Ovarian cancer and isolated cardiophrenic lymph nodes metastases: a systematic review

Victoria Psomiadou[1], Alexandros Fotiou[2], Christos Iavazzo[1]

[1]Metaxa Memorial Cancer Hospital, Piraeus, Greece

[2]Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens Medical School, Attikon Hospital, Athens, Greece

Abstract

Currently, there is limited information available on the best course of action for advanced epithelial ovarian cancer (OC) with isolated extra-peritoneal disease in the cardiophrenic lymph nodes. Recently, there have been numerous reports of successful surgical removal of metastatic cardiophrenic lymph nodes in patients with OC, mostly during primary or interval cytoreduction procedures. However, the optimal management of isolated, extra-peritoneal cardiophrenic lymph node metastasis (ICLNM) remains unclear, since this clinical scenario is rather uncommon in OC and chemotherapy is so far the indicated treatment for patients with from advanced stage disease. We searched the English-language literature for cases of OC with ICLNM or recurrence, evaluating the feasibility and safety of surgical excision. From 2009 to 2022 only 11 cases were reported. In seven the tumor was of serous histology. ICLN was detected in five cases with primary disease and in the remaining six it was recurrence of OC. The primary disease was treated in 10/11 patients with primary cytoreduction while the other received systemic chemotherapy. The ICLNM was removed in all the patients, in 10 via video-assisted thoracic surgery and in one via transdiaphragmatic incision. Median follow-up was 10 months. (J Turk Ger Gynecol Assoc. 2025; 26: 49-54)

Keywords: Ovarian cancer, cardiophrenic lymph nodes, isolated metastasis

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Introduction

The existing literature reports that cardiophrenic lymph node metastasis (CLNM) affects 2.3% of ovarian cancer (OC) patients. Extra-abdominal metastases associated with OC were once considered a very poor prognostic indicator, with systemic therapy being the only treatment modality. Recently, extra-abdominal cytoreductive surgery has become increasingly popular as a proactive treatment choice for certain patients with thoracic metastases. This approach has been shown to enhance outcomes and extend survival for such patients, highlighting the importance of early intervention in these cases. Interestingly, the outcome for patients with CLNMs arising from OC is estimated to be less poor than that of other International Federation of Gynecology and Obstetrics (FIGO) stage IVB OC patients, reaching 68.9-72.3 months (1). Unfortunately, despite the better prognosis and the rising incidence of these cases, a consensus guideline approach has not yet been validated, and although much has been written regarding the management of intra-abdominal lymph node metastatic sites, little is known about the optimal approach in cases of isolated cardiophrenic lymph node metastasis (ICLNMs). More specifically, a recent study by Boria and Chiva (2) proposed that cardiophrenic lymph node resection can be safely performed in selected patients, but no survival benefit has been demonstrated to date. However, a recent study by Nasioudis et al. (3) indicated a higher survival rate in patients with OC isolated distant lymph node metastases compared to those with stage IV disease from other metastatic sites, potentially even comparable to patients

Address for Correspondence: *Victoria Psomiadou*
e-mail: *psomiadouvictoria@gmail.com* ***ORCID:*** *orcid.org/0000-0003-2028-6977*

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with stage IIIC disease. As a result, the removal of isolated cardiophrenic lymph nodes in FIGO stage IVB OC continues to be a topic of debate, and the present analysis seeks to clarify the feasibility and outcomes of such cytoreductive surgery in this specific group. Consequently, the reported cases of solitary extra-peritoneal cardiophrenic metastasis of OC that underwent surgical intrathoracic debulking were reviewed.

Material and methods

Data sources

The electronic databases PubMed and Google Scholar were searched by two authors (V.P. and A.F.). The literature search was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses guidelines (4). The search strategy used in both databases, included the combination of the keywords: (OC OR tubal OR peritoneal) AND (isolated cardiophrenic lymph node) AND (metastasis OR involvement). All databases were searched up to December 2023. The references of relevant articles were also manually searched for additional studies. Studies in languages other than English were excluded. The initially identified studies were screened, based on their title and abstracts against inclusion criteria. At the end of this initial search, all records considered eligible were included for full-text assessment.

Study selection criteria

All selected articles were in English and referred to studies on humans. Moreover, for a study to be included and it had to demonstrate histological or radiological diagnosis of ICLNM of an ovarian, tubal or peritoneal carcinoma. Review articles and studies with patients diagnosed with multiple metastatic sites and/or extended disease were excluded. Figure 1 demonstrates the selection strategies. All authors' agreed by consensus regarding the final decision on both inclusion and exclusion of the papers.

Results

The initial search yielded 27 citations, with an additional three studies included from manual bibliography searches. Four studies were excluded for being literature reviews, nine for focusing on radiological criteria, and 12 for discussing management options or surgical techniques related to cardiophrenic lymph node resection. Ultimately, five articles were chosen for analysis, as summarized in Table 1 (5-9).

Study results

Five studies with a total of 11 patients were investigated. In seven (63.6%) the primary tumor was of serous histology. By the time of the diagnosis of ICLNM, four (36.4%) had a primary and six (54.5%) had recurrent disease. For the treatment of the primary disease, nine (81.9%) underwent primary

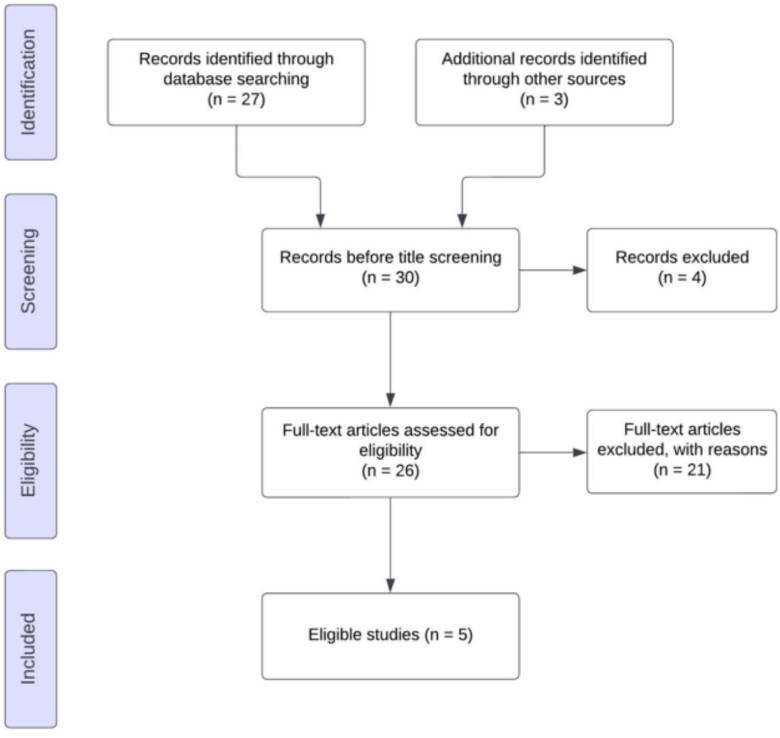

Figure 1. PRISMA flow-diagram

Table 1. Studies reporting data on isolated cardiophrenic lymph node metastasis in patients with ovarian cancer.

First author year	Number of patients	Age of patient (range)	Serous histology	Other histology	Primary disease	Recurrence	Main symptoms	Primary disease treatment		ISLN resection	LN treated with systematic therapy	Follow-up (mo)
								Chemo therapy	Surgical debulking			
Case series												
Euscher, (2004)	8	Median: 49.5 (30-68)	8	0	7	0	1: Neurological paraneoplastic syndrome	7	4	4	2	Median: 29 (12-166)
Blanchard, (2007)	7	NM	NM	NM	0	7	NM	NM	7	5	2	NM
Case reports												
Piura, (1989)	1	48	1	0	1	0	Mass	1	1 (secondary)	1	1	20
Mayadevi, (2005)	1	59	1	0	1	0	Mass	0	1	0	1	24
Gontier, (2006)	1	76	1	0	0	0	Mass	0	1	0	1	24
Keepanasseril, (2008)	1	33	0	1	1	0	Mass	0	1	0	1	10
He, (2013)	1	60	1	0	1	0	Bilateral mass	0	1	0	1	6
Puri, (2015)	1	65	0	1	0	1	Mass	0	1	0	1	NM
Kemal, (2016)	1	64	1	0	1	0	Mass	1	0	0	1	NM
Dhilon, (2013)	1	68	0	1	0	1	No	0	1	0	1	NM
Holmess, (2017)	1	32	0	1	0	1	Mass	0	1	1	0	NM
Tanaka, (2018)	1	65	1	0	0	1	Immobile mass	0	1	1	1	20
Baharudin, (2019)	1	28	1	0	1	0	Mass	1	1	1	0	12
Piciu, (2020)	1	75	0	1	0	1	Mass	NM	NM	0	1	NM

NM: Not mentioned

cytoreduction while one (9%) received a combination of neoadjuvant chemotherapy (NACT) and surgical resection. The median age at the time of diagnosis of the metastases was 50 years. The ICLNM was found at the right side in two patients (18%), on the left side in one (9%) and bilaterally in another two patients (18%) while for the other five the side was not specified. All 11 patients (100%) underwent surgical excision of the ICLN, in one case in conjunction with systemic therapy, but the included studies (5-9), showed variations in the method of treatment. Video-assisted thoracic surgery (VATS) was the most popular approach (n=10, 90.9%) while only one patient (9%) underwent transdiaphragmatic incision. Complications were reported in two (18%), one with pleural effusion that required medical treatment after VATS and one with postoperative chylothorax and chest liver herniation following a transdiaphragmatic resection. The mean follow-up of the patients was 10 months.

Discussion

The CPLNs are located in the thoracic cavity, typically positioned behind the sternum and between the diaphragm and the heart. These lymph nodes receive drainage from various organs, including the diaphragm, anterior part of the liver, pleura, and anterior chest wall. Diagnosing and reducing intrathoracic metastases originating from OC present significant challenges. Limited information is available on intrathoracic metastases specific to OC. Nevertheless, advances in surgical techniques, instrumentation, and perioperative care have made intrathoracic diagnosis and reduction safe and effective procedures (5).

This review showed that surgical lymph node dissection may be a viable management strategy for certain subsets of OC patients with ICLNM, with the goal of achieving improved survival rates. Our results align with a recent study from the Memorial Sloan Kettering Cancer Center team, which highlighted the safety and feasibility of intrathoracic cytoreduction in 178 advanced-stage OC patients. The study also suggested that this approach could result in significantly enhanced progression-free survival (PFS) and overall survival (OS) in carefully selected patients who can undergo tumor-free surgery, despite having extra-abdominal tumor burden. Furthermore, in the same study it was stated that instead of automatically considering NACT for patients with operable stage IV disease, it is now recommended to assess their eligibility for primary debulking surgery (PDS). Recent data shows promising results when comparing NACT to PDS, suggesting that high tumor burden stage IV patients may not always require NACT, as previously suggested (10).

The original classification of FIGO stage IV OC grouped patients based on disease burden, prognosis, and management recommendations. This included extra-peritoneal disease, such as pleural effusion, parenchymal liver metastases, and extra-abdominal lymph node involvement, such as the supraclavicular lymph nodes. However, in the 2014 revision, patients with pleural effusion were considered a separate category from those with parenchymal disease or metastases to extra-abdominal lymph nodes. Nasioudis et al. (3) reported that isolated distant lymph node metastases have a more favorable prognosis than stage IV disease with metastases in other sites, and are comparable to patients with stage IIIC disease. Zang et al. (11) compared stage IV OC patients with extra abdominal or intrahepatic metastasis and found that women with isolated supraclavicular lymphadenopathy or malignant pleural effusion had better survival rates than other stage IV patients. A study by Deng et al. (12) with 1,481 patients showed that the site of distant metastases significantly affects the overall prognosis in FIGO stage IV OC. These authors estimated a lower OS for parenchymal metastases compared to distant lymph node metastases. Similarly, in a comprehensive study, Hjerpe et al. (13) found that women with stage IV serous OC who only have lymph nodes as distant metastatic sites tend to have a longer survival compared to other stage IV patients. A recent review by Pergialiotis et al. (14) demonstrated that in OC patients with isolated lymph node recurrence (ILRN), survival was prolonged compared to recurrences in other sites. This type of recurrence seems to be less aggressive and can be treated with a combination of secondary cytoreduction and standard chemotherapy in selected cases (14), aligning with the previous research conducted by Uzan et al. (15), which proposed that patients with a prior isolated OC nodal recurrence may have a more favorable prognosis when undergoing surgical resection followed by chemoradiation or radiation therapy.

Regarding the identification of such rare metastases, radiology appears to play an essential role. More specifically, 10 out of 11 patients diagnosed with ICLNM were operated with VATS, meaning no abdominal surgery was performed. As a result, in those cases the isolated cardiophrenic metastasis diagnosis was based on imaging, in seven cases by computed tomography (CT) and in the other three by fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning. Only one patient underwent abdominal exploration during the complete cytoreduction and the initial radiological finding was confirmed by anatomopathological analysis. Typically, CT is the preferable radiological method for OC patients surveillance and staging and usually cardiophrenic lymph nodes larger than 5 mm are considered suspicious. However, according to Boria and Chiva (2), the confirmation rates in the final histological examination vary from 45-95%. Nevertheless, Hynninen et al. (16) demonstrated the inferiority of FDG PET/CT in detecting histologically confirmed supradiaphragmatic lymph node metastases when compared to conventional CT

and highlighted the correlation of this finding to the presence of ascites and subdiaphragmatic carcinomatosis compared to patients without it. Another possible method to localize suspicious CPLNs and to guide their surgical eradication was presented by Moro et al. (17) who performed intraoperative transdiaphragmatic ultrasound during a cytoreduction surgery and after the abdominal debulking was completed.

The optimal approach for dissection remains uncertain. In the majority of the centers that have reported cases of resection of cardiophrenic LNs, VATS has been used, but also transdiaphragmatic incision has been successfully conducted by Leray et al. (8). Interestingly, Minig et al. (18) and Yang et al. (19) proposed the subxiphoid approach to resect cardiophrenic lymph nodes, suggesting that it reduces the possibility of opening the pleural cavity, since it avoids a diaphragmatic incision and in most of the cases liver mobilization. Khatib et al. (20) also presented their approach via the subxiphoid route in order to resect prepericardiac and costophrenic lymph nodes without opening the diaphragm and with acceptable morbidity for patients.

Nevertheless, none of the studies manages to quantify any survival benefit of thoracic cytoreduction since the impact of ICLNM dissection has not been fully elucidated. Moreover, complications such as pleural effusion and pneumothorax are relatively common, while major complications also occur in 0-9% of patients (2). In our analysis, two cases (20%) reported complications: one involved pleural effusion requiring medical treatment after a VATS approach, and the other included chylothorax, atelectasis, and thoracotomy for chest liver herniation following a transdiaphragmatic incision.

However, a recent meta-analysis (21) has demonstrated that optimal tertiary cytoreduction surgery with an absence of residual tumor was associated with improved OS and PFS compared to suboptimal tertiary cytoreductive surgery and this is in line with previous retrospective analysis of tertiary cytoreduction (22,23). Recently Bruno et al. (24) reported proposed minimally invasive tertiary cytoreductive surgery because a patient presented with a pelvic ILRN, with a highly predictable optimal cytoreduction. Their experience confirmed that tertiary cytoreductive surgery may be considered an effective therapeutic option for management of ILRN, even in patients with *BRCA 1* or *BRCA 2* mutation-associated carcinoma already treated with PARPi. In particular, the personalization of the strategy and the achievement of a complete cytoreduction must be the aim of the treatment of these kind or recurrences. In this context, surgical excision may play a role if curative treatment for the abdominal disease is feasible. CLNMs are rare, with fewer than 10 eligible patients identified for this review. The scarcity of reported cases may be attributed to variations in the quality of radiological diagnosis of metastatic nodes. Most primary data comes from case series and reports, posing risks of selection and publication biases and only two databases (PubMed and Google) were included, thus representing a slight selection bias. The limitations in primary data restrict definitive conclusions on the optimal treatment of ICLNM. Therefore, the conclusions drawn are not recommendations due to the small sample sizes.

Conclusion

Our findings may be less robust than original, higher-quality evidence. Further single-center case series are unlikely to significantly contribute to the existing knowledge base. Therefore, there is a need for more extensive and impactful research in this area. Due to the rarity of ICLNM, traditional study recruitment methods may not reach the necessary patient numbers for meaningful results, making a multinational registry essential for additional data. Furthermore, expert consensus opinions would benefit clinical teams treating patients with ICLNM. Currently, this review serves as a summary of the current understanding in this field, offering a contemporary overview to assist clinicians in treating patients with ICLNM from primary or recurrent OC.

Footnotes

Author Contributions: *Surgical and Medical Practices: V.P., A.F., C.I., Concept: V.P., A.F., C.I., Design: V.P., A.F., C.I., Data Collection or Processing: V.P., A.F., C.I., Analysis or Interpretation: V.P., A.F., C.I., Literature Search: V.P., A.F., C.I., Writing: V.P., A.F., C.I.*

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