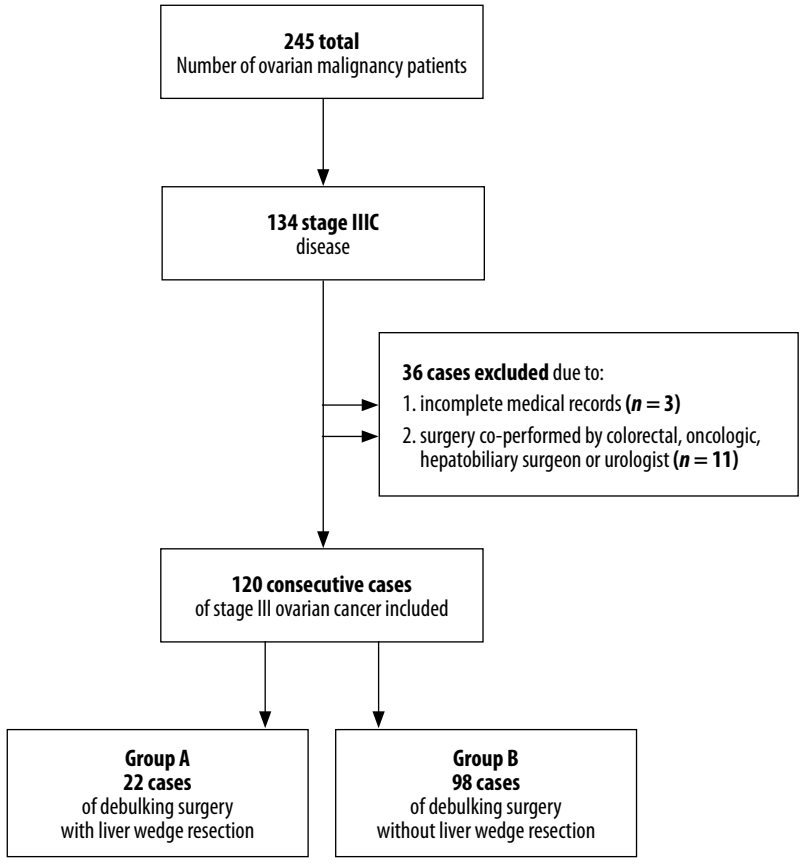

Fig. 1. Number of patients eligible to the study

There were no significant differences in the incidence of mAEs and sAEs between the two analyzed groups (Tab. 2).

Learning curve endpoints

The median operating time in the 120 consecutive cases was 345.00 min (IQR: 195.50). No significant differences between Group A and B were observed (Tab. 2). The median intraoperative blood loss in the whole cohort was 2,120.00 mL (IQR: 1,422.50), and similarly, Groups A and B did not differ in a significant way (Tab. 2). Again, there were no significant differences in median postoperative hospital stay between the analyzed groups, and the median postoperative hospital stay for the entire cohort was 11.00 days (IQR: 7.00) (Tab. 2).

In Group A, the CUSUM analysis of operating time indicated that procedure no. 10 was the cut-off point of gaining a stable and repeatable surgical experience; in Group B, this point was established at procedure no. 56 (Fig. 2). When the entire cohort was analyzed, it was procedure no. 53 that was identified as the cut-off point of stable and repeatable operating time (Fig. 2). Intraoperative blood loss analysis of both groups allowed us to identify cases no. 10 and no. 53 as the cut-off points of procedure stabilization. In the entire cohort, the stabilization of intraoperative blood loss was achieved at procedure no. 62 (Fig. 3). Postoperative hospital stay stabilized after procedure no. 8 and no. 56 in Groups A and B, respectively; and after procedure no. 63 in the entire cohort (Fig. 4).

Patient safety

In the entire cohort, 62 (51.66%) mAEs occurred. There were 9 (41.00%) and 53 (54.08%) mAEs identified in groups A and B, respectively. When it comes to the prevalence of mAE, there was no significant difference between these two groups (Tab. 2). Additionally, 42 (35.00%) cases of sAE were reported in the entire cohort, specifically, 8 (36.36%) in Group A and 34 (34.69%) in Group B. Again, there was no statistical difference in the incidence of sAEs between the two groups (Tab. 2). Furthermore, CUSUM analysis of mAEs and sAEs showed that in the entire cohort, the incidence of mAEs stabilized after procedure 53, and a stable decrease in sAEs was accomplished after the procedure 61 (Figs. 5, 6). The stabilization of AEs was gained with the procedures 12 and 47, respectively for Group A, as well as procedures 17 and 56 in Group B (Figs. 5, 6).

DISCUSSION

Our findings on operating time and intraoperative blood loss during debulking surgery in advanced ovarian cancer

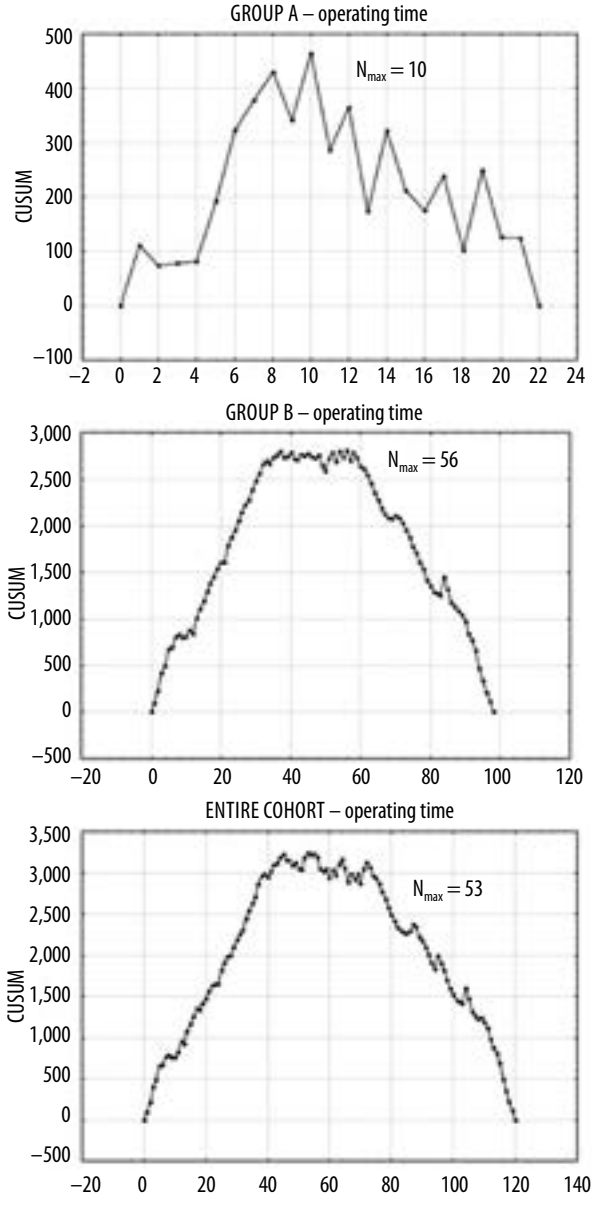

Fig. 2. Cumulative sum control chart of operative (CUSUM) operating in Group A, Group B and the entire cohort against the number of patients

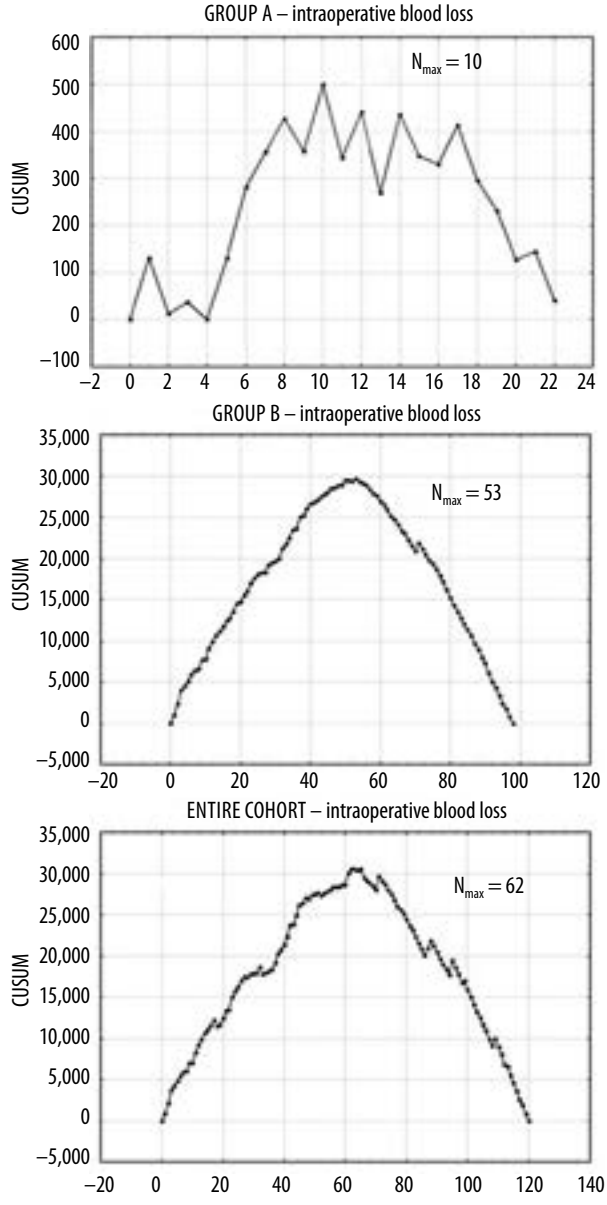

Fig. 3. Cumulative sum control chart of operative (CUSUM) intraoperative blood loss in Group A, Group B and the entire cohort against the number of patients

are comparable with the findings of Nishikimi et al., proving that upper abdominal complex surgery performed by a well-trained gynecologic oncologists team is a safe and feasible procedure with optimal oncological outcomes[11,12]. A further detailed analysis showed that liver wedge resection during a cytoreductive surgery in women with FIGO stage IIIC ovarian malignancy does not significantly impact either the operating time, intraoperative blood loss, or postoperative hospital stay. This procedure also did not impact the shape of a learning curve for the operating time, intraoperative blood loss, or postoperative hospital stay. A forward shift of several cases after this procedure stabilization was gained in the entire cohort compared to Group B was due to an increase in number of analyzed cases rather than a result of gaining surgical skills. In Group A, the learning curves for operating time, intraoperative blood loss, and postoperative hospital stay remained irregular and different in shape compared to Group B and the entire cohort.

The prevalence of mAEs and sAEs in our study remain comparable with other results[11,12]. Liver wedge resection did not increase the prevalence of mAEs or sAEs. Comparable learning curves of mAEs and sAEs in Group B and the entire cohort additionally confirm that the fact that liver wedge resection is performed by a gynecologic oncologist does not impact the final outcome of the cytoreductive surgery in advanced ovarian cancer. These findings remain

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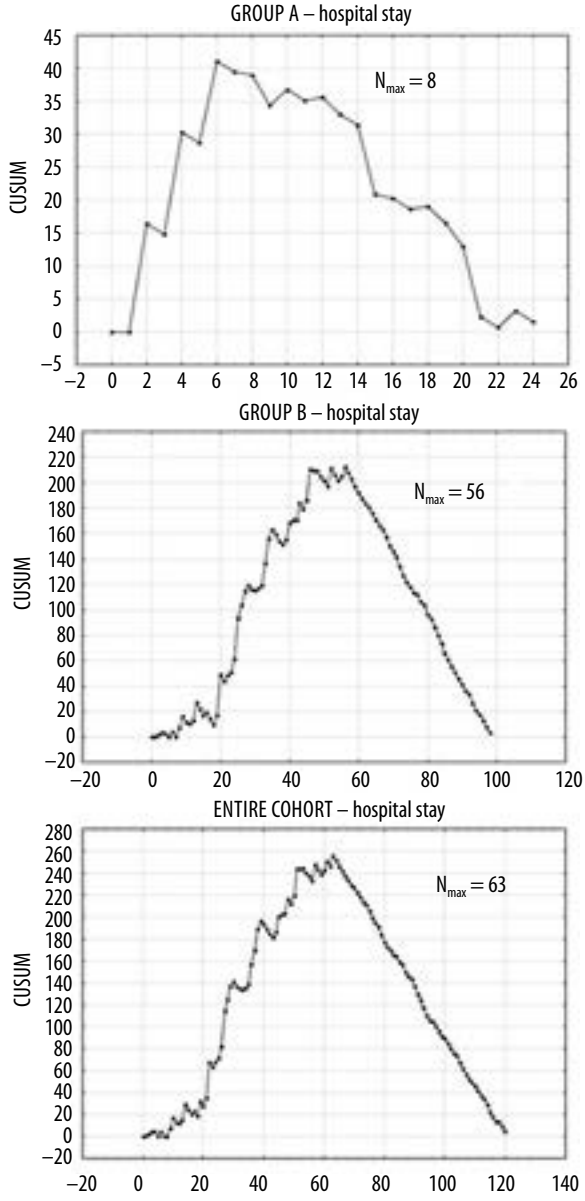

Fig. 4. Cumulative sum control chart of operative (CUSUM) postoperative hospital stay in Group A, Group B and the entire cohort against the number of patients

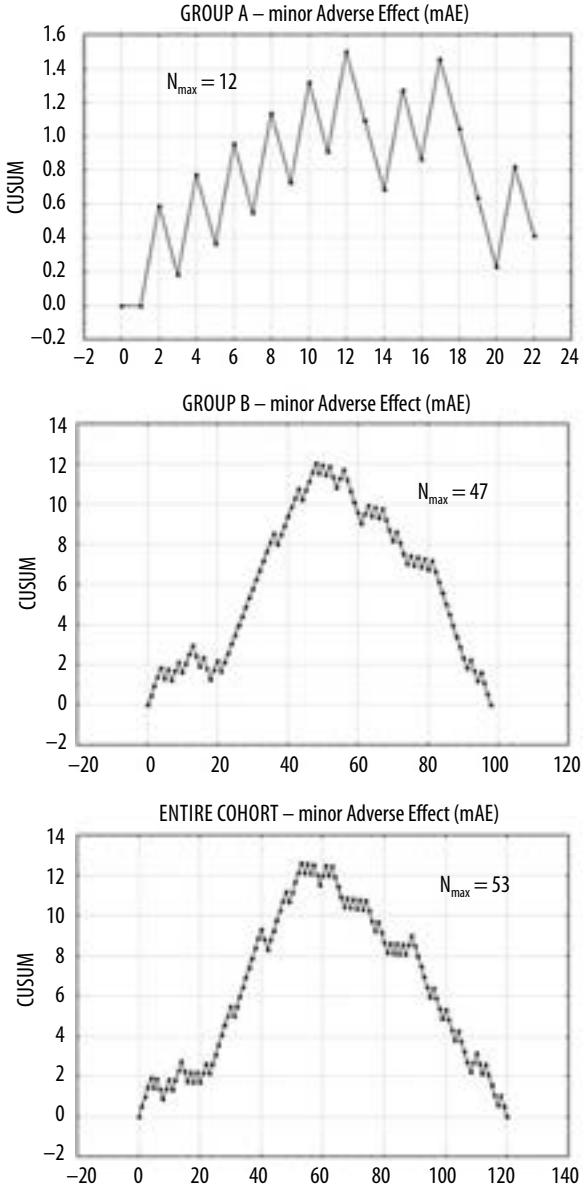

Fig. 5. Cumulative sum control chart of operative (CUSUM) minor Adverse Effect (mAE) in Group A, Group B and the entire cohort against the number of patients

consistent with what Bacalbasa et al. postulated based on a literature review, namely, that properly performed surgical procedures involving liver in women suffering from ovarian cancer not only do not increase the risk of postoperative AEs, but also significantly increase the overall survival rate[13]. In another study, Bacalbasa et al. concluded that resection of liver metastases in women with ovarian cancer performed as part of a primary, secondary and even tertiary or quaternary cytoreductive surgery is beneficial in terms of survival rate and indicate that liver resection remains safe with no mortality and 25% morbidity rates[14]. This conclusion stays in consistency with Roh et al., who analyzed 4 cases of liver wedge resections, 13 cases of unisegmentectomy, and 1 bisegmentectomy as part of a secondary cytoreductive surgery for recurrent ovarian cancer, and concluded that hepatic resection for recurrent ovarian cancer is safe and even associated with a favorable outcome and a low risk of AEs[15].

The large sample size of patients with stage IIIC ovarian cancer proven with a histopathological report and a relatively substantial number of patients who underwent liver wedge resection is the major strength of this study. We are, however, aware of its limitations. Firstly, we were unable to analyze neither the operative time of liver wedge resection, nor the intraoperative blood loss directly connected with this procedure. Based on the learning curves

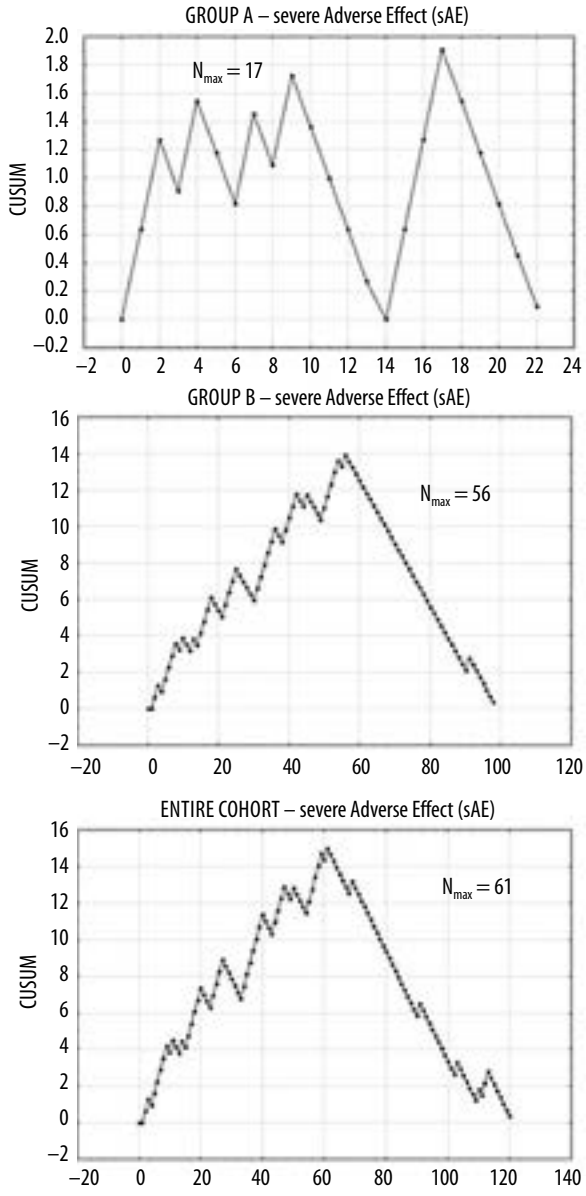

Fig. 6. Cumulative sum control chart of operative (CUSUM) severe Adverse Effect (sAE) in Group A, Group B and the entire cohort against the number of patients

in Group A, these data should be interpreted with caution. Secondly, the cytoreductive surgeries were not performed by a single gynecologic oncologist, but by a team consisting of two gynecologic oncologists and a rotating third member under training in obstetrics and gynecology. Therefore, we analyzed gaining surgical experience in a debulking surgery performed due to an advanced ovarian cancer by an operating team, and not by a single surgeon. This can be explained by the fact that a high-complexity surgery performed in women with advanced ovarian cancer, usually in combination with upper abdominal surgery, and additionally, bowel and liver resection, requires an experienced surgical team and this kind of experience can be hardly gained by a single, even highly skilled and practized surgeon, as concluded by Nishikimi et al.[11].

In conclusion, wedge liver resection performed as part of cytoreductive surgery in women with advanced ovarian cancer can be performed safely and feasibly by gynecologic oncologists. It does not increase the risk of mAEs or sAEs, nor significantly affects operating time, intraoperative blood loss or postoperative hospital stay.

Institutional Review Board statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the Jagiellonian University (protocol code: 1072.6120.238.2021; date of approval: 29 September 2021).

Informed consent statement

Patient consent was waived as the study involved retrospective analysis of anonymous data.

Conflict of interest

The authors declare no conflict of interest.

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