CASE REPORT

Relevance of enlarged cardiophrenic lymph nodes in determining prognosis of patients with advanced ovarian cancer

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SUMMARY

Ovarian cancer often presents at an advanced stage with widespread peritoneal and/or extra-abdominal metastases. Complete cytoreduction is the mainstay of treatment for disease confined to peritoneum. But in patients with distant metastases, the role and rationale is less obvious. One of the most common sites of extra-abdominal disease is the cardiophrenic lymph node (CPLN). In this paper, we described the management of a patient with International Federation of Gynecology and Obstetrics (FIGO) stage IVB epithelial ovarian carcinoma and widespread peritoneal and extra-abdominal metastases to the CPLN, who underwent complete cytoreduction including excision of enlarged CPLN, following neoadjuvant chemotherapy. We examined the literature to determine the prognostic value of enlarged CPLN and their relevance in managing patients with advanced ovarian cancer and found it as an adverse prognostic factor. Transdiaphragmatic excision of CPLN is feasible without major complications. But as its correlation with overall or progression-free survival is not yet evident, large-scale prospective studies are warranted.

BACKGROUND

Ovarian cancer is the seventh most common cancer in women worldwide, with 239 000 new cases diagnosed in 2012.¹ Patients with early-stage ovarian cancer are often asymptomatic, and as a result, approximately 75% of ovarian cancer is diagnosed at an advanced stage (FIGO IIIC–IV).² The 5-year survival rate ranges from approximately 30% to 50%.¹

The mainstay of treatment for stage III epithelial ovarian cancer (EOC) confined to the peritoneum is optimal cytoreduction. This has been shown to significantly improve overall survival (OS) and progression-free survival (PFS).³ The benefit of complete cytoreductive surgery has also been shown for selected patients with stage IV EOC, even in the presence of extra-abdominal distant disease.^{4,5}

One of the most common sites of extra-abdominal disease in patients with peritoneal metastases is the cardiophrenic lymph node (CPLN).⁶ In this paper, we aim to examine the prognostic relevance of enlarged CPLN in the management of patients with advanced ovarian cancer and report on a patient with FIGO stage IVB EOC, who underwent

complete cytoreduction including excision of involved CPLN.

CASE PRESENTATION

The patient presented here is a 43-year-old, para 3, gravida 3, premenopausal Indian woman, who presented with a persistent painless umbilical ulcer of 1½ months' duration, which was progressively enlarging and discharging serous, foul-smelling fluid. She denied any trauma to her abdomen prior to the ulcer formation and had no fever nor abdominal distension or discomfort. In addition, she had no weight loss, shortness of breath, vaginal discharge or bleeding, changes in bowel habit or early satiety. She has a known medical history of type 2 diabetes and asthma. She denied any family history of malignancy.

The patient initially saw a primary care physician for the umbilical ulcer, who treated her with antibiotics for 2 weeks, along with dressing of the wound, but as it was not improving, she was referred to a tertiary care hospital.

On examination, she was alert, comfortable, with no conjunctival pallor or scleral icterus. An umbilical ulcer, overlying a hard subcutaneous nodule, with a foul-smelling serous fluid discharge was noted. Her abdomen was mildly distended but non-tender. A large pelvic mass was palpated that extended beyond the pubic symphysis. On digital rectal examination, there was no obvious pouch of Douglas mass, but the pelvic mass was felt at the tip of the examining finger with no rectal mucosal abnormalities.

INVESTIGATIONS

After the initial consultation, a contrast enhanced CT scan of her abdomen and pelvis was performed. This revealed a 13.2×17.6×16.0 cm loculated, mixed cystic solid mass extending from the pelvis into the abdomen. The lesion demonstrated heterogeneous enhancement and appeared to arise from the right ovary and was suspicious for an ovarian tumour. A 6.5×5.3 cm left ovarian cyst with internal septations was also present. There was associated free fluid in the lower abdomen but no gross ascites. The umbilicus contained a soft tissue nodule measuring 2.0×3.0 cm. The liver, kidneys, spleen, pancreas, bladder and adrenals were unremarkable. In addition, several enlarged lymph nodes were noted at the aortocaval region, measuring up to

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Figure 1 Contrast-enhanced CT scan of abdomen and pelvis showing (A) right CPLN, (B) left CPLN and (C) mixed cystic solid right ovarian mass along with the Sister Mary Joseph nodule. CPLN, cardiophrenic lymph node.

1.2 cm. The right CPLN measured 2.1×0.6 cm and left CPLN measured 1.2×0.7 cm (figure 1).

Her biochemical investigation revealed an elevated cancer antigen (CA)-125 of 1156 IU/mL (normal <351 IU/mL). An incisional biopsy of her umbilical nodule was subsequently performed and the histology revealed a high-grade carcinoma in keeping with a high-grade serous carcinoma of ovarian/peritoneal origin. The lesional cells immunoprofile were positive for CK7, WT1, PAX8, ER (Estrogen receptor : 80% showing 1 to 2+ staining intensity) and negative for CK20, CDX2 and GATA3.

As part of her staging work-up, a positron emission tomography (PET)-CT scan was ordered, which gave radiological findings similar to that of the CT scan. The CPLN measured 2.2×0.8 cm on the right (Maximum standardized uptake value, SUV_{max} 6.2) and 1.3×0.7 cm on the left (SUV_{max} 3.4) (figure 2). Additionally, she was noted to have significant ascites with suspicious peritoneal metastases scalloping the right hepatic lobe, splenic capsule and splenic flexure.

In view of her extensive disease, she underwent three cycles of neoadjuvant chemotherapy with paclitaxel and carboplatin and achieved a good response. A CT scan of her thorax, abdomen and pelvis postneoadjuvant chemotherapy showed interval decrease in the size of the bilateral ovarian masses; the right ovarian solid-cystic mass was 15×11 cm and the left ovarian lesion was 7.7×7.3 cm. The previously noted peritoneal nodules were barely discernible, and there was a decrease in prominence of the 18F-fluorodeoxyglucose (FDG) avid bilateral CPLN and intra-abdominal nodes. The umbilical soft tissue nodule was also barely discernible on the scan. Her CA-125 had also decreased to 285 from 1156 IU/mL.

TREATMENT

Her case was discussed at the multidisciplinary tumour board meeting and the recommendation was for complete cytoreductive surgery along with resection of bilateral CPLN, followed by adjuvant chemotherapy.

She was optimised for surgery and underwent a laparotomy. Intraoperatively, a small amount of ascites, a 20 cm right ovarian solid cystic tumour, a 7 cm left ovarian tumour, a normal uterus and bilateral tubes were found. There were a few tumour deposits seen on the small bowel and descending colon mesentery, greater omentum and both diaphragmatic surfaces. There were no obvious liver metastases visualised or palpated. The pelvic and para-aortic lymph nodes were enlarged up to the level of the left renal vein.

She underwent cytoreductive surgery that included a total hysterectomy with bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, omentectomy, stripping of bilateral subdiaphragmatic peritoneum and resection of the Sister Mary Joseph nodule, en-bloc with the umbilicus. A subxiphoid approach was then used to assess and resect bilateral CPLN. The right pleural cavity was breached during excision of the right CPLN while three left CPLN were excised without entering the left pleural cavity. The right diaphragm was repaired primarily with non-absorbable sutures and a right chest tube was inserted. There was no residual disease at the end of the surgery.

The patient was nursed in the surgical high-dependency ward postoperatively and made an uneventful recovery, with no significant abdominal or pulmonary complications. The right chest tube was removed on the 4th postoperative day (POD), and she was discharged on the POD 11.

Figure 2 PET-CT scan showing the FDG avid (A) Right CPLN, (B) Left CPLN and (C) Right ovarian mass along with the Sister Mary Joseph nodule. FDG, 18F-fluorodeoxyglucose; PET, positron emission tomography.

OUTCOME AND FOLLOW-UP

The final histology revealed a high grade serous carcinoma of bilateral ovaries with right ovarian surface involvement, and lymphovascular invasion. The right fallopian tube was also involved by the tumour. The omentum, mesenteric nodules, right subdiaphragmatic peritoneum, and right pelvic peritoneum were positive for metastatic carcinoma. Additionally, 11 out of 19 para-aortic lymph nodes, 3 out of 18 right pelvic lymph nodes and 3 out of 6 presacral lymph nodes were positive for metastatic carcinoma. All 14 left pelvic lymph nodes were negative for malignancy. One right CPLN and three left CPLNs were positive for metastatic carcinoma.

Further, six cycles of adjuvant chemotherapy with paclitaxel and carboplatin have been planned for her that started on the POD 25.

DISCUSSION

Methodology

PubMed, Cochrane Library and Google Scholar were searched for articles published in English on cardiophrenic lymph node and ovarian cancer from January 1990 to August 2017 to investigate the relevance of CPLN in determining prognosis of patients with advanced epithelial ovarian cancer. Twenty-one items were found in PubMed, 377 articles were found in Google scholar. The reference lists of relevant articles were also searched. A total of 41 relevant articles were found which were used as references. Fourteen of those were summarised in a table.

Literature review and discussion

FIGO stage IV ovarian carcinoma is defined as the presence of distant metastasis excluding peritoneal metastases. This includes pleural effusion with positive cytology (stage IVA), lung parenchymal metastases and metastases to extra-abdominal organs including inguinal lymph nodes and lymph nodes outside of the abdominal cavity (stage IVB).⁷ These extra-abdominal metastases are found to be present in 12%–33% of the patients at initial diagnosis.⁸ Overall, median survival for patients with stage IV disease ranges from 15 to 29 months, with an estimated 5-year survival of approximately 20%.⁸ In presence of CPLN, the patient discussed above, suffered from stage IVB ovarian cancer.

The terminology for lymph nodes at the low anterior mediastinum is not uniform, and they have been referred to as precordial, paracardial, mediastinal, retrosternal, epiphrenic, supradiaphragmatic or CPLN.⁹ CPLN has also been described in patients with lung, oesophageal and colorectal cancer and in patients with lymphoma.¹⁰ In patients with EOC, enlarged CPLN has been reported in up to 10.5% of patients.¹¹ Even isolated bilateral CPLN metastasis from previously resected ovarian carcinoma, with no peritoneal and pleural involvement has been reported.¹² It has been described as a possible predictive parameter for the failure of optimal debulking surgery¹³ and are associated with impaired OS.¹⁴

Over the past three decades, it has been established that one of the most important prognostic factors in patients with stage III EOC is optimal abdominal cytoreduction at initial surgery.⁴ This benefit has also been shown for patients with stage IV EOC, although, in these patients, disease has spread to extra-abdominal sites.⁴

The criteria for optimal cytoreductive surgery have changed over time: before the year 2002, optimal cytoreduction was considered if the residual tumour was <2 cm in size. Beyond 2002, this cut-off was changed to <1 cm and subsequently complete cytoreduction, with no macroscopic tumour left behind, was the

designated gold standard.¹⁵ Since then, numerous studies have demonstrated a survival advantage for patients who undergo 'optimal' versus 'suboptimal' cytoreduction.^{16–20}

Although various cut-off points have been used to define optimal cytoreduction (residual disease ranging from 0 to 3 cm), the Gynecologic Oncology Group currently uses 1 cm as a cut-off.²¹ It is also important to note that for patients who are suboptimally cytoreduced, survival is equivalent regardless of residual tumour size,^{13 22 23} which emphasises the importance of complete cytoreduction.

Chi *et al* demonstrated that along with traditional primary cytoreductive surgery, incorporating procedures such as resection of diaphragm, peritonectomy, splenectomy, distal pancreatectomy, partial hepatectomy, cholecystectomy and portal caval dissection to address tumour deposits in the upper abdomen has led to improved optimal cytoreduction rate without any significant change in complication rates and length of hospitalisation.¹⁹ In another study, Chi *et al* identified the amount of residual disease as a significant prognostic factor ($P < 0.001$). He showed that patients with no gross residual disease achieved a median OS of 106 months compared with patients with residual tumour of >0.5 cm ($P < 0.01$).²³ Even in patients with unresectable liver metastasis, optimal debulking of extrahepatic disease was associated with a significant survival advantage.²⁴ There is a statistically significant positive correlation between per cent maximal cytoreduction and log median survival time in patients with FIGO III and IV EOC, and this correlation remained significant after controlling for all other variables ($P < 0.001$).²⁵ Though Mert *et al* has described that there is no difference in OS between patients with 'no gross residual disease' versus 'residual disease' when abnormal CPLNs were present (median OS, 38.4 vs 37.5 months, $P = 0.99$).²⁶

The presence of enlarged CPLN at presentation appears to be associated with a poorer prognosis and is significantly associated with a lower rate of complete response, a shorter disease-free interval and a shorter OS.^{6 11 26 27} The diagnosis of involved CPLN is important as it can define patients having stage IV as opposed to stage III disease.^{6 28}

Cytoreductive surgery for advanced ovarian cancer does not routinely include opening of the thorax. Even systematic lymphadenectomy does not commonly extend to lymph nodes above the diaphragm. However, in patients with suspicious CPLN detected on preoperative CT scan or by intraoperative assessment based on the degree of diaphragm involvement and palpation of the pericardial space, >85% had histologically confirmed metastasis.^{9 28–30} Hynninen *et al* proposed that preoperative FDG PET/CT diagnosed CPLN metastases in 67% of patients with advanced stage epithelial ovarian cancer, which was significantly higher than conventional imaging (33%).³¹

In our patient, the CPLNs were seen on both preoperative CT scan and PET/CT, which were tested positive for metastatic carcinoma on histology.

The surgical procedure of CPLN dissection is feasible without major complications if performed by experienced surgeons. Transabdominal CPLN dissection via an incision in the diaphragm, instead of video-assisted thoracic surgery (VATS), is also feasible as a part of the cytoreductive surgery without significant morbidities.^{28 30 32–34} In our case, as the enlarged CPLN was seen on preoperative CT scan, we planned to perform the CPLN dissection via the transdiaphragmatic route and completed it without any significant morbidity. The patient recovered well in the postoperative period and was discharged home on POD 11.

CPLN colonisation is frequently associated with extensive intrathoracic disease, typically represented by pleural

Table 1 Review of literature: CPLN in ovarian cancer

Studies	Patients (n)	Patients group	Objective	Result
Chi <i>et al</i> ²³	465	FIGO IIIC	Analyse survival rates at very specific residual disease diameters to determine the optimal goal of primary cytoreduction for bulky stage IIIC EOC	Amount of residual disease as a significant prognostic factor ($P=0.001$) Median overall survival in relation to the five residual disease categories was: no gross residual, 106 months; gross ≤ 0.5 cm, 66 months; 0.6–1.0 cm, 48 months; 1–2 cm, 33 months; >2 cm, 34 months. Removal of all evidence of macroscopic disease is associated with prolonged survival and should be the goal of primary cytoreductive surgery.
Bristow <i>et al</i> ²⁴	84	FIGO IV	Survival impact of surgical cytoreduction and of debulking extrahepatic disease in the subgroup of patients with liver metastasis	Median survival of optimally cytoreduced patients was 38.4 months compared with 10.3 months for patients with suboptimal residual disease. Optimal resection of both extrahepatic and hepatic disease had a median survival of 50.1 months, compared with a median survival of 27.0 months for the patients with optimal extrahepatic disease but suboptimal residual hepatic tumour.
Bristow <i>et al</i> ²⁵	81 cohorts, 6885	FIGO III and IV	Relative effect of per cent maximal cytoreductive surgery and other prognostic variables on survival	Each 10% increase in maximal cytoreduction was associated with a 5.5% increase in median survival time. When actuarial survival was estimated, cohorts with $<25\%$ or $\geq 25\%$ maximal cytoreduction had a mean weighted median survival time of 22.7 months, whereas cohorts with more than 75% maximal cytoreduction had a mean weighted median survival time of 33.9 months—an increase of 50%.
Chang <i>et al</i> ¹⁸	18 relevant studies, 13 257 patients	FIGO IV	To quantify the impact of complete cytoreduction to no gross residual disease on overall survival among patients with advanced-stage ovarian cancer	Each 10% increase in the proportion of patients undergoing complete cytoreduction to no gross residual disease was associated with a significant and independent 2.3-month increase (95% CI 0.6 to 4.0, $P=0.011$) in cohort median survival compared with a 1.8-month increase (95% CI 0.6 to 3.0, $P=0.004$) in cohort median survival for optimal cytoreduction (residual disease ≤ 1 cm).
Raban <i>et al</i> ¹¹	72	FIGO IIIC	Comparison between patients with CPLN at initial diagnosis and controls	CPLN were related with lower cytoreduction rate, shorter DFI and OS.
Holloway <i>et al</i> ⁶	78	Recurrence	Detection of enlarged CPLN on CT scan	Enlarged CPLN detected in 28% cases. Detection is a significant adverse prognostic factor for OS and PFS.
Kolev <i>et al</i> ¹⁴	212	FIGO III–IV	Retrospective revision of supradiaphragmatic LN and OS	Cut-off ≥ 5 mm largest axis 50-month median survival without adenopathy versus 45 months with adenopathy. All underwent attempted primary cytoreduction followed by systemic chemotherapy. None had any supradiaphragmatic nodes removed at primary cytoreduction.
Prader <i>et al</i> ⁹	196	FIGO IIIC–IVB	Surgical management of CPLN	Cut-off ≥ 10 mm shortest axis 90% histologically positive Transdiaphragmatic excision of CPLN is a feasible part of cytoreductive surgery.
Kim <i>et al</i> ²⁹	31	FIGO IV	Whether the preoperative diameter of CPLN along the short and long axes, determined by CT scan predicts CPLN metastasis in patients with advanced epithelial ovarian cancer.	The probability of detecting CPLN metastasis in patients with advanced ovarian cancer was approximately 85% when the short axis of the CPLN was >7 mm in preoperative CT scans.
Perri <i>et al</i> ²⁷	218	FIGO IIIC–IV	Rates of optimal abdominal pelvic cytoreduction and the sites of recurrence Potential impact of thoracic cytoreduction on treatment results in patients with intrathoracic spread	Patients with CPLNs of this size may be candidates for CPLN dissection to confirm the pathological diagnosis. Optimal abdominopelvic cytoreduction was achievable in stage IV patients, although in significantly fewer patients than in stage IIIC. Sites of recurrence were rarely thorax alone (6.8%). Thoracic debulking is likely to change the course of disease in only a few patients and thus should be carefully individualised.
Eisenkop ⁴²	24	FIGO IIIC and IV	To determine possible benefits of thoracoscopy for the management of patients with advance epithelial ovarian cancer	The median and estimated 5-year survival for the entire cohort was 28.9 months and 42%, respectively. Log-rank analysis revealed the probability of survival to be improved by the performance of thoracoscopy (performed versus not performed, $P=0.05$). Permits complete cytoreduction for some patients who might otherwise have unrecognised macroscopic residual intrathoracic disease.
Yoo <i>et al</i> ³²	11	FIGO IV	Feasibility of the transabdominal CPLN dissection via incised diaphragm in patients with ovarian cancer by gynaecological oncologists instead of the conventional VATS	Metastasis was identified in 45% (5/11) of ≥ 5 mm CPLN on preoperative CT. There was no significant morbidity related to CPLN dissection and mortality associated with surgery. Ten patients achieved the no gross residual disease and one patient accomplished gross residual 1 (residual disease measuring ≤ 1 cm in maximal diameter).
Garbi <i>et al</i> ²³	22	FIGO IVB	To define the safety and feasibility of surgical transdiaphragmatic resection of enlarged CPLN as a part of upfront debulking surgery	All patients who underwent CPLN resection had an extensive disease (median peritoneal cancer index, 18), and more than 77% required complex surgical procedures (complexity score, 3). No residual abdominal disease less than 5 mm at the end of surgery was described in 20 (90%) out of 22. Transdiaphragmatic enlarged CPLN resection seems to be safe and feasible procedure when indicated to achieve no or minimal tumour residual disease.
LaFargue <i>et al</i> ⁴⁰	11	FIGO IVB	To further define the preoperative, intraoperative and postoperative characteristics of patients undergoing transdiaphragmatic resection of CPLNs in advanced gynaecological cancer and delineate the associated short-term morbidities	Malignancy was identified in 86% of lymph node submitted. The overall postoperative morbidity associated with CPLN resection was low, with the most common finding being a small pleural effusion present on chest X-ray between POD 3 and 5 (5%). Transdiaphragmatic CPLN resection is a feasible procedure with relatively minor short-term postoperative morbidities that can be used to achieve cytoreduction to no gross residual disease.

Some part of this table is reproduced from Prader *et al*⁹ with permission from Elsevier.

CPLN, cardiophrenic lymph node; EOC, epithelial ovarian cancer; DFI, disease-free interval; OS, overall survival; PFS, progression-free survival; POD, postoperative day; VATS, video-assisted thoracic surgery.

Learning points

- The presence of enlarged cardiophrenic lymph node (CPLN) is an adverse prognostic factor for epithelial ovarian cancer.
- With the knowledge that optimal cytoreduction improves survival, excision of the CPLN may contribute to the survival benefit in selected patients, especially if this can be achieved with low morbidity, through a transdiaphragmatic route.
- Larger prospective studies would aid in the assessment of the relevance and impact of CPLN dissection as a part of cytoreductive surgery for stage IV ovarian cancer.

effusion,^{35 36} though isolated bilateral CPLN involvement without pleural effusion also has been reported.¹² When pleural or lung parenchymal disease is suggested by the presence of a pleural effusion, the use of VATS could be helpful in staging and guiding the management of the patient.^{36–41} In those patients, a cytoreduction through VATS should be considered an option.^{4 12 36 42}

Details of relevant reviewed literatures are summarised in table 1.

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