Risks and benefits of systematic lymphadenectomy during interval debulking surgery for advanced high grade serous ovarian cancer

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Running head: Lymphadenectomy in ovarian cancer

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Synopsis

The impact of lymphadenectomy in patients with ovarian cancer undergoing neoadjuvant chemotherapy with interval debulking surgery is debated. We found that lymphadenectomy did not enhance recurrence-free and overall survival at the cost of increased post-operative complications.

Abstract (200 words)

Background: Lymphadenectomy is debated in patients with ovarian cancer. The aim of our study was to evaluate the impact of lymphadenectomy in patients with high-grade serous ovarian cancer receiving neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS).

Methods: A retrospective, unicentric study including all patients undergoing NACT and IDS was carried out from 2005-2018. Patients with and without lymphadenectomy were compared in terms of recurrence free survival (RFS), overall survival (OS), and complication rates.

Results: We included 203 patients. Of these, 133 had a lymphadenectomy (65.5%) and 77 had involved nodes (57.9%). Patients without a lymphadenectomy were older, had a more extensive disease and less complete CRS. No differences were noted between the lymphadenectomy and no lymphadenectomy group concerning 2-year RFS (47.4% and 48.6%, p=0.87, respectively) and 5-year OS (63.2% versus 58.6%, p=0.41, respectively). Post-operative complications tended to be more frequent in the lymphadenectomy group (18.57% versus 31.58%, p=0.09). In patients with a lymphadenectomy, survival was significantly altered if the nodes were involved (positive nodes: 2-year RFS 42.5% and 5-year OS 49.4%, negative nodes: 2-year RFS 60.7% and 5-year OS 82.2%, p= 0.03 and p<0.001 , respectively).

Conclusion: Lymphadenectomy during IDS does not improve survival and increases post-operative complications.

Key words:

Epithelial ovarian cancer; lymphadenectomy; interval debulking surgery; neo-adjuvant chemotherapy.

Introduction

Epithelial ovarian cancer (EOC) is a gynecologic malignancy responsible of 313 959 new cases and is the 7th cause of death by cancer in women in 2019 worldwide [1]. The standard of care is defined by surgery followed by platinum-based chemotherapy [2,3]. The main prognostic factor is the completion of a complete macroscopic cytoreductive surgery (CRS), i.e. with no residual disease [4,5]. However, a large proportion of EOCs are discovered at an advanced stage where primary CRS is deemed impossible. These patients benefit from a neoadjuvant chemotherapy (NACT) followed by an interval debulking surgery (IDS) depending on the therapeutic response [4].

Pelvic and aortic lymphadenectomy have been part of the standard guidelines during primary CRS for many years. However, the recent LION study has shown that systematic lymphadenectomy was associated with an increase in post-operative complications with no benefit on recurrence-free survival (RFS) and overall survival (OS) in patients with advanced EOC undergoing primary CRS followed by chemotherapy, and without any preoperative or per-operative suspicion of nodal involvement, after appropriate imaging and clinical assessment [6].

Little data exists on the benefit of a systematic lymphadenectomy for patients undergoing NACT followed by IDS [7–13]. Current evidence is based on small retrospective studies. Moreover, due to the different inclusion criteria (optimal residual disease, histological subtype) and the lymphadenectomy modalities (systematic or selective), the results differ from one study to another. Indeed, two studies have found that a lymphadenectomy could enhance OS [9,10] whereas most have not found a survival benefit from a systematic lymphadenectomy[7,8,10–12]. In this specific setting, more information is needed to fuel the debate on the importance of a systematic lymphadenectomy.

The aim of this study was therefore to assess the impact of a systematic lymphadenectomy during IDS, in terms of survival and morbidity for patients with an advanced EOC.

Material and methods

Population

The data of all patients with advanced EOC were retrospectively collected in our department from 2005 to 2018. Our department is accredited for the surgical management of advanced EOC by the European Society of Gynecologic Oncology (ESGO). We included all patients with an advanced EOC (stage IIB-IV according to the 2014 classification of the International Federation of Gynecology and Obstetrics (FIGO)) who underwent a NACT followed by IDS [14]. Others histological subtypes than high grade serous ovarian cancer (HGSOC) were excluded to strengthen the conclusion of our study for the most frequent histology. This study was conducted in accordance with our institutional ethic guidelines for retrospective studies and was approved by the ethics committee of the National College of French Gynecologists and Obstetricians (2021-GYN- 0305).

Data regarding patient characteristics (age, body mass index (BMI), American society of anesthesiology (ASA) score, identified genetic mutation), tumor attributes (FIGO stage, histological type and grade, CA 125 tumor marker), neoadjuvant and adjuvant treatment (chemotherapy) surgical management (surgical route, extent of surgery), oncologic outcomes (RFS and OS, death, location of recurrence) and adverse events after surgery (intra- and post-operative complications) were collected. Information regarding race / ethnicity is not available in our study because French directives do not authorize studies on these data.

Surgery

Therapeutic management was decided for each woman during multidisciplinary tumor boards that included surgeons, oncologists, radiation oncologists, radiologists, pathologists and nuclear medicine physicians. All patients had an initial evaluation (laparoscopy and computed tomography (CT)) with a histological confirmation of their advanced ovarian cancer. Their disease was considered too extensive to undergo primary CRS. Resectability was systematically assessed by an experienced senior surgeon. Patients then received a platinum-based NACT and underwent a second evaluation (laparoscopy and/or CT) after 3-6 cycles of chemotherapy. The choice of the number of NACT cycles was left to the medical

team. Patients who were considered operable with an objective of no post-operative residual disease underwent an IDS, that included at least peritoneal cytology, bilateral salpingo-oophorectomy, total hysterectomy, omentectomy, appendectomy (depending on histology) and eventually a pelvic/para-aortic lymphadenectomy. The extent of the surgery (digestive resection, splenectomy, diaphragmatic peritonectomy…) depended on the spread of the disease and was carried out with the goal of complete macroscopic cytoreduction. Lymphadenectomy was performed according to patient comorbidities, extent of surgery and depended on ongoing research protocols. After IDS, patients had platinum-based adjuvant chemotherapy and targeted therapies (bevacizumab, PARP inhibitors) if indicated by the tumor board.

Residual disease was defined according to the completeness of cytoreduction score (CC) at the end of the intervention and separated in CC0 (no residual tumor), CC1 (residual tumor less or equal to 2.5mm), CC2 (residual tumor superior to 2.5mm but inferior or equal to 2.5cm), and CC3 (strictly superior to 2.5cm). Staging was assessed by the FIGO stage and the peritoneal carcinomatosis index (PCI) defined by Sugarbaker [15]. The PCI was evaluated at the initial laparoscopy and before the IDS.

Survival

RFS and OS were compared between the patients who underwent a lymphadenectomy and those who did not. RFS and OS were respectively defined as the time from the date of the initial diagnosis to the date of the first tumor recurrence or the date of death, of any cause. 2-year RFS and 5-year OS were also assessed.

The location of the recurrences was separated into peritoneal, nodal (above or below the left renal vein or over the diaphragm) and metastatic.

Among the patients who underwent a lymphadenectomy, we also compared the survival rates between the patients who had a positive histological lymphadenectomy (N+) to those who did not (N-).

Post- and per-operative complication

Peri- and post-operative morbidities were assessed according to the Clavien-Dindo classification [16]. Major complications were defined by a grade over 3. Grade 3 complications require a surgical,

endoscopic, or radiological intervention (with or without anesthesia) and grade 4 complication are considered life-threatening complication. Grade 5 complications result in patient demise.

The 30-day mortality was also assessed.

Statistical analysis

Continuous variables were expressed using the mean +/- the standard deviation or using the median and range. They were compared with a student-t test or a Wilcoxon test in case of non-parametric distributions. Categorical values were expressed using an absolute number and a percentage. They were compared with a chi2 test or Fischer's exact test.

A Kaplan Mayer curve was used to graphically express the differences in RFS and OS. A log rank test compared the two curves. A multivariate analysis was performed using the Cox regression model and including the variables with a p-value <0.05 in univariate analysis for survival analysis.

All statistical tests were two-sided, and the significance level was 0.05. Data were analyzed using R studio version 1.1447 and an Excel database (Microsoft, Redmond, WA).

Results

Patient's characteristics

A total of 631 patients were diagnosed with an EOC in our institution from 2005 to 2018. Only patients with high-grade serous ovarian cancer (HGSOC) were selected for further analysis as the number of patients with other histology were insufficient (n=28) to draw solid conclusion regarding the value of systematic lymphadenectomy in these populations. Of these, 203 had an initially non-operable advanced disease and underwent NACT followed by IDS. One hundred and thirty-three (65.5%) had a lymphadenectomy and 70 (34.5%) did not (Figure 1). Of these, 57.89% (77/133) had positive lymph nodes.

The populations did not differ in terms of BMI, menopausal status, ASA score and BRCA mutation. Patients in the no lymphadenectomy group were older (average 68.37 years old versus 62.33, $p<0.001$).

Patients had similar tumor marker CA 125 and FIGO stage. Patients who did not undergo a lymphadenectomy had a non-significant higher PCI score on initial exploratory laparoscopy (average 19.72 versus 21.54, $p=0.15$). The two groups did not differ concerning NACT treatment (type, number of cycles). The median follow-up was 32 (4-120 months) and 26 (5-103 months) in the lymphadenectomy and no lymphadenectomy group, respectively ($p=0.41$).

Patient characteristics are summarized Table 1.

Surgery

Of the 133 patients who received a lymphadenectomy, 122 had both a pelvic and para-aortic lymphadenectomy. Concerning the other patients : 3 only had a pelvic lymphadenectomy, and 8 only had a para-aortic lymphadenectomy.

The mean number of nodes removed for the entire population was 31.37 (+/- 17): 22.5 (+/- 12.9) and 12.2 (+/- 7.7) for para-aortic and pelvic lymphadenectomy, respectively.

Patients in the no lymphadenectomy group had more extensive disease according to the PCI score (average 8.45 versus 12.12, p<0.001) (Table 2). They also had a significantly higher residual disease score (CC2, 21.43% versus 0.75%, p<0.001).

Per and post-operative complications

In the whole population, 27.09% (55/203) of the patients presented a post-operative complication. Post-operative complications tended to be more frequent in the group with a lymphadenectomy (18.57 versus 31.58, p=0.09). The Clavien Dindo classification was similar in both groups. Per-operative complications and the 30-day mortality did not differ (Table 2).

Survival

No differences were noted between the lymphadenectomy and no lymphadenectomy group concerning 2-year RFS (47.4% and 48.6%, p=0.87, respectively) and 5-year OS (63.2% versus 58.6%, p=0.41, respectively). Median RFS was 21 months in the lymphadenectomy group and 17 months in the no lymphadenectomy group. Median OS was 28 months in the lymphadenectomy group and 20 months in the no lymphadenectomy group. The Kaplan-Meyer curves did not differ neither for RFS (log-rank test, p=0.3) nor for OS (p=0.6) (Figure 2).

Lymphadenectomy was not associated with RFS (HR = 0.83 IC95%= 0.58-1.19, p=0.32). Only PCI was associated with RFS after multivariate analysis (Table 3).

Likewise, lymphadenectomy was not associated with OS (HR= 0.89 IC95%= 0.57-1.41, p=0.64). Only PCI was associated with OS after multivariate regression model (Table 3).

The location of recurrences was similar even though there was a non-significance increase of nodal recurrences in the no lymphadenectomy group (38.57% versus 34.59%, p=0.68) (Table 2). In the lymphadenectomy group, nodal recurrences were mainly over the left renal vein (17/46, 36.9%) and over the diaphragm (25/46, 47.8%).

Survival according to definitive lymph node status

206 Of the 133 patients who benefitted from a lymphadenectomy, 59.4% had a positive lymphadenectomy
207 on definitive analysis. Seventy-one patients (53.4%) had a positive para-aortic lymphadenectomy
208 (average: 3 positive nodes) and 48 (36.1%) a positive pelvic lymphadenectomy (average: 2 nodes).
209 The 2-year RFS and 5-year OS was significantly altered in the positive lymphadenectomy group
210 (positive lymph nodes: 2-year RFS 42.5% and 5-year OS 49.4%, negative nodes: 2-year RFS 60.7%
211 and 5-year OS 82.2%, $p= 0.03$ and $p<0.001$, respectively)
212 The survival curves were significantly different with an altered RFS ($p<0.001$) and OS ($p<0.001$) in the
213 positive lymphadenectomy group (Figure 3). After multivariate analysis, positive pathological nodes
214 were significantly associated with a worse OS and RFS (supplementary Table 1).

Discussion

In this study, we aimed to enrich the ongoing debate on the therapeutic value of systematic lymphadenectomy during IDS after NACT in patients with an advanced HGSOC (FIGO stage IIB-IV). We found that a systematic lymphadenectomy did not statistically improve RFS or OS, at the expense of higher post-operative complications. In the sub-group of patients benefitting from a systematic lymphadenectomy, patients with histological positive nodes presented an altered survival rate.

The LION study, a randomized controlled trial comparing systematic lymphadenectomy to no lymphadenectomy, found that systematic lymphadenectomy did not impact RFS or OS and increased post-operative complications. However, this study only assessed patients who benefitted from primary CRS with FIGO stage IIB-IV EOC, and without any preoperative or per-operative suspicion of nodal involvement, after appropriate imaging and clinical assessment [6]. Several retrospective works are in accordance with our findings and have suggested that systematic lymphadenectomy during IDS after NACT does not improve survival of patients [7,11,12]. Two studies showed that lymphadenectomy enhanced OS. Indeed, Eoh et al. found an improved OS in patients with an optimal CRS undergoing systematic lymphadenectomy. However, in their work, they compared systematic lymphadenectomy to selective lymphadenectomy (suspicious nodes) [10]. Moreover, Eoh et al. had the highest rate of positive lymph nodes (54-66%) and of incomplete CRS (63-33%). Likewise, Song et al. suggested an altered OS in patients not undergoing a lymphadenectomy if complete CRS was achieved [9].

Studies have found positive lymph nodes in 44-55.7% of patients undergoing primary CRS with systematic lymphadenectomy [6,17,18]. However, after NACT this rate drops to 11-54 % [7,8,19,20]. In our work, 57.89% (77/133) of the 157 patients who benefitted from a lymphadenectomy had involved lymph nodes on definitive pathologic analysis. Despite the removal of these involved nodes, these patients did not present an improved OS, questioning the importance of the residual peritoneal tumor burden. Iwase et al. found the same results with a significant decrease in the 2-years RFS and 5-years OS in patients with a positive lymphadenectomy versus a negative lymphadenectomy (62% and 56% versus 26% and 24%, respectively $p<0.001$) [8]. Nodal metastasis could be more chemotherapy

resistant such as Morice et al. suggested [20]. Moreover, it can be hypothesized that removing lymph nodes decreases the immunologic response thus promoting tumor proliferation [21]. One French multicentric study found that nodal status did not impact survival. This study found a small number of metastatic nodes (11%) compared to the high number in our study (57.89%) [7]. However, no hasty conclusion can be made concerning this subgroup as our work was not designed to analyze this. Indeed, in order to conclude on the necessity of a lymphadenectomy in histologically node positive patients, a study comparing lymphadenectomy versus no lymphadenectomy in node positive patients is needed. Defining this population pre-operatively is a major concern in ovarian cancer management as imaging and per-operative palpation cannot accurately predict lymph node involvement [22–25]. Likewise, our study did not evaluate the impact of a lymphadenectomy of an "unusual site" such as hepatoceliac nodes or omental nodes for too few patients underwent this procedure. These regions are systematically assessed yet rarely dissected in our work [26–28].

The two groups in our study presented different characteristics. Indeed, patients in the no lymphadenectomy group were older with a more extensive disease. These patients were therefore more likely to not undergo a complete CRS and a morbid lymphadenectomy. However, despite the inferior rate of complete cytoreduction (CC0) in the no lymphadenectomy group, these patients did not present an altered survival. On the contrary, patients who benefitted from a lymphadenectomy were initially fitter, and presented similar survival rates. It could be hypothesized that the lymphadenectomy itself generated a morbidity, altering their prognosis (31.58% post-operative complications versus 18.57%, p=0.09), even if the effective of our groups did not allow us to reach significant result.

More post-operative complications were noted in the lymphadenectomy group, yet this difference did not reach significance (31.58% versus 18.57%, p=0.09). The Clavien Dindo classification, per-operative complications and the 30-day mortality were similar in both groups. It has been shown that a lymphadenectomy is a source of complications with notably longer operative times and transfusion rates [11,12]. Moreover, post-operative complications and extensive surgery can cause delay in adjuvant chemotherapy initiation [29].

In the no lymphadenectomy group, 28.57% of the patients had residual post-operative intraabdominal tumor versus 12.03% in the lymphadenectomy group. In this retrospective nonrandomized study, we chose to include patients who did not achieve complete cytoreduction. Excluding this population with the poorest prognosis would have resulted in a selection bias.

To our surprise, the patterns of recurrences did not differ between the two groups with 34.59% (46/133) and 38.57% (27/70) of nodal recurrences in the lymphadenectomy and no lymphadenectomy group (p=0.68). This cannot be explained by the quality of the lymph node dissection as a satisfactory number of nodes were removed in our study (22.5 and 12.2 nodes for para-aortic and pelvic lymphadenectomy, respectively) [30–32]. Moreover, studies with more extensive lymphadenectomies found similar results [7,8,12]. Only Eoh et al. found more nodal recurrences in patients benefitting from a selective rather than from a systematic lymphadenectomy (45.5% vs 23.5%, p = 0.022) [10]. Among the 27 patients with a nodal recurrence in the no lymphadenectomy, group only 3 had a salvage lymphadenectomy. Likewise, only 6 patients had a complementary adenectomy among the 46 patients with a nodal recurrence in the lymphadenectomy group. These patients did not have an isolated lymph node recurrence and had multiple lesions. It has been shown that patients with multiple lesions probably benefit less from a salvage lymphadenectomy [33].

Several limits must be noted. First, this was a retrospective, single site study. Since patients with more morbidities were more likely to not undergo a lymphadenectomy, a multivariate analysis was performed to limit confounding bias. Only patients with HGSOC were included in order to obtain a homogeneous population. Likewise, all patients were included regardless of their initial node status to avoid a selection bias. Indeed, accurately defining histologically positive patients pre-operatively is complex. Neither imaging nor per-operative palpation can precisely predict lymph node involvement [20-23]. In the LION trial, despite the selection of node negative patients by imaging and per-operative palpation, 55.7% had histologically positive nodes [6].

298 Our results issued from a large population treated at an expert center point out that a systematic
299 lymphadenectomy during IDS after NACT in patients with an advanced HGSOC (FIGO stage IIB-IV)
300 does not statistically improve RFS nor OS, at the expense of a non-significant higher post-operative
301 complication rate. A large prospective randomized trial is needed to close this debate.
302

Conflict of interests

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Conflicts of interest: None

Author contribution

Louise Benoit : Conceptualization ; Data curation; Formal analysis ; Investigation; Methodology; Roles/Writing - original draft

Koual Meriem : Conceptualization; Supervision; Validation ; Writing - review & editing.

Le Frère-Belda Marie-Aude: Conceptualization ; Supervision; Validation ; Writing - review & editing.

Zerbib Jonathan: Data curation; Formal analysis ; Investigation

Nguyen-Xuan Huyen-Thu: Conceptualization ; Supervision; Validation ; Writing - review & editing.

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Bats Anne-Sophie: Conceptualization ; Formal analysis ; Investigation; Methodology ; Supervision; Validation ; Writing - review & editing.

Azaïs Henri: Conceptualization ; Formal analysis ; Investigation; Methodology ; Supervision; Validation ; Writing - review & editing.

Data availability

The data that support the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Figure 1. Flow chart of patients with a stage IIB-IV epithelial ovarian cancer who underwent neo-adjuvant chemotherapy followed by interval debulking surgery

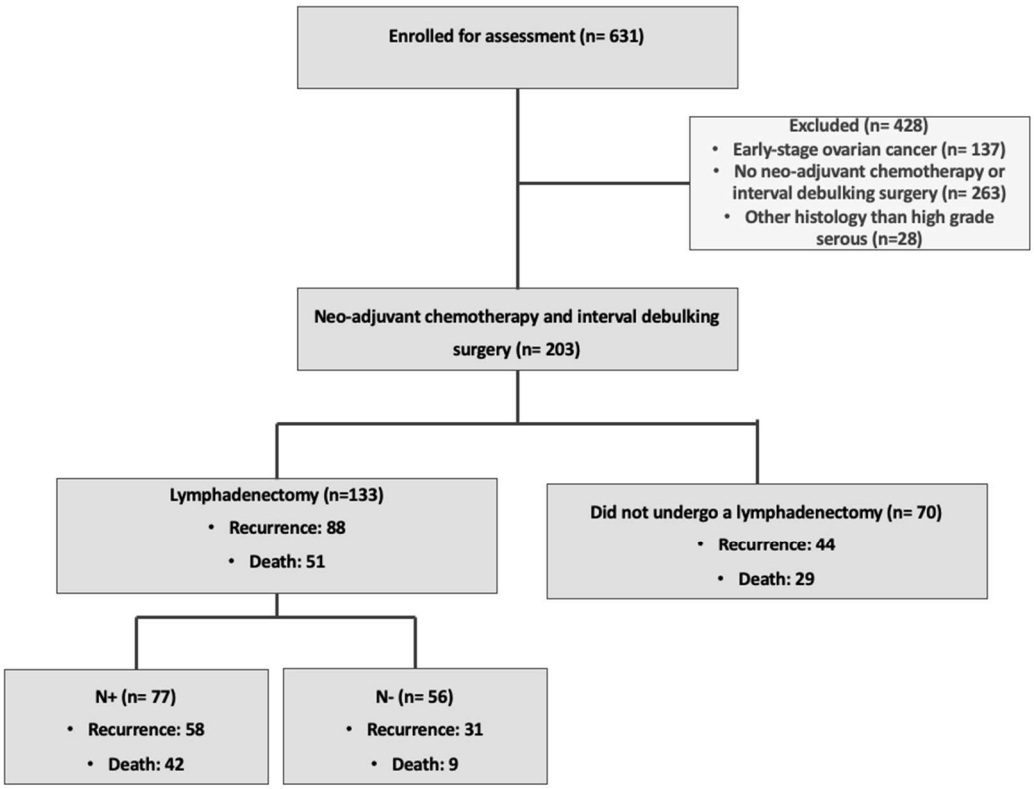


Figure 2: Patients with a stage IIB-IV high grade serous ovarian cancer who underwent neo-adjuvant chemotherapy followed by interval debulking surgery either with or without systematic lymphadenectomy (LND)

A. Recurrence free survival (RFS) of patients with a stage IIB-IV ovarian cancer who underwent neo-adjuvant chemotherapy followed by interval debulking surgery (p=0.3)

B. Overall survival (OS) of patients with a stage IIB-IV ovarian cancer who underwent neo-adjuvant chemotherapy followed by interval debulking surgery (p=0.6)

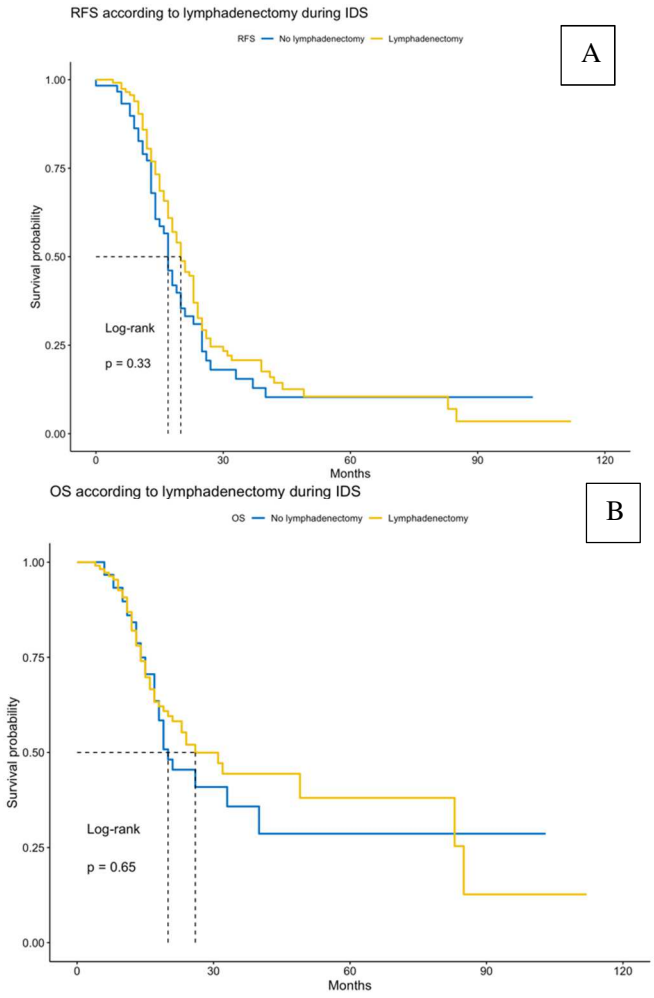
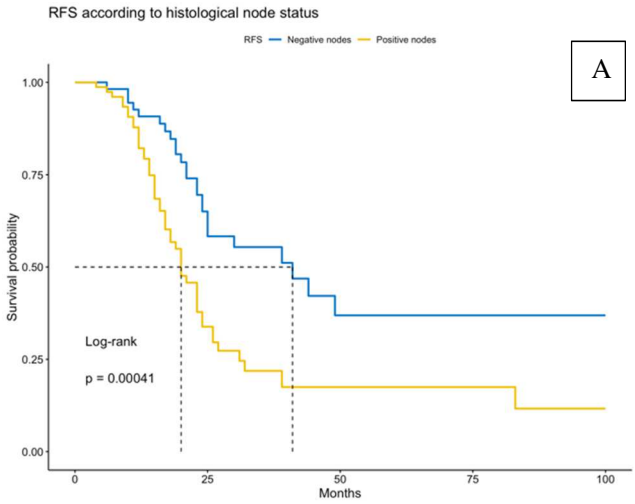


Figure 3. Patients with a stage IIB-IV high-grade serous ovarian cancer who underwent neoadjuvant chemotherapy followed by interval debulking surgery with a systematic lymphadenectomy

A. Recurrence free survival (RFS) according to node status after neo-adjuvant chemotherapy ($p<0.001$)

B. Overall survival (OS) according to node status after neo-adjuvant chemotherapy ($p<0.001$)



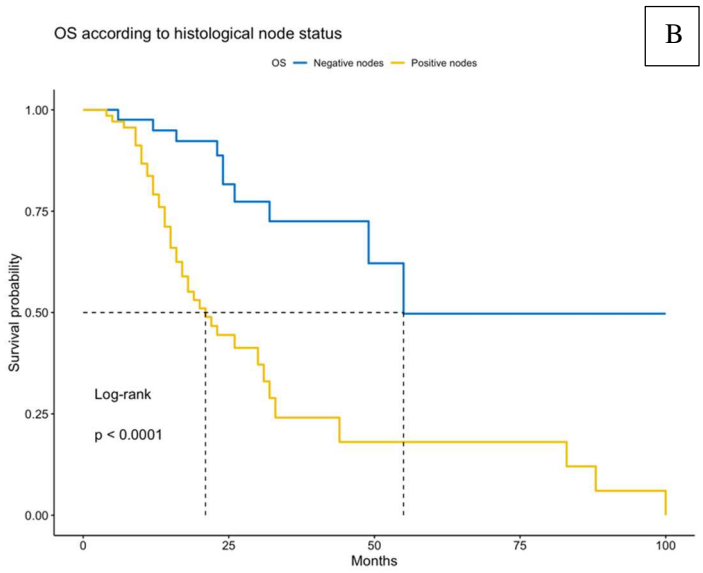


Table 1. Patient characteristics

Patient characteristics		**Lymphadenectomy N=133 (%)**	**No lymphadenectomy N=70 (%)**	**p**
Age (years)	Mean+/- SD	62.33 +/- 10.65	68.37 +/-10.95	**<0.001**
BMI (kg/m^2)	Mean+/- SD	23.62 +/- 4.71	24.07 +/- 5.35	0.57
Menopause	Yes No NA	107 (80.45) 22 (16.54) 4 (3.01)	60 (85.71) 8 (11.43) 2 (2.86)	0.44
BRCA mutation	Yes	22 (16.54)	6 (8.57)	0.43
ASA score	1 2 3 4 NA	32 (24.06) 44 (33.08) 12 (9.02) 0 45 (33.83)	8 (11.43) 32 (45.71) 11 (15.71) 1 (1.43) 18 (25.71)	0.06
CA125 (U/ml)	Mean +/- SD	1976 +/-3504	2587 +/- 3865	0.28
PCI score on initial exploratory laparoscopy	Mean +/- SD	19.72 +/- 7.78	21.54 +/- 6.46	0.15
FIGO stage	IIIA IIIB IIIC IV NA	2 (1.5) 2 (1.5) 79 (59.4) 42 (31.58) 8 (6.02)	2 (2.86) 4 (5.71) 38 (54.29) 19 (27.14) 7 (10)	0.30
NACT by Carboplatin and Paclitaxel		128 (96.24)	68 (97.14)	1
Number of NACT cycles	Mean +/- SD	4.39 +/-1.42	4.6 +/-1.55	0.34
Adjuvant chemotherapy	Yes No	198 (81.2) 25 (18.8)	51 (72.86) 19 (27.14)	0.23

Abbreviations: PCI = peritoneal carcinomatosis index, NACT= neo-adjuvant chemotherapy, ASA= American society of anesthesiology, BMI= body mass index, FIGO = International Federation of Gynecology and Obstetrics, SD= standard deviation

Table 2. Surgical characteristics and post-operative and per operative complications

Surgical and post-operative characteristics		**Lymphadenectomy N=133 (%)**	**No lymphadenectomy N=70 (%)**	**p**
Interval debulking surgery				
PCI	Mean +/- SD	8.45 +/- 5.91	12.12 +/- 8.12	**<0.001**
Completeness of Cytoreduction score (CC)	CC0 CC1 CC2 NA	116 (87.22) 15 (11.28) 1 (0.75) 1 (0.75)	48 (68.57) 5 (7.14) 15 (21.43) 2 (2.86)	**<0.001**
Survival				
Recurrence		87 (65.41)	44 (62.86)	1
Death		51 (38.35)	29 (41.43)	1
Location of recurrence	Peritoneal	65 (48.87)	32 (45.71)	0.77
	Nodal	46 (34.59)	27 (38.57)	0.68
	Metastasis	25 (18.8)	19 (27.14)	0.23
Per and post-operative complications				
Peri-operative complications	Yes No NA	33 (24.81) 97 (72.93) 3 (2.26)	10 (14.29) 56 (80) 4 (5.71)	0.14
Post-operative complications	Yes No NA	42 (31.58) 88 (66.17) 3 (2.26)	13 (18.57) 53 (75.71) 4 (5.71)	0.09
Clavien Dindo grade of post-operative complications	1-2 3 4-5	25 (59.52) 12 (28.57) 5 (11.91)	9 (69.23) 4 (30.76) 0	0.48
30-day mortality	Yes No NA	1 (0.75) 132 (99.25)	0 68 (97.14) 2 (2.86)	1

Abbreviations: SD= standard deviation, PCI = peritoneal carcinomatosis index

Table 3. Cox regression model of univariate and multivariate analysis of variables associated with recurrence free survival (A) or overall survival (B)

A.

Variables associated with recurrence-free survival		Univariate			Multivariate		
		HR	**IC**	**p**	**HR**	**IC**	**p**
Peritoneal Carcinomatosis index		1.05	1.03-1.08	**<0.001**	1.05	1.02-1.09	**<0.001**
Completeness of Cytoreduction score (CC)	Reference = CC0			**<0.001**			0.60
	CC1	1.9	1.03-3.45		0.79	1.02- 1.08	
	CC2	3.4	1.63-7.09		1.56	0.60- 4.01	

B.

Variables associated with overall survival		Univariate			Multivariate		
		HR	**IC**	**p**	**HR**	**IC**	**p**
Peritoneal Carcinomatosis index		1.05	1.02-1.09	**<0.001**	1.04	1.01-1.08	**0.02**
Completeness of Cytoreduction score (CC)	Reference = CC0			**<0.001**			0.28
	CC1	3.18	1.7-5.81		1.59	0.70- 3.60	
	CC2	2.4	1.17-4.89		0.85	0.30- 2.43	

Abbreviations: HR= hazards ratio, IC= confidence interval 95%