Impact of Pelvic and Para-aortic Lymphadenectomy in Advanced Ovarian Cancer After Neoadjuvant Chemotherapy

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Abstract. *Aim: The aim of our study was to evaluate the impact of systemic pelvic and para-aortic lymphadenectomy on survival in patients with advanced ovarian cancer after neoadjuvant chemotherapy. Patients and Methods: This multi-centric descriptive study included patients with initially inoperable advanced ovarian cancer, undergoing neoadjuvant chemotherapy followed by cytoreductive surgery with no residual tumor between 1998 and 2012. They were distributed into two groups depending on if they underwent lymphadenectomy or not during the interval surgery. Results: Among the 101 included patients, 54 underwent lymphadenectomy and 47 did not. The multivariate analysis for overall survival showed no significant difference between the two groups [hazard ratio (HR)=1.88, confidence interval (CI)=0.89-3.94; p=0.08]. The multivariate analysis for progression-free survival showed no significant difference (HR=1.43, 95% CI=0.86-2.39; p=0.17). Conclusion: In patients with advanced ovarian cancer, treated by neoadjuvant chemotherapy and interval surgery with no residual tumor, lymphadenectomy does not seem to improve the survival rate.*

Ovarian cancer is the fifth most commonly diagnosed cancer in women in Europe, and the most deadly of gynecological cancers (1, 2). Primary debulking surgery, including pelvic and para-aortic lymphadenectomy, is the cornerstone of treatment of advanced ovarian cancer. The aim of debulking surgery is to obtain no gross residual tumor. Indeed, the prognostic value of complete debulking has been reported in several cases (3). In order to achieve this goal, in patients where optimal primary surgery is unachievable, neoadjuvant chemotherapy and interval debulking surgery seem to give the same results in term of overall survival (4, 5). Nowadays, almost 70% of patients with advanced ovarian cancer are treated by neoadjuvant chemotherapy and interval debulking surgery (6).

The definition of optimal cytoreductive surgery has evolved. In patients with optimal intra-abdominal debulking (residual tumor <1 cm) at the time of primary cytoreduction, systematic lymphadenectomy has been shown to improve progression-free survival without any impact on overall survival (7). Another study has shown a significant impact on overall survival when there is no gross residual tumor (8). But in patients with small residual tumors up to 1 cm, the effect on overall survival barely reached significance (8). The impact of chemotherapy on lymph node metastasis is not well known (9). Only one study investigated the prognostic role of lymphadenectomy in patients with optimal surgery defined as a residual tumor <1 cm (10). But no study found on patients without residual tumor, which may be the best condition to show the true impact of lymphadenectomy.

The aim of the present study was to investigate the prognostic role of pelvic and para-aortic lymphadenectomy after neoadjuvant chemotherapy, at the time of interval cytoreductive surgery without gross residual tumor.

Patients and Methods

This multi-centric descriptive study was conducted at the University Hospitals of Strasbourg (Department of Obstetrics and Gynecology Hautepierre, Department of Obstetrics and Gynecology CMCO Schiltigheim, Department of General and Visceral Surgery Hautepierre) and Cancer Institutes of Lorraine (Centre Alexis Vautrin, France) and Alsace (Centre Paul Strauss, Strasbourg).

We selected all patients with advanced ovarian cancer [stage III or IV according to the International Federation of Gynecology and

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Obstetrics (FIGO) classification (11)], diagnosed between January 1998 and December 2012. The diagnosis was made by ascites puncture or by surgical assessment (laparoscopy or laparotomy). Patients in whom optimal surgery was judged as unachievable (or by imaging in stage IV ovarian cancer or by laparoscopy in stage III) were selected. These patients were treated by neoadjuvant chemotherapy and interval surgery. Only the patients in whom the interval reductive surgery conducted to the absence of residual tumor were included (R0).

Exclusion criteria were: surgical removal during the assessment surgery more than adnexectomy, peritoneal biopsies and omental biopsy, persistence of gross residual tumor, incomplete lymphadenectomy (only pelvic lymphadenectomy, or selective lymphadenectomy).

The patients were separated into two groups: Group 1: without lymphadenectomy: patients in whom a pelvic and para-aortic lymphadenectomy during the interval surgery were not performed; group 2: with lymphadenectomy: patients in whom a pelvic and para-aortic lymphadenectomy during the interval surgery were performed.

The realization or not of pelvic and para-aortic lymphadenectomy was surgeon-dependent without any other objective criteria. The only condition for lymphadenectomy to be realized was the absence of macroscopic residual tumor as evaluated by the surgeon.

Information concerning postoperative follow-up, adjuvant chemotherapy and signs of progression were collected until patient's death or until November 2014. We systematically researched mortality data by requesting information from town councils for patients with a follow-up of less than 5 years.

We collected: the age at diagnosis, the body mass index (BMI), comorbidity using Charlsons' score (12), the diagnostic mode (ascites puncture or surgery: laparoscopy or laparotomy), the number of neoadjuvant and adjuvant chemotherapy cycles, chemotherapy type (platinum and taxane, other platinum-based, without platinum), histological type and grade of the tumor, residual tumor after chemotherapy as evaluated by Sugarbaker's score (13) at the beginning of interval surgery, Aletti score for abdominal surgery complexity (14), length of time for the surgical procedure, number of transfusions, postoperative complications according to Dindo-Clavien classification (15), the date of diagnosis first progression and the date of death.

The primary study end-point was the overall survival of patients with advanced cancer after neoadjuvant surgery according to the association or not of lymphadenectomy during the interval surgery. The overall survival was defined by the time between the interval surgery and the date of death or the date of latest follow-up. The secondary endpoints were progression-free survival (defined by the time between the interval surgery and the date of first progression diagnosis) and postoperative complications.

This study was approved by the Institutional Ethics Committee from the University Hospitals of Strasbourg and was declared to the French Data Protection Agency (CNIL/1867044).

Statistic analysis. A descriptive analysis of all included patients was performed. Patients' characteristics were compared using Wilcoxon's test for quantitative variables, and Chi square or Fischer's exact tests for qualitative variables.

Survival curves were constructed using the Kaplan–Meier method, with the log-rank test applied to detect differences between groups.

A bivariate analysis was performed using log-rank test and a multivariate analysis was performed using Cox regression models with stepwise adjustment on year of diagnosis, age at diagnosis, comorbidity, the center (Nancy or Strasbourg), the histological type and grade. We used R 3.0.2 (16) and the 'survival package' (17, 18) to perform statistical analysis.

Results

The characteristics of the 101 patients included in the study are summarized in Table I: 47 did not undergo lymphadenectomy (group 1), and 54 did (group 2).

Patients' characteristics, the histological type and grade and the neoadjuvant treatment were similar in the two groups (Table II). The distribution of FIGO stage and diagnosis mode were different in the two groups. Stage IV was more frequent in group 1 (n=20, 42.6%) than in group 2, n=11, 20.4%), p=0.01. The diagnosis method was less often (p<0.001) laparoscopy in group 1 (n=11, 23.4%) than in group 2 (n=34, 63%).

The characteristics of the surgical outcomes are summarized in Table II. The length of time for the procedure and the number of transfusions were significantly higher in group 2. The rate of postoperative complications was similar in the two groups.

The median number (interquartile range) of lymph nodes removed during lymphadenectomy was 11.5 (8-15.8) in the pelvis and 15.5 (8-23.8) in the para-aortic region. Among the patients with lymphadenectomy (group 2), 22 (40.7%) had metastatic lymph nodes, and 16 (29.6%) patients had at least one metastatic lymph node. Patients of group 2 were more often treated by adjuvant chemotherapy: 51 patients (94.4%) *versus* 36 patients (76.6%) (p=0.01). The median follow-up was 34 months.

The median overall survival time was 35.3 months: 36.3 months in group 1 and 33.1 months in group 2. The 5-year overall survival rate was 29%: 35% in group 1 and 25.8 % in group 2. The Kaplan–Meier curves are shown in Figure 1. The log-rank test for differences between the two was not significant (p=0.42). After adjusting for group, center, year of diagnosis, age at diagnosis, histological type and grade, and Sugarbaker score, we did not find a difference in overall survival between the two groups [hazard ratio (HR)=1.88, 95% confidence interval (CI)=0.89-3.94; p=0.088] (Table III).

The median progression-free survival time was 10.5 months: 9.7 months in group 1 and 10.4 months in group 2. The Kaplan–Meier curves are shown in Figure 2. The log-rank test was not significant (p=0.79). After adjusting for group, center, year of diagnosis, age at diagnosis, histological type and grade, and Sugarbaker score, we did not find a difference in progression-free survival between the two groups (HR=1.43, 95% CI=0.86-2.39; p=0.17).

Table I. *Patient, tumor and neoadjuvant chemotherapy (NACT) treatment characteristics*.

Characteristic	Group 1: Without lymphadenectomy	Group 2: With lymphadenectomy	*p*-Value
No. of patients	47	54	
From Nancy	23 (48.9)	7 (13.0)	
From Strasbourg	24 (51.1)	47 (87.0)	
Year of diagnosis			
1997-2002	6 (12.8)	3 (5.6)	
2003-2007	19 (40.4)	15 (27.8)	
2008-2011	22 (46.8)	36 (66.7)	
At diagnosis			
Age, years*			0.40
≤55	14 (29.8)	22 (40.8)	
56-69	22 (46.8)	24 (44.4)	
≥71	11 (23.4)	8 (14.8)	
BMI, kg/m^2*	25.2 (22.6-28.7)	24.5 (22.4-27.3)	0.789
Missing	3	1	
Performance status (ECOG), no. (%)	0.60		
0-1	22 (50.0)	27 (50.0)	
2-4	22 (50.0)	25 (50.0)	
Missing	3	2	
Comorbidity score (Charlson), no. (%)	0.79		
0	32 (68.1)	35 (64.8)	
≥1	15 (31.9)	19 (35.2)	
Gynecologic cancer history, no. (%)	0.84		
Personal	3 (6.4)	5 (9.3)	
Family	9 (19.1)	9 (16.7)	
None	35 (74.5)	40 (74.1)	
Known mutation, no. (%)	5 (10.6)	4 (7.4)	0.73
FIGO stage, no. (%)			0.01
III	27 (57.4)	43 (79.6)	
IV	20 (42.6)	11 (20.4)	
Histological subtype, no. (%)			0.22
Serous	38 (82.6)	47 (87.0)	
Other	8 (17.4)	7 (13.0)	
Missing	1	0	
Grade, no. (%)			0.60
1-2	12 (33.3)	12 (25.6)	
3	24 (66.7)	31 (74.4)	
Missing	11	11	
Staging surgery, no. (%)			<0.001
Laparoscopy	11 (23.4)	34 (63.0)	
Laparotomy	12 (25.5)	7 (13.0)	
None	24 (51.1)	13 (24.0)	
NACT			
No. of cycles *	6 (4-6)	5 (4-6)	0.152
Type, no. (%)			0.99
Platin and taxane	45 (95.7)	51 (94.4)	
Other platin-based	2 (4.3)	3 (5.6)	
Response to NACT at 3 cycles, no. (%)		0.30	
Complete	6 (18.7)	9 (33.3)	
Partial	19 (59.4)	16 (53.4)	
Stable disease or progression	7 (21.9)	4 (13.3)	
Not evaluable/missing	15	24	

*Median (interquartile range). ECOG, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics.

Table II. *Operative outcomes and adjuvant treatment characteristics.*

	Group 1: Without lymphadenectomy n=47	Group 2: With lymphadenectomy n=54	*p*-Value
Debulking surgery			
Time from diagnosis to debulking surgery, months *	5.8 (4.5-8.0)	5.3 (4.3-6.0)	
Sugarbaker PCI, no (%)	0.14		
0	8 (17.4)	14 (25.9)	
1-5	15 (32.6)	25 (46.3)	
6-10	13 (28.3)	7 (13.0)	
>10	10 (21.7)	8 (14.8)	
Missing	1	0	
Surgery time, min*	240 (177.5-295)	320 (270-370)	<0.001
RBC transfusion, no. of cases (%)	11 (33.3)	33 (70.2)	0.002
RBC no. *	2 (2-3)	2 (2-4)	
missing	14	7	
Hospital stay (days)*	10.5 (9.0-14.2)	10 (8-15)	0.67
Post-operative complications (Dindo), no (%)		0,43	
None	14 (31.8)	13 (25.5)	
Grade I-II	28 (63.6)	32 (62.7)	
Grade III-IV	2 (4.6)	6 (11.8)	
Missing	3	3	
Time from debulking surgery to 1st adjuvant cycle (days)*	40 (29.2-49)	36.5 (30.2-48.8)	0.71
Adjuvant therapy			
No. (%)	36 (76.6)	51 (94.4)	0.01
No. of cycles*	3 (2-4)	3 (2-3)	0.96
Type, no. (%)	(of 36 patients)	(of 51 patients)	0.58
Platin and taxan	23 (69,7)	30 (66.7)	
Other platin based	8 (24.2)	14 (31.1)	
Without platin	2 (6,1)	1 (2.2)	
Type missing	3	7	
Chemotherapy lines after progression, no.*	3 (1.8-3.0)	1 (0.2-2.0)	0.028

*Median (interquartile range). PCI: Peritoneal cancer index.

Table III. *Multivariate Cox analysis for overall survival adjusted by center.*

		Univariate analysis			Multivariate analysis		
Variable		Hazard ratio	95% CI	*p*-Value	Hazard ratio	95% CI	*p*-Value
Type of surgery	Without lymphadenectomy	Ref.		0.42	ref.		0.088
	With lymphadenectomy	1.27	0.71-2.28		1.88	0.89-3.94	
Year of diagnosis	1997-2002	Ref.		0.86	ref.		0.68
	2003-2007	0.93	0.35-2.50		1.07	0.38-3.04	
	2008-2011	0.81	0.30-2.14		0.78	0.26-2.36	
Age at diagnosis, years	≤55	Ref.		0.42	ref.		0.29
	56-69	1.18	0.79-1.75		1.26	0.82-1.98	
	≥70	2.36	1.59-3.50		2.53	1.63-3.95	
Grade	1-2	Ref.		0.08	ref.		0.09
	3	2.19	0.96-4.98		2.4	0.88-5.21	
	Missing value	1.25	0.45-3.45		1.21	0.32-3.12	
Histological type	Serous	Ref.		0.034	ref.		0.013
	Other	2.4	1.14-5.03		2.64	1.35-6.94	
Sugarbaker score	0	Ref.		0.22	ref.		0.024
	1-4	1.49	0.61-3.67		1.04	0.53-3.34	
	5-8	1.92	0.71-5.19		1.8	0.79-6.02	
	≥9	2.45	0.99-6.08		3.35	1.45-9.59	

Discussion

In this study, we did not find any significant difference, neither in overall nor in progression-free survival between patients who underwent pelvic and para-aortic lymphadenectomy or not after neoadjuvant chemotherapy and optimal (R0) interval cytoreductive surgery for advanced ovarian cancer.

Our findings are consistent with those published by Fagotti *et al*. (10). In their case–control study, they focused on the impact of lymphadenectomy after neoadjuvant chemotherapy, and found no significant improvement of survival in patients undergoing pelvic and para-aortic lymphadenectomy (Table IV). Furthermore, similarly to our study, the duration of surgery as well as the rate of blood transfusion were significantly increased in this group of patients. However, in their study, 20% of the patients presented intraperitoneal residual tumor (10). Dell' Anna *et al*., in a randomized clinical trial, found also no significant improvement of survival in patient undergoing systematic pelvic and para-aortic lymphadenectomy (19). In our study, we included only patients without any intraperitoneal residual tumor.

The significance of optimal cytoreductive surgery has evolved, and in fact there is increasing evidence that only complete resection without any residual tumor should be considered (3). On the other hand, the risk of lymph node metastasis increases with advancement of stage in ovarian cancer, reaching up to 50% and 77% in stages III and IV, respectively (20).

Both arguments appear to be in total agreement with previous studies, which have shown that systematic lymphadenectomy at the time of primary cytoreduction improved the progression-free survival rate without any impact on overall survival (7). Chan *et al*. published a retrospective study in 2007 on 13918 patients with advanced ovarian cancer. For all patients, a more extensive lymph node dissection was associated with an improved 5-year disease-specific survival (26.1%, 35.2%, 42.6%, 48.4%, 47.5%, and 47.8% for those with dissection of 0, 1, 2-5, 6-10, 11-20, and >20 nodes, respectively; $p<0.001$) (21). In multivariate analysis, the extent of lymph node dissection and the number of positive nodes were independent prognostic factors for disease-specific survival in women with advanced ovarian cancer (21).

Du Bois *et al*., in an exploratory analysis of three prospective randomized trials investigating chemotherapy regimens in advanced ovarian cancer with no macroscopic residual tumor, showed a significant impact of lymphadenectomy on overall survival. The 5-year survival rate was 67.4% in the group treated with lymphadenectomy *versus* 59.2% in group without lymphadenectomy ($p=0.0166$) (8). All of these studies were conducted at the time of primary cytoreductive surgery (Table IV).

Table IV. *Studies on the impact of lymphadenectomy in advanced ovarian cancer between 2005 and 2015.*

Author	Year	Type of study	N With L/ Without L	Chemotherapy	Residual tumor	Overall survival		Overall survival HR (CI)	*p*-Value	Progression-free survival		Progression-free survival HR (CI)	*p*-Value
						With L	Without L			With L	Without L		
Panici *et al.* (7)	2005	Randomized	216/211	Adjuvant	0-2 cm			0.96 (0.73-1.26)	0.77			0.76 (0.60-0.96)	0.02
Du Bois *et al.* (8)	2010	Analysis of 3 randomized studies	658/338	Adjuvant	0			0.75 (0.60-0.93)	0.0102				
			390/556	Adjuvant	1-10 mm			0.85 (0.73-1.04)	0.1202				
Dell' Anna *et al.* (19)	2012	Randomized	158/150	Adjuvant. L during second look	<1 cm			1.04 (0.733-1.49)	0.81			1.18 (0.87-1.59)	0.29
Fagotti *et al.* (10)	2012	Case–control study	50/101	Neoadjuvant	<1 cm	69% (2 years)	88% (2 years)		0.777	36%	25%		0.834
Our study	2015	Retrospective	54/47	Neoadjuvant	0	25.8% (5 years)	35% (5 years)	1.88 (0.89-3.94)	0.088			1.43 (0.86-2.39)	0.17

L: Lymphadenectomy; HR: Hazard ratio; 95% CI: 95% confidence interval.

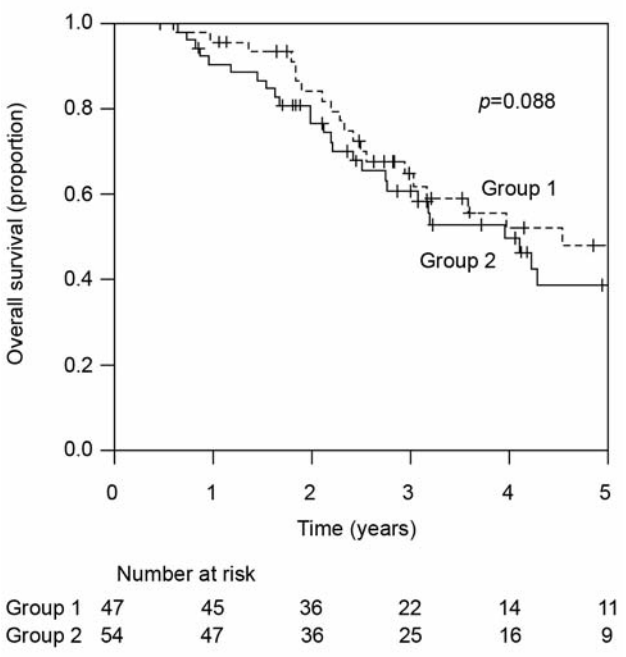

Figure 1. *Overall survival in patients with advanced ovarian cancer treated by neoadjuvant chemotherapy and interval debulking surgery without (group 1) and with (group 2) lymphadenectomy.*

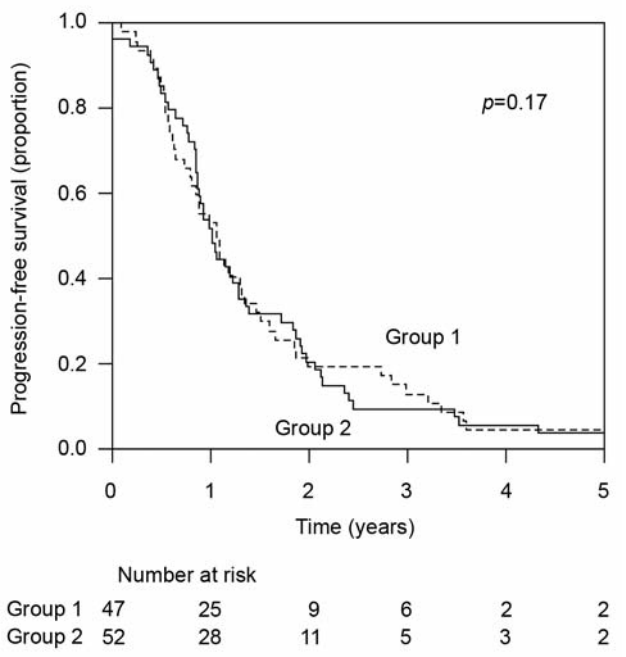

Figure 2. *Progression-free survival in patients with advanced ovarian cancer treated by neoadjuvant chemotherapy and intervall debulking surgery without (group 1) and with (group 2) lymphadenectomy.*

In our study, similarly to other published data, we found metastatic implants in retrieved lymph nodes despite neoadjuvant chemotherapy. Joulie *et al*. have shown that the frequency of lymph node involvement is similar when lymphadenectomy is performed before or after chemotherapy, which suggests that nodal metastases are not totally inhibited by chemotherapy (9). Consequently, survival improvement secondary to para-aortic lymphadenectomy could be expected.

Our adverse results could be explained by neoadjuvant chemotherapy that preceded surgery. In fact, according to some authors, the absence of macroscopic residual tumor at interval debulking surgery has a lower prognostic value than at the time of primary cytoreductive surgery (22). They explain this by the fact that microscopical reduction of peritoneal lesions after neoadjuvant chemotherapy is not complete. Knowing that, the recurrence and the terminal evolution of ovarian cancer are mostly linked to the intraperitoneal evolution, microscopic peritoneal lesions could be a more important risk factor of recurrence than lymph node metastasis.

Concerning the operative morbidity of para-aortic lymphadenectomy: in our study it was mainly represented by increased duration of surgery and by the number of transfused patients. It was otherwise similar in both groups. Indeed, complications are more related to cytoreductive surgery than to lymphadenectomy.

In our study, the characteristics of patients undergoing or not pelvic and para-aortic lymphadenectomy after optimal cyto-reductive surgery (R0) were quite similar concerning the age, BMI, associated morbidity and the performance status. There was, however, more initially 'pleural' stage IV cases in group of patients not undergoing lymphadenectomy. This could be an argument justifying the choice of surgeons not to perform lympadenectomy, however, this was not a standard option for this group of patients and some patients with stage IV disease underwent lymphadenectomy. The most probable explanation for this management discrepancy would be the lack of recommendation and the low level of evidence concerning the benefit of systemic lymphadenectomy after neoadjuvant chemotherapy.

Our study is retrospective and multicentric, this could have induced multiple bias and this could have influenced our results, although multivariate analyses were performed in the attempt to reduce these inherent biases. The absence of a significant difference in survival between the two groups can also be explained by a lack of power of the study.

In conclusion, in our study of patients with advanced ovarian cancer, treated by neoadjuvant chemotherapy and interval cytoreductive surgery without macroscopic residual tumor, lymphadenectomy does not seem to improve the overall nor the progression-free survival rate. These results should be confirmed by further controlled studies.

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