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Review

Current Status of Metastatic Cardiophrenic Lymph Nodes (CPLNs) in Patients With Ovarian Cancer: A Review

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Abstract. *Background: One of the most common sites of extra-abdominal disease spread of advanced stage ovarian cancer is the cardiophrenic lymph node (CPLN) region. The role and impact of extra-abdominal cytoreduction is not obvious in patients with cardiophrenic lymph node metastases. Materials and Methods: We examined the relevant and currently available literature to determine the prognostic value and management of enlarged CPLNs in ovarian cancer patients. Results: Transdiaphragmatic excision of CPLNs or via video-assisted thoracoscopic surgery (VATS) is achievable without major complications. The most common postoperative complications were pleural effusion, pneumothorax and pneumonia. On preoperative CT scan, the cut-off size of suspicious CPLNs is not uniform and is indicated as 5 to 10 mm short-axis dimension. Conclusion: CPLNs were detected in up to 60% of patients and malignancy was pathologically confirmed in 45-95% of the cases. The presence of enlarged CPLNs was found to be a negative prognostic factor, although its impact on progression-free and overall survival is not yet clarified and needs further investigation.*

Ovarian cancer is the most lethal gynecologic malignancy in developed countries (1). It is mainly due to the fact that over 75% of cases are diagnosed in advanced stages International Federation of Gynecology and Obstetrics (FIGO IIIC-IV) with significant peritoneal and/or extra-abdominal metastases (2). The most important prognostic factor is the achievement of complete macroscopic cytoreduction, which may significantly improve overall survival (OS) and progression-free survival (PFS) (3, 4). The positive impact of complete cytoreduction on median survival has been proved by a meta-analysis of 18 studies with more than 13,000 patients (5). Based on the guidelines, removal of all visible tumors by ultraradical surgery is also recommended (6-8). In support of this, the benefits of this practice have been detected in patients who had FIGO stage III and stage IV epithelial ovarian cancer (EOC) with extra-abdominal disease spread (9). Overall, 12-33% of patients had stage IV disease at initial diagnosis, and those with distant parenchymal metastases or metastatic cardiophrenic lymph nodes had a poorer prognosis compared to stage IIIC patients (10).

It is known that one of the most common extra-abdominal predilection sites of tumor spread is the group of cardiophrenic lymph nodes. According to the current 2014 FIGO classification (11), extra-abdominal lymph node metastases, including cardiophrenic lymph nodes (CPLNs), are upstaged to stage IVB as distant metastases. The complex afferent lymph drainage coming from different regions of the upper abdomen and lower mediastinum provides a metastatic spread route resulting in the enlargement of CPLNs in many abdominopelvic and thoracic malignancies, such as lymphoma, hepatocellular carcinoma, or colorectal, pancreatic, lung, and ovarian cancers (12-15). However, determining the significance of enlarged CPLNs identified on CT scan is still challenging in the clinical practice and causes difficulty in the preoperative decision-making process, even in specialized centers. In this regard, resection of cardiophrenic lymph nodes has been proposed (12, 16). The expanding literature also suggests that enlarged cardiophrenic lymph nodes suspicious for malignancy worsen survival in advanced ovarian cancer (17-19), but their correlation with poor overall and progression-free survival is not yet clarified. Another issue is the inconsistent terminology of CPLNs of the

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low anterior mediastinum: these lymph nodes have been referred to as paracardiac, mediastinal, supradiaphragmatic, retrosternal or cardiophrenic.

In order to predict the probability of complete cytoreduction, high-resolution imaging modalities, such as CT and PET/CT, are used to preoperatively assess the location and extent of tumor spread. PET/CT is more accurate in the detection of pathologic cardiophrenic lymph nodes than CT, especially if they are smaller than 1 cm in size (13). Therefore, lymph node size is a potential clinical indicator of nodal metastasis, but the optimal size cut-off for pathologic CPLNs is still unknown on preoperative imaging. It should be noted that this indicator has different values in the available studies and has never been standardized (20). In the meantime, a short-axis cut-off of 5 mm has been proposed for a normal cardiophrenic lymph node size (13, 21). According to the revised RECIST guidelines (Response Evaluation Criteria in Solid Tumors version 1.1), lymph nodes are considered to be pathologic, irrespectively of their location, when their short-axis is >10 mm (22). On the other hand, the European Society of Urogenital Radiology (ESUR) has defined pathologic cardiophrenic lymph nodes at a cut-off of ≥5 mm short-axis dimension (23). The QAS (Qualitative Assessment Scale) alternative scoring system, which calculates scores based on the size, heterogeneity, and architecture of the lymph node, has also been recommended for use (18).

Enlargement of cardiophrenic lymph nodes was reported in 5-62% of patients with advanced stage ovarian cancer, depending on the applied cut-off diameter of lymph nodes and the selected patient cohort (17, 18, 20, 24-28). Surgical resection of cardiophrenic lymph nodes is still not a routine procedure, and is performed only in a few highly specialized centers to achieve a macroscopically complete tumor resection. The procedure aims to decrease the rate of residual disease and to pathologically identify FIGO stage IV diseases by video-assisted thoracoscopic surgery (VATS) or through a subxiphoid or large transdiaphragmatic incision. According to the LION (Lymphadenectomy in ovarian neoplasms) study, there is a clear recommendation for the removal of enlarged intra-abdominal lymph nodes by cytoreductive surgery if macroscopically complete intraabdominal resection is possible (29). Even though the benefits of maximal-effort cytoreductive surgery in the abdominal compartment are well defined, the significance and management for the extra-abdominal spread of ovarian cancer remain unclear. Currently, there is no specific recommendation regarding the management of extra-abdominal cardiophrenic lymph nodes. Nevertheless, CPLN involvement should not preclude primary cytoreduction if complete cytoreduction can be achieved (25, 30).

Since the available results raise a number of questions regarding the extra-abdominal lymphatic metastases in ovarian cancer, the purpose of this review is to examine the relevant publications in terms of anatomy, characteristics, treatment, and clinical significance of metastatic cardiophrenic lymph nodes in patients with ovarian cancer.

Materials and Methods

To investigate anatomy, surgical procedures, and relevance of CPLNs in the prognosis of patients with advanced primary and recurrent ovarian cancer, PubMed and Cochrane Library were searched for English language articles published after March 2021. Our search words were the following: cardiophrenic lymph node, supradiaphragmatic lymph node, paracardiac lymph node, and ovarian cancer. We excluded articles containing mostly radiological aspects, except for those with clinical or prognostic importance. The reference lists of relevant articles were also researched. A total of 38 relevant articles were found and used as references. Two physicians (M.A., S.P.) independently carried out data extraction.

Anatomy. The cardiophrenic space is filled with adipose tissue and may contain small, visible lymph nodes. These are physiological, and usually there are less than two of them, each with a diameter of <5 mm (21). Cardiophrenic lymph nodes are between the diaphragm and the pericardium directly behind the xiphoid process of the sternum. Anatomically, CPLNs belong to the group of parietal thoracic lymph nodes often called anterior diaphragmatic, supradiaphragmatic, prepericardiac, and retrosternal lymph nodes as well (31-34).

Lymph nodes of the cardiophrenic region were classified as diaphragmatic lymph nodes and were divided into two major subgroups by Rouvière in 1932. The first group is called the anterior prepericardiac group consisting of 3 lymphoid aggregations situated on the diaphragm: a single median group lying in the retroxiphoid region, and two lateral groups behind the 7th anterior costochondral joint. These nodes drain the afferent lymphatics from certain parts of the diaphragm, the anterior part of the liver, and the anterior chest wall while emptying their content into the internal mammary chain. The second major group includes the middle and lateropericardiac (or juxtaphrenic) lymph nodes. It is called the "posterior lymphatic pathway" (35) consisting of two lymphoid tissue aggregations indicated by their position relative to the phrenic nerve: (a) right-sided aggregations are normally present, lie adjacent and usually anterior to the inferior vena cava; (b) left-sided aggregations are often absent. Their afferent lymphatics drain from various parts of the diaphragm, the pericardium, the liver, and the deep lymphatic vessels inferior to the diaphragm (iliac, para-aortic, and mesenteric), and gather the content of the superficial lymphatic vessels caudal to the umbilicus (33, 35, 36). In addition, Gray's Anatomy lists a third, posterior group of supradiaphragmatic lymph nodes that lie posteromedial to the inferior vena cava and adjacent to the esophagus, extending to the aortic hiatus of the diaphragm (37). For easier orientation, Figure 1 represents the major anatomic landmarks of the cranial surface of the diaphragm.

As it has been described by Abu-Hijleh *et al*. (38), peritoneal fluid, which may contain tumor cells, enters the subperitoneal lymphatic lacunae (a plexus of flattened terminal lymphatics) in between muscle fibers of the diaphragm, hence peritoneal fluid can pass through the stomata serving as the main drainage channels. From these lacunae, fluid enters the lymphatics through the diaphragm and drains into the parasternal lymph nodes. Negative intrathoracic pressure further stimulates lymph flow upwards towards the diaphragm.

Based on animal studies, collecting lymphatics drain primarily into the internal mammary chain (anterior route) rather than to the

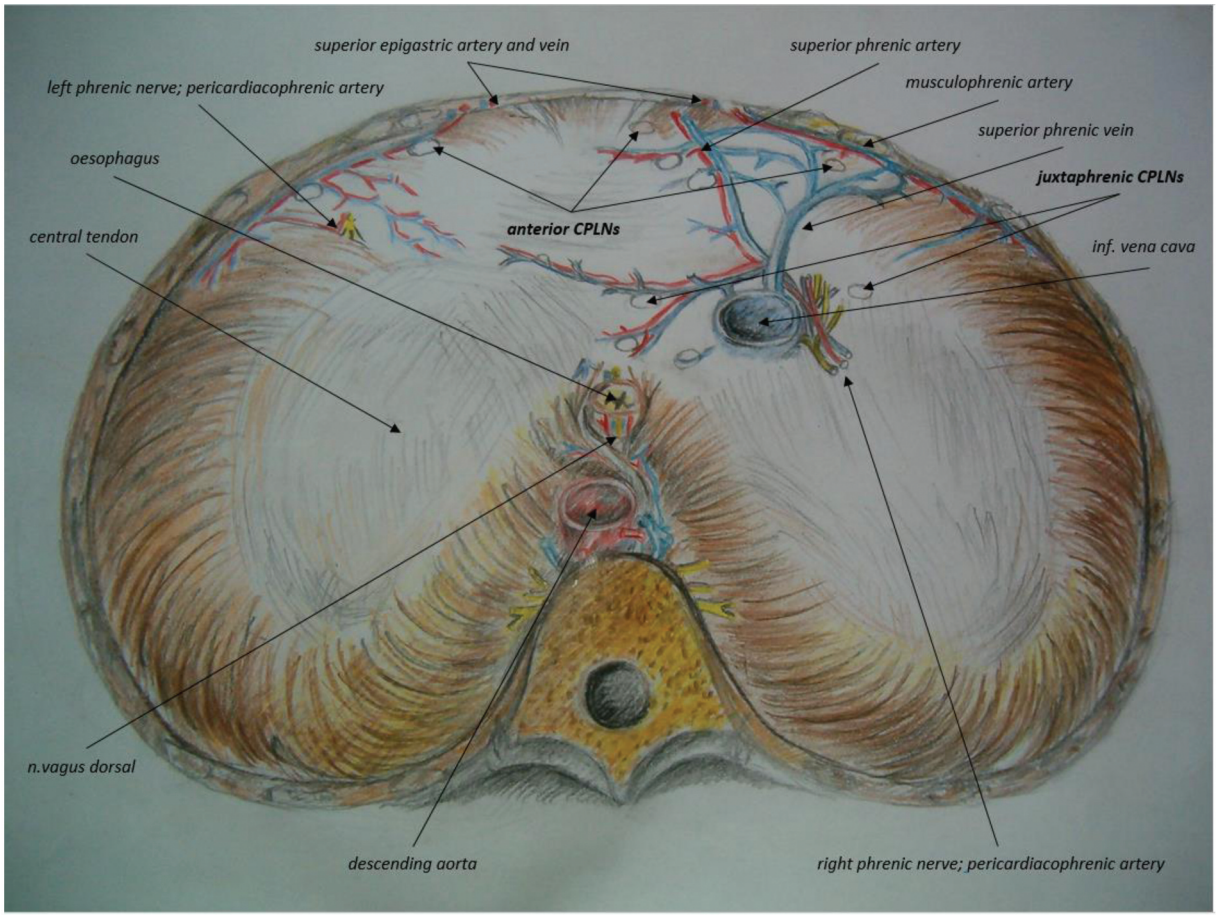

Figure 1. *Color illustration of diaphragm and related structures from a cranial view, without displaying lungs and heart.*

posterior lymphatic pathways that transport lymph to the great veins after being filtered by the mediastinal lymph nodes (38). Furthermore, a dominantly right-sided lymphatic drainage has been found in dogs, which can explain the frequently present right anterior location of metastasized cardiophrenic lymph nodes (39). As several researchers have previously described (15, 17, 25, 26, 28, 35, 40), cardiophrenic lymph nodes act as nodal stations for the lymphatic drainage of the upper abdomen (33, 36), making it obvious why CPLNs have a high predictive value for the carcinosis of this location. This predictive value was 94.6% in the study of Luger *et al*. (17).

The occurrence and location of radiologically positive cardiophrenic lymph nodes was published in the paper by Prader *et al*. (20). In their study involving 217 patients, the right anterior region was the most often affected location (in 93.5% of the cases). This observation was in line with data of other researchers who found that metastatic lymph nodes were predominantly present at this site, followed by left-sided, midline, and bilateral locations (17, 26, 27, 41, 42).

Results

The issue of enlarged and metastatic cardiophrenic lymph nodes was addressed in various ways by different authors. The existing literature describes the transdiaphragmatic procedure and the video-assisted thoracoscopic surgery as possible approaches for the resection of cardiophrenic lymph nodes (25). Certain researchers made their conclusions based only on the findings of CT or PET/CT without removing lymph nodes, whereas others performed lymph node resection by transdiaphragmatic intervention or by video-assisted thoracoscopic surgery. Currently, CT scans have a slice thickness of ≤5 mm; thus, this modality can provide a representative picture of the status of intra- and extra-abdominal lymph nodes if they are ≥5 mm, independently from other lymph node cut-off values.

Defining pathologic lymph node size and imaging characteristics indicative of metastatic disease has proven to be challenging with varying cut-offs between 5 to 10 mm in the short-axis, as these values have never been standardized. Nevertheless, for an effective treatment strategy, it is crucial to determine the features of abnormal CPLNs. McIntosh *et al*. (43) searched for the optimal threshold and defined it at 5 mm in the short-axis; this

Table I. *Studies in which removal of cardiophrenic lymph nodes was not performed.*

Authors	Patient group	Number of patients	Objective	Conclusion
Holloway *et al*., 1997 (26)	Primary and recurrent	78	Detection of enlarged CPLN on CT scan with a cut-off of >5 mm short-axis	CPLN detection rate was 28%, which is a significant adverse prognostic factor for OS and PFS.
Kolev *et al*., 2010 (27)	Primary	212	Prognostic value of enlarged CPLN in comparison with a control group of patients without CPLN enlargement	CPLN detected in 43% of all cases. The cut-off was >5 mm in the largest axis. Worse survival rates were found in patients with CPLN. Median survival without and with adenopathy was 50 and 45 months, respectively.
Hynninen *et al*., 2012 (35)	Primary	30	Detection of supradia-phragmatic LN with FDG PET/CT	CPLN detected in 43% of all cases. Supradiaphragmatic lymph node metastasis was a common finding in advanced EOC as well as in ascites. The EOC cells may permeate through the diaphragm from the peritoneal cavity to CPLNs and PSLNs.
Raban *et al*., 2015 (24)	Primary	72 (31 with CPLNs and 41 as controls without CPLN)	Prognostic value of enlarged CPLNs in comparison with control subjects without CPLN enlargement with a cut-off of >10 mm short-axis	CPLN detected in 10.5% of all cases. The presence of enlarged CPLNs showed shorter DFS and OS.
Mert *et al*., 2017 (18)	Primary	28	Prognostic significance of abnormal CPLNs in OC using preoperative CT scan with cut-offs of a) >7 mm or b) ≥10 mm short-axis	CPLN detected in 11.1% of all cases. Patients with abnormal CPLNs had worse survival rates than patients without abnormal CPLNs despite complete tumor resection.
McIntosh *et al*., 2017 (43)	Primary	88	Prognostic significance and optimal size threshold of CPLN	CPLN detected in 43% of all cases. The presence of CPLN was associated with shorter PFS and OS. Size threshold was 5 mm short-axis.
Luger *et al*., 2020 (17)	Primary	178	Prognostic value of enlarged CPLNs in comparison with control subjects without CPLN enlargement	CPLN detected in 50% of all cases. The cut-off was ≥5 mm short-axis. The presence of enlarged CPLN was associated with impaired PFS and OS.
Larish *et al*., 2020 (44)	Recurrent	27	Recurrence patterns in patients with CPLN at initial diagnosis	Patients with CPLN were more likely to experience recurrence in the thoracic region.
Oommen *et al*., 2021 (40)	Primary	42	Clinical significance of enlarged CPLN in comparison with control subjects without CPLN enlargement on preoperative CT scan with cut-offs of ≥7 mm and ≥5 mm	CPLN detected in 41.5% of all cases. The presence of enlarged CPLN showed shorter DFS. No differences in OS.
Luengas-Wuerzinger *et al*., 2021 (70)	Primary	66	Analyzing the role of the CPLN status before and after NACT with cut off >5 mm	Response to NACT can also be measured by the size CPLN in advanced ovarian cancer

CPLN: Cardiophrenic lymph node; OS: overall survival; FDG PET/CT: fluorodeoxyglucose positron emission tomography/computer tomography; PFS: progression-free survival; DFS: disease-free survival; EOC: epithelial ovarian cancer; CT: computer tomography; PSLN: parasternal lymph node; NACT: neoadjuvant chemotherapy.

value was associated with significantly shorter PFS and OS. On the contrary, Kim *et al*. (15) defined the optimal cut-off at >7 mm in the short-axis, and in their study, 86% was the positive predictive value of enlarged CPLNs. Furthermore, Hynninen *et al*. (35) believe that defining a threshold (thus separating benign from malignant) is unnecessary as lymph node metastases may be microscopic, while ascites and carcinosis can also lead to lymph node enlargement. Therefore, they recommend PET/CT in the first place for diagnostics.

Table II. *Studies in which removal of cardiophrenic lymph nodes was performed through a transdiaphragmatic resection.*

Authors	Patient group	Number of patients	Objective	Conclusion
Patel *et al*., 1999 (49)	Recurrent	5	Unusual pattern of isolated supradiaphragmatic disease	Relapse without peritoneal metastases 3-5 years after complete primary abdominopelvic resection.
Yoo *et al*., 2013 (16)	Primary and recurrent	11	Transabdominal CPLN resection instead of VATS with a cut-off of ≥5 mm short-axis	Transabdominal CPLN can substitute conventional VATS in 45% (5/11) of histologically positive CPLNs.
LaFargue *et al*., 2016 (50)	Primary and recurrent	11	Technique and perioperative outcomes of transdiaphragmatic LN resection	Transdiaphragmatic CPLN resection is achievable with minor short-term postoperative morbidities.
Prader *et al*., 2016 (28)	Primary	30	Surgical management of CPLN resection with a cut-off of ≥10 mm short-axis	CPLN detected in 15.3% of all cases. Transdiaphragmatic CPLN resection is achievable during cytoreductive surgery.
Garbi *et al*., 2017 (51)	Primary	22	To define the safety and feasibility of surgical transdiaphragmatic resection of enlarged CPLNs with a cut-off of ≥5 mm short-axis	Transdiaphragmatic enlarged CPLN resection is a safe and feasible procedure when indicated to achieve no or minimal residual tumor disease.
Salehi *et al*., 2018 (42)	Primary	24	To assess the accuracy of imaging for CPLN metastases, and to compare surgical outcomes between women with and without CPLN resection at PDS with a cut-off of >8 mm short-axis	CPLN detected in 13% of all cases. Resection of CPLN metastases is achievable. The prognostic significance of CPLN metastases is still unclear.
Lopes *et al*., 2019 (41)	Primary and recurrent	24	To evaluate the clinical outcomes after CPLN resection with a cut-off of ≥8 mm short-axis	Resection of CPLN should be performed when complete cytoreduction is achievable.
Prader *et al*., 2019 (20)	Primary	52	Prognostic impact and potential role of CPLN resection with a cut-off of ≥5 mm short-axis	CPLN detected in 62% of all cases. CPLN metastases are associated with impaired PFS and OS after macroscopically CR. The impact of CPLN resection remains unclear.
Pinelli *et al*., 2019 (52)	Primary during IDS after NACT	7	Transabdominal CPLN resection when full-thickness resection is required to achieve CR with a cut-off of ≥7 mm short-axis	CPLN detected in 57% of all cases after NACT. Intraoperative assessment is less accurate during IDS compared to PDS.

CPLN: Cardiophrenic lymph node; PDS: primary debulking surgery; IDS: interval debulking surgery; NACT: neoadjuvant chemotherapy; CR: complete tumor resection; EOC: epithelial ovarian cancer; PSLN: parasternal lymph node; LN: lymph node.

The vast majority of authors agreed that an enlarged CPLN is a prognostic factor in patients with ovarian cancer. Data from Luger *et al*. (17) and Mert *et al*. (18) showed that patients who underwent intraabdominal macroscopically complete resection and had been diagnosed with enlarged CPLN on preoperative CT scans, had shorter overall survival than the control subjects without CPLN. This difference was found to be significant by Luger *et al*. (17) for both progression-free survival (HR=2.02, 95% CI=1.14-3.55 p=0.015) and overall survival (HR=2.46, IQR=1.54-3.93, p=0.0001). A significant difference was also reported for PFS and OS by Raban *et al*. (24) who reported shorter PFS (median PFS value was 9.0 *vs*. 24.0 months, respectively; p=0.0097) in patients with CPLN, while OS was shorter as well (median OS value was 31.7 *vs*. 61.3 months, respectively; p=0.001). Patients who underwent optimal cytoreduction (<1 cm) had also been shown to have differences regarding OS according to Kolev *et al*. (27), who found a median survival rate of 55 months in patients without adenopathy and 50 months with supradiaphragmatic adenopathy. After conducting further investigations, Mert *et al*. (18) reported that in cases with intra-abdominal residual disease after surgery (0.1-1.0 cm), no significant OS differences could be found between the two study groups, irrespective of enlarged CPLNs (median OS value was 37.5 *vs*. 28.5 months; respectively; p=0.49).

In contrast to these findings, Oommen *et al*. (40) published that CPLNs detected by CT did not have an adverse effect on overall survival (p=0.272), but they negatively affected the rates of recurrence-free survival (p=0.008) after primary or interval cytoreductive surgery. In addition to this, significantly more patients with CPLN had interval surgery than patients without enlarged CPLN (61.9%

vs. 32.2%, respectively). Table I includes the details of the studies where CPLN removal was not performed.

Next, we examined those studies where cardiophrenic lymph nodes were removed by transdiaphragmatic resection (Table II). The transdiaphragmatic approach for removing enlarged CPLNs is performed at the time of abdominal diaphragm peritonectomy or full-thickness resection. If full-thickness resection is not required due to diaphragmatic infiltration, a linear ventral muscle incision is created retrosternally on the diaphragm near the CPLN of interest (subxiphoid approach). At this point, the anterior insertion of the diaphragm at the xiphoid process must be dissected and separated. It is followed by the exploration of the anterior mediastinal space when metastatic lymph nodes are grasped and extracted prior to closing the diaphragmatic defect (16, 45, 46, 47). If there is a need for full-thickness resection during intra-abdominal cytoreduction due to diaphragmatic infiltration, the pleural space has to be explored more precisely both visually and by palpation to exclude an extensive disease, such as pleural or pericardial carcinosis, or parenchymal lung disease (45). Additionally, lymph nodes located in posterior regions can also be removed by this method. These techniques require preceding hepatic mobilization, and during such interventions, a pericardial opening can rarely occur (3% of the cases) (48).

Prader *et al*. (20) found an inverse association between the size of CPLNs and the rate of complete cytoreduction. According to their data, the larger the CPLN, the lower the probability of achieving complete cytoreduction. They reported a significant difference in 5-year survival between patients who had negative CPLN and those with positive (54% *vs*. 21%, respectively; p=0.019). Comparing the cohorts of patients in whom macroscopically complete tumor resection could be achieved, the difference was even more significant: 5-year OS was 69% *vs*. 30% in CPLN negative and positive cases, respectively (p=0.009) (20). During further investigation of those 52 patients who underwent CPLN resection, no significant prognostic impact of CPLN resection could be observed compared to the control group who did not have CPLN resection prior to 2014 (20). The same result was reported by Lee *et al*. (53) who found that patients who underwent supradiaphragmatic debulking experienced no benefit in PFS and OS compared to patients who did not undergo this procedure. Pinelli *et al*. (52) published the only study that verified the accuracy and feasibility of CPLN removal during interval cytoreductive surgery after neoadjuvant chemotherapy (NACT). They found that intraoperative assessment of the samples was less accurate during interval cytoreductive surgery than in primary cytoreductive surgery.

In addition to this, video-assisted thoracoscopic surgery (VATS) is performed separately to the abdominal cytoreduction, or concurrently with the abdominal procedures. Table III shows those studies where CPLN resection happened *via* VATS, while Table IV includes studies in which CPLNs were removed both *via* VATS and through a transdiaphragmatic approach.

Thoracic surgical intervention *via* VATS requires the application of a double-lumen endotracheal tube and single-lung ventilation; the ability to manage hemodynamic shifts resulting from single-lung ventilation is also crucial. Most of the time this procedure is performed by thoracic surgeons in oncology centers in a multidisciplinary setting. The patient is placed in the lateral decubitus position with the help of an axillary roll. In the three-port technique, one port is inserted into the seventh or eighth intercostal space along the posterior axillary line for the introduction of the camera. The second port is placed into the eighth intercostal space, and the third port goes into the fourth or fifth intercostal space in the mid-axillary line (56). CPLNs are usually resected by using standard electrocauterization or a vessel-sealing device. One of the advantages of this procedure is that the pleural cavity can be explored accurately without opening the diaphragm, and this method does not only have diagnostic potential, but lesions can be removed at the same time. The only disadvantages are that the patient must be repositioned for intraabdominal surgery, and the insertion of a chest tube is inevitable (16). Juretzka *et al*. (57) recommended the use of VATS in patients with moderate to large pleural effusion prior to abdominal cytoreduction, and reported that 65% of these patients had gross intrathoracic disease identified at VATS. In line with this, Di Guilmi *et al*. (58) detected pleural disease in 57% of their patients with pleural effusion. However, in the latter case, pleural carcinosis was the most common finding and the main cause of FIGO stage IV EOC.

As it can be seen in Table V, enlarged CPLNs have been shown to predict a pathologically confirmed metastatic disease in 45-95% of patients. These patients had radiographically confirmed abnormal cardiophrenic lymph nodes and underwent surgical resection based on specific lymph node cut-off values (≥5 mm, ≥7 mm, ≥10 mm). The median CPLN diameter ranged from 7.65 to 16 mm, while the median number of removed CPLNs was between 1.5 and 3, and in general, 1 to 3 lymph nodes were removed. Enlarged metastases were suspected and pathologically confirmed cardiophrenic lymph nodes were reported in 10.5-62% of the studies. The majority of these publications revealed that the presence of enlarged CPLNs significantly correlates with the occurrence of peritoneal carcinosis, particularly with diaphragmatic involvement, and predicts poor prognosis as well (20, 26, 35, 41, 53). The peritoneal carcinosis rate reported by Cowan *et al*. (25) was 81% in patients with enlarged CPLNs. In addition, we reviewed studies in which authors found pathologically confirmed FIGO stage IVB ovarian cancer and provided PFS and OS data. These data are shown in Table VI.

Table III. *Cardiophrenic lymph nodes resection via video-assisted thoracoscopic surgery.*

Authors	Patient group	Number of patients	Objective	Conclusion
Montero *et al*., 2000 (31)	Primary	1	Case report about the first CPLN resection *via* VATS	VATS enables the accurate pathological diagnosis and intrathoracic resection of pleural and CPLN metastases. Metastatic CPLN detected in 78% of all cases.
Lim *et al*., 2009 (12)	Primary and recurrent	12	To assess the benefit of VATS in pathological diagnosis and intrathoracic cytoreduction of CPLN and pleural metastasis	
Ragusa *et al*., 2011 (54)	Primary and recurrent	2	Resection of isolated bilateral cardiophrenic angle lymph node metastases	More investigation is required to make the indication of surgery more appropriate.
Lee *et al*., 2018 (53)	Primary	10	To determine the prognostic significance of CPLN detection by PET/CT	The presence of CPLN is an unfavorable prognostic factor. The resection of CPLNs did not improve PFS nor OS.
Hamaji *et al*., 2018 (55)	Primary and recurrent	6	Experiences about thoracoscopic resection of PET/CT-positive mediastinal lymph nodes. 3/6 patients with CPLN	No perioperative or long-term mortality was noted.

CPLN: Cardiophrenic lymph node; OS: overall survival; PFS: progression-free survival; VATS: video-assisted thoracoscopic surgery; PET/CT: positron emission tomography and computed tomography.

Table IV. *Cardiophrenic lymph nodes resection via video-assisted thoracoscopic surgery and transdiaphragmatic approach.*

Authors	Patient group	Number of patients	Objective	Conclusion
Kim *et al*., 2016 (15)	Primary and recurrent	31	Prediction of optimal cut-off of CPLN metastasis using CT scan	The CPLN short axis was >7 mm with a positive predictive value of 86%. Metastatic CPLN detected in 61% (19/31) of all cases.
Cowan *et al*., 2017 (25)	Primary	54	Feasibility, safety, and clinical outcomes of CPLN resection. 48 (89%) patients underwent transdiaphragmatic resection, while 6 (11%) patients had VATS.	CPLN resection can help to identify extra-abdominal disease progression, and it is safe, feasible, and does not delay chemotherapy.

CPLN: Cardiophrenic lymph node; CT: computer tomography; VATS: video-assisted thoracoscopic surgery.

Several researchers published a low rate of complications possibly related to CPLN resection; the most common complications were of pulmonary nature (pleural effusion, pneumothorax, and pneumonia), with a prevalence rate of 7%. Accordingly, they concluded that CPLN resection is a feasible and safe technique (16, 25, 28). Regarding the duration of the CPLN procedure, a specific time of 65 minutes was given for VATS by Lim *et al*. (12), 28 minutes for transdiaphragmatic approach by Lopes *et al*. (41), and 30 minutes for transabdominal cardiophrenic lymph node dissection (CPLND) by Yoo *et al*. (16).

Discussion

Our review demonstrates that the clinical and prognostic significance of enlarged CPLNs is unclear. In this systematic review, a total of 302 patients were identified in whom CPLN resection was performed. The number of CPLN positive cases in the studies varied between 1 and 54 with data collection of 3 to 16 years, and further follow-up times were 6 to 120 months. In the published literature, progression-free survival ranged between 3 and 24 months, whereas overall survival was found to be 30 to 70.1 months.

Table V. *Studies about the pathological processing of cardiophrenic lymph nodes.*

Authors	Median diameter of CPLN in mm	Metastasis in CPLNs	Median number of removed CPLNs	Median number of metastatic lymph nodes
Lim *et al*., 2009 (12)	8.9 (range=5.3-16.1)	78% (7/9)	3 (range=1-10)	3 (range=1-10)
Yoo *et al*., 2013 (16)	10 (range=7-17)	45% (5/11)	3 (range=1-12)	1 (range=0-10)
La Frague *et al*., 2016 (50)	16 (range=2-25)	86% (18/21)	1.9 (range=1-4)	No data
Prader *et al*., 2016 (28)	10	90% (27/30)	2 (range=1-12)	1 (range=0-5)
Garbi *et al*., 2017 (51)	No data	95% (21/22)	1.7 (range=1-8)	No data
Cowan *et al*., 2017 (25)	13 (range=6-29)	94.4% (51/54)	3 (range=1-23)	2 (range=0-22)
Salehi *et al*., 2018 (42)	No data	83% (20/24)	No data	No data
Lee *et al*., 2018 (53)	7.65	80% (8/10)	2.6 (range=1.4-14.1)	No data
Prader *et al*., 2019 (20)	8.5	84.6% (44/52)	No data	No data
Lopes *et al*., 2019 (41)	14 (range=8-25)	87% (21/24)	1.5 (range=1-6)	No data
Pinelli *et al*., 2019 (52)	No data	57% (4/7)	No data	No data

CPLN: Cardiophrenic lymph node.

According to the available data, no study has been able to prove the benefits of CPLN resection in terms of overall survival or progression-free survival so far. Based on the aforementioned results, our main finding is that the enlargement of cardiophrenic lymph nodes indicates the presence of extensive tumor load and advanced lymphatic metastases. Together, these conditions have an adverse effect on prognosis. Even though several animal experiments have been conducted and radiological studies and clinical experience are available, the exact lymphatic drainage routes and tumor metastatic pathways are still not completely explored. This is particularly relevant for the connections of parietal mediastinal lymph nodes. In addition, costophrenic (middle mediastinal) and paracaval (posterior mediastinal) lymph nodes may occur as a result of different metastatic disease progression as well (32, 33, 38, 39, 59, 60). There is little information available about the two apertures of the diaphragm – the Larrey's cleft (Trigonum sternocostale sinistrum) and the Morgagni's foramen (Trigonum sternocostale dextrum) – through which ascites and tumor cells can enter the thoracic cavity (61). For this reason, it is essential to have a better understanding of the role of these metastatic pathways. As some radiological findings indicate, Hynninen *et al*. (35) also suggested that the anterior metastatic lymph route originates from the cardiophrenic lymph nodes and continues in the mammarian lymph nodes while the lateral paracardiac group empties its content into the anterior mediastinal lymphatic chain.

Macroscopically complete resection is the main prognostic and surgical factor that can be influenced in advanced ovarian cancer. Maximal-effort cytoreductive surgery and extended surgical procedures are beneficial, especially in stage IV cancer patients, in whom microscopic residual disease is linked with the best outcome (62, 63). Several studies have demonstrated that patients with optimal (<1 cm) or microscopic residual disease had better survival chances compared to those with suboptimal resection (62, 64, 65). There is increasing evidence that the presence of enlarged and suspicious cardiophrenic lymph nodes is associated with poor prognosis, lower overall and disease-free survival rates (18, 26, 27). However, the removal of metastatic enlarged CPLNs with macroscopically complete tumor resection would lead to better survival rates, theoretically. In contrast with this, the results of Prader *et al*. (20) have proved that even the resection of positive cardiophrenic lymph nodes could not result in a significant survival benefit compared to patients who did not have their positive CPLNs resected. They also indicated a 5-year survival rate of 69% in CPLN negative patients, while this number was 30% in CPLN positive patients (with complete resection).

Table VI. *Progression-free survival and overall survival in pathologically proven cardiophrenic lymph node metastases (FIGO stage IVB).*

Authors	Median PFS (months)	Median OS (months)
Yoo *et al*., 2013 (16)	24	No data
Garbi *et al*., 2017 (51)	3, 5, 8 (3 relapses)	No data
Cowan *et al*., 2017 (25)	17.2	70.1
Lee *et al*., 2018 (53)	14	31.5
Lopes *et al*., 2019 (41)	12	30

CPLN: Cardiophrenic lymph node; OS: overall survival; PFS: progression-free survival.

In view of these results, substantial questions may arise. One of the most important questions is whether there is a clear need for removing these lymph nodes, as the only accepted indication of this procedure from which we expect survival benefit is the pathologically proven diagnosis of FIGO stage IVB cancer. Without lymph node resection, a

residual tumor mass can remain after surgery, and therefore the procedure cannot be called macroscopically complete or optimal tumor resection, aggravating the prognosis. As recommended by some authors, the presence of enlarged cardiophrenic lymph nodes should not rule out surgery and CPLN removal if macroscopically complete cytoreduction is achievable. On the other hand, CPLNs tend to be an important indicator for extended peritoneal carcinosis, thus these patients should be admitted to appropriate gynecologic oncology centers (25, 28). Corresponding results show the intraabdominal residual disease having a greater prognostic impact than positive cardiophrenic lymph nodes (17, 20). Another problem may develop if metastatic CPLNs are pathologically confirmed, as mentioned in 45-95% of the cases, as it can cause a significant shift in disease staging, and thus in prognosis. Prader *et al*. (28) reported a FIGO stage shift from FIGO stage IIIC to IVB in 30% and from FIGO stage IVA to IVB in 13% of cases. This means a considerable deterioration of prognosis for patients (28). As the original FIGO stage and FIGO stage IVB do not make a difference between inguinal, axillary, and cardiophrenic lymph nodes and metastases of the abdominal wall, all of them are considered distant metastases. Overall, there is a lack of clinical relevance and prognostic accuracy (11).

Discussing this issue further, Nasioudis *et al*. (66) studied the survival rates of 11,152 patients with FIGO stage III and IV ovarian cancer, distinguishing 3 subgroups in the latter group. They found that the prognosis of FIGO stage IVB patients was similar to those who had FIGO stage III disease with pelvic or paraaortic lymph node metastases (OS was 55 and 53 months, respectively). According to their understanding, this was due to the involvement of inguinal lymph nodes. However, FIGO stage IVB patients with distant lymph node metastases had longer survival than those with distant parenchymal metastases (OS was 39 and 30 months, respectively) (66). In support of these data, the retrospective study of Ataseven *et al*. (67) revealed that FIGO stage IVB patients with abdominal wall metastases had significantly longer overall survival compared to other stage IVB patients (58 *vs*. 25 months, respectively), while the OS was similar to that of those with stage IIIC. Moreover, the same authors found that OS of patients with FIGO stage IVA ovarian cancer was almost identical to that of stage IVB patients who had at least 2 metastatic manifestations (25 *vs*. 28 months, respectively) (68). Whether there is a difference in prognosis in terms of CPLNs compared to other FIGO stage IVB patients is still unknown.

Finally, as it has been suggested by Mert *et al*. (18) and Nasser *et al*. (69), there is a concern that tumor dissemination arising from adverse tumor biology is difficult to manage by surgical resection. Results from the LION study have revealed that in advanced stage ovarian cancer, systematic lymphadenectomy of radiologically non-suspicious lymph nodes has no benefits regarding survival rates. However, the resection of bulky lymph nodes is still recommended for the achievement of complete cytoreduction, thus for better prognosis (29). Nevertheless, no attention has been paid to the presence and resection of frequently enlarged extra-abdominal cardiophrenic lymph nodes in this setting.

Conclusion

The impact of cardiophrenic lymph node resection on overall and progression-free survival remains uncertain, and no recommendation can be made based on evidence to date. Therefore, CPLN removal allowing complete macroscopic resection is still advocated if this is the only extra-abdominal tumorous manifestation of the disease. In order to clarify these questions, a prospective, randomized, and multicentric clinical trial, analogous to the LION study, should be conducted with the involvement of a large group of patients, extending the trial's scope to extra-abdominal lymph nodes as well. To gain comparable data, it is necessary to make a consensus on CPLN size to predict the pathologic diameter of cardiophrenic lymph nodes.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

Miklos Acs wrote the paper, conceived and designed the analysis, collected data. Pompiliu Piso conceived and designed the analyses. Sonia Prader wrote the paper, collected data.

References

1 Siegel RL, Miller KD and Jemal A: Cancer statistics, 2016. CA Cancer J Clin *66(1)*: 7-30, 2016. PMID: 26742998. DOI: 10.3322/caac.21332

2 Marsden DE, Friedlander M and Hacker NF: Current management of epithelial ovarian carcinoma: a review. Semin Surg Oncol *19(1)*: 11-19, 2000. PMID: 10883019. DOI: 10.1002/1098-2388(200007/08)19:1<11::aid-ssu3>3.0.co;2-3

3 du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I and Pfisterer J: Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer *115(6)*: 1234-1244, 2009. PMID: 19189349. DOI: 10.1002/cncr.24149

4 Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL and Montz FJ: Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol *20(5)*: 1248-1259, 2002. PMID: 11870167. DOI: 10.1200/JCO.2002.20.5.1248

5 Chang SJ, Hodeib M, Chang J and Bristow RE: Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: a meta-analysis. Gynecol Oncol *130(3)*: 493-498, 2013. PMID: 23747291. DOI: 10.1016/j.ygyno.2013.05.040

6 National Comprehensive Cancer Network: Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer NCCN Guidelines Version 1, 2021. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1453 [Last accessed on November 2, 2021]

7 Lavoue V, Huchon C, Akladios C, Alfonsi P, Bakrin N, Ballester M, Bendifallah S, Bolze PA, Bonnet F, Bourgin C, Chabbert-Buffet N, Collinet P, Courbiere B, De la Motte Rouge T, Devouassoux-Shisheboran M, Falandry C, Ferron G, Fournier L, Gladieff L, Golfier F, Gouy S, Guyon F, Lambaudie E, Leary A, Lecuru F, Lefrere-Belda MA, Leblanc E, Lemoine A, Narducci F, Ouldamer L, Pautier P, Planchamp F, Pouget N, Ray-Coquard I, Rousset-Jablonski C, Senechal-Davin C, Touboul C, Thomassin-Naggara I, Uzan C, You B and Daraï E: Management of epithelial cancer of the ovary, fallopian tube, primary peritoneum. Long text of the joint French clinical practice guidelines issued by FRANCOGYN, CNGOF, SFOG, GINECO-ARCAGY, endorsed by INCa. (Part 2: systemic, intraperitoneal treatment, elderly patients, fertility preservation, follow-up). J Gynecol Obstet Hum Reprod *48(6)*: 379-386, 2019. PMID: 30936025. DOI: 10.1016/j.jogoh.2019.03.018

8 Orr B and Edwards RP: Diagnosis and treatment of ovarian cancer. Hematol Oncol Clin North Am *32(6)*: 943-964, 2018. PMID: 30390767. DOI: 10.1016/j.hoc.2018.07.010

9 Ataseven B, Grimm C, Harter P, Heitz F, Traut A, Prader S and du Bois A: Prognostic impact of debulking surgery and residual tumor in patients with epithelial ovarian cancer FIGO stage IV. Gynecol Oncol *140(2)*: 215-220, 2016. PMID: 26691222. DOI: 10.1016/j.ygyno.2015.12.007

10 Ataseven B, Chiva LM, Harter P, Gonzalez-Martin A and du Bois A: FIGO stage IV epithelial ovarian, fallopian tube and peritoneal cancer revisited. Gynecol Oncol *142(3)*: 597-607, 2016. PMID: 27335253. DOI: 10.1016/j.ygyno.2016.06.013

11 Prat J and FIGO Committee on Gynecologic Oncology: Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet *124(1)*: 1-5, 2014. PMID: 24219974. DOI: 10.1016/j.ijgo.2013.10.001

12 Lim MC, Lee HS, Jung DC, Choi JY, Seo SS and Park SY: Pathological diagnosis and cytoreduction of cardiophrenic lymph node and pleural metastasis in ovarian cancer patients using video-assisted thoracic surgery. Ann Surg Oncol *16(7)*: 1990-1996, 2009. PMID: 19408045. DOI: 10.1245/s10434-009-0486-5

13 Farmakis S, Vejdani K, Muzaffar R, Parkar N and Osman MM: Detection of Metastatic Disease in Cardiophrenic Lymph Nodes: FDG PET/CT versus contrast-enhanced CT and implications for staging and treatment of disease. Front Oncol *3*: 260, 2013. PMID: 24102048. DOI: 10.3389/fonc.2013.00260

14 Vock P and Hodler J: Cardiophrenic angle adenopathy: update of causes and significance. Radiology *159(2)*: 395-399, 1986. PMID: 3961172. DOI: 10.1148/radiology.159.2.3961172

15 Kim TH, Lim MC, Kim SI, Seo SS, Kim SH and Park SY: Preoperative prediction of cardiophrenic lymph node metastasis in advanced ovarian cancer using computed tomography. Ann Surg Oncol *23(4)*: 1302-1308, 2016. PMID: 26714941. DOI: 10.1245/s10434-015-5015-0

16 Yoo HJ, Lim MC, Song YJ, Jung YS, Kim SH, Yoo CW and Park SY: Transabdominal cardiophrenic lymph node dissection (CPLND) *via* incised diaphragm replace conventional video-assisted thoracic surgery for cytoreductive surgery in advanced ovarian cancer. Gynecol Oncol *129(2)*: 341-345, 2013. PMID: 23290988. DOI: 10.1016/j.ygyno.2012.12.023

17 Luger AK, Steinkohl F, Aigner F, Jaschke W, Marth C, Zeimet AG and Reimer D: Enlarged cardiophrenic lymph nodes predict disease involvement of the upper abdomen and the outcome of primary surgical debulking in advanced ovarian cancer. Acta Obstet Gynecol Scand *99(8)*: 1092-1099, 2020. PMID: 32112653. DOI: 10.1111/aogs.13835

18 Mert I, Kumar A, Sheedy SP, Weaver AL, McGree ME, Kim B and Cliby WA: Clinical significance of enlarged cardiophrenic lymph nodes in advanced ovarian cancer: Implications for survival. Gynecol Oncol *148(1)*: 68-73, 2018. PMID: 29129390. DOI: 10.1016/j.ygyno.2017.10.024

19 Blanchard P, Plantade A, Pagès C, Afchain P, Louvet C, Tournigand C and de Gramont A: Isolated lymph node relapse of epithelial ovarian carcinoma: outcomes and prognostic factors. Gynecol Oncol *104(1)*: 41-45, 2007. PMID: 16952391. DOI: 10.1016/j.ygyno.2006.06.039

20 Prader S, Vollmar N, du Bois A, Heitz F, Schneider S, Ataseven B, Bommert M, Waltering KU, Heikaus S, Koch JA, Alesina PF, Traut A and Harter P: Pattern and impact of metastatic cardiophrenic lymph nodes in advanced epithelial ovarian cancer. Gynecol Oncol *152(1)*: 76-81, 2019. PMID: 30463683. DOI: 10.1016/j.ygyno.2018.11.001

21 Sussman SK, Halvorsen RA Jr, Silverman PM and Saeed M: Paracardiac adenopathy: CT evaluation. AJR Am J Roentgenol *149(1)*: 29-34, 1987. PMID: 3495988. DOI: 10.2214/ajr.149.1.29

22 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45(2)*: 228-247, 2009. PMID: 19097774. DOI: 10.1016/j.ejca.2008.10.026

23 Forstner R, Sala E, Kinkel K, Spencer JA and European Society of Urogenital Radiology: ESUR guidelines: ovarian cancer staging and follow-up. Eur Radiol *20(12)*: 2773-2780, 2010. PMID: 20839002. DOI: 10.1007/s00330-010-1886-4

24 Raban O, Peled Y, Krissi H, Goldberg N, Aviram A, Sabah G, Levavi H and Eitan R: The significance of paracardiac lymph-node enlargement in patients with newly diagnosed stage IIIC ovarian cancer. Gynecol Oncol *138(2)*: 259-262, 2015. PMID: 26001327. DOI: 10.1016/j.ygyno.2015.05.007

25 Cowan RA, Tseng J, Murthy V, Srivastava R, Long Roche KC, Zivanovic O, Gardner GJ, Chi DS, Park BJ and Sonoda Y: Feasibility, safety and clinical outcomes of cardiophrenic lymph node resection in advanced ovarian cancer. Gynecol Oncol *147(2)*: 262-266, 2017. PMID: 28888540. DOI: 10.1016/j.ygyno.2017.09.001

26 Holloway BJ, Gore ME, A'Hern RP and Parsons C: The significance of paracardiac lymph node enlargement in ovarian cancer. Clin Radiol *52(9)*: 692-697, 1997. PMID: 9313735. DOI: 10.1016/s0009-9260(97)80034-7

27 Kolev V, Mironov S, Mironov O, Ishill N, Moskowitz CS, Gardner GJ, Levine DA, Hricak H, Barakat RR and Chi DS: Prognostic significance of supradiaphragmatic lymphadenopathy identified on preoperative computed tomography scan in patients

undergoing primary cytoreduction for advanced epithelial ovarian cancer. Int J Gynecol Cancer *20(6)*: 979-984, 2010. PMID: 20683405. DOI: 10.1111/IGC.0b013e3181e833f5

28 Prader S, Harter P, Grimm C, Traut A, Waltering KU, Alesina PF, Heikaus S, Ataseven B, Heitz F, Schneider S and du Bois A: Surgical management of cardiophrenic lymph nodes in patients with advanced ovarian cancer. Gynecol Oncol *141(2)*: 271-275, 2016. PMID: 26972337. DOI: 10.1016/j.ygyno.2016.03.012

29 Harter P, Sehouli J, Lorusso D, Reuss A, Vergote I, Marth C, Kim JW, Raspagliesi F, Lampe B, Aletti G, Meier W, Cibula D, Mustea A, Mahner S, Runnebaum IB, Schmalfeldt B, Burges A, Kimmig R, Scambia G, Greggi S, Hilpert F, Hasenburg A, Hillemanns P, Giorda G, von Leffern I, Schade-Brittinger C, Wagner U and du Bois A: A randomized trial of lymphadenectomy in patients with advanced ovarian neoplasms. N Engl J Med *380(9)*: 822-832, 2019. PMID: 30811909. DOI: 10.1056/NEJMoa1808424

30 Boria F and Chiva L: Role of cardiophrenic lymph node removal in advanced ovarian cancer. Int J Gynecol Cancer *31(2)*: 307, 2021. PMID: 33273019. DOI: 10.1136/ijgc-2020-002207

31 Montero CA, Gimferrer JM, Baldo X and Ramirez J: Mediastinal metastasis of ovarian carcinoma. Eur J Obstet Gynecol Reprod Biol *91(2)*: 199-200, 2000. PMID: 10869796. DOI: 10.1016/s0301-2115(99)00275-4

32 Aronberg DJ, Peterson RR, Glazer HS and Sagel SS: Superior diaphragmatic lymph nodes: CT assessment. J Comput Assist Tomogr *10(6)*: 937-941, 1986. PMID: 3782563. DOI: 10.1097/00004728-198611000-00007

33 Castellino RA and Blank N: Adenopathy of the cardiophrenic angle (diaphragmatic) lymph nodes. Am J Roentgenol Radium Ther Nucl Med *114(3)*: 509-515, 1972. PMID: 5011400. DOI: 10.2214/ajr.114.3.509

34 Libshitz I and Holbert JM: Anterior diaphragmatic lymph nodes. Lymphology *21(2)*: 99-104, 1988. PMID: 3221720.

35 Hynninen J, Auranen A, Carpén O, Dean K, Seppänen M, Kemppainen J, Lavonius M, Lisinen I, Virtanen J and Grénman S: FDG PET/CT in staging of advanced epithelial ovarian cancer: frequency of supradiaphragmatic lymph node metastasis challenges the traditional pattern of disease spread. Gynecol Oncol *126(1)*: 64-68, 2012. PMID: 22542580. DOI: 10.1016/j.ygyno.2012.04.023

36 Rouvière H: Anatomie des Lymphatiques de l`Homme. Paris, Masson et Cie, 1932.

37 Warwick R and Williams TL: Gray`s Anatomy 35th British edition. Philadelphia, Saunders, 1973.

38 Abu-Hijleh MF, Habbal OA and Moqattash ST: The role of the diaphragm in lymphatic absorption from the peritoneal cavity. J Anat *186 (Pt 3)*: 453-467, 1995. PMID: 7559120.

39 Szabó G, Magyar Z and Serényi P: Lymphatic drainage of the peritoneal cavity in experimental ascites. Acta Med Acad Sci Hung *32(3-4)*: 337-348, 1975. PMID: 1235450.

40 Oommen I, Chandramohan A, Raji PS, Thomas A, Joel A, Samuel Ram T and Peedicayil A: Clinical significance of CT detected enlarged cardiophrenic nodes in ovarian cancer patients. Abdom Radiol (NY) *46(1)*: 331-340, 2021. PMID: 32577780. DOI: 10.1007/s00261-020-02618-z

41 Lopes A, Rangel Costa RL, di Paula R, Anton C, Calheiros Y, Sartorelli V, Kanashiro YM, de Lima JA, Yamada A, Pinto GLS, Vianna MR, Nogueira Dias Genta ML, Ribeiro U Jr and Dos Santos MO: Cardiophrenic lymph node resection in cytoreduction for primary advanced or recurrent epithelial ovarian carcinoma: a cohort study. Int J Gynecol Cancer *29(1)*: 188-194, 2019. PMID: 30640703. DOI: 10.1136/ijgc-2018-000073

42 Salehi S, Mohammar R, Suzuki C, Joneborg U, Hjerpe E, Torbrand C and Falconer H: Cardiophrenic lymph node resection in advanced ovarian cancer: surgical outcomes, pre- and postoperative imaging. Acta Oncol *57(6)*: 820-824, 2018. PMID: 29182048. DOI: 10.1080/0284186X.2017.1409434

43 McIntosh LJ, O'Neill AC, Bhanusupriya S, Matalon SA, Van den Abbeele AD, Ramaiya NH and Shinagare AB: Prognostic significance of supradiaphragmatic lymph nodes at initial presentation in patients with stage III high-grade serous ovarian cancer. Abdom Radiol (NY) *42(10)*: 2513-2520, 2017. PMID: 28429056. DOI: 10.1007/s00261-017-1158-8

44 Larish A, Mert I, McGree M, Weaver A, Sheedy S and Cilby W: Recurrence patterns in patients with abnormal cardiophrenic lymph nodes at ovarian cancer diagnosis. Int J Gynecol Cancer *30(4)*: 504-508, 2020. PMID: 31953350. DOI: 10.1136/ijgc-2019-000981

45 Bristow RE, Karlan BY and Chi DS: Surgery for Ovarian Cancer. CRC Press Taylor & Francis Group, 2015.

46 Grimm C, Harter P, Heitz F and du Bois A: The sandwich technique of diaphragmatic stripping or full-thickness resection for advanced ovarian cancer: how to keep it short and simple. Int J Gynecol Cancer *25(1)*: 131-134, 2015. PMID: 25347091. DOI: 10.1097/IGC.0000000000000309

47 Minig L, Arraras M, Zorrero C, Martinez P, Patron M and Peñalver JC: A different surgical approach for cardiophrenic lymph node resection in advanced ovarian cancer. Ecancermedicalscience *11*: 780, 2017. PMID: 29225687. DOI: 10.3332/ecancer.2017.780

48 Einenkel J, Ott R, Handzel R, Braumann UD and Horn LC: Characteristics and management of diaphragm involvement in patients with primary advanced-stage ovarian, fallopian tube, or peritoneal cancer. Int J Gynecol Cancer *19(7)*: 1288-1297, 2009. PMID: 19823067. DOI: 10.1111/IGC.0b013e3181a3a833

49 Patel SV, Spencer JA, Wilkinson N and Perren TJ: Supradiaphragmatic manifestations of papillary serous adenocarcinoma of the ovary. Clin Radiol *54(11)*: 748-754, 1999. PMID: 10580766. DOI: 10.1016/s0009-9260(99)91178-9

50 LaFargue CJ, Sawyer BT and Bristow RE: Short-term morbidity in transdiaphragmatic cardiophrenic lymph node resection for advanced stage gynecologic cancer. Gynecol Oncol Rep *17*: 33-37, 2016. PMID: 27354998. DOI: 10.1016/j.gore.2016.05.006

51 Garbi A, Zanagnolo V, Colombo N, Aletti G, Achilarre MT, Bocciolone L, Landoni F, Rizzo S, Biffi R and Maggioni A: Feasibility of transabdominal cardiophrenic lymphnode dissection in advanced ovarian cancer: Initial experience at a tertiary center. Int J Gynecol Cancer *27(6)*: 1268-1273, 2017. PMID: 28498236. DOI: 10.1097/IGC.0000000000000983

52 Pinelli C, Morotti M, Casarin J, Tozzi R, Alazzam M, Mavroeidis VK and Soleymani Majd H: The feasibility of cardiophrenic lymphnode assessment and removal in patients requiring diaphragmatic resection during interval debulking surgery for ovarian cancer. J Invest Surg *34(7)*: 756-762, 2021. PMID: 31809609. DOI: 10.1080/08941939.2019.1690077

53 Lee IO, Lee JY, Kim HJ, Nam EJ, Kim S, Kim SW, Lee CY, Kang WJ and Kim YT: Prognostic significance of supradiaphragmatic lymph node metastasis detected by ^{18}F-FDG PET/CT in advanced epithelial ovarian cancer. BMC Cancer *18(1)*: 1165, 2018. PMID: 30477469. DOI: 10.1186/s12885-018-5067-1

54 Ragusa M, Vannucci J, Capozzi R, Daddi N, Avenia N and Puma F: Isolated cardiophrenic angle node metastasis from ovarian primary. report of two cases. J Cardiothorac Surg *6*: 1, 2011. PMID: 21208441. DOI: 10.1186/1749-8090-6-1

55 Hamaji M, Yamaguchi K, Koyasu S and Date H: Thoracoscopic resection of fluorodeoxyglucose-avid mediastinal lymph nodes associated with advanced ovarian carcinoma. Thorac Cardiovasc Surg *67(8)*: 692-696, 2019. PMID: 30086572. DOI: 10.1055/s-0038-1667325

56 Cameron JL and Cameron AM: Current Surgical Therapy, 11th edn. Ann R Coll Surg Engl *97(2)*: 165, 2015.

57 Juretzka MM, Abu-Rustum NR, Sonoda Y, Downey RJ, Flores RM, Park BJ, Hensley ML, Barakat RR and Chi DS: The impact of video-assisted thoracic surgery (VATS) in patients with suspected advanced ovarian malignancies and pleural effusions. Gynecol Oncol *104(3)*: 670-674, 2007. PMID: 17150248. DOI: 10.1016/j.ygyno.2006.10.010

58 Di Guilmi J, Salvo G, Mehran R, Sood AK, Coleman RL, Lu KH, Vaporciyan A and Ramirez PT: Role of video-assisted thoracoscopy in advanced ovarian cancer: a literature review. Int J Gynecol Cancer *26(4)*: 801-806, 2016. PMID: 26937753. DOI: 10.1097/IGC.0000000000000680

59 Forstner R, Meissnitzer M and Cunha TM: Update on imaging of ovarian cancer. Curr Radiol Rep *4*: 31, 2016. PMID: 27110476. DOI: 10.1007/s40134-016-0157-9

60 Cho CS, Blank N and Castellino RA: CT evaluation of cardiophrenic angle lymph nodes in patients with malignant lymphoma. AJR Am J Roentgenol *143(4)*: 719-721, 1984. PMID: 6332470. DOI: 10.2214/ajr.143.4.719

61 Iancu I, Chiriac V, Cozma N and Stancu N: [Larrey's cleft—Morgagni's foramen (superiority of anatomical terms)]. Rev Med Chir Soc Med Nat Iasi *74(2)*: 429-432, 1970. PMID: 5447571.

62 Winter WE 3rd, Maxwell GL, Tian C, Sundborg MJ, Rose GS, Rose PG, Rubin SC, Muggia F, McGuire WP and Gynecologic Oncology Group: Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage IV epithelial ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol *26(1)*: 83-89, 2008. PMID: 18025437. DOI: 10.1200/JCO.2007.13.1953

63 Bristow RE, Montz FJ, Lagasse LD, Leuchter RS and Karlan BY: Survival impact of surgical cytoreduction in stage IV epithelial ovarian cancer. Gynecol Oncol *72(3)*: 278-287, 1999. PMID: 10053096. DOI: 10.1006/gyno.1998.5145

64 Aletti GD, Dowdy SC, Gostout BS, Jones MB, Stanhope CR, Wilson TO, Podratz KC and Cliby WA: Aggressive surgical effort and improved survival in advanced-stage ovarian cancer. Obstet Gynecol *107(1)*: 77-85, 2006. PMID: 16394043. DOI: 10.1097/01.AOG.0000192407.04428.bb

65 Eisenhauer EL, Abu-Rustum NR, Sonoda Y, Levine DA, Poynor EA, Aghajanian C, Jarnagin WR, DeMatteo RP, D'Angelica MI, Barakat RR and Chi DS: The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stages IIIC-IV epithelial ovarian cancer. Gynecol Oncol *103(3)*: 1083-1090, 2006. PMID: 16890277. DOI: 10.1016/j.ygyno.2006.06.028

66 Nasioudis D, Chapman-Davis E, Frey MK, Caputo TA, Witkin SS and Holcomb K: Should epithelial ovarian carcinoma metastatic to the inguinal lymph nodes be assigned stage IVB? Gynecol Oncol *147(1)*: 81-84, 2017. PMID: 28716307. DOI: 10.1016/j.ygyno.2017.07.124

67 Ataseven B, du Bois A, Harter P, Prader S, Grimm C, Kurzeder C, Schneider S, Heikaus S, Kahl A, Traut A and Heitz F: Impact of abdominal wall metastases on prognosis in epithelial ovarian cancer. Int J Gynecol Cancer *26(9)*: 1594-1600, 2016. PMID: 27654263. DOI: 10.1097/IGC.0000000000000826

68 Ataseven B, Harter P, Grimm C, Heitz F, Heikaus S, Traut A, Kahl A, Kurzeder C, Prader S and du Bois A: The revised 2014 FIGO staging system for epithelial ovarian cancer: Is a subclassification into FIGO stage IVA and IVB justified? Gynecol Oncol *142(2)*: 243-247, 2016. PMID: 27208538. DOI: 10.1016/j.ygyno.2016.05.021

69 Nasser S, Kyrgiou M, Krell J, Haidopoulos D, Bristow R and Fotopoulou C: A review of thoracic and mediastinal cytoreductive techniques in advanced ovarian cancer: Extending the boundaries. Ann Surg Oncol *24(12)*: 3700-3705, 2017. PMID: 28861808. DOI: 10.1245/s10434-017-6051-8

70 Luengas-Wuerzinger V, Rawert F, CLAßEN-VON Spee S, Baransi S, Schuler E, Carrizo K, Mallmann P and Lampe B: Role of the cardiophrenic lymph node status after neoadjuvant chemotherapy in primary advanced ovarian cancer. Anticancer Res *41(10)*: 5025-5031, 2021. PMID: 34593451. DOI: 10.21873/anticanres.15317

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