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Cardiophrenic lymph node resection in cytoreduction for primary advanced or recurrent epithelial ovarian carcinoma: a cohort study

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HIGHLIGHTS

- Cardiophrenic lymph nodes may be a site of metastasis of ovarian cancer.
- Histologically positive cardiophrenic lymph nodes likely indicate a future recurrence.
- Resection should be considered in cases of suspicious involvement and to achieve complete cytoreduction.

ABSTRACT

Objectives To evaluate the clinical outcomes of epithelial ovarian carcinoma patients who underwent cardiophrenic lymph node resection.

Methods We retrospectively reviewed the records of all surgically treated patients with advanced epithelial ovarian carcinoma (stages IIIC–IV) who underwent cardiophrenic lymph node resection between 2002 and 2018. Only those in whom cardiophrenic lymph node involvement was the only detectable extra-abdominal disease were included. Patients with suspected cardiophrenic lymph node metastasis on staging images underwent a transdiaphragmatic incision to access the para-cardiac space after complete abdominal cytoreduction achievement. Data on disease-free survival, overall survival, and surgical procedures performed concurrently with cardiophrenic lymph node resection were collected.

Results Of the total 456 patients, 29 underwent cardiophrenic lymph node resection; of these, 24 patients met the inclusion criteria. Twenty-two, one, and one patients had high grade serous epithelial ovarian carcinoma, low grade epithelial ovarian carcinoma, and ovarian carcinosarcoma, respectively. Ten patients had recurrent disease (recurrence group). Fourteen patients underwent cytoreduction during primary treatment (primary debulking group); four underwent cytoreduction after neoadjuvant chemotherapy. Cardiophrenic lymph node resection was performed on the right side in 19 patients, left side in three, and bilaterally in two. The average procedural duration was 28 minutes, with minimal blood loss and no severe complications. Twenty-one patients had cardiophrenic lymph node positivity. The median disease-free intervals were 17 and 12 months in the recurrent and primary debulking surgery groups, respectively. The mediastinum was the first recurrence site in 10 patients. Five patients developed brain metastases. Five patients had an overall survival beyond 50 months.

Conclusions Although rare, the cardiophrenic lymph nodes may be a site of metastasis of ovarian cancer. Although their presence might indicate future recurrence, some patients may achieve long-term survival. Resection should be considered in cases of suspicious involvement to confirm extra-abdominal disease and achieve complete cytoreduction.

INTRODUCTION

Patients with primary or recurrent epithelial ovarian carcinoma, who undergo complete cytoreduction, have better overall survival rates and longer disease-free intervals than those with residual disease.[1–3] Debulking surgery is performed to achieve complete surgical resection in patients with advanced or recurrent epithelial ovarian carcinoma.[4 5] Procedures of a more radical nature have been introduced for complete cytoreduction achievement, including the resection of distant metastases at extra-abdominal sites.[2] Accordingly, a survival benefit was observed in a selected population of patients with stage IV disease or with recurrent but completely resectable disease.[1–3 5 6]

The cardiophrenic lymph nodes, also referred to as superior diaphragmatic or para-cardiac lymph nodes, are located in the most basal portion of the mediastinum between the heart and the diaphragm. They are classified as anterior pre-pericardiac and middle latero-pericardiac, as well as right and left, using the midline as a reference.[7 8] In patients with ovarian carcinoma, enlarged (size >8 mm) cardiophrenic lymph nodes detected via imaging may represent metastatic disease,[4 8] particularly if the patient has extensive tumor spread in the upper abdomen.

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Cardiophrenic lymph node resection is used for appropriate staging and complete cytoreduction.[7–9] As they are unusual sites of metastatic disease, cardiophrenic lymph nodes may go unnoticed in staging examinations.[10] There is an 85% probability of detecting cardiophrenic lymph node metastasis in advanced ovarian carcinoma if the short axis of the nodes exceeded 7 mm.[11]

Cardiophrenic lymph node enlargement has been associated with a reduced likelihood of achieving complete chemotherapy response and shorter disease-free interval and overall survival.[11] However, the prognostic impact of cardiophrenic lymph node resection remains uncertain, particularly when complete cytoreduction is feasible. Furthermore, the disease progression status following complete cytoreduction in confirmed ovarian carcinoma metastases patients remains unknown.[12]

In this study, we reviewed our experiences with the management of women with primary or recurrent epithelial ovarian carcinoma who underwent surgical resection of the cardiophrenic lymph nodes during cytoreductive debulking surgery with the achievement of a complete abdominal cytoreduction. We aimed to report on patient outcomes and long-term follow-up results.

METHODS

This retrospective cohort review included patients with epithelial ovarian carcinoma who underwent cardiophrenic lymph node resection as part of a secondary or primary cytoreduction (including primary debulking and after neoadjuvant chemotherapy) from 2002 through June 2018 at the Instituto Brasileiro de Controle do Cancer and the Instituto do Cancer do Estado de Sao Paulo.

Cardiophrenic lymph nodes were considered suspicious if the short axis size was ≥8 mm on preoperative computed tomography (CT) or magnetic resonance imaging (MRI).[8 11] Patients were also considered for resection if they exhibited 18-fluorine fluorodeoxyglucose uptake in the cardiophrenic lymph nodes on positron emission tomography (PET-CT).[13] For all patients, the cardiophrenic lymph nodes were the only detectable site of extra-abdominal disease. Patients with parenchymal disease at other sites were excluded. Cardiophrenic lymph node resection was performed only after the achievement of complete abdominal cytoreduction. In all cases, the right and/or left para-cardiac spaces were accessed via a transdiaphragmatic approach to reach the fat pad containing the lymph nodes.

Data regarding disease-free survival, overall survival, first recurrence site, and the surgical procedures performed concurrently with cardiophrenic lymph node resection were collected. Disease status at diagnosis, patient characteristics, and diagnostic imaging reports were recorded.

To observe possible disease recurrence, patients were followed-up for at least 6 months after cardiophrenic lymph node resection and/or until death. Overall survival and follow-up durations were calculated from the ovarian carcinoma diagnosis date to the date of the last follow-up or death. Disease-free survival was calculated from the date of cardiophrenic lymph node resection to the first date of progression. Kaplan–Meier analyses were used to estimate overall survival, disease-free survival, and follow-up durations. Patients were staged according to the 2014 International Federation of Gynecology and Obstetrics classification.

Surgical Technique

To ensure adequate diaphragm exposure, a midline abdominal incision extending to the xyphoid process was made and an external retraction device was used. In some cases, liver mobilization was necessary. After adequate exposure, a longitudinal incision was made in the direction of the diaphragm muscle fibers to gain access to the pleural and cardiophrenic spaces. The incision was made to the left or the right of the midline, according to the lymph node topography on preoperative imaging exams, and approximately 2.0 cm lateral to the midline to avoid damage to the diaphragmatic vessels and nerve or the hepatic vein on the right side. If diaphragmatic resection was required during debulking, the lymph nodes were resected through the incised diaphragm. Our approach was similar to those previously described.[4 14]

After identifying the fat pad containing the suspected lymph nodes, the resection was performed using surgical metal clips or a sealing cut device, avoiding any pericardial damage. An approximation of the opened diaphragm was performed via a continuous suture using long lasting absorbable suture thread. Aspiration and, if necessary, thoracostomy were performed when closing the diaphragm. Details on the surgical technique are presented in Figure 1.

RESULTS

During the study period, 456 patients with International Federation of Gynecology and Obstetrics stage IIIC–IV epithelial ovarian carcinoma were surgically treated at both participating institutions. Twenty-nine cytoreductive procedures involving cardiophrenic lymph node resection were identified (6.3%). Five patients with histologically positive cardiophrenic lymph nodes were not included in the study; of these, three with recurrent disease were excluded because of the presence of either parenchymal or other extra-abdominal diseases concomitant with cardiophrenic lymph node resection. Two patients who underwent primary cytoreduction were also excluded due to a follow-up <6 months. Hence 24 patients were included in the study: 22 patients had high grade serous epithelial ovarian carcinoma, 1 patient had low grade serous epithelial ovarian carcinoma, and 1 patient had histologically diagnosed high grade carcinosarcoma. Median age at resection was 56 years (range 45–76 years).

Ten platinum sensitive patients were treated for recurrent disease with secondary cytoreduction. Of these patients, all had International Federation of Gynecology and Obstetrics stage IIIC disease at diagnosis, and nine had previously undergone complete primary cytoreduction. The disease-free survival interval to histologically confirmed cardiophrenic lymph node metastasis ranged from 13 to 61 months (median 28 months). One patient in this subgroup received platinum-based chemotherapy prior to secondary cytoreduction. The remaining 14 patients underwent resection as part of the primary treatment; of these, 7 received neoadjuvant chemotherapy comprising carboplatin plus taxane (3–6 cycles) because of large volume disease and/or a poorer performance status.

A total of 19, 3, and 2 patients underwent resection of the right, left, and bilateral cardiophrenic lymph nodes, respectively. An average of 1.5 (range 1–6) lymph nodes were resected. In 21 (87%) patients, the cardiophrenic lymph node was positive for metastatic
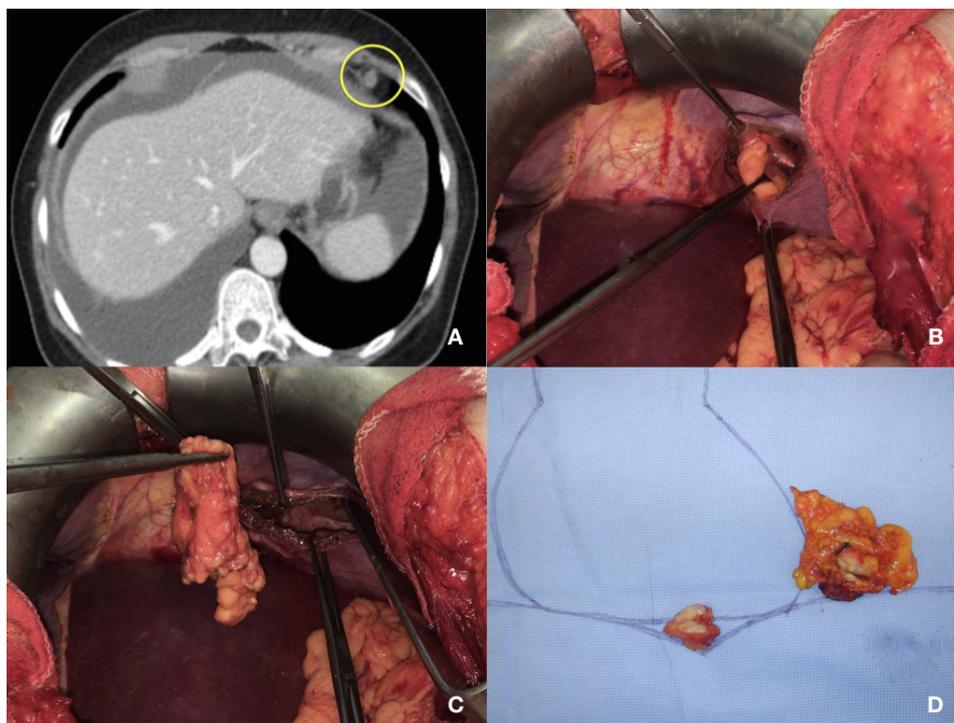
Figure 1 Stepwise resection of the cardiophrenic lymph nodes: suspicious diagnostic features on images, surgical techniques, and resection specimens. (A) Enlarged (15 mm) left cardiophrenic lymph node identified on computed tomography. (B) Incision of the left diaphragm and traction of the fat pad containing cardiophrenic lymph nodes. (C) Resected fat pad containing left cardiophrenic lymph nodes. (D) Macroscopic image of specimens from bilateral cardiophrenic lymph node resection.

disease. Twelve patients in the primary treatment group were upstaged from stage IIIC to IV based on cardiophrenic lymph node positivity. Of the five patients who underwent neoadjuvant chemotherapy, three had residual viable tumor cells in the lymph nodes and two achieved complete pathological response in the resected tissue, with signs of tumor regression. We considered these cardiophrenic lymph nodes to be positive. One patient in the recurrence group with cardiophrenic lymph node negativity had a low grade serous carcinoma and was the only patient who underwent chemotherapy prior to secondary cytoreduction; no sign of tumor regression was observed in the resected lymph node.

The average duration of cardiophrenic lymph node resection was 28 minutes, with minimal blood loss. In all cases, the diaphragm was primarily sutured without mesh or graft requirement. Twenty-three patients underwent thoracostomy with a 28-Fr chest tube or pigtail pneumothorax drainage system. The chest tubes were removed after an average of 48–72 hours (range 2–7 days). The most common thoracic complications were non-complicated pulmonary atelectasis in six patients, while four reported moderate to severe pain due to chest tube placement. The pericardium was opened in two cases; in the first, the opening was incidental, while in the second, the pericardium and phrenic nerve were resected due to contiguous tumor invasion. Pericardial openings occurred during right sided dissection and were kept open per the surgeon's decision in both cases. No deaths occurred within 60 days of the procedure, and no other major cardiophrenic lymph node resection specific complications, such as thoracic lymphatic fistula, intrathoracic hemorrhage, pleuritis, or pneumonia, were reported.

The average size of the enlarged cardiophrenic lymph nodes was 14 mm (range 8–25 mm). In three patients with histologically negative nodes, cardiophrenic lymph node sizes of 10, 14, and 20 mm, as measured by CT and/or MRI, were observed. Thirteen patients exhibited 18-fluorine fluorodeoxyglucose uptake in the cardiophrenic lymph nodes on PET–CT images, and all had histologically positive lymph nodes.

The surgical procedures performed concurrently with cardiophrenic lymph node resection included modified radical hysterectomy with bilateral salpingo-oophorectomy, omentectomy, rectosigmoidectomy, pelvic and para-aortic lymphadenectomy, diaphragmatic stripping or resection, partial gastrectomy, splenectomy, distal pancreatic resection, and Glisson's liver capsule resection. One patient only underwent cardiophrenic lymph node resection. The associated surgical procedures and patient characteristics are described in Table 1.

None of the 21 patients with cardiophrenic lymph node positivity were lost to follow-up. Nineteen of these patients underwent postoperative platinum-based chemotherapy. Eighteen of the 21 patients developed recurrence, and 11 died of causes related to the disease. Of the deceased patients, four died of brain metastasis within an average of 12 months after recurrence. One patient died 4 months after surgery of causes unrelated to cancer. The two remaining patients without recurrent disease were followed-up for 9 and 18 months, respectively. The median estimated disease-free survival intervals of the recurrence and primary debulking groups were 17 (95% confidence interval (CI) 15.8 to 18.1) and 12 (95% CI 7.2 to 16.7) months, respectively, and the corresponding median

Table 1   Patient characteristics and procedures associated with cytoreduction surgery

	Primary (n=12)	Recurrent (n=9)
Age (years) (median (range))	58 (38–79)	
Chemotherapy prior to resection (n)	7	1
Cardiophrenic lymph node size (mm) (median (range))	13 (8–25)	
No of resected cardiophrenic lymph nodes (median (range))	2 (1–6)	1 (1–2)
No of positive cardiophrenic lymph nodes (median (range))	2 (1–5)	1 (1–2)
Associated procedures (n (%))		
Diaphragmatic peritonectomy/resection	10 (83)	5 (55)
Splenectomy	4 (33)	3 (33)
Distal pancreatectomy	0	2 (22%)
Hepatic capsule resection	5 (41)	4 (44)
Cholecystectomy	6 (50)	2 (22)
Partial gastrectomy	1 (8)	2 (22)
Pelvic lymphadenectomy	9 (40)	4 (44)
Para-aortic lymphadenectomy	9 (40)	3 (33)
Modified radical hysterectomy	11 (91)	1 (11)
Bilateral adnexectomy	11 (91)	0
Rectosigmoidectomy	6 (50)	1 (11)
Omentectomy	12 (100)	3 (33)

overall survival durations were 66 (95% CI 9.8 to 122.1) and 30 (95% CI 22.5 to 37.4) months, respectively. The median follow-up durations of the recurrence and primary debulking groups were 49 (95% CI 0 to 119.8) and 30 (95% CI 22.5 to 37.4) months, respectively. Figure 2 presents the Kaplan–Meier estimations of disease-free survival and overall survival for both groups. Five patients with histologically positive cardiophrenic lymph nodes (four of whom belonged to the recurrence group) achieved survival durations >48 months (range 48–120 months) from the date of cardiophrenic lymph node resection.

In 10 patients, the mediastinum was the first site of disease recurrence, with synchronous metastases in other sites, such as the peritoneum (n=3), lung (n=2), pleura (n=1), brain (n=1), and brain and peritoneum (n=1). Five other patients first developed peritoneal recurrences without mediastinal metastases. Of these, one patient each also developed recurrences in the brain and pleura. Two additional patients developed recurrence in the brain only. One patient only developed pleural recurrence. The sites involved sites are described in Figure 3.

DISCUSSION

In this study, we analyzed a cohort of patients with epithelial ovarian carcinoma who underwent resection of the cardiophrenic lymph nodes during primary or secondary cytoreduction, and found that although rare, cardiophrenic lymph nodes may be ovarian cancer metastasis sites and potential indicators of future recurrence.

The maximal surgical debulking effort philosophy has changed the concept of cytoreduction for ovarian cancer treatment.[1] Significant correlations between complete disease resection and increased overall survival and disease-free survival were observed even among patients with primary advanced stage or recurrent disease.

This approach includes the use of more radical surgical procedures in the upper abdomen and extra-abdominal sites, particularly if limited disease is detectable, with consequent improvements in the cytoreduction rates.[15 16]

Cardiophrenic lymph nodes, considered extra-abdominal sites,[2 3 5] may be a site of metastatic disease in patients with epithelial ovarian carcinoma who have extensive upper abdominal disease, particularly with diaphragmatic involvement.[4 10 17 18] Cardiophrenic lymph node enlargement has been associated with a lower complete chemotherapeutic response rate, as well as shorter disease-free and overall survival intervals.[4 11–13 17 18] However, limited evidence is available regarding the long-term outcomes of histologically positive cardiophrenic lymph nodes, and the prognostic impact remains uncertain, particularly in cases of complete cytoreduction.

Although cardiophrenic lymph node involvement should not contraindicate a complete cytoreduction procedure, it may be a marker of advanced disease.[10] If cardiophrenic lymph node involvement is suspected, resection should be considered in primary treatment settings as these patients could be upstaged to International Federation of Gynecology and Obstetrics stage IVB or in a recurrent disease setting if complete cytoreduction is feasible.

The paucity of reports on enlarged cardiophrenic lymph nodes is likely due to a lack of extensive research on these entities; additionally, data relevant to epithelial ovarian carcinoma have only recently been published.[4 8 10 13 19 20] Given the high positivity rates in previous reports,[4 10] a cardiophrenic lymph node with a short axis >8 mm may provide important information to surgeons. A short axis cut-off of 5 mm has been suggested as a normal cardiophrenic lymph node size.[18] A recent study reported a 90% positive predictive value for histologically proven cardiophrenic lymph nodes, using a short axis diameter of 10 mm on preoperative CT as
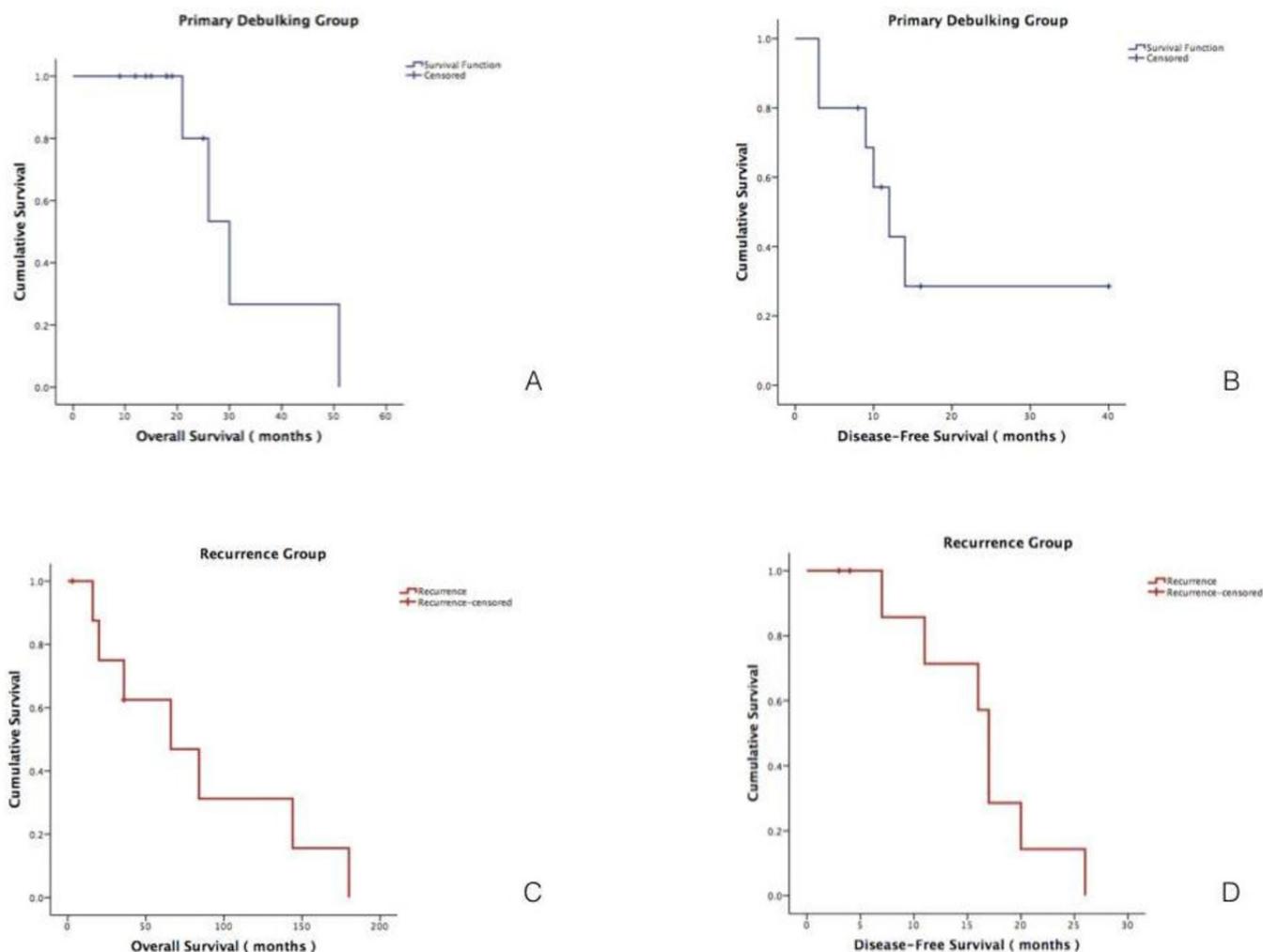
Figure 2 Kaplan–Meier curves of (A) the median disease-free survival of 12 (95% confidence interval (CI) 7.2–16.7) months and (B) median overall survival of 30 (95% CI 22.5–37.4) months in the primary debulking group. Kaplan–Meier curves of (C) median disease-free survival of 17 (95% CI 15.8–18.1) months and (D) median overall survival of 66 (95% CI 9.8–122.1) months in the recurrence group.
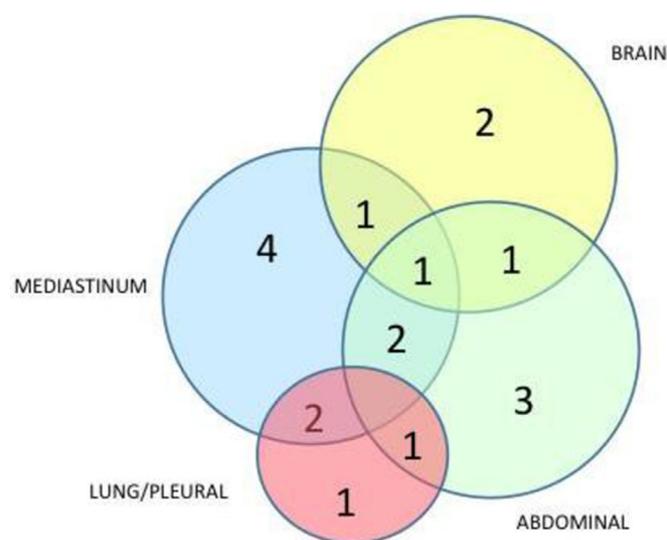

Figure 3 First sites of metastatic disease in patients undergoing cardiophrenic lymph node resection with disease positive nodes. The number of patients with metastatic disease per site are indicated.

a reference.[4] In our cohort, the cardiophrenic lymph nodes were not identified in seven radiological reports, and cardiophrenic lymph node resection was considered only after a multidisciplinary review of the imaging scans.

In our study, PET–CT yielded a sensitivity of 100%. However, given the high rate of positivity (±90%) associated with cardiophrenic lymph node sizes >8 mm[4 12] on CT or MRI, we do not consider PET–CT to be essential, especially in public service settings where this modality is not always available. However, PET–CT may be highly specific and can be ordered if the diagnosis is unclear.

The existing literature describes various techniques and possible approaches for cardiophrenic lymph node resection used at specialty centers. Lim et al reported nine cases of cardiophrenic lymph node resection performed using video assisted thoracic surgery.[6] In 2013, Yoo et al reported on a series of 11 patients with primary and recurrent disease in which cardiophrenic lymph node resection was performed transdiaphragmatically. The authors discussed some advantages of this technique, including the lack of a need to change the patient's position for video assisted thoracic surgery, feasibility of procedural performance by a gynecologic oncologist, and lack of requirement for chest tube insertion.[20] In

a series by Cowan et al, cardiophrenic lymph node resection was performed either using video assisted thoracic surgery or via the transdiaphragmatic or subxiphoid approach.[19] In the subxiphoid approach, the anterior insertion of the diaphragm is dissected in an attempt to leave this muscle intact and not open the pleural space.[21] However, some surgeons do resect or divide the cartilage within the xiphoid process cartilage.[22] Nevertheless, in all of our cases, it was possible to dissect and resect the cardiophrenic lymph nodes on the sides via the transdiaphragmatic approach, without additional procedures. In addition, thoracic drainage was performed in nearly all cases according to the surgeon's discretion, with the intent to monitor or treat any possible thoracic complications, especially in cases involving diaphragm muscle resection. However, some groups do not routinely perform thoracic drainage, opting instead for air aspiration during diaphragmatic closure.[12]

Our study had some limitations, particularly pertaining to the retrospective design and limited number of cases. In a retrospective study of 54 patients with stage IIIC–IV disease who underwent complete or suboptimal cytoreduction, although the reported disease-free survival and overall survival durations were 17.1 and 70.1 months, respectively, 83% of the patients experienced recurrence.[19] In our cohort, most patients experienced recurrence and these recurrences frequently occurred in unusual sites, such as the brain and mediastinum, despite our use of stricter inclusion criteria—namely, the cardiophrenic lymph node being the only detectable site of extra-abdominal disease and absence of parenchymal metastases. Furthermore, although all patients with longer follow-ups developed recurrences, some achieved long-term overall survival.

Further, the incidence of brain metastases in our cohort was higher than expected; this pattern of recurrence may have affected survival outcomes. In contrast with the reported symptomatic brain metastasis incidence rate of 1% in patients with epithelial ovarian carcinoma,[23] five patients in our study (27%) developed recurrence in the brain. Dvoretsky et al published an autopsy series of 100 patients with ovarian cancer in which the incidence of brain metastases was 6%. Moreover, 63% and 29% of the cases had diaphragmatic and mediastinal involvement, respectively, and these disease spread patterns are very similar to those in our cohort.[24] Güth et al published autopsy results from 166 patients with epithelial ovarian cancer in which the incidence of brain metastases was 2.4%. However, 66.3% of the patients in that study harbored metastases to extra-abdominopelvic sites.[25] Nevertheless, we were unable to identify the reason for the higher incidence of cardiophrenic lymph node metastases and brain recurrence in our cohort.

CONCLUSION

Cardiophrenic lymph node resection is a feasible procedure associated with low morbidity, and should be considered in cases of suspected cardiophrenic lymph node involvement, to achieve complete cytoreduction and confirm extra-abdominal disease. Notably, survival was affected by tumor biology and the treatments administered after cardiophrenic lymph node resection, including multiple chemotherapy regimens and secondary or tertiary cytoreduction, in some cases. Nevertheless, complete resection of all visible disease in cases with recurrent or primary epithelial

ovarian carcinoma may significantly contribute to longer survival. Further, cardiophrenic lymph node metastasis in ovarian cancer is uncommon. Although our findings are not conclusive, histological cardiophrenic lymph node positivity likely indicates future recurrence. Further studies with larger cohorts are needed to confirm these findings and assess the impact of cardiophrenic lymph node resection on long-term outcomes (overall survival and disease-free survival).

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