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Deep epigastric lymph nodes implication in patients' recurrence pattern after cytoreductive surgery in ovarian peritoneal metastases

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ABSTRACT

Introduction: Although complete cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC) offers a good prognosis in patients with peritoneal metastasis of ovarian cancer (PMOC), recurrences are quite common. These recurrences can be intra-abdominal or systemic in nature. Our objective was to study and illustrate the global recurrence pattern in patients operated for PMOC, shedding light on a previously overlooked lymphatic basin at the level of the epigastric artery, the deep epigastric lymph nodes (DELN) basin.

Patients and methods: This was a retrospective study including patients with PMOC who underwent surgery with curative-intent, from 2012 until 2018, at our cancer center, and who presented with any type of disease recurrence on follow-up. CT-scans, MRIs and PET-scans were reviewed in order to determine solid organs and lymph nodes (LN) recurrences.

Results: During the study period, 208 patients underwent CRS ± HIPEC, 115 (55.3%) presented with organ or lymphatic recurrence over a median follow-up of 81 months. Sixty percent of these patients had radiologically enlarged LN involvement. The pelvis/pelvic peritoneum was the most common intra-abdominal organ recurrence site (47%), while the retroperitoneal LN was the most common lymphatic recurrence site (73.9%). Previously overlooked DELN were found in 12 patients, with 17.4% implication in lymphatic basin recurrence patterns.

Conclusion: Our study revealed the potential role of the DELN basin, previously overlooked in the systemic dissemination process of PMOC. This study sheds light on a previously unrecognized lymphatic pathway, as an intermediate checkpoint or relay, between the peritoneum, an intra-abdominal organ, and the extra-abdominal compartment.

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1. Introduction

Ovarian cancer (OC) is the most common cause of gynecological cancer-associated death in women worldwide [1]. Patients with early stage OC present with few symptoms, and approximately 80% of them present with advanced stages of the disease at diagnosis, with a 5-year survival rate of <50% [2]. Classically, these patients have peritoneal metastases with ascites, which is reported as peritoneal carcinomatosis on morphological abdominal imaging. Current standard treatment consists of a combination of complete cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC) and adjuvant platinum- and taxane-based intravenous chemotherapy [3]. Upfront CRS is preferred, but interval CRS with perioperative chemotherapy has been shown to yield similar outcomes and is reserved for patients with extensive peritoneal disease, allowing for a decrease in post-operative complications [4]. Local and systemic recurrences are common, with 75% involving the peritoneum (40% peritoneum-only), 38% nodal metastases, and 8% isolated distant metastases, leading to poor prognosis, with a median DFS and OS of 10–57 and 22–64 months, respectively [1,5,6].

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The intra- and extra-abdominal lymphatic systems have been reported to play a major role in disease dissemination, influencing the pattern of recurrence and outcomes of patients with OC [4]. Clinically, patients with advanced OC without pelvic and retroperitoneal lymph nodes (LN) on initial imaging do not benefit from systemic pelvic and para-aortic lymphadenectomy. However, patients with suspected pelvic and/or retroperitoneal LN still benefit from a significant 16% gain in 5-year survival, with a median OS of 103 months in the lymphadenectomy group versus 84 months in patients without lymphadenectomy [7–9].

In peritoneal carcinomatosis, two major lymphatic pathways of systemic dissemination, from the intra-abdominal to the extra-abdominal compartment, have been reported: the *trans*-diaphragmatic and retroperitoneal pathways, both leading to the cardiophrenic angle LN (CPALN) described by Elias et al. and/or to the hiatal LN [10–12]. Recently, a new intra-abdominal lymphatic pathway has been reported as a potential relay for tumor cells between the peritoneum and the extra-abdominal compartment, known as the deep epigastric LN (DELN), along the inferior epigastric artery. This anterior retroperitoneal route has been described in patients with colorectal (CRC) and ovarian cancer, presenting with peritoneal metastases (PM), and is considered an additional drainage basin for the peritoneum [13,14]. Its implication in patients' recurrence patterns after cytoreductive surgery for PMCRC was previously illustrated, but never in PMOC [15]. Globally, the mechanism of systemic dissemination from peritoneal metastases remains poorly understood.

The objective of our study was to evaluate the global recurrence pattern of patients with PMOC treated with CRS ± HIPEC while focusing on the newly described DELN basin.

2. Patients and methods

2.1. Study design and population

This retrospective study included patients treated for PMOC with curative intent (CCR-0/R1) by CRS ± HIPEC from 2012 to 2018 at our comprehensive cancer center, Institut Jules Bordet, who presented with any type of disease recurrence on follow-up. All patients treated for PMCRC were followed up systematically, including clinical examination with a CT scan and a blood test, every three months for the first 2 years, every four months from the third to the fifth year, and once a year thereafter. Patients suspected of recurrence on CT underwent ^{18F}FDG-PET/CT. This study was approved by the ethical committee of the Institut Jules Bordet (CE3405).

2.2. Imaging modalities and imaging review

All CT scans of the patients included in the study were reviewed to identify recurrent metastatic sites and enlarged LNs in the whole body. The CT scans reviewed were those through which recurrence was diagnosed before any chemotherapy was initiated, and not during an inflammatory event (intestinal occlusions, or any other infectious processes).

Two senior radiologists and one surgeon retrospectively reviewed the CT images. The reviewers were aware that all patients had recurrent OC after CRS but were blinded to their clinical data, official CT reports, pathological findings, and each other's findings. MRI and/or FDG scans were performed in patients with suspected metastatic lesions to confirm disease recurrence and/or detect systemic, extra-abdominal metastatic disease.

The array of CT features evaluated included all metastatic sites in two categories: radiological lymphatic basin involvement and radiological organ recurrences. In patients with radiological LN involvement, we re-assessed the enlarged LNs in nine different locations: the intra-abdominal compartment basins: posterior retroperitoneal LN (RPLN), anterior retroperitoneal or deep epigastric LN (DELNs), anterior thoracic or cardiophrenic angle LN (CPALNs), and extra-abdominal compartment basins (axillary, clavicular, cervical, inguinal, internal mammary, and mediastinal LN). The criteria used to define an LN as suspicious for malignant involvement were clustered distribution, round shape, heterogeneous texture, irregular margins, extracapsular spread, ill-defined borders, degree of necrosis, microcalcifications, ring enhancement, and size: cervical LNs >10–15 mm, chest >10 mm, abdomen and pelvis > 8–10 m [16], and DELNs and CPALNs > 7–10 mm [17]. For organ-based recurrences, two subgroups were used: intra-abdominal organ metastases and distant organ metastases.

2.3. Statistical analysis

A descriptive analysis was performed to show the proportion of involvement of each organ and lymphatic basin in PMOC recurrence. A global pattern of recurrence was devised and illustrated for better and easier interpretation. The clinical, demographic, and histopathological characteristics of the patients were calculated. The median PCI, OS, and DFS were calculated for the recurrence population and for each category of patients with respect to recurrence sites. DFS was defined as the interval between CRS and recurrence, and OS as the interval between the diagnosis of PMOC and death.

3. Results

3.1. Whole population characteristics

Between 2012 and 2018, 208 patients presented with PMOC at our institution and were operated on with curative intent using CRS ± HIPEC. Table 1 summarizes the characteristics of the entire population. The median age of the patients was 61 years [19]. Most patients had FIGO stage III (147, 70.7%), and the majority underwent neoadjuvant chemotherapy before CRS (142, 68.3%). The most common histological type of OC was serous (177, 85%), and 70.2% of the patients had poorly differentiated tumor pathology. HIPEC was performed in 23 patients (11.1%) and the median CRS time was 322 min. The median OS was 68 months [59.1–76], with 1-, 3 and 5-years OS of 95%, 77.9%, and 58%, respectively. The median DFS was 22 months [18.6–25.4], with 1-, 3 and 5-years DFS of 72.7%, 33.6%, and 22%, respectively.

3.1.1. Radiological intra- and extra-abdominal solid organs' recurrence

After a median follow-up period of 81 months [71,6–90.3], 115 patients (55.3%) presented with recurrence (Table 2). Ninety-six (83.5%) patients had intra-abdominal organ recurrence (86 patients (74.8%) intra-abdominal only and 10 patients (8.7%) had combined intra-/extra-abdominal recurrences), 29 (25.2%) had distant organ recurrence (19 patients (16.5%) extra-abdominal-only). Table 2 details the characteristics of the patients presenting with recurrences according to site: organs and lymphatic basins. The most common site for intra-abdominal organ recurrence was the peritoneum (78.3%), particularly the pelvis (47%), followed by the liver (43.5%) and spleen (10%), with the lungs being the most common (16.5%). The median DFS for the recurrence group was 15 months and the median OS was 60 months.

3.1.2. Radiological intra- and extra-abdominal lymphatic basins' recurrence

Among patients with disease recurrence, 69 (60%) had radiological LN involvement on CT scan, either intra-abdominal-only (25

Table 1
Patients' pre-, intra-, and post-operative characteristics: demographic, clinical and histopathological (IQR: interquartile range; BMI: body mass index; PCI: peritoneal carcinomatosis index; NAC: neoadjuvant chemotherapy, pre-cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; CRS: cytoreductive surgery).

Variables	N (%)
Median Age [IQR] *in years*	61 [19]
Median BMI [IQR] kg/m^2	23.9 [6]
Median PCI [IQR]	7.5 [12]
NAC	
Yes	142 (68.3%)
No	66 (31.7%)
FIGO stage	201 (96.7%)
I	15 (7.2%)
II	12 (5.8%)
III	147 (70.7%)
IIIA	10 (4.8%)
IIIB	15 (7.2%)
IIIC	122 (58.7%)
IVa[a]	27 (13%)
Primary tumor histology	
Serous	177 (85.1%)
Other or mixed	31 (14.9%)
Degree of differentiation	
Well	32 (15.4%)
Moderate	30 (14.4%)
Poor	146 (70.2%)
HIPEC	
No	185 (88.9%)
Yes	23 (11.1%)
Median CRS time [IQR] *in min*	322 [269]
Median DFS (95% CI) *in months*	22 (18.6–25.4)
Median OS (95% CI) *in months*	68 (59.1–76)[a]

**Relative risk within the concerned category.
[a] Patients with FIGO IVa were included, with resectable peritoneal disease, and in whom CRS was complete.

patients, 21.7%), extra-abdominal-only (58 patients, 50.4%), or combined (35 patients, 27.8%).

Twelve patients had enlarged DELN on CT scan (Figs. 1 and 2), representing 17.4% of those with lymphatic recurrences. All patients with DELN (100%) had concomitant intra-abdominal recurrent metastases, with the pelvis being the most involved site in 58.3% of cases. These LN were either too small to be seen, especially when the radiologist was not particularly looking for them (Fig. 1A, B, 2A, 2B), or too large and interpreted as intra-abdominal deposits, mainly anterior abdominal wall nodules (Fig. 1C, D, 2C, 2D). The DELN was enlarged on the right side in seven patients, on the left in four patients, and one patient had bilateral LN enlargement.

The anterior retroperitoneal and mediastinal lymphatic pathways, represented by the DELN and CPALN, are involved in approximately 51% of the lymphatic recurrence basins. In the extra-abdominal compartment, the CPALN had the highest involvement proportion (33.3%), followed by the mediastinal and internal mammary basins (16 and 15%, respectively) and the axillary LN (11.6%). The global pattern of recurrence in patients with PMOC after CRS ± HIPEC is summarized in Fig. 3.

4. Discussion

Our study reports previously overlooked DELN as a metastatic site in patients with recurrent PMOC initially treated with curative-intent CRS ± HIPEC. This confirms the implication of this anterior retroperitoneal LN basin, following the epigastric vessels, as a potential lymphatic pathway for systemic dissemination from the intra-peritoneal to the extra-peritoneal space and from the intra-abdominal to the extra-abdominal compartment. The DELN basin has never been described in patients with recurrent ovarian cancer [18–24].

The pathophysiological mechanism of dissemination from the peritoneal space to the systemic compartment remains poorly understood and is of paramount importance to better understand the underlying mechanisms and different pathways of dissemination.

In our study, a radiologically enlarged DELN, reported as a suspected metastatic site on CT scan of recurrent OC, was found in 17.4% of patients, which constitutes a high proportion of involvement among other lymphatic basins. Interestingly, 100% of patients with enlarged DELN had concomitant peritoneal recurrences, as shown in our results section, Table 2. This strengthens the relationship between DELN involvement and peritoneal disease, similar to the results obtained when we studied the implications of this lymphatic basin in patients with recurrent PMCRC after CRS [15]. Although in PMCRC, the DELN was enlarged in 8% of the recurrence group versus 17.4% in PMOC, both groups of patients shared the fact that in 100% of cases with DELN involvement, the peritoneum was involved in the recurrence pattern.

The two major prognostic factors in patients with PMOC and PMCRC are PCI and completeness (CCR-0) of CRS [25,26]. Given the high morbidity associated with CRS ± HIPEC, the need for new prognostic factors to better select patients who are the most suited to benefit from this intervention is important [27]. Whether DELN basin involvement is a prognostic factor in PMOC remains to be determined. Among the different lymphatic pathways responsible for distant metastatic dissemination of PMOC, CPALNs are considered to play a central role [17,28,29]. Furthermore, CPALNs have been shown to have a high prognostic value in patients with PMCRC, for instance, as robust clinical predictors for the systemic dissemination of PM [30,31]. Investigations of the route of metastatic dissemination to these nodes are still underway. The DELN pathway offers an alternative dissemination pathway, which is a route for lymphatic drainage of the peritoneum. Instead of considering the DELN basin only as an indicator of metastatic disease, it could also be considered as an intermediate checkpoint between the peritoneal surface and the extra-abdominal compartment, in the same way as has been described for the involvement of the CPALN pathway, through diaphragmatic passage of the tumor cells into the diaphragmatic stomata [15,30].

In this study, we describe the recurrence pattern in lymphatic basins and solid organs based on morphologic imaging in patients treated for PMOC by curative CRS ± HIPEC. Whether this systemic dissemination follows certain rules, similar to the lymphatic dynamics dictating intra-abdominal seeding of peritoneal metastases, is yet to be determined. The metastatic trend might be related to the location of the primary tumor, its genetic characteristics, its stage, as well as to the location, extent and pattern of peritoneal metastases seeding.

Our study has several limitations. First, it was a retrospective study. Second, our sample size was not large enough to determine the impact of several clinical and pathological factors on the involvement of the anterior lymphatic route and the prognostic value of different variables, including DELN. However, we observed a clear relationship between peritoneal recurrence and DELN involvement. Third, the evaluation of metastatic sites is based on morphological CT-scan and has not been confirmed by histopathology. However, this is the current standard method of evaluating recurrent disease in association with other biochemical tumor markers. All patients were treated for recurrent disease, and no additional suspected metastatic sites were found on the reviewed CT-scan of patients without recurrence.

A prospective study is currently being conducted at our institution (EudraCT: 2021-003270-31) to harvest DELN in patients presenting with PMOC treated with curative intent by CRS ± HIPEC, in order to understand the relationship between the involvement of these nodes, the extent and location of peritoneal carcinomatosis, and their recurrence pattern on follow-up.

Table 2
Affected organs and radiologically enlarged lymph node basins involvement in patients with recurrent ovarian cancer, after curative-intent cytoreductive surgery for peritoneal metastases of ovarian origin *(OC: ovarian cancer; PCI: peritoneal carcinomatosis index; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; LN: lymph nodes; CPALN: cardiophrenic angle LN; RPLN: retroperitoneal LN; DELN: deep epigastric LN, CI: confidence interval; IQR: interquartile range).* [a]

	Patients with Recurrent OC after CRS ± HIPEC Total N = 115 (55.3%)	Radiological LN involvement		Patients with Radiological LN involvement N = 69 patients (RR)[a]								
		No	Yes	Axillary	Clavicular LN	Cervical	Inguinal	Internal mammary	Mediastinal	CPALN	RPLN	DELN
		N = 46 (40%)	N = 69 (60%)	N = 8 (11.6%)[a]	N = 6 (8.7%)[a]	N = 3 (4.3%)[a]	N = 6 (8.7%)[a]	N = 10 (14.5%)[a]	N = 11 (15.9%)[a]	N = 23 (33.3%)[a]	N = 51 (73.9%)[a]	N = 12 (17.4%)[a]
Median PCI [IQR]	9 [13]	10.5 [11]	8 [15]	5 [8]	5.5 [9]	4 [n/a]	5 [7]	14 [16]	6 [11]	14 [17]	6.5 [15]	5 [8]
Intra-abdominal Organ Recurrence	96 (83.5%)	41 (89.1%)	55 (79.7%)	5 (62.5%)	4 (66.7%)	2 (66.7%)	6 (100%)	10 (100%)	7 (63.6%)	20 (87%)	41 (80.4%)	12 (100%)
Pelvis/Pelvic peritoneum	54 (47%)	22 (47.8%)	32 (46.4%)	2 (25%)	3 (50%)	0	4 (66.7%)	6 (60%)	2 (18.2%)	13 (56.5%)	23 (45.1%)	7 (58.3%)
Non-pelvic peritoneum	36 (31.3%)	16 (34.8%)	20 (29%)	2 (25%)	2 (33%)	1 (33%)	3 (50%)	5 (50%)	4 (36.4%)	7 (30.4%)	13 (25.5%)	5 (41.7%)
Liver	50 (43.5%)	21 (45.7%)	29 (42%)	2 (25%)	1 (16.7%)	0	3 (50%)	5 (50%)	3 (27.3%)	11 (47.8%)	20 (39.2%)	4 (33.3%)
Spleen	9 (10%)	7 (15.2%)	5 (7.2%)	0	0	0	2 (33.3%)	1 (10%)	0	1 (4.3%)	2 (3.9%)	2 (16.7%)
Stomach	5 (4.3%)	1 (2.2%)	4 (5.8%)	0	0	0	1 (16.7%)	0	0	1 (4.3%)	3 (5.9%)	1 (8.3%)
Adrenals	1 (0.9%)	0	1 (1.4%)	0	0	1 (33.3%)	0	0	0	1 (4.3%)	1 (2%)	0
Distant Organ Recurrence *(any site)*	29 (25.2%)	10 (21%)	19 (27.5%)	5 (62.5%)	3 (50%)	0	1 (16.7%)	3 (30%)	5 (45.5%)	4 (17.4%)	15 (29.4%)	4 (33.3%)
Lungs	19 (16.5%)	4 (8.7%)	15 (21.7%)	3 (37.5%)	3 (50%)	0	1 (16.7%)	2 (20%)	5 (45.5%)	3 (13%)	11 (21.6%)	3 (25%)
Bones	1 (0.9%)	1 (2.2%)	0	0	0	0	0	0	0	0	0	0
Breast	4 (3.5%)	1 (2.2%)	3 (4.3%)	2 (25%)	0	0	0	1 (10%)	0	1 (4.3%)	3 (5.9%)	1 (8.3%)
Brain	5 (4.3%)	4 (8.7%)	1 (1.4%)	0	0	0	0	0	0	0	1 (2%)	0
Median DFS [95%CI] (in months)	15 [13–17]	15 [10–20]	17 [14–20]	25 [14–18]	8 [0–25]	29 [19–39]	8 [0–19]	15 [0–30]	20 [17–23]	21 [10–32]	19 [14–24]	14 [4–24]
Median OS [95%CI] (in months)	60 [53–67]	69 [49–79]	55 [45–65]	87 [26–148]	38 [3–73]	66 [48–84]	55 [30–80]	43 [15–71]	55 [43–67]	54 [28–80]	57 [40–74]	64 [40–88]

[a] RR: relative risk of positivity for each lymphatic basin, within the group of patients with radiologically involved LN.

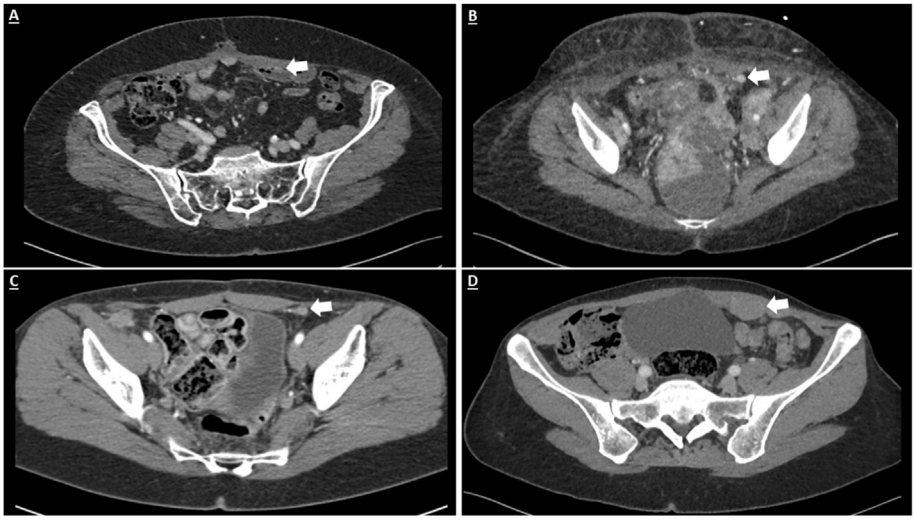

Fig. 1. Radiologically enlarged *Left deep epigastric lymph nodes* at the level of the inferior epigastric artery, as seen on CT-scan, in 4 patients presenting with recurrent ovarian cancer, in the anterior retroperitoneal compartment.

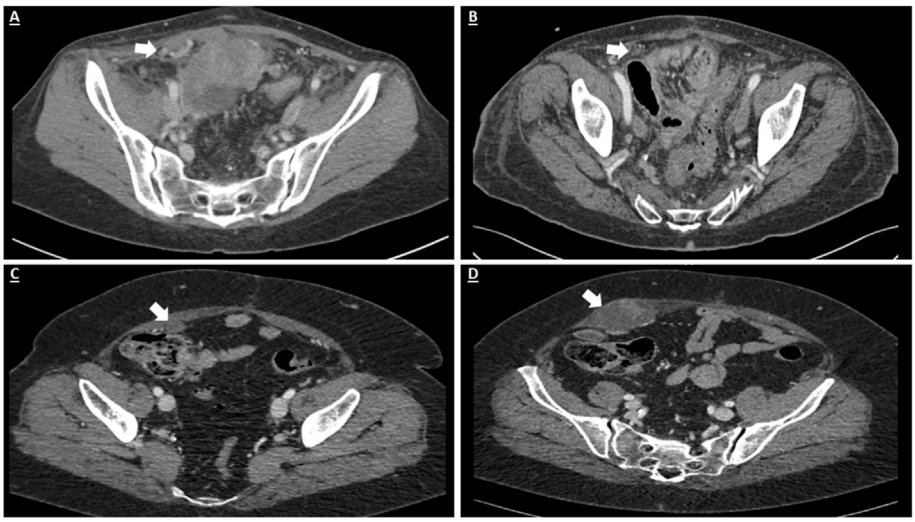

Fig. 2. Radiologically enlarged *Right deep epigastric lymph nodes* at the level of the inferior epigastric artery, as seen on CT-scan, in 4 patients presenting with recurrent ovarian cancer, in the anterior retroperitoneal compartment.

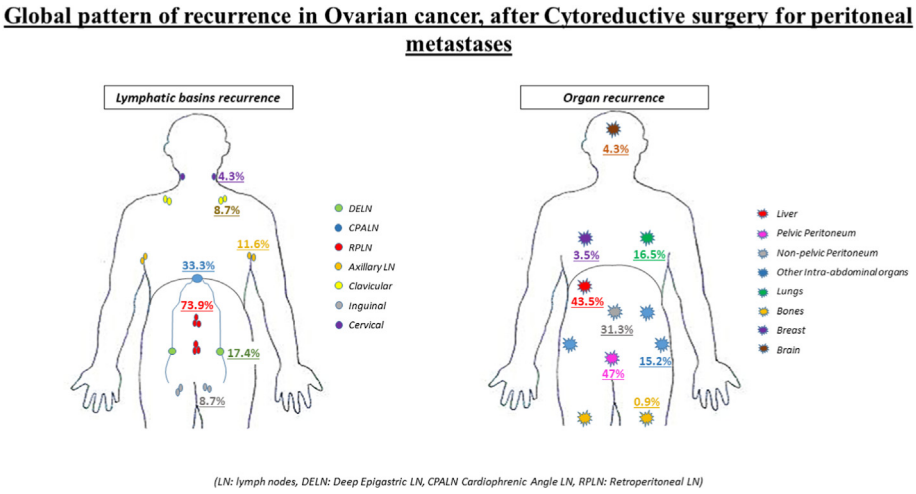

Fig. 3. Lymphatic and organ-based recurrence patterns, in patients with peritoneal metastases of ovarian cancer, after curative-intent cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy.

5. Conclusion

The pattern of recurrence observed in our study correlates with that reported in the literature. Herein, we report the involvement of a new lymphatic pathway for dissemination in patients with recurrent OC. The presence of suspected DELN in these patients was strongly associated with peritoneal recurrence.

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Data availability statement

Research data supporting this publication are available upon the Editor's request.

CRediT authorship contribution statement

Antoine El Asmar: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Investigation, Writing – original draft, Writing – review & editing. **Michael Vouche:** Data curation, Investigation, Validation, Visualization, Writing – review & editing. **Florin Pop:** Data curation, Formal analysis, Investigation, Visualization, Writing – review & editing. **Laura Polastro:** Conceptualization, Investigation, Methodology, Project administration, Validation. **Marie Chintinne:** Conceptualization, Methodology, Supervision, Validation. **Isabelle Veys:** Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization. **Vincent Donckier:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. **Gabriel Liberale:** Conceptualization, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

Authors declare no conflict of interest.

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