

**Prognostic factors of overall survival for patients with  
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neo-adjuvant chemotherapy followed by interval  
debulking surgery: A multicenter cohort analysis from  
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L. Vincent, C. Jankowski, L. Ouldamer, M. Ballester, S. Bendifallah, P.A.  
Bolze, C. Akladios, H. Costaz, V. Lavoué, G. Canlorbe, et al.

► **To cite this version:**

L. Vincent, C. Jankowski, L. Ouldamer, M. Ballester, S. Bendifallah, et al.. Prognostic factors of overall survival for patients with FIGO stage IIIc or IVa ovarian cancer treated with neo-adjuvant chemotherapy followed by interval debulking surgery: A multicenter cohort analysis from the FRANCOGYN study group. *EJSO - European Journal of Surgical Oncology*, WB Saunders, In press, 10.1016/j.ejso.2020.04.029 . hal-02638428

**HAL Id: hal-02638428**

**<https://hal-univ-rennes1.archives-ouvertes.fr/hal-02638428>**

Submitted on 28 May 2020

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**Credit author statement**

Study concepts: LV, CJ, CC

Study design: LV, CJ, CC

Data acquisition: LV, CJ, SD

Quality control of data and algorithms: LV, CJ, SD

Data analysis and interpretation: LV, CJ, SD

Statistical analysis: LV, CJ

Manuscript preparation: LV, CJ, CC

Manuscript editing: LV, CJ, LO, MB, SB, PAB, CA, HC, VL, CU, PC, CT, CH, AB, SD,  
MMP, JF, LB, LA, CC

Manuscript review: LV, CJ, LO, MB, SB, PAB, CA, HC, VL, CU, PC, CT, CH, AB, SD,  
MMP, JF, LB, LA, CC

**Prognostic factors of overall survival for patients with FIGO stage IIIc or IVa ovarian cancer treated with neo-adjuvant chemotherapy followed by interval debulking surgery: a multicenter cohort analysis from the FRANCOGYN study group.**

Vincent L<sub>a,b,\*</sub>, Jankowski C<sub>a</sub>, Ouldamer L<sub>c,d</sub>, Ballester M<sub>e</sub>, Bendifallah S<sub>f</sub>, Bolze PA<sub>g</sub>, Akladios C<sub>h</sub>, Costaz H<sub>a</sub>, Lavoué V<sub>i</sub>, Canlorbe G<sub>j,k</sub>, Collinet P<sub>l</sub>, Touboul C<sub>m</sub>, Huchon C<sub>n</sub>, Bricou A<sub>o</sub>, Dridi S<sub>a,b</sub>, Padéano MM<sub>a</sub>, Bengrine L<sub>p</sub>, Arnould L<sub>q</sub>, Coutant C<sub>a,b</sub>; Groupe de Recherche FRANCOGYN

**\*Corresponding author:** Laura Vincent, Department of Surgical Oncology Georges-Francois Leclerc Cancer Center, 1 Professor Marion's street, Dijon, France; lvincent@cgfl.fr, 03 80 73 75 09, fax: 03 80 73 75 29

<sup>a</sup> Department of Surgical Oncology, Georges-Francois Leclerc Cancer Center, 1 Professeur Marion street, 21000 Dijon, France

<sup>b</sup> University of Burgundy, 7 Jeanne d'Arc boulevard, 21000 Dijon, France

<sup>c</sup> Department of Gynecology, Centre Hospitalier Universitaire de Tours, 2 Tonnelé boulevard, 37000 Tours, France,

<sup>d</sup> INSERM U1069 Université François-Rabelais, 10 Tonnelé boulevard, 37000 Tours, France

<sup>e</sup> Department of Gynecologic and Breast Surgery, Groupe Hospitalier Diaconesses Croix Saint Simon, 125 Avron street, 75020 Paris, France

<sup>f</sup> Department of Gynaecology and Obstetrics, Tenon University Hospital, Assistance Publique des Hôpitaux de Paris (AP-HP), 4 Chine street, 75020 Paris, France

<sup>g</sup> Gynecological Surgery Service, CHU Lyon-Sud, 165 Grand Revoyet road, 69495 Pierre-Bénite, France

<sup>h</sup> Department of Surgical Gynecology, University Hospital of Strasbourg, Molière avenue 67200 Strasbourg, France

<sup>i</sup> Department of Gynecological Surgery, Rennes University Hospital, 16 Bulgarie boulevard 35200 Rennes, France

<sup>j</sup> Department of Gynecologic and Breast Surgery and Oncology, AP-HP, Pitié-Salpêtrière University Hospital, 47-83 Hôpital boulevard, 75013 Paris, France

<sup>k</sup> INSERM, UMR S 938, Sorbonne University, 75005 Paris, France

<sup>l</sup> Department of Gynecological Surgery, Jeanne de Flandre University Hospital, Eugène Avinée avenue 59000 Lille, France

<sup>m</sup> Department of Obstetrics and Gynaecology, Centre Hospitalier Intercommunal, 40 Verdun avenue 94010 Créteil, France

<sup>n</sup> Department of Gynecology, Centre Hospitalier de Poissy, 10 Champ Gaillard street 78300 Poissy, France

<sup>o</sup> Department of Gynaecology, Bobigny University, AP-HP, Hôpital Jean-Verdier, 14 Juillet avenue, 93140 Bondy, France

<sup>p</sup> Department of Medical Oncology, Georges-Francois Leclerc Cancer Center, Dijon, 1 Professeur Marion street, 21000 France

<sup>q</sup> Department of Anatomopathology, Georges-Francois Leclerc Cancer Center, 1 Professeur Marion street, 21000 Dijon, France

**1 ABSTRACT**

2 **Introduction.** The aim of this study was to identify prognostic factors of overall survival in  
3 patients with FIGO stage IIIc or IVa ovarian cancer (OC) treated by neo-adjuvant  
4 chemotherapy (NAC) followed by interval debulking surgery.

5 **Materials and Methods.** Data from 483 patients with ovarian cancer were retrospectively  
6 collected, from January 1, 2000 to December 31, 2016, from the FRANCOGYN database,  
7 regrouping data from 11 centers specialized in ovarian cancer treatment. Median overall  
8 survival was determined using the Kaplan-Meier method. Univariate and multivariate analysis  
9 were performed to define prognostic factors of overall survival.

10 **Results.** The median overall survival was 52 after a median follow up of 30 months. After  
11 univariate analysis, factors significantly associated with decreased overall survival were; no  
12 pelvic and/or para-aortic lymphadenectomy ( $p=0.002$ ), residual disease (CC1/CC2/CC3) after  
13 surgery ( $p<0.001$ ), positive cytology after NAC ( $p<0.001$ ), omental disease after NAC  
14 ( $p=0.002$ ), no pathologic complete response (pCR) ( $p=0.002$ ). In multivariate analysis, factors  
15 significantly associated with decreased overall survival were; residual disease after surgery  
16 (HR=1.93; CI95% (1.16-3.21),  $p=0.01$ ) and positive cytology after NAC (HR=1.59; CI95%  
17 (1.01-2.55),  $p=0.05$ ). Patients with no residual disease after surgery had a median overall  
18 survival of 64 months versus 35 months for patients with residual disease. Patients with  
19 negative cytology after NAC had a median overall survival of 71 months versus 43 months  
20 for patients with positive cytology after NAC.

21 **Conclusion.** In this first and largest French based retrospective study, complete cytoreductive  
22 surgery in ovarian cancer remains the main prognostic factor of overall survival.

23

24 **KEYWORDS:** ovarian cancer, neoadjuvant chemotherapy, interval debulking surgery,  
25 overall survival.

1 **ABBREVIATIONS:**

2 BMI: Body Mass Index

3 CCS: Complete Cytoreductive Surgery

4 HE4: Human Epididymal protein 4

5 IDS: Interval Debulking Surgery

6 LVSI: Lymphovascular Space Invasion

7 NAC: Neo-adjuvant chemotherapy

8 OC: Ovarian cancer

9 OS: Overall survival

10 pCR: pathologic Complete Response

11 PFS: Progression Free Survival

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26 Declarations of interest: none

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## 1 1. INTRODUCTION

2 In France, ovarian cancer (OC) is the eighth leading cause of cancer in women. Incidence in  
3 France in 2018 was 4985 cases and mortality rate was 3927 deaths/year (1).

4 In approximately 70% of cases, patients with OC are diagnosed at an advanced stage, stage  
5 IIIc International Federation of Gynecology and Obstetrics (FIGO) or higher, and have  
6 peritoneal carcinomatosis (2,3). The prognosis of advanced OC (stage IIIc or IVa FIGO)  
7 remains poor, with a median overall survival (OS) estimated at 30 months according to the  
8 European Organization for the Research and Treatment of Cancer (EORTC) (4).

9 OC management is based on a complete resection surgery, preceded or not by neo-adjuvant  
10 platinum-based chemotherapy. Complete resection is a prognostic factor of survival, but  
11 excision of peritoneal carcinomatosis lesions might be impossible (5). Performing a neo-  
12 adjuvant chemotherapy (NAC) followed by an interval debulking surgery (IDS) decrease  
13 surgical resection and thus surgical morbidity without affecting patient survival. A  
14 randomized study conducted by the EORTC comparing primary surgery to NAC followed by  
15 IDS, demonstrated no significant difference in terms of recurrence-free survival and OS. NAC  
16 followed by complete resection surgery became the standard of care in patients with  
17 unresectable epithelial OC (4,6,7).

18 Residual tumors in the operative specimens are evaluated by pathological examinations,  
19 allowing histological response definitions. Studies have shown a prognostic impact of  
20 complete histological response or pathologic complete response (pCR) on progression-free  
21 survival (PFS) and OS. Petrillo *et al.*, studied the prognostic impact of pCR after NAC in  
22 unresectable OC. In this study, pCR was significantly associated with longer PFS and OS (8).  
23 However, pCR is a rare event in these advanced OC receiving NAC (approximately 6%) (9).  
24 Therefore it is interesting to identify other factors associated with OS in OC, receiving NAC  
25 to optimize patient management, in particular regarding adjuvant treatments after IDS. In fact,

1 identifying subgroups with worse OS could allow us to adapt adjuvant treatment. Two three-  
2 phase randomized studies (ICON 7 and GOG-218) have demonstrated a progression free  
3 survival (PFS) benefit of adding bevacizumab as adjuvant therapy in poor prognosis sub  
4 group's patients (10,11).

5 The objectives of this study are to identify prognostic factors of OS in patients with stage IIIc  
6 or IVa OC treated with taxane/platinum-based NAC and IDS and to evaluate the prognostic  
7 impact of pCR.

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9

## 10 **2. MATERIALS AND METHODS**

### 11 *2.1. Population*

12 Data from 483 patients with OC, stage IIIc or IVa treated by NAC followed by IDS were  
13 retrospectively collected, from January 1, 2000 to December 31, 2016, from the  
14 FRANCOGYN database regrouping data from 11 French centers specialized in OC treatment:  
15 "Georges-François Leclerc Cancer Center" Dijon, "International Hospital" Créteil,  
16 "University hospital Lyon Sud", "Jean Verdier Hospital" Bondy, "La Pitié-Salpêtrière  
17 Hospital" Paris, "Jeanne de Flandre University Hospital" Lille, "Hospital of Poissy",  
18 "University Hospital" Rennes, "University Hospital", Strasbourg, "Hôpital Tenon" Paris and  
19 "University Hospital", Tours. NAC was decided after a diagnostic laparoscopy. The research  
20 protocol was approved by the Institutional Review Board of the French College of Obstetrics  
21 and Gynecology (CEROG 2014-GYN-020). The inclusion criteria were: inoperable initial  
22 stage FIGO IIIc or IVa OC, treated by taxane/platinum-based NAC followed by IDS.

### 23 *2.2. Clinical and pathological variables*

24 The clinical and pathological variables studied were: age, body mass index (BMI), CA125  
25 serum level during evaluation and after NAC, FIGO stage, menopause, BRCA mutation, and

1 histological type. Concerning chemotherapy, the variables studied were: number of NAC  
2 cycles, NAC protocol, and bevacizumab treatment.

3 Surgery variables studied were: Fagotti score, digestive resection, pelvic lymphadenectomy or  
4 para-aortic lymphadenectomy, macroscopic residual tumor, and intraoperative capsular  
5 rupture.

6 Pathology variables studied were: peritoneal cytology, lymphovascular space invasion  
7 (LVSI), omentum invasion, grade of serous tumors, differentiation, involvement of pelvic and  
8 para-aortic nodes and histological response.

### 9 *2.3. Definition of the histological response*

10 At the end of IDS, an anatomopathological examination of the surgical specimens was carried  
11 out to define histological response in three types: complete response, partial response and no  
12 response. Pathologic complete response (pCR) was defined by the absence of invasive  
13 residual tumor in operative specimens. Partial histological response was defined by the  
14 presence of degenerative changes of the tumor cells. Absence of a histological response was  
15 defined by the absence of anatomopathological response to NAC. An expert in gynecological  
16 pathology performed histology in all cases.

### 17 *2.4. Statistical analysis*

18 Univariate and multivariate analysis were performed to identify clinical, pathological,  
19 chemotherapy and surgery variables significantly associated with OS. To identify factors  
20 associated with OS, each variable was tested in univariate analysis using the log-rank test.  
21 Survival medians were defined according to the Kaplan-Meier method. Variables included in  
22 multivariate analysis had a  $p$  value equal or inferior to 0.10, a significant confidence interval  
23 (CI) in univariate analysis and less of 20% missing data.



1 Multivariate analysis was performed according to a Cox model. Results were considered  
2 significant when  $p$  value was equal or inferior to 0.05. Survival curves obtained using the  
3 Kaplan-Meier method and compared according to the log-rank test. Patients were censored at  
4 death or at 137 months if alive.

5 Data were managed with an Excel database (Microsoft Corporation, Redmond, WA, USA)  
6 and analyzed using R 3.3.1 software (R Foundation, Vienna, Austria), available online  
7 (<http://lib.stat.cmu.edu/R/CRAN/>). The research protocol was approved by the institutional  
8 review board of the French College of Obstetricians and Gynecologists (CEROG 2016-GYN-  
9 1003).

10

### 11 **3. RESULTS**

#### 12 *3.1. Population characteristics at initial evaluation*

13 Data from 483 patients with NAC-treated OC followed by IDS were retrospectively collected  
14 from 11 French expert centers.

15 Population characteristics are summarized in Table 1. The average age was 61.5 years (+/- 11  
16 years). BMI was in average 25.1 kg/m<sup>2</sup> (+/- 5.3 kg/m<sup>2</sup>). 83.2% patients were menopausal.  
17 Thirty-eight patients had a germline mutation BRCA gene (7.9%) but the BRCA gene status  
18 was unknown for 72.9% of patients. Three hundred and fifty-eight patients had FIGO stage  
19 IIIc (74.1%) and 97 FIGO stage IVa (20.1%). The majority of patients had a serous ovarian  
20 tumor (81.6%).

21 Of the NAC protocols used, 442 patients received taxane/platinum-based chemotherapy  
22 (91.5%). Ninety-eight patients received adjuvant therapy with bevacizumab (20.3%).

23 The mean CA125 serum level was 2181 U/ml (+/- 4499 U / ml), 247 patients had a CA125  
24 level  $\leq 1000$  U/ml (51.2%), 115 patients had a CA125 between 1000 and 3000 U/ml (23.8%),  
25 and 87 patients had a CA125  $\geq 3000$  U / ml (18%).

1 Three hundred and sixty-one patients underwent exploratory surgery, of which 291 had  
2 exploratory laparoscopy (80.6%), 44 had exploratory laparotomy (12.2%) and 4 had a  
3 conversion to laparotomy (1.1%). In this surgical evaluation, sixty-nine patients had a Fagotti  
4 score lower than 8 (14.3%) and 199 patients had a Fagotti score  $\geq$  8 (41.2%). Initial peritoneal  
5 cytology was positive in 179 patients (69.8%).

### 6 3.2. *Evaluation after NAC*

7 Regarding the number of NAC cycles, 195 patients received 2 or 3 or 4 cycles (40.4%), 200  
8 patients received 5 or 6 cycles (41.4%), 170 patients received 6 cycles (35.2 %) and 47  
9 patients had more than 6 cycles (9.7%) (table 2).

10 Regarding radiological evaluation after NAC, 238 patients had a TAP scan (49.3%) and 35  
11 patients underwent a PET scan (7.2%). In this radiological evaluation, 56 patients had ascites  
12 (11.6%) and omentum invasion was found in 70 patients (14.5%). With respect to lymph node  
13 assessment, 36 patients had suspicious pelvic nodes (7.5%) and 33 patients had suspicious  
14 para-aortic nodes (6.8%). Eight patients seem to have small bowel involvement (1.7%) and 22  
15 patients seem to have colon involvement (4.6%).

### 16 3.3. *Characteristics of IDS and histological response after NAC*

17 The Characteristics of IDS and histological response after NAC are summarized in table 2.  
18 After NAC, the average CA125 level was 152U/ml (+/- 316U/ml). One hundred and thirty  
19 patients had a CA125 level  $\leq$ 35 U/ml (26.9%) and 120 patients had a CA125 level  $>$ 35 U / ml  
20 (24.8%).

21 During IDS, Fagotti score was less than 8 for 105 patients (21.7%) and  $\geq$  8 for 65 patients  
22 (13.5%). Bowel resection was performed in 140 patients (28.9%). Three hundred and  
23 seventeen patients underwent pelvic and para-aortic lymphadenectomy (65.6%), 14 patients  
24 had only pelvic lymphadenectomy (2.9%) and 8 patients received a para-aortic

1 lymphadenectomy only (1.7%). Among 36 patients with positive pelvic lymph nodes on  
2 imaging, 24 patients had a pelvic lymphadenectomy and 22 had a para-aortic  
3 lymphadenectomy. Among patients with negative nodes on imaging, 114 patients had a pelvic  
4 lymphadenectomy and 110 patients had a para-aortic lymphadenectomy. Among 33 patients  
5 with positive para-aortic lymph nodes on imaging, 23 had a para-aortic lymphadenectomy.  
6 After IDS, three hundred and fifty-five patients had no visible residual tumor CC0 (73.5%)  
7 and 106 had a CC1 or CC2 or CC3 macroscopic residual tumor (21.9%).  
8 After histopathological analysis, 31 patients had a pCR (6.4%), 403 patients had a partial  
9 histological response (83.4%) and 8 patients showed no response to NAC (1.7%). Capsular  
10 rupture was found in 100 patients (20.7%). Peritoneal cytology was positive for 230 patients  
11 (47.6%), omentum was invaded for 281 patients (58.2%). One hundred and nineteen patients  
12 had positive pelvic lymph nodes (24.7%) and para-aortic lymph nodes were metastatic in 258  
13 patients (53.4%).

#### 14 3.4. *Univariate and multivariate analysis of OS*

15 Univariate analysis of OS is summarized in table 1 and 2. Median follow-up was 30 months  
16 and median OS was 52 months.

17 In univariate analysis, age, BMI, menopausal status, germline BRCA mutation, FIGO stage,  
18 histological type, NAC protocol, CA 125 at evaluation, Fagotti's score before NAC, and  
19 adjuvant bevacizumab didn't significantly affected OS (table 1). At the contrary, positive  
20 peritoneal cytology at evaluation was associated with worse OS ( $p=0.04$ ).

21 Regarding the characteristics of IDS, the absence of pelvic and/or para-aortic  
22 lymphadenectomy, and the absence of complete cytoreductive surgery (CCS); CC1/CC2/CC3  
23 was associated with worsen OS (respective  $p$  value: 0.002 and  $<0.001$ ). There was no  
24 significant difference of OS regarding patients with surgical resection ( $p=0.23$ ).

1 Concerning pathological analysis after IDS, variables significantly associated with a decrease  
2 in OS were positive peritoneal cytology at evaluation ( $p=0.04$ ) and after NAC ( $p<0.001$ ),  
3 omentum invasion at evaluation ( $p=0.02$ ) and after NAC ( $p=0.002$ ), para-aortic  
4 lymphadenectomy after NAC ( $p=0.01$ ), presence of LVSI ( $p=0.04$ ), absence of pCR  
5 ( $p=0.002$ ) and capsular rupture ( $p=0.03$ ).

6 Among significant variables in univariate analysis ( $p\leq 0.10$ ), only those with less than 20%  
7 missing data were studied in multivariate analysis. These variables were: absence of pelvic  
8 and /or para-aortic lymphadenectomy, presence of residual tumor during interval surgery,  
9 positive peritoneal cytology after NAC, omentum invasion after NAC and absence of pCR.  
10 After multivariate analysis, the presence of residual tumor (CC1/CC2/CC3) and positive  
11 peritoneal cytology after NAC were significantly associated with a decrease in OS  
12 (respectively HR = 1.93, 95%CI (1.16-3.21),  $p=0.01$  and HR = 1.59, 95%CI (1.01-2.55),  
13  $p=0.05$ ) (figure 1).

14 The median OS of patients with no visible residual tumor (CC0) was 64 months, while that of  
15 patients with a CC1, CC2 and CC3 was 35 months. The median OS of patients with a positive  
16 peritoneal cytology after NAC was 43 months, and 71 months for patients with negative  
17 peritoneal cytology after NAC. Survival curves according to residual tumor and peritoneal  
18 cytology results are shown in figure 2.

19

#### 1 4. DISCUSSION

2 This is the first and largest French based retrospective study examining the outcome for  
3 patients with stage IIIc or IVa OC treated with NAC. It confirms that CCS remains the main  
4 prognostic factor. In our study, 73.5% of patients underwent macroscopically complete  
5 resection (CC0) during IDS, and 106 were CC1/CC2/CC3. This rate is relatively high  
6 compared to literature data where this level varies between 30 and 85% (2,12–15). We have  
7 also shown that the presence of residual tumor after ICS is one of the major prognostic factors  
8 of decreased OS of stage IIIc or IVa OC treated with NAC. The median OS of patients with  
9 no visible residual tumor (CC0) was 64 months, while that of patients with a CC1, CC2 and  
10 CC3 was 35 months. The importance of residual tumor has been shown in many studies (16).  
11 Indeed, in 2009, Du Bois *et al.* demonstrated in an analysis of 3 randomized studies (AGO-  
12 OVAR 3, 5 and 7) that CCS for stage IIb to IV OC was associated with significant  
13 improvement in OS: the median OS was 99 months for patients with no residual tumor, 36  
14 months for patients with a residual tumor of 1 to 10 mm and 29 months for patients with a  
15 residual tumor strictly larger than 10 mm ( $p<0.0001$ ) (17). Similarly, Bristow *et al.* showed  
16 that the 24.5 months median OS was significantly associated with CCS ( $p=0.027$ ). Indeed, a  
17 10% increase in CCS rate, increased median survival by 1.9 months (18). However, it is  
18 sometimes difficult to compare data from literature as the definition of CCS varies according  
19 to studies, that often define CCS as residual tumor of less than 1 cm (4,9,15,19–21). In our  
20 study, CCS was not defined by a residual tumor less than 1 cm but by absence of residual  
21 tumor (CC0), limiting the biases associated to this factor. Obtaining no residual tumor after  
22 surgery is increased by NAC as demonstrated by Lee *et al.*(22). Similarly, the EORTC-NCIC  
23 study demonstrated that obtaining a residual tumor of less than 1 cm concerned 41.6% of  
24 patients during primary surgery and 80.6% after IDS (23). In addition, the CHORUS study  
25 conducted by Kehoe *et al.*, showed the non-inferiority of the NAC compared to the primary

1 surgery, therefore it seemed interesting to perform a NAC in patients with major peritoneal  
2 dissemination to reduce peri-operative morbidity/mortality and to increase CCS rate (13).  
3 However, Hacker *et al.* demonstrated that primary CCS remained the gold standard for  
4 patients with OC immediately resectable. In fact, inflammation after NAC can make surgery  
5 complicated and ovarian tumors sensitivity to platinum salts can't be predicted (24).

6 In the present study, residual tumor seems to predominate over pCR, that does not appear to  
7 be significantly associated with OS in multivariate analysis ( $p=0.5$ ). Furthermore, pCR rate is  
8 6%, similar to what has been previously reported (9). This low rate can be explained by the  
9 peritoneal diffusion of OC. However, many studies have demonstrated the importance of  
10 histological response after NAC, since NAC is significantly associated with PFS. Rose *et al.*  
11 showed that pCR rate was 19.9%. In this study, PFS was 16.1 months in a pCR, 13.5 months  
12 in a partial response and 11.7 months when no response was observed ( $p=0.018$ ) (25).  
13 Therefore, Petrillo *et al.*, searched for predictors of pCR. Only the FIGO stage was  
14 significantly associated with pCR ( $p=0.21$ ) (8).

15 Taking in consideration the previously described data, it seemed important to identify other  
16 prognostic factors of OS and PFS of IIIc or IVa ovarian stage cancers, to adapt neoadjuvant  
17 and adjuvant therapies to subgroups at risk. Scores for predicting OS could be created and  
18 implemented using different variables such as the CA125 marker, the presence of BRCA  
19 mutation, omental disease. Indeed, Rutten *et al.*, created a nomogram based on clinical-  
20 pathological variables, to estimate the 5-year survival of patients with OC treated by primary  
21 surgery or IDS. The variables used in this nomogram were age, primary surgery or IDS, post-  
22 surgical residual tumor, histological type, FIGO stage, WHO performance status, ascites  
23 amount and BRCA status. The total number of points resulting from all variables analysis  
24 allowed defining 1-year, 3-year and 5-year survival (26).

1 In our study, a CA125 serum level higher than or equal to 3000 U/ml at evaluation was  
2 significantly associated with decreased OS in univariate analysis ( $p=0.08$ ). As missing data  
3 rate was higher than 20%, this marker was not studied in multivariate analysis. Nevertheless,  
4 several authors have shown interesting results with this marker. Mahdi *et al.*, showed that a  
5 CA125 level of less than 20 U/ml was a predictor of progression-free survival (HR = 0.37,  
6 95%CI (0.20-0.66),  $p<0.001$ ) but not OS (HR = 0.64, 95%CI (0.34-1.21),  $p=0.17$ ) (27). Other  
7 markers could also be used for their prognostic value. The human epididymal protein 4 (HE4)  
8 is overexpressed in serous and endometrioid-type OC and can be used for both diagnosis and  
9 follow-up of these cancers (28). Thus, Chudecka *et al.* demonstrated that post-treatment  
10 normalization or a 50% reduction in HE4 was significantly associated with increased  
11 recurrence-free survival and OS (29). Similarly, a meta-analysis performed by Yuang *et al.*,  
12 showed that a high pre-operative HE4 level had a negative impact on OS (HR=1.91, 95%CI  
13 (1.40-2, 61),  $p<0.001$ ) (30).

14 Pathological variables such as omental disease could also be implemented in these scores. In  
15 our study, omentum invasion after NAC was significantly associated with decreased OS in  
16 univariate analysis but was no longer in multivariate analysis. On the other hand, Le *et al.*  
17 demonstrated that omentum involvement and its response to NAC were prognostic factors of  
18 PFS (20). Given these different data, the combination of biological and pathological criteria  
19 could be helpful to identify subgroups with poor prognosis.

20 In our study, the presence of BRCA1/2 mutation was not significantly associated with OS, in  
21 contrast with previously reported data but there were missing data for 72.9% of patients. The  
22 prognostic value of a BRCA1/2 mutation was assessed in a large number of retrospective  
23 cohorts and a recent meta-analysis involving 34 studies concluded that patients with a  
24 BRCA1/2 mutation had a benefit in terms of PFS (HR = 0.62, 95%CI (0.53-0.73),  $p=0.261$ )  
25 and OS (HR = 0.67, 95%CI(0.57-0.78),  $p=0.001$ ) and this benefit was more important in

1 patients with a BRCA2 mutation (31). In another study, the presence of a BRCA1/2 mutation  
2 was associated with a better prognosis in the short term ( $p=0.03$ ) but was not found after 10  
3 years of follow-up (32). These data might be explained by a higher sensitivity of patients with  
4 a BRCA mutation to platinum-based chemotherapy, as demonstrated by Gorodnova *et al.*  
5 (33).

6 In recent years, the development of molecular biology and genomics has revolutionized the  
7 treatment and understanding of neoplastic diseases, particularly breast cancer. This is still not  
8 the case for OC. Mendiola *et al.* demonstrated that 5 overexpressed genes found in malignant  
9 ovarian tumors (ANGPT1, CD34, CD44, MMP7, PDGFB) were favorable prognostic factors  
10 of OS of high-grade serous OC (34). Mutation identification or new biomarkers associated  
11 with survival will be necessary to define subgroups of patients with poor prognosis leading to  
12 treatment intensification. In fact, the use of bevacizumab as an adjuvant is still not consensual  
13 and is depended on the benefit/risk balance in patients with stage IIIc/IVa OC treated with  
14 NAC. Thus, no prognostic score objectively defines patients belonging to high-risk  
15 subgroups, who require this adjuvant treatment. Finally, identifying new biomarkers may lead  
16 to the development of new therapies such as targeted therapies that may improve the bad  
17 prognosis of this pathology.

18

## 19 **5. CONCLUSION**

20 This is the first and largest French based retrospective study about prognostic factors of OS in  
21 stage IIIc or IVa OC treated with NAC. It confirms that CCS remains the main prognostic  
22 factor (HR = 1.93, 95%CI (1.16-3.21),  $p=0.01$ ) and residual tumor after IDS seems to  
23 predominate over pCR ( $p=0.5$ ). At the time of personalized medicine in oncology, identifying  
24 clinical, pathological, surgical, molecular or genomic factors, prognosis of OS and PFS would



1 optimize patient management leading to treatment intensification in subgroups with poor  
2 prognosis.

3

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**Table 1 : Univariate analysis of prognostic factors of OS in population characteristics**

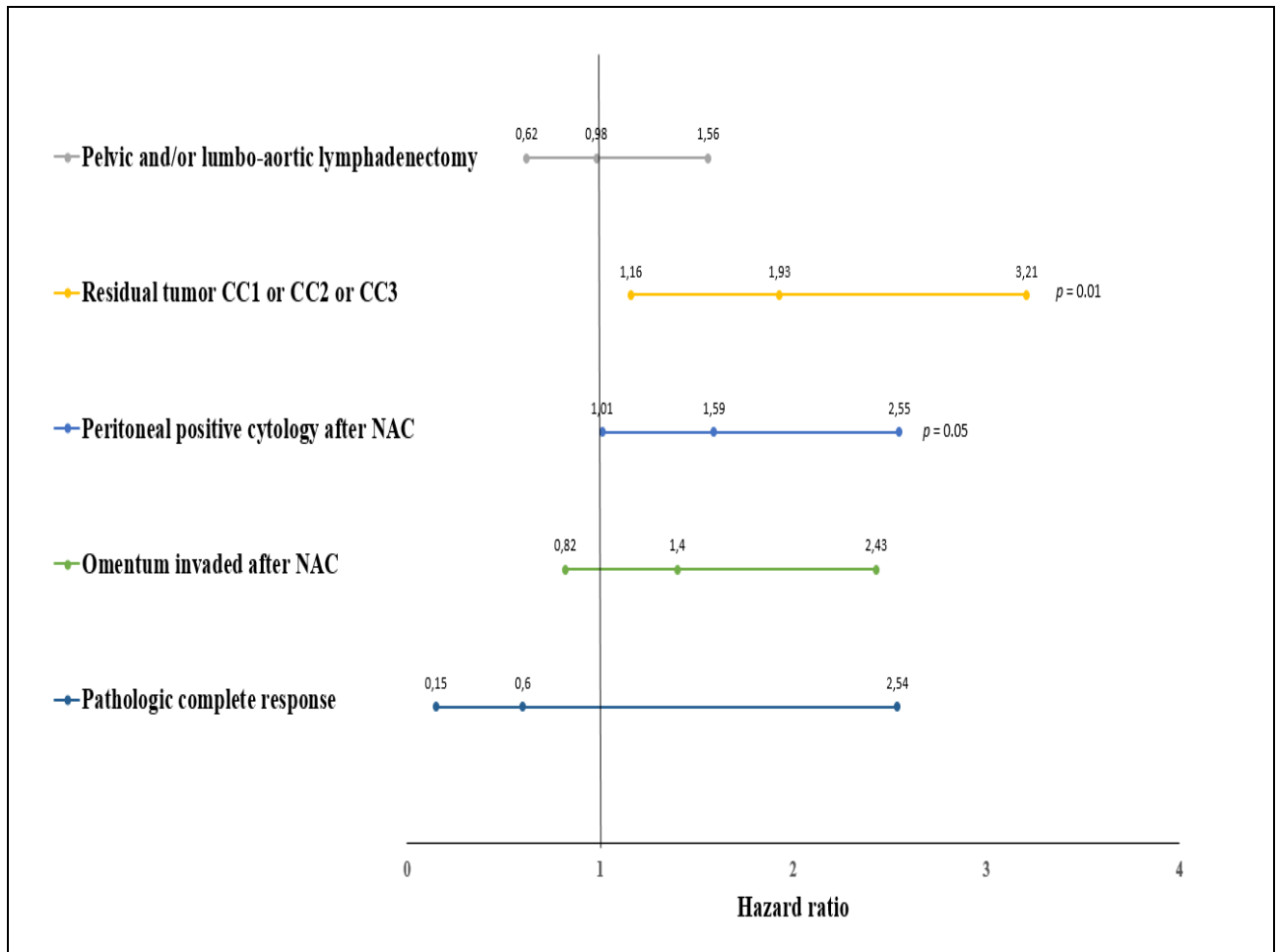
Variables	Values (n = 483)	Median overall survival (months)	p
Age at diagnosis (mean ± SD, years)	61.5±11		
≤ 50 (reference)	78 (16.1%)	60	
50 to 70	284 (58.9%)	54	0.75
≥ 70	120 (24.8%)	43	0.13
Unknown	1 (0.2%)		
BMI (mean ± SD, years)	25,1±5.3		
≤ 25	252 (52.2%)	46	
>25	187 (38.7%)	53	0.15
Unknown	44 (9.1%)		
Menopause			
Yes	402 (83.2%)	50	
No	47 (9.7%)	69	0.22
Unknown	34 (7.1%)		
BRCA mutation			
Yes	38 (7.9%)	73	
No	93 (17.1%)	67	0.28
Unknown	352 (72.9%)		
FIGO stage			
IIIc	358 (74.1%)	54	
IVA	97 (20.1%)	46	0.08
Unknown	28 (5.8%)		
Histological type			
Serous (reference)	394 (81.6%)	54	
Endometrioid	22 (4.6%)	48	
Clear cells	11 (2.3%)	42	
Other	22 (4.6%)	46	0.7
Unknown	34 (7%)		
NAC protocol			
Taxane/platinum-based chemotherapy	442 (91.5%)	53	
Others	41 (8.5%)	41	0.3
CA125 at evaluation (U/ml)			
≤ 1000 (reference)	247 (51.2%)	55	
1000 to 3000	115 (23.8%)	46	0.61
≥ 3000	87 (18%)	41	0.08
Unknown	34 (7%)		
Fagotti score before NAC			
< 8 (reference)	69 (14.3%)	69	
≥ 8	199 (41.2%)	46	0.1
Unknown	215 (44.5%)		
Peritoneal cytology at evaluation			
Positive (reference)	176 (69.8%)	46	
Negative	31 (12.3%)	74	<b>0.04</b>
Unknown	276		
Adjuvant bevacizumab			
Yes (reference)	98 (20.3%)	46	
No	255 (52.8%)	54	0.87
Unknown	130 (26.9%)		

Abbreviations : BMI = body mass index; FIGO = International Federation of Gynecology and Obstetrics, NAC = neo-adjuvant chemotherapy

**Table 2: Univariate analysis of prognostic factors of OS after IDS**

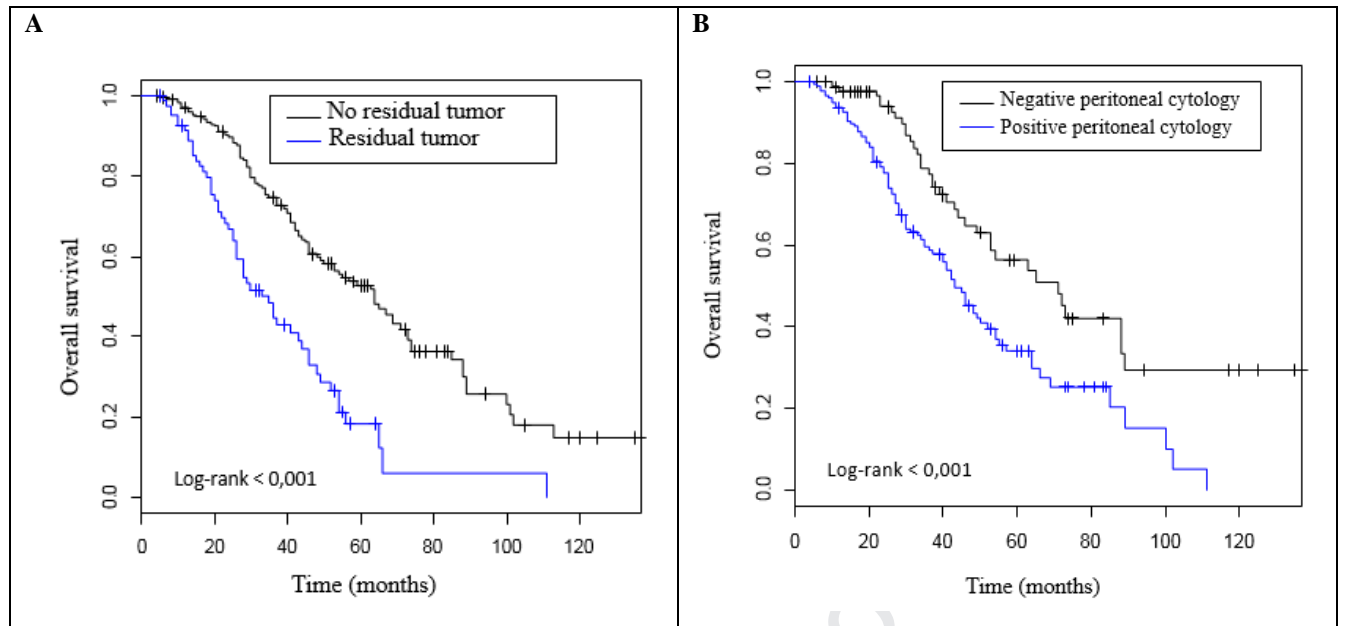
Variables	Values (n = 483)	Median overall survival (months)	p
<b>Fagotti score after NAC</b>			
< 8	105 (21.7%)	43	0.1
≥ 8	65 (13.5%)	49	
Unknown	313 (64.8%)		
<b>CA125 post NAC (mean±SD, U/ml)</b>			
≤ 35	130 (26.9%)	54	0.22
> 35	120 (24.8%)	46	
Unknown	233 (48.3%)		
<b>Surgical resections</b>			
<b>Digestive resections</b>			
Yes	140 (28.9%)	54	0.23
No	342 (70.8%)	46	
Unknown	1 (0.2%)		
<b>Pelvic and para-aortic lymphadenectomy</b>			
Yes	317 (65.6%)	60	<0.001
No	151 (31.3%)	44	
Unknown	1 (0.2%)		
<b>Residual tumor after IDS</b>			
CC1/CC2/CC3	106 (21.9%)	64	<0.001
CC0	355 (73.5%)	35	
Unknown	22 (4.6%)		
<b>Peritoneal cytology after NAC</b>			
Positive	230 (47.6%)	43	<0.001
Negative	153 (31.7%)	51	
Unknown	100 (20.7%)		
<b>Pathological response to NAC</b>			
None (reference)	8 (1.7%)	24	0.2
Partial	403 (83.4%)	49	
Complete	31 (6.4%)	66	
Unknown	41 (8.5%)		
<b>Capsular rupture</b>			
None	113 (23.4%)	72	0.03
Yes	100 (20.7%)	42	
Unknown	270 (55.9%)		
<b>Invaded omentum after NAC</b>			
Yes	281 (58.2%)	44	0.002
No	101 (20.9%)	73	
Unknown	101 (20.9%)		
<b>Invaded pelvic nodes after NAC</b>			
Yes	113 (35.6%)	53	0.073
No	180 (56.8%)	65	
Unknown	24 (7.6%)		
<b>Invaded para-aortic nodes after NAC</b>			
Yes	125 (39.4%)	49	0.01
No	139 (43.8%)	74	
Unknown	53 (16.8%)		
<b>Embolus</b>			
Yes	47 (9.7%)	41	0.04
No	80 (16.6%)	72	
Unknown	356 (73.7%)		

Abbreviations : NAC = Neo-adjuvant chemotherapy; CC0 = no visible residual tumor; CC1/CC2/CC3 = macroscopic residual tumor



**Fig 1. Prognostic factors of overall survival in multivariate analysis.**

NAC = neo-adjuvant chemotherapy; CC0 = no visible residual tumor; CC1 or CC2 or CC3= macroscopic residual tumor.



**Fig 2. Estimation of overall survival according to residual tumor (A) and peritoneal cytology (B) after interval debulking surgery in Stage IIIc or IVa ovarian cancer patients treated with NAC.**



## **CONFLICTS OF INTEREST**

None.

## **ACKNOWLEDGEMENTS**

Medical writing assistance was provided by Isabel Grégoire, PhD, Centre Georges François Leclerc.