

Postoperative Intestinal Fistula in Primary Advanced Ovarian Cancer Surgery

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Background: Advanced ovarian cancer (AOC) requires an aggressive surgery with large visceral resections in order to achieve an optimal or complete cytoreduction and increase the patient's survival. However, the surgical aggressiveness in the treatment of AOC is not exempt from major complications, such as the gastrointestinal fistula (GIF), which stands out among others due to its high morbidity and mortality.

Methods: We evaluated the clinicopathological features in patients with AOC and their association with GI. Data for 107 patients with AOC who underwent primary debulking surgery were analyzed retrospectively. Clinicopathological features, including demographic, surgical procedures and follow-up data, were analyzed in relation to GIF.

Results: GIF was present in 11% of patients in the study, 5 (4.5%) and 7 (6.4%) of colorectal and small bowel origin, respectively. GIF was significantly associated with peritoneal cancer index (PCI) >20, more than 2 visceral resections, and multiple digestive resections. Overall and disease-free survival were also associated with GIF. Multivariate analysis identified partial bowel obstruction and operative bleeding as independent prognostic factors for survival. The presence of GIF is positively associated with poor prognosis in patients with AOC.

Conclusion: Given the importance of successful cytoreductive surgery in AOC, the assessment of the amount of tumor and the aggressiveness of the surgery to avoid the occurrence of GIF become a priority in patients with AOC.

Keywords: advanced ovarian cancer surgery, complications, intestinal leakage, intestinal fistula

Introduction

According to the Spanish Society against Cancer (AECC), ovarian cancer is usually diagnosed between 45 and 75 years of age, and up to 75% of the cases are diagnosed in advanced stages, resulting in a poor prognosis. In 2016, there were approximately 3412 cases of ovarian cancer in Spain, 1960 of those case were lethal.¹ However, the introduction of advanced ovarian cancer (AOC) surgery, which strives to achieve complete cytoreduction, aims to increase survival and provide a definitive cure in some cases.² Such surgery is considered highly aggressive and often results in serious postoperative complications that could reach a rate of 38% reported in some systematic revisions and may cause an increase in patient mortality and the delay or impossibility of adjuvant oncological treatment.³ A multidisciplinary approach of AOC has been implemented by the Multidisciplinary Unit of Abdominal Pelvic Oncology Surgery (MUAPOS), at the General University Hospital in Castellon since 2013 and was able to increase the patients' survival in the past few years.⁴ An effort has been made in order

to identify risk and prognostic factors retrospectively in patients who suffered complications, for instance, gastrointestinal fistulae, creating a predictive model for major complications after extensively primary debulking in order to predict morbidity. The study concluded that risk factors for major complications are: five or more visceral resections, rectosigmoid resection, glossectomy, and pelvic peritonectomy.⁵ We have currently taken a particular interest in the gastrointestinal fistulae (GIF), one of the most feared adverse events of extensive cytoreduction since rectosigmoid, jejunum and/or ileum resections are necessary for approximately 50% of the AOC surgeries.⁵ Some factors favor the occurrence of digestive fistula, in the immediate or late postoperative period, such as hydroelectric imbalance and malnutrition, in addition to the intestinal resection and/or neoadjuvant chemotherapy. This usually leads to aggressive treatments and prolonged hospitalizations.⁶⁻⁹

The objective of this study is twofold, to address the results concerning the GIF collected at the MUAPOS at the General University Hospital in Castellon, and to investigate the relationship with the survival of patients who experienced GIF.

Patients and Methods

Patients with stage IIIc and IV ovarian, peritoneal, and fallopian tube carcinoma who underwent primary cytoreduction, with intestinal resections (rectosigmoid, jejunum, ileum and/or colon), at the MUAPOS of the University General Hospital of Castellon in Spain from January 2013 to January 2018, were included. All of the patients had an Eastern Cooperative Oncology Group (ECOG) Score <3. Patients who were at risk of unresectability according to the advanced ovarian cancer management guide of the MUAPOS¹⁰ received neoadjuvant chemotherapy and were excluded from this study. A prospective analytical study was carried out based on a retrospective analysis of the data.

Demographic, clinicopathological, and follow-up data were analyzed. Debulking status was defined: Complete (Group A): no residual; Optimal (Group B): residual tumor <1 cm; Suboptimal (Group C): residual tumor >1 cm. For this study, complications grade I–II and grade III–IV were categorized in Minor and Major, respectively, according to the Clavien-Dindo classification.¹¹ When collecting data from complications, cancer-related procedures, ie diagnostic thoracentesis for staging, were not considered. For the diagnosis of malnutrition were used anthropometric, clinic and laboratory parameters. Mainly studied parameters

were age, albumin prior to the intervention, peritoneal carcinomatosis index, chemotherapy administration and tumor staging.

GIF was defined as any exit of material from the digestive tract, which can remain in the abdominal cavity in the form of a collection (anastomosis leakage) or go outside either spontaneously or through a drain (true fistula).¹² In the same way, GIF was categorized into the rectosigmoid anastomosis, related to colonic anastomosis, and related to small bowel anastomosis which includes genuine small bowel fistulae, gastro-jejunal, duodenal, and those related to anastomosis between the colon and small bowel.

The patients were staged following the International Federation of Obstetrics and Gynecology (FIGO)¹³ staging system, and the quantitative assessment of the carcinomatosis distribution was done following Sugabaker's Peritoneal Carcinomatosis Index (PCI) (categorized in 1–10, 11–20, >20).¹⁴ The PCI was determined at the time of surgery by the same surgical team. Patients were informed of this study, and written informed consent was obtained from all the participants included in the study. The Ethics and Clinical Research Committee of the General University Hospital in Castellon also gave its approval. All procedures performed in this study were under the ethical standards of our Hospital and the 1964 Declaration of Helsinki.

Statistical Analysis

Statistical analysis was directed to compare two groups: Presence of GIF vs Absence of GIF. Means and Standard deviation were used for summarizing quantitative variables, counts and percentages for summarizing qualitative variables. For univariate statistics, the Mann–Whitney test was used to compare groups of quantitative non-parametric variables, and CHI-squared or Fisher's exact test to compare qualitative variables. As for the descriptive and univariate statistical analysis of overall and disease-free survival associated with the event of a GIF, Kaplan–Meier curves and Log Rank test were used. Medians and 95% Confidence Intervals of survival were calculated. To identify the most influential independent factors in the appearance of GIF a multivariate analysis was performed with all significant and almost significant variables from the univariate analysis that has been included in a backwards-stepwise model of binary logistic regression, with the condition that those whose p is less than 0.05 remain in the final model and more than

Table I Clinicopathological Characteristics of All Patients

	Total n=107	No n=95 (89%)	Yes n=12 (11%)	P value
Age	60±10.5	60±10.6	62±10.6	0.52
FIGO stage				0.49
III	80 (74.8%)	72 (75.8%)	8 (66.7%)	
IV	27 (25.2%)	23 (24.2%)	4 (33.3%)	
Charlson	2±2.2	2±2.1	3±2.4	0.36
Charlson category				0.31
CHR0	40 (37.4%)	36 (37.9%)	4 (33.3%)	
CHR1–3	33 (30.8%)	31 (32.6%)	2 (16.7%)	
CHR4–8	34 (31.8%)	28 (29.5%)	6 (50%)	
Preoperative malnutrition				0.090
No	83 (77.6%)	76 (80%)	7 (58.3%)	
Yes	24 (22.4%)	19 (20%)	5 (41.7%)	
Duration (min) of surgery	440±163	434±162.8	490±162.2	0.26
Operative PCI	14±9.4	13±9.1	20±9.9	0.027
Operative PCI category				0.14
I–10	43 (41.7%)	41 (45%)	2 (16.7%)	
11–20	35 (34.0%)	30 (33%)	5 (41.7%)	
+20	25 (24.3%)	20 (22%)	5 (41.7%)	
Ascitis				0.98
NO	80 (74.8%)	71 (74.7%)	9 (75%)	
SI	27 (25.2%)	24 (25.3%)	3 (25%)	
Partial bowel obstruction				0.017
No	94 (87.9%)	86 (90.5%)	8 (66.7%)	
Yes	13 (12.1%)	9 (9.5%)	4 (33.3%)	
Diffuse intestinal or mesos infiltration				0.25
No	85 (79.4%)	77 (81.1%)	8 (66.7%)	
Yes	22 (20.6%)	18 (18.9%)	4 (33.3%)	
Major invasion of wall or retroperitoneum				0.44
No	96 (89.7%)	86 (90.5%)	10 (83.3%)	
Yes	11 (10.3%)	9 (9.5%)	2 (16.7%)	
Tumor blocks or retractions				0.42
No	89 (83.2%)	80 (84.2%)	9 (75%)	
Yes	18 (16.8%)	15 (15.8%)	3 (25%)	
Diaphragmatic invasion				0.81
No	96 (89.7%)	85 (89.5%)	11 (91.7%)	
Yes	11 (10.3%)	10 (10.5%)	1 (8.3%)	

0.15 are removed. A Network analysis using JASP software . JASP (Version 0.13.1) URL = {<https://jasp-stats.org/>} was performed with the most significant risk factors (p<0.15) for GIF in the multivariate analysis to show the strength of their correlations. The remaining analysis of

statistical data was performed using the IBM-SPSS software version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). A p-value <0.05 was considered statistically significant.

Table 2 Principal Procedures Concerning GIF

	Total N=107	GIF No N=95 (89%)	GIF Yes N=12 (11%)	P value
Peritonectomy				0.06
No	24 (22.4%)	22 (92%)	2 (8%)	
Complete	31 (29%)	24 (77%)	7 (23%)	
Partial	52 (48.6%)	49 (94%)	3 (6%)	
Fulguration or excision of nodules				0.39
No	57 (53.3%)	52 (91%)	5 (9%)	
Yes	50 (46.7%)	43 (86%)	7 (14%)	
Visceral resection				0.85
No	20 (18.7%)	18 (90%)	2 (10%)	
Yes	87 (81.3%)	77 (89%)	10 (11%)	
Bowel resection				0.56
No	25 (23.4%)	23 (92%)	2 (8%)	
Yes	82 (76.6%)	72 (88%)	10 (12%)	
Type of bowel resection				0.13
No	25 (23.4%)	23 (92%)	2 (8%)	
Rectum-Sigmoid	15 (14.0%)	15 (100%)	0	
Colon	20 (18.7%)	19 (95%)	1 (5%)	
Small bowel	22 (20.6%)	19 (86%)	3 (14%)	
Multiple	25 (23.4%)	19 (76%)	6 (24%)	
Pancreas and/or spleen resection				0.86
No	78 (72.9%)	69 (89%)	9 (11%)	
Yes	29 (27.1%)	26 (90%)	3 (10%)	
Number of visceral resections	4±3.1	3±2.8	6±4.1	<0.001
Grouped number of visceral resections				0.07
0–2	44 (41.1%)	42 (96%)	2 (4%)	
>2	63 (58.9%)	53 (84%)	10 (16%)	
Digestive anastomosis				0.06
No	45 (42.1%)	43 (96%)	2 (4%)	
Yes	62 (57.9%)	52 (84%)	10 (16%)	
Mean digestive anastomosis per patient	0.9±0.1	0.8±0.1	1.3±0.3	0.13
Grouped number of digestive anastomosis per patient				0.20
0–1	86 (80.4%)	78 (91%)	8 (9%)	
>1	21 (19.6%)	17 (81%)	4 (19%)	
Definitive stoma				0.99
No	89 (83.2%)	79 (89%)	10 (11%)	
Yes	18 (16.8%)	16 (89%)	2 (11%)	
Lymphadenectomy				0.76
No	49 (45.8%)	43 (88%)	6 (12%)	
Yes	58 (54.2%)	52 (90%)	6 (10%)	
Operative bleeding cc	1926±887	1856±893	2483±611	0.02
Grouped operative bleeding cc				0.01
0–1000	17 (15.9%)	17 (100%)	0	
1000–2000	57 (53.3%)	53 (93%)	4 (7%)	
2000–3000	24 (22.4%)	17 (71%)	7 (29%)	
+3000	9 (8.4%)	8 (89%)	1 (11%)	

(Continued)

Table 2 (Continued).

	Total N=107	GIF No N=95 (89%)	GIF Yes N=12 (11%)	P value
Cytoreduction				0.83
Group A	84 (78.5%)	74 (88%)	10 (12%)	
Group B	8 (7.5%)	7 (88%)	1 (12%)	
Group C	15 (14%)	14 (93%)	1 (7%)	
Cytoreduction				0.54
Group A + B	92 (86%)	81 (88%)	11 (12%)	
Group C	15 (14%)	14 (93%)	1 (7%)	
Length of stay	22±20.7	19±14.6	49±38.1	<0.001
Grade CLAVIEN-DINDO				<0.001
No complication	50 (46.7%)	50 (100%)	0	
I	11 (10.3%)	11 (100%)	0	
II	13 (12.1%)	13 (100%)	0	
III	27 (25.2%)	17 (63%)	10 (37%)	
IV	6 (5.7%)	4 (67%)	2 (33%)	
Complication grade				<0.001
No complication	50 (46.7%)	52 (100%)	0	
Minor (I–II)	24 (22.4%)	24 (100%)	0	
Major (III–IV)	33 (30.9%)	19 (58%)	12 (42%)	
Radiologically or endoscopically intervention				<0.001
No	89 (83.2%)	84 (94%)	5 (6%)	
Yes	18 (16.8%)	11 (61%)	7 (39%)	
Surgical reintervention				<0.001
No	90 (84.1%)	86 (96%)	4 (4%)	
Yes	17 (15.9%)	9 (53%)	8 (47%)	
90 days mortality				0.002
No	103 (96.3%)	92 (91%)	9 (9%)	
Yes	4 (3.7%)	3 (50%)	3 (50%)	
Disease recurrence				0.95
No	49 (45.8%)	38 (78%)	5 (22%)	
Yes	58 (54.2%)	51 (88%)	7 (12%)	
Type of disease recurrence				0.88
Peritoneal	16 (27.6%)	14 (88%)	2 (12%)	
Metastases	31 (53.4%)	27 (87%)	4 (13%)	
Both	11 (19%)	9 (82%)	2 (18%)	

Results

During the study period, 107 patients met the inclusion criteria. Given the preexisting interest to study prognostic factors related to GIF, the patients were divided into two groups: those who did not present this type of complication (95 patients) and those that did present it (12 patients), meaning that 11% of the patients in the study suffered from a GIF, 5 (4.5%) and 7 (6.4%) of colorectal and small bowel origin, respectively. Of the 12 GIF patients, 4 patients were true fistulas and 8 anastomosis leakage.

Table 1 summarizes the clinicopathologic characteristics of patients. Table 2 summarizes the characteristics of the surgery and outcomes.

The average age in the group of GIF was 62 years, compared to the 60 years in the other group. Concerning the average duration of surgery, in the group of GIF, it was 510 minutes, compared to the 450 minutes in the other group. GIF incidence was higher (31%) in the presence of partial bowel obstruction than in its absence (8%). Logically, the percentage of bowel resections in GIF was

Table 3 The Final Model of Backward-Stepwise Logistic Regression Based on the Variables Associated with Univariate Incidence Risk of GIF

GIF	Odds Ratio	CI 95%	p value
Operative bleeding (mL)	1.01	1.001–1.022	0.016
Partial bowel obstruction	6.26	1.406–27.671	0.015

12%, compared to those who did not, which was 8%. A total operative PCI mean of 20 was higher in the GIF group, while the group that did not present the complication had a mean of 13. Eighty-three patients (78%) did not receive any kind of nutritional support, while 24 (22%) received nutritional supplements and/or parenteral nutrition. GIF incidence was higher (21%) in the presence of preoperative malnutrition than in its absence (8%).

Principal procedures with anastomotic leakage are shown in Table 2. GIF had a higher incidence (23%) when complete peritonectomy was performed than when not (8%) performed. Multiple intestinal resections were done in the majority of cases of GIF, and the number of visceral resections was more than 2 in the 16% of patients with GIF. When blood loss was higher than 2000 mL, it was associated with GIF in 29% of patients. The type of cytoreduction was not associated with the rate of GIF. However, there was more incidence of GIF when complete or optimal cytoreduction (group A+B) (12%) was performed than when it was suboptimal (group C) (7%). No fistula was observed when only a colorectal anastomosis was performed. In exclusively colonic anastomoses, we found 1 (5%) fistula, compared to 3 (14%) in only small bowel anastomosis, and 6 (24%) when multiple colorectal and small bowel anastomoses were performed. No protective stoma was performed.

The number of GIF with or without definitive stoma was identical (11%). Significant complications were found in 33 (31%) patients, 19 (58%) and 12 (42%) without and with GIF. Finally, about the surgical reoperation, it was required in 17 (16%) patients, 8 (47%) of those presenting

a GIF. In those who did not require reoperation, only 4 (4%) presented GIF.

Multivariate analysis (Table 3) revealed that partial bowel obstruction and operative bleeding are the only independent risk factors for the appearance of GIF.

Network analysis was performed with the most significant risk factors ($p < 0.15$) in the multivariate analysis to show the strength of their correlation. The matrix of weights correlations and paths are shown in Table 4 and Figure 1.

Cumulative survival analysis using Kaplan-Meier curves in the presence or absence of a GIF is shown in Figure 2 and Table 5. Median survival was 16 months (95% CI 0–35.3) and 37.63 months (95% CI: 29.7–45.4) in patients with and without GIF. Median disease-free interval in months (Figure 3) was 12 (95% CI: 3.8–20.1) and 19.6 (95% CI: 9.5–29.6). Kaplan-Meier survival curves were also constructed, specifying the type of fistula (Figure 4). Cumulative survival for Colorectal and small bowel fistula and absence of GIF were 16, 6.5 and 37.6 months, respectively. The disease-free interval for the different types of GIF was 19.6 months (95% CI: 9.5–29.6) for the absence of GIF and 12 (95% CI: 0–36.5) and 5.8 (95% CI: 3.0–8.5) for Colorectal and Small bowel fistulas, respectively (Figure 5).

Discussion

In this study, partial bowel obstruction and Operative bleeding are the most important predictive factors in the appearance of GI fistulas in advanced ovarian cancer surgery.

In most studies on peritoneal carcinomatosis originating from ovarian cancer, it has been observed that the

Table 4 Network Weights Matrix of Correlations

	Charlson	Fistula	PCI	Bleeding	Obstruction
Charlson	–	0.141	–0.067	–0.163	0.137
Fistula	0.141	–	0.322	0.374	0.457
PCI	–0.067	0.322	–	0.221	0.269
Bleeding	–0.163	0.374	0.221	–	–0.039
Obstruction	0.137	0.457	0.269	–0.039	–

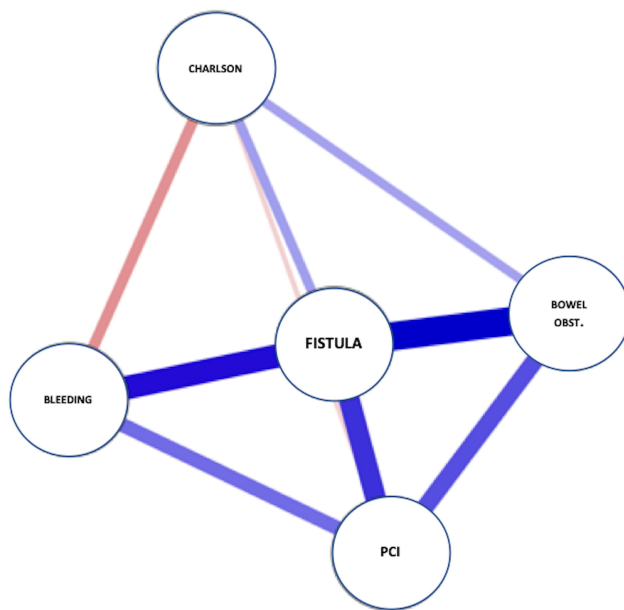


Figure 1 Network paths of correlations.

complete or optimal cytoreduction and platinum-based chemotherapy are the only factors that are clearly associated with a better survival rate in these patients.⁴ According to our MUAPOS database, 86% of our patients benefitted from an optimal cytoreduction (Group A+B), 11% of those developed a gastrointestinal fistula.

Now it is time to distinguish anastomosis leakage from fistula in digestive surgery:

Fistula and leaks are terms, which are often used interchangeably. However, technically, they are somewhat different as we stated in the method section.¹² These terms are usually employed in the same clinical situations, but their repercussion in terms of morbidity is not the same. While anastomosis leakage can be resolved frequently with radiological intervention, GIF frequently requires a surgical approach and the clinical repercussion is worse for the patient. These different definitions are not usually recorded in the literature.¹²

There is significant variability of GIF/leakages rates in the literature which can range from 4% to 20%.¹⁵ In our data, half of the anastomotic leaks were treated by interventional radiology so they could be considered anastomosis leakage instead of real fistulas. Moreover, no GIF fistulas were observed in cases of simple colorectal resections. Like other authors, we have stated that GIF of colorectal origin is more frequent in cases of multiple bowel resections.¹⁶

The different types of GIF are more frequently associated with two or more visceral resections as we can see in our data. As previously described,^{17,18} the tumor burden affects the number of resections performed in patients with advanced ovarian cancer so that with a high tumor load, quantified as a PCI > 20, more than 3 resections would be performed to achieve optimal cytoreduction.

Survival in patients with fistula decreases compared to patients without it; surely this is because the hospital stay is

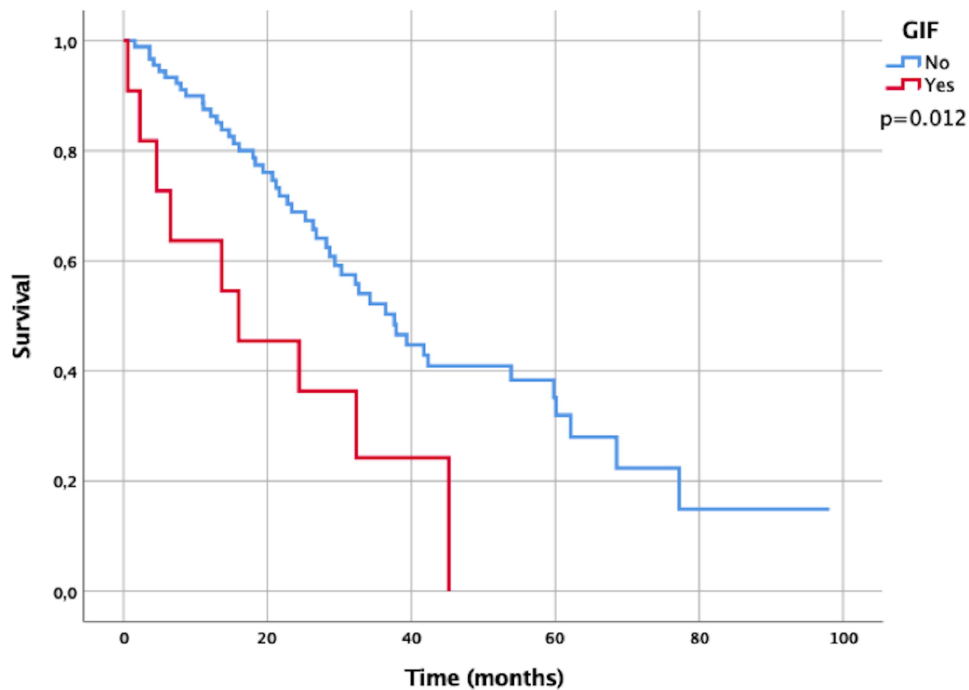


Figure 2 Overall survival according to the existence or absence of GIF.

Table 5 Median Survival in Months in Patients with or Without GIF

	Median Survival (Months)	Median CI 95%	Hazard Ratio (GIF vs No GIF)	Hazard Ratio CI 95%
GIF	16	4.6–45.2	2.4	1.33–10.02
No GIF	38	28.6–59.8		
Global	34	28.2–45.2		

prolonged and causes patients not to start or to delay the onset of chemotherapy and this impacts negatively in survival.^{6–8,16} Moreover, survival among different types of GIFs is different. We observe that survival is worse in cases of small bowel fistulas. This negative impact on survival is probably caused by the impact on the general condition of the patient, in the form of dehydration and renal failure, which is frequently associated with this type of fistula.^{19,20}

It has been described that malnutrition status is a risk factor for anastomosis leakage in ovarian cancer surgery.²¹ In our results, five patients (21%) with GIF had malnutrition status at the time of surgery.

The network analysis represents either symmetric relations or asymmetric relations between the variables that influence the appearance of GIF.²² As we can see in the graph, there is a strong correlation between bowel obstruction, bleeding, and

PCI with the appearance of GIF. It is well known that with a high tumor burden quantified as a high PCI number, the risk of bowel obstruction increases, and the bleeding produced during surgery is higher.^{17,18,23–25} Multivariate analysis revealed that partial bowel obstruction increases six times the risk of postoperative digestive fistula, along with an increase of operative bleeding. Both variables were the only independent risk factors in our study, and they were both surrogates variables of the tumor burden and the extent of surgery. It is well known that the state of intestinal occlusion or subocclusion could generate an inflammatory environment in the intestinal wall and therefore more prone to fistulization; in this situation, any suture in this area may heal worse.

Strengths of this study include the homogeneous cohort of patients, in a tertiary hospital with a uniform approach to the treatment of AOC, making it relevant for those at highest risk for GIF. One of our main limitations here is the retrospective design and analysis of the data, which difficult the reproduction in other environments.

Conclusions

The digestive fistula in the postoperative period derives from multiple risk factors. In other words, it is multifactorial. Specifically, in this study, some factors have more weight than others, such as intraoperative bleeding and the presence of partial bowel obstruction. But in Table 4 it can be seen that

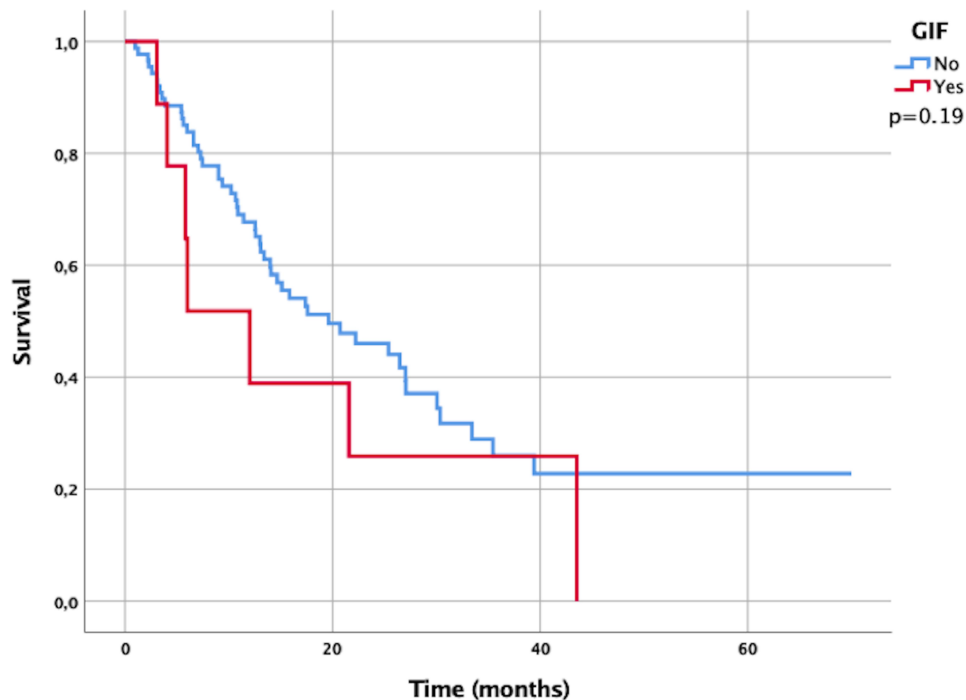


Figure 3 Disease-free survival according to the existence or absence of GIF.

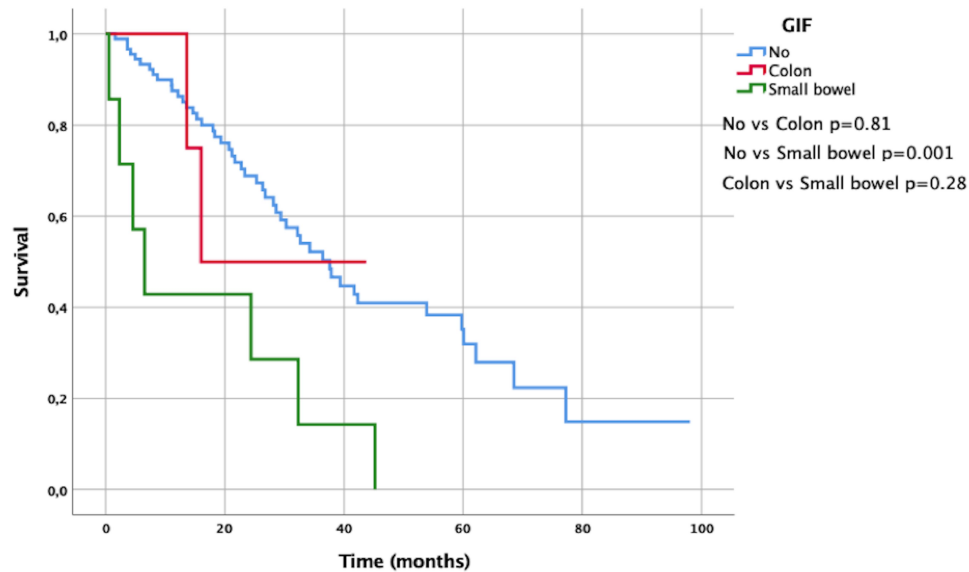


Figure 4 Overall survival for different types of GIF.

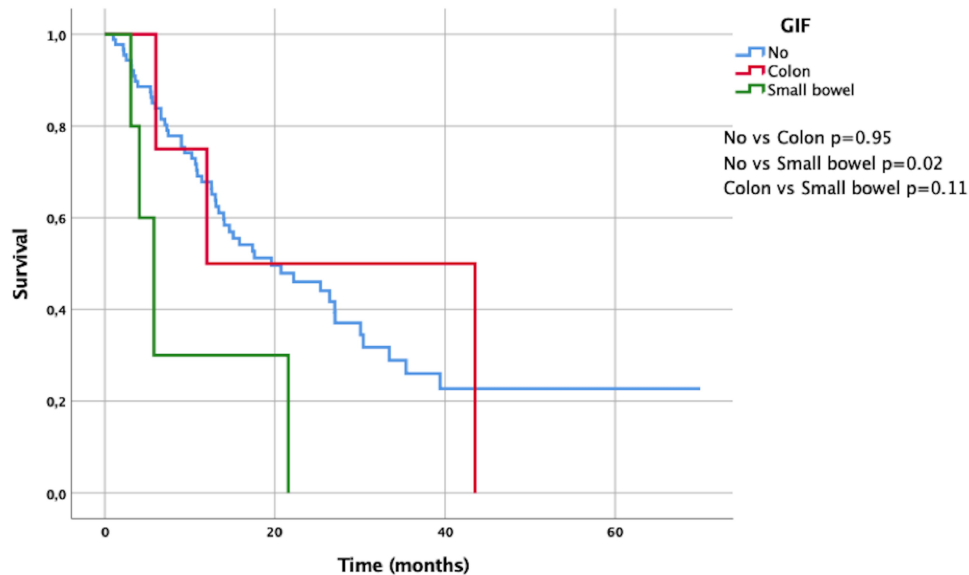


Figure 5 Disease-free survival for different types of GIF.

there are other risk factors that are highly correlated with fistulas, such as the extent of the disease itself (PCI), and comorbidity, and very strikingly, that there are cross-correlations (covariance) between them. A maximum effort to achieve a complete cytoreduction in a context of a lot of peritoneal diseases and in a debilitated patient will suppose a highly aggressive surgery that will carry the highest risk of postoperative complications, including fistulas and probably they, therefore, jeopardize further treatment.

Assuming correct execution of the surgical technique, the best prevention of fistula (and other

complications) can only consist of planning the intervention aimed at achieving the maximum cytoreduction possible with the least possible surgical aggression. Probably, combining both things depends to a very high degree on the technical training and experience of the surgical team.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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