Are nodal metastases in ovarian cancer chemoresistant lesions? Analysis of nodal involvement in 105 patients treated with preoperative chemotherapy

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Summary

Background: To report the rates of nodal involvement in epithelial ovarian cancer (EOC) in patients who underwent initial lymphadenectomy (before chemotherapy) and patients who underwent lymphadenectomy after chemotherapy.

Study design: The rates of nodal involvement in 205 patients with EOC who underwent complete bilateral pelvic and para-aortic lympadenectomy between 1985 and 2001 were analyzed: 100 women underwent this surgical procedure before chemotherapy (initial surgery) and 105 at the end of chemotherapy (second-look surgery for 77 patients with 6 courses of a *platinum*-based regimen) or during chemotherapy (interval debulking surgery for 28 patients with 3 courses of a *platinum*-based regimen containing *paclitaxel*).

Results: The overall frequency of lymph-node involvement was 35% (35/100) in patients treated with initial surgery, 54% (15/28) in the interval debulking surgery group and 36% (28/77) in the second-look surgery group. In patients with Stage III disease, the rates of nodal involvement in patients treated with initial surgery, interval debulking surgery (with *paclitaxel*-based regimen) and second-look surgery were respectively: 53% (15/28), 58% (15/26) and 48% (20/42). The rates of nodal involvement in patients who underwent lymphadenectomy prior to or after chemotherapy were not statistically different whatever the stage of the disease. Adding *paclitaxel* to the platinum-based regimen does not seem to improve node sterilization rates.

Conclusions: The rates of nodal involvement seem to be similar in patients treated before or after chemotherapy. Such results suggest that nodal metastases are not as chemosensitive as peritoneal lesions. However, further studies are needed to evaluate the therapeutic value of lymphadenectomy in patients with nodal involvement.

Key words: Ovarian cancer; Chemotherapy; Nodal involvement; Para-aortic lymphadenectomy; Chemoresistance.

Introduction

Treatment of epithelial ovarian cancer (EOC) is based (in most of cases) on surgery followed by postoperative adjuvant chemotherapy. The strongest prognostic factor is the presence and size of residual tumor at the end of initial surgery [1-4]. Thus, the aim of initial surgery is to be optimal, completely removing the tumor and not leaving any residual disease at the end of cytoreductive surgery. Optimal surgery is possible for all disease stages (I, II, IIIA and B disease according to the FIGO 1987). Standard surgery is defined as peritoneal washing, hysterectomy, salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymphadenectomies and multiple peritoneal biopsies (with peritoneal resection, bowel resection and/or splenectomy, if necessary).

At present, the interest of surgical management of lymph nodes is under discussion. EOC is the gynecological tumor which spreads most frequently to pelvic and/or para-aortic lymph nodes. If we believe in "optimal cytoreductive surgery" and the need to remove all tumor sites in order to improve survival, then pelvic and para-aortic lymphadenectomy should be performed to achieve this objective. However, no randomized study has demonstrated the therapeutic value of lymphadenectomy. Furthermore, some authors have recently argued that lymphadenectomy, and particularly para-aortic lymphadenectomy, should not be performed in EOC [5]. This approach could be feasible if positive lymph nodes could be cured with adjuvant chemotherapy (without surgical resection). In our institution, pelvic and para-aortic lymphadenectomy has been performed routinely since 1985 for ovarian and cervical cancer [6, 7]. The aim of this study was to compare the rates of nodal involvement in patients treated with initial surgery and in patients treated with chemotherapy before lymphadenectomy.

Materials and Methods

From July 1985 to July 2001, 205 patients with EOC who underwent a complete bilateral pelvic and para-aortic lymphadenectomy in our institution were analyzed. The surgical procedure has been described in a previous publication [6, 7]. Briefly, pelvic and para-aortic lymphadenectomies were performed using an open transperitoneal approach, up to the level of the left renal vein. Pelvic lymph node dissection included removal of the common iliac, external iliac and obturator node groups. The para-aortic lymph nodes removed were located in the presacral, para-caval, intercavo-aortic and para-aortic area, the latter being divided into infra- and supra- mesenteric nodes.

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Two groups of patients were studied:

1. Patients who underwent initial lymphadenectomy (before potential chemotherapy).

This first group consisted of patients with incompletely staged disease who had not undergone lymphadenectomy during initial surgery but were restaged surgically and were submitted to pelvic and para-aortic lymphadenectomies before possible adjuvant chemotherapy. Most of these patients had their initial surgical procedure outside our institution and were referred to us so that surgery could be completed (particularly lymphadenectomy). The disease stage in these patients was based on macroscopic and histological evidence of tumor spread determined during the examination of diverse specimens (peritoneal washing cytology, ovaries, tubes, uterus, omentum and peritoneum) removed during initial surgery (before knowing the nodal status). Some patients with Stage IA or IB grade 1 or 2 disease (without peroperative rupture of the tumor) were submitted to surgery alone. All other patients received postoperative platinum-based chemotherapy.

2. Patients who underwent lymphadenectomy after initial chemotherapy.

This group comprised two different categories of patients:

– Some patients treated with an optimal (residual disease < 2 cm) surgical procedure (hysterectomy, bilateral salpingo-oophorectomy and omentectomy) initially but without a lymphadenectomy (because the initial surgical procedure was performed outside our institution or patients were in a poor medical condition at the end of intra-abdominal debulking surgery) received adjuvant chemotherapy. Second-look surgery including a pelvic and para-aortic lymphadenectomy was then performed after completion of adjuvant chemotherapy. The disease stage in these patients was determined based on the assessment of peritoneal cytology, ovaries, tubes, uterus, omentum and peritoneum at initial surgery performed before chemotherapy (before knowing the nodal status).

– The other group of patients who received chemotherapy before undergoing lymphadenectomies included patients who were submitted to "interval debulking surgery". Since 1996, patients with "unresectable" Stage IIIC or IV disease have received neo-adjuvant chemotherapy (a *platinum* + *paclitaxel* regimen) followed by interval debulking surgery including pelvic and para-aortic lymphadenectomy (in optimally debulked patients) [8]. Resectability of these patients was determined during an initial surgical procedure (laparoscopy or laparotomy). Interval debulking surgery was followed by chemotherapy.

The decision to select patients treated in another institution without lymphadenectomy for initial restaging surgery or to perform a lymphadenectomy at the time of second-look surgery depended on several factors: the time since initial surgery, tumor prognostic factors (stage, histologic subtype and tumor grade) and the extent of initial surgery (complete or incomplete resection). If patients had initial prognostic factors indicating that adjuvant therapy was needed (stage > IB and/or grade 3) and if the interval between initial surgery and when the patient was sent to our institution was too long, initial chemotherapy (before lymphadenectomy) was performed. Finally, among the patients referred to us from another institution, some had already received adjuvant chemotherapy.

The histological analysis was performed on lymphatic tissue. Lymph nodes were stained with hematoxylin and eosin and counted in order to determine whether metastatic spread had occurred. Nodal involvement was defined as the presence of tumor cells inside the lymph nodes whatever the extent of the involvement (micrometastases, metastases > 2 mm or macrometastases) or the status of the nodal capsule (presence or absence of involvement of the nodal capsule). The rates of nodal involvement in these three groups were studied.

Statistical analysis

The $\chi 2$ test was used to compare the percentage of nodal involvement in two groups (1. initial lymphadenectomies and 2. lymphadenectomies performed after chemotherapy including patients who had undergone interval debulking surgery and patients who had undergone second-look surgery). A p value of < 0.05 was considered significant.

Results

The median age was 50 years (range 16.1-70.4 years). Patient characteristics are detailed in Table 1. The distribution of disease stages was not similar in the three groups studied. However, this difference was corrected because the rates of nodal involvement were analyzed according to the disease stage (Table 2).

Pelvic and para-aortic lymphadenectomy were performed during restaging surgery in 100 patients (before chemotherapy). One hundred and five patients received chemotherapy before lymphadenectomy: 28 during interval debulking surgery and 77 at the time of second-look surgery. All 28 patients treated with neo-adjuvant chemotherapy followed by interval debulking surgery received a median number of three (range 2-4) courses of the *platinum* + *paclitaxel* regimen before surgery. Patients (n = 77) who underwent lymphadenectomy at the time of second-look surgery received a median number of six (range 4-12) courses of *platinum*-based chemotherapy.

The median number of pelvic and para-aortic lymph nodes removed per patient were 11 (range 2-55) and 14 (range 1-61), respectively. The median number of lymph nodes removed according to the treatment group were: 14 pelvic (range, 1-35) and 14 para-aortic (range, 1-41) in the "initial surgery" group; 14 pelvic (range, 8-32) and 16 para-aortic (range, 5-61) in the "interval debulking surgery" group and four pelvic (range, 1-28) and 14 para-aortic (range, 9-18) in patients who underwent lymphadenectomy at the time of second-look surgery. The total number of lymph nodes removed according to the treatment group were: 1,686 (781 pelvic and 905 para-aortic) in the "initial surgery" group; 964 (435 pelvic and 529 para-aortic) in the "interval debulking surgery" group and 627 (207 pelvic and 420 para-aortic) in the "second-look surgery" group. The overall frequency of lymph-node involvement was 38% (78/205). A median of four lymph nodes were involved when nodes were metastatic (range 1-29). Only pelvic lymph nodes were involved in six (8%) patients. Only para-aortic nodes were involved in 32 (41%) patients. Both lymph node groups were involved in 40 (51%) patients. The percentages of patients with metastatic lymph nodes (/total of removed lymph nodes) according to treatment groups were: 31/1,686 (2%) in the "initial surgery" group, 113/964 (12%) in the "interval debulking surgery" group and 28/627 (4%) in patients who underwent lymphadenectomy at the time of second-look surgery.

Details on nodal involvement according to the treat-

ment group are reported in Table 2. The overall frequency of lymph-node involvement in patients treated with initial surgery, interval debulking surgery and second-look surgery was 35% (35/100), 54% (15/28) and 36% (28/77), respectively. The rates of lymph-node metastasis in "early-stage" disease (Stage I and II) according to the surgical treatment ("initial surgery" vs "second-look surgery") were respectively: 19% (11/57) and 21% (6/28) for Stage I disease and 50% (4/8) and 33% (2/6) for Stage II disease. Details on nodal involvement in patients with Stage I disease according to substages (Stage IA, IB and IC) and according to the tumor grade are reported in Table 2. In advanced-stage disease (Stages III and IV), the rates of nodal involvement in patients who had undergone initial surgery were 59% (20/34), compared to 55% (15/27) in patients submitted to interval debulking surgery (with the *paclitaxel*-based regimen) and to 48% (20/42) in patients submitted to second-look surgery. The rates of nodal involvement before and after chemotherapy were not statistically different in these two groups of patients whatever the disease stage (Stage I, II and III) (Table 2). These rates were not compared for Stage IV disease because the number of patients was low (n = 7).

Discussion

In this study, the rates of nodal involvement in patients treated with initial surgery or after chemotherapy are similar to those observed by other authors (Table 3) [9-15]. As previously observed by some authors, the rate of nodal involvement, particularly in patients with "early-stage" disease ("I" or "II") is similar before or after chemotherapy (Table 2). Such results suggest that metastatic lymph nodes are not chemosensitive lesions. Kimball *et al.* evaluated the DNA content and S-phase fraction using flow cytometry in primary ovarian tumors, peritoneal metastases and lymph-node metastases in 35 patients treated for Stage III or IV EOC. Diploid cell lines and a low S-phase were found significantly more frequently in metastatic lymph nodes than in peritoneal metastases or ovarian tumors [16]. Such data could explain why metastatic lymph nodes do not seem to be as chemosensitive as peritoneal lesions.

Our series is original in two respects. Firstly, to our knowledge, it presents the largest series of patients submitted to a para-aortic lymphadenectomy after (or during) chemotherapy (105 patients). The second originality of this series concerns the preoperative chemother-

Table 1. — *Characteristics of patients according to the treatment group.*

	No. chemotherapy initial surgery	Interval debulking surgery	Chemotherapy Second-look surgery	Total*	p value
Stage					
I**	57 (57%)	0	28 (36%)	28 (26%)	< 0.001***
IA	44 (77%)	0	16 (57%)	16 (57%)	
IB	7 (12%)	0	5 (18%)	5 (18%)	0.06****
IC	6 (11%)	0	7 (25%)	7 (25%)	
II**	8 (8%)	1 (4%)	6 (8%)	7 (7%)	
III+IV	35 (35%)	27 (96%)	43 (56%)	70 (67%)	
Histologic subtypes					
Serous	46 (46%)	23 (82%)	41 (53%)	64 (61%)	
Mucinous	22 (22%)	0	3 (4%)	3 (3%)	< 0.001
Endometrioid	24 (24%)	1 (4%)	19 (25%)	20 (19%)	
Other	8 (8%)	4 (14%)	14 (18%)	18 (17%)	
Grade					
Grade 1	27 (27%)	3 (11%)	1 (1%)	4 (4%)	
Grade 2	33 (33%)	16 (57%)	39 (51%)	55 (52%)	< 0.001
Grade 3	29 (29%)	6 (21%)	24 (31%)	30 (29%)	
Not stated	11 (11%)	3 (11%)	13 (17%)	16 (15%)	
Stage I & Grade					
Grade 1	22 (39%)	0	0	0	
Grade 2	22 (39%)	0	18 (64%)	18 (64%)	< 0.001*****
Grade 3	11 (19%)	0	3 (11%)	3 (11%)	
Not stated	2 (3%)	0	7 (25%)	7 (25%)	
Stage I & Histology					
Serous	16 (28%)	0	10 (36%)	10 (36%)	
Mucinous	19 (33%)	0	1 (4%)	1 (4%)	< 0.002******
Endometrioid	18 (32%)	0	9 (32%)	9 (32%)	
Other	4 (7%)	0	8 (28%)	8 (28%)	
Laterality					
Right	19 (19%)	5 (18%)	9 (12%)	14 (13%)	
Left	38 (38%)	1 (4%)	18 (23%)	19 (18%)	< 0.001
Bilateral	41 (41%)	22 (78%)	49 (64%)	71 (68%)	
Not stated	2 (2%)	0	1 (1%)	1 (1%)	
Total	100	28	77	105	

*: Total of patients who received chemotherapy before lymphadenectomy; **: Stage of the disease before knowledge of the nodal status; ***: p value between Stage I versus II+III+IV; ****: p value between Stage IA versus IB+IC; *****: p value between grade 1 versus 2+3; ******: p value between mucinous versus others subtypes.

Table 2. — *Nodal involvement according to the type of treatment in the present series.*

Stage	Initial surgery	Interval debulking surgery	Preoperative chemotherapy Second-look surgery	Total	p value *
Stage I**	11/57 (19%)	0	6/28 (21%)	6/28 (21%)	0.82
IA	7/44 (16%)	0	3/16 (18%)	3/16 (18%)	
IB	1/7 (14%)	0	2/5 (40%)	2/5 (40%)	
IC	3/6 (50%)	0	1/7 (14%)	1/7 (14%)	
Stage I/grade 1**	0/22 (0%)	0	0	0/22 (0%)	
Stage I/grade 2**	4/22 (18%)	0	5/18 (28%)	5/18 (28%)	
Stage I/grade 3**	6/11 (55%)	0	1/3 (33%)	1/3 (33%)	
Stage I/unknown grade**	1/2 (50%)	0	0/7 (0%)	0/7 (%)	
Stage II*	4/8 (50%)	0/1	2/6 (33%)	2/7 (28%)	0.4
Stage III	15/28 (53%)	15/26 (58%)	20/42 (48%)	35/68 (51%)	0.85
Stage IV	5/6 (83%)	0/1	0	0/1	ND***
Total	35/100 (35%)	15/28 (54%)	28/77 (36%)	43/105 (41%)	0.38

*: Value determined comparing patients treated with initial surgery and preoperative chemotherapy; **disease stage before knowing nodal status; ***:Not determined.

Table 3. — *Literature review of nodal involvement following lymphadenectomy at the time of second-look surgery.*

Authors	No. of patients*	Stage	Type CT**	Rate of nodal involvement	
				No. preop. CT**	Preoperative CT**
Burghardt [9]	26	I-IV	17 PL	59/97 (61%)	17/26 (65%)
Wu [10, 11]	15	III	38/59 (64%)	14/15 (93%)	14/15 93%)
Di Re [12]	88	I-IV	PL	–	33/88 (27%)
Scarabelli [13]	30	III-IV	PL	23/30 (76%)	21/30 (70%)
Baiocchi [14]	58	I-IV	42 PL	–	15/58 (23%)
Zinzindohoue [15]	34	I-IV	PL	24/52 (46%)	18/34 (53%)
Present series ***	105	I-IV	77PL/28 PL+PC	35/100 (35%)	43/105 (41%)
Total	350	I-IV		179/338 (53%)	161/356 (45%)

*: number of patients who received preoperative chemotherapy; **CT: Chemotherapy; PL: *platinum*-based regimen; PC: *paclitaxel*; ***: Second-look surgery and interval debulking surgery.

apy regimen. To date, no publication had focused on the nodal status of patients treated with a *paclitaxel* regimen although several randomized studies have demonstrated that the *paclitaxel* regimen yields a higher survival rate [17, 18]. The combination of *paclitaxel* and platinum is considered the reference first-line regimen by several teams in EOC. This drug was used in our series of patients who underwent interval debulking surgery. The rates of nodal involvement in patients with Stage III disease were not statistically different at respectively, 53% (15/28), 58% (15/25) and 48% (20/42) in patients who underwent lymphadenectomy initially, at the time of interval debulking surgery or at the time of second-look surgery (Table 2). Such results suggest that adding the *paclitaxel* regimen do not seem to increase the rate of nodal sterilization.

It is difficult to compare patients with Stage III disease in the three treatment groups. Patients treated with interval debulking surgery had more massive spread (with unresectable intra-abdominal disease) than patients in the other two groups. Consequently, the rate of nodal involvement in patients with bulky Stage III or IV disease was probably higher than in patients with a similar disease stage but in whom complete initial surgery was possible (due to a smaller tumor burden). The rate of nodal involvement might have been higher had patients not received neoadjuvant chemotherapy. The absence of a statistical difference between nodal involvement in patients who underwent interval debulking surgery and patients who underwent lymphadenectomy initially does not necessarily signify that chemotherapy had no impact on nodal metastases. Furthermore, the number of chemotherapy courses delivered before lymphadenectomy was different: a median number of three courses were given in the interval debulking surgery group and six courses were given in patients who underwent a lymphadenectomy at the time of second-look surgery. The comparability of patients with Stage III disease is therefore limited due to these two biases.

Our results raise also the question of the therapeutic value of lymphadenectomy in EOC. We were unable to investigate this point in the present series because there was no group of patients in whom lymph nodes were not removed. Several retrospective studies have emphasized the therapeutic value of resecting metastatic nodes in Stage III/IV disease [19, 20]. Spirtos *et al.* reported that the survival rates obtained in optimally debulked patients with Stage III and IV disease were similar irrespective of whether nodes were negative or microscopically or macroscopically positive [19]. However, none of these series were randomized. Consequently, the therapeutic value of nodal "debulking" has yet to be confirmed even if lymph-node metastases do not seem to be as chemosensitive as peritoneal lesions. An ongoing multicentric international randomized study is attempting to clarify the therapeutic value of lymph-node resection for patients with advanced-stage disease.

In the present series, the rates of nodal involvement in patients with Stage I disease were similar in patients who underwent lymphadenectomy before chemotherapy or at the time of second-look surgery. However, several biases could modulate this result: the percentage of patients with stage IB and IC disease was higher among patients who underwent second-look surgery than in the initial surgery group (43% vs 23%). Furthermore, the percentage of patients with grade 2 and 3 tumors was higher in the "second-look surgery" group. The percentage of patients with serous tumors was also statistically higher in the "second-look" group whereas mucinous tumors were more frequent in initial surgery group. Finally, the percentage of patients with bilateral tumors was higher among patients who underwent lymphadenectomy at the time of second-look surgery (Table 1). We know that the rate of nodal involvement is higher in patients with grade 2 and 3 tumors (compared to grade 1), in patients with Stage IB and IC disease (compared to Stage IA disease), in patients with serous tumors (compared to mucinous lesions) and in patients with bilateral tumors (compared to unilateral) [7]. As a result of all these adverse prognostic factors, the rate of initial nodal involvement (before chemotherapy) in patients who underwent lymphadenectomy at the time of second-look surgery would probably have been spontaneously higher than in patients who underwent initial lymphadenectomy. As was the case in patients with Stage III disease, the absence of statistical difference for nodal involvement in Stage I disease does not necessarily signify that chemotherapy had no influence on nodal metastases. Moreover, the rates of nodal involvement in patients with Stage II disease were statistically different (50% in the "initial surgery" group vs 33% in the "second-look surgery" group - Table 2). However, the number of patients was very low (15 patients) in this subgroup, so firm conclusions cannot be drawn. Nevertheless, even if we cannot firmly exclude a therapeutic effect of chemotherapy on metastatic lymph-node metastases because of the previously mentioned potential biases in this study, in none of the substages of the disease (Stage I, II or III) was chemotherapy able to sterilize nodal involvement completely in patients who underwent lymphadenectomy at the time of second-look surgery.

Our results also raise the question of the therapeutic value of lymphadenectomy in early-stage disease, a point which is still under discussion. A large randomized study on the benefit of adjuvant chemotherapy in early-stage EOC was recently published about the benefit of adjuvant chemotherapy in early stage EOC [21]. This series involved 448 patients: 224 received adjuvant chemotherapy and 224 were submitted to surgery alone [21]. One hundred and fifty-one patients had been optimally staged and 297 had not. The benefit of adjuvant therapy in terms of survival was limited to the subgroup of patients in whom staging was suboptimal (absence of lymphadenectomy), and thus with a higher risk of unappreciated residual disease than in patients in whom staging was adequate. Such results could suggest that chemotherapy does have an effect on residual lymph-node metastasis [21]. When we examined the data in this trial in detail, we found that optimal surgical staging was defined as: inspection and palpation of the peritoneal surface, peritoneal washings, multiple peritoneal biopsies and "sampling of iliac and peri-aortic nodes". The term "sampling" can be misleading as sampling can involve a complete lymphadenectomy, a bilateral dissection or simply nodal picking. In fact, the number of patients who had a complete bilateral pelvic and para-aortic lymphadenectomy was not specified in this study. The results of Trimbos *et al.'s* important trial demonstrated that adjuvant chemotherapy had an effect on suboptimally staged disease sterilizing potential residual peritoneal disease. However, if the number of patients with complete lymphadenectomy in that trial was very low, the results would not necessarily signify that adjuvant chemotherapy had an effect on potential nodal metastases. Recent retrospective studies seem to suggest that the removal of isolated positive nodes in patients with EOC and the absence of peritoneal disease have a therapeutic value [22, 23]. The only way to demonstrate a potential therapeutic value of lymphadenectomy would be to conduct a randomized trial including patients with EOC, treated *"a priori"* by surgery alone (Stage IA & IB disease with grade 1 or 2 tumors) with adequate staging in the peritoneal cavity (peritoneal cytology, multiple peritoneal biopsies) who would be randomized to two arms, one in which a complete bilateral lymphadenectomy would be performed and no lymphadenectomy in the other arm. But as the rate of nodal involvement is low in these substages of the disease (10% to 15%), a very high number of patients (> 600) would have to be accrued to demonstrate a potential benefit for the survival. Furthermore, as the percentage of Stage IA and IB disease is low, the feasibility of such a trial seems to be questionable and probably unrealistic.

The results of our study seem to suggest that the rates of nodal involvement is similar for patients operated on before or after chemotherapy. Apparently, adding the *paclitaxel*-based regimen did not improve the rate of nodal sterilization. However, there were several biases in the present series. Randomized studies are needed to evaluate the therapeutic value of lymph-node resection in EOC. Such a study is ongoing in patients with advanced-stage (III and IV) EOC, but definitive results will not be available before a couple more years.

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