Behaviour and Prognosis of Ovarian Cancer With Rare Metastatic Sites

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Research Article

Keywords: Ovarian cancer, Debulking, Rare presentation, Non-regional node metastasis

Posted Date: October 27th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-708828/v1

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Abstract

**Purpose:** Ovarian cancer is the commonest gynecologic malignancy in Egypt. Although metastasis from ovarian cancer is common, there are still sites with rarely reported deposits as non-regional nodes, bone, and brain.

**Methods:** This is a cohort study where we retrospectively a group of patients over 7 years period recruited from the data system of a cancer centre. All the recruited patients suffered a rare distant metastasis from ovarian cancer.

**Results:** Nearly half of the patients already had metastasis at the time of the initial presentation, while the rest developed during the disease course. Debulking was feasible in nearly half of the patients with long overall and progression-free survival. Tumours with non-regional nodal metastases tend to have excellent survival.

**Conclusion:** we recommend offering these patients optimal debulking and considering those with a non-regional nodal spread as having a curable disease.

Introduction:

Ovarian cancer is ranked the 8th most commonly diagnosed cancers and cancer-related mortality in females worldwide, while it ranked the 4th among the most frequently diagnosed cancers in Egyptian females (1, 2). Although ovarian cancer lies behind breast cancer in prevalence, it is three times more fatal (3). This could be attributed to many factors including late presentation and/or diagnosis, non-specific symptoms, and advanced disease stage at the presentation that is ultimately followed by poor prognosis and high mortality rate (4).

Ovarian cancer spreads mainly by direct extension to the adjacent organs or transperitoneal spread of detached cancerous cells to the peritoneum, bowel, and abdominal viscera. The lymphatic spread of ovarian carcinoma to pelvic and paraaortic lymph nodes is also common, while the hematogenous spread is less commonly reported. The prognosis of ovarian cancer patients with distant metastases is generally poor regardless of the site of distant metastasis. Notably, the rare sites of distant metastases are not deeply explored in literature representing a great challenge for oncologists in managing these cases (5, 6). In this study, we retrospectively addressed this cohort of patients to detect their clinical characteristics and survival patterns.

**Methods:**

This is a retrospective cohort study where all patients diagnosed with FIGO stage IV ovarian cancer presented with a rare site metastasis as defined by metastasis to sites other than peritoneum, liver, and lung. or developed this rare pattern of metastasis throughout their disease course from a tertiary centre were included from August 2012 to September 2019. These patients were followed up to the end of
January 2021. Demographics, site of ovarian cancer rare metastasis, preoperative, operative, postoperative, pathologic, and oncologic follow-up data were retrieved from a prospectively maintained electronic database.

OAS was calculated from the date of diagnosis with rare metastasis, while progression-free survival was calculated as time span lived without recurrence or progression.

We used the statistical software SPSS (Statistical Package for Social Scientists SPSS 22.0; Armonk, NY: IBM Corp) for analysis of the study results. Continuous variables were presented as mean and standard deviation if normally distributed or median and range when non normally distributed. Independent samples t-test was used to compare parametric data whereas the Mann-Whitney U test was used to compare non-parametric data. Categorical data were compared by Pearson's Chi-square test or Fischer-Exact test when appropriate. A p-value < 0.05 was considered statistically significant.

Results:

Out of 1135 ovarian cancer patients, 48 patients with FIGO stage IV rare metastatic sites were enrolled. The mean age at diagnosis of primary ovarian cancer was 57.8 +/-10.8 years. Mean BMI was 33.7 +/-7.8 kg/m2. 34 of the study patients received neoadjuvant therapy, 31 of them received it because of the predicted inability to achieve R0 resection, in 2 patients for pleural effusion, and 1 patient due to pulmonary metastasis. In nearly 60% of the patients who received neoadjuvant therapy, regression occurred with complete response in 3 cases.

In most of the patients, the pathology was serous carcinoma (87.5%) and the majority (66.7%) were high grade. The cancer was affecting both ovaries in 64.4% of cases. In 58.5% the omentum, peritoneum, or both were involved in the malignant process.

Considering the normal range of CA125 in our centre (up to 35 IU/ml), all patients except one had an elevated level at diagnosis of ovarian cancer (Table 1).

The commonest site of rare metastasis was non-regional nodes (inguinal then cervical then axillary) in 56.3% followed by bone and brain with 12.5% each. The rare metastasis was presented within primary diagnosis in 26 cases, while as a recurrence in 22 cases. Non-operative biopsy from rare metastasis was done in 30 cases. In 60% of the patients, a biopsy was taken from the rare metastasis, which was commonly FNAC in 58.6% of biopsied patients. In 20 patients (41.7%) the rare metastasis was surgically resected (Table 2).

Two patients with non-regional node metastasis achieved pathologic complete response in the resected nodes as a result of neoadjuvant chemotherapy.

By the end of follow-up, recurrence after treatment of the rare ovarian metastasis occurred in 17 (35.4%) patients and 25 (52.1%) patients were dead. The estimated median overall survival after rare metastases
diagnosis was 29 (95%CI = 19.8–38.2), while the median progression-free survival was 15 (95%CI = 9.4–20.6) months.

The patients with non-regional node metastasis had significantly better overall survival from visceral/skeletal metastasis (estimated median OS 39 vs. 13 months), P-value = .003. with the highest mortality rate for those with Sister Mary Joseph's nodule (100%) followed by those with bone metastasis (66.6%) during the follow-up period. Also, the non-regional node group had significantly better PFS (estimated median 29 vs. 13), P-value = .034 (Fig. 1).

Also, the surgical resection of these metastases did not improve either overall or progression-free survival, with estimated median OS 38 vs 25 months (P-value = .17) for resection and non-surgical treatment respectively, and estimated median PFS 29 vs. 14 months (P-value = .24), respectively (Fig. 2).

**Discussion:**

Ovarian cancer was typically reported in the literature to metastasize to the peritoneal cavity. Notably, other rare sites of metastases had been reported either at the primary diagnosis or during the disease course. These sites included the bone, brain, skin, breast, non-regional lymph nodes, and rare intra-abdominal organs (5). In the present study, we retrospectively reviewed the demographics, disease characteristics, and prognosis of this unique cohort of patients from a single centre.

It is crucial to understand the pattern of distant metastasis from ovarian cancer as this impacts the patient’s survival. In their study, Deng et al. analysed the prognostic significance of the site of ovarian cancer distant metastasis. They reported the distant lymph node metastatic site to be associated with better survival than the other sites of distant metastasis including liver, bone, brain, and lungs (6). This was previously reported also by Hjerpe et al. where the median overall survival for patients with non-regional lymph node metastases was significantly higher than the other distant metastasis (41.4 vs 25.2-or 26.8-months) (7). Moreover, ovarian cancer patients suffering from distant lymph node metastases experienced a better prognosis when treated by surgery and chemotherapy (6). In our study, non-regional lymph node metastases were the most reported rare metastatic sites (56.3%) and these patients experienced significantly better overall survival from visceral/skeletal metastasis (estimated median OS 39 vs. 13 months. Moreover, they had significantly higher progression-free survival (estimated median 29 vs. 13 months).

Inguinal nodal metastasis from ovarian carcinoma represented the most common site of rare metastasis in our patients (29.2%). This could be explained by altered lymphatic drainage pathway of the ovaries either through the round ligament, or the gubernaculum or due to surgical excision of the primary pathway to the paraaortic and iliac lymph nodes (8).

Axillary and intramammary nodal metastasis from ovarian cancer is very rare and whenever found represents a diagnostic dilemma. Two pathways could explain the spread of ovarian cancer to axillary nodes through the superior diaphragmatic lymph nodes. The first follows an anterior pathway to the
prepericardial nodes then the subclavian lymph trunk ending eventually the axillary lymph nodes, while the other one is posteriorly through inferior diaphragmatic nodes to superficial umbilical lymphatics that end in cisterna chyli that is continuous into the thoracic duct which ends at the junction between the left subclavian and internal jugular veins (9). It should be mentioned that thorough clinical, radiological, and pathological interpretation is crucial to differentiate these patients from primary breast carcinomas with ovarian metastasis (10). In our study, axillary and intramammary nodal metastasis was reported in 7 patients (14.6%), 3 patients presented as a recurrent event through their disease course.

Thanks to the recent advances in imaging technology, the incidence of brain metastasis from ovarian cancer had been reportedly increasing in the recent literature (11). Brain metastasis is more commonly reported with breast and lung carcinomas. On the other hand, the incidence of brain metastasis from ovarian cancer in literature ranged from 0.3–12% (12). Surgery, chemotherapy, and radiation therapy were the most commonly used treatment modalities in these patients (5). In the present study, brain metastasis was the second common (12.5%) after non-regional nodal metastasis. This was reported in 6 patients out of them only one patient was presented with this rare metastatic pattern in her first presentation, while the other 5 patients presented with brain metastasis in the form of recurrence. All patients were managed by chemoradiation while one patient performed surgical resection.

Bone metastasis was rarely reported from ovarian carcinoma. Most of the available evidence from the literature is derived from case reports and retrospective studies. The incidence of ovarian cancer patients who developed bone metastasis ranged from 0.82–3.74% (6, 13). This could be explained by either direct, hematogenous, lymphatic, and transperitoneal spread. The vertebral venous system was thought to be the route of the spread of ovarian cancer to the vertebrae in some studies (13). In our study, bone metastasis was reported in six patients (12.5%), three of them were confined to lumbar vertebrae, while one patient had hip bone metastasis and the other two had multiple sites bone metastasis.

Diagnosis of splenic metastasis is a rare event. Interestingly, splenic metastasis from breast, lung, colorectal carcinoma and melanoma were more commonly reported than from ovarian cancer. Moreover, splenic capsular metastasis was more commonly encountered in ovarian cancer as a part of widespread peritoneal carcinomatosis rather than isolated parenchymal metastasis (14). In the present study, three patients were diagnosed with parenchymal splenic metastasis one of them presented as recurrent. All patients were managed by splenectomy.

The treatment strategy of ovarian cancer patients with rare distant site metastasis is still not standardized. The treatment is mainly individualized per each case within the scope of the multimodal approach aiming at improving the patient's survival. Although previous studies reported a better impact of surgery on patient's survival particularly in patients with non-regional lymph node metastasis (6, 7), we found no survival benefit of surgery among the whole cohort of patients with rare distant metastatic sites of ovarian cancer.

It is worth mentioning that this study had some limitations. The retrospective nature and the small sample size along with the variation in clinical presentation and management of the disease might have
affected some of the results. The patients included in this study were managed all over nearly seven years in which some advances and changes in the management protocols might have been achieved.

**Conclusion:**

Ovarian cancer can metastasize to rare sites, the commonest are non-regional nodes. Rare metastasis can equally occur in association with the primary diagnosis as well as a recurrence. Non-regional nodes had better survival trends than other rare sites of metastasis, and as such those patients should be treated with curative intent. Although surgical treatment is feasible in nearly half the cases with an accepted overall and progression-free survival, we could not detect the survival benefit of resection of these metastases.

**Abbreviations:**

| Abbreviation | Definition |
|--------------|------------|
| FIGO         | Fédération Internationale de Gynécologie et d'Obstétrique |
| SPSS         | Statistical Package for Social Scientists |
| BMI          | Body mass index |
| CA 125       | Cancer antigen 125 |
| CI           | Confidence interval |
| OS           | Overall survival |
| PFS          | Progression free survival |

**Declarations:**

- **Ethics approval and consent to participate:** All procedures performed in the study involving human participants were following the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval was obtained from the institutional review board at our faculty, (MFM-IRB) under code number R/21.01.1180.

- **Competing Interest:** All authors declare they have no conflict of interest

- **Availability of data and material:** All the clinical, radiological & pathological data used in this manuscript is available on Mansoura University medical system

- **Funding:** no funding was received

- **Author contributions:** All authors have read and approved the manuscript. MZ conceptualization, data collection, writing & revision. RA: Data collection, writing. OH: Data collection, revision. IH: Data validation, revision.

- **Code availability:** N/A
Disclosures and funding source: The authors declare no conflict of interest. No funding sources.

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| Parameter                                    | Value                                      |
|---------------------------------------------|--------------------------------------------|
| Age at diagnosis of ovarian cancer mean +/- SD | 57.8 +/- 10.8                              |
| BMI mean +/- SD                             | 33.7 +/- 7.8                               |
| CA125 level                                 |                                            |
| Normal                                      | 1 (2.1%)                                   |
| Elevated                                    | 44 (91.7%)                                 |
| Median (range)                              | 478 (16-5000)                              |
| Neoadjuvant                                 |                                            |
| No                                          | 14 (29.2%)                                 |
| Yes                                         | 34 (70.8%)                                 |
| Indication for NAC                          |                                            |
| Optimal debulking non-achievable            | 28 (58.3%)                                 |
| Pleural effusion                            | 2 (4.2%)                                   |
| Pulmonary metastasis                        | 1 (2.1%)                                   |
| Supraclavicular metastasis                  | 1 (2.1%)                                   |
| Peritoneal & inguinal metastasis            | 1 (2.1%)                                   |
| Response to NAC                             |                                            |
| Regression                                  | 20 (41.7%) (3 complete)                    |
| Stable disease                              | 11 (22.9%)                                 |
| Progression                                 | 2 (4.2%)                                   |
| Surgery                                     |                                            |
| No                                          | 5 (10.4%)                                  |
| Interval debulking                          | 28 (58.3%)                                 |
| Primary suboptimal debulking                | 6 (12.5%)                                  |
| Primary optimal debulking                   | 5 (10.4%)                                  |
| TAHBSO                                      | 3 (6.3%)                                   |
| Excision of fungation                       | 1 (2.1%)                                   |
| Pathology                                   |                                            |
| Serous                                      | 42 (87.5%)                                 |
|                                |      |
|--------------------------------|------|
| **Adenocarcinoma**             | 4 (8.3%) |
| **Mixed Mullerian**            | 1 (2.1%)  |
| **Endometrioid**               | 1 (2.1%)  |
| **Grading**                    |      |
| Low                            | 4 (8.3%) |
| Moderate                       | 2 (4.2%) |
| High                           | 32 (66.7%) |
| Undifferentiated               | 2 (4.2%) |
| **Side**                       |      |
| Unilateral                     | 12 (25%) |
| Bilateral                      | 31 (64.6%) |
| **Nodal resection**            |      |
| No                             | 16 (33.3%) |
| Pelvic                         | 19 (39.6%) |
| Pelvic and para-aortic         | 8 (16.7%) |
| **Peritoneal/omental infiltration** |      |
| Free                           | 17 (35.4%) |
| Infiltrated omentum            | 16 (33.3%) |
| Infiltrated peritoneum         | 1 (2.1%)  |
| Both infiltrated               | 7 (14.6%) |
| **Ascites cytology**           |      |
| Reactive                       | 8 (16.7%) |
| Mg                             | 21 (43.8%) |
| **LN status**                  |      |
| Free                           | 18 (37.5%) |
| Infiltrated                    | 9 (18.8%) |
| **Adjuvant therapy**           |      |
| No                             | 5 (10.4%) |
| Yes                            | 38 (79.2%) |
| **Recurrence/progression**     |      |
|             |      |
|-------------|------|
| **No**      | 15 (31.3%) |
| **Yes**     | 31 (64.6%)  |

| **Pattern of recurrence** |      |
|---------------------------|------|
| **Solitary**              | 13 (43.3%)* |
| **Multiple**              | 17 (56.7%)* |

* Valid percent
| Parameter                                      | Value          |
|------------------------------------------------|----------------|
| **Presentation of rare metastasis**           |                |
| Primary                                       | 26 (54.2%)     |
| Recurrent                                     | 22 (45.8%)     |
| **Site of rare metastasis**                   |                |
| Inguinal nodes                                | 14 (29.2%)     |
| Axillary nodes                                | 6 (12.5%)      |
| Cervical nodes                                | 7 (14.6%)      |
| Parenchymal splenic                           | 3 (6.3%)       |
| Intramammary nodes                            | 1 (2.1%)       |
| Bone                                          | 6 (12.5%)      |
| Brain                                         | 6 (12.5%)      |
| Sister Mary nodule                            | 5 (10.4%)      |
| **Diagnostic biopsy**                         |                |
| No                                            | 17 (35.4%)     |
| Yes                                           | 30 (62.5%)     |
| · FNAC                                        | 17 (58.6%)*    |
| · CNB                                         | 8 (27.6%)*     |
| · Excisional                                  | 4 (13.8%)*     |
| **Resection of rare metastasis**              |                |
| No                                            | 28 (58.3%)     |
| Yes                                           | 20 (41.7%)     |
| **Number of resected non-regional nodes**     | 2 (1-17)       |
| **Number of infiltrated non-regional nodes**  | 1 (0-6)        |
| **Recurrence/persistence after rare metastasis treatment** |  |
| No                                            | 29 (60.4%)     |
| Yes                                           | 17 (35.4%)     |

*Valid percent
Figure 1

A diagram showing the distribution of the sites of metastasis among the study group
Figure 2

Overall survival and progression-free survival of non-regional LNs metastasis vs other sites
Figure 3

Effect of surgical intervention on the overall survival and progression-free survival

Supplementary Files

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