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The Effect of Upper Abdominal Surgery on Complication Profile in Ovarian Cancer

Gurkan Kiran[1], Fatma Basak Tanoglu[1]*, Caglar Cetin[1], Ozge Pasin[2]

[1]Department of Obstetrics and Gynecology, Bezmialem University Faculty of Medicine, Istanbul, Turkey
[2]Department of Biostatistics, Bezmialem University, Faculty of Medicine, Istanbul, Turkey

***Corresponding author:**
Fatma Basak Tanoglu, MD
Bezmialem Vakif University Hospital
İskender Paşa Mh Adnan Menderes Bulvarı, Vatan Cad, 34093 Fatih
Istanbul, 34093, Turkey
Fax: +90 (212) 453 18 69
Tel: +90 212 453 1700
E-mail: basaktanoglu3@gmail.com
Orcid ID: 0000-0002-0843-9160

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Rezumat

Complicațiile intervențiilor chirurgicale de citoreducție din abdomenul superior în cancerul ovarian

Introducere: În contextul diseminării peritoneale superficiale a cancerului ovarian, procedurile chirurgicale în etajul abdominal superior sunt adesea necesare pentru a obține citoreducția chirurgicală optimă. Acest studiu compară ratele de mortalitate şi morbiditate ale pacienților la care s-au practicat intervenții chirurgicale de citoreduție tumorală în etajele abdominale superior şi inferior în instituția noastră.

Material şi metode: Pacienții cu intervenții chirurgicale de citoreducție tumorală pentru afecțiuni ovariene maligne din 2014 până în 2020 au fost identificați retrospectiv dintr-o bază de date instituțională. Citoreducția abdominală superioară a fost definită anatomic ca rezecții tumorale practicate în apropierea ligamentului lui Treitz. Au fost analizate rezultatele perioperatorii şi postoperatorii.

Rezultate: Au fost efectuate în total 148 de intervenții chirurgicale. Toate procedurile au fost efectuate de un singur medic ginecolog. În urma evaluării procedurilor citoreductive, s-a constatat că, leziunile diafragmei, transfuzia de sânge, spitalizarea, atelectazia, pneumonia, pleurezia, infecția plăgii şi necesarul de terapie intensivă s-au dovedit a fi semnificativ mai mari din punct de vedere statistic la pacienții care au suferit o intervenție chirurgicală în abdomenul superior, comparativ cu pacienții cu proceduri efectuate în abdomenul inferior (p=0,001, p=0,017, p=0,002, p=0,045, p=0,006, respectiv p=0,005).

Concluzie: La pacientele programate pentru intervenție chirurgicală citoreductivă pentru diagnosticul de cancer ovarian, chirurgia abdominală superioară este o procedură viabilă, deşi prezintă un

risc mai mare de complicații comparativ cu chirurgia abdominală inferioară. Chirurgia abdominală superioară poate fi considerată în cazul cancerului ovarian avansat atunci când pacienții prezintă un profil de complicații acceptabil, luând în considerare posibilul beneficiu în termeni de supraviețuire.

Cuvinte cheie: cancer ovarian, chirurgie citoreductivă, Complicație postoperatorie, morbiditatea post-operatorie

Abstract

Introduction: Due to the superficial peritoneal spread of ovarian cancer, upper abdominal surgical procedures are often required to achieve optimal surgical cytoreduction. This study compares the mortality and morbidity rates of patients undergoing upper and lower abdominal cytoreductive surgery in our institution.

Material and Methods: Patients who underwent cytoreductive surgery for ovarian malignancies from 2014 to 2020 were retrospectively identified from an institutional database. Upper abdominal cytoreduction was defined anatomically as debulking of disease proximal to the ligament of Treitz. Perioperative and postoperative outcomes were analyzed.

Results: A total of 148 operations were performed. A single gynecologic oncologist performed all procedures. When all cytoreductive procedures were evaluated, diaphragm injury, blood transfusion, hospital stay, atelectasis, pneumonia, effusion, wound infection and need for intensive care were found to be statistically significantly higher in patients who underwent upper abdominal surgery compared to patients in the lower abdominal surgery group (p=0.001, p=0.017, p=0.002, p=0.045, p=0.006, p=0.005, respectively).

Conclusion: In patients scheduled for cytoreductive surgery with the diagnosis of ovarian cancer, upper abdominal surgery is a viable procedure, although it carries a higher risk of complications compared to lower abdominal surgery alone. Upper abdominal surgery in advanced ovarian cancer can be applied to patients with an acceptable complication profile when the possible survival advantage is considered.

Key words: ovarian cancer, cytoreductive surgery, postoperative complication, postoperative morbidity

Introduction

Ovarian cancer is the disease with the highest mortality among gynecological malignancies. Despite other cancers with higher incidence rates, such as endometrial and cervical cancer, death rates from ovarian cancer remain high. According to the 2020 World Cancer Report, the five-year survival rate is below 30% (1). The main reason is that the disease can often be diagnosed at an advanced stage, and the recurrence rate is high after standard treatment. Staging surgery in the early stages and chemotherapy applied after primary cytoreductive surgery in the advanced stages are accepted as the gold standard in managing the disease. Residual tumor size after primary cytoreductive surgery is the most important prognostic factor in ovarian cancer (2). However, complete resection without residual macroscopic tumor can be achieved in only 33% of patients (3). Studies show that aggressive cytoreductive surgery improves the rates of complete resection and the prognosis of patients with advanced disease (4). The recurrence of advanced-stage ovarian cancer is more

common in the intraperitoneal region (5,6). Aggressive cytoreductive surgery improves the rates of complete resection and the prognosis of patients with advanced disease (7). Studies show that aggressive cytoreductive surgical approaches in which gastrointestinal and upper abdominal surgery are applied are associated with reduced intra-abdominal recurrence rates. Upper abdominal procedures in this context of ovarian cancer include diaphragm stripping or resection, distal pancreatectomy, splenectomy, and partial hepatectomy.

Although many studies emphasize the importance of upper abdominal surgery included in the procedure for survival, there are limited studies in the literature focusing on complications of upper abdominal surgery (8). The present study aims to compare the mortality and morbidity profile of patients who underwent combined upper and lower abdominal cytoreductive surgery with those who underwent isolated lower abdominal surgery in our center.

Materials and Methods

This is a retrospective study in which patients with ovarian cancer who underwent staging or cytoreductive surgery by a single gynecologist oncologist between January 2014 and December 2020 in the Department of Obstetrics and Gynecology, Bezmialem Vakıf University Faculty of Medicine, were included. The Non-interventional Ethics Committee decision number of the study was 2022/216. Data were collected by reviewing electronic patient records, including radiology reports, laboratory tests, pathology/surgery reports, and hospitalizations in other departments. Patients between the ages of 17-80 admitted to the oncology outpatient clinic and referred from other outpatient clinics with a preliminary diagnosis of ovarian cancer, operated on by us, and whose postoperative data were accessible were included in the study. Patients whose pathology results were reported as non-ovarian malignancy or benign and whose postoperative data could not be reached were excluded from the study.

Demographic characteristics (age, body mass index, ASA, and ECOG scores); physical examination, laboratory tests (CA125 values), and imaging findings (presence of ascites); primary of the peritoneal tumor, surgical stages, histopathological features and grade in the final pathology reports, type and degree of cytoreduction, whether simultaneous pelvic-paraaortic lymph node dissection was performed; operation-related variables (intraoperative and postoperative complications, blood transfusion, ICU need, hospitalization time, mortality in the first 30 days) of the patients were analyzed through the hospital database. Statistical evaluation was performed using the collected data. Upper abdominal cytoreduction was defined anatomically as debulking of the disease proximal to the ligament of Treitz. Two groups were formed; the group in which upper and lower abdominal cytoreduction was performed and the group in which only lower abdominal cytoreduction was performed. The two groups were compared in terms of the parameters mentioned above.

Morbidity was defined as any adverse event: complications occurring within 30 days of surgery were described as early, and those occurring later were defined as late complications. Mortality was defined as death occurring within 30 days of surgery. Complications were divided into two groups: intraoperative and postoperative. Intraoperative complications were determined as vascular, gastrointestinal, urinary, and diaphragm damage. Postoperative complications were determined as atelectasis, pneumonia, effusion, bleeding, abscess, ileus, wound infection, anastomotic leakage, hernia, and deep vein thrombosis.

Statistical Analysis

The descriptive statistics of the qualitative variables in the study are given as numbers and percentages, and the descriptive statistics of the quantitative variables are presented as mean, median, standard deviation, minimum and maximum. Pearson chi-square and Fisher exact tests were used in group comparisons

regarding the ratios of qualitative variables. The conformity of the quantitative data to the normal distribution was investigated using the Shapiro-Wilk test. The independent sample t-test (student t-test) was used to compare two independent groups regarding the means of normally distributed variables. The Mann-Whitney U test compares two independent groups regarding the medians of non-normally distributed variables. The statistical significance level was taken as 0.05 in the calculations, and the statistical analyzes were performed with the SPSS (version 28) package program.

Results

A total of 148 patients who met the criteria were included in the study. Fifty-five patients underwent upper and lower abdominal cytoreductive surgery (Group 1), while only lower abdominal cytoreductive surgery (Group 2) was performed in 93 patients. The characteristics are shown in *Table 1.* The median age of the patients in group 1 was 61(22-87), the median value of BMI was 26.5(17.9-35.7) kg/m^2, while the median age of the patients in group 2 was 53(17-83), and the median BMI value was 25.6(18.7-40.8) kg/m^2. The presence of ascites and high CA125 value in Group 1 were statistically significantly higher when compared to Group 2. When the ASA and ECOG scores of the patients were compared, no statistical significance was found. The cytoreductive procedures applied to the patients are shown in *Table 2.* In most patients, the disease was of ovarian origin (85.8%), and the histological type was serous ovarian carcinoma (70.2%). Lower abdominal surgery was performed in the %62.8 of patients, while both upper and lower abdominal surgery was performed in 37.1% of the patients. When compared in terms of disease stage, patients who underwent upper and lower abdominal cytoreduction had more advanced disease (stage IIIA and above) (p< 0.001). The pelvic and paraaortic lymphadenectomy and serous histological type rate were higher in the group undergoing upper + lower abdominal surgery than in the other group (p<0.001). Optimal and suboptimal cytoreduction surgery rates were similar

Table 1. Baseline of patient characteristics.

Variables	Group 1 Upper+Lower (n=55)	Group 2 Lower (n=93)	P value
Median Age; [IQR]	61 [22-87]	53 [17-83]	0.006
BMI*; median; [IQR]; (kg/m^2)	26.5 [17.9-35.7]	25.6 [18.7-40.8]	0.274
ASA**; n(%)			0.010
1	5 (9.1)	26 (28)	
2	33 (60)	5 (37.6)	
3	15 (27.3)	30 (32.3)	
4	2 (3.6)	2 (2.2)	
ECOG***; n(%)			0.170
0	5 (9.1)	21 (22.6)	
1	17 (30.9)	29 (31.2)	
2	28 (50.9)	35 (37.6)	
3	5 (9.1)	8 (8.6)	
Preoperative Ascites; n(%)			<0.001
Present	41 (74.5)	43 (46.2)	
Not present	14 (25.5)	50 (53.8)	
CA125; median; [IQR]; U/ml	647 [14-16614]	130 [3-12230]	<0.001

Data are expressed as median, minimum, maximum or number (%).
$p \leq 0.05$ significant difference, comparison of groups
*Body Mass Index; ** American Society of Anesthesiology; ***Eastern Cooperative Oncology Group

Table 2. The procedures of abdominal cytoreductive surgery in all groups.

Procedure	N (%)
TAH + BSO* + Omentectomy + Apendectomy + PPLND**	55 (37.1)
TAH + BSO + Omentectomy	65 (43.9)
Splenectomy	9 (6.0)
Diaphragm Peritonectomy	34 (22.9)
Colon Resection	17 (11.4)
Resection of the tumor on the surface of liver	4 (2.7)
Liver Lobectomy	2 (1.3)
Distal Pancreatectomy	1 (0.6)
Inguinal Lymphadenectomy	2 (1.3)

Data are expressed as number (%)
* Total Abdominal Hysterectomy + Bilateral Salpingoopherectomy
** Pelvic and Paraaortic Lymphadenectomy

Table 3. Clinicopathologic characteristics of patients.

Variables	Group 1 (n=55) Upper + Lower	Group 2 (n=93) Lower	P value
Primary Tumor			0.218
Ovarian cancer	46 (83.6)	81 (87.1)	
Tubal cancer	2 (3.6)	7 (7.5)	
Primary peritoneal cancer	7 (12.7)	5 (5.4)	
Stage of Disease			<0.001
IA	0 (0)	19 (22.6)	
IB	0 (0)		1 (1.2)
IC	0 (0)		9 (10.7)
IIA	0 (0)	6 (7.1)	
IIB	0 (0)	2 (2.4)	
IIIA	2 (3.6)		4 (4.8)
IIIB	1 (1.8)	10 (11.9)	
IIIC	38 (69.1)	25 (29.8)	
IVA	7 (12.7)	4 (4.8)	
IVB	7 (12.7)	4 (4.8)	
Tumor Grade			0.002
1	2 (3.6)	18 (21.4)	
2	5 (9.1)	14 (16.7)	
3	48 (87.3)	52 (61.9)	
Histologic Type			<0.001
Serous	50 (89.3)	54 (56.3)	
Mucinous	1 (1.8)	6 (6.3)	
Endometrioid	1 (1.8)	15 (15.6)	
Clear Cell	1 (1.8)	3 (3.1)	
Others	3 (5.4)	9 (9.4)	
Cytoreductive Surgery			0.105
PDS	38 (69.1)	76 (81.7)	
IDS	15 (27.3)	12 (12.9)	
Secondary	2 (3.6)	5 (5.4)	
Pelvic Lymphadenectomy			<0.001
Performed	47 (85.5)	37 (40.7)	
Not performed	8 (14.5)	54 (59.3)	
Paraaortic Lymphadenectomy			<0.001
Performed	46 (83.6)	40 (44)	
Not performed	9 (16.4)	51 (56)	
Cytoreduction			0.296
Optimal	43 (78.2)	79 (84.9)	
Suboptimal	12 (21.8)	14 (15.1)	

Data are expressed as number (%). $p \leq 0.05$ significant difference, comparison of groups.

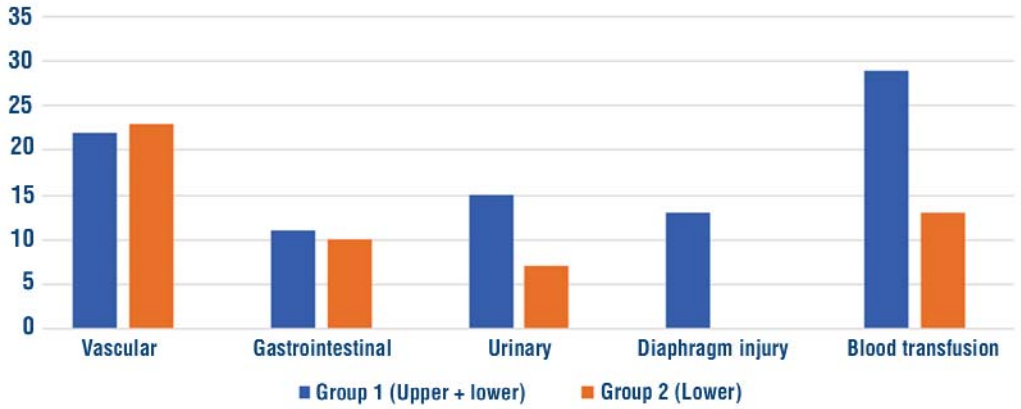


Figure 1. Percentage distribution of intraoperative complications.

between both groups (p=0.296). The clinicopathological features of the patients are shown in *Table 3*.

One patient in each group died within 30 days of surgery due to progression of the existing disease. There was no statistically significant difference between the groups regarding intraoperative vascular, gastrointestinal, and urinary complications. As expected, diaphragm damage and blood transfusion were higher in group 1 (p=0.001; p=0.017) (*Fig. 1*). The postoperative hospital stay was significantly longer in group 1 than in group 2 (p=0.002). Again, postoperative complications such as atelectasis, wound infection, and the need for intensive care unit were statistically higher in group 1 (p=0.045; p= 0.006; p=0.005, respectively) (*Fig. 2*). Both groups were similar regarding other complications (*Table 4*). According to the univariate analysis, no association was observed between the groups regarding postoperative hospital stay and type of surgery (*Table 5*). Only two variables (diaphragmatic peritonectomy and colon resection) were significantly associated with a more extended postoperative hospital

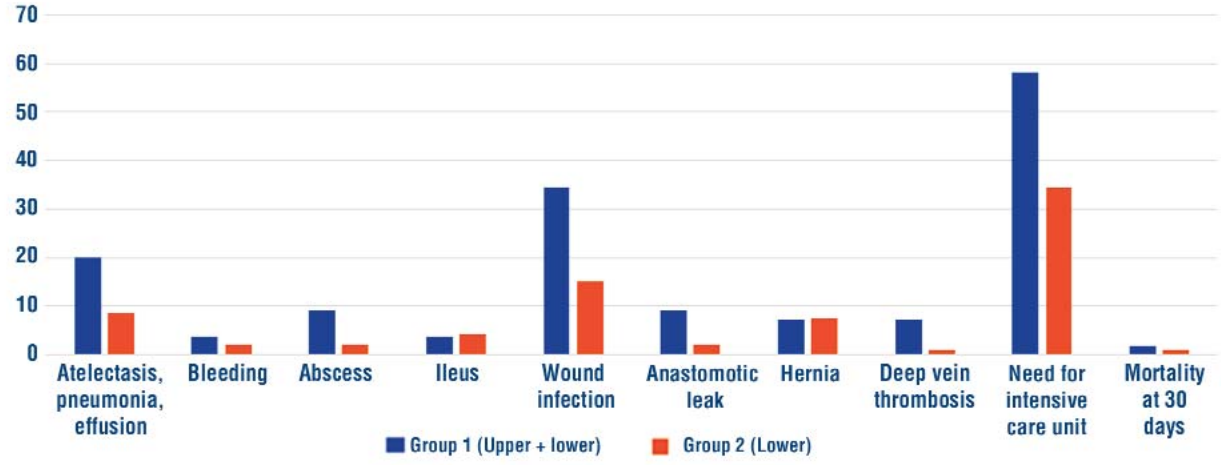


Figure 2. Percentage distribution of postoperative complications.

Table 4. Perioperative and postoperative morbidity and mortality between groups.

Variables	Group 1 Upper + Lower (n=55)	Group 2 Lower (n=93)	P value
Intraoperative Complications n (%)			
Vascular	12 (21.8)	21 (22.6)	0.914
Gastrointestinal	6 (10.9)	9 (9.7)	0.810
Urinary	8 (14.5)	6 (6.5)	0.104
Diaphragma injury	7 (12.7)	0 (0)	0.001
Blood transfusion	16 (29.1)	12 (13)	0.017
Postoperative Complications n (%)			
Length of stay; median; [min-max]; d	8 [1-45]	6[1-68]	0.002
Atelectasis, pneumonia, effusion	11 (20)	8 (8.6)	0.045
Bleeding	2 (3.6)	2 (2.2)	0.628
Abscess	5 (9.1)	2 (2.2)	0.102
Ileus	2 (3.6)	4 (4.3)	1
Wound infection	19 (34.5)	14 (15.1)	0.006
Anastomotic leak	5 (9.1)	2 (2.2)	0.102
Hernia	4 (7.3)	7 (7.5)	0.955
Deep vein thrombosis	4 (7.3)	1 (1.1)	0.064
Need for intensive care unit	32 (58.2)	32 (34.4)	0.005
Mortality at 30 days	1 (1.8)	1 (1.1)	1

Data are expressed as median, minimum, maximum or number (%).
$p \leq 0.05$ significant difference, comparison of groups.

Table 5. Length of hospital stay according to the surgical procedures performed.

Surgical Procedure(s)	N	Mean ± SD	Median (Minimum-Maximum)	P value
TAH+BSO+ Omentectomy				
Yes	131	9.98 ± 9.48	7.00 (1.00-68.00)	0.913
No	16	8.44 ± 4.49	8.00 (2.00-18.00)	
TAH+BSO+ Omentectomy + Appendectomy+ PPLND				
Yes	62	9.03 ± 9.27	7.00 (3.00-68.00)	0.216
No	85	10.38 ± 8.93	8.00 (1.00-50.00)	
Splenectomy				
Yes	9	9.56 ± 6.11	8.00 (5.00-25.00)	0.578
No	138	9.83 ± 9.24	7.00 (1.00-68.00)	
Diaphragm Peritonectomy				
Yes	36	10.67 ± 8.04	8.00 (1.00-44.00)	0.050
No	111	9.53 ± 9.40	7.00 (1.00-68.00)	
Colon Resection				
Yes	18	12.78 ± 7.41	9.50 (4.00-27.00)	0.004
No	129	9.40 ± 9.22	7.00 (1.00-68.00)	
Liver Lobectomy				
Yes	7	14.00 ± 13.87	8.00 (6.00-45.00)	0.138
No	140	9.60 ± 8.78	7.00 (1.00-68.00)	

Data are expressed as median, minimum, maximum, mean ± standard deviation or number.
$p \leq 0.05$ significant difference, comparison of groups.

stay (p=0.050; p=0.004).

Discussion

Ovarian cancer tends to spread to the anatomical regions and organs of the upper abdomen, and therefore, upper abdominal surgery has a key role in achieving an optimal cytoreduction rate (9). In recent years, positive effects of complete cytoreduction on survival

have been demonstrated in ovarian cancers with extensive upper abdominal involvement. As a result, the surgical management of the disease is improving daily (10,11). However, the recent LION study reported that systematic pelvic and paraaortic lymphadenectomy was not associated with longer-term overall or progression-free survival in patients with advanced ovarian cancer who underwent intra-abdominal macroscopic complete resection and had normal lymph nodes, both preoperatively and intraoperatively, then not performing lymphadenectomy (12). While complex surgeries for ovarian cancer directly increase costs, it appears to provide valuable benefits without compromising long-term survival (13,14,15). Few studies in the literature show the complication rates of extensive cytoreductive surgeries, including upper abdominal surgery. A cohort study by Chi et al. examined the major complication rates after primary cytoreduction in patients with ovarian cancer and reported that the most common complications were pleural effusion requiring drainage, pancreatic leak requiring drainage, and intra-abdominal collection. The overall major complication rate within 30 days after surgery was 22%, and the mortality rate was 1.4% (16). In the observational study involving 353 patients and comparing standard and radical surgery, Ren et al. reported the rates of grade 3-4 complications as 8% and 2.9% in patients undergoing upper abdominal surgery and standard surgery, respectively (17). In the literature review by Chéreau et al., the most common complications in patients who underwent aggressive cytoreductive surgery were intestinal fistula (1.4 to 8.2%), septic complications (3.7 to 41.4%), lymphocyst formation (0.6 to 32%), and pulmonary complications in diaphragmatic surgery (0. to 59%) (18). On the other hand, Xu et al. evaluated the postoperative complications of 5223 patients who underwent debulking surgery for epithelial ovarian cancer between 2004 and 2013. They reported that although the complication rates in patients who underwent aggressive cytoreduction were found to be statistically significantly higher, aggressive cytoreduction improves overall and disease-free survival (19). Similar to previous studies, we found that the intraoperative and postoperative complication rates observed in the combined upper and lower abdominal surgery groups were acceptable compared to the standard surgery groups (8,20), suggesting that combined upper and lower abdominal surgery can be safely performed in suitable patients.

The extent of diaphragmatic resection, pleural patency, and liver mobilization are all risk factors for pulmonary and pleural morbidity. The incidence of pulmonary complications varies between 20% and 70% in different studies (21,22). However, there are studies showing that diaphragm surgery can be performed safely without increasing the postoperative morbidity rate by improving the perioperative and postoperative management of these patients (23,24,25). In our study, the rate of postoperative pulmonary complications among all patients was 12.8% (19/148). While the incidence of pulmonary complications in patients undergoing upper abdominal surgery was 20%, it was 8.6% in those with only lower abdominal surgery. We attribute the incidence of pulmonary complications in patients undergoing upper abdominal surgery to prolonging the operation time and interventions to the diaphragm. The literature describes different physical interventions such as deep breathing exercises, intermittent positive pressure breathing, spirometry, oxygen therapy, and early ambulation to prevent pulmonary complications after diaphragmatic surgery. However, strong evidence has yet to be shown about their effectiveness (26). All patients in our study underwent similar exercises after the surgical procedure to avoid pulmonary complications.

Among the upper abdominal procedures performed in advanced ovarian cancer surgery, the surgical procedure associated with the most severe complication is pancreatic resection. In the literature, the complication rate related to pancreatic resection is 30-60%, and the mortality rate is 5% (27,28). Complications are generally in the form of

leakage from the residual pancreas or fistula. The pancreatic fistula is the most common complication after distal pancreatectomy, and its incidence varies widely, ranging from 3% to 49% (29). In our series, a distal pancreatectomy was performed in 1 patient associated with upper abdominal surgery, and no postoperative complications were observed.

Benedetti Panici et al. (8) showed that surgical procedures involving the upper abdominal region (diaphragmatic, gastric, pancreatic resection, and splenectomy) were significantly associated with a longer postoperative hospital stay. Yalcin et al. showed no relationship between the types of upper abdominal surgery procedures and the length of hospital stay. However, they found this period to be longer in patients with severe complications and attributed it to a longer treatment period (30). In our study, postoperative hospital stay was significantly longer in patients with only diaphragmatic peritonectomy and colon resection. We attribute the reasons for prolonged hospitalization in these patients to pulmonary complications and the need to ensure anastomosis safety in patients undergoing colon resection.

Consistent with the available literature, our institutional experience of combined upper and lower abdominal cytoreduction in advanced ovarian cancer is associated with acceptable perioperative and postoperative morbidity and mortality (8,16). In our study, diaphragm damage, pulmonary complications, and wound infection were significantly higher in the group that underwent combined upper and lower abdominal cytoreduction compared to the group that underwent isolated lower abdominal cytoreduction. Our study, in which we found similar morbidity and perioperative results between combined cytoreductions and isolated lower abdominal cytoreductions, confirms the safety and feasibility of combined cytoreductions and the potential value of a collaborative surgical approach.

The limitations of our study are its retrospective design, the relatively small sample size, and the inability to analyze data on disease recurrence and survival due to the need for more patient information. The strengths of our study are that the surgical procedures are performed in a single center by the same surgeon. In addition, the fact that our hospital is a tertiary center has enabled us to receive support from other surgical branches when necessary in the procedures performed during the operation.

Conclusions

In conclusion, our current study has shown that performing upper abdominal surgical procedures, especially in patients with advanced ovarian cancer, is not associated with severe postoperative complications. It was demonstrated that applying existing methods to achieve optimal cytoreduction is acceptable in terms of mortality and morbidity risk.

Conflicts of Interests

The authors declared no potential conflicts of interest.

Financial Disclosure

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References

1. Wild CP, Weiderpass E, Stewart BW. World Cancer Report: Cancer Research for Cancer Prevention. Lyon, France: International Agency for Research on Cancer; 2020.
2. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol. 2002;20(5): 1248-59.
3. Du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer. 2009;115(6):1234-44.
4. Chi DS, Eisenhauer EL, Zivanovic O, Sonoda Y, Abu-Rustum NR, Levine DA et al. Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. Gynecol Oncol. 2009; 114(1):26-31.
5. Cormio G, Rossi C, Cazzolla A, Resta L, Loverro G, Greco P et al. Distant metastases in ovarian carcinoma. Int J Gynecol Cancer. 2003;13(2):125-9.
6. Ferrandina G, Legge F, Salutari V, Paglia A, Testa A, Scambia G. Impact of pattern of recurrence on clinical outcome of ovarian cancer patients: clinical

considerations. Eur J Cancer. 2006;42(14):2296-302.
7. Tate S, Nishikimi K, Matsuoka A, Shozu M. Aggressive surgery for advanced ovarian cancer decreases the risk of intraperitoneal recurrence. Int J Clin Oncol. 2020;25(9):1726-1735.
8. Benedetti Panici P, Di Donato V, Fischetti M, Casorelli A, Perniola G, Musella A, et al. Predictors of postoperative morbidity after cytoreduction for advanced ovarian cancer: Analysis and management of complications in upper abdominal surgery. Gynecol Oncol. 2015;137(3):406-11.
9. Eisenhauer EL, Abu-Rustum NR, Sonoda Y, Levine DA, Poynor EA, Aghajanian C, et al. The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stages IIIC-IV epithelial ovarian cancer. Gynecol Oncol. 2006;103(3):1083-90.
10. Ro Rodriguez N, Miller A, Richard SD, Rungruang B, Hamilton CA, Bookman MA et al. Upper abdominal procedures in advanced stage ovarian or primary peritoneal carcinoma patients with minimal or no gross residual disease: an analysis of Gynecologic Oncology Group (GOG) 182. Gynecol Oncol. 2013;130(3):487-92.
11. Hiu, S., Bryant, A., Gajjar, K., Kunonga, P. T., & Naik, R. Ultra-radical (extensive) surgery versus standard surgery for the primary cytoreduction of advanced epithelial ovarian cancer. The Cochrane database of systematic reviews. 2022;8(8):CD007697.
12. Harter P, Sehouli J, Lorusso D, Reuss A, Vergote I, Marth C, et al. A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms. N Engl J Med. 2019;380(9):822-832.
13. Angioli R, Plotti F, Aloisi A, Capriglione S, Terranova C, Ricciardi R et al. Does extensive upper abdomen surgery during primary cytoreduction impact on long-term quality of life? Int J Gynecol Cancer. 2013;23(3): 442-7.
14. Liberale G, Pop CF, Polastro L, Kerger J, Moreau M, Chintinne M, et al. A radical approach to achieve complete cytoreductive surgery improve survival of patients with advanced ovarian cancer. J Visc Surg. 2020; 157(2):79-86.
15. Tate S, Nishikimi K, Matsuoka A, Otsuka S, Shozu M. Highly Aggressive Surgery Benefits in Patients With Advanced Ovarian Cancer. Anticancer research. 2022;42(7):3707–3716.
16. Chi DS, Zivanovic O, Levinson KL, Kolev V, Huh J, Dottino J et al. The incidence of major complications after the performance of extensive upper abdominal surgical procedures during primary cytoreduction of advanced ovarian, tubal, and peritoneal carcinomas. Gynecol Oncol. 2010;119(1): 38-42.
17. Ren Y, Jiang R, Yin S, You C, Liu D, Cheng X, et al. Radical surgery versus standard surgery for primary cytoreduction of bulky stage IIIC and IV ovarian cancer: an observational study. BMC Cancer. 2015;15:583.
18. Chéreau E, Ballester M, Lesieur B, Selle F, Coutant C, Rouzier R, et al. Complications of radical surgery for advanced ovarian cancer. Gynecol Obstet Fertil. 2011;39(1):21-7. French
19. Xu Z, Becerra AZ, Justiniano CF, Aquina CT, Fleming FJ, Boscoe, F. P et al. Complications and Survivorship Trends After Primary Debulking Surgery for Ovarian Cancer. J Surg Res. 2020;246:34-41.
20. Eng OS, Raoof M, Blakely AM, Yu X, Lee SJ, Han ES et al. A collaborative surgical approach to upper and lower abdominal cytoreductive surgery in ovarian cancer. J Surg Oncol. 2018;118(1):121-126.
21. Cliby W, Dowdy S, Feitoza SS, Gostout BS, Podratz KC. Diaphragm resection for ovarian cancer: technique and short-term complications. Gynecol Oncol. 2004;94(3):655-60.
22. Eisenhauer EL, D'Angelica MI, Abu-Rustum NR, Sonoda Y, Jarnagin WR, Barakat RR et al. Incidence and management of pleural effusions after diaphragm peritonectomy or resection for advanced mullerian cancer. Gynecol Oncol. 2006;103(3):871-7.
23. Bacalbasa N, Balescu I, Balalau C, Ionescu O, Stoica C. Association of Diaphragmatic Surgery as Part of Cytoreductive Effort in Advanced Stage Ovarian Cancer. In vivo (Athens, Greece). 2018; 32(2):431-436.
24. Einenkel J, Ott R, Handzel R, Braumann UD, Horn LC. Characteristics and management of diaphragm involvement in patients with primary advanced-stage ovarian, fallopian tube, or peritoneal cancer. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society. 2009;19(7):1288–1297.
25. Zapardiel I, Peiretti M, Zanagnolo V, Biffi R, Bocciolone L, Landoni F, et al. Diaphragmatic surgery during primary cytoreduction for advanced ovarian cancer: peritoneal stripping versus diaphragmatic resection. Int J Gynecol Cancer. 2011;21(9):1698-703.
26. Thomas JA, McIntosh JM. Are incentive spirometry, intermittent positive pressure breathing, and deep breathing exercises effective in the prevention of postoperative pulmonary complications after upper abdominal surgery? A systematic overview and meta-analysis. Phys Ther. 1994;74(1):3-10; discussion 10-6.
27. Gouma DJ, van Geenen RC, van Gulik TM, de Haan RJ, de Wit LT, Busch OR et al. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. Ann Surg. 2000;232(6):786-95.
28. Connor S, Raraty MG, Howes N, Evans J, Ghaneh P, Sutton R et al. Surgery in the treatment of acute pancreatitis--minimal access pancreatic necrosectomy. Scand J Surg. 2005;94(2):135-42.
29. Nishikimi K, Tate S, Matsuoka A, Otsuka S, Shozu M. Predictors of post-operative pancreatic fistula after splenectomy with or without distal pancreatectomy performed as a component of cytoreductive surgery for advanced ovarian cancer. J Gynecol Oncol. 2022;33(3):e30.
30. Yalcin Y, Tatar B, Erdemoglu E, Erdemoglu E. The parameters to estimate postoperative severe complications classified through Clavien-Dindo after upper abdominal surgery in patients with primary and recurrent ovarian cancer. Ginekol Pol. 2019;90(10):557-564.