Bevacizumab Does Not Reduce the Lymphocele Rate in Advanced Ovarian Cancer After Complete Cytoreductive Surgery

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Abstract. *Background/Aim: We aimed to evaluate the impact of bevacizumab on the lymphocele rate in patients after complete cytoreductive surgery for advanced ovarian cancer. Patients and Methods: This retrospective study included patients with advanced ovarian cancer who had undergone complete cytoreductive surgery with pelvic and para-aortic lymphadenectomy at the Gustave Roussy Institute from 2005 to 2014. The introduction of bevacizumab was discussed in a multidisciplinary meeting. Results: During the study period, 247 patients were included; 24.6% of patients (61 patients) received adjuvant bevacizumab. The rate of symptomatic lymphocele was 34% (84 patients). In the lymphocele group, patients tended to receive adjuvant bevacizumab more often than did the control group (32% and 21%, respectively, p=0.05). In multivariate analysis, bevacizumab was not significantly associated with the risk of symptomatic lymphocele (hazard ratio(HR)=1.62, 95% confidence interval(CI)=0.87-3.01, p=0.12). Conclusion: Adjuvant bevacizumab has no impact on the formation or duration of symptomatic lymphocele in patients after complete cytoreductive surgery for advanced ovarian cancer.*

Ovarian cancer is the seventh most common malignancy among females worldwide, with an estimated incidence of about 239,000 new cases in the 2012 (1). More than 75% of cases are diagnosed at advanced stages due to the absence of symptoms in early stages and the prognosis is, therefore, poor (2). Treatment of advanced stages includes complete cytoreductive surgery, which is a major prognostic factor (3-5), and adjuvant chemotherapy. Para-aortic and pelvic lymph node dissection is an integral part of surgical staging, and its benefit in terms of disease-free and overall survival (OS) have been demonstrated in retrospective studies (6, 7). In the only existing randomized trial, lymphadenectomy positively affected progression-free survival (8).

Complete cytoreductive surgery increases the risk of postoperative complications and lymphocele is one of the most frequent complications, but remains unstudied in the literature (9). Most lymphoceles are asymptomatic and resorb spontaneously (10). However, symptomatic lymphoceles can cause fever, abdominal pain, tenesmus, hydronephrosis, leg oedema and deep vein thrombosis. Symptomatic lymphoceles do not seem to have an impact on survival but do require needle aspiration, drainage or further surgery, which can prolong the hospital stay and delay the administration of adjuvant chemotherapy (11). The risk factors for lymphocele development are unclear. The extent of surgery and the number of lymph nodes removed seem to be risk factors in ovarian cancer (11). In gynaecological cancer, the extent of lymphadenectomy, presence of lymph node metastases, body mass index (BMI), lack of lymphatic vessel ligation and use of drainage have also been described as risk factors for lymphocele formation (10, 12-16). Yet, the lymphocele rate remains high because no clear management strategy has been established to reduce the risk of lymphocele formation (17) or to treat this complication.

The treatment strategy for advanced ovarian cancer was recently modified with the introduction of bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, in first-line treatment, combined with chemotherapy, and as maintenance therapy. Two trials, the International Collaboration on Ovarian Neoplasms (ICON) 7 (18) and Gynecologic Oncology Group (GOG) 02-18 (19) showed that adding bevacizumab to first-line adjuvant therapy prolonged recurrence-free survival by 2 or 4 months in

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Key Words: Lymphocele, ovarian cancer, bevacizumab, lymphadenectomy, surgery.

patients with advanced epithelial ovarian cancer. The ICON 7 trial also showed that the benefits in terms of both recurrence-free survival and OS were greater among patients at high risk of progression (18). Since these trials, bevacizumab has been increasingly prescribed and the effect of this treatment has already been studied for malignant ascites in ovarian cancer and yielded a positive symptomatic benefit (20-23) but has never been studied on lymphoceles.

To our knowledge, this is the first study to investigate the impact of bevacizumab on the lymphocele rate in patients after complete cytoreductive surgery for advanced ovarian cancer.

Patients and Methods

Study population. This retrospective study included patients with advanced ovarian cancer, stages IIIB, IIIC, and IV according to the 1988 International Federation of Gynaecology and Obstetrics (FIGO) classification (24), who had received surgical treatment at our Institute from 2005 to 2014. All patients had undergone complete cytoreductive surgery with para-aortic and pelvic lymph node dissection. Patients were classified into a group with symptomatic lymphocele and a control group (without symptomatic lymphocele) and then into adjuvant bevacizumab group and control group (without adjuvant bevacizumab). Symptomatic lymphocele was defined as the presence of a lymphocele causing fever, abdominal pain, occlusion, and ureteral or vascular obstruction. Symptomatic lymphoceles systematically required needle aspiration, drainage under ultrasound or computed tomography guidance or further surgery. The following patient characteristics and surgical data were collected: age, BMI before surgery (kg/m²), 1988 FIGO cancer stage, histological type (serous, mucinous, or other), type of surgery (standard, radical, or supra-radical), number of lymph nodes removed, lymph node involvement, and the length of hospital stay after surgery. Data on adjuvant therapy were also collected: neoadjuvant chemotherapy, adjuvant chemotherapy, the interval (days) between surgery and the initiation of chemotherapy, adjuvant bevacizumab, number of cycles, the interval (days) between surgery and initiation of bevacizumab, adverse events, and reasons for stopping bevacizumab early. In the group with symptomatic lymphocele, the number of needle aspiration or drainage events, and the interval (days) between the first and last such events were collected. In cases of repeated aspiration or drainage, a cytological analysis was performed.

Treatment and follow-up. Complete cytoreductive surgery was defined as no postoperative macroscopic residual tumour. Standard surgery comprised total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal biopsies in the pelvis and paracolic gutters, and systematic para-aortic and pelvic lymphadenectomy. Radical surgery included standard surgery with the Hudson procedure. In the latter, a rectosigmoidal resection along with resection of the reproductive organs and the pelvic peritoneum was accomplished using an *en bloc* retroperitoneal approach (25). Supra-radical surgery was performed in patients requiring resection of the diaphragm (full-thickness resection or partial or complete peritoneotomy), cholecystectomy, splenectomy, any bowel resection beyond removal of the sigmoid or an appendectomy, and resection of the bladder or ureter. Systematic lymphadenectomy included resection of pelvic and para-aortic lymph nodes. Pelvic lymphadenectomy included the removal of the common iliac, external and obturator nodal groups. Para-aortic lymphadenectomy was performed *via* a transperitoneal approach. The upper limit of the para-aortic dissection was the left renal vein. The pre-sacral chain, paracaval chain, and intercaval aortic chain were removed. The left para-aortic chain with the infra-mesenteric and supra-mesenteric groups was removed.

At the end of surgery, a pelvic drain with/without a retroperitoneal drain was left in place in the aortic area. In the case of diaphragmatic surgery or splenectomy, another drain was placed in the upper abdominal area. A low-pressure drain was always used. Withdrawal of drainage depended on the surgeons and outcomes. Drains were usually removed when the volume of fluid collected was less than 300-500 ml/day.

Patient follow-up included clinical examination and blood marker determination and the use of imaging techniques according to the findings every 4 months during the first 2 years, every 6 months up to 5 years, and then yearly thereafter.

Statistical analysis. The quantitative and qualitative variable results are expressed as medians and as frequencies and percentages, respectively. The statistical analysis was based on Student's *t*-test and the Mann–Whitney test for parametric and non-parametric continuous variables, respectively, and the chi-square test or Fisher's exact test, as appropriate, for categorical variables. *p*-Values of less than 0.05 were considered to denote significant differences. To assess the association between different variables and the occurrence of symptomatic lymphoceles, we used logistic regression analysis. Hazard ratios (HR) and the 95% confidence interval (CI) were calculated. Univariate analysis was followed by multivariate analysis. Variables in the univariate analysis had to reach a level of significance of 0.2 or had to be considered as a risk factor for lymphocele in the literature in order to be included in the multivariate model. The Kaplan–Meier method was used to estimate the survival distribution and survival rates were compared using the log-rank test. Data were managed with an Excel database (Microsoft, Redmond, WA, USA) and analysed using the R 2.15 software, available online.

Results

Two hundred and forty-seven patients had undergone complete cytoreductive surgery including a para-aortic and pelvic lymphadenectomy. Eighty-four patients (34%) had a symptomatic lymphocele and 61 patients (25%) had received adjuvant chemotherapy with bevacizumab. Table I shows the characteristics of patients with (lymphocele group) and without a lymphocele (control group). There was no difference between the two groups in terms of age, BMI, FIGO stage, histological subtype, type of surgery, number of para-aortic and pelvic nodes removed and chemotherapy characteristics (neoadjuvant and adjuvant, with or without bevacizumab). There was no difference between the two groups in terms of number of cycles of bevacizumab and the delay between complete cytoreductive surgery and the first cycle of bevacizumab. Conversely, the median hospital stay

Table I. *Characteristics of the two groups of patients included in this study.*

Characteristic	Lymphocele group (n=84)	Control group (n=163)	*p*-Value
Mean age (range), years	53.4 (23.3-74.0)	54.4 (25.2-70.3)	0.51
Mean BMI (range), kg/m^2	25.5 (17.4-40.4)	24.5 (16.5-36.1)	0.14
Median hospital stay (range), days	14 (5-102)	12 (7-73)	0.03
FIGO stage, n (%)			0.11
IIIB	0	4 (2%)	
IIIC	74 (88%)	149 (92%)	
IV	10 (12%)	10 (6%)	
Histology, n (%)			0.28
Serous	66 (80%)	119 (73%)	
Mucinous	1 (1%)	8 (5%)	
Other	16 (19%)	35 (22%)	
Unknown	1	1	
Surgery, n (%)			
Standard	14 (17%)	42 (26%)	0.10
Radical	6 (7%)	19 (11%)	0.26
Supra-radical	64 (76%)	102 (63%)	0.03
Median no. of lymph nodes removed (range)			
Total	50 (17-95)	42 (6-123)	0.05
Pelvic	18 (6-47)	17 (1-54)	0.05
Para-aortic	31 (6-70)	24 (5-82)	0.12
Patients with involved nodes, n (%)	62 (74%)	108 (66%)	0.22
Median no. of nodes involved (range)	4 (1-31)	5 (1-85)	0.33
Chemotherapy			
Neoadjuvant, n (%)	58 (69%)	103 (63%)	0.35
Adjuvant, n (%)	78 (93%)	147 (93%)	0.95
Bevacizumab, n (%)	27 (32%)	34 (21%)	0.05
Median no. of cycles of bevacizumab (range)	16 (2-36)	16 (1-36)	0.69
Median delay between surgery and bevacizumab (range), days	60 (33-100)	56 (27-134)	0.43

BMI: Body mass index; FIGO: International Federation of Gynaecology and Obstetrics.

was significantly longer in the lymphocele group than in the control group, with 14 and 12 days, respectively (*p*=0.03).

Table II shows the results of multivariate analysis of the risk of lymphocele formation: no independent factor was associated with the risk of developing a symptomatic lymphocele postoperatively. Bevacizumab was not associated with the risk of developing a symptomatic lymphocele (HR=1.62 95% CI=0.87-3.01, *p*=0.12).

Table III shows the characteristics of the population with and without adjuvant bevacizumab. Both groups were comparable in terms of demographic characteristics (age and BMI), FIGO stage and type of surgery. Nevertheless, the group treated with adjuvant bevacizumab more frequently had serous histology (88.5% *vs*. 71.5%) and less frequently mucinous histology (none *vs*. 4.8%) than the group not treated with bevacizumab (*p*=0.01). In addition, the group treated with adjuvant bevacizumab had more lymph nodes removed (49 *vs*. 43.5, *p*=0.02) than the group without bevacizumab.

Table IV shows that bevacizumab had no impact on radiological drainage. Eighty-four patients (34%) developed symptomatic lymphoceles. Thirty-two patients (38%) with a

Table II. *Multivariate analysis of the association between variables and the occurrence of symptomatic lymphocele.*

Covariate	HR (95% CI)	*p*-Value
Bevacizumab therapy	1.62 (0.87-3.01)	0.12
Supra-radical surgery	1.78 (0.97-3.38)	0.06
FIGO stage IV	2.1 (0.79-5.56)	0.12
>40 Lymph nodes removed	1.58 (0.90-2.83)	0.11
Lymph node involvement	1.40 (0.75-2.65)	0.29
Age >60 years	1.11 (0.61-2.01)	0.72
BMI>25 kg/m^2	1.04 (0.98-1.1)	0.16

HR: Hazard ratio, CI: confidence interval, BMI: body mass index, FIGO: International Federation of Gynaecology and Obstetrics.

symptomatic lymphocele had undergone only one needle aspiration (or drainage) and 12 at least two needle aspirations or drainage, with a median number of 3.5 (range=2-20). The median delay between surgery and the first needle aspiration was 34 days (range=8-317 days).

Table III. *Characteristics of the population treated with and without (Control) adjuvant bevacizumab.*

Characteristic	Bevacizumab (n=61)	Control group (n=186)	*p*-Value
Mean age (range), years	57.9 (23-70)	54.1 (24-74)	0.88
Mean BMI (range), kg/m^2	24.0 (17-36)	24.8 (16-40)	0.83
FIGO stage, n (%)			0.99
IIIB	1(2%)	3 (2%)	
IIIC	55 (90%)	168 (90%)	
IV	5 (8%)	15 (8%)	
Histology, n (%)			0.01
Serous	54 (88%)	131(71%)	
Mucinous	0	9 (5%)	
Other	7 (12%)	44 (24%)	
Unknown		2	
Surgery, n (%)			0.21
Standard	9 (14.8%)	47 (25%)	
Radical	6 (9.8%)	19 (10%)	
Supra-radical	46 (75.4)	120 (65%)	
Median no. of lymph nodes removed (range)			
Total	49 (19-123)	44 (6-108)	0.02
Pelvic	17 (6-54)	17 (1-54)	0.32
Para-aortic	30 (7-82)	26 (5-73)	0.01
Patients with involved nodes, n (%)	44 (72%)	125 (67%)	0.47
Median no. of nodes involved (range)	5 (1-85)	4 (1-62)	0.23
Symptomatic lymphocele	27 (44%)	57 (31%)	0.05

BMI: Body mass index; FIGO: International Federation of Gynaecology and Obstetrics.

Table IV. *Impact of adjuvant bevacizumab on drainage of symptomatic lymphocele.*

Characteristic	Bevacizumab	Control group	*p*-Value
No. of patients with only one needle aspiration/drainage	10 (37%)	22 (38%)	0.89
Median no. of needle aspirations/drainage if >1, (range)	8 (2-16)	4 (2-20)	0.54
Median delay between first and last needle aspiration/drainage (range), days	33 (4-357)	74 (5-400)	0.33

In the bevacizumab-treated and the control groups, the median follow-up times were 27.1 (range=13.7-75.3) months and 40.8 (range=1.3-107.4) months, respectively.

Discussion

The risk factors for development of lymphocele are unclear. The extent of surgery and number of lymph nodes removed seem to be risk factors in ovarian cancer (11). In gynaecological cancer, the extent of the lymphadenectomy, the presence of lymph node metastases, the BMI, the lack of lymphatic vessel ligation and the use of drainage have also been described as risk factors for lymphocele formation (10, 12-16).

Our results show that bevacizumab did not reduce the lymphocele rate after complete cytoreductive surgery in advanced ovarian cancer. To our knowledge, our series is the largest in the literature (247 patients having undergone complete cytoreductive surgery and a complete para-aortic and pelvic lymphadenectomy) to investigate the lymphocele rate in the bevacizumab era.

Lymphocele occurs very frequently after complete para-aortic and pelvic lymphadenectomy but has been poorly studied. The only study which raised the question of the frequency of symptomatic lymphocele after cytoreductive surgery in advanced ovarian cancer found a rate of 28% (11). It broached the issue of the quality of life of patients who had undergone extensive and complete surgery. In our study, 34% of patients had developed a symptomatic lymphocele which required at least one needle aspiration (or drainage) and 14% had undergone more than one needle aspiration. Regarding the hospital stay, we found it was significantly longer for patients with symptomatic lymphocele but only by approximately 2 days, which confirms the result of the study

reported by Gauthier *et al.* (11). We did not find a significant delay in the introduction of adjuvant treatment unlike that previous study, which is very important because adjuvant therapy is a decisive step in the treatment of patients with advanced ovarian cancer.

These results do not challenge the indication for systematic lymphadenectomy for this subgroup of patients if we consider the quality of life and survival associated with lymphocele. In the literature, several studies showed the benefit of lymphadenectomy in optimal surgery (6-8). More precisely, Du Bois *et al.* found that total lymphadenectomy afforded an OS benefit for patients with advanced ovarian cancer and cytoreductive surgery with no residual tumour (HR=0.74, 95% CI=0.59-0.94, *p*=0.0123) (6). This signifies that lymphadenectomy is an important prognostic factor for such patients as well as there being no residual tumour at the end of surgery. Panici *et al.* reported that systematic lymphadenectomy alone afforded a benefit for progression-free survival but in women who had undergone optimal surgery (residual tumour ≤1 cm in 60% of cases and no residual tumour in 37% of cases). Our population had undergone complete cytoreductive surgery at a major referral centre applying guidelines and with surgeons highly experienced in extensive surgery.

In our study, we found no risk factor for symptomatic lymphocele formation. In the literature, Gautier *et al.* found that undergoing supra-radical surgery was an independent risk factor for symptomatic lymphocele formation in a multivariate analysis in ovarian cancer, as well as removal of more than 40 lymph nodes in the univariate analysis. Despite a larger study population, we did not identify supra-radical surgery and the number of lymph nodes removed (>40) as significant risk factors in our multivariate analysis (HR=1.78, 95% CI=0.97-3.38, *p*=0.06 and HR=1.58, 95% CI=0.90-2.83, *p*=0.11 respectively). Other factors such as a high BMI, the extent of the lymphadenectomy and the presence of lymph node metastasis have been described to promote the formation of lymphocele in gynaecological cancer (10, 12, 16). None of these factors were proven to be independent risk factors in our study, that confirms previous results.

In the literature, therapy with intravenous or intraperitoneal bevacizumab seems to be beneficial in patients with malignant ascites in ovarian cancer and decreases the number of needle aspirations required (20-23). The hypothesis put forward for this benefit was the expression of VEGF in the fluid. Kobold *et al.* showed that VEGF was overexpressed in malignant ascites in comparison with non-malignant ascites (21). We did not verify VEGF expression in lymphoceles but it seems obvious that it would be low after complete cytoreductive surgery. Unsurprisingly, bevacizumab did not reduce the lymphocele rate (HR=1.62, 95% CI=0.87-3.01, *p*=0.12 in the multivariate analysis) nor did it lower the number of needle aspirations (or drainage) required.

One potential bias of our retrospective study was the number of lymph nodes removed, which was significantly higher in the bevacizumab-treated group (49 *versus* 44 in the group without bevacizumab). Several studies have demonstrated the benefit of total lymphadenectomy in terms of survival for patients with advanced ovarian cancer who had undergone optimal surgery (6-8) and the number of lymph nodes removed was a prognostic factor with a cut-off point of 10 lymph nodes in the study conducted by Rouzier *et al.* (7). In our study, all the patients had undergone complete cytoreductive surgery with no residual tumour and pelvic and para-aortic lymphadenectomy, and only two of them had fewer than 10 lymph nodes removed in the entire study population. Finally, our study showed that the number of lymph nodes removed was not a risk factor for lymphocele development in the multivariate analysis.

A second potential bias was the cancer histological types: there were more patients with serous tumours and fewer with mucinous histology in the bevacizumab-treated group than in the group without bevacizumab. Du Bois *et al.* found that a mucinous histological type was a strong prognostic factor for survival *versus* a serous histological type in debulked advanced ovarian cancer (3). In our study, the number of mucinous tumours was very low in the two groups (1% and 5% in the groups treated without and with bevacizumab, respectively). These very low numbers reduced the impact of this potential bias.

Conclusion

Adjuvant bevacizumab has no impact on the formation or the duration of symptomatic lymphocele.

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