Cardiophrenic lymph nodes in advanced ovarian cancer

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ABSTRACT

Epithelial ovarian cancer most commonly presents at advanced stages, and prognosis is influenced by residual disease following cytoreduction. The significance of cardiophrenic lymph node resection at the time of cytoreductive surgery in advanced ovarian cancer remains a topic of debate. Enlarged cardiophrenic lymph nodes are detected through high-resolution imaging; however, the optimal imaging technique in determining feasibility of node resection remains uncertain. Similarly, the impact of excision of cardiophrenic lymph nodes on progression-free and overall survival remains elusive. The indications for resection of cardiophrenic lymph nodes are not addressed in standard ovarian cancer guidelines. Patients with cardiophrenic lymph nodes exceeding 1 cm in size may be considered for resection if complete intra-abdominal cytoreduction is feasible to no gross residual. The surgical approach might be either by open access or by video-assisted thoracoscopic surgery (minimally invasive approach), and major complications following cardiophrenic lymph nodes resection are low. Pathological cardiophrenic lymph nodes are associated with a poorer overall prognosis and can serve as a prognostic parameter; however, the therapeutic benefit of cardiophrenic lymph nodes resection remains inconclusive.

INTRODUCTION

Epithelial ovarian cancer routinely is diagnosed in advanced stages, and prognosis is influenced by residual disease following cytoreduction.[1] The standard treatment is complete cytoreductive surgery, either as the primary treatment or after neoadjuvant chemotherapy, combined with carboplatin plus paclitaxel-based chemotherapy.[2] Retrospective data have shown that each 10% increase in maximal cytoreduction, has been associated with a 5.5% increase in median survival time.[3] However, only 12.3% of patients with stage IV achieve complete cytoreduction.[4]

A potential prognostic factor in advanced ovarian cancer is the cardiophrenic lymph node status.[5] These lymph nodes encompass the mediastinum, cardiac base, diaphragm, and chest wall. Enlarged cardiophrenic lymph nodes may be detected through high-resolution imaging techniques; however, the optimal imaging and its predictive value for successful node resection remain unknown.[6]

While the excision of enlarged cardiophrenic lymph nodes has been shown to be feasible without added complications, its impact on progression-free and overall survival remains a subject of controversy.[7] Performing a systematic pelvic and para-aortic lymphadenectomy of unsuspicious nodes was once standard practice in ovarian cytoreductive surgery. However, the results of the LION trial demonstrated no survival benefit, leading to abandonment of this practice.[8] Despite these advances made in the abdomino-pelvic lymph node removal management, evidence remains limited regarding the therapeutic benefits of removing cardiophrenic lymph nodes when they are positive for disease. A single meta-analysis and systematic review[5] revealed no evidence of a therapeutic benefit of pathological cardiophrenic lymph nodes removal in patients achieving complete cytoreduction in advanced epithelial ovarian cancer. Currently, there are no established guidelines recommending surgical indications for patients with enlarged cardiophrenic lymph nodes.[2 9]

This review highlights the distinctive characteristics of cardiophrenic lymph node involvement in patients with newly diagnosed advanced ovarian cancer and provides an update on its diagnostic considerations, as well as insights into both medical and surgical management impact on survival outcomes.

ANATOMY OF SUPRADIAPHRAGMATIC LYMPH NODES

Supradiaphragmatic lymph nodes play an essential role in the lymphatic drainage of the thoracic and abdominal regions. They are categorized into two main groups: visceral and parietal lymph nodes. The visceral nodes are responsible for receiving lymphatic drainage from the anterior and middle mediastinal structures, including the lungs and tracheobronchial tree. Their location within the mediastinum places these lymph nodes in close proximity to essential thoracic organs, making them crucial in maintaining fluid balance and immune function within the chest cavity. The parietal group comprises extrapleural lymph nodes that receive lymphatic drainage

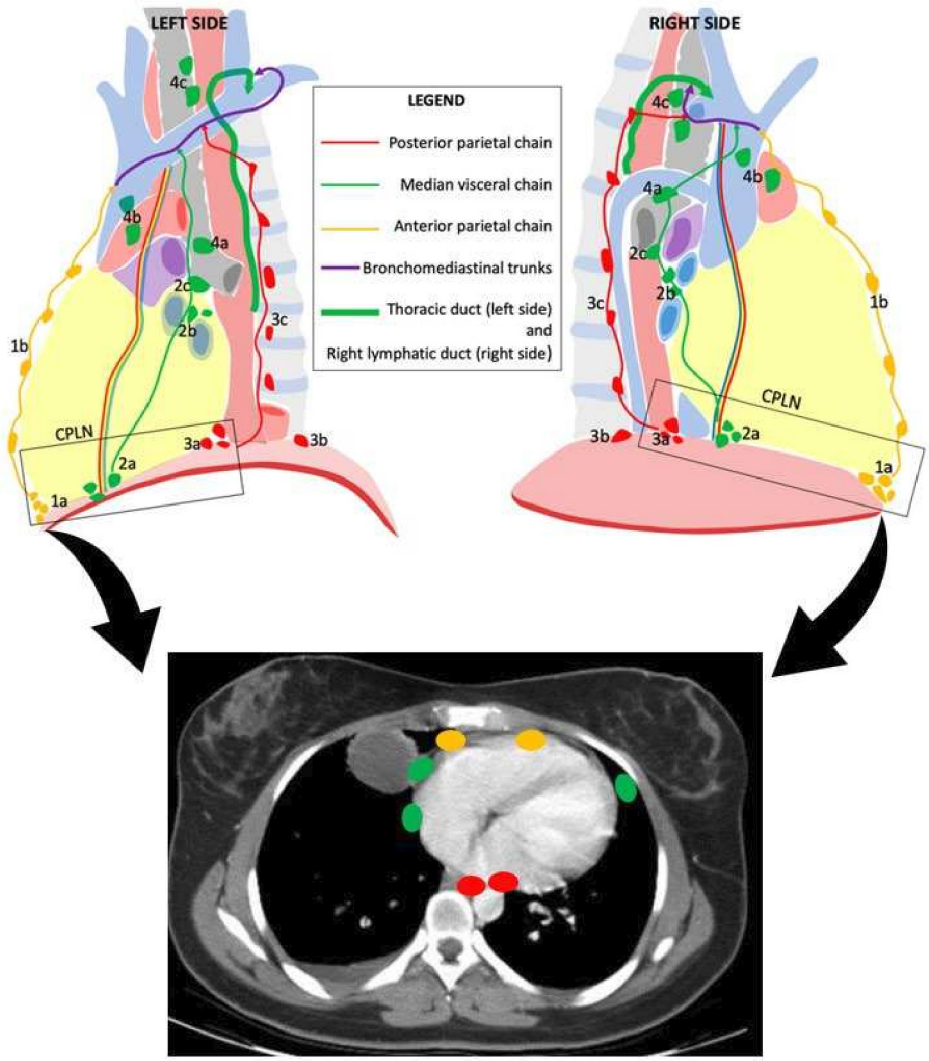

Figure 1 Axial CT scan showing the location of the cardiophrenic lymph nodes (CPLN). These nodes are classified into an anterior group (yellow), a middle or lateral group (green), and a posterior group (red).

from musculoskeletal structures of the thorax. Key nodes within this group include the cardiophrenic nodes, parasternal nodes, prevertebral nodes, and retrocrural nodes.

The cardiophrenic lymph nodes represent the caudal portion of the mediastinal lymph nodes and are located within the fatty tissue surrounding the base of the heart in an extrapleural space. Based on their position in relation to the heart, they are further divided into three subgroups (Figure 1):

a. Anterior (retroxiphoid) cardiophrenic nodes: collecting lymph from the anterior chest, supra-umbilical abdominal wall, anterior diaphragm, liver surface, and medial breast.
b. Median or lateral (lateropericardial) cardiophrenic nodes: draining lymph from intrathoracic organs through the paraesophageal and median tracheobronchial chains.
c. Posterior (juxta-esophageal) cardiophrenic nodes: collecting lymph from the chest wall, posterior pleura, esophagus, and posterior diaphragm ending in the left thoracic duct, right lymphatic duct, or Pirogoff's angle.

Precise anatomical classification allows us to identify the lymph nodes in imaging studies and during surgical procedures. The complex interplay between these lymphatic chains highlights the multiple potential routes of disease dissemination. Thus, knowledge of these lymphatic pathways and their relationship to the cardiophrenic lymph nodes is important in assessing the involvement of these nodes in advanced ovarian cancer.

IMAGING

Enlarged cardiophrenic lymph nodes are found in 10.5–62% of patients with advanced epithelial ovarian cancer, depending on the radiological size classification of a pathological node.[10–14] There is no current consensus regarding which radiological short axis cardiophrenic lymph nodes length should be considered pathological, with current cut-off values varying from 5 to 10 mm.[10 11 13 15 16] This lack of standard classification makes prognostication and diagnosis challenging. The European Society of Urogenital Radiology (ESUR) states that cardiophrenic lymph nodes larger than 5 mm might have a negative prognostic impact and should be regarded as suspicious.[17] However, the Response Evaluation Criteria in Solid

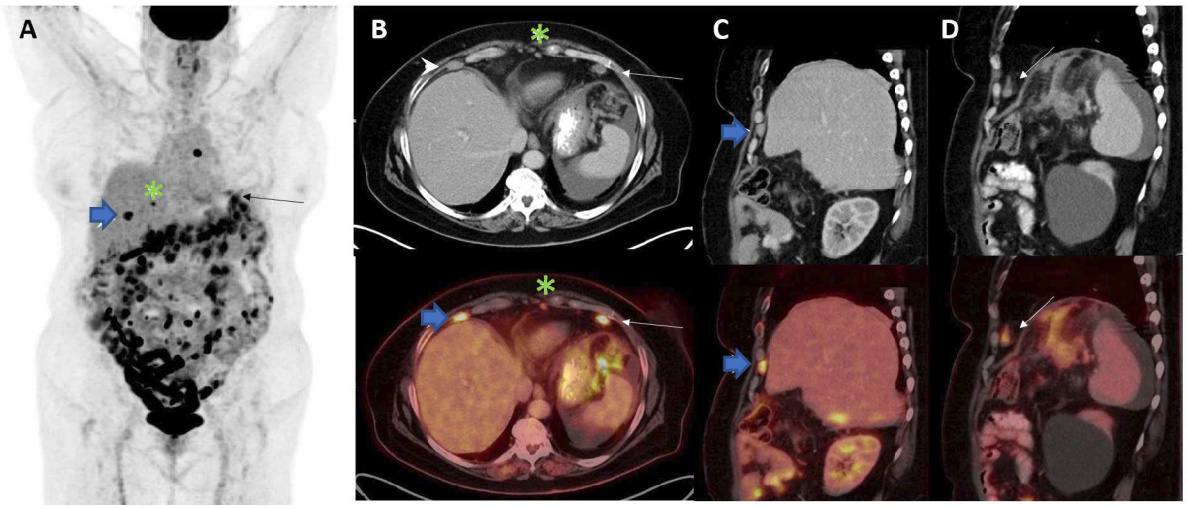

Figure 2 PET/CT for staging purposes shows internal mammary nodes (*) and bilateral cardiophrenic nodes with high metabolism indicative of tumorous disease: two right (* and arrow-head) and one left (arrow). From right to left: maximum intensity projection PET image (A), CT and fused PET/CT images on axial view (B) and sagittal view (C, D) of right (C) and left (D) cardiophrenic nodes.

Tumors (RECIST) guideline 1.1 defined lymph nodes as pathologically enlarged when their short axis is >10 mm, regardless of location.[18]

Additionally, international gynecological oncology guidelines[2 9] do not provide any specific recommendations regarding the optimal imaging technique for the detection of pathological cardiophrenic lymph nodes in ovarian cancer. Enlarged cardiophrenic lymph nodes detected through pre-operative imaging have shown the ability to predict pathologically confirmed metastatic disease in 57–95% of patients, depending on the imaging used, the type of surgery (primary or interval debulking), and the specific cut-off value applied (≥5 mm, ≥7 mm, ≥10 mm).[10 11 16 19–22]

CT is considered the best available imaging technique for pre-surgical evaluation and staging purposes. It is the most widely used imaging modality as it provides adequate resolution and accuracy within a short examination time period and is readily available worldwide.[17 23] MRI can also be used with high detection accuracy; however, due to limited availability, higher costs, and longer examination time is mostly used for cases in which CT scanning is contraindicated or unavailable.[17] Lastly, 18F-FDG positron emission tomography/computed tomography (PET/CT) has emerged as an alternative imaging technique for pre-operative assessment and treatment planning in patients with advanced ovarian cancer. PET/CT (Figure 2) combines metabolic functional imaging with an accurate anatomic visualization when performed with an intravenous contrast agent and may increase the likelihood of detecting cardiophrenic lymph nodes <10 mm in size in comparison with CT alone.[13 20 24] This increase in accuracy over other imaging techniques based on morphology and size criteria alone is probably because PET/CT detects higher glucose metabolism in a non-enlarged pathological lymph node.[25] However, the European Association of Nuclear Medicine[23] (EANM) states that the available evidence is limited and no definitive conclusions can be drawn regarding the replacement of diagnostic CT by PET/CT in treatment planning such as tumor resectability evaluation or predictive value before a debulking surgery.

SURGICAL INDICATIONS

The surgical indications for resection of cardiophrenic lymph nodes in advanced ovarian cancer remain uncertain, with specific recommendations in international guidelines lacking.[2 9] The surgical indications can vary based on different factors, such as pre-operative imaging, size cut-off values, and the extent of intra-abdominal carcinomatosis or thoracic involvement. Importantly, involvement of cardiophrenic lymph nodes has been associated with a higher rate of intra-abdominal carcinomatosis, especially in the upper abdomen.[5 26] The most significant impact on improving overall and progression-free survival is achieving optimal debulking, defined as no residual macroscopic disease (<1 cm) after surgery.[1] The degree of carcinomatosis plays a crucial role in determining the feasibility of achieving complete debulking, which in turn contributes to the uncertainty surrounding surgical indications for removal of cardiophrenic lymph nodes.

In general, patients with cardiophrenic lymph nodes with a short-axis diameter greater than 1 cm may be potential candidates for cardiophrenic lymph nodes resection in advanced ovarian cancer. Using this higher cut-off value for cardiophrenic lymph nodes size can enhance sensitivity in predicting metastatic disease. The location of the enlarged cardiophrenic lymph nodes should not preclude from its removal. Instead, it might influence the choice of the surgeon who performs the resection. If cardiophrenic lymph nodes are outside the gynecologic oncologist's range of expertise, a cardiothoracic surgery consultation should be considered. However, dissection of cardiophrenic lymph nodes should be considered only for those patients in whom complete intra-abdominal disease resection can be achieved, with no evidence of other extra-abdominal involvement present.

Pre-operative radiological assessment of cardiophrenic lymph nodes might decrease after neoadjuvant chemotherapy (about 57% correlation with post-operative pathology),[19] therefore, primary debulking surgery may be the optimal time for cardiophrenic lymph nodes resection. Neoadjuvant chemotherapy probably has an impact on the macroscopic structure of lymph nodes, resulting in chemotherapy-induced fibrosis following tumor regression. This fibrotic effect may also make the radiological and intra-operative assessment of bulky nodes more complex. However, if an enlarged cardiophrenic lymph node is still detected after neoadjuvant chemotherapy, the same criteria applied in the upfront surgery may be considered. This applies when complete intra-abdominal resection can be achieved, and there is no evidence of other extra-abdominal disease

SURGICAL TECHNIQUE AND APPROACHES

There are various surgical approaches for the excision of cardiophrenic lymph nodes in the context of ovarian cancer cytoreduction. The two most used methods of access are the transdiaphragmatic approach and the transxiphoid approach. The transdiaphragmatic approach is mainly used for posterior and medial cardiophrenic lymph nodes, whereas the transxiphoid approach might be employed for resecting anterior cardiophrenic lymph nodes

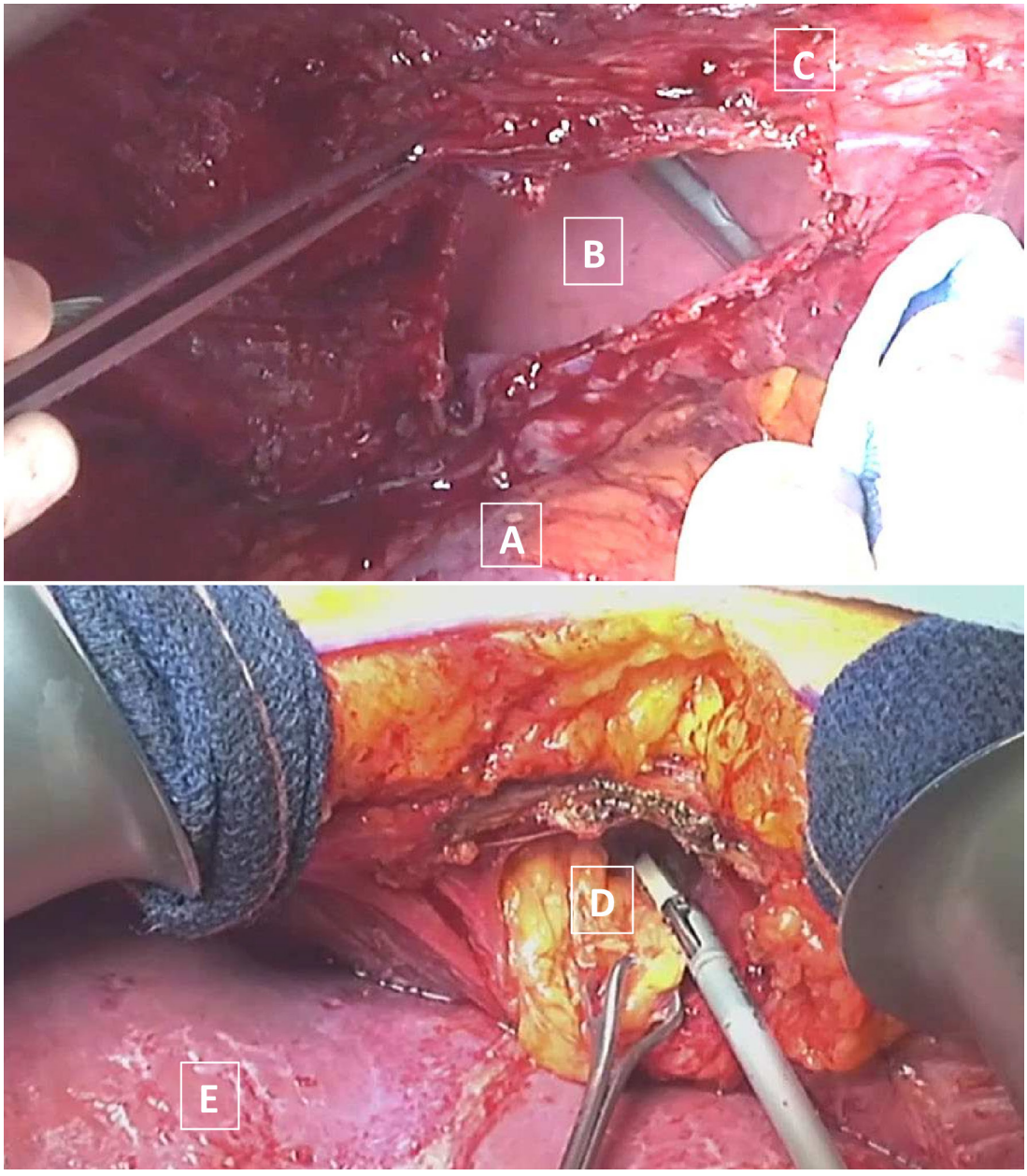

Figure 3 Anatomy of the cardiophrenic lymph node. In the upper image, the transdiaphragmatic approach is shown after liver mobilization: (A) kidney; (B) lung after performing a right incision of the diaphragm; (C) diaphragm. The lower image illustrates the transxiphoid approach: (D) lymphofatty tissue involving anterior cardiophrenic lymph nodes; (E) liver. Images courtesy of Professor Alejandra Martínez.

(Figure 3).[27] The transdiaphragmatic approach usually entails a liver mobilization and requires a diaphragmatic incision, and therefore can be performed at the time of the abdominal portion of the cytoreduction. The subxiphoid approach does not require the opening of the diaphragm or pleural space and can also be considered when a diaphragmatic resection is not required.

For the transdiaphragmatic approach, a transabdominal cardiophrenic lymph nodes resection requires a generous incision from the xiphoid to the pubic symphysis. A fixed upper abdominal retractor such as the Thompson Surgical Retractor (Surgi-One Medical Technologies Inc., Burlington, Ontario, Canada) is generally recommended. Adequate mobilization of the liver is essential for initial access to the cardiophrenic space. Bashir et al[28] recommend first dividing the round ligament of the liver, then the falciform ligament, as well as the anterior and posterior leaves of the right coronary ligament (which are also inclusive of the right triangular ligament). The hepatic veins and inferior vena cava should be identified and visualized to prevent injury.

The diaphragm peritonectomy is performed by incising the diaphragm in a curvilinear fashion beneath the right costal margin. A series by Prader et al[10] describes starting at the anterior mediolateral margin of the centrum tendineum, approximately 1–2 cm laterally to the midline to avoid damaging the hepatic vein as well as the diaphragmatic vessels and nerve. As the mobilized liver is pushed caudally and posteriorly, the incision should then follow the direction of the muscle fibers to the ventral abdominal wall along a length of approximately 5 cm. Dissection using either electrocautery or scissors have both been reported.[10 28 29] This, then allows access to the parietal and visceral pleura, the interlobular space, and the mediastinum. The cardiophrenic lymph nodes can now undergo resection, which has been described usung a Ligasure device (Medtronic. Minneapolis, Minnesota, USA).[10] Attention should be paid to the pericardium to avoid injury. The diaphragmatic defect should undergo closure with a simple, full-thickness interrupted technique using prolene, polypropylene, or polydioxanone, size 1–0 or 2–0, sutures.[10 28 29]

The transxiphoid approach was first described by Minig et al.[30] One should proceed with initial separation of the anterior insertions of the diaphragm at the xiphoid appendix, allowing for incision at the parietal peritoneum and upper fibers of the transversus abdominis muscle. Additionally, Martínez-Gómez et al[27] described a transxiphoid approach to access the retroxiphoid lymph nodes. In this technique, the xiphoid process is resected along with incision of the ventral diaphragmatic fibers to give access to the anterior mediastinum.

Video-Assisted Thorascopic Surgery

Video-assisted thorascopic surgery with the assistance of cardiothoracic surgeons has become more widely used in the management of advanced ovarian cancer involving the thoracic cavity. This form of minimally invasive thoracic surgery is considered a safe approach that allows for the rapid assessment of the extent of disease, providing different options for the management of advanced ovarian cancer, including obtaining tissue for pathological diagnosis and treating pleural effusions.[31–34] Moreover, video-assisted thorascopic surgery can be performed to triage patients for either primary cytoreductive surgery or neoadjuvant treatment. A study by Boerner et al investigated 100 patients with suspected intrathoracic ovarian cancer metastasis and moderate-to-large pleural effusions who underwent video-assisted thorascopic surgery.[33] The authors introduced an updated treatment algorithm,[32] suggesting primary surgery for patients without intrathoracic disease seen on the video-assisted procedure, and neoadjuvant chemotherapy, possibly followed by intrathoracic cytoreduction, for those with unresectable disease.

For video-assisted thorascopic surgery approach, it is recommended to anticipate the potential need for conversion to an open thoracotomy. It is commonly performed in a lateral decubitus position to provide optimal surgical access to thoracic structures along with table arching to separate the ribs (Figure 4). It is important during positioning to relieve any pressure on the intercostal nerves to avoid injury. The standard video-assisted thorascopic surgery anterior approach involves three incisions forming a triangular configuration. Most commonly, the first port for the thoracoscope is placed at the seventh or eighth intercostal space in the mid-axillary line to allow for inspection of the pleural cavity. A window of roughly 5 cm in length is commonly placed at the fifth or sixth intercostal space in the mid-clavicular line. An additional port can be made at the seventh intercostal space in the post-scapular line.[35] The triangular port placement permits a panoramic view of the pleural cavity.[36] Assessment with the video thoracoscope and corresponding procedural components can then be performed.

Video-assisted thorascopic surgery procedures should be performed with an experienced anesthesia team. Anesthesia preparations for these procedures are similar to that of an open pulmonary resection. A protective ventilation strategy is employed to minimize acute lung injury. Maximal collapse of the operative lung is required for optimal surgical visualization during the procedure.[37] Typically, fluid management during the procedure is restricted to <6 mL/kg per hour or 1–2 L in total to minimize the risk of post-operative pulmonary complications; however, this must be balanced with consideration of a possible lengthy cytoreduction surgery following lung resections.[38]

COMPLICATIONS: PREVENTION AND MANAGEMENT

The published literature shows a low rate of major complications following cardiophrenic lymph nodes resection.[10 16 22 39] Pulmonary complications are the most common, with pleural effusion occurring in 9–55% of patients and uncomplicated pulmonary atelectasis in 25%.[29] However, it is difficult to assess whether all cardiothoracic complications are directly related to cardiophrenic lymph nodes resection, given the large number of procedures performed during cytoreductive surgery. Complications following a video-assisted thorascopic surgery procedure are rare and can be minimized through the proper selection of patients. Excessive bleeding has been shown to occur in up to 2% of cases.[40] Additionally, other complications include damage to surrounding organs at the time of port placement, prolonged air leak, infections, pain, and recurrence at the port site.

Cowan et al[39] published a single-center experience of 54 patients who underwent resection of cardiophrenic lymph nodes via video-assisted thoracic surgery (n=6) and a transdiaphragmatic approach (n=48), with the majority having a chest tube placed (n=51). Post-operatively, four patients (7.4%) developed pulmonary complications. However, it was not

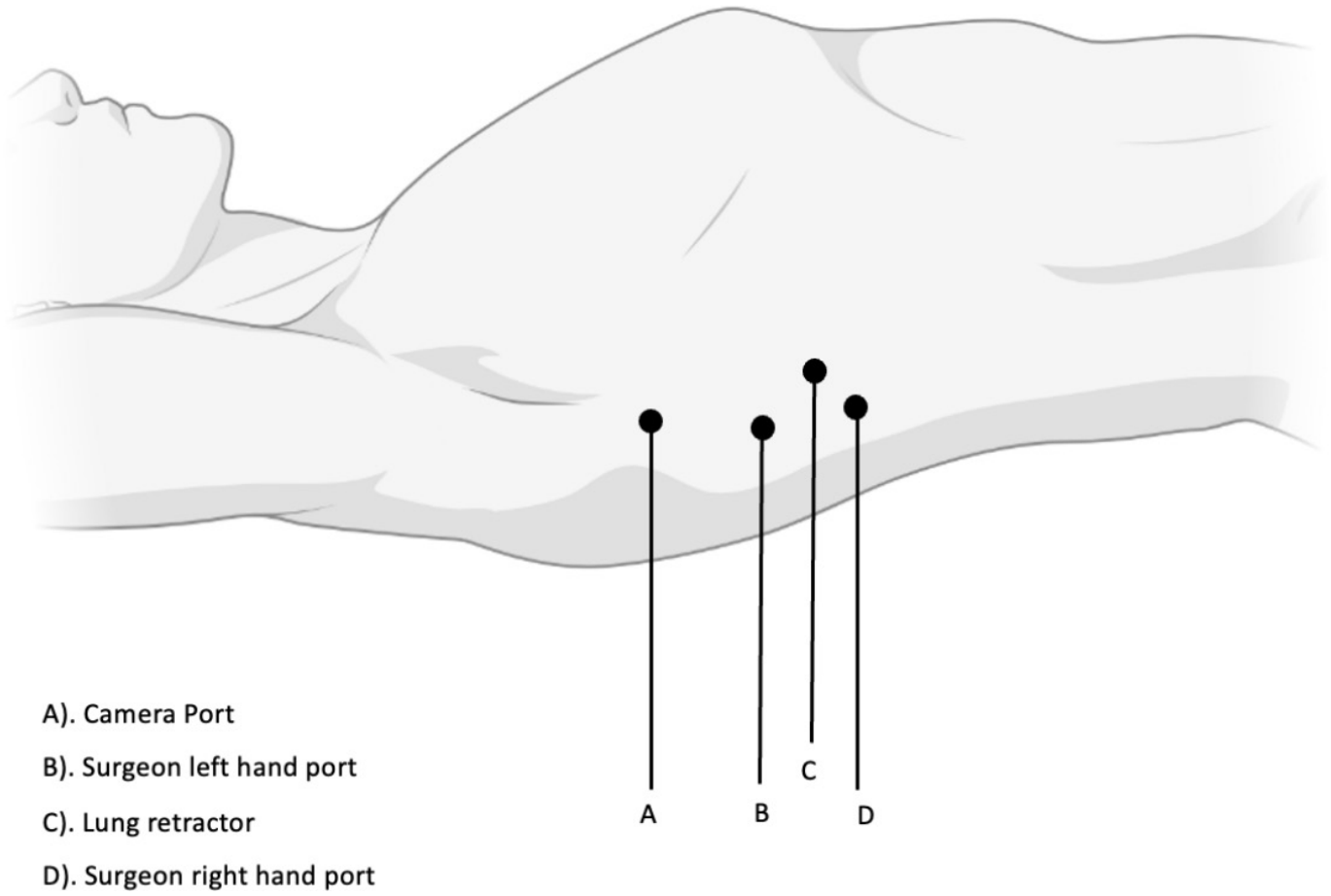

Figure 4 Patient position and entry: video-assisted thorascopic surgery access.

specified if complications were more likely in the group receiving video-assisted thorascopic surgery or transdiaphragmatic surgery.

Another study by Prader et al reported no direct procedure related complications following transabdominal resection of cardiophrenic lymph nodes in 30 patients.[10] Furthermore, Lim et al 2009 described a series of nine patients who underwent cardiophrenic lymph nodes resection via video-assisted thorascopic surgery, with two patients developing a right pleural effusion successfully managed with a chest tube placement.[21]

The placement of a chest tube has been suggested to prevent complications after cardiophrenic lymph nodes resection. Notably, a recent study conducted by Cianci et al[41] evaluated the role of intra-operative thoracostomy tube placement as a preventive measure for post-operative complications after diaphragmatic resection. This single-center prospective randomized trial found that intra-operative placement of a thoracostomy tube following diaphragmatic resection is effective in preventing post-operative thoracic complications, regardless of the extension of the resection. Currently, although there is no consensus on the routine use of tube placement at the time of surgery, it could be considered if a large pleural effusion, extensive pre-operative ascites >500 mL, or large diaphragmatic resection is observed.[10 16 22 29 39 42–44]

ONCOLOGIC IMPLICATIONS CARDIOPHRENIC LYMPH NODES

Controversy remains as to whether removal of pathologically enlarged cardiophrenic lymph nodes at primary debulking surgery confers a survival benefit, and further investigation is needed. According to certain authors, the presence of enlarged cardiophrenic lymph nodes should not automatically preclude surgery and cardiophrenic lymph nodes removal if achieving macroscopically complete cytoreduction is possible.[10 39] However, other proponents argue that it may serve more as an indicator of advanced-stage disease, and prognosis is not solely dependent on the isolated factor of lymph nodes involvement; but rather, it might be an indirect marker for other relevant factors.[45]

As enlargement of cardiophrenic lymph nodes has been described as an independent negative prognostic factor, some authors sought to evaluate the role of surgery to achieve macroscopic gross resection in the abdomen and also in the thorax.[4 46] In line with this, some evidence suggests that the presence of non-resected abnormal cardiophrenic lymph nodes may lead to a decrease in overall survival, even when complete intra-abdominal resection is achieved (median overall survival, 38.4 vs 69.6 months, p=0.08).[13] Additionally, a recent meta-analysis[5] found that patients with cardiophrenic lymph nodes involvement had a pooled median progression-free survival rate of 17.7 months (95% CI 7.9 to 27.4), whereas patients without pathological cardiophrenic lymph nodes had a median progression-free survival rate of 15.3 months (95% CI 3.5 to 27.1). However, it is important to note that most of the studies included in the analysis were series of cases reporting outcomes after cardiophrenic lymph nodes resection. When focusing only on studies that had a control group directly

comparing survival outcomes based on cardiophrenic lymph node resection, the authors did not find significant differences in survival rates. Frequently, the lack of data on potential confounding factors, such as rate of complete intra-abdominal debulking surgery, the use of primary or adjuvant chemotherapy, histological-type, and genetic factors, may hinder the ability to determine the true reasons behind these observed survival results.

In contrast, other studies showed that survival relies on complete macroscopic intra-abdominal resection even if enlarged cardiophrenic lymph nodes are resected,[11 20 26] suggesting that cardiophrenic lymph nodes do not have a therapeutic effect. Prader et al[11] conducted a matched cohort analysis involving 52 patients per group, which did not demonstrate any significant impact on survival in patients who underwent cardiophrenic lymph node resection. The possibility of peritoneal sanctuary housing occult ovarian cancer cells might outweigh the potential risk associated with lymph node involvement.

According to published data, patients with enlarged cardiophrenic lymph nodes at the time of initial diagnosis might have a higher recurrence rate (81.5% vs 57.4%) than those without pathological nodes.[47] Recurrence pattern maybe different in those with pathological cardiophrenic lymph nodes, showing a higher rate of synchronous recurrence in the thorax, abdomen, and pelvis (50.0% (n=11/22) vs 25.0% (n=32/128)) and a less likely isolated recurrence in the pelvis or abdomen (40.9% (n=9/22) vs 68.0% (n=87/128)).[47] Thus, involvement of cardiophrenic lymph nodes may represent a surrogate marker of a higher likelihood of extensivecarcinomatosis, especially disease in the upper abdomen, conferring a decreased rate of complete intra-abdominal disease resection.[45] Figure 5 shows the comprehensive approach to managing cardiophrenic lymph node involvement in advanced epithelial ovarian cancer.

Limitations in the Literature

The role of removing enlarged cardiophrenic lymph nodes during debulking surgery for ovarian cancer remains a topic with limited quality evidence, hindered by various biases and challenges. The studies conducted in this context are predominantly retrospective cohort studies, with inherent limitations such as missing data and multiple potential biases including control selection. Adding to the complexity, the enlargement of these lymph nodes often signifies extensive tumor load and advanced lymphatic metastases, making it challenging to isolate their true impact. Additionally, there is a scarcity of studies analyzing patient matching, variations in treatment

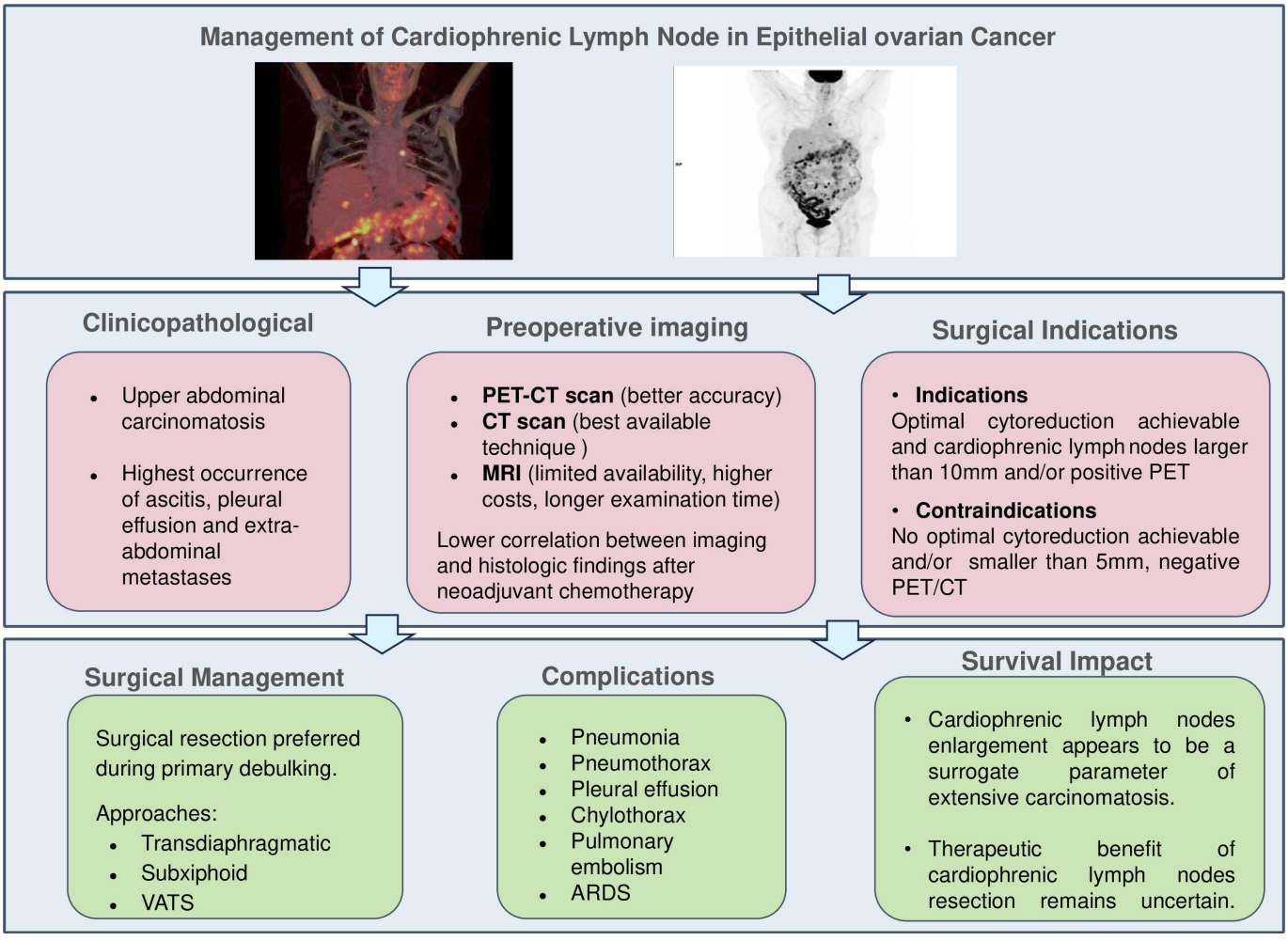

Figure 5 Overall management of cardiophrenic lymph node involvement in advanced epithelial ovarian cancer. ARDS, acute respiratory distress syndrome. CT, computed tomography; MRI, magnetic resonance imaging; PET, 18F-FDG positron emission tomography; VATS, video-assisted thorascopic surgery,

regimens, or reporting rates of optimal debulking surgeries, introducing confounding variables that complicate data interpretation.

While the results should be approached with caution due to retrospective design limitations, one notable issue is that most studies base survival impact comparisons of cardiophrenic lymph nodes solely on imaging, lacking histological confirmation or other interventions. This can introduce multiple biases, particularly in those patients with advanced disease. Moreover, isolated cardiophrenic lymph node involvement without other extra-abdominal or inoperable extensive intra-abdominal disease is rare. Thus, while prospective randomized trials would be ideal to establish the role of cardiophrenic lymph nodes, the low prevalence stage of disease makes such trials challenging and unfeasible.

CONCLUSION

Positive cardiophrenic lymph nodes may reflect advanced-stage disease characterized by extensive carcinomatosis and, as a result, the prognosis for these patients is generally unfavorable. Considering that such patients require more aggressive surgery to achieve optimal cytoreduction, a neoadjuvant approach might be favored, especially for frail patients. However, if pre-operative imaging shows enlarged cardiophrenic lymph nodes and the patient qualifies for upfront debulking surgery, their removal should be considered only for those patients in whom complete cytoreduction is feasible. It remains unclear whether the benefit of removing cardiophrenic lymph nodes arises from their direct removal or from other indirect indicators of a more favorable prognosis that enable the successful achievement of complete cytoreduction.

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