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Feasibility, safety and clinical outcomes of cardiophrenic lymph node resection in advanced ovarian cancer

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HIGHLIGHTS

- CPLN resection during PCS for ovarian cancer is feasible and safe.
- CPLN resection may be associated with improved surgical and survival outcomes.
- CPLN should be done at an expert center by a multidisciplinary team of specialists.

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ABSTRACT

Objectives. Surgical resection of enlarged cardiophrenic lymph nodes (CPLNs) in primary treatment of advanced ovarian cancer has not been widely studied. We report on a cohort of patients undergoing CPLN resection during primary cytoreductive surgery (CRS), examining its feasibility, safety, and potential impact on clinical outcomes.

Methods. We identified all patients undergoing primary CRS/CPLN resection for Stages IIIB-IV high-grade epithelial ovarian cancer at our institution from 1/2001–12/2013. Clinical and pathological data were collected. Statistical tests were performed.

Results. 54 patients underwent CPLN resection. All had enlarged CPLNs on preoperative imaging. Median diameter of an enlarged CPLN: 1.3 cm (range 0.6–2.9). Median patient age: 59y (range 41–74). 48 (88.9%) underwent transdiaphragmatic resection; 6 (11.1%) underwent video-assisted thoracic surgery. A median of 3 nodes (range 1–23) were resected. A median of 2 nodes (range 0–22) were positive for metastasis. 51/54 (94.4%) had positive nodes. 51 (94.4%) had chest tube placement; median time to removal: 4d (range 2–12). 44 (81.4%) had peritoneal carcinomatosis. 19 (35%) experienced major postoperative complications; 4 of these (7%) were surgery-related. Median time to adjuvant chemotherapy: 40d (range 19–205). All patients were optimally cytoreduced, 30 (55.6%) without visible residual disease. Median progression-free survival: 17.2mos (95% CI 12.6–21.8); median overall survival: 70.1mos (95% CI 51.2–89.0).

Conclusions. Enlarged CPLNs can be identified on preoperative imaging and may indicate metastases. Resection can identify extra-abdominal disease, confirm Stage IV disease, obtain optimal cytoreduction. In the proper setting it is feasible, safe, and does not delay chemotherapy. In select patients, it may improve survival.

1. Background

Women with suspected advanced epithelial ovarian cancer (EOC) should be evaluated by a gynecologic oncologist to determine the appropriate initial treatment modality [1]. This evaluation usually includes imaging of the chest, abdomen, and pelvis, to determine the extent of disease and the feasibility of optimal surgical resection [1,2]. A 2001 survey of gynecologic oncologists revealed that the presence of upper abdominal disease and/or disease in "hazardous locations" were the most common reasons given for deciding against a primary cytoreductive surgery (CRS) [3]. The authors also reported that surgeons who were familiar with diverse surgical approaches were more

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likely to perform riskier procedures, and had more optimal outcomes [3]. Numerous studies have noted that gynecologic oncologists are expanding the surgical armamentarium for EOC, diversifying their skill sets and participating in a multidisciplinary team approach to treatment [4–6]. Several studies have also reported significant increases in survival, as well as a minimal but acceptable increase in morbidity, as a result of this shift in the surgical paradigm [7–10].

Cardiophrenic lymph nodes (CPLNs), also referred to as paracardiac and supradiaphragmatic lymph nodes, are located just above the diaphragm. The region anterior to the pericardium normally houses 0–2 visible lymph nodes, each usually measuring <5 mm in diameter [11]. In diseases such as advanced EOC, where there is often a large peritoneal and abdominal tumor burden, these lymph nodes can serve as a common site for metastases [12,13].

Suspicious nodes are generally larger than 5 mm in diameter and are readily identified on computed tomography (CT) scans. In women with ovarian cancer, these enlarged nodes are usually indicative of metastatic disease [13]. Positive CPLN is an independent negative prognostic factor and indicates that the patient has Stage IVB disease. However, the evidence suggests that optimal debulking surgery (resulting in minimal or no visible residual disease)—even if it requires a "radical" surgical procedure—is associated with an increased median overall survival (OS) in the setting of Stage IV disease [14–16].

Surgical resection of enlarged CPLNs in the primary treatment of advanced ovarian cancer has not been widely studied. In this study we report on a cohort of patients that underwent CPLN resection at the time of primary CRS at a single institution. We discuss the feasibility and safety of the procedure, and assess outcomes.

2. Methods

After Institutional Review Board approval, we identified patients with Stage IIIB-IV ovarian cancer who underwent primary CRS for high-grade EOC at our institution (Memorial Sloan Kettering Cancer Center) from January 2001 to December 2013. Patients were included if they had undergone a supradiaphragmatic resection with the intent of removing one or more CPLN(s) for diagnosis and/or treatment of ovarian cancer. Patients were excluded if they received neoadjuvant chemotherapy (NACT). Patients were also excluded if their primary surgery was not performed with the intent of optimal cytoreduction, (e.g., surgery for bowel obstruction or palliative indications). CPLN resection was performed either by a thoracic surgeon via video-assisted thoracic surgery (VATS), or by a gynecologic oncologist or other consulting surgeon via a transdiaphragmatic or subxiphoid approach. Transdiaphragmatic resection is accomplished by opening the diaphragm directly to enter the thoracic cavity and access the pericardial fat pad containing the CPLNs. Alternatively, the subxiphoid approach utilizes the upper portion of the laparotomy incision and leaves the diaphragm intact, entering the pleural space anterior to the diaphragm and pericardium.

We collected pertinent clinical, surgical, pathologic, outcome, and follow-up data for this cohort. Descriptive analyses were performed. Complications were graded according to an institutional surgical complication grading system [17]. Perioperative complications were defined as any adverse event related to operative treatment occurring within 30 days of surgery, including death. All patients had routine preoperative radiologic imaging. All radiologic reports and images were reviewed by the surgical team. The size (cm), location, quantity, and tumor burden of the CPLNs, and the presence of pleural effusions, were collected from radiologic, pathologic, and operative reports. Peritoneal carcinomatosis was defined as the presence of ≥20 tumor nodules, as noted at the time of surgery or as documented on preoperative CT scans. Residual disease was defined as the greatest dimension in diameter (cm) of the largest residual tumor nodule, as documented in the operative report. Optimal cytoreduction was defined as ≤1 cm of residual disease on completion of CRS. Time to adjuvant chemotherapy was defined as the number of days from postoperative day 1 to the first day of chemotherapy.

Progression-free survival (PFS) was calculated from the date of CRS to the date of first progression, last follow-up, or death. OS was defined as time elapsed (in months) from the date of CRS to the date of last follow-up, or death. Follow-up data were collected until September 2016. The Kaplan-Meier method was used to generate survival curves [18].

3. Results

Of the 985 patients at our institution who underwent primary CRS for Stage IIIB-IV high-grade EOC from January 2001 to December 2013, we identified 54 patients who underwent surgical resection of the CPLN(s). The median age in this group was 59 years (range 41–74). In all 54 cases, enlarged or suspicious CPLNs were documented on preoperative CT reports. The median diameter of an enlarged CPLN was 1.3 cm (range 0.6–2.9). Preoperative pleural effusion was noted in 13 (24%) patients. Peritoneal carcinomatosis was documented in 44 (81%) patients. Patient and tumor characteristics are shown in Table 1.

An intraoperative consulting surgeon performed transdiaphragmatic CPLN resection in 31 (57%) patients; a gynecologic oncologist performed the procedure in 17 (31%) patients. The other 6 (11%) patients underwent a VATS procedure by a thoracic surgeon prior to their abdominal CRS. A median of 3 nodes (range 1–23) were resected. Upon histopathologic review, a median of 2 nodes (range 0–22) were positive for metastatic disease. Fifty-one of the 54 (94%) patients had nodes that were positive for metastatic disease. In 51 (94%) patients, a chest tube was placed at the time of the procedure; the median time to removal of the chest tube was 4 days (range 2–12). Fifty-three (98%) patients underwent one or more extensive upper abdominal procedures at the time of CRS. This included diaphragmatic stripping/resection in 49 (91%) patients, resection of tumor from the porta hepatis in 19 (35%), splenectomy in 14 (26%), cholecystectomy in 12 (22%), liver resection in 10 (19%), and distal pancreatectomy in 3 (6%) patients. Median estimated blood loss (EBL) was 1000 mL. Median operative time was 450 min. Forty-eight (88%) patients had an epidural

Table 1
Patient and Tumor Characteristics.

Patient and tumor characteristics ($n = 54$) variable	No. of patients (%)
Median age (range)	59 years (41–74)
Median BMI (range)	27 (19–45)
Median pre-operative albumin (range)	4.2 (2.7–4.9)
BRCA status	
Negative	26 (48)
BRCA 1 positive	4 (7)
BRCA 2 positive	4 (7)
Status Unknown	20 (37)
ASA	
2	21 (39)
3	33 (61)
Primary site of disease	
Ovary	34 (63)
Fallopian Tube	16 (29)
Peritoneum	4 (7)
Tumor histology	
High grade serous	51 (94)
Carcinosarcoma	2 (4)
Clear cell	1 (2)
Preoperative serum CA-125	
0–500	19 (35)
501–1000	7 (48)
1001–2000	10 (19)
2001–3000	4 (26)
3001–4000	2 (4)
4001–5000	5 (9)
> 5000	1 (2)
Ascites	
≤ 500	29 (54)
> 500	25 (46)

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