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Lymphocele following Cytoreductive Surgery and Hipec for locally Advanced Ovarian Cancer

Antonios-Apostolos K Tentes* and Dimitrios Kyziridis

Abstract

Background and Aim: Lymphocele is a frequent complication of ovarian cancer. This study attempts to investigate the incidence of lymphocele after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).

Methods: Clinical and pathologic variables were correlated to the formation of lymphocele in patients with ovarian cancer who underwent CRS in combination with HIPEC.

Results: In 148 women treated with CRS plus HIPEC, giant lymphoceles were found in 20 patients (13.5%) and asymptomatic lymphoceles in 37 patients (25%). Lymphoceles were more frequently formed in patients a) with complete or near-complete cytoreduction (p=0.008), b) with abdomino-pelvic lymph node dissection (p=0.017), c) with a PCI=14-20 (p=0.005), d) with infiltrated large bowel lymph nodes (p=0.026). The abdomino-pelvic lymph node dissection (p=0.017, 95% CI=0.205-0.854) and the infiltrated large bowel lymph nodes (p=0.027, 95% CI=0.222-0.912) were indicated as independent variables for lymphocele formation.

Conclusions: The number of patients treated with CRS and HIPEC complicated with lymphocele formation does not appear to differ from the number of patients treated with conventional cytoreduction. The independent variables of lymphocele formation are the extent of lymph node resection and the infiltration of the resected large bowel lymph nodes.

Keywords: Ovarian cancer; Cytoreductive Surgery; HIPEC; Lymphocele.

Introduction

Lymphocele is a complication experienced by approximately 1-60% of patients who undergo pelvic surgery [1-3]. Lymphoceles are frequently formed after gynecological, urological, rectal surgery associating pelvic or abdominopelvic lymph node dissection [4] or even after renal transplantation [5]. They usually develop 3 to 8 weeks after surgery, although some are formed one year after initial surgery [1]. Most lymphoceles are small in size and asymptomatic, often incidental findings in routine follow-up that regress spontaneously [7]. In contrast, large lymphoceles are usually found in 5-18% of the patients, are symptomatic, prolong hospitalization, and delay adjuvant therapy [7]. The large lymphoceles may compress adjacent structures (ureter, urinary bladder, colon and rectum, or even large vessels), cause hydronephrosis, urinary urgency, pain, abdominal discomfort, and pulmonary insufficiency but the most severe complications are infection, micturition, resumption of bowel movement, pain, lymphedema, or leg swelling [7-9].

Pelvic and para-aortic lymph node (abdomino-pelvic) dissection is part of staging and treatment for gynecologic malignancies with controversial therapeutic benefit. The results of the LION study has demonstrated that pelvic and para-aortic lymph node dissection does not offer survival benefit to all ovarian cancer patients [10] and have influenced the new French recommendations which accept that systematic lymphadenectomy is no more recommended always [11]. Even if systematic lymphadenectomy is not routinely performed as part of the locally advanced ovarian cancer

Affiliation:
Euromedica Kyanous Stavros, Peritoneal Malignancy Program, Viziis 1 Thessaloniki, 54636, Greece

***Corresponding author:**

Antonios-Apostolos K Tentes, Euromedica Kyanous Stavros, Peritoneal Malignancy Program, Viziis 1 Thessaloniki, 54636, Greece.

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treatment, extensive cytoreduction with lymphadenectomy of other viscera is very frequently part of surgery resulting to lymphocele formation. Low anterior resection of the rectum is part of pelvic peritonectomy procedure which is very frequently performed in ovarian cancer. Lymphocele does not usually complicate typical low-anterior resection of the rectum. The patients are at great risk to form lymphocele if low-anterior resection is performed with resection of the pelvic peritoneum combined with intraperitoneal hyperthermic chemotherapy. The purpose of the study is to report the incidence and the treatment of lymphoceles in patients with gynecologic malignancies who undergo extensive cytoreductive surgery (CRS) in combination with hyperthermic intraperitoneal chemotherapy (HIPEC), and review of the literature.

Materials and Methods

The files of the patients with locally advanced ovarian cancer who underwent CRS in combination with HIPEC from July 2018 until July 2024 were retrieved. The data were retrospectively collected in a prospectively maintained database and analyzed. The patients' age, the performance status (PS), the ASA (American Society of Anesthesiologists) stage, the tumor volume (TV), the extent of previous surgery (PSS), the extent of peritoneal carcinomatosis (PCI), the completeness of cytoreduction (CC-score), the number of peritonectomy procedures (PP), the HIPEC procedure, the administration of intravenous chemotherapy concomitant to HIPEC, the estimated blood loss (BL), the number of the transfused blood units during surgery (BU), the number of the transfused fresh frozen plasma units (FFP), the duration of surgery (DS), the complications (morb), the number of the resected lymph nodes, the number of the resected and infiltrated lymph nodes of the retroperitoneal area- of the large bowel-of remote sites, the histopathologic type of the tumor, and the degree of differentiation (G) were all recorded in detail.

The performance status was assessed according to Karnofsky performance scale. Implantations with maximal diameter > 0.5 cm were assessed as large-volume tumors and those with maximal diameter < 0.5 cm as small-volume tumors [12]. The blood loss was estimated in ml. The duration of surgery was estimated in minutes. The standard peritonectomy procedures included greater omentectomy with or without splenectomy, lesser omentectomy, right and left subdiaphragmatic peritonectomy, right and left parietal peritonectomy, pelvic peritonectomy, and cholecystectomy with or without resection of the omental bursa. Right colectomy, subtotal colectomy, segmental intestinal resection, subtotal or total gastrectomy, and distal pancreatectomy were other visceral resections than those included in standard peritonectomy procedures that were considered separately as additional peritonectomy procedures.

Maximal abdominal exploration was possible through a midline abdominal incision from the xiphoid process to the symphysis pubis. The PSS was estimated according to previous surgical reports. The tumor volume was evaluated after complete lysis of the adhesions and the extent of peritoneal carcinomatosis was estimated using the peritoneal cancer index (PCI). The completeness of cytoreduction was assessed using the CC-score after the completion of surgery. CC-0 surgery was considered complete cytoreduction and CC-1 surgery as near-complete cytoreduction [12]. Standard peritonectomy procedures were always used for cytoreduction [13,14]. The gall-bladder was routinely removed even if there were no visible implants on its surface. Abdomino-pelvic (pelvic and para-aortic) lymph node dissection was performed after cytoreductive surgery. Abdominal lymphadenectomy included the resection of the entire tissue above and between the aorta and the inferior vena cava below the left renal vein, at the right side across the right ureter, the right major psoas muscle, and the ascendind colon, at the left side across the mesentery of the descending and the sigmoid colon, the inferior mesenteric vessels, and the left ureter, as well as the mid-common iliac level below the bifurcation of the aorta. Pelvic lymphadenectomy included the resection of the common-external and internal iliac vessels, the obturator, and the pre-sacral lymph nodes.

After tumor resection and before the reconstruction of the alimentary tract, HIPEC was performed for 90 min at 42.5-43^{0}C using the open abdominal (Coliseum) technique. The skin edges of the abdominal cavity were adequately elevated in order to contain >3 liters of prime solution. A heater circulator with two roller pumps, one heat exchanger, one reservoir, an extracorporeal system of two inflow and two outflow tubes, and 4 thermal probes was used for HIPEC (Sun Chip, Gamida Tech, Paris, France). The prime solution of 2-3 liters of normal saline or Ringer's lactate was instilled rapidly, and as soon as the mean abdominal temperature reached 40^{0}C, the cytostatic drugs were administered in the abdomen. Cis-platin (50mg/m^2) combined with doxorubicin (15mg/m^2) was used for 90 min in HIPEC in addition to ifosphamide (1300mg/m^2), and mesna (260mg/m^2), which were administered IV.

The continuity of the gastrointestinal tract was reconstructed after the completion of HIPEC. Proximal stoma defunctioning was always performed in those cases in which more than two gastrointestinal anastomoses needed to be protected.

All patients remained in the ICU for at least 24 hours. The complications were recorded in detail and their severity was evaluated according to Clavien-Dindo classification [15]. All the resected specimens were histopathologically examined in detail and all patients were scheduled to receive adjuvant chemotherapy one month after surgery.

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All patients were followed-up every 3 or 4 months during the first year after surgery and every 6 months later. Follow-up included physical examination, hematologic-biochemical examinations, tumor markers (CEA, CA-125), thoracic and abdominal imaging (CT-scan, or MRI, or PET-CT scan). The recurrences and the sites of recurrence were recorded in detail. The disease-free survival was estimated as the time from initial surgery until the time of recurrence. The overall survival was estimated as the time from initial diagnosis until the time of death or until the time of the last examination.

Statistical analysis

Statistical analysis was possible using SPSS (Statistical Package for Social Sciences, version 17). The proportion of patients with a given characteristic was compared by chi-square analysis or by Pearson's test. Logistic regression analysis was used to identify the independent variables of lymphocele formation. A p value < 0.05 was considered statistically significant. All patients signed an informed consent. The Ethical Committee of the Hospital approved the publication of the study.

Results

The files of 148 women, treated from 2018 until 2024, with locally advanced ovarian cancer were retrieved and analyzed. No patient was lost during follow-up. Lymphoceles were found in 57 patients (38.5%). Giant lymphoceles were identified in 20 patients who comprise 13.5% of the total. During the same period asymptomatic lympoceles were identified in 37 patients (25%). The clinical characteristics of the patients are listed in table 1.

Table 1: Clinical characteristics.

Variable	No (lower-upper limit)	%
Age (mean)	60.6+-11.3 (22-86)	
PCI (mean)	13+-8 (1-31)	
Blood loss (mean)	186+-182 (0-850) ml	
Blood units (mean)	1+-1 (0-6)	
FFP units (mean)	2+-2 (0-8)	
Hospitalization (mean)	13+-6 (8-61) days	
Time to diagnosis (mean)	3+-1 (2-6) months	
Peritonectomy procedures (mean)	7+-3 (1-12)	
Performance status		
90-100%	144	97.3
70-80%	4	2.7
ASA class		
I	135	91.2
II	13	8.8
PSS		
PSS-0	50	33.8
PSS-1	35	23.6
PSS-2	35	23.6
PSS-3	28	18.9
Tumor volume		
Large volume	140	95.3
Small volume	7	4.7
CC		
CC-0	88	59.9
CC-1	44	29.9
CC-2	16	4.1
CC-3	9	6.1
Lymph node dissection		
Abdomino-pelvic	83	56.1
Conventional	65	43.9
HIPEC	133	89.9
IV chemotherapy	126	85.1
Morbidity	40	27
In-hospital mortality	5	3.4
Recurrence	44	29.7
Sites of recurrence		
Distant	23	15.5
Local-regional	23	15.5
Histologic type		
Serous	131	88.6
Endometrioid	9	6.1
Mucinous	1	0,6
Others	7	4.7
Degree of differentiation		
G1	3	2
G2	8	5.4
G3	137	92.6

In 45 patients (31%) the retroperitoneal lymph nodes were found positive. In 56 patients (38.6%) the large bowel lymph nodes were positive, and in 30 patients (20.7%) distant lymph nodes were positive.

Univariate analysis has demonstrated that the age, the performance status, the ASA class, the extent of previous surgery, the tumor volume, the use of HIPEC or IV chemotherapy during HIPEC, the blood loss during the operation, the units of transfused blood or FFP, the morbidity, the number of the resected lymph nodes, the number of the infiltrated retroperitoneal lymph nodes, the number of the infiltrated remote lymph nodes, the histopathologic type of the tumor, and the degree of differentiation of the tumor did not affect the development of lymphocele ($p>0.05$).

In contrast it has been demonstrated that the formation of lymphoceles has been related to the completeness of

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cytoreductive surgery, to the type of lymph node dissection, to the extent of the peritoneal dissemination, and to the infiltration of the resected large bowel lymph nodes. Lymphoceles were more frequently formed in patients with CC-0 or CC-1 cytoreduction (p=0.008), in patients with abdomino-pelvic lymph node dissection (p=0.017), in patients with a PCI 14-20 (p=0.005), and in those with infiltrated large bowel lymph nodes (p=0.026) (Table 2).

Table 2: Univariate analysis for lymphocele formation.

Variable	Pts with lymphocele	Pts without lymphocele	P value
Performance status			
90-100%	56 (98.2%)	88 (96.7%)	0.573
70-80%	1 (1.8%)	3 (3.3%)	
ASA class			
I	50 (87.7%)	85 (93.4%)	0.234
II	7 (12.3%)	6 (6.6%)	
PSS			
PSS-0	25 (43.9%)	25 (27.5%)	
PSS-1	15 (26.3%)	20 (22%)	0.064
PSS-2	11 (19.3%)	24 (26.4%)	
PSS-3	6 ((10.5%)	22 (24.2%)	
Tumor volume			
Large volume	54 (94.7%)	86 (95.5%)	0.711
Small volume	3 (5.3%)	4 (4.4%)	
CC-score			
CC-0	28 (49.1%)	60 (66.7%)	
CC-1	26 (45.6%)	18 (20%)	0.008
CC-2	1 (1.8%)	5 (5.6%)	
CC-3	2 (3.5%)	7 (7.8%)	
Lymph node dissection			
Abdomino-pelvic	39 (68.4%)	44 (48.4%)	0.017
Conventional	18 (31.6%)	47 (51.6%)	
HIPEC	53 (93%)	80 (87.9%)	0.282
IV chemotherapy	50 (87.7%)	76 (73.5%)	0.484
Recurrence	15 (26.3%)	29 (31.9%)	0.472
Age			
<70	45 (78.9%)	77 (84.6%)	0.378
>70	12 (21.1%)	14 (15.4%)	
PCI			
0-13	25 (43.9%)	58 (64.4%)	0.005
14-20	24 (42.1%)	16 (17.8%)	
21-39	8 (14%)	16 (17.8%)	
Blood loss			
0-200ml	40 (70.2%)	63 (69.2%)	0.377
201-500ml	17 (29.8%)	25 (27.5%)	
501-850	0 (0%)	3 (3.3%)	
Transfused blood units			
0-1	51 (89.5%)	75 (82.4%)	0.291
2-3	6 (10.5%)	13 (14.3%)	
3-6	0 (0%)	3 (3.3%)	

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Transfused FFP units			0.335
0-2	32 (56.1%)	57 (62.6%)	
3-4	25 (43.9%)	32 (35.2%)	
5-8	0 (0%)	2 (2.2%)	
Morbidity	39 (68.4%)	69 (75.8%)	0.324
Retroperitoneal lymph nodes	19 (33.9%)	26 (20.2%)	0.55
Large bowel lymph nodes	28 (50%)	28 (31.5%)	0.026
Other lymph nodes	14 (25%)	16 (18%)	0.449
Degree of differentiation			0.982
G1	1 (1.8%)	2 (2.2%)	
G2	3 (5.4%)	5 (5.6%)	
G3	52 (92.9%)	83 (92.2%)	
Histopathologic type			0.564
Serous	49 (87.5%)	80 (88.9%)	
Endometrioid	4 (7.1%)	5 (5.6%)	
Mucinous	1 (1.8%)	0 (0%)	
Other	2 (3.6%)	5 (5.6%)	
No of resected lymph nodes			0.137
0-20	9 (16.1%)	24 (26.7%)	
>20	47 (83.9%)	66 (73.3%)	

Table 3: Multivariate analysis of lymphocele formation.

Variable	HR	P value	95% CI
Lymph node dissection	5.721	0.017	0.205-0.854
Large bowel lymph nodes	4.903	0.027	0.222-0.912

Multivariate analysis has demonstrated that the type of lymph node dissection (p=0.017, 95% CI=0.205-0.854) and the infiltrated large bowel lymph nodes (p=0.027, 95% CI=0.222-0.912) are independent variables of lymphocele formation (Table 3).

Discussion

Symptomatic lymphoceles are usually diagnosed earlier than asymptomatic. The mean time of diagnosis is 3.7 months for symptomatic and 5 months for asymptomatic lymphoceles [7]. A small minority of symptomatic lymphoceles develop after 10 years following pediatric reconstructive urologic procedures [16]. Asymptomatic lymphoceles are considered complications with limited clinical significance [17] in contrast to symptomatic which are usually large, compress adjacent tissues, may be infected, affect the quality of life [17-19], and require therapeutic intervention [20]. Percutaneous catheter drainage is initially the most efficient method and is almost always attempted. Alternative therapeutic methods include percutaneous fine needle aspiration, sclerotherapy, and marsupialization [20]. Infected lymphoceles may be successfully treated by percutaneous catheter drainage in combination with antibiotic administration [21].

Lymphoceles are more frequently found in the left side of the pelvis probably because there is difference in lymphatic drainage [22,23]. In our study giant lymphoceles were found in 13.5% of the patients and asymptomatic smaller lymphoceles in 25% which implies that the total proportion of patients with lymphoceles is not different from the proportion of lymphocele in patients treated with conventional cytoreduction.

Risk factors of lymphocele formation are the metastatic lymph nodes, the number of the dissected lymph nodes, the BMI, the dissection of para-aortic lymph nodes, the use of anticoagulants, the surgeon's experience, the use of pelvic drains, the ligation techniques and the hemostatic agents, the adjuvant radiotherapy, and the type of surgery (open or laparoscopic) [23-26]. In laparoscopic surgery the incidence of lymphocele formation is lower because of less tissue damage, reduced peritoneum handling and tissue bleeding, less contamination, and less postoperative adhesions. Smoking, prior abdominal surgery, and younger age are other risk factors that have been identified for lymphocele formation [27]. In one prospective randomized study it has been shown that the development of lymphoceles is not influenced by the extent of retroperitoneal lymph node dissection [2].

Titanium clipping or coagulation of the lymphatic vessels

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has been used to seal the lymphatic vessels during pelvic lymph node dissection to reduce the incidence of lymphocele development. No difference has been identified in lymphocele formation between clipping and coagulation of the lymphatic vessels [28]. Partial peritoneal closure with wide pelvic drainage in patients with laparotomic retroperitoneal lymph node dissection has been considered to reduce the incidence of lymphocele but has not been still proved [29]. Gelatin-thrombin matrix has been successfully used in sealing the lymphatic vessels after pelvic lymph node dissection and has shown to reduce the incidence of lymphocele formation [30].

Collagen-fibrin patch has been successfully used to prevent lymphocele formation [31] but the results of another similar study showed reduction of the volume drain but no difference in the incidence of lymphocele formation [32].

The purpose of cytoreductive surgery is the resection of the entire macroscopically visible tumor which is possible by performing standard peritonectomy procedures [13]. The most frequently performed peritonectomy procedures are greater omentectomy with or without splenectomy, and pelvic peritonectomy procedure. Intraperitoneal cancer cells are accumulated at the greater omentum which is the most significant site of peritoneal fluid absorption or are directed at the pelvis by gravity developing large volume tumors [33]. Greater omentectomy deprives the patient of the ability to seal surfaces that have undergone surgical manipulations and as a consequence the development of lymphoceles is easier. Pelvic peritonectomy procedure leaves widely opened the areas behind the bladder and in front of the rectum. The pelvis is another anatomic region in which lymphoceles may easily develop. In general, cytoreductive surgery combined with abdomino-pelvic lymph node resection and HIPEC leaves unprotected many anatomic structures from lymphatic drainage.

In extended peritoneal dissemination surgical manipulations will be extensively performed and the lymphatic vessels will remain unsealed and will contribute to the formation of lymphoceles. The results of our study have shown that the development of lymphoceles is related to the extent of peritoneal dissemination. Complete or near complete cytoreductive surgery usually requiring extensive surgical manipulations is another variable responsible for the formation of lymphocele. In addition, after CRS and HIPEC a small amount of the prime solution remains in the abdominal cavity and contributes to the formation of lymphoceles.

No patient has been lost during follow-up. The strength of the study is based to the fact that all patients have undergone surgery by the same surgical and anesthesiological team with the same surgical and anesthesiological principles. As a retrospective study, it includes certain biases. For example, the BMI, smoking, or the time of lymphocele formation are variables that have not been included in the analysis. The type of cytoreduction (primary, secondary or interval) has also not been included. As a consequence, the conclusions of the study cannot be reliably used. Future trials are needed to establish all the variables that are related to lymphocele formation.

Conclusions

The number of patients treated with CRS and HIPEC complicated with lymphocele formation does not appear to differ from the number of patients treated with conventional cytoreduction. The independent variables of lymphocele formation are the extent of lymph node resection and the infiltration of the resected large bowel lymph nodes.

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