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Prognostic impact of initial tumor load and intraperitoneal disease dissemination patterns in patients with advanced ovarian cancer undergoing complete cytoreductive surgery

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Abstract

Introduction: Complete removal of disease is the most important prognostic factor for patients with advanced epithelial ovarian carcinoma. However, the influence of carcinomatosis distribution on prognosis is unknown and the prognostic impact of implant size according to their location is poorly studied. Our objective was to assess the impact of peritoneal carcinomatosis quantitative and qualitative localizations on progression free survival (PFS) in patients with advanced epithelial ovarian carcinoma (AEOC) after complete cytoreductive surgery.

Methods: We conducted a monocentric cohort study, retrospective from October 2001 to July 2014. Inclusion criteria were high-grade AEOC patients without residual disease (CC0) after primary debulking surgery (PDS) or after interval debulking surgery (IDS) following neoadjuvant chemotherapy (NACT). Peritoneal carcinomatosis was assessed according to qualitative criteria and quantitative criteria.

Results: One hundred and one patients were included. Median PFS was 21·2 months and median OS was 62·2 months. On the whole population, involvement of adipocytes-enriched areas tended to be associated with a decreased PFS and was significantly associated with a decreased OS. Any localization was associated with PFS or OS in the "IDS" subgroup. In the "PDS" subgroup, PCI score and involvement of the right mesocolic area were associated with a decreased PFS.

Conclusion: Initial tumor load has not been found associated with PFS after complete surgery. Adipocytes-enriched areas and right mesocolic areas involvement were associated with poor prognosis in patients receiving primary debulking surgery. Larger-scale studies are needed to assess whether initial tumor load has a prognostic impact even after complete cytoreductive surgery is achieved.

Keywords: ovarian cancer, survival, peritoneal carcinomatosis, tumor load

Introduction

Complete removal of visible disease is the most important prognostic factor in patients with advanced epithelial ovarian carcinoma (AEOC) [1]. Extensive surgery to the upper abdomen (supra-radical surgery) has increased the rate of complete surgery allowing to validate the concept of maximal surgical effort which requires the development of high-level surgical skills [2]. Carcinomatosis is a peritoneal disease related to the dissemination of tumor cells of carcinomatous origin on parietal and visceral peritoneum through the blood, lymphatic and peritoneal fluid circulation. Stagnation sites for fluid in the peritoneal cavity are logically main sites of tumor deposits (cul-de-sac of Douglas, lower quadrant of the right mesocolic space (ileocecal junction), superior surface of the sigmoid mesocolon, the right parieto-colic gutter and the duodenum) [3]. Similarly, the areas of reabsorption of peritoneal fluid, such as diaphragmatic doms or the small and large omentum, are physiopathologically areas of concentration of tumor cells. In addition, other patterns of carcinomatosis dissemination have been suggested. The frequency of omental involvement with peritoneal carcinomatosis may be due to the presence of adipocytes that stimulate the growth of ovarian tumor cells through a transfer of energy [4]. The impact of tumor load on prognosis is controversial. Some authors conclude that there is no influence of the initial tumor burden if surgery is complete, while others conclude that the tumor burden influences morbidity, overall survival and recurrence-free survival even after obtaining a zero tumor residue [5–8]. Furthermore, the issue on prognosis of the impact of the initial distribution, i.e. localization of carcinomatosis, rather than only tumor load is unsolved.

Our objective was to investigate the relationship between initial total tumor burden, qualitative and quantitative distribution of peritoneal carcinomatosis on prognosis, in patients

with AEOC and no residual disease after surgery. Our primary endpoint was PFS in the overall population, our secondary endpoint was PFS in two subgroups: patients with primary debulking surgery (PDS) and patients with interval debulking surgery (IDS).

Patients and Methods

We conducted a retrospective study in a teaching hospital (Hôpital Européen Georges Pompidou, Paris, France) of a prospectively maintained database concerning all patients diagnosed with ovarian cancer between October 2005 to April 2018. We use a systematic standardized operative report including a descriptive location of carcinomatosis (quantitative and qualitative) as well as a description and calculation of PCI (peritoneal carcinomatosis index). Inclusion criteria were: AEOC of serous subtype (FIGO stage III/IV), treated from October 2005 to July 2014 in order to have a sufficient follow-up, absence of residual macroscopic disease after PDS or IDS after NACT, high histological grade and explicit initial operative report. Patients had systematically a pre-therapeutic thoraco-abdomino-pelvic CT scan and a diagnostic laparoscopy. All cases were discussed in multidisciplinary meetings. Patients data including clinical and biological characteristics, pathology, surgical data and chemotherapy characteristics were extracted. The tumor load was defined by the initial PCI. Quantitative criteria were defined according to the PCI score as a continuous variable, but regarding also the number of areas affected, the number of area quoted 1 (inferior to 0·5cm), 2 (0·5 to 5cm) or 3 (superior to 5cm). Concerning the peritoneal carcinomatosis distribution, we focused on qualitative criteria regarding embryologic origin, adipocyte richness, anatomical localizations using the transverse mesocolon and the mesentery as reference. Embryologic origin was divided in anterior intestine (abdominal oesophagus, stomach, anterior part of the duodenum, hepatic parenchyma, gallbladder, hepatic, cystic and common bile duct and ventral and dorsal pancreatic buds), middle intestine (posterior part of the

duodenum, small intestine, caecum, appendix, right colon, proximal part of the transverse colon) and posterior intestine (distal part of the transverse colon, sigmoid and rectum), according to visual initial evaluation. Adipocytes rich areas corresponded to the greater and lesser omentum, the mesentery and mesocolon. Anatomical localizations were classified as supra mesocolic or infra mesocolic; infra mesocolic localizations were separated into right, left and central according to their location compared to the mesentery. The presence of supra-diaphragmatic adenopathy was evaluated thanks to the pre-operative thoracic and abdominal CT.

Study data were collected and managed using REDCap electronic data capture tools hosted by the CARPEM translational research platform at HEGP, AP-HP, Paris, France[9]. The data were described as mean ± standard deviation or median [min-max] for quantitative variables and by numbers (percentage) for qualitative variables. Univariate survival analysis (PFS and OS) were performed with the logrank test, comparing the Kaplan-Meier curves of the variables involved. The date of cancer diagnosis was considered the beginning of the follow-up. The point date was 25th April 2018. The variables reaching a significance of 0·1 were then included in a multivariate Cox model, adjusted to the main prognostic factors (age, PCI CA125 as a continuous variable, FIGO stage, constitutional BRCA status, antiVEGF therapy) to identify independent prognostic factors. A secondary, exploratory analysis was then carried out to evaluate PFS and OS in the following subgroups: "primary debulking surgery" or "interval debulking surgery". Statistical analysis were carried out using software R version 3.1.0 (http://lib.stat.cmu.edu/R/CRAN). This study was registered to the CNIL (Commission Nationale de l'Informatique et des Libertés (n°1875581), French national authority for personal data protection).

Results

One hundred and one patients were included in the study. Median follow-up was 50·5 months [3·3-171·6], 55.5 months [3·3-171·6] and 45·2 months [9·8-135] in the whole population, the PDS group and the IDS group respectively. Median progression-free survival (PFS) was 21·2 months (19-25·3), 26·9 months (22-date point) and 17·4 months (14·8-22·5) in the whole population, the PDS group and the IDS group respectively. Median overall survival (OS) was 62·2 months (52-96·5), 83·4 months (53·8-date point) and 55·4 months (40-96·5) in the whole population, the PDS group and the IDS group respectively (**Fig. 1**).

Population characteristics are described in **Table 1**. Median age was 62 years old. Six patients (5·9%) had stage IIIA, 9 (8·9%) patients had stage IIIB, 64 (63·4%) patients had stage IIIC and 22 (21·8%) patients had stage IV, according to 2009 FIGO classification. Chemotherapy protocols were based on the association of paclitaxel and carboplatin. Three patients had neoadjuvant and adjuvant anti VEGF in the ANTHALYA trial and 35 patients had only adjuvant anti VEGF [10].

Surgical data are shown in **Table 2**. Forty patients (39·6%) had radical surgery and sixty-one patients (60·4%) had supra radical surgery [11]. Twenty patients (19·8%) had a bowel resection. 24% of patients didn't undergo lymphadenectomy because they were randomized in an ongoing multicentric French trial (Pelvic and Aortic-Cava Lymphadenectomy Randomized for Ovarian Cancer, CARACO, ClinicalTrials.gov Identifier: NCT01218490).

Thirteen patients (12·7%) had supra diaphragmatic adenopathy diagnosed on pre-operative thoracic and abdominal CT scan. Qualitative evaluation of peritoneal carcinomatosis is presented and compared between PDS group and IDS group in **Table 3.** Twenty patients (19·8%) had an involvement of structures originating from the anterior

intestine. Regarding quantitative criteria: two patients (1·9%) had all areas of the PCI affected reflecting an extensive disease; one patient (0·9%) had all areas of the PCI quoted 1, and one patient (0·9%) had all areas of the PCI quoted 3. Only 13 patients (12·8%) were free of area quoted 3 and 43 patients (42·2%) were free of area quoted 1. The mean PCI was 14 (±9). These results show that a vast majority of patients had extensive and bulky peritoneal carcinomatosis. Patients receiving neoadjuvant chemotherapy had significantly more aggressive disease with more intestinal involvement, more bilateral diaphragmatic involvement and more stage IV disease (**table 3**).

We first investigated the relationship between tumor load, peritoneal distribution and survival in the total population. On multivariate analysis, PCI (HR 1.04 (1·0-1·09) p=0·05) and adipocytes-enriched areas involvement (HR 2·07 (0·87-4·93) p=0·10) showed a trend to decreasing PFS, while it was not statistically significant. Adipocytes-enriched areas involvement remains significantly associated with a decreased OS (HR=4.36 (1·21-15·74) p=0·02), as well as para-aortic lymph node involvement (HR=3.77 (1·65-8·64) p=0·0007). Seromuscular intestinal infiltration was not associated with prognosis. Results of multivariate analysis are summarized in **table 4A**.

We subsequently investigated the relationship between tumor load, peritoneal distribution and survival in the two subgroups of patients with primary debulking surgery and patients with interval debulking surgery. On multivariate analysis, we found an association with a decreased PFS only in the PDS subgroup for the following factors: PCI (HR=1·18 (1·06-1·32) p=0·003) and right infra-mesocolic area involvement (HR= 3·37 (1·20-9·50) p= 0·02). We found an association with a decreased OS in both PDS and NAC subgroups for para-aortic lymph node involvement (HR= 3.87 (1·05-14·23) p= 0·03) and (HR= 3.25 (1·08-

9·74) p= 0·03) respectively. The results of multivariate analysis are presented in **tables 4B** and **4C**.

Discussion

Our study investigated, among patients with advanced high grade serous ovarian adenocarcinoma undergoing complete debulking surgery, the association between initial tumor burden, dissemination patterns, specific localization of disease and prognosis. We observed that in the whole population, the involvement of adipocytes-enriched areas had an impact on OS and PFS and that in the PDS subgroup, the involvement of the right infra-mesocolic space decreased PFS. None of peritoneal carcinomatosis localizations had any impact "IDS" subgroup. Nevertheless, patients with neoadjuvant chemotherapy had a higher tumor burden than patients with primary debulking surgery. Patients requiring NACT appear as an interesting group, with greater tumor load and different qualitative extension. The relative impact of these parameters should be better studied.

The impact of the initial tumor burden on the survival of patients with advanced ovarian cancer in complete resection is controversial in the literature. In the 2000s, when obtaining a zero tumor residue became the main goal of cytoreductive surgery, some authors conclude that there was no influence of the initial tumor burden in case of complete macroscopic resection, while others conclude that tumor burden influences overall survival and survival without recurrence, even after a complete removal of the tumor [14,15]. Most of studies focused on the impact of the tumor burden on prognosis but not on specific regions. *Rosendahl et al.* showed recently that specific regions were more predictive of survival than the entire PCI but they did not focus their analysis on patients with a complete cytoreduction [8]. It is still difficult to find in the literature a study focused on the prognosis impact of specific region involvement in patients with complete cytoreduction rather than the impact on prediction of

resectability.

Few studies have evaluated quantitative criteria such as the impact of implants size or confluence on survival in advanced ovarian cancer. In our study, we investigated the quantitative distribution of the tumor burden using the quantitative classification of PCI and we found, in univariate analysis, that for each additional zone reaching a score 3, the risk of recurrence was multiplied by 1·10. In their retrospective study on different types of cancer (ovary, stomach, colon, pseudomyxoma.), *Spiliotis et al*. showed that the increase in the number of affected areas was associated with a poorer prognosis [12]. In the EORTC randomized study, a small initial tumor burden was associated with better OS, although the initial tumor burden was assessed by laparoscopy or laparotomy only in 34·6% in the "primary surgery" group and 38·3% in the "interval surgery" group [13]. The study by *Martinez et al*. went further and found an influence of the size of the implants in the supra-mesocolic region on the PFS with a HR 1·39 [1·05-1·84] for 0-25mm implants and 1·52 [1·08-2·12] for implants larger than 25mm [14].

Regarding lymph node involvement, para-aortic lymph node involvement was significantly associated with poorer prognosis. It has been shown that ovarian carcinoma with isolated lymph node involvement without carcinomatosis has a better prognosis. In our study, all patients with para-aortic lymph node involvement had associated peritoneal carcinomatosis. We also found in univariate analysis that supradiaphragmatic lymph node (SDLN) involvement was associated with poorer prognosis but this was not confirmed in multivariate analysis probably because of too small sample size. In our study, this diagnosis was estimated with CT scan or PET/CT without any histological confirmation. Patient with SDLN involvement were more likely to receive NAC and these lymph nodes were not resected, making difficult their evaluation and the analysis of its prognostic impact. The prognostic impact of SDLN involvement has been recently studied by *Lee et al* [16]. They showed that

patients with stage IV disease with SDLN involvement detected on PET/CT had a poorer prognosis than patients with stage III disease, but the same prognosis than patients with stage IV disease with another metastasis. In their study, resection of suspicious SDLN did not improve survival rates.

We chose to study qualitative criteria based on the physiology of peritoneal fluid circulation and on the role of tumor microenvironnement. Peritoneal fluid circulation results of a pressure gradient in the abdominal cavity. There are four peritoneal recesses where flow can be temporarily arrested: the Douglas pouch, the right lower quadrant, the right paracolic gutter and the sigmoid colon [3,17]. These regions are the most involved in case of carcinomatosis. In our study, right mesocolic lesions were found to be significantly associated with a decrease in PFS in the PDS subgroup. In the study by *Spiliotis et al*. the involvement of zones 4, 5 and 8 of PCI (right and left mesocolic) was associated with a better prognosis than the zones 9, 10, 11 of PCI (proximal and distal jejunum and proximal ileum) [12]. The hypothesis of the distribution of peritoneal carcinomatosis lesions according to the peritoneal fluid circulation had never been mentioned in the literature before. However, according to an *in vitro* study, the peritoneal fluid contains CD90 + / CD45- cells which, when co-cultured with gastric cancer cells, give cells with a mesothelial profile that favor the development of peritoneal metastases [18]. Histological analysis of these peritoneal metastases showed that these cells with mesothelial profile were embedded in the fibrous zone forming the microenvironment of the metastasis. This study thus raises the hypothesis of floating cells in the peritoneal fluid which, when in contact with cancer cells (primary lesion), favor the development of peritoneal metastases. Within tumor microenvironment, adipocytes have been shown to promote growth, invasion and metastasis [4]. Therefore, we studied the influence of involvement of areas rich in adipocytes (large and small epiploon, mesentery, mesocolon). In multivariate analysis, this involvement was significantly associated with a decrease in

survival in our whole population. Obesity was not associated with involvement of areas rich in adipocytes. These results are difficult to extrapolate due to the lack of literature. Some authors described the presence in the omentum of "milky spots" composed of immune cells and stromal cells which, together with the adipocytes, play a role in the dissemination of peritoneal carcinomatosis [19].

We analyzed the locations of peritoneal carcinomatosis according to their embryological origin, which had never been described in the literature. We observed that involvement of structures originating from the medium (posterior part of the duodenum, small intestine, caecum, appendix, right colon, proximal part of the transverse colon) and posterior intestine (distal part of the transverse colon, sigmoid and rectum) was associated with a decrease in PFS and OS in univariate analysis. We also found that involvement of the right paracolic gutter was associated with a decreased PFS in multivariate analysis in patients receiving primary surgery, which may correspond to the involvement of the caecum, appendix and right colon. We saw in our comparison that patients in the IDS group had a more aggressive disease with more intestinal involvement and in particular more involvement of the right side of the mesentery. This specific location may have a significant prognostic impact.

The major strength of our study is to provide detailed information on initial surgical findings and disease spread patterns. Limitations are the retrospective design of the study and limited number of cases, making subgroup analysis difficult.

Conclusion

In summary, the impact on survival of the initial tumor load in patients with complete resection remains unsolved. Some dissemination patterns appear to be associated with a decreased PFS (increase in the number of affected areas, involvement of adipocytes-enriched areas and the presence of right paracolic lesions). Thus, identifying patients with an initial

tumor distribution at greater risk of recurrence would allow a tailored follow-up to diagnose recurrences earlier in order to improving their overall survival. Recent studies suggested that molecular subtypes are associated with peritoneal disease dissemination patterns and surgical outcomes [20]. Indeed, the mesenchymal subtype is associated with the presence of upper abdominal disease and with a decreased rate of complete primary debulking surgery. Initial molecular profiling of AEOC, as well as imaging and laparoscopic peritoneal disease scoring, could allow to selecting patients more likely to receive neoadjuvant chemotherapy or to undergo supra-radical primary debulking surgery.

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References

[1] 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;20:1248–59.

[2] 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;114:26–31.

[3] Canis M, Botchorishvili R, Rabischong B, Houlle C, Wattiez A, Mage G, et al. Péritoine. EMC-Gynécologie 2002;75-A-10:1–11.

[4] Nieman KM, Kenny HA, Penicka CV, Ladanyi A, Buell-Gutbrod R, Zillhardt MR, et al. Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. Nat Med 2011;17:1498–503.

[5] Gasimli K, Braicu EI, Richter R, Chekerov R, Sehouli J. Prognostic and Predictive Value of the Peritoneal Cancer Index in Primary Advanced Epithelial Ovarian Cancer Patients After Complete Cytoreductive Surgery: Study of Tumor Bank Ovarian Cancer. Ann Surg Oncol 2015;22:2729–37.

[6] Eisenkop SM, Spirtos NM, Friedman RL, Lin WC, Pisani AL, Perticucci S. Relative influences of tumor volume before surgery and the cytoreductive outcome on survival for patients with advanced ovarian cancer: a prospective study. Gynecol Oncol 2003;90:390–6.

[7] Horowitz NS, Miller A, Rungruang B, Richard SD, Rodriguez N, Bookman MA, et al. Does aggressive surgery improve outcomes? Interaction between preoperative disease burden and complex surgery in patients with advanced-stage ovarian cancer: an analysis of GOG 182. J Clin Oncol 2015;33:937–43.

[8] Rosendahl M, Harter P, Bjorn SF, Hogdall C. Specific Regions, Rather than the Entire Peritoneal Carcinosis Index, are Predictive of Complete Resection and Survival in Advanced Epithelial Ovarian Cancer. Int J Gynecol Cancer 2018;28:316–22.
[9] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inf 2009;42:377–81.
[10] Rouzier R, Gouy S, Selle F, Lambaudie E, Floquet A, Fourchotte V, et al. Efficacy and safety of bevacizumab-containing neoadjuvant therapy followed by interval debulking surgery in advanced ovarian cancer: Results from the ANTHALYA trial. Eur J Cancer 2017;70:133–42.
[11] Chi DS, Franklin CC, Levine DA, Akselrod F, Sabbatini P, Jarnagin WR, et al. Improved optimal cytoreduction rates for stages IIIC and IV epithelial ovarian, fallopian tube, and primary peritoneal cancer: a change in surgical approach. Gynecol Oncol 2004;94:650–4.
[12] Spiliotis J, Halkia EE, Kalantzi N, Giassas S, Lianos E, Efstathiou E, et al. Mapping the location of peritoneal metastases using the peritoneal cancer index and the correlation with overall survival: a retrospective study. J Buon 2015;20 Suppl 1:S64-70.
[13] Vergote I, Trope CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 2010;363:943–53.
[14] Martinez A, Ngo C, Leblanc E, Gouy S, Luyckx M, Darai E, et al. Surgical Complexity Impact on Survival After Complete Cytoreductive Surgery for Advanced Ovarian Cancer. Ann Surg Oncol 2016;23:2515–21.
[15] Berek J. Lymph node-positive stage IIIC ovarian cancer: a separate entity? Int J Gynecol Cancer 2009;19 suppl2: S18-20.
[16] Lee IO, Lee, Jung-Yun, Kim, Hyun Jeong, Nam, Eun Ji, Kim, Sunghoon, Kim, Sang Wun, et al. Prognostic significance of supradiaphragmatic lymph node metastasis detected by 18F-FDG PET/CT in advanced epithelial ovarian cancer. - PubMed - NCBI n.d. https://www.ncbi.nlm.nih.gov/pubmed/30477469 (accessed April 4, 2019).
[17] Meyers MA. Distribution of intra-abdominal malignant seeding: dependency on dynamics of flow of ascitic fluid. Am J Roentgenol Radium Ther Nucl Med 1973;119:198–206.
[18] Kitayama J, Emoto S, Yamaguchi H, Ishigami H, Watanabe T. CD90+ mesothelial-like cells in peritoneal fluid promote peritoneal metastasis by forming a tumor permissive microenvironment. PLoS One 2014;9:e86516.
[19] Clark R, Krishnan V, Schoof M, Rodriguez I, Theriault B, Chekmareva M, et al. Milky spots promote ovarian cancer metastatic colonization of peritoneal adipose in experimental models. Am J Pathol 2013;183:576–91.
[20] Torres D, Kumar A, Wallace SK, Bakkum-Gamez JN, Konecny GE, Weaver AL, et al. Intraperitoneal disease dissemination patterns are associated with residual disease, extent of surgery, and molecular subtypes in advanced ovarian cancer. Gynecol Oncol 2017;147:503–8.

Figure 1: survival curves: A, B, C Progression-free survival of whole population, PDS groupe and IDS group. D, E, F Overall survival of whole population, PDS group and IDS group.

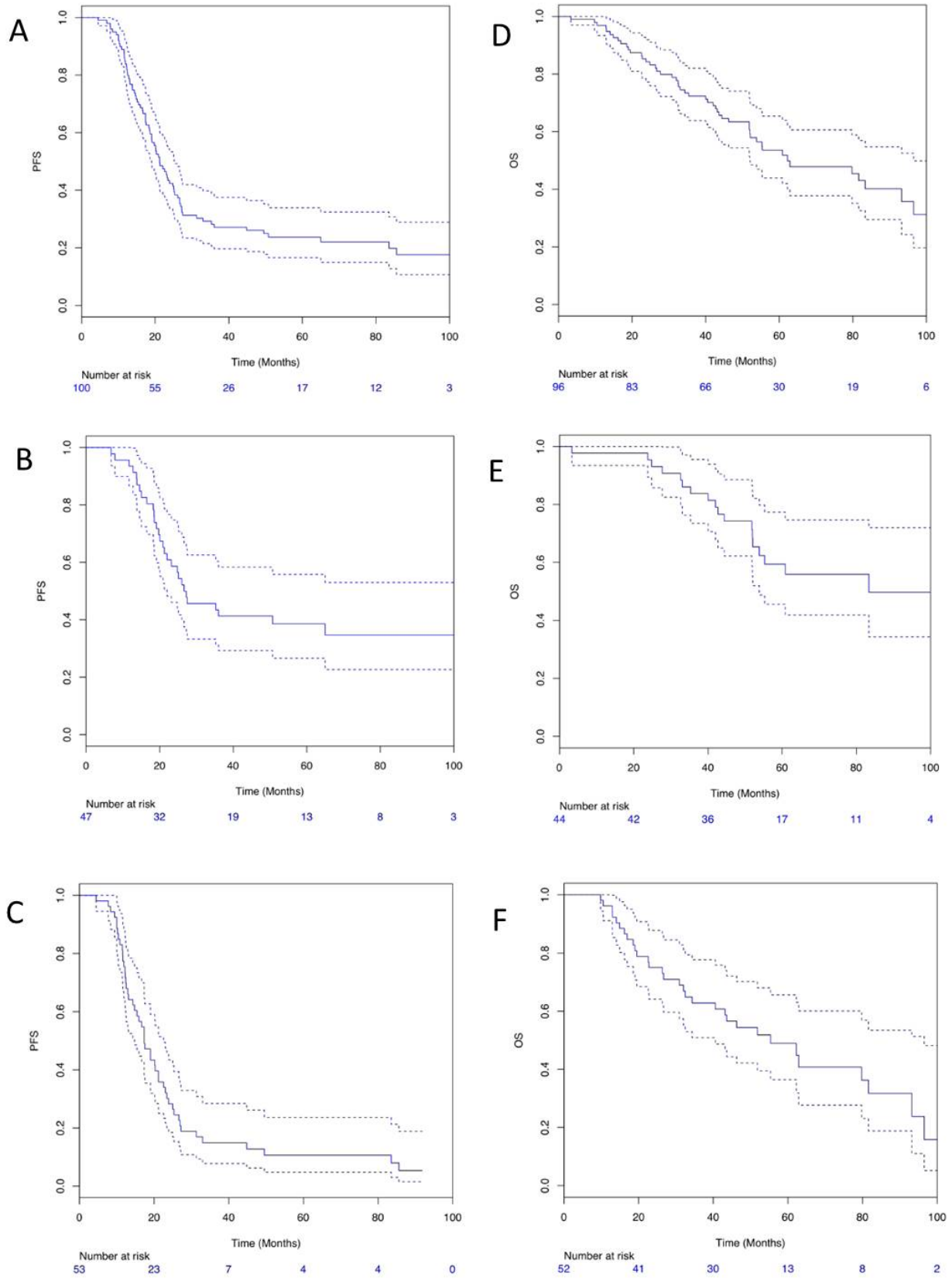

Table 1: patients characteristics

Characteristics	**N=101**
Age (median, range)	62 [39-84]
ASA **< 3** **≥ 3** NA	87 (85.3%) 13 (12.8%) 1 (1.9%)
Body Mass Index (mean ± standard deviation)	23.3 ±4.2
FIGO Stage **III** **IV**	 79 (78.2%) 22 (21.8%)
CA 125 (median, range)	660 [9-125 000]
BRCA status **Unknown** **Negative** **BRCA1** **BRCA2**	 39 (38.6%) 47 (46.5%) 9 (8.9%) 6 (6%)
PCI (mean ± standard deviation)	14 ± 9
Surgery Primary debulking surgery Interval debulking surgery	 48 (47.5%) 53 (52.5%)
Chemotherapy Neo-adjuvant only Adjuvant only Neo-adjuvant + adjuvant **AntiVEGF therapy**	 7 (7%) 47 (46.5%) 47 (46.5%) 38 (37.6%)

Table 2: surgical procedures

Surgical procedures	N (%)
Radical surgery	
TH-BSO	101 (100%)
Pelvic lymphadenectomy	77 (76.2%)
Para-aortic lymphadenectomy	77 (76.2)
Radical omentectomy	100 (99%)
Anterior pelvic exenteration	2 (2%)
Posterior pelvic exenteration	39 (38.6%)
Douglassectomy	65 (65%)
Supra-radical surgery	
Right diaphragmatic stripping	61 (60.4%)
Left diaphragmatic stripping	34 (33.7%)
Visceral resection	
Liver resection	5 (5%)
Splenectomy	9 (9%)
Small bowel	9 (8.9%)
Large bowel	11 (11%)
Coeliac lymphadenectomy	1 (1.1%)

TH-BSO: total hysterectomy and bilateral salpingo-oophorectomy

Table 3: qualitative distribution of peritoneal carcinomatosis, comparison between WP (whole population), PDS group (primary debulking surgery) and IDS group (interval debulking surgery).

Carcinomatosis localization	**WP N= 101**	**PDS N=48**	**IDS N=53**	**p**
Embryologic primitive intestine				
Anterior intestine	20 (19.8%)	7 (14.6 %)	13 (28.9%)	0.09
Medium intestine	38 (37.6%)	8 (16.7%)	30 (66.7%)	<0.0001
Posterior intestine	53 (52.5%)	19 (40.4%)	34 (75.6%)	0.0007
Areas rich in adipocytes	72 (77.4%)	28 (58.3%)	44 (97.8%)	<0.0001
Infra-mesocolic				
Left side of the mesentery	66 (64.7%)	21 (43.8%°	33 (62.3%)	0.0625
Right side of the mesentery	51 (57.8%)	13 (27.1%)	38 (71.7%)	<0.0001
Supra-mesocolic	72 (78.3%)	28 (59.6%)	44 (97.8%)	<0.0001
Diaphragmatic cupola				
Unilateral	21 (23%)	14 (29.8%)	7 (15.5%)	
bilateral	45 (49%)	10 (21.3%)	35 (77.8%)	<0.0001
Paracolic gutters				
Right paracolic gutter	8 (9.3%)	2 (4.3%)	6 (15.4%)	<0.0001
Left paracolic gutter	1 (1.2%)	1 (2.1%)	0	
Both	29 (33.7%)	5 (10.6%)	24 (61.5%)	
Susdiaphragmatic nodes	13 (13.1%)	2 (4.2%)	11 (21.6%)	0.01
FIGO Stage				
IIIa	6 (5.9%)	5 (10.4%)	1 (1.9%)	
IIIb	9 (8.9%)	8 (16.7%)	1 (1.9%	
IIIc	64 (63.4%)	32 (66.7%)	32 (60.4%)	
IV	22 (21.8%)	3 (6.2%)	19 (35.8%)	<0.0002

Table 4: multivariate analysis of progression free survival and overall survival. A, total population; B, primary debulking surgery subgroup; C, interval debulking surgery subgroup.

A: total population

PFS	**HR [95% CI]**	**p**
Infra-mesocolic involvement	1.49 [0,75-2.98]	0,25
PCI	1.04 [1.0-1,09]	**0,05**
Adipocytes-enriched areas involved	2.07 [0,87-4.95]	0,1
OS		
PCI	1.05 [1.0-1,1]	0,08
Total Nb of PCI areas involved	1,03 [0,94-1,14]	0,46
Adipocytes-enriched areas involved	4.36[1.20-15.74]	**0.02**
Para-aortic lymph node involvement	3.77 [1.65-8.64]	**0.0007**

B: primary debulking surgery

PFS	**HR [95% CI]**	**p**
Infra-mesocolic right side involvement	3.37 [1.2-9.5]	**0.02**
PCI	1.18 [1.06-1,32]	**0,003**
OS		
age	1.05 [1.0-1,1]	0,08
Infra-mesocolic right side involvement	1.87 [0,49-7.11]	0,36
PCI	1.1[0.97-1.27]	0.1
Para-aortic lymph node involvement	3.87 [1.05-14.23]	0.03

C: interval debulking surgery

PFS	**HR [95% CI]**	**p**
age	1.64 [0.76-3.5]	0.2
PCI	1.04 [0.98-1,1]	0,2
OS		
age	1.99 [0.88-4.50]	0.09
PCI	1.03[0.97-1.10]	0.3
Para-aortic lymph node involvement	3.25 [1.08-9.74]	**0.03**