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Change of Fagotti score is associated with outcome after neoadjuvant chemotherapy for ovarian cancer

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ABSTRACT

Objective To investigate whether a change in the Fagotti score (Δ Fagotti) following neoadjuvant chemotherapy is predictive of resection to no residual disease (R0) and survival in women diagnosed with ovarian cancer.

Methods Women treated with neoadjuvant chemotherapy for newly diagnosed ovarian cancer between January 2012 and June 2021 at the Bern University Hospital were included in this retrospective cohort study. Fagotti scores before and after neoadjuvant chemotherapy treatment were assessed for a potential association with resection status at interval debulking surgery defined as no residual disease (R0), macroscopic residual disease with a diameter of 0.1–1 cm (R1) or >1 cm (R2), and survival.

Results During the study period, 130 patients received neoadjuvant chemotherapy, mainly in response to advanced ovarian cancer International Federation of Gynecology and Obstetrics (FIGO) stages IIIC (68.5%) or IV (20.8%). 91 patients (70%) experienced a relapse and 81 (62%) died due to their disease. Median overall survival was 40 months (95% CI 30.6 to 49.4). Fagotti scores dropped from a mean of 7.8 (95% CI 7.14 to 8.42) at diagnosis to 3.9 (95% CI 3.34 to 4.46, $p < 0.001$) after neoadjuvant therapy. This decrease was associated with resection status during interval debulking surgery (mean Δ Fagotti -4.9 in R0, -2.2 in R1, -0.6 in R2, $p < 0.001$). Women whose Fagotti score declined more than 2 points after neoadjuvant chemotherapy ($n = 51/88$, 58%) survived significantly longer (median overall survival of 42 vs 32 months, $p = 0.048$).

Conclusion Fagotti scores and Δ Fagotti scores are associated with complete cytoreduction at interval debulking surgery and longer overall survival in women treated with neoadjuvant chemotherapy for ovarian cancer. These markers are valuable for individualized patient treatment planning and should always be performed after neoadjuvant therapy.

INTRODUCTION

Approximately 75% of patients with ovarian cancer are diagnosed at an advanced International Federation of Gynecology and Obstetrics (FIGO) stage. Cytoreductive surgery followed by platinum-based chemotherapy remains the cornerstone of treatment for ovarian cancer. The residual tumor diameter after surgery is one of the most important determinants of

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The Fagotti score is a laparoscopic index highly predictive for completeness of cytoreduction at primary debulking surgery in women with advanced ovarian cancer; however, the prognostic value of the change of the score (Δ Fagotti) during neoadjuvant chemotherapy has not yet been analyzed.

WHAT THIS STUDY ADDS

⇒ This is the first study showing that Δ Fagotti tracks with outcome after neoadjuvant chemotherapy for ovarian cancer. The Fagotti score after neoadjuvant treatment strongly correlates with resection status, and progression-free and overall survival.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Fagotti scores are valuable for individualized patient treatment planning and should be routinely assessed at time of interval debulking surgery.

patient survival,^{1,2} but a complete macroscopic upfront cytoreduction can be achieved in only 30–40% of women with FIGO stage III/IV disease.^{3,4} Neoadjuvant chemotherapy followed by interval debulking surgery has become the standard of care for patients with ovarian cancer, in whom a complete tumor resection seems unachievable.⁵ Two randomized controlled phase III trials have shown an equivalent progression-free and overall survival after interval versus primary debulking surgery in these patients, with the benefit of less complex surgical interventions and a lower rate of post-operative complications.^{6,7}

Pre-operative radiologic assessment of the tumor burden and of the level of serum biomarkers correlate poorly with the surgical resection status. However, laparoscopic assessment of the intra-abdominal tumor spread is a useful measure to predict tumor resectability and guide treatment decisions for newly diagnosed ovarian cancer; numerous scores have been developed for this purpose.^{8–11} In 2006, Fagotti et al proposed a laparoscopic index predictive of optimal cytoreduction based on peritoneal carcinomatosis, omental cake, diaphragmatic involvement, bowel or gastric infiltration, mesenteric retraction,

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and liver metastases.¹¹ This predictive index value, or 'Fagotti score', was further refined and validated for patients after neoadjuvant chemotherapy.^{12–13} Visualization and appropriate assessment of carcinomatous lesions after chemotherapy, however, may be difficult due to chemotherapy-induced fibrosis, with the risk of underestimating the remaining tumor load.¹⁴

Similar to primary debulking surgery, complete cytoreduction at interval debulking surgery is an important prognostic factor for patients with advanced ovarian cancer.¹⁵ Other prognostic markers include the nadir of the serum biomarker cancer antigen 125 (CA125) after chemotherapy, a decrease in tumor burden assessed by imaging according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and histological chemotherapy response score,^{16–18} although with controversial data regarding their individual prognostic value.^{19–20}

At the time of primary debulking surgery, the Fagotti score is an independent prognostic factor for both progression-free and overall survival of patients.²¹ To the best of our knowledge, the change in Fagotti score (Δ Fagotti) after neoadjuvant chemotherapy has not yet been analyzed with regard to its potential prognostic value. We expect that a systematic assessment of the score will improve identification of patients with a favorable response to chemotherapy, in whom debulking surgery should be performed.

Here, we investigate whether a change in the Fagotti score following neoadjuvant chemotherapy (Δ Fagotti) is associated with surgical resection status and with survival of women diagnosed with advanced ovarian cancer.

METHODS

In this retrospective, single-center cohort study, all women treated with neoadjuvant chemotherapy for newly diagnosed primary ovarian, Fallopian tube, or peritoneal cancer between January 2012 and June 2021 at the Bern University Hospital, Bern, Switzerland were included.

Upon approval of the cantonal ethics committee Bern (BASEC ID 2018–00479), clinical parameters of study participants with a signed consent form were collected from the prospectively maintained institutional database. After a thorough review of all surgical reports and available video and photo documentation, status of intra-abdominal tumor spread, amount of ascites, and surgical resection status were assessed and a Fagotti score determined by two independent trained surgeons both before and after neoadjuvant chemotherapy.²² The surgeons evaluating the scores were blinded for patient survival. In case of divergent scores, the tumor spread was re-assessed collectively and a score determined by discussion. Extensive peritoneal carcinosis, infiltrating or confluent diaphragmatic involvement, omental cake, small bowel metastases requiring resection or miliary carcinomatosis, mesenteric root retraction, stomach infiltration, and liver surface metastases each contributed two points to the Fagotti score, resulting in a possible score range of 0–14. Follow-up information was updated in February 2022; this update included data on adjuvant treatment, maintenance therapies, treatment of recurrence, survival, and cause of death.

Treatment

In this tertiary referral center, treatment for ovarian cancer usually consists of a diagnostic laparoscopy with biopsies to verify tumor histology and to evaluate surgical resectability, followed by three cycles of neoadjuvant chemotherapy with carboplatin and paclitaxel if a primary R0 resection is not achievable. The standard dosage of intravenous (IV) chemotherapy is carboplatin area under the receiver operating characteristic (ROC) curve 5 mg/mL/min and paclitaxel 175 mg/m² every 3 weeks. Other possible treatment schedules include weekly administration of paclitaxel at 80 mg/m² and the addition of bevacizumab (7.5 mg/kg 3-weekly IV) in women with FIGO stage IV disease. Patients showing a partial or complete response based on RECIST/Gynecological Cancer Intergroup (RECIST 1.1/GCIG) criteria of CT scans and a decline of CA125 serum marker after three cycles undergo another diagnostic laparoscopy and interval debulking surgery, if an optimal cytoreduction seems attainable.²³ Adjuvant treatment consists of three cycles of carboplatin and paclitaxel as indicated above, with bevacizumab in FIGO III R1 and FIGO IV disease.

Since 2019, genetic counseling and testing for mutations of *BRCA1*, *BRCA2*, and other genes of the homologous recombination DNA repair pathway is recommended for all patients with newly diagnosed non-mucinous ovarian cancer. In women without germline mutations, tumor tissue is tested for somatic homologous recombination deficiency. On identification of an homologous recombination mutation, maintenance therapy with a poly(ADP-) ribose polymerase (PARP) inhibitor with olaparib (300 mg twice daily) or niraparib (200 mg daily) for 36 months or up to disease progression is recommended. According to the PAOLA-1 trial, a therapy combining bevacizumab (15 mg/kg 3-weekly IV) for 15 months with a PARP inhibitor is considered in patients with FIGO stage IV disease.²⁴

Endpoints

The primary outcome of this study was progression-free survival, calculated as the interval between the date of first diagnosis and the date of recurrence. Recurrence was defined as an increase of CA125 >35 kU/L or diagnosis of progressive tumor burden on CT scans or MRI.

Secondary endpoints included overall survival and surgical resection status at interval debulking surgery as indicated on the surgical report. Complete surgical cytoreduction with no macroscopic visual tumor left was classified as R0 resection. R1 and R2 were defined as macroscopic residual disease with a diameter of 0.1–1 cm (R1) or >1 cm (R2), respectively.

Statistical Analysis

Univariate logistic regression was applied to analyze the association of the Fagotti score at diagnosis, after neoadjuvant chemotherapy and absolute Δ Fagotti with progression-free and overall survival. Statistical significance was determined using log-rank (χ^2 test). A p value <0.05 was defined as significant. Using a Cox regression survival function, progression-free and overall survival were calculated for women with different Δ Fagotti scores.

A multivariate logistic regression model including surgical Fagotti scores before and after administration of chemotherapy, as well as resection status at interval surgery, was calculated for progression-free and overall survival.

Table 1 Patient characteristics

Parameter	N (%)	Median (range)
All patients	130 (100)	
Age at diagnosis (years)		66 (24–91)
Menopausal status		
Pre-/peri-menopausal	15 (11.5)	
Post-menopausal	115 (88.5)	
ECOG performance status		
ECOG 0–1	97 (75.2)	
ECOG \geq 2	32 (24.8)	
BMI (kg/m ²)		23 (17–53)
CA125 at diagnosis (kU/l)		736 (25–26 296)
Histologic subtype		
High-grade serous	116 (89.2)	
Mucinous	4 (3.1)	
Other	7 (5.4)	
Unknown	3 (2.3)	
FIGO stage		
I/II	9 (6.9)	
IIIA/B	5 (3.8)	
IIIC	89 (68.5)	
IVA	10 (7.7)	
IVB	17 (13.1)	
Indication for neoadjuvant chemotherapy		
Advanced FIGO stage	119 (91.5)	
Comorbidities	5 (3.8)	
Thromboembolic event	2 (1.5)	
Other	4 (3.1)	
Number of neoadjuvant chemotherapy cycles		
2 to 4	113 (86.9)	
>4	17 (13.1)	

BMI, body mass index; CA125, cancer antigen 125; ECOG, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics.

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences, International Business Machines (IBM), Armonk, NY) software, version 25, and R studio, version 2022.02.0.

RESULTS

During the study period, 130 patients (18.8% of 693 women treated for ovarian cancer) underwent neoadjuvant chemotherapy and met the study inclusion criteria. Initial diagnosis was based on either a diagnostic laparoscopy with biopsies (n=107), puncture of ascites and/or pleural effusion (n=18), or image-guided biopsy (n=5). Patient characteristics are presented in [Table 1](#).

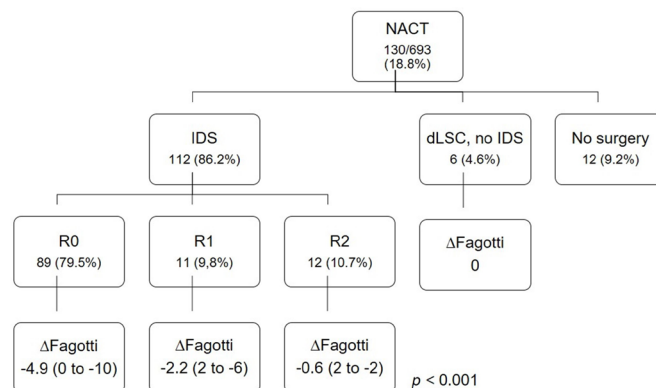


Figure 1 Overview on patient treatment status at interval debulking surgery and Δ Fagotti. Absolute number of patients are indicated. For Δ Fagotti, mean values and range are shown. Statistical significance of association between Δ Fagotti and resection status calculated with one-way analysis of variance (ANOVA). dLSC, diagnostic laparoscopy; IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; R0, R1, R2, resection status; Δ Fagotti, absolute change in Fagotti score before and after neoadjuvant chemotherapy.

Nine women had neoadjuvant treatment despite early FIGO stage I/II disease, mainly due to comorbidities. Most patients underwent chemotherapy with carboplatin and paclitaxel (n=118, 90.8%). In six (4.5%) patients, bevacizumab was added, and five (3.8%) patients were treated with carboplatin monotherapy due to comorbidities, frailty, or anaphylactic reaction to paclitaxel. Before interval debulking surgery, a mean of 3.56 cycles (range 2–9, median 3) were administered. Notably, one patient only had two cycles, whereas the majority was treated with three to four cycles (86.2%). Data on homologous recombination status was available for 49 patients; a germline or somatic *BRCA1/2* mutation was detected in 14 women (28.6%).

Δ Fagotti Correlation With Surgical Resection After Neoadjuvant Chemotherapy

After neoadjuvant therapy, surgery was performed on 118 patients ([Figure 1](#)). In six patients, an intended debulking surgery was omitted because of persistent gross intra-abdominal tumor burden with Fagotti scores of 8 to 14 (mean 9.7) during diagnostic laparoscopy. A Fagotti score both before and after neoadjuvant chemotherapy could be determined in 88 patients as some women had their diagnostic workup in external clinics with no video or photo documentation available; for 30 patients, only one score was available. There was a high concordance of the scores assessed between the surgeons (Pearson's correlation coefficient $r=0.85$, 95% CI 0.78 to 0.90). Overall, the mean Fagotti score dropped from 7.8 (range 0–14, 95% CI 7.14 to 8.42) at diagnosis to 3.9 following treatment (range 0–12, 95% CI 3.34 to 4.46, $p<0.001$) ([Figure 2](#)).

Complete tumor resection was achieved in 79.5% (n=89) of all interval debulking surgeries, which was performed by laparoscopy in two patients with FIGO stage I or II; 90.6% of patients with a low Fagotti score ≤ 6 after neoadjuvant chemotherapy (n=96) had an R0 resection; only two patients had an R2 resection due to FIGO IVB disease with non-resectable liver and lung metastases.

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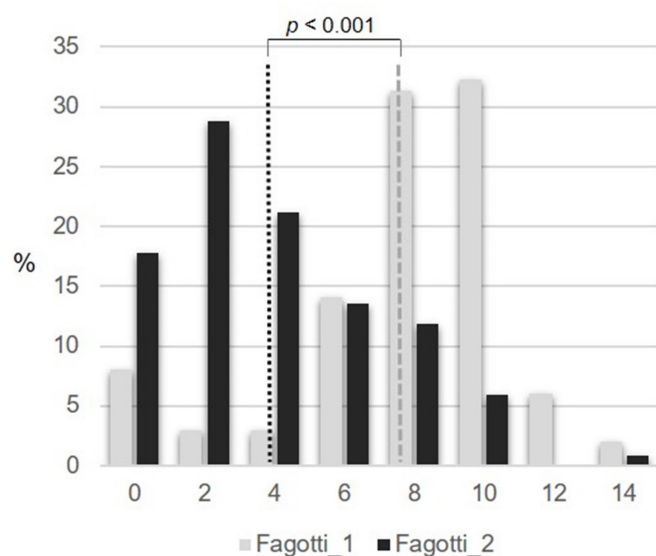


Figure 2 Distribution of Fagotti scores before and after neoadjuvant chemotherapy. Proportion of patients with a respective Fagotti score at initial diagnosis (Fagotti_1, gray bars) and after neoadjuvant chemotherapy (Fagotti_2, black bars) are shown. The dashed and pointed lines indicate mean Fagotti_1 (mean 7.78 ± 3.218 SD) and Fagotti_2 (mean 3.90 ± 3.081 SD), respectively. Statistical significance analyzed by Student's t-test.

The Fagotti score stayed high (≥ 8) in 22 out of 118 patients (18.6%) after neoadjuvant treatment. R0 resection in this group was achieved only in two women with a Fagotti score of 8, whereas the majority ($n=16$; 72.7%) had gross residual disease after interval debulking surgery.

Δ Fagotti correlated strongly with resection status at interval surgery. Women in whom an R0 resection was achieved had a significantly higher Δ Fagotti score compared with patients with macroscopic residual disease (Δ Fagotti -4.9 in R0, -2.2 in R1, -0.6 in R2, $p < 0.001$) (Figure 1).

Positive Predictive Value of Δ Fagotti

The association between change in Fagotti score after neoadjuvant chemotherapy and resection status was further investigated by determining positive predictive values (PPV) of different cutoffs of the score for an R0 resection. A Δ Fagotti score greater than -2 had a PPV of 87% for an R0 resection in this cohort (OR 6.0, 95% CI 2.15 to 16.8) (Online supplemental table S1). Higher PPVs to predict an R0 resection were found for absolute Fagotti scores at interval debulking surgery of either ≤ 6 (PPV 90.6%, sensitivity 97.8%) or ≤ 4 (PPV 95%, sensitivity 85.4%).

Fagotti Score After Neoadjuvant Chemotherapy Correlates With Survival

Overall, 91 patients (70%) experienced a relapse and 81 patients (62%) died due to their disease. Median overall survival was 40 months (95% CI 30.6 to 49.4 months). Using a univariate regression analysis, several clinical parameters were tested for their association with survival in patients with FIGO stage III or IV ovarian cancer ($n=121$). Fagotti scores at diagnosis, at interval debulking surgery,

as well as Δ Fagotti, were associated with progression-free and overall survival (Table 2).

In multivariate regression including the same clinical parameters, only the absolute Fagotti score after neoadjuvant therapy was significantly associated with progression-free survival (HR 1.49, 95% CI 1.17 to 1.90, $p=0.001$) (Online supplemental table S2).

After neoadjuvant chemotherapy, 81.4% of all women undergoing surgery had a Fagotti score of 6 or lower ($n=96/118$). On average, they had a significantly longer progression-free survival compared with patients with a persistent Fagotti score >6 (median 23 vs 10 months; HR 3.77, 95% CI 2.2 to 6.3, $p < 0.001$) (Figure 3A). A decline in the Fagotti score below 8 after neoadjuvant treatment was further associated with a longer overall survival of 52 compared with 19 months (HR 3.97, 95% CI 2.3 to 6.8, $p=0.000$).

Δ Fagotti and Overall Survival After Neoadjuvant Chemotherapy

To analyze the prognostic value of Δ Fagotti, progression-free and overall survival were determined using a Cox regression survival function, stratifying for Δ Fagotti score of ≥ -2 . Women whose Fagotti score declined more than 2 points after chemotherapy ($n=51/88$, 58%) tended to have a longer progression-free survival (HR 1.29, 95% CI 0.79 to 2.1, $p=0.309$). Furthermore, they survived significantly longer than patients with a Δ Fagotti of -2 or less (median overall survival 42 vs 32 months; HR 1.71, 95% CI 1.004 to 2.907, $p=0.048$) (Figure 3B).

DISCUSSION

Summary of Main Results

This is the first analysis of Δ Fagotti as a novel measure for response to chemotherapy at the time of interval debulking surgery for ovarian cancer. Our study shows that both Fagotti score after neoadjuvant chemotherapy and Δ Fagotti are useful to predict a complete cytoreduction. Independent of surgical resection status, we identified the Fagotti score after neoadjuvant treatment as an important prognostic factor for progression-free and overall survival of women with advanced stage ovarian cancer.

Results in the Context of Published Literature

A complete (R0) or optimal (R0/R1) surgical cytoreduction belong to the most important determinants for survival and remains the overall aim of both primary and interval debulking surgery. The EORTC-55971, CHORUS, and SCORPION trials led to a paradigm shift towards neoadjuvant treatment of women with bulky, advanced FIGO stage IIIC and IV ovarian cancer to increase the chance of complete surgical tumor resection and improve patient outcome.^{6 7 25} Both a relatively low rate of complete cytoreduction and the missing evaluation of tumor resectability at primary diagnosis unfortunately limit the strengths of these three trials. A predictive score for optimal cytoreduction at interval debulking surgery proposed by Ghisoni et al considers age, CA125 at diagnosis, and Peritoneal Cancer Index and shows an accuracy of 85.8% in predicting complete cytoreduction at interval debulking surgery.²⁶ The KELIM (elimination rate constant K) score, reflective for the reduction of CA125 during neoadjuvant chemotherapy, is an additional measure for chemosensitivity and predictive for

Table 2 Hazard ratios (HR) of different clinical parameters for survival of patients*

Parameter	Progression-free survival		Overall survival	
	HR (95% CI)	P value	HR (95% CI)	P value
Fagotti_2	1.2 (1.1 to 1.3)	0.00000052	1.2 (1.1 to 1.3)	0.0000017
R status	1.6 (1.2 to 2.1)	0.002	1.7 (1.3 to 2.3)	0.000094
Fagotti_1	1.1 (1 to 1.3)	0.017	1.1 (1 to 1.3)	0.021
ECOG	1.4 (1.1 to 1.9)	0.02	1.8 (1.3 to 2.5)	0.00016
Δ Fagotti	0.92 (0.85 to 1)	0.045	0.92 (0.84 to 1)	0.046
Age	1 (0.99 to 1)	0.39	1 (0.99 to 1)	0.13
Menopause	1.2 (0.73 to 2)	0.45	0.95 (0.59 to 1.5)	0.83
BMI	1 (0.96 to 1.1)	0.65	1 (0.94 to 1.1)	0.88

*Univariate regression analysis of clinical parameters including Fagotti score before (Fagotti_1) and after (Fagotti_2) neoadjuvant chemotherapy, change in Fagotti score (Δ Fagotti), surgical resection (R) status, performance status, age, menopausal state, and BMI. BMI, body mass index; ECOG, Eastern Cooperative Oncology Group performance status.

completeness of cytoreduction at interval debulking surgery and survival.²⁷

In our cohort, an R0 resection was achieved in 80% of all patients after neoadjuvant chemotherapy. The resection rate at interval surgery was significantly associated with Fagotti score after chemotherapy and Δ Fagotti. We found that >90% of women with either a Fagotti score ≤ 6 after neoadjuvant treatment, or with a Δ Fagotti > -2 had an R0 resection at interval debulking surgery. Comparing survival after an R1 resection at primary surgery with R0 resection during interval debulking surgery, Ghirardi et al found a superior outcome after complete cytoreduction at interval surgery.²⁸ The ongoing prospective randomized controlled TRUST trial is expected to shed light on differences in outcome after neoadjuvant chemotherapy versus primary debulking surgery.²⁹

A recent survey showed that diagnostic laparoscopy for suspected ovarian cancer is performed in around 80% of European centers, but despite its potential utility, decisions about the treatment strategy were based on laparoscopic scores in only about one third of all participating centers.³⁰ To date, intra-operative scores assessing tumor resectability have been developed in the upfront setting to guide primary treatment decisions. An evaluation of the intra-abdominal tumor spread after neoadjuvant chemotherapy, however, provides additional information on the chemotherapy response of the tumor, with a potential prognostic value. Indeed, our analysis showed that the Fagotti score after neoadjuvant treatment is significantly associated with both progression-free and overall

survival, which was independent of the surgical resection status in a multivariate analysis.

Fagotti et al proposed to assess only four out of seven parameters of their pelvic index score in the neoadjuvant setting, that is, mesenterial retraction, bowel and stomach infiltration, and superficial liver metastasis.³¹ Using the same score at initial diagnosis and after neoadjuvant chemotherapy, however, allows a direct evaluation of the therapy-induced change, which is why the same laparoscopic features were evaluated before and after neoadjuvant chemotherapy to calculate the Fagotti scores in this cohort. The present study confirms that an evaluation of the same score at different points in time during treatment is valuable both to estimate the effect of prior chemotherapy and to predict patient outcome.

Findings arising from the present study provide evidence of the utility of a laparoscopic assessment after neoadjuvant chemotherapy in order to prevent futile laparotomies in patients who would benefit more from further cycles of chemotherapy instead of an incomplete cytoreductive surgery.³²

Strengths and Weaknesses

The main limitation of this study lays in the retrospective evaluation of the Fagotti score, as the routine assessment of the score was implemented in our center only in 2019. The lack of some video or photo documentation may result in an underestimation of Fagotti. On the other hand, an evaluation of the scores before and after neoadjuvant chemotherapy by two independent surgeons ensured

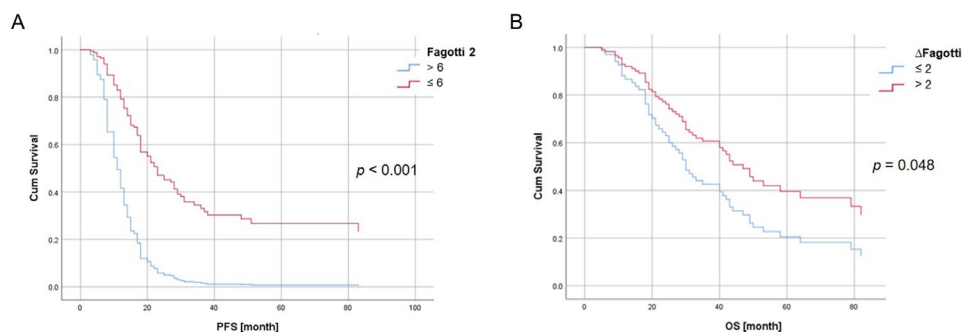


Figure 3 Cox regression analysis indicating progression-free survival (PFS) according to Fagotti score after neoadjuvant chemotherapy (Fagotti 2) (A) and overall survival (OS) of patients stratified for Δ Fagotti (B). P, χ^2 test.

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consistent scoring within the cohort and over the years, and there was a low rate of inter-observer variability. The long follow-up period—from 2012 to 2022—and the consistency in surgical and oncological treatment provided in a single tertiary referral hospital are additional strengths.

Implications for Practice and Future Research

In light of the strong association found in this study between the absolute Fagotti score after neoadjuvant chemotherapy with resection status, progression-free and overall survival, we propose to routinely assess the score at the time of interval debulking surgery. A systematic evaluation of the score may identify patients with persistent high intra-abdominal tumor burden and a low probability of complete surgical tumor resection, in whom debulking surgery should not be attempted.

CONCLUSION

To the best of our knowledge, the present study is the first to provide an in-depth analysis of the change of Fagotti score induced by neoadjuvant chemotherapy and its prognostic value. Future prospective trials are needed to validate these findings. Novel markers such as Δ Fagotti may foster the current paradigm shift towards a more personalized counseling and treatment approach for women diagnosed with ovarian cancer.

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