Recurrent ovarian cancer with supraclavicular lymph node metastasis: a report of two cases and literature review

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Recurrent ovarian cancer is commonly associated with lymphatic metastasis, however, supraclavicular lymph node is a rare site for metastasis. Few studies have investigated whether local debulking surgery would benefit patients with supraclavicular lymph node metastasis. We report two such cases, review the literature and discuss the potential for local debulking surgical treatment for this rare scenario. Both cases were diagnosed with recurrent ovarian cancer, with the first having left supraclavicular lymph node metastasis, while the second had right supraclavicular lymph node metastasis. Cervical lymphadenectomy was performed to relieve local symptoms in both cases followed by chemotherapy. The first case died of hepatic hilar metastasis 6 months after the surgery while the second case has to date (January 2020) survived without any recurrence 12 months postoperatively. A comprehensive search in the PubMed, Embase, and Cochrane databases was performed. According to the limited study and our cases, we conclude the lymphadenectomy appears to provide potential benefit to patients with oligometastasis like right supraclavicular lymph node metastasis.

Keywords
Ovarian cancer; Surgery; Supraclavicular lymph node

1. Introduction

Recurrent ovarian cancer is commonly associated with lymphatic metastasis, however, supraclavicular lymph node (SCLN) is a rare metastasis site, which is reflected by a lack of studies in the literature [1–6]. SCLN metastases are considered to be distant metastases, in which systemic chemotherapy is typically recommended as the main treatment. Secondary tumor reduction surgery is controversial in the guidelines on recurrent ovarian cancer. Especially for SCLN metastasis, it is unclear whether surgery would provide a benefit to patient displaying symptoms of compression and chemotherapy resistance [7]. Few studies have discussed the significance of local debulking surgery in SCLN metastasis [8]. In this manuscript, we summarise the published literature on this topic, report two cases presenting in our hospital and discuss the potential of local debulking surgical treatment for this rare scenario.

2. Case Report

2.1 Case 1

A 57-year-old woman diagnosed with stage III low-grade serous adenocarcinoma underwent surgery. Following surgery, she had 6 cycles of adjuvant chemotherapy (paclitaxel, 135–175 mg/m² and carboplatin, 350 mg/m²). She was found to have recurrent ovarian cancer nine years after the initial surgical treatment. Her left SCLN was found enlarged with symptoms of local compression for 6 months (multiple, clustered lesions, measured 5 cm, confirmed metastasis of low-grade adenocarcinoma by core needle biopsy). PET-CT scan showed hepatic portal lesions with high clinical suspicion of simultaneous metastasis (the second primary cancer would not be considered based on her stage III disease during the initial exploration and the location of the lesions adjacent to the hepato-biliary system), while no obstructive jaundice was observed and bilirubin levels were normal. The tumor marker blood test (Ca125) was 22.18 U/mL in blood. The SCLN metastases continued to increase during the subsequent palliative chemotherapy (paclitaxel, 135–175 mg/m² and cis-platinum, 70 mg/m²) even though abdominal lesions were stable. Left cervical lymphadenectomy was performed to relieve neck compression. The lymphadenectomy included left cervical lymph nodes in regions III, IV and V. After the lymphadenectomy, palliative chemotherapy was continued (liposome paclitaxel, 135–175 mg/m² and oxaliplatin, 130 mg/m²). Two months later, the abdominal metastases progressed and obstructive jaundice developed. The patient died of hepatic hilar metastasis 6 months after the lymphadenectomy.

2.2 Case 2

A 73-year-old woman diagnosed with stage III high-grade ovarian serous adenocarcinoma underwent surgery. Following the surgery, she had 8 cycles of adjuvant chemotherapy (paclitaxel, 135–175 mg/m² and carboplatin, 350 mg/m²). The patient was found to have recurrent ovarian cancer two years after the initial treatment. Her right SCLN was enlarged (a maximum mass of 8.0 × 6.0 cm, also confirmed metastasis of low-grade adenocarcinoma by pathology) in 2 months and Ca125 was 1020 U/mL without...
any other organ metastasis (PET-CT scan confirmed). She was treated with palliative chemotherapy (paclitaxel, 135–175 mg/m$^2$ and carboplatin, 350 mg/m$^2$) but the enlargement of the neck mass continued causing pressure on the local surrounding skin. Right cervical lymphadenectomy was performed and the Ca125 levels decreased to 108.70 U/ml after surgery. In order to completely remove the tumor, the internal jugular vein and vagus nerve were sacrificed during the operation because of tumor invasion. Postoperative chemotherapy (8 cycle liposome paclitaxel, 135–175 mg/m$^2$ and nedaplatin, 80–100 mg/m$^2$) was delayed 2 months because of surgical complications of chylous leak and hoarseness. At present, one year after surgery, the patient lives well without any recurrence and Ca125 has reduced to 18.70 U/mL (Figs. 1, 2, 3).

3. Discussion

Ovarian cancer is the fifth leading cause of cancer death in women and is the second most common cause of death from gynecological cancers. It is often metastasized by intraperitoneal spread and may metastasize by the lymph nodes. Among lymphatic metastasis, intraperitoneal metastatic lymph nodes are more common in these patients while supraclavicular lymph nodes are treated as distant metastasis which are very rare [9–11]. A comprehensive search in the PubMed, Embase, and Cochrane databases was performed to identify studies on ovarian cancer with SCLN metastasis. Only 6 studies (all case reports) have reported such cases, including two patients in right SCLN metastasis (2 studies) and five patients in left SCLN metastasis (4 studies). Details of these cases are shown in Table 1. There are no consistent patterns among the 6 studies. There is 1 case of occult ovarian cancer with right supraclavicular lymph node as the first manifestation [4] and 3 cases which are lack of specific
information, including follow-up [1, 2]. The significance of surgical intervention is not mentioned in most cases and only one case in right side undergo surgery and show the efficacy of it [6]. With such a rare case, the quality of the reports is so variable that it is difficult to guide the treatment of such patients. More clinical experience should be accumulated in treating such patients at present.

We report two cases of recurrent ovarian cancer with SCLN metastasis who underwent surgical treatment which enabled us to consider possible effective surgical treatment of such diseases. Case 1 was a patient whose cancer had metastasized to multiple organs after treatment a few years earlier. Although neck surgery can improve local discomfort, the intra-abdominal lesions were poorly controlled and the overall survival did not improve. Given the current available of many targeted and immune drugs for systemic therapy, the need for neck surgery may now be reduced. A number of studies (GOG 0218 [12], ICON 7 [13], OCEANS [14, 15], GOG0213 [16], AURELIA [17]) proposed that bevacizumab combined with chemotherapy could improve progression free survival compared with chemotherapy alone. Bevacizumab was then approved by the FDA for use in first-line chemotherapy for ovarian cancer and in patients with recurrence. Other studies of antivascular-targeted drugs, such as abelesepp [18, 19], trebananib [20, 21] and apatinib [22], were also being studied. Some PARP inhibitors (olaparib, rucaparib, niraparib) [23–25] and immunotherapy (nivolumab, avelumab) [26, 27] might offer new promise for the treatment of advanced ovarian cancer. The first case was treated initially almost ten years ago and then bevacizumab combined with chemotherapy was not recommended in the guideline, however, the second case could not afford the bevacizumab although we recommended to her. If our cases had undergone the targeted therapy, they might have better control for metastasis. With the development of drugs, under the premise of stable disease by drug control, it seems more meaningful to debate how surgery could improve quality of life and prolong the survival.

Case 2 was a patient with relatively ‘oligometastases’, while the local neck lesion was still progressing despite the control of systemic chemotherapy. After surgical resection, the lesion disappeared and Ca125 decreased significantly. Although it was difficult to recover from postoperative complications, the patient improved her quality of life with sequential systemic therapy and lives well until now. This also gives us a reflection on whether palliative resection should be attempted in patients with relatively oligometastases ovarian cancer.

It is well known that for advanced and recurrent tumors, systemic treatment is the primary approach and the need for surgery is controversial. It seems a ‘absolute truth’ in ovarian cancer, while a new study [28] published in N Engl J Med recently suggests that secondary surgical cytoreduction for recurrent ovarian cancer surgery provide no survival benefits. Distant metastasis of malignant tumor is considered as an operative contraindication, however, many surgeons challenged the authority in the long course of history. In the 1990s, Hellman and Weichselbaum jointly proposed the concept of oligometastasis [29]. Oligometastasis was a period of mild invasion of tumor organisms, which existed in the transitional stage between limited primary focus and extensive metastasis. In this period, the number of metastatic tumors was limited and the metastatic organs were specific. Subsequently, a large number of studies on resectable oligometastatic tumors were published, among the fields of lung cancer [30], colorectal cancer [31], prostate cancer [32] and breast cancer [33], which had brought us successful experience in surgical treatment for advanced cancer. Limited to the pathogenesis of ovarian cancer, the definition of ‘oligometastases’ may not quite similar to other tumors. However, in the context of other tumors, the localized, isolated lesions seem to be provided a new opportunity for surgical treatment.
Table 1. Cases of Ovarian Cancer with Supraclavicular Lymph Node Metastasis in Published.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Age of Onset (y)</th>
<th>Pathological type</th>
<th>Initial Staging</th>
<th>Initial Therapy</th>
<th>Regimen</th>
<th>Cycle Ca125 at Metastasis (U/mL)</th>
<th>Side of SCLN</th>
<th>Diameter of SCLN (cm)</th>
<th>Sequential Therapy</th>
<th>Ca125 after Therapy (U/mL)</th>
<th>Lymphadenotomy</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayadivi S</td>
<td>2005</td>
<td>UK</td>
<td>55</td>
<td>Serous cystadenocarcinoma (occult cancer)</td>
<td>IV</td>
<td>Radiotherapy</td>
<td>N/A</td>
<td>N/A</td>
<td>Right</td>
<td>N/A</td>
<td>Surgery + ACT (carboplatin)</td>
<td>100</td>
<td>N</td>
<td>5y no recurrence</td>
</tr>
<tr>
<td>Fanti S [2]</td>
<td>2006</td>
<td>Italy</td>
<td>51</td>
<td>Poorly differentiated cancer</td>
<td>IV</td>
<td>Surgery + ACT</td>
<td>TC + topotecan</td>
<td>N/A</td>
<td>273</td>
<td>Left</td>
<td>N/A</td>
<td>N/A</td>
<td>14</td>
<td>N</td>
</tr>
<tr>
<td>Cebesoy FB [1]</td>
<td>2008</td>
<td>Turkey</td>
<td>64</td>
<td>Serous-papillary carcinoma</td>
<td>IV</td>
<td>Surgery</td>
<td>N/A</td>
<td>N/A</td>
<td>Left</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N</td>
<td>N/A</td>
</tr>
<tr>
<td>Tanaka T [6]</td>
<td>2012</td>
<td>Japan</td>
<td>65</td>
<td>Serous adenocarcinoma</td>
<td>IV</td>
<td>Surgery + ACT</td>
<td>TC</td>
<td>6</td>
<td>Right</td>
<td>1.5</td>
<td>wTC<em>5 + Lymphadenectomy + wTc</em>4</td>
<td>Normal</td>
<td>Y</td>
<td>20 m no recurrence</td>
</tr>
<tr>
<td>Rahman M [5]</td>
<td>2012</td>
<td>Japan</td>
<td>49</td>
<td>Serous carcinoma</td>
<td>IV</td>
<td>Surgery + ACT</td>
<td>TC</td>
<td>N/A</td>
<td>Left</td>
<td>3</td>
<td>Second line chemotherapy (CPT-11/Gemcitabin)</td>
<td>N/A</td>
<td>N</td>
<td>PFS 6 m, OS 2y</td>
</tr>
<tr>
<td>Hong L [3]</td>
<td>2018</td>
<td>China</td>
<td>45</td>
<td>Serous carcinoma</td>
<td>IV</td>
<td>NACT + surgery + HIPEC + ACT</td>
<td>TC/TP 2/4</td>
<td>290.4</td>
<td>Left</td>
<td>N/A</td>
<td>N/A</td>
<td>14.6</td>
<td>N</td>
<td>3y no recurrence</td>
</tr>
</tbody>
</table>

SCLN, supraclavicular lymph node; UK, United Kingdom; N/A, not available; ACT, adjuvant chemotherapy; TC, paclitaxel plus carboplatin; wTC, weekly paclitaxel plus carboplatin; PFS, progresses free survival; OS, overall survival; NACT, neoadjuvant chemotherapy; TP, paclitaxel plus platinum; N, no; Y, yes.
While it is not possible to be definitive using two case reports, comparing Case 1 and Case 2 can motivate some hypotheses. For example, seen from the oncologic view, the left SCLN often receives lymphatic reflux from the abdominal cavity, which always means the existence of simultaneous abdominal organ lesions. Left SCLN metastasis is a hallmark of primary abdominal tumors like gastric carcinoma [34]. While anatomically the right SCLN is relatively isolated it is easier to achieve an ‘oligometastases’ state. A similar phenomenon can be found in the study reviewed. Mayadevi [4] report the case of occult ovarian cancer with right SCLN metastasis as a starting performance. The right SCLN is also ‘oligometastases’ state in this patient and she accepted local radiotherapy. After the following ovarian cancer treatment, she lived well without recurrence for 5 years. We hypothesize that systemic treatment is sub-optimal for patients with SCLN metastasis for treatment of the oligometastatic lesion. In contrast local therapy, such as surgical excision, may be a more effective treatment, especially for the isolated lesions in the right side.

Therefore, for such patients, indications for surgical treatment should be more strictly controlled. First we need to make sure that the primary lesion is controllable, and check that metastatic lesions do cause the patient discomfort. Secondly, the preoperative evaluation should be sufficient to determine that there is no other important organ metastasis (multiple metastases or oligometastasis). Furthermore, full consideration should be given to the patient's general condition, whether the patient can tolerate the operation and her expected survival. In addition, surgical risks and anticipated complications should be considered. Newer medications need to be considered. If there are no more effective nonsurgical treatments available, then surgery may be a choice.

Last but not least, we still hope more such cases will be accumulated. According to the NCCN guideline [7], patients of recurrent ovarian cancer who meet the following conditions could be considered for secondary tumor reduction: (1) Relapse more than 6 months after completing prior chemotherapy; (2) The lesions can be completely removed; (3) No ascites; (4) Encourage patients to participate in clinical trials to evaluate whether the secondary tumor reduction surgery really benefits. Even though, some scholars, based on the study mentioned above [28], argue that secondary surgical cytoreduction for recurrent ovarian cancer surgery did not result in overall survival but brought about significant decline in quality of life. When we reviewed the study, it contained 240 patients to secondary cytoreduction in the study, however, as for the metastasis sites of these patients, it was very mixed. In the subgroup analysis, it divided ‘disease site’ into four parts: liver, extrabdominal, both and other. As we all know, large organ metastasis sites resection, such like liver, always lead to the worse prognosis and postoperative complications, which accord with the conclusion. No details of the SCLN subgroup data were mentioned in the study so that we cannot generalize the conclusion into this special subgroup curply. For the lack of treatment experiences on SCLN metastasis, it is premature to say that surgical treatment is meaningless in all cases of recurrent ovarian cancer metastasis. Even if the treatment did not improve the survival, it seems to offer a potential way to relieve the discomfort of neck compression for advanced patients using palliative surgery. We need to accumulate more such cases to explore the therapeutic significance of oligometastases in ovarian cancer.

Author contributions
BL and QPL designed the study. BL, PLZ and YZB performed the surgery. AYL provided help on the follow-up. PLZ and AYL analyzed the data. PLZ and BL wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
All subjects gave their informed consent for inclusion before they participated in the study.

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Conflict of interest
The authors declare no conflict of interest.

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