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Prognostic impact of celiac lymph node involvement in patients after frontline treatment for advanced ovarian cancer

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ABSTRACT

Introduction: Completeness of cytoreduction is the most important prognostic factor in patients with advanced ovarian cancer (OC). Extensive upper abdominal surgery has allowed to increase the rate complete cytoreduction and the feasibility of resection of celiac lymph nodes (CLN) and porta hepatis disease in these patients has been demonstrated. The aim of our study was to assess the prognostic impact of CLN involvement in patients with primary advanced OC undergoing a complete cytoreductive surgery (CRS).

Material and methods: We designed a retrospective unicentric study. We reviewed data from patients who underwent CLN resection with or without porta hepatis disease resection, within upfront or interval complete CRS in the frontline treatment of advanced epithelial OC between January 2008 and December 2015. Patients were classified in two groups according to CLN status. Univariate and multivariate analyses were conducted. Survival rates were estimated using Kaplan-Meier method.

Results: Forty-three patients were included and positive CLN were found in 39.5% of them. The median disease-free survival in the group of patients with positive and negative CLN were 11.3 months and 25.8 months, respectively. In multivariable analysis, both CLN involvement and high peritoneal cancer index were independently associated with decreased disease-free survival. Computed tomography re-reading by an expert radiologist has good sensitivity for detection of positive CLN.

Conclusion: CLN involvement and high preoperative tumor burden are independently associated with decreased survival after complete cytoreduction for OC. CLN involvement is a marker of diffuse disease and an independent risk factor for early recurrent disease.

Introduction

Completeness of cytoreduction has demonstrated to have a more significant influence on survival of patients with advanced ovarian cancer (OC) than the extent of the metastatic disease present before the surgery [1]. In the last decades, there has been an evolution in the surgical approach of advanced OC. The incorporation of extensive upper abdominal procedures (UAP) has allowed to almost double the rate of optimal cytoreduction [2,3]. Celiac lymph nodes (CLN) and porta hepatis (PH) are one of the disease sites, which can hinder a complete cytoreduction. In order to improve complete cytoreduction rates, we demonstrated the feasibility with an acceptable morbidity of the resection of CLN and PH disease in patients with advanced or recurrent OC [4]. Moreover, we showed that disease in CLN in primary or recurrent OC was a

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marker of disease severity and that these patients had a worse oncologic outcome [5].

The aim of our study was to evaluate the prognostic impact of CLN involvement in a homogeneous cohort of patients who underwent a complete cytoreductive surgery (CRS) for a primary diagnosis of advanced OC (FIGO stage IIIC-IV).

Materials and methods

Patients and study design

A computer-generated search of our institution patient database was carried out to retrospectively identify all patients who underwent CLN resection with or without PH disease resection, within upfront or interval complete CRS in the frontline treatment of advanced (FIGO stage IIIC-IV) epithelial ovarian, fallopian or primary peritoneal cancer between January 2008 and December 2015 at the French Comprehensive Cancer Center, Institut Claudius Regaud – Institut Universitaire du Cancer de Toulouse, France. Institutional Review Board approval was obtained from our center.

Preoperative assessment, surgery principles and chemotherapy treatment

All the patients underwent a preoperative imaging study including a computed tomography (CT) of the chest, abdomen and pelvis. In selected cases of extra-abdominal disease suspicion, a positron emission tomography was performed.

All the surgical procedures were performed by two experienced oncological surgeons. The surgical technique of CRS was performed following Surgarbaker principles of peritonectomy [6] and the CLN and PH disease resection was carried out as we previously described [4]. The extent and distribution of the disease throughout the 13 abdominopelvic regions were evaluated with the peritoneal cancer index (PCI). The main goal of the surgery was to obtain a complete cytoreduction, evaluated using the Completeness Cytoreduction score [7]. The indication of CLN or PH disease resection was based on the intraoperative findings of suspicious lymph nodes (those measuring more than 1 cm and/or indurated at palpation) or carcinomatosis in the PH peritoneum, respectively. We used Aletti Score to quantify the surgical complexity [8] and we evaluated postoperative complications following Clavien-Dindo Classification [9].

The indication of neoadjuvant chemotherapy was based on the sum of procedures required to achieve complete cytoreduction, on medical comorbidities, and on the potential to tolerate an extensive procedure. Patients with deep infiltration of the small bowel mesentery, diffuse carcinomatosis involving large parts of the small bowel, stomach, infiltration of the duodenum or pancreas (not limited to the pancreatic tail), or more than two bowel resections required to eradicate the disease were considered for neoadjuvant chemotherapy. After three cycles of platinum and taxane-based chemotherapy, a clinical, biological and imaging evaluation of the response to chemotherapy were performed. In case of poor response or bad performance status, three additional cycles of chemotherapy where administered before the surgery. Adjuvant chemotherapy was administered, when feasible, within 2 months after the surgery with carboplatin and paclitaxel until completing a total of six cycles. In case of poor response with important residual disease, two to three cycles of chemotherapy or antiangiogenic maintenance treatment with bevacizumab were added after discussion at the tumor board. To evaluate the accuracy of an expert radiologist for the detection of CLN involvement, all the preoperative CTs a double lecture by an experienced radiologist of our center (G.B.).

Study data

Medical records were carefully examined, and patient demographic data with particular emphasis on operative records to detail the extent and distribution of the disease spread, surgical procedures, histologic data, and follow-up data were included.

Statistical analysis

Data were summarized by frequency and percentage for categorical variables and by median and range for continuous variables. Comparisons between groups were performed using the Chi-squared or Fisher's exact test for categorical variables and the Mann-Whitney test for continuous variables. Disease-free survival (DFS) was defined as the time from the date of diagnosis until relapse or death, patients alive and disease-free were censored at last follow-up news. Overall survival (OS) was defined as the time from the date of diagnosis until death, patients alive were censored at last follow-up news. Survival data were summarized using the Kaplan-Meier method with their 95% confidence intervals. Univariable analysis was performed using the log-rank test for categorical variable and the Cox model for continuous variable. Multivariable analysis was performed using the Cox model and hazard ratios were estimated with their 95% confidence intervals (CI). Sensitivity and specificity were estimated with their 95% CI (Binomial exact). All reported p values were 2-sided. For all the statistical tests, differences were considered significant at 5% level. Statistical analyses were conducted using STATA 13 (StataCorp, Texas, USA) software.

Results

During the study period, 150 patients underwent a complete CRS for frontline treatment of advanced epithelial OC. Of them, 43 (28.7%) underwent CLN resection and 22/43 (51.2%) also received PH disease resection. Metastatic involvement was identified in 17/43 (39.5%) patients. There were not significant differences in baseline characteristics between patients with positive and negative CLN, view Table 1.

Table 1. Baseline characteristics of patients with CLN resection.

All patients underwent a pelvic peritonectomy, total hysterectomy, bilateral adnexectomy, total infragastric omentectomy and pelvic and paraaortic lymphadenectomy by laparotomy. A complete cytoreduction was achieved in all of them [7]. Patients with positive CLN had a significantly higher PCI and number of affected anatomic regions. CLN involvement was also significantly associated with high scores of Surgical Complexity Score (SCS) of Aletti, large bowel resection and left diaphragm stripping.

When analyzing the different regions of PCI, even if not significant, we observed a trend toward more extensive disease in the group of patients with positive CLN, with a higher score of upper abdomen PCI and of small bowel PCI, view Table 2.

Table 2. Surgical data of patients with CLN resection.

Positive CLN were significantly associated with PH disease and paraaortic lymph node (PALN) involvement. In the same line, the number of PALN affected was higher in patients with CLN involvement, view Table 3.

Table 3. Anatomopathological findings of patients with CLN resection.

A significantly higher fluid loss (blood plus ascites) during surgery was observed in the patients with CLN involvement with a median (range) of 2300 (332–6860) ml vs. 1257.5 (300–3800) ml in patients with negative CLN, $p = 0.028$. We did not find significant differences in operative time between the patients with positive and negative CLN with a median (range) of 264 (119–522) minutes

Table 1
Baseline characteristics of patients with celiac lymph node resection.

	Overall n = 43	Negative CLN n = 26	Positive CLN n = 17	*p*-value
Age (years) median (range)	61 (22–75)	60 (22–74)	65 (48–75)	0.115
BMI (kg/m^2) median (range)	23 (16.6–37.1)	22.9 (16.6–33.8)	24 (18.8–37.1)	0.345
WHO performance status classification n (%)				
0	23 (53.5)	15 (57.7)	8 (47.1)	0.494
≥1	20 (46.5)	11 (42.3)	9 (52.9)	
Preoperative CA-125 (UI/ml) median (range)	857 (13–15000)	722.5 (13–15000)	1365 (47–3000)	0.846
Missing	7	4	3	
FIGO stage n (%)				
IIIC	36 (83.7)	23 (88.5)	13 (76.5)	0.407
IV	7 (16.3)	3 (11.5)	4 (23.5)	

CLN: celiac lymph nodes.
BMI: body mass index.
WHO: World Health Organization.
CA-125: cancer antigen 125.
FIGO: International Federation of Gynecology and Obstetrics.

Table 2
Surgical data of patients with celiac lymph node resection.

	Overall n = 43	Negative CLN n = 26	Positive CLN n = 17	*p*-value
Type of surgery n (%)				
Upfront	18 (41.9)	10 (38.5)	8 (47.1)	0.576
Interval	25 (58.1)	16 (61.5)	9 (52.9)	
Intraoperative findings				
PCI median (range)	22 (5–33)	17 (5–28)	25.5 (10–33)	**0.011**
Missing	*2*	*1*	*1*	
Upper abdomen PCI median (range)	7 (0–9)	6 (0–9)	8 (2–9)	0.157
Missing	2	1	1	
Small bowel PCI median (range)	2 (0–8)	2 (0–7)	3 (0–8)	0.098
Missing	*2*	*1*	*1*	
No. affected anatomic regions median (range)	11 (3–13)	10 (3–13)	11 (7–13)	**0.040**
Missing	2	1	1	
Ascites (ml) median (range)	200 (0–5000)	150 (0–4500)	1000 (0–5000)	0.087
Surgical procedures n (%)				
Small bowel resection	4 (9.3)	2 (7.7)	2 (11.8)	1.000
Large bowel resection	22 (51.2)	9 (34.6)	13 (76.5)	**0.007**
If large bowel resection, rectosigmoid resection [n = 22]	18 (81.8)	6 (66.7)	12 (92.3)	0.264
Multiple bowel resection	6 (14)	3 (11.5)	3 (17.6)	0.666
Right diaphragm stripping	40 (93)	23 (88.5)	17 (100)	0.266
Left diaphragm stripping	23 (53.5)	10 (38.5)	13 (76.5)	**0.015**
f diaphragm stripping, diaphragm resection [n = 40]	11 (27.5)	7 (30.4)	4 (23.5)	0.730
Liver resection	2 (4.7)	2 (7.7)	0	0.510
Cholecystectomy	17 (39.5)	10 (38.5)	7 (41.2)	0.859
Lesser omentum resection	33 (76.7)	18 (69.2)	15 (88.2)	0.269
PH resection	22 (51.2)	11 (42.3)	11 (64.7)	0.151
Splenectomy	27 (62.8)	14 (53.8)	13 (76.5)	0.133
Distal pancreatectomy	8 (18.6)	5 (19.2)	3 (17.6)	1.000
Partial gastrectomy	3 (7)	2 (7.7)	1 (5.9)	1.000
Extended peritonectomy	37 (86)	20 (76.9)	17 (100)	0.066
Glissonectomy	6 (14)	4 (15.4)	2 (11.8)	1.000
Mesentery or bowel vaporization	13 (30.2)	8 (30.8)	5 (29.4)	0.925
Partial abdominal wall resection	7 (16.3)	3 (11.5)	4 (23.5)	0.407
Aletti Score median (range)	10 (4–16)	9 (4–14)	12 (7–16)	**0.011**

CLN: celiac lymph nodes.
PCI: peritoneal cancer index.
Upper abdomen PCI: sum of 1 (right upper), 2 (epigastrium) and 3 (left upper) regions score.
Small bowel PCI: sum of 9 (upper jejunum), 10 (lower jejunum), 11 (upper ileum) and 12 (lower ileum) regions score.
PH: porta hepatis.
Extended peritonectomy: peritonectomy of more than three abdominal regions.
p-value < 0.05 was considered significant and highlighted in bold font.

and 242 (124–432) minutes, respectively; $p = 0.502$. In the same line, there were no differences in the length of hospitalization stay in the two groups with a median (range) of 22 (11–43) days in CLN positive patients vs. 18 (8–93) days in CLN negative patients; $p = 0.183$). There were no differences in major surgical complications (grade 3–5) between the two groups of patients (7/17 (41.2%) in CLN positive vs. 6/26 (23.1%) in CLN negative; $p = 0.206$).

The median overall follow-up was 61.7 months (95% CI = [44.0–81.4]). During the study period, 33 (76.7%) out of the 43 patients relapsed, 17/26 (65.4%) in the group with negative CLN and 16/17 (94.1%) in the group of positive CLN. Out of the 9 patients with metastatic lung progression, 7 had positive CLN at diagnosis, just as 4 of the 5 patients with metastatic hepatic relapse. Also, CLN were found to be involved in 5 of the 7 women who had mediastinal lymph node progression. Relapse within the 6 months after the end of the chemotherapy was significantly associated with CLN involvement, 2/26 (7.7%) in the group with negative CLN vs. 8/17 (47.1%) in the group with positive CLN ($p = 0.007$).

Table 3
Anatomopathological findings of patients with celiac lymph node resection.

	Overall n = 43	Negative CLN n = 26	Positive CLN n = 17	*p*-value
Anatomopathological findings				
Histologic subtype n (%)				
Serous high grade	33 (76.7)	19 (73.1)	14 (82.4)	1.000
Serous low grade	7 (16.3)	4 (15.4)	3 (17.6)	
Endometrioid	1 (2.3)	1 (3.8)	0	
Mixed	1 (2.3)	1 (3.8)	0	
Carcinosarcoma	1 (2.3)	1 (3.8)	0	
Chemotherapy Response Score [n = 25] n (%)				
Type 1: no or minimal tumor response	10 (40%)	4 (25%)	6 (66.7%)	0.238
Type 2: partial tumor response	10 (40%)	8 (50%)	2 (22.2%)	
Type 3: near-complete tumor response	4 (16%)	3 (18.8%)	1 (11.1%)	
Type 3': complete tumor response	1 (4%)	1 (6.3%)	0	
No. CLN removed median (range)	2 (1–6)	2.5 (1–6)	2 (1–6)	0.872
No. positive CLN median (range)	0 (0–5)	0 (0–0)	1 (1–5)	
PH confirmed disease n (%)	17 (39.5)	7 (26.9)	10 (58.8)	**0.037**
PALN involvement n (%)	31 (72.1)	14 (53.8)	17 (100)	**0.002**
No. positive PALN median (range)	3 (0–24)	1.5 (0–13)	5 (1–24)	**0.001**
> **4 positive PALN** n (%)	19 (44.2)	7 (26.9)	12 (70.6)	**0.009**

CLN: celiac lymph nodes.
Chemotherapy Response Score developed by Böhm et al.
PH: porta hepatis.
PALN: paraaortic lymph nodes.
p-value < 0.05 was considered significant and highlighted in bold font.

The median DFS for all patients was 19.4 months (95% CI = [13.3–25.8]). The median DFS in the group of patients with positive and negative CLN were 11.3 months (95% CI = [8.1–19.4]) and 25.8 months (95% CI = [18.5 – not reached]), respectively; $p < 0.001$. Fig. 1 displays the DFS curves according to the CLN status.

The median OS for all patients was 73.1 months (95% CI = [37.2 – not reached]). The median OS in the group of patients with positive CLN was 31.6 months (95% CI = [16.6–80.7]) and in the group with negative CLN it was not reached (95% CI = [48.0 – not reached]); $p = 0.007$. Fig. 1 shows the OS curves according to the CLN status.

Fig. 1. Disease-free and overall survivals according to CLN status.

In univariable analysis, we found that age, FIGO stage, neoadjuvant chemotherapy, histologic grade, presence of ascites and small bowel PCI were not associated neither with DFS nor with OS; whereas CLN involvement (HR: 3.79, p < 0.001 and 3.13, p = 0.007), PCI (HR: 1.12, p < 0.001 and 1.11, p = 0.002), upper abdomen PCI (HR: 1.34, p < 0.001 and 1.35, p = 0.007) and SCS of Aletti (HR: 1.14, p = 0.027 and 1.25, $p = 0.005$) were significantly associated with DFS and OS, respectively. Confirmed disease at the PH and number of positive PALN were significantly associated with OS and DFS, respectively (Table 4).

Table 4. Univariable disease-free and overall survival analysis.

In multivariable analysis, we included clinically relevant variables. Both CLN involvement (HR: 2.66, 95% CI = [1.14–6.21], $p = 0.024$) and high PCI (HR:1.11, 95% CI = [1.03–1.20], $p = 0.008$) were independently associated with decreased DFS, whereas number of positive PALN was not (HR: 0.97, 95% CI = [0.91–1.04], $p = 0.407$).

The sensitivity and the specificity of the re-reading of the CT by an expert radiologist in identifying positive CLN were 76.5% (95% CI = [50.1–93.2]) and 52.0% (95% CI = [31.3–72.2]), respectively. In contrast, the sensitivity and the specificity of the non-expert radiologist were 20.0% (95% CI = [4.3–48.1]) and 95.7% (95% CI = [78.1–99.9]), respectively.

Table 5 summarizes the available studies evaluating the role of CLN resection.

Table 5. Available studies assessing the role of CLN resection in patients with advanced epithelial ovarian cancer.

Discussion

Residual tumor after CRS is one of the most important prognostic factors of survival of patients with advanced OC [10–12]. Size of residual tumor has been significantly associated with decreased survival [13]. In the upper abdomen, there are some specific disease sites such as the PH, which can preclude a complete cytoreduction [13–18]. In the last decades, the use of extensive UAP in the surgical

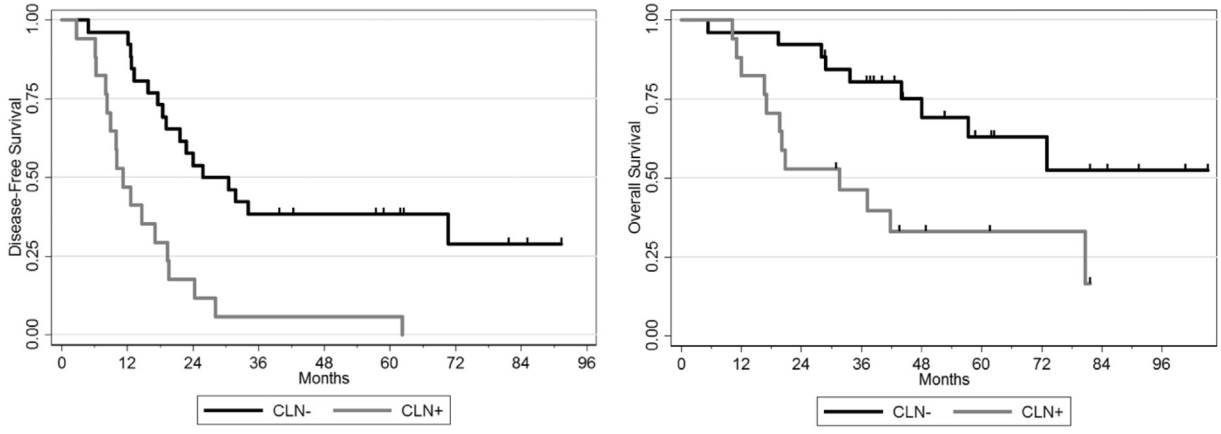

Fig. 1. Disease-free and overall survivals according to celiac lymph node status.

Table 4
Univariable disease-free and overall survival analysis.

	Disease-free survival			Overall survival		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)	1.02	[0.98–1.05]	0.330	1.03	[0.98–1.08]	0.200
FIGO stage IV	0.63	[0.24–1.64]	0.342	0.39	[0.09–1.68]	0.189
Neoadjuvant CT	1.15	[0.58–2.30]	0.687	0.98	[0.41–2.36]	0.967
PCI	1.12	[1.05–1.19]	**< 0.001**	1.11	[1.04–1.18]	**0.002**
Upper abdomen PCI	1.34	[1.13–1.58]	**< 0.001**	1.35	[1.09–1.68]	**0.007**
Small bowel PCI	1.05	[0.91–1.21]	0.508	1.05	[0.89–1.24]	0.564
Ascites (dl)	1.02	[0.99–1.04]	0.171	1.00	[0.97–1.04]	0.930
Aletti Score	1.14	[1.02–1.29]	**0.027**	1.25	[1.07–1.47]	**0.005**
High histologic grade	0.73	[0.29–1.83]	0.507	1.07	[0.29–3.96]	0.919
Positive CLN	3.79	[1.87–7.69]	**< 0.001**	3.13	[1.31–7.49]	**0.007**
No. positive PALN	1.06	[1.01–1.11]	**0.027**	1.04	[0.97–1.11]	0.242
PH confirmed disease	1.93	[0.97–3.83]	0.057	2.36	[0.99–5.64]	**0.047**

HR: hazard ratio.
FIGO: International Federation of Gynecology and Obstetrics.
CT: chemotherapy.
PCI: peritoneal cancer index.
Upper abdomen PCI: sum of 1 (right upper), 2 (epigastrium) and 3 (left upper) regions score.
Small bowel PCI: sum of 9 (upper jejunum), 10 (lower jejunum), 11 (upper ileum) and 12 (lower ileum) regions score.
CLN: celiac lymph nodes.
PALN: paraaortic lymph nodes.
PH: porta hepatis.
p-value < 0.05 was considered significant and highlighted in bold font.

Table 5
Available studies assessing the role of CLN resection in patients with advanced epithelial ovarian cancer.

Author and year	Disease of included patients	Number of patients included in the study n	Number of patients with CLN or PH disease resection n	Number of patients with reported histopathological disease in CLN or PH n (%)	Morbidity related to CLN or PH disease resection n (%)	Prognostic outcome of patients with disease in CLN or PH
Song et al., 2011	Primary and recurrent epithelial ovarian cancer	155	11 (PH disease resection)	11 (100) with PH disease	0 (0)	median PFS 8 months (range 1–13)
Martinez et al., 2011	Primary and recurrent epithelial ovarian cancer	28	28 (CLN and/or PH disease resection)	15/26 (57.7) with CLN involvement 19/28 (67.9) with PH disease	1 (3.6)	–
Raspagliesi et al., 2013	FIGO stage IIIC-IV epithelial ovarian cancer	37	5 (CLN resection) 4 (PH disease resection)	5 (100) with CLN involvement 4 (100) with PH disease	2 (5.4)	–
Martinez et al., 2014	Primary and recurrent epithelial ovarian cancer	41	41 (CLN and/or PH disease resection)	23 (56.1) with CLN involvement	–	median PFS 9 months (95% CI [5-16]) median OS 27 months (95% CI [9-40])
Tozzi et al., 2016	FIGO stage IIIC-IV epithelial ovarian cancer	216	31 (CLN and/or PH disease resection)	31 (100) with PH disease and/or CLN involvement	0 (0)	–
Gallotta et al., 2017	FIGO stage IIIC-IV epithelial ovarian cancer	85	85 (CLN resection)	45 (52.9%) with CLN involvement	0 (0)	median PFS 16 months (95% CI [12–19]) median OS 43 months (95% CI [32–54])
Angeles et al., 2019	FIGO stage IIIC-IV epithelial ovarian cancer	43	43 (CLN resection)	17 (39.5)	0 (0)	median DFS 11 months (95% CI [8-19]) median OS 32 months (95% CI [17–81])

CLN: celiac lymph node involvement.
PH: porta hepatis.
PFS: progression-free survival.
CI: confidence interval.
OS: overall survival.
DFS: disease-free survival.

approach of OC has significantly increased the rate of optimal primary cytoreduction [2,3]. Our team, as well as other workgroups, demonstrated that resection of enlarged CLN and metastatic disease of the PH was both feasible and with an acceptable morbidity [4,19–22]. However, gynecologic surgeons are often not familiar with this kind of surgical procedure as they are uncommonly required in CRS for OC. Moreover, surgery at the PH requires high level surgical skills as it contains important anatomical structures such as the hepatic artery, the portal vein and the common bile duct. It is possible in these cases to work with an interdisciplinary team in order to achieve complete cytoreduction [20].

Incidence of CLN involvement

The real incidence of CLN involvement in patients with advanced epithelial OC is unclear and probably underestimated, as systematic hepato-celiac lymphadenectomy is not performed. In fact, CLN resection is only performed in case of suspicious bulky

lymph nodes [22]. In our series, CLN resection was performed when intraoperative suspicious CLN were found. The procedure was done in 28.7% of patients with a complete CRS. Among the patients with CLN resection, 39.5% had CLN involvement. Hence, our estimated incidence of CLN involvement is 11.3% (17/150).

Risk factors of CLN involvement

In a retrospective study, Rodriguez et al. found that patients requiring UAP due to disease spread at this location had higher preoperative disease overall volume when compared to patients that did not require this kind of procedure [23]. We found similar results in our series, as disease extension measured by the PCI and the number of affected regions was significantly associated with CLN involvement. Disease spread to the upper abdomen was also more frequent in the patients with positive CLN, and left diaphragm stripping was performed more frequently. CLN involvement was also associated with confirmed anatomo-pathological disease in the PH.

CLN involvement was significantly associated with large bowel resection and disease spread to small bowel mesentery. In a series of patients undergoing rectosigmoid resection during primary or interval debulking surgery for advanced OC, Gallotta et al. found mesenteric lymph node involvement in 47% of patients. Mesenteric lymph node involvement was associated with depth of bowel infiltration and with isolated celiac trunk or aortic lymph node recurrences [24]. Salani et al. studied the same kind of patients and found that mesenteric involvement was correlated with bowel wall involvement and tumor spread to pelvic and PALN [25]. In the same line, another workgroup found invasion of the muscularis propria and retroperitoneal lymph node metastasis significantly correlated with mesenteric lymph node involvement [26]. Even if we did not evaluate mesenteric lymph node involvement, our results also suggest an increased risk of CLN involvement when disease spreads to the bowel or the mesentery. In fact, a longitudinal pattern of ovarian tumor spread from bowel wall lymphatics through mesenteric lymph nodes and, subsequently, to the upper lymph node stations has already been described [27]. Due to the proximity of the nodes at the base of the mesentery and the retroperitoneum, mesenteric lymph nodes metastasis could spread into the retroperitoneum and ascend along the paraaortic or aortocaval group [28].

On the other hand, CLN involvement was associated with PALN involvement. In fact, in our study, all the patients with positive CLN had PALN involvement. Among the patients with CLN involvement, the 71% (12/17) had more than four positive PALN. Our results are biologically plausible as drainage from paraaortic nodes immediately below the left renal vein to the CLN has been demonstrated [29]. Lymphadenectomy in ovarian neoplasm (LION) randomized trial (NCT00712218) aimed to evaluate the impact on overall survival of systematic lymphadenectomy in patients with OC stage IIB-IV undergoing complete PDS with pre and intraoperatively clinical negative lymph nodes. Results presented at the last ASCO meeting showed that microscopic metastases were present in 56% of the patients in LNE arm. Despite this finding, there were not significant differences in OS between the two arms [30]. Our results suggest presence of occult lymph node involvement upper to the renal vein and could explain the absence of benefit of systematic lymphadenectomy in these patients.

Prognostic impact of CLN involvement

In our study, CLN involvement was associated with short-term recurrence and resistance to platin-based chemotherapy. We found a gain of DFS and OS in patients with negative CLN. These results are concordant with our previous study, in which disease in the CLN was associated to decreased survival and resistance to chemotherapy in patients with primary and recurrent OC [5]. Furthermore, CLN involvement was found to be a high-risk marker for metastatic and mediastinal lymph node progression. More than 80% of patients with hepatic or lung metastasis at recurrent disease had positive CLN.

In multivariable analysis, high PCI and CLN involvement were both independently associated with decreased DFS. Even if residual tumor has a more important prognostic impact than initial extent of tumor burden [1], our series showed that in patients with complete cytoreduction, PCI remained an independent risk factor of decreased DFS. These findings are similar to other studies. The survival benefit obtained by an optimal cytoreduction seemed to decrease with increasing initial tumor volume [31]. In a previous study, our workgroup found that complex surgical procedures involving two or more visceral resections, tumor volume and extension of the disease before surgery decreased survival rates [32].

Patients with different degree of disease extension to the upper abdomen and patients with positive CLN are both included in stage IIIC of FIGO classification. Other authors have suggested to modify current FIGO staging system [33]. We believe that FIGO stage IIIC should be subdivided depending on criteria like PCI score or CLN status in order to define a subgroup with a poorer prognosis. Due to their poor prognosis, another option would be to consider patients with CLN involvement as a FIGO stage IVB, analogously to patients with cardiophrenic lymphatic involvement, which are currently included in this subgroup stage [34].

Benefit of extensive CRS procedures in CLN positive patients remains unclear. In our study, patients with CLN involvement underwent more complex procedures with higher median Aletti SCS when compared to patients with negative CLN. There were no differences in surgical postoperative complications depending on CLN status, but the overall rate of postoperative major complications was high (13/43–30.2%). Extensive procedures have a non-negligible morbidity and can decrease patient's quality of life [2,35–38].

Patients with CLN involvement have poor prognosis even after complete CRS. Medical personalized strategies with new target therapies may be a way to improve their outcome. It would be interesting to identify these patients preoperatively to tailor the optimal surgical timing and to intensify treatment modalities. We found a good sensitivity (77%) for the detection of CLN involvement by the double lecture of the CT performed by an expert radiologist, while the sensitivity of a non-expert radiologist was poor (20%). The low specificity of the expert radiologist could be explained by the enlargement of the reactive CLN, probably due to tumoral burden.

The main limitations of our study are its unicentric retrospective design and the small sample size. However, even if CLN resection is an uncommon procedure in surgical approach of advanced OC, the population of our study is homogeneous as all patients were primary diagnosed of advanced epithelial OC and underwent a complete cytoreduction, which can allow to better assess survival of these patients. Another important strength of this study is the long follow-up of our patients.

Conclusion

CLN involvement and high PCI score are independently associated with a decreased DFS after complete CRS for OC. CLN involvement is a marker of diffuse disease and an independent risk factor for early recurrent disease. Medical personalized strategies with new target therapies may be the best option to improve survival in these patients. These findings should be confirmed in further prospective and multicentric studies.

Conflict of interest

None.

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