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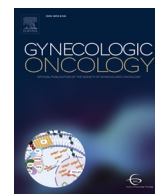


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## Optimal timing of interval debulking surgery for advanced epithelial ovarian cancer: A retrospective study from the ESME national cohort

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### HIGHLIGHTS

- The goal of interval debulking surgery (IDS) is complete resection.
- IDS should not be performed after >3–4 neoadjuvant chemotherapy (NACT) cycles.
- Almost half of patients treated by IDS are operated after ≥5 NACT cycles in France (delayed IDS).
- Patients treated by delayed IDS have worse progression free survival than after standard IDS (3–4 NACT cycles).
- The quality of real-world data extracted from electronic-health records requires improvement to reduce missing data.

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### ABSTRACT

**Objective.** Interval debulking surgery is recommended after 3–4 cycles (standard IDS) of neoadjuvant chemotherapy (NACT) for epithelial ovarian cancer (EOC) not able to received upfront complete debulking surgery. However, real world practices frequently report performing IDS after ≥5 NAC cycles (delayed IDS). The aim of this work was to evaluate the impact on survival of the number of NACT cycles before IDS.

**Methods.** We identified from a French national database, women with newly diagnosed EOC who underwent IDS from January 2011 to December 2016. Progression free survival (PFS) and overall survival (OS) were compared using Cox model with adjustments for confounding factors provided by two propensity score methods: inverse probability of treatment weighting (IPTW) and matched-pair analysis.

**Results.** 928 patients treated by IDS for which our propensity score could be applied were identified. After a median follow-up of 49.0 months (95% CI [46.0;52.9]); from the IPTW analysis, median PFS was 17.6 months

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Prognosis  
Propensity score

and 11.5 months (HR = 1.42; CI 95% [1.22–1.67];  $p < 0.0001$ ); median OS was 51.2 months and 44.3 months (HR = 1.29; CI 95% [1.06–1.56];  $p = 0.0095$ ) for the standard and delayed IDS groups. From the matched-pair analysis (comparing 352 patients for each group), standard IDS was associated with better PFS (HR = 0.77; CI 95% [0.65–0.90];  $p = 0.018$ ) but not significantly associated with better OS (HR = 0.84; CI 95% [0.68–1.03];  $p = 0.0947$ ).

**Conclusions.** Carrying IDS after  $\geq 5$  NACT cycles seems to have a negative effect on patients survival. The goal of IDS surgery is complete resection and should not be performed after  $> 3$ –4 NACT cycles.

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## 1. Introduction

Primary debulking surgery (PDS) followed by taxane and platinum based adjuvant chemotherapy remains the standard of care for advanced EOC although several clinical trials have reported no disadvantage for NACT [1–3]. Complete gross resection is required, as the presence of post-operative tumor residue has a strong negative impact on survival [4].

When complete PDS is not feasible, NACT followed by interval debulking surgery (IDS) is recommended [1]. Four randomized trials have compared IDS with PDS. In these trials, 3–4 cycles of NACT were allowed, with a total of 6–8 peri-operative chemotherapy cycles [2,3,5,6]. In daily practice, many teams report a number  $\geq 5$  NACT cycles leading to delayed IDS [7–10]. The reasons for increasing the number of NACT cycles are various, mainly related to persistent tumor unresectability after 3–4 cycles but also to logistical set-up of IDS, medical complications requiring delayed surgery or other medical reasons [10]. Results regarding the impact on survival of increasing the number of NACT cycles beyond 4 are contradictory [11]. Some retrospective studies found that  $\geq 5$  NACT cycles appear to be associated with a decrease in PFS and OS, despite a non-inferior complete surgery rate [7,10,12–14]. Other studies argue that delayed IDS does not seem to affect the prognosis [8,9,15–17]. The main limitations of these retrospective studies are related to the selection of patients who have undergone delayed IDS. Indeed, patients with poor prognostic factors such as altered general condition, stage IV disease according to the International Federation of Gynecology and Obstetrics (FIGO) classification at initial presentation, or poor chemosensitivity are more likely to be proposed for delayed IDS [7]. The challenge related to the timing of IDS lies in identifying prognostic factors to guide the clinician to the optimal treatment strategy.

The French national Epidemiological Strategy and Medical Economics (ESME) cohort of patients aims to centralize existing real-world patient data in oncology [18]. It compiles data from the patients' electronic medical records, inpatient hospitalization records, and pharmacy records. The ESME-ovarian cancer (OC) database compiles data on consecutive patients diagnosed and/or treated (whatever the stage of OC disease) since 2011 at one of the 18 French Comprehensive Cancer Centers (FCCC). It offers a large real-world multicenter cohort, with demographics, tumor characteristics, clinical features, clinical events, and treatment-related data that may lead to a better knowledge of OC evolution.

The aim of our study was to evaluate PFS and OS according to the timing of IDS: after 3–4 cycles or  $\geq 5$  cycles of NACT and to identify prognostic factors associated with survival in patients with advanced epithelial ovarian cancer in the ESME-OC cohort.

## 2. Patients and methods

### 2.1. Study design and selection criteria

This retrospective non-interventional study analyzed data from the ESME-OC database of Unicancer. The ESME-OC database (NCT03275298) is a centralized deidentified structured database derived from electronic

health records and of consecutive patients suffering from OC and treated at one of the 18 cancer centers in the Unicancer network since 01/01/2011. Our overall study population was defined as all female patients aged  $\geq 18$  years diagnosed with FIGO III/IV ovarian cancer and treated by IDS at a FCCC between January 01, 2011 and December 31, 2016. The standard and delayed IDS populations were defined as patients treated by IDS after 3–4 or  $\geq 5$  cycles of NACT, respectively. All types of chemotherapy regimens were accepted. All patients with early stage (FIGO I-II), with FIGO stage III-IV treated by PDS or those who had only received 1–2 NACT cycles before IDS were excluded from the analysis. Patients with aberrant delays between the start of NACT and IDS ( $> 9$  NACT cycles and a delay since diagnosis of more than one year) were also excluded. Data were extracted on January 6th, 2020.

The ESME-OC database is managed according to the good epidemiology and pharmacoepidemiology practices guidelines. The data are updated on a yearly basis and are subject to data management process aimed at ensuring the quality of data analyzed.

### 2.2. Objectives of the study

The primary objective of this study was to assess the PFS according to whether patients had undergone standard or delayed IDS. PFS is defined as the time from debulking surgery to the first documented date of progression, or death from any cause, whichever occurred first (the last date of follow-up being censored). Indeed, the number of neoadjuvant chemotherapy cycles was recorded prior to interval debulking surgery and is therefore a known baseline covariate at the time of surgery.

The secondary endpoints of the study were:

- OS depending on whether the patient had undergone standard or delayed IDS. OS is defined as the time from the date of surgery to death from any cause, last date of follow-up being censored.
- Identification of prognostic factors for both OS and PFS.

### 2.3. Data collection and statistical analysis

Continuous variables were described by the number of observations (N), the median, minimum, maximum, mean and standard deviation. The Student *t*-test or Wilcoxon test were used to compare the distribution of continuous variables. Categorical variables were described by the number of observations (N) and the frequency (%) of each modality. Missing categories were counted. Percentages were calculated in the overall population excluding missing data. The Chi-square test was used to compare proportions (or the Fisher's exact test if the expected frequencies were  $< 5$ ).

Median follow-up was estimated using the reverse Kaplan-Meier method for OS and PFS. The Kaplan-Meier method was used to estimate survival rates and median survival times and their associated 95% confidence interval (95% CI). The survival distribution of both treatment arms was compared using the Log-rank test.

A propensity score was used to balance the covariates observed between subjects in the two treatment study groups. Logistics regression was used to develop the propensity score and was defined as the probability that a subject would receive standard or delayed IDS given the

following covariates: age at diagnosis, Eastern Cooperative Oncology Group performance status (ECOG PS) at diagnosis (0,1, ≥2), FIGO stage (III, IV), pathological subtype (serous + endometrioid vs other). Only those patients with data available for all propensity score variables were considered for the analysis of OS and PFS.

Once the probability was estimated, the Inverse Probability of Treatment Weights (IPTW) method was used to attribute weights to each treatment [19]. In order to demonstrate the robustness of this finding, a sensitivity analysis was performed using the propensity score matching method. Patients were matched on the same variables as for the IPTW method.

A Cox proportional hazard analysis was performed to identify OS and PFS prognostic factors. A univariate analysis was performed with Cox model analysis (IPTW propensity score method) for each variable of interest. The analysis was performed on the following parameters: age at diagnosis, family history of cancer, body mass index (BMI), ECOG PS, pathological subtype, FIGO stage, BRCA 1/2 mutation status, CA 125 (U/ml) value at diagnosis, ascites at diagnosis, gastrointestinal resection during debulking surgery, complete gross resection status, chemotherapy regimen and the rhythm of NACT administration, time from the last NACT cycle until debulking surgery and administration of adjuvant bevacizumab. Variables with  $p$ -value <0.20 (at univariate analysis) were selected for the multivariate analysis. A Cox proportional hazards model was performed.

Statistical analyses were performed on the Unicancer external server using SAS 9.4 statistical software. All statistical tests were two-sided and the significance threshold was set at 5% (i.e.  $p < 0.05$ ).

### 3. Results

#### 3.1. Population demographics

Out of the 10,263 patients included in the ESME-OC database, we identified 2059 patients diagnosed from 01/01/2011 until 12/31/2016 treated with IDS for FIGO stage III/IV OC (Fig. 1). Demographics are detailed in Table 1. The median age at diagnosis was 63.0 years. Patients with FIGO stage III represent 68.7% of the global population. Most of the patients had a good performance status at diagnosis (PS 0 = 33.6% and PS 1 = 48.9%). Serous carcinoma represented 73.6% of the cohort including 3.6% low-grade serous carcinoma. A personal history of breast cancer concerned 8.9% patients and a family history of cancer was available for 1569 patients, including a quarter (28.4%) with a family history of breast and/or OC. BRCA1/2 deleterious mutations (germline and/or somatic) were identified in 27.4% of the patients with data available.

The number of neoadjuvant cycles ranged from 3 to 9, with a median of 4. Regarding neoadjuvant chemotherapy regimens, 94.5% of patients received carboplatin and paclitaxel and 2.8% had carboplatin monotherapy. More than half (54.0%) of the patients received the combination of carboplatin and paclitaxel every 3 weeks (D1 = D21). >80% of patients with available data had a complete IDS (82.4%). An anti-angiogenic treatment by bevacizumab was provided as adjuvant therapy in 446 patients representing 25.9% and 22.1% of standard and delayed IDS populations. None patients received a poly (adenosine diphosphate-ribose) polymerase inhibitor (PARPi) in maintenance considering the inclusion period of the study.

#### 3.2. Clinical and surgical discrepancies between standard and delayed IDS populations (Table 1)

Among patients treated by IDS, 1120 (54.4%) had standard IDS and 939 (45.6%) patients had delayed IDS. Approximately the same fraction of patients benefited from standard IDS after 3 cycles (48.9%) and 4 cycles (51.1%). Most patients treated by delayed IDS received 6 cycles of NACT (74.2%). The proportion of FIGO Stage IV OC and the number of patients with ECOG PS ≥ 2 were higher in the delayed IDS than in the standard IDS population: 39.9% vs 24.1% and 21.4% vs 15.0%, respectively.

1052 (93.9%) and 787 (83.8%) of patients benefited from adjuvant chemotherapy with a mean (standard deviation) of 3.4 (1.4) and 2.9 (1.5). The mean (standard deviation) number of peri-operative chemotherapy cycles (neoadjuvant + adjuvant) was 5.9 (2.0) and 7.6 (1.9) in the standard and delayed IDS arms respectively. Clinical characteristics including age at diagnosis, BMI, pathological subtype, initial CA 125 value were globally similar between the two groups. At the time of surgery, complete gross resection was obtained in 84.7% and 79.1% of patients with data available in the standard and delayed IDS groups. The use of the propensity score allowed a balanced distribution of all the variables among the two treatment groups (standard and delayed IDS) (Supplementary material 1).

#### 3.3. Progression-free survival analysis

Among the cohort treated by IDS, 928 patients (559/1120 and 369/939 patients) had data available for each propensity score variable and were included in the PFS analysis using the IPTW propensity score method. The overall demographics of this population of 928 patients were comparable to the overall population of 2059 patients treated by IDS (Table 1).

The median PFS was 16.1 months (CI 95% [14.9–17.1]) for the global population. Median PFS was 17.6 months (CI 95% [16.1–19.0]) and 11.5 months (CI 95% [10.6–13.1]) for patients of the standard and delayed IDS groups respectively (HR = 1.42; CI 95% [1.22–1.67];  $p < 0.001$ ). From the sensitivity analysis performed using the propensity score matching method, the final samples were of 352 patients in each arm. For the global population, the median PFS was 14.3 months (CI 95% [12.6–16.1]). For patients in the standard and delayed IDS groups the median PFS was 16.6 months (CI 95% [15.1–18.0]) and 11.8 months (CI 95% [10.8–13.5]) respectively. (HR = 1.30; CI 95% [1.10–1.53];  $p = 0.018$ ) (Fig. 2).

268 patients were kept in prognostic identification for PFS analysis due to missing data. PFS univariate Cox regression analysis identified delayed IDS (HR = 1.30; CI 95% [0.95–1.77];  $p = 0.10$ ); abnormal BMI ( $p = 0.199$ ); PS 1 at diagnosis (HR = 1.32; CI 95% [0.98–1.77];  $p = 0.09$ ); PS >1 at diagnosis (HR = 1.55; CI 95% [0.95–2.53];  $p = 0.09$ ); residual disease after surgery (HR = 1.39; CI 95% [1.02–1.90];  $p = 0.04$ ); interval between last NACT cycle and IDS >4 weeks (HR = 1.26; CI 95% [0.94–1.68];  $p = 0.13$ ) as negatively associated with PFS. BRCA1/2 mutation (HR = 0.70; CI 95% [0.51–0.98];  $p = 0.04$ ) was positively associated with PFS. In a multivariate analysis including those six variables, delayed IDS remained an independent negative PFS-prognostic factor (HR = 1.49; CI 95% [1.02–2.18];  $p = 0.04$ ), as well as an interval between last NACT cycle and IDS >4 weeks ( $p = 0.002$ ); normal BMI ( $p = 0.03$ ) and BRCA1/2 mutation ( $p = 0.03$ ) remained independent positive PFS-prognostic factors. (Table 2).

We assessed PFS in patients with available data for propensity score variables and the presence or not of residual disease after IDS. From the 53 patients with postoperative tumor residue, survival rate at two years were 29.4% (CI 95% [12.6–48.3]) in the standard IDS group and 18.9% (CI 95% [4.2–37.8]) in the delayed IDS group. There was no difference in PFS between the two treatment arms (HR = 1.31; CI 95% [0.66–2.59];  $p = 0.43$ ). For the 215 patients with complete gross resection, survival rate at two years were 44.1% (CI 95% [35.7–54.6]) and 25.2% (CI 95% [14.7–37.8]) respectively. There was no difference in PFS between the two treatment arms (HR = 1.39; CI 95% [0.94–2.05];  $p = 0.10$ ) (Fig. 3).

#### 3.4. Overall survival analysis

Regarding the OS analysis on 928 patients, with a median follow-up of 49.0 months (CI 95% [46.0–52.9]), 450 events occurred. In the whole population, median OS was 49.7 months (CI 95% [45.6–54.1]). Median OS was 51.2 months (CI 95% [46.4–61.2]) and 44.3 months (CI 95% [38.2–52.1]) in patients receiving the standard and delayed IDS groups, respectively (HR = 1.29; CI 95% [1.06–1.56];  $p = 0.009$ ). From the



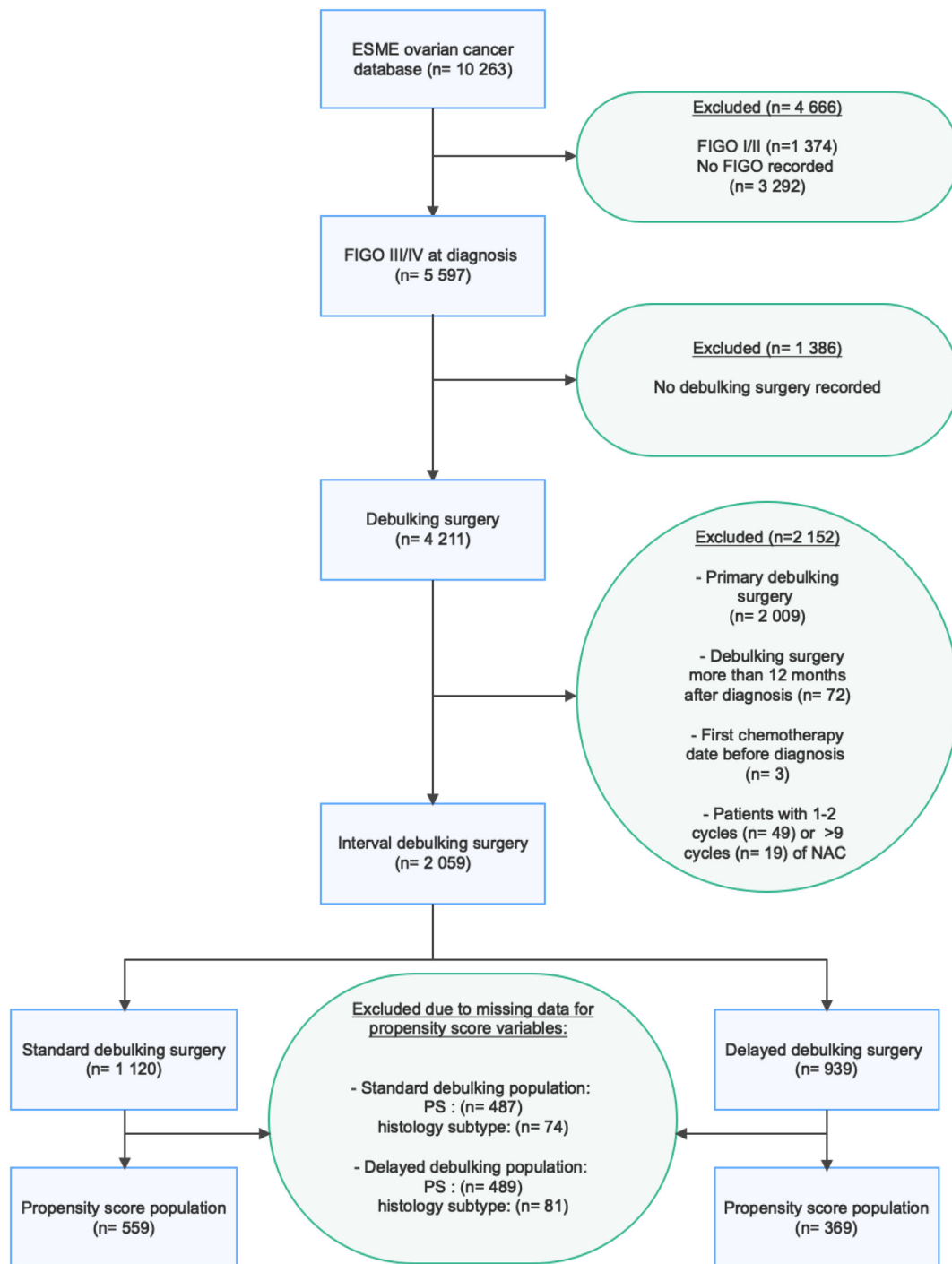


Fig. 1. Consort flow chart of number of patients included for analysis.

sensitivity analysis performed using the propensity score matching method for the global population, median OS was 49.1 months (CI 95% [44.5–54.1]). In patients from the standard and delayed IDS groups, median OS was 53.1 months (CI 95% [44.7–61.3]) and 47.3 months (CI 95% [39.5–52.7]) respectively (HR = 1.20; CI 95% [0.97–1.47];  $p = 0.09$ ) (Fig. 4).

Two-hundred sixty-eight patients were kept in prognostic identification for OS analysis due to missing data. Age at diagnosis (HR = 1.02; CI 95% [1.00–1.04];  $p = 0.11$ ); History of previous other cancer (HR = 1.40; CI 95% [0.87–2.26];  $p = 0.168$ ); ASA score > 1 ( $p = 0.13$ ); residual disease after surgery (HR = 1.78; CI 95% [1.11–2.86];  $p = 0.02$ ); interval

between last NACT cycle and IDS >4 weeks (HR = 1.42; CI 95% [0.90–2.23];  $p = 0.13$ ) were negative OS-prognostic factors. BRCA1/2 mutation (HR = 0.71; CI 95% [0.46–1.10];  $p = 0.13$ ); gastrointestinal resection during IDS (HR = 0.72; CI 95% [0.49–1.06];  $p = 0.09$ ); pathological subtype (HR = 0.70; CI 95% [0.40–1.21];  $p = 0.197$ ) were positive OS-prognostic factors. In a multivariate analysis including those eight variables, BRCA1/2 mutation (HR = 0.33; CI 95% [0.14–0.74];  $p = 0.007$ ) remained an independent positive OS-prognostic factor. History of previous other cancer (HR = 2.69; CI 95% [1.23–5.88];  $p = 0.01$ ) and residual disease after surgery (HR = 2.04; CI 95% [1.14–3.64];  $p = 0.02$ ) remained independent negative OS-prognostic factors (Table 2).

**Table 1**  
Demographics on the whole IDS population and for the population selected for the IPTW. Data are notified as N (% of cases with data available) unless otherwise specified.

	Unadjusted total cohort			Cohort selection for IPTW (before adjustment)		
	Standard IDS population N = 1120	Delayed IDS population N = 939	Global population N = 2059	Standard IDS population N = 559	Delayed IDS population N = 369	Global Population N = 928
<b>Age at diagnosis (years)</b>						
Mean (std)	62.4 (10.8)	62.8 (10.2)	62.6 (10.6)	62.6 (11.2)	63.9 (9.6)	63.1 (10.6)
Median (min; max)	63.0 (20; 88)	63.0 (22; 87)	63.0 (20; 88)	64.0 (20; 88)	65.0 (30; 87)	64.0 (20; 88)
Missing	0	0	0	0	0	0
<b>BMI at diagnosis</b>						
Mean (Std)	24.8 (5.2)	25.4 (5.2)	25.0 (5.2)	24.8 (5.3)	25.4 (5.2)	25.0 (5.2)
Median (min; max)	24.0 (13; 59)	24.5 (16; 47)	24.1 (13; 59)	23.9 (13; 59)	24.3 (16; 44)	24.0 (13; 59)
Missing	394	409	803	40	38	78
<b>Personal history of breast cancer</b>						
Yes	107 (9.9%)	77 (8.6%)	184 (9.3%)	55 (10.0%)	35 (9.8%)	90 (9.9%)
No	976 (90.1%)	818 (91.4%)	1794 (90.7%)	495 (90.0%)	321 (90.2%)	816 (90.1%)
Missing	37	44	81	9	13	22
<b>Family history of breast/ovarian cancer</b>						
Yes	243 (28.7%)	202 (28.0%)	445 (28.4%)	127 (28.1%)	94 (30.8%)	221 (29.2%)
No	604 (71.3%)	520 (72.0%)	1124 (71.6%)	325 (71.9%)	211 (69.2%)	536 (70.8%)
Missing	273	217	490	107	64	171
<b>FIGO stage</b>						
III	850 (75.9%)	564 (60.1%)	1414 (68.7%)	416 (74.4%)	213 (57.7%)	629 (67.8%)
IV	270 (24.1%)	375 (39.9%)	645 (31.3%)	143 (25.6%)	156 (42.3%)	299 (32.2%)
Missing	0	0	0	0	0	0
<b>ECOG PS at diagnosis</b>						
0	213 (36.3%)	116 (29.5%)	329 (33.6%)	205 (36.7%)	109 (29.5%)	314 (33.8%)
1	286 (48.7%)	193 (49.1%)	479 (48.9%)	271 (48.5%)	185 (50.1%)	456 (49.1%)
2	76 (12.9%)	61 (15.5%)	137 (14.0%)	72 (12.8%)	55 (14.9%)	127 (13.7%)
3–4	12 (2.1%)	23 (5.9%)	35 (3.6%)	11 (2.0%)	20 (5.4%)	31 (3.3%)
Missing	533	546	1079	0	0	0
<b>ASA Score</b>						
I	72 (10.9%)	53 (11.0%)	125 (10.9%)	22 (6.6%)	13 (6.1%)	35 (6.4%)
II	481 (72.5%)	328 (67.8%)	809 (70.5%)	255 (76.6%)	153 (71.5%)	408 (74.6%)
III + IV	110 (16.6%)	103 (21.3%)	213 (18.6%)	56 (16.8%)	48 (22.4%)	104 (19.0%)
Missing	457	455	912	226	155	381
<b>Ascites at diagnosis</b>						
Yes	298 (93.4%)	261 (96.0%)	559 (94.6%)	159 (90.9%)	113 (95.8%)	272 (92.8%)
No	21 (6.6%)	11 (4.0%)	32 (5.4%)	16 (9.1%)	5 (4.2%)	21 (7.2%)
Missing	801	667	1468	384	251	635
<b>Pathological subtype</b>						
Serous	802 (76.7%)	599 (69.8%)	1401 (73.6%)	442 (79.1%)	278 (75.3%)	720 (77.6%)
Endometrioid	18 (1.7%)	12 (1.4%)	30 (1.6%)	5 (0.9%)	6 (1.6%)	11 (1.2%)
Others $\Sigma$	226 (21.6%)	247 (28.8%)	473 (24.8%)	112 (20.0%)	85 (23.0%)	197 (21.2%)
Missing	74	81	155	0	0	0
<b>BRCA1/2 mutation</b>						
Positive	191 (26.5%)	136 (28.6%)	327 (27.4%)	105 (27.0%)	57 (26.6%)	162 (26.9%)
Negative	529 (73.5%)	339 (71.4%)	868 (72.6%)	284 (73.0%)	157 (73.4%)	441 (73.1%)
Missing	400	464	864	170	155	325
<b>CA 125 value (U/mL) before first NACT cycles</b>						
Mean (Std)	2357.0 (8300.5)	2197.2 (4383.3)	2284.1 (6798.8)	1959.3 (4830.2)	2063.5 (3972.5)	2001.3 (4501.3)
Median (min; max)	900.0 (5;161,849)	941.5 (1; 60,955)	922.0 (1;161,849)	827.5 (6; 83,142)	889.0 (1; 43,735)	859.0 (1; 83,142)
Missing	299	251	550	101	59	160
<b>Neoadjuvant chemotherapy regimen</b>						
Carboplatine +Paclitaxel	1073 (95.9%)	871 (92.8%)	1944 (94.5%)	533 (95.3%)	342 (92.7%)	875 (94.3%)
Carboplatine alone	20 (1.8%)	38 (4.0%)	58 (2.8%)	16 (2.9%)	14 (3.8%)	30 (3.2%)
Others	26 (2.3%)	30 (3.2%)	56 (2.7%)	10 (1.8%)	13 (3.5%)	23 (2.5%)
Missing	1	0	1	0	0	0
<b>Carboplatine + Paclitaxel administration <math>\Phi</math>:</b>						
Every 3 weeks	426 (51.9%)	360 (56.9%)	786 (54.0%)	248 (50.5%)	177 (53.4%)	425 (51.6%)
Dose dense	120 (14.6%)	54 (8.5%)	174 (12.0%)	79 (16.1%)	32 (9.6%)	111 (13.5%)
Weekly	265 (32.3%)	205 (32.4%)	470 (32.3%)	134 (27.3%)	91 (27.4%)	225 (27.3%)
Others	10 (1.2%)	14 (2.2%)	24 (1.7%)	30 (6.1%)	32 (9.6%)	62 (7.5%)
Missing	299	306	605	68	37	105

(continued on next page)

Table 1 (continued)

	Unadjusted total cohort			Cohort selection for IPTW (before adjustment)		
	Standard IDS population N = 1120	Delayed IDS population N = 939	Global population N = 2059	Standard IDS population N = 559	Delayed IDS population N = 369	Global Population N = 928
<b>NACT cycles</b>						
3	548 (48.9%)	0	548 (26.6%)	257 (46.0%)	0	257 (27.7%)
4	572 (51.1%)	0	572 (27.8%)	302 (54.0%)	0	302 (32.5%)
5	0	105 (11.2%)	105 (5.1%)	0	52 (14.1%)	52 (5.6%)
6	0	697 (74.2%)	697 (33.9%)	0	260 (70.5%)	260 (28.0%)
7	0	77 (8.2%)	77 (3.7%)	0	33 (8.9%)	33 (3.6%)
8	0	30 (3.2%)	30 (1.5%)	0	12 (3.3%)	12 (1.3%)
9	0	30 (3.2%)	30 (1.5%)	0	12 (3.3%)	12 (1.3%)
<b>Number of cycles before IDS</b>						
Mean (Std)	3.5 (0.5)	6.1 (0.8)	4.7 (1.5)	3.5 (0.5)	6.1 (0.8)	4.6 (1.4)
Median (min;max)	4.0 (3; 4)	6.0 (5; 9)	4.0 (3; 9)	4.0 (3;4)	6.0 (5;9)	4.0 (3;9)
<b>Complete gross resection</b>						
Yes	599 (84.7%)	398 (79.1%)	997 (82.4%)	293 (81.8%)	147 (73.9%)	440 (79.0%)
No	108 (15.3%)	105 (20.9%)	213 (17.6%)	65 (18.2%)	52 (26.1%)	117 (21.0%)
Missing	413	436	849	201	170	371
<b>Gastrointestinal resection</b>						
No	417 (37.2%)	369 (39.3%)	786 (38.2%)	193 (34.5%)	148 (40.1%)	341 (36.7%)
Yes	703 (62.8%)	570 (60.7%)	1273 (61.8%)	366 (65.5%)	221 (59.9%)	587 (63.3%)
<b>Post-operative death <math>\Omega</math></b>	3 (0.3%)	3 (0.3%)	6 (0.3%)	1 (0.2%)	2 (0.5%)	3 (0.3%)
<b>Adjuvant chemotherapy</b>						
No	68 (6.1%)	152 (16.2%)	220 (10.7%)	23 (4.1%)	46 (12.5%)	69 (7.4%)
Yes	1052 (93.9%)	787 (83.8%)	1839 (89.3%)	536 (95.9%)	323 (87.5%)	859 (92.6%)
Mean (Std)	3.4 (1.4)	2.9 (1.5)	3.2 (1.4)	3.4 (1.5)	2.9 (1.3)	3.2 (1.5)
<b>Total Number of chemotherapy cycles</b>						
Mean (Std)	5.9 (2.0)	7.6 (1.9)	6.7 (2.1)	5.9 (2.1)	7.6 (1.8)	6.6 (2.1)
<b>Adjuvant Bevacizumab <math>\Gamma</math></b>	272 (25.9%)	174 (22.1%)	446 (24.3%)	169 (31.5%)	91 (28.2%)	260 (30.3%)

$\Delta$  Confidence interval 95%.

$\Sigma$  Others pathological subtype:

Brenner, clear cell, undifferentiated, carcinosarcoma, other carcinoma, germinal, others tumors.

$\Phi$  Carboplatine + paclitaxel regimen:

Every 3 weeks: Carboplatine AUC 5 – D1 + Paclitaxel 175 mg/m<sup>2</sup> – D1 D1=D21.

Dose dense (3 weeks on 4): Carboplatine AUC 5 D1 + Paclitaxel 80 mg/m<sup>2</sup> – D1-D8-D15 D1 = D21.

Weekly: Carboplatine AUC 2 D1-D8-D15 + Paclitaxel 60 mg/m<sup>2</sup> – D1-D8-D15 D1 = D21.

$\Omega$  Post-operative death:

Death of any cause occurring within 30 days after surgery.

$\Gamma$  at least one cycle.

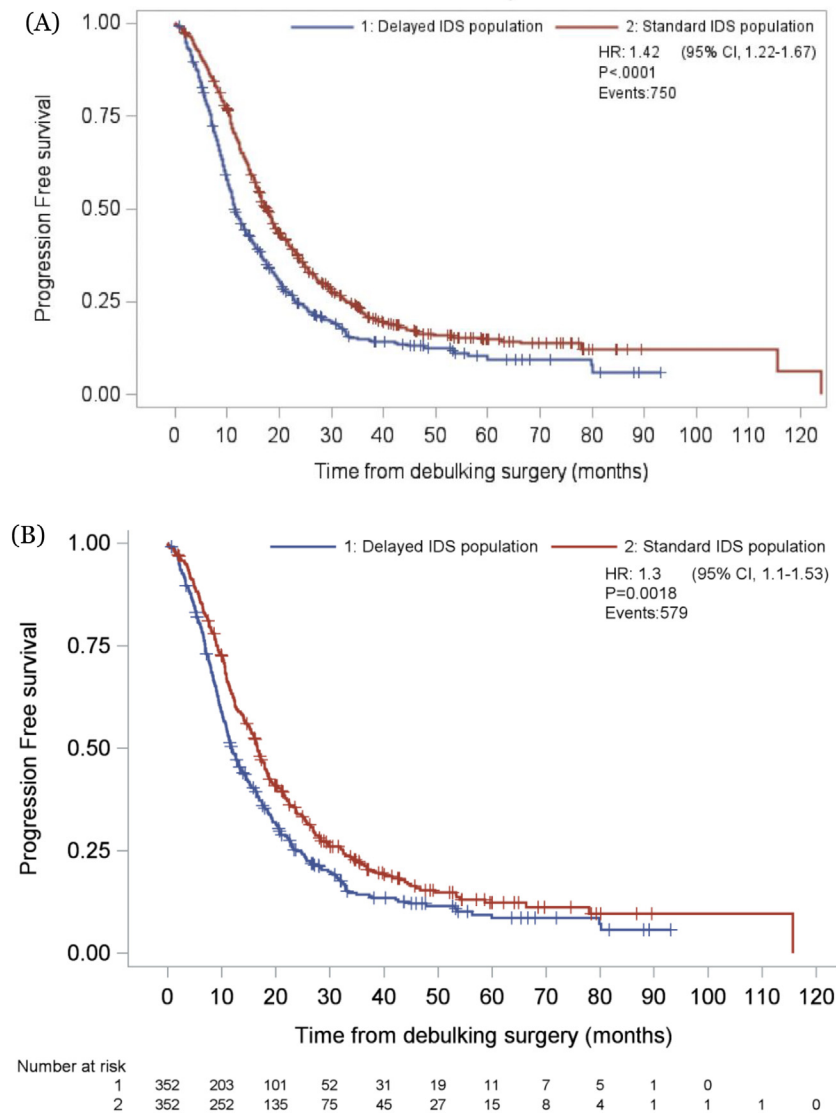
#### 4. Discussion

On a population of 928 women with newly diagnosed FIGO stage III-IV ovarian cancer, the present analysis of the French national ESME-OC Unicancer database shows a significant increase in PFS and a trend towards improved OS in patients treated by standard IDS compared to delayed IDS. Even though the international guidelines recommend performing IDS after  $\leq 4$  cycles of NACT for patients who are not eligible for PDS [20], our results show that delayed IDS was very common (45.6% of IDS) in clinical practice in France from 01/01/2011 until 12/31/2016. Our study is consistent with several retrospective studies suggesting that a greater number of NACT cycles may be associated with worse outcomes [10,13]. Bristow and Chi examined the link between the number of NACT cycles and survival, and found that each increase in the number of cycles above 3 was associated with a decrease of 4.1 months in median survival time [21]. Liu et al. studied 199 women with OC receiving NACT and did not find any significant difference in progression-free or overall survival when comparing 3 versus 4 neoadjuvant cycles. However, receiving  $\geq 5$  NACT cycles was associated with a poorer OS even after adjusting on the completeness of cytoreduction [10]. Others have corroborated these findings and suggest that the number of neoadjuvant cycles should not exceed 4 [7,13]. However, only a prospective randomized clinical trial will answer this question.

Complete gross resection is a major prognostic factor identified for all debulking surgery, regardless of the timing (PDS [2,3,5,6] or IDS

[7,12,14,22]) in the initial management of EOC but also for secondary debulking surgery when a relapse occurs [23–25]. Our multivariate Cox model analysis also shows a negative impact on OS for patients with a postoperative tumor residue ( $p = 0.02$ ). In our study, a complete gross resection rate of 84.7% was observed in the standard IDS population and this rate was 79.1% in the delayed IDS population for patients with available data. These rates were higher than all retrospective studies evaluating the timing of IDS over earlier or similar inclusion periods [26] suggesting that, over time, the quality of the assessment of pre-operative tumor resectability had improved. This also suggests that increasing the number of NACT cycles is not associated with an increase in the rate of complete debulking surgery. Almost all retrospective studies comparing the rate of complete surgery between standard and delayed IDS show similar results [11].

The overall analysis of retrospective studies suggesting the potential deleterious effect of delaying IDS remains controversial particularly in experts centers. In fact, as all patients are discussed in multidisciplinary team meeting in order to decide whether patients are treated by NACT or upfront surgery, the same multidisciplinary team will also proceed to a decision after analysis of response to first line (3 or 4 cycles) chemotherapy. It is obvious that patients with poor medical conditions and/or partial clinical/radiological response might be considered for continuing NACT resulting in a selection of patients with poor prognosis. This is therefore extremely difficult to draw any conclusions as long as a randomized trial is conduct. Patients receiving NACT and *a fortiori*  $>4$  cycles



**Fig. 2.** Kaplan Meier curves for progression free survival (PFS) depending on the timing of interval debulking surgery (IDS).

(A): PFS for each treatment strategy using propensity score IPTW method.

(B): PFS for each treatment strategy using propensity score matching method.

P = log rank p-value; HR = Hazard ratio; 95% CI = Confidence interval 95%.

before surgery had worse prognostic factors with more advanced disease at the time of presentation or tumors that were more resistant to chemotherapy. From a molecular point of view, this fact is supported by the theory of Goldie and Coldman based on the possible development of resistant tumors due to a lack of initial surgery or standard IDS leading to the selection of resistant tumor cells due to the repetition of NACT cycles [27]. Certain clinical features such as altered general condition and FIGO stage IV may also lead to delayed IDS [20]. We evaluated the survival of the standard and delayed IDS populations using a propensity score including 4 variables (age at diagnosis, ECOG PS at diagnosis, FIGO stage and pathological subtype) to compare patients independently of these 4 factors. Our results suggest that, if the patient's general condition allows surgery, IDS after 3–4 cycles of NACT should be preferred to IDS after  $\geq 5$  cycles of NACT even for patients with FIGO stage IV. Patients who remain unfit for IDS after cycle 4 of NACT have a poorer prognosis, which does not seem to be mitigated by surgical efforts as confirmed by the prognostic impact on PFS of having standard IDS rather than delayed IDS in our population.

International guidelines recommend an interval between the last NACT cycle and IDS shorter than 4 weeks [28]. In our population, a delay of  $>4$  weeks has indeed a significant negative impact on PFS in multivariate analysis. This reinforces the concept that for patients resectable after 3 cycles of NACT, a 4th cycle permitting the logistic setup of the IDS is fully justified. Our results also show that the rate of bowel resections and postoperative mortality were globally overlapping between the two populations, suggesting that there was no increase in the complexity of surgical procedures in the event of delayed IDS. It is important to remember that, in this population, excessively morbid surgery that might alter patient's quality of life must be avoided [29].

Targeted therapy including antiangiogenic vascular endothelial growth factor inhibitor (VEGFi) and PARPi are currently used in adjuvant first treatment line for a large majority of patients with advanced EOC [20]. Bevacizumab, a VEGFi, can be proposed for patients with high risk of recurrence (stage FIGO IV and suboptimal tumor cytoreduction stage FIGO III) [30]. PARPi are actually recommended in maintenance after a platinum-based doublets for all patients with



**Table 2**  
Cox regression progression free and overall survival analysis.

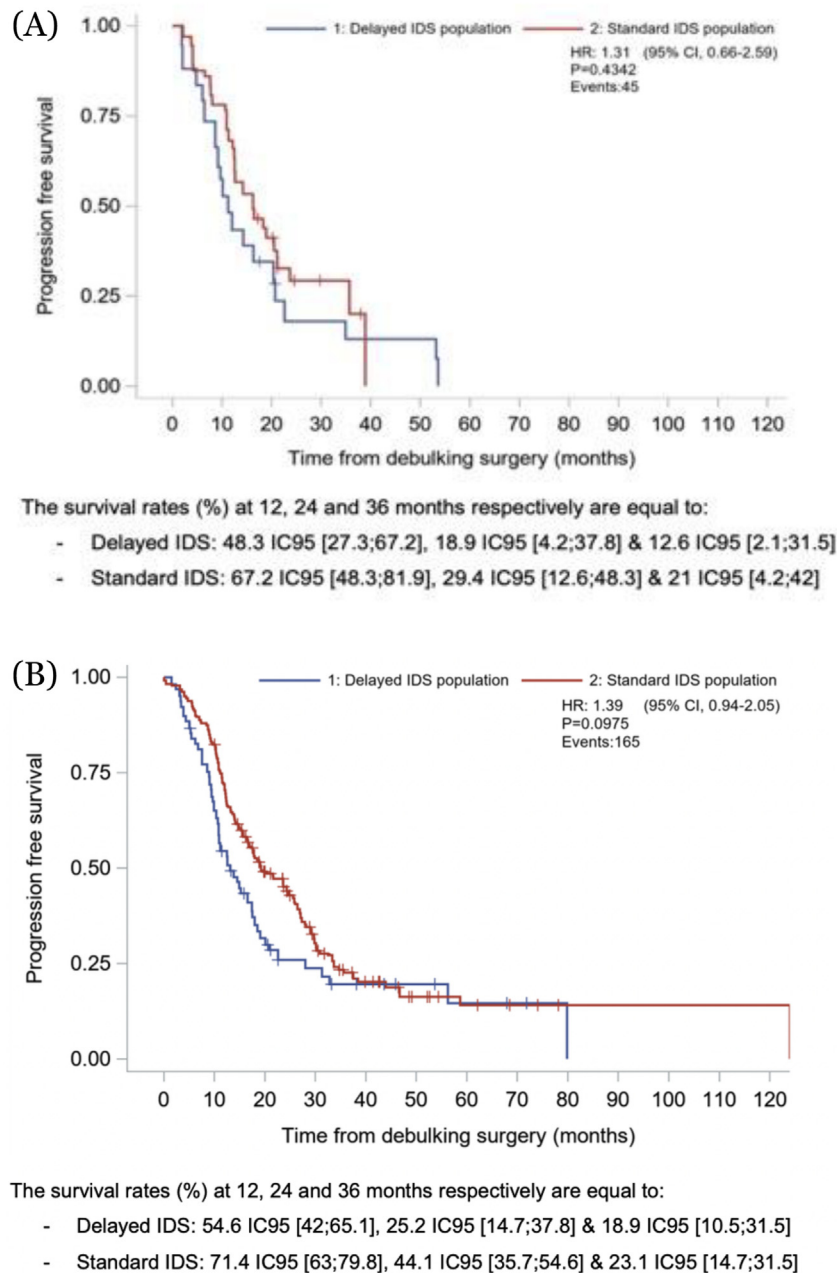
		Progression free survival				Overall survival			
		Univariate analysis (N = 268)		Multivariate analysis		Univariate analysis (N = 268)		Multivariate analysis	
		Hazard Ratio [95CI]	p-value	Hazard Ratio[95CI]	p-value	Hazard Ratio [95CI]	p-value	Hazard Ratio [95CI]	p-value
Age at inclusion, years	<65 vs ≥65	0.87 [0.66;1.14]	0.3240			1.02 [1.00;1.04]	<b>0.1080</b>	1.01 [0.98;1.04]	0.6042
Family history of breast/ovarian cancer (N = 236)	No vs yes	0.87 [0.63;1.21]	0.4150			0.80 [0.49;1.30]	0.3630		
Other cancer	No vs yes	0.89 [0.63;1.26]	0.5184			1.40 [0.87;2.26]	<b>0.1677</b>	2.69 [1.23;5.88]	<b>0.0133</b>
BMI	Normal vs overweight	0.88 [0.59;1.31]	0.1994	1.25 [0.84;1.85]	<b>0.0263</b>	0.98 [0.52;1.87]	0.9985		
	Normal vs Obese	1.28 [0.95;1.72]		0.61 [0.34;1.11]		0.97 [0.59;1.58]			
	Normal vs underweight	0.86 [0.43;1.69]		0.30 [0.09;0.98]		0.96 [0.55;1.68]			
PS at diagnosis	0 vs 1	1.32 [0.98;1.77]	0.0949	1.33 [0.91;1.95]	0.1624	1.19 [0.79;1.79]	0.6039		
		1.55 [0.95;2.53]		1.69 [0.91;3.15]		1.31 [0.67;2.58]			
Pathological subtype	0 vs ≥2								
	Serous + endometrioid vs Others	1.00 [0.72;1.39]	0.9967			0.70 [0.40;1.21]	<b>0.1973</b>	0.51 [0.23;1.16]	0.1095
FIGO stage	III vs IV	1.13 [0.84;1.52]	0.4266			1.05 [0.70;1.60]	0.8018		
BRCA1/2 mutation	Negative vs positive	0.70 [0.51;0.98]	0.0358	0.64 [0.42;0.97]	<b>0.0349</b>	0.71 [0.46;1.10]	<b>0.1267</b>	0.33 [0.14;0.74]	<b>0.0075</b>
CA 125 (U/mL)	≤500 vs >500	1.10 [0.84;1.44]	0.5031			1.03 [0.70;1.52]	0.8808		
Ascites at diagnosis (N = 77)	No vs yes	0.71 [0.31;1.65]	0.4310			1.19 [0.18;7.83]	0.8528		
Treatment strategy	Standard vs delayed IDS	1.30 [0.95;1.77]	0.0988	1.49 [1.02;2.18]	<b>0.0416</b>	0.97 [0.62;1.51]	0.8936		
Chemotherapy regimen	Carboplatine + Paclitaxel vs carboplatine alone	2.01 [0.70;5.80]	0.3858			5.31 [2.67;10.56]	<0.0001	NA	
		0.74 [0.21;2.62]				0.00 [0.00;0.00]			
	Carboplatine + paclitaxel versus others								
Duration between last cycle of NACT and debulking surgery	≤4 weeks vs >4 weeks	1.26 [0.94;1.68]	0.1286	1.85 [1.26;2.73]	<b>0.0018</b>	1.42 [0.90;2.23]	0.1297	1.92 [0.95;3.9]	0.0696
Rhythm of administration of carboplatine + paclitaxel	Weekly vs Every 3 weeks	1.16 [0.83;1.61]	0.4552			1.34 [0.80;2.25]	0.2810		
	Weekly vs others	1.27 [0.87;1.84]				1.63 [0.89;2.97]			
ASA score (N = 172)	I vs II	0.93 [0.45;1.92]	0.2145			1.06 [0.41;2.72]	<b>0.1299</b>	0.89 [0.35;2.25]	0.2648
	I vs II + III	1.36 [0.62;3.02]				1.94 [0.69;5.48]		1.48 [0.53;4.12]	
Residual tumor	No vs yes	1.39 [1.02;1.90]	<b>0.0374</b>	1.33 [0.89;1.98]	0.1607	1.78 [1.11;2.86]	<b>0.0163</b>	2.04 [1.14;3.64]	<b>0.0162</b>
Gastrointestinal resection	No vs yes	0.98 [0.74;1.29]	0.8586			0.72 [0.49;1.06]	<b>0.0937</b>	0.74 [0.42;1.31]	0.3024
Bevacizumab	No vs yes	0.95 [0.73;1.25]	0.7196			0.92 [0.60;1.42]	0.7141		

germline or somatic pathogenic BRCA1/2 variants and/or genomic instability [31]. The combination of these two treatments in maintenance for patients having a response after first-line platinum–taxane chemotherapy appears to provide a significant benefit in PFS in patients with homologous-recombination deficiency positive tumors, including those without a BRCA1/2 mutation [32]. Performing a standard IDS allows for an earlier initiation of adjuvant treatment combining these therapies that target several hallmarks of cancer [33]. Diversifying the mechanisms of antitumor action reduces the risk of the emergence of resistant clones and tumor relapse [27].

The main strength of our study is the size of the global population treated by IDS, thanks to use of the French national ESME-OC Unicancer database. Indeed, to the best of our knowledge, this is the largest cohort reported in a retrospective study to have analyzed the optimal timing of IDS for advanced EOC. The application of a propensity score balancing the distribution of patients according to known confounding factors also strengthens the validity of the survival results obtained in this study. However, the use of baseline variables in the construction of the propensity score is a limit of our study. It would be interesting to incorporate variables reflecting the response obtained after 3–4 cycles of NACT. Indeed, the tumor response obtained after 3–4 cycles of NACT is the main factor influencing the decision to perform a standard or delayed IDS. The kinetic of CA 125 decrease could for example be incorporate. This variable has already proven its predictive and prognostic

utility according to the KELIM score in the situation of platinum-resistant relapse for patients treated in the first line with PDS followed by adjuvant chemotherapy [34]. The major limitation of our study was the small number of “complete case” patients for the analysis of prognostic factors. Nevertheless, the prognostic factors identified in the multivariate analysis are consistent with those in the literature, suggesting that the prognostic value of the timing of IDS should be considered [7,8,10,12,16,17]. The ESME-OC is the largest electronic health record (EHR) database collecting data on patients with OC in France. It will provide a wide range of valuable data and help us answer many scientific questions. Our work illustrates that the major issue with this type of database is missing data. Possible approaches to improve data collection include reinforcing the training of the research assistants who collect the data or standardizing EHRs on a national level in order to ensure that certain clinical characteristics are systematically recorded during patient management. In the near future, artificial intelligence could also be used to improve collection of this type of data, particularly via the natural language processing method, to enhance the research of prognostic factors for cancer from EHR [35,36].

The optimal timing of IDS has been identified by the Gynecologic Cancer InterGroup (GCIG) as one of the main issues to be resolved in the future to optimize the management of patients with advanced EOC [37]. There are currently several ongoing prospective randomized trials evaluating the optimal number of neoadjuvant cycles to be



**Fig. 3.** Kaplan Meier curves for progression free survival (PFS) depending on the presence of a macroscopic tumor residue after interval debulking surgery (IDS) in the propensity score population.

(A): PFS for patients with macroscopic tumor residue after IDS ( $n = 53$ ); Delayed IDS ( $n = 21$ ) versus standard IDS ( $n = 32$ )

(B): PFS for patients with complete gross resection after IDS ( $n = 215$ ); Delayed IDS ( $n = 62$ ) versus standard IDS ( $n = 153$ )

P = log rank  $p$ -value; HR = Hazard ratio; 95% CI = Confidence interval 95%.

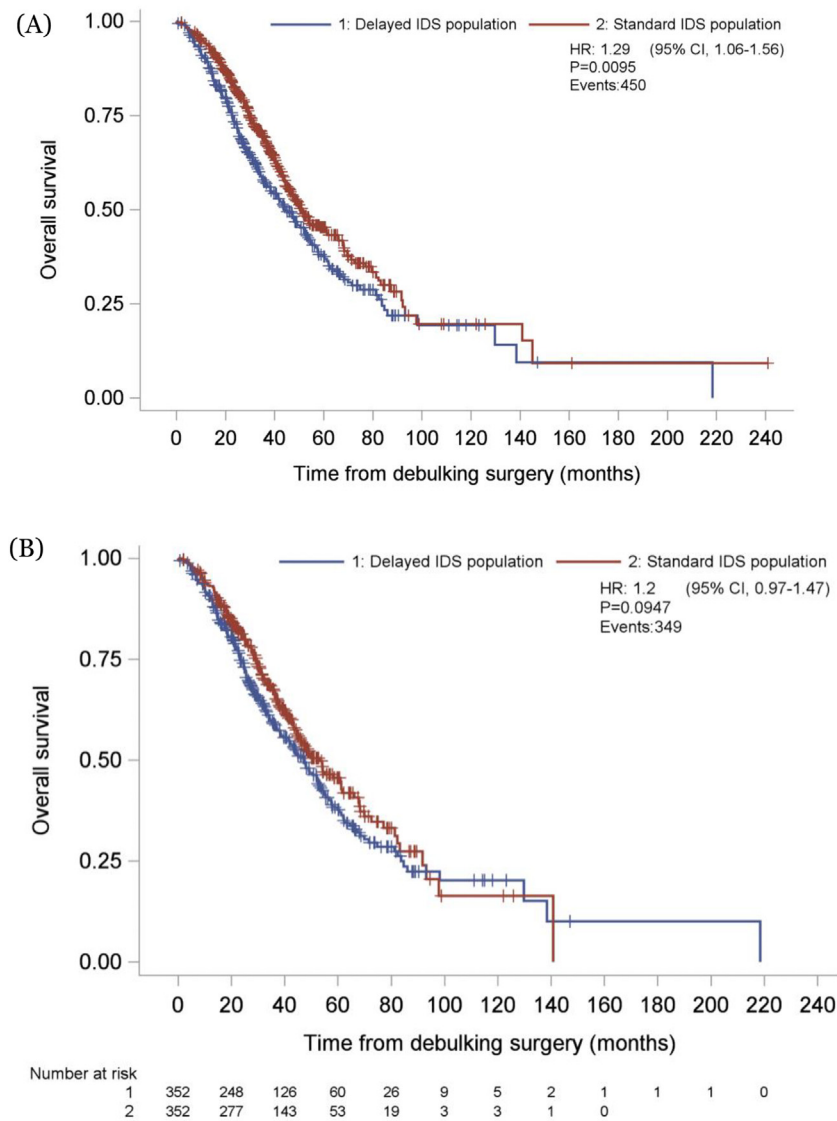
administered for advanced OC. These include the CHRONO trial (NCT03579394) conducted by the ARCAGY-GINECO cooperative group, comparing PFS when IDS is performed after 3 versus 6 NACT cycles for FIGO stage IIIB-IV patients who were initially inoperable but considered eligible for IDS after 3 cycles (i.e. randomization is performed after these 3 cycles) [38]. The GOG-01 trial (NCT02125513), also compares the complete resection rate of IDS performed after 3 versus 6 NACT cycles for FIGO stage IIIB-IV patients.

In conclusion, our data suggest that patients with newly diagnosed FIGO stage III-IV OC who are not eligible for PDS should be operated after 3–4 cycles of NACT. Patients treated by IDS after  $\geq 5$  cycles of NACT present worse survival outcomes. Prospective randomized trials

should be pursued to clarify the optimal timing of IDS. The quality of real-world data extracted from electronic-health records requires improvement with new technologies such as artificial intelligence.

#### Ethics approval

In compliance with French regulations, the ESME-OC database (NCT03275298) was authorized by the French data protection authority (initial authorization N°DE- 2017-311 and subsequent amendment obtained on 14-Oct-2019 in accordance with European regulations). No formal dedicated informed consent is required but participating centers handle process to ensure that patients are informed about the re-use of their electronically recorded data.



**Fig. 4.** Kaplan Meier curves for overall survival (OS) depending on the timing of interval debulking surgery (IDS). (A): OS for each treatment strategy using propensity score IPTW method. (B): OS for each treatment strategy using propensity score matching method. P = log rank p-value; HR = Hazard ratio; 95% CI = Confidence interval 95%. The median follow-up is 49.0 months; 95% CI [46.0;52.9]. The median follow-up are 48.4 months; CI 95% CI [44.9;52.6] and 53.0 months; 95% CI [47.0;60.1] for standard and delayed populations respectively.

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**Declaration of Competing Interest**

All the authors declare that they have no conflicts of interest to disclose related to this work.

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ygyno.2022.08.005>.

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