Lymphocele and Ovarian Cancer: Risk Factors and Impact on Survival

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Identify risk factors for lymphoceles after cytoreductive surgery in ovarian cancer.
2. Describe the impact of lymphoceles on outcomes in women with ovarian cancer.

CME

This article is available for continuing medical education credit at CME.TheOncologist.com.

ABSTRACT

Introduction. We describe the incidence, impact on survival, and the risk factors for symptomatic lymphoceles in patients with ovarian cancer.

Methods. This retrospective study includes patients with ovarian cancer who had complete cytoreductive surgery and para-aortic and pelvic lymphadenectomy performed in our institute from 2005 to 2011. Patients were classified into two groups: patients with symptomatic lymphoceles and a control group.

Results. During the study period, 194 patients with epithelial ovarian cancer underwent cytoreductive surgery and a lymphadenectomy without macroscopic residual disease. Fifty-four patients had symptomatic lymphoceles (28%). In the multivariate analysis, only supraradical surgery was significantly and independently associated with

the risk of symptomatic lymphoceles occurring postoperatively. Median follow-up was 24.8 months (range, 1–74 months). Survival rates were not significantly different between the symptomatic lymphocele group and the control group. Two-year disease-free survival rates were 54% for the lymphocele group and 48% for the control group. Two-year overall survival rates were 90% for the lymphocele group and 88% for the control group.

Conclusions. Symptomatic lymphoceles occur frequently after cytoreductive surgery in ovarian cancer. Supraradical surgery is an independent risk factor. The occurrence of symptomatic lymphoceles does not decrease survival. Nevertheless, further studies are needed to reduce the risk of lymphoceles in such patients. *The Oncologist* 2012;17:1198–1203

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INTRODUCTION

Treatment of advanced-stage ovarian carcinoma includes cytoreductive surgery (CRS). The prognostic value of complete debulking has been reported in several studies [1–3]. Para-aortic and pelvic lymphadenectomy is an integral part of surgical staging. The impact on survival remains unclear. With complete cytoreduction, para-aortic and pelvic lymphadenectomy seem to have an impact on disease-free survival (DFS) and overall survival (OS) rates in retrospective studies. However, in the only one randomized trial, lymphadenectomy positively affected progression-free survival rates but had no impact on OS rates [4–6]. The German AGO (Arbeitsgemeinschaft Gynäkologische Onkologie) study group has initiated a large international trial in an attempt to answer the clinically relevant question of whether systematic lymph node dissection influences the overall survival rates of patients with advanced ovarian cancer. Pending the results, lymphadenectomy is currently recommended.

However, CRS and lymphadenectomy increase postoperative complications [7]. Lymphoceles are the most frequent complications of the lymphadenectomy procedure in gynecologic cancer [8–10]. Since the 1990s, the incidence of severe morbidities after CRS has decreased, including infections, postoperative bleeding, and bowel fistulae). However, the rate of lymphoceles remains high and no clear management strategy has been established to reduce the risk.

The incidence of lymphoceles is related to the detection method of systematic screening with diagnostic imaging (ultrasound or computed tomography) according to the symptoms. Asymptomatic lymphocysts do not pose a problem and can be ignored. However, symptomatic lymphocysts can cause fever, abdominal pain, tenesmus, hydronephrosis, leg edema, and deep vein thrombosis; in addition, they can potentially postpone systemic treatment [8, 11]. Treatment of symptomatic lymphoceles includes antibiotics, needle aspiration, drainage, or surgery.

The risk factors for lymphocele development are unclear [12–14]. They may include the extent of the lymphadenectomy, the number of lymph nodes removed, the presence of metastases to the lymph nodes, body mass index (BMI), and the use of drainage. Furthermore, the effect of symptomatic lymphoceles on survival rates is not known.

The majority of previous studies reported the incidence of lymphoceles in mixed gynecological cancers with a pelvic lymphadenectomy alone [9, 12, 14]. The incidence of symptomatic lymphoceles after complete cytoreductive surgery and para-aortic and pelvic lymphadenectomy in ovarian cancer is not specifically described in the literature.

The purpose of this study was to describe the incidence, the impact on survival, and the risk factors for symptomatic lymphoceles after CRS and para-aortic and pelvic lymphadenectomy for patients with ovarian cancer.

PATIENTS AND METHODS

This retrospective study included patients with epithelial ovarian cancer who received surgical treatment in our institute from 2005 to 2011. All the patients who had undergone com-

plete cytoreductive surgery with a para-aortic and a pelvic lymphadenectomy were retrieved from our surgery database.

Patients were classified into two groups: the symptomatic lymphocele group and the control group (without lymphoceles). A 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 or drainage under ultrasound or computed tomography guidance.

The following patient characteristics were collected: age, BMI before surgery (kg/m^2), International Federation of Gynecology and Obstetrics cancer stage, histology of cancer (serous, mucinous, or other), neoadjuvant chemotherapy, adjuvant chemotherapy, and the interval (days) between surgery and the initiation of chemotherapy. Surgical data were also collected: the type of surgery (standard, radical, or supra-radical), number of lymph nodes removed, lymph node involvement, number of lymph involved nodes, and the length of the hospital stay after surgery. In the symptomatic lymphocele group, symptoms and the number of needle aspiration or drainage events were collected. In case of repeated aspiration or drainage, a cytological analysis was performed.

Patient follow-up included a clinical examination and blood marker determination every 4 months during the first 2 years, every 6 months up to 5 years, and then yearly thereafter. OS was calculated in months from the date of the diagnosis to the date of death or the last follow-up for surviving patients. DFS was calculated in months from the date of the diagnosis to the date of the first recurrence or the date of the last follow-up for patients without recurrence.

Patients had received chemotherapy according to standard protocols, with platinum-based chemotherapy most often including paclitaxel.

Surgical Treatment Details

Complete cytoreductive surgery was defined as no postoperative macroscopic residual tumor. Standard surgery included a 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, rectosigmoid resection along with resection of the reproductive organs and the pelvic peritoneum was accomplished in an en bloc retroperitoneal approach [15].

Supraradical surgery had been 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.

A systematic lymphadenectomy included pelvic and para-aortic lymph node resection. A pelvic lymphadenectomy included the removal of the common iliac, external and obturator node groups. A para-aortic lymphadenectomy was performed using a transperitoneal approach. The upper limit of the para-aortic dissection was the left renal vein. The presacral chain, paracaval chain, and intercaval aortic chain were removed.

Table 1. Patient characteristics

	Symptomatic lymphocele group (n = 54)	Control group (n = 140)	p-value
Age, median yrs (range)	53 (23–74)	56 (25–77)	.28
Body mass index, median kg/m ² (range)	24.3 (19–41)	23.6 (17–36)	.19
Hospital stay, median days (range)	14 (5–55)	12 (7–73)	.01
FIGO stage, n (%)			.5
Stage I	1 (1.8)	5 (3.6)	
Stage II	1 (1.8)	4 (2.9)	
Stage III	45 (83.3)	122 (87.1)	
Stage IV	7 (13)	9 (6.4)	
Histology, n (%)			.6
Serous	36 (66.7)	96 (68.6)	
Mucinous	2 (3.7)	8 (5.7)	
Other	16 (29.6)	36 (25.7)	
Surgery, n (%)			.08
Standard	11 (20.4)	49 (35)	
Radical	5 (9.3)	17 (12.1)	
Supraradical	38 (70.4)	74 (52.9)	
Total lymph node count, median (range)	48 (17–95)	40 (6–108)	.02
Pelvic lymph node count, median (range)	20 (7–41)	16 (0–54)	.04
Para-aortic lymph node count, median (range)	28 (6–60)	22 (0–73)	.04
Lymph node involvement, n (%)	39 (72.2)	85 (60.7)	.13
Number of lymph nodes involved, median (range)	2 (0–31)	2 (0–62)	.52
Delay between surgery and chemotherapy, median days (range)	36 (13–105)	32 (14–103)	.01
Neoadjuvant chemotherapy, n (%)	38 (70.4)	85 (60.7)	.21
Adjuvant chemotherapy, n (%)	47 (87)	121 (86.4)	.71

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

The left para-aortic chain with the inframesenteric and supramesenteric groups was removed. Hemostasis and lymphostasis were carefully performed using coagulation and clips. The pelvic and paracolic peritoneum were not closed.

At the end of surgery, a pelvic drain and a retroperitoneum drain were systematically left in place in the aortic area. For 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. Usually, drains were removed when the volume of fluid collected was less than 100 mL/day.

Statistical Analysis

The quantitative and qualitative variable results were expressed as medians and as frequency and percentage, respectively. We used the Pearson χ^2 or Fisher exact tests to compare qualitative variables. We compared quantitative variable distributions with the Wilcoxon test. To assess the association between different variables and the occurrence of symptomatic lymphoceles, we used a logistic regression analysis. Odds ratios and the 95% confidence interval (CI) were calculated.

Variables considered were age >60 years, BMI >25, neoadjuvant chemotherapy, serous histology, lymph node count >40, lymph node involvement, and supraradical surgery.

A univariate analysis was followed by a multivariate analysis. Variables in the univariate analysis had to reach a level of significance of $\leq 5\%$ to be included in the multivariate model. The significance threshold chosen for all the statistical analyses was 0.05. The Kaplan-Meier method was used to estimate the survival distribution and survival rates were compared using the log-rank test.

RESULTS

During the study period, 194 patients with epithelial ovarian cancer underwent complete cytoreductive surgery with a lymphadenectomy without macroscopic residual disease. In all, 54 patients developed symptomatic lymphoceles (28%) and 140 patients did not receive any treatment for a lymphocele (72%).

The demographic and surgical characteristics of the patients are summarized in Table 1. Patients in the symptomatic lymphocele group had undergone supraradical surgery more

often, had a more extensive lymphadenectomy, and had a longer hospital stay. Furthermore, the initiation of chemotherapy had been slightly delayed in this group.

In the lymphocele group, symptoms included pain (72%), fever (26%), ureteral compression (15%), occlusion (7%), and venous compression (2%). A total of 35% of lymphoceles were located in the abdominal area (19/54) and 65% in the pelvic area (35/54).

The median number of needle aspiration or drainage events was 2 (range, 1–15). The median time from surgery to the first aspiration or drainage was 30.5 days (range, 9–260). Percutaneous transcatheter ethanol sclerotherapy was performed in three cases. Surgery to remove lymphocyst was required in four cases (7%). Carcinoma cells were never diagnosed at the cytological analysis.

In the univariate analysis, supraradical surgery and the removal of ≥ 40 lymph nodes were significantly associated with the risk of a symptomatic lymphocele occurring postoperatively (Table 2). The multivariate analysis showed that only supraradical surgery was significantly and independently associated with the risk of a symptomatic lymphocele occurring (OR = 2.04, 95% CI: 1.04–4.01; $p = .04$). This was not the case when ≥ 40 lymph nodes were removed (OR = 0.99, 95% CI: 0.97–1.00; $p = .12$).

The median follow-up of the study was 24.8 months (range, 1–74 months). In the lymphocele and the control groups, median follow-up times were 26.0 months (range, 2–74 months) and 24.7 months (range, 1–72 months), respectively.

DFS and OS times were not significantly different between the two groups. Median DFS times were 2.1 and 2 years in the symptomatic lymphocele group and the control group, respectively. Two-year DFS rates were 54% (95% CI: 39%–68%) in the lymphocele group and 48% (95% CI: 38%–58%) in the control group (Fig. 1). There was no significant difference between the two groups (log-rank $p = .65$). Two-year OS rates were 90% (95% CI: 76%–96%) for the lymphocele group and 88% (95% CI: 81%–93%) for the control group (Fig. 2). There was no significant difference between the two groups (log-rank $p = .70$).

DISCUSSION

Lymphoceles occur frequently after gynecological surgery, in up to 60% of cases [8, 10, 12]. Most lymphoceles are asymptomatic and regress spontaneously [12]. Lymphocysts often occur after a pelvic lymphadenectomy and cervical or endometrial cancer [9, 12, 14, 16]. In ovarian cancer, the incidence of lymphoceles varied considerably according to the rate of lymphadenectomies and the extent of surgery. In a study by Morice et al., the rate of symptomatic lymphoceles was 26% in a population of 80 patients with ovarian cancer or cervical cancer treated with a pelvic and a para-aortic lymphadenectomy [8]. In an equivalent study, Chereau et al. described 7% of symptomatic lymphoceles in a population of 143 patients with ovarian cancer, of whom 59% had para-aortic lymphadenectomy and 71% had complete debulking surgery [17].

A study by Chi et al. required only three drainage events for infected or uninfected collections after 141 extensive upper abdominal surgical procedures for patients with advanced ovar-

ian cancer. However, a para-aortic lymphadenectomy was performed in only 33% of cases [18]. In our study, all patients underwent complete surgery and an extensive lymphadenectomy. During a complete para-aortic lymphadenectomy, most of the lymphatic efferent vessels in the lower part of the para-aortic area converge to form the right and left lumbar trunks, which join the cisterna chyli on the posteromedial side of the abdominal aorta. Damage to lymphatic vessels and trunks during surgery leads to lymphorrhea. A lymphocele is a collection of lymph fluid that appears typically within 8 weeks after surgery [12, 19]. An extensive lymphadenectomy and multiple surgical procedures can explain the high rate of symptomatic lymphoceles in our study.

In the literature, several factors are believed to promote the occurrence of lymphoceles: high BMI, the extent of the lymphadenectomy, the number of lymph nodes removed, the presence of lymph node metastases, and the absence of ligation of lymph vessels [9, 11, 12, 16]. However, none of these factors were proven to be independent risk factors. In our study, variables such as a BMI $> 25 \text{ kg/m}^2$, a lymph node count > 40 , and lymph node involvement were not independently significant. (We chose 40 lymph nodes as an arbitrary cutoff point according to our median lymph node count.)

Supraradical surgery was the only one independent risk factor for the occurrence of symptomatic lymphoceles. Supraradical surgery can disturb peritoneal absorption properties due to the extensive peritonectomies required to achieve macroscopically complete surgery and the formation of postoperative adhesions. Furthermore, inflammation can increase these phenomena and thus contribute to lymphorrhea [20].

The impact of lymphoceles on the survival times of patients with ovarian cancer is unknown. Delayed chemotherapy is feared. Repeated aspiration or drainage events and infectious complications could disrupt treatment and exert an adverse impact on survival. Despite negative cytology, there is concern that lymphoceles may be the first symptom of recurrence. In our study, delays in the initiation of chemotherapy were significantly higher in the lymphocele group. Unlike that observed in a cervical carcinoma study, the start of chemoradiation therapy was not delayed by lymphoceles after a laparoscopic para-aortic lymphadenectomy [21]. However, according to our results, symptomatic lymphoceles had no impact on survival. DFS and OS rates were equivalent in both groups.

There are a number of limitations inherent to our study design that must be acknowledged. The main drawback of our study is that we maintained routine retroperitoneal drainage in place in the pelvis and abdomen. Drains are considered to be foreign bodies, which contribute to inflammation and increase lymphorrhea [22]. Paradoxically, prophylactic drainage does not prevent lymphocysts but induces iatrogenic morbidity by increasing the incidence of symptomatic lymphocysts [8, 14, 22]. However, the population of patients with advanced ovarian cancer in the studies by Benedetti-Panici et al and by Morice et al was clearly smaller than the group in our study.

Cytoreductive surgery with frequent peritoneal and digestive resections performed as well as lymphadenectomy is very specific. Data concerning drainage are poor in such

Table 2. Univariate analysis of the association between variables and the occurrence of symptomatic lymphoceles

	Symptomatic lymphocele group (n = 54)	Control group (n = 140)	p-value	Odds ratio	95% confidence interval
Age >60 years	15 (27.8)	38 (27.1)	.93	0.97	0.48–1.96
Body mass index >25	25 (46.3)	51 (35.7)	.22	0.67	0.36–1.27
Neoadjuvant chemotherapy	38 (70.4)	85 (60.7)	.21	1.54	0.78–3.02
Serous histology	36 (66.7)	96 (68.6)	.95	0.98	0.5–1.91
Lymph node count >40	35 (64.8)	65 (46.4)	.02	2.13	1.11–4.07
Lymph node involvement	39 (72.2)	85 (60.7)	.13	1.68	0.85–3.38
Supraradical surgery	38 (70.4)	74 (52.9)	.03	2.12	1.08–4.15

Data are n (%).

Figure 1. Disease-free survival rates for patients with ovarian cancer in the symptomatic lymphocele group versus the control group (no lymphocele).

cases. A randomized study aimed at determining the usefulness of drainage in radical and supraradical surgery would be of interest. We therefore continued to use systematic drainage to keep an eye on the risk of hemorrhage and anastomotic leakage following cytoreductive surgery when frequent peritoneal and digestive resections were also performed with lymphadenectomy.

Another weakness is the lack of data on the albumin level. Protein loss from plasma with lowered oncotic pressure could increase leakage of lymph fluid and the occurrence of lymphocysts [23]. Furthermore, a low albumin level could increase postoperative morbidity due to infection [24, 25].

In conclusion, lymphoceles are frequent postoperative complications after cytoreductive surgery for patients with ovarian cancer. Supraradical surgery seems to be an indepen-

Figure 2. Overall survival rates for patients with ovarian cancer in the symptomatic lymphocele group versus the control group (no lymphocele).

dent risk factor for the occurrence of symptomatic lymphoceles. These moderate complications do not reduce overall and disease-free survival rates for these patients. Nevertheless, further studies are needed to reduce the risk of lymphoceles in such patients.

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