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Behavior and Prognosis of Ovarian Cancer with Rare Metastatic Sites

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Abstract

Background: Ovarian cancer is the most prevalent 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.

Method: We retrospectively recruited a group of patients over a 7-year period from the data system of a cancer center. All the recruited patients suffered from a rare distant metastasis from ovarian cancer. We used statistical software (SPSS) for the 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 utilized to compare parametric data, whereas non-parametric data were compared through the use of the Mann-Whitney U test. Categorical data were compared with Pearson's Chi-square test or Fischer-Exact test when appropriate. A P-value < 0.05 was considered to be statistically significant.

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

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

Keywords: Ovarian neoplasms, Cytoreduction surgical procedure, Rare diseases, Lymphatic metastases

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Introduction

Ovarian cancer is ranked as the 8th most commonly diagnosed cancer and cause of cancer-related mortality in females worldwide. In Egypt, it is ranked the 4th among the most frequently diagnosed cancers among females.[1, 2] Although ovarian cancer lies behind breast cancer in prevalence, it is three times more fatal.[3] This could be attributed to numerous factors, including late

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presentation and/or diagnosis, non-specific symptoms, and an 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 para-aortic lymph nodes is also prevalent, while the hematogenous spread is less frequently reported. The prognosis of metastatic ovarian cancer is not usually favorable, independent of the site of spread. Notably, the rare sites of distant metastasis 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.

Material and Method

This is a retrospective study where we recruited all the patients diagnosed with Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage IV ovarian cancer presenting with a rare site metastasis, as defined by metastasis to sites other than peritoneum, liver, and lung. There were also subjects who developed this rare pattern of metastasis throughout their disease course from a tertiary center from August 2012 to September 2019. These patients were followed up until 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.

Overall survival (OS) was calculated from the date of diagnosis with rare metastasis, while progression-free survival (PFS) was calculated as time lived without recurrence or progression.

Ethics approval and consent to participate

All the procedures performed in the study involving human participants were following the ethical standards of the institutional research committee as well as 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 the code number R/21.01.1180. A written consent with an explanation of the lines of management and the possible complications was signed by every patient before starting the treatment.

We used the statistical software SPSS (Statistical Package for Social Scientists SPSS 22.0; Armonk, NY: IBM Corp) for the 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 utilized to compare parametric data, whereas non-parametric data were compared through the use of the Mann-Whitney U test.

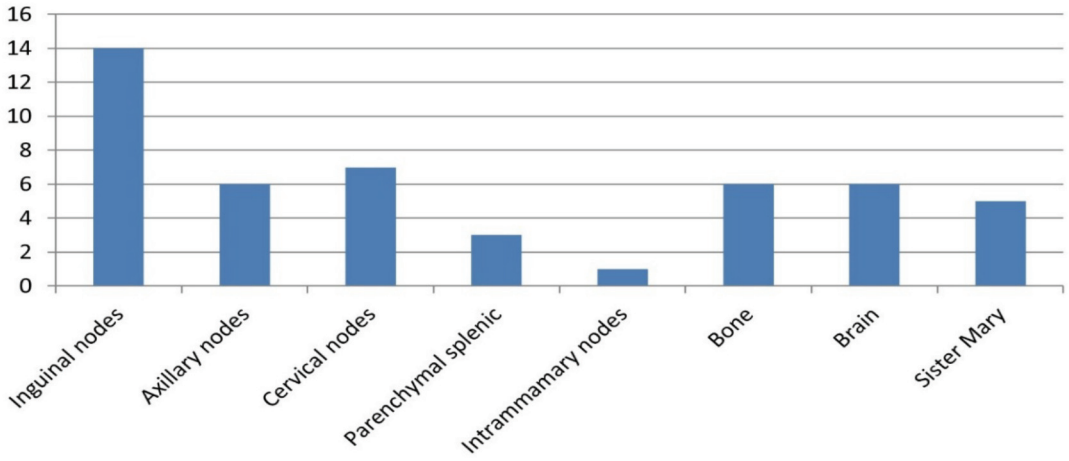

Figure 1. This figure illustrates a diagram showing the distribution of the sites of metastasis among the study group.

Table 1. Clinical and epidemiological data (continued)

Parameter	Value
Age at diagnosis of ovarian cancer (mean ±SD)	57.8 +/- 10.8 years
BMI (mean ± SD)	33.7 +/-7.8 (Kg/m^2)
CA125 level	
Normal	1 (2.1%)
Elevated	44 (91.7%)
Median (range)	478 (16-5000) (IU/ml)
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 and inguinal metastases	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%)
Total Abdominal hysterectomy + bilateral salpingoophrectomy	3 (6.3%)
Excision of fungation	1 (2.1%)
Pathology	
Serous carcinoma	42 (87.5%)
Dedifferentiated/ undifferentiated carcinoma	4 (8.3%)
Carcinosarcoma	1 (2.1%)
Endometrioid carcinoma	1 (2.1%)
Grading	
Low	4 (8.3%)
Moderate	2 (4.2%)
High	32 (70.9%)
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%)
Malignant	21 (43.8%)
Lymph node status	
Free	18 (37.5%)
Infiltrated	9 (18.8%)

*Valid percent; BMI: Body mass index; SD: Standard deviation; CA 125: Cancer antigen 125; NAC: Neoadjuvant chemotherapy

Table 1. Clinical and epidemiological data (continued)

Parameter	Value
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; BMI: Body mass index; SD: Standard deviation; CA 125: Cancer antigen 125; NAC: Neoadjuvant chemotherapy

Categorical data were compared via Pearson's Chi-square test or Fischer-Exact test when appropriate. A *P*-value < 0.05 was considered to be statistically significant.

Results

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

In most patients, the pathology was serous carcinoma (87.5%), the majority of which (70.9%) were high grade. The cancer was affecting both ovaries in 64.4% of the cases. In 58.5% of them,

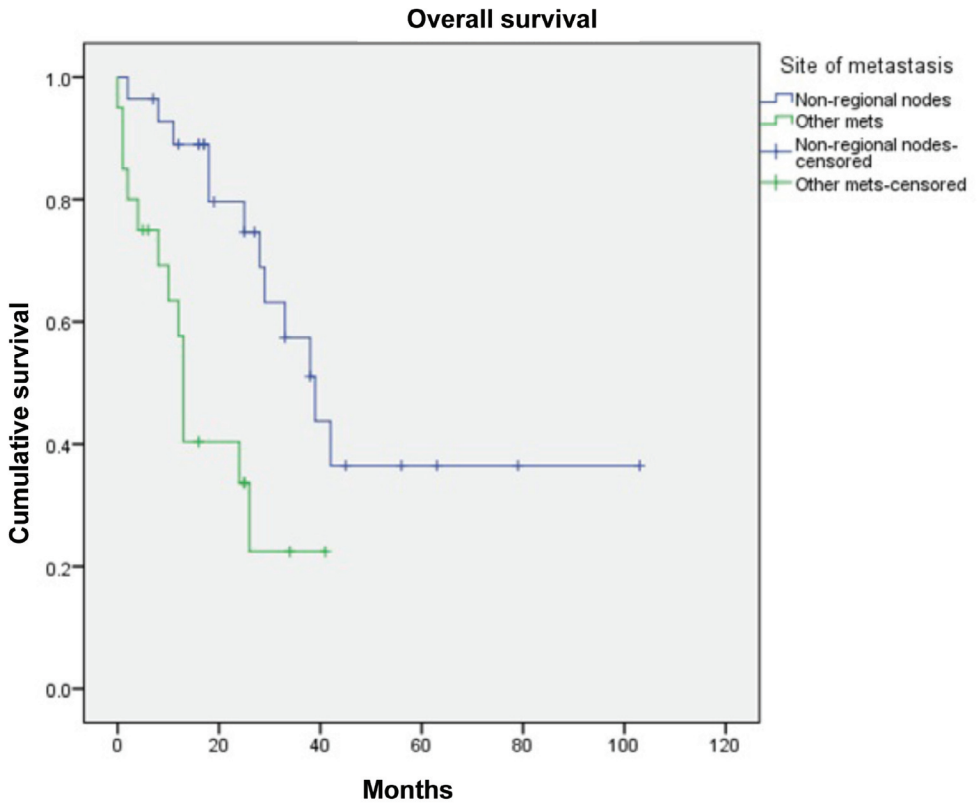

Figure 2. This figure compares the overall survival and progression-free survival of non-regional lymph node metastasis to those of other sites.

Table 2. Presentation and management of rare metastasis

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 Joseph 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; FNAC: Fine needle aspiration cytology; CNB: Core needle biopsy

the omentum, peritoneum, or both were involved in the malignant process.

Considering the normal range of cancer antigen 125 (CA125) in our center (up to 35 IU/ml), all the patients, except one, had an elevated level at diagnosis of ovarian cancer (Table 1).

The most common site of rare metastasis was non-regional nodes (inguinal, cervical, and axillary, respectively), being 56.3%, followed by bone and brain being 12.5% each. Rare metastasis was presented within primary diagnosis in 26 cases, while it was 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 fine needle aspiration cytology (FNAC) in 58.6% of the biopsied subjects. 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 the follow-up, recurrence after treatment of the rare ovarian metastasis occurred in 17 (35.4%) patients, whereas 25 (52.1%) were dead. The estimated median OS after rare metastases diagnosis was 29 (95% confidence interval (CI) = 19.8-38.2), while the median PFS was 15 (95% CI = 9.4-20.6) months.

The patients with non-regional node metastasis had significantly better OS from visceral/skeletal metastasis (estimated median OS 39 vs. 13 months, $P = 0.003$), 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. Additionally, the non-regional node group had significantly better PFS (estimated median 29 vs. 13, $P = 0.034$) (Figure 1).

Moreover, the surgical resection of these metastases did not improve OS or PFS, with an

estimated median OS of 38 vs. 25 months (P = 0.17) for resection and non-surgical treatment, respectively, and an estimated median PFS of 29 vs. 14 months (P = 0.24), respectively (Figures 2 and 3).

Discussion

Hereby, we explored the clinicoepidemiological characteristics and survival trends of ovarian cancer patients with rare site metastases from a tertiary cancer center over a nearly 7-year period. Metastasis to non-regional lymph nodes was the most common site; these patients had better survival than others. Despite the acceptable overall and disease-free survival of the surgery, we could not report any survival benefits from surgical resection in those patients. Ovarian cancer was typically reported in the literature to metastasize to the peritoneal cavity. Of note, other rare sites of metastases have 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 our study, non-regional lymph node metastases were the most reported rare metastatic sites (56.3%); these patients experienced significantly better OS from visceral/skeletal metastasis (estimated median OS of 39 vs. 13 months). Moreover, they had significantly higher PFS (estimated median of 29 vs. 13 months). 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. analyzed 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 also previously reported by Hjerpe et al. who found the median OS for patients with non-regional lymph node metastases to be significantly higher than that of the other distant metastases (41.4 vs. 25.2- or 26.8-months).[7]

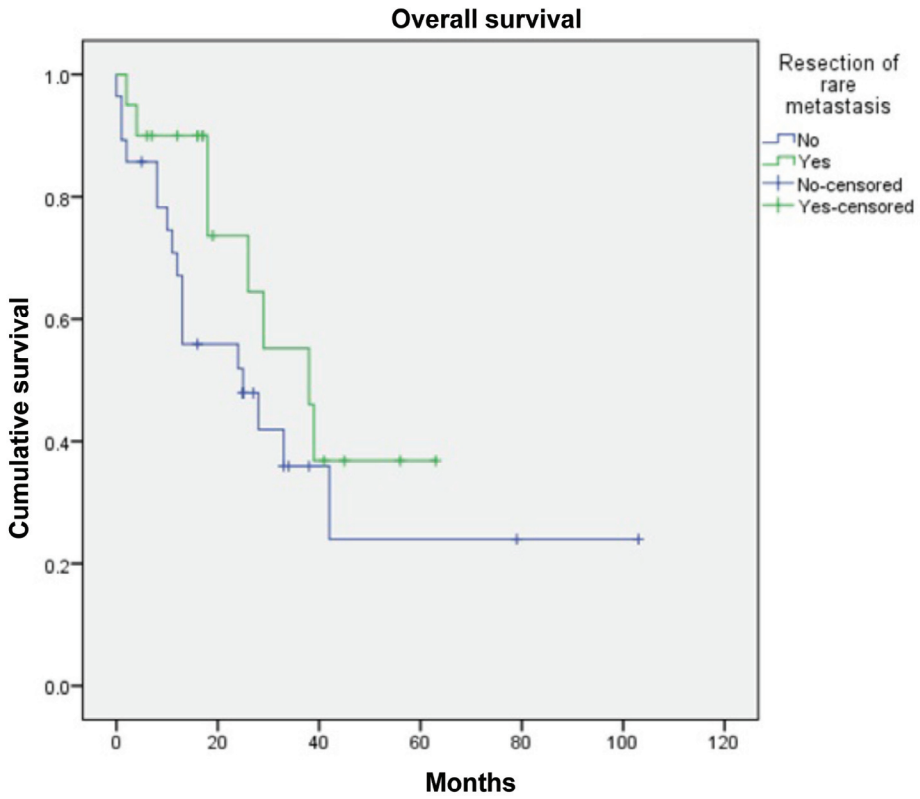

Figure 3. This figure compares the effect of surgical intervention on the overall survival and progression-free survival.
Cum: Cumulative

Furthermore, ovarian cancer patients suffering from distant lymph node metastases experienced a better prognosis when treated with surgery and chemotherapy.[6]

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 surgical excision of the primary pathway to the para-aortic and iliac lymph nodes.[8]

In our study, axillary and intramammary nodal metastases were reported in seven patients (14.6%), while three patients presented as a recurrent event throughout their disease course. Axillary and intramammary nodal metastasis from ovarian cancer is very rare and whenever found, it represents a diagnostic dilemma. Two pathways could explain the spread of ovarian cancer to axillary nodes through the superior diaphragmatic lymph nodes. The first one follows an anterior pathway to the prepericardial nodes, followed by the subclavian lymph trunk, and ending eventually in the axillary lymph nodes. Meanwhile, the second one is posteriorly through the inferior diaphragmatic nodes to superficial umbilical lymphatics ending in cisterna chyli that is continuous into the thoracic duct and ends at the junction between the left subclavian and internal jugular veins.[9,10] It should be mentioned that thorough clinical, radiological, and pathological interpretation is crucial to differentiate these patients from primary breast carcinomas with ovarian metastasis.[11]

In the present work, brain metastasis was the second most common (12.5%) after non-regional nodal metastasis. This was reported in six patients out of whom only one presented with this rare metastatic pattern in her first presentation. However, the other five patients presented with brain metastasis in the form of recurrence. All the patients were managed via chemoradiation, while one performed surgical resection. Thanks to the recent advances in imaging technology, the incidence of brain metastasis from ovarian cancer had been increasingly reported in the recent literature.[12] 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% to 12%.[13] Surgery, chemotherapy, and radiation therapy were the most frequently used treatment modalities in these patients.[5]

Herein, bone metastasis was reported in six patients (12.5%), three of whom were confined to lumbar vertebrae, while one had hip bone metastasis and the other two had multiple sites of bone metastasis. 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% to 3.74%.[6, 14] This could be explained by either direct, hematogenous, lymphatic, or transperitoneal spread. The vertebral venous system was thought to be the route of ovarian cancer spread to the vertebrae in some studies.[14]

In the present paper, three patients were diagnosed with parenchymal splenic metastasis, one of whom presented as recurrent. All the subjects were managed with splenectomy. Diagnosis of splenic metastasis is a rare event. Interestingly, splenic metastasis from breast, lung, colorectal carcinoma, and melanoma were more commonly reported than that from ovarian cancer. Moreover, splenic capsular metastasis was more frequently observed in ovarian cancer as a part of widespread peritoneal carcinomatosis rather than isolated parenchymal metastasis.[15]

The treatment strategy for 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 to improve the patient's survival. Although previous studies have reported a better impact of surgery on patients' survival, particularly in those 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.

The present research is one of the few studies

discussing the characteristics and prognosis of ovarian cancer patients with rare metastatic sites. Of note, our work had certain 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 during which some advances and changes in the management protocols might have been achieved.

Conclusion

Ovarian cancer can metastasize to rare sites, the most common of which 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; therefore, those patients should be treated with curative intent. Although surgical treatment is feasible in nearly half the cases with an accepted OS and PFS, we could not detect the survival benefit of resection of these metastases

Availability of data and material

All the clinical, radiological, and pathological data used in this manuscript are available on the medical system of Mansoura University.

Conflict of Interest

None declared.

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