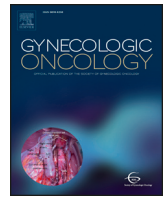




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## Sites of distant metastases and overall survival in ovarian cancer: A study of 1481 patients

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### HIGHLIGHTS

- The most common distant metastatic site of ovarian cancer was liver, followed by distant lymph nodes, lung, bone and brain.
- The site of distant metastases was an independent prognostic factor for ovarian cancer patients with distant metastases.
- Lung metastases had the worst overall survival and distant lymph node metastases had the best overall survival.
- The number of distant metastatic sites did not affect overall survival of patients with ovarian cancer.
- Prognostic factors were identified for organ-specific distant metastases.

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### ABSTRACT

**Objective.** To assess the association between patterns of distant metastases and overall survival in metastatic ovarian cancer and identify prognostic factors for site-specific distant metastases.

**Methods.** Data was obtained from the SEER database between 2010 and 2014. Univariate and multivariate Cox proportional hazard models were used to identify variables associated with overall survival. Survival times between different groups were compared using Kaplan-Meier analysis and log-rank tests.

**Results.** We analyzed 1481 patients. The most common distant metastatic site was liver, followed by distant lymph nodes, lung, bone, and brain. The site of distant metastases was an independent prognostic factor for overall survival. Using liver metastases as reference, overall survival was lower for lung metastases ( $p = 0.0297$ ) and higher for distant lymph node metastases ( $p = 0.0006$ ). Using distant lymph nodes as reference, distant metastases to the liver ( $p = 0.0006$ ), lung ( $p < 0.0001$ ), brain ( $p = 0.0455$ ), and bone ( $p = 0.0138$ ) were all associated with worse overall survival. The number of metastatic sites did not affect overall survival. We also found that surgery and chemotherapy affected overall survival for patients with distant lymph node metastases only; age, histological subtype, surgery, and chemotherapy affected overall survival for patients with liver metastases only, while histological subtype and chemotherapy affected overall survival for patients with lung metastases only.

**Conclusions.** The site of distant metastases affected overall survival in metastatic ovarian cancer. Patients with specific distant metastatic sites should receive special treatment and management. The identified prognostic factors can help clinician evaluate the prognosis for ovarian cancer patients with distant metastases.

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### 1. Introduction

Ovarian cancer is one of the most common tumors in women, with the highest mortality rate among gynecology malignancies. The majority of ovarian cancer patients are diagnosed at advanced stage (stage III–

IV). Ovarian cancer has historically been called the “silent killer” because approximately 62% of the disease occurs as distant disease [1]. Ovarian cancer can metastasize through the intraperitoneal route, lymphatic channels, and hematogenous route [2]. The prognosis of metastatic ovarian cancer is poor and only limited advances have been made that shed light on the epidemiology of ovarian cancer metastases.

The most common sites of metastatic ovarian cancer include peritoneum, liver and lymph nodes [2–4]. Occasionally, distant sites such as bone and brain may be involved [5, 6]. Currently, ovarian cancer patients with distant metastases are considered to have similar poor

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prognoses regardless of metastatic sites. However, the distant sites where primary ovarian cancer metastasizes may have different effects on the survival of patients with ovarian cancer. Understanding the patterns of distant metastases in ovarian cancer is crucial to improving treatments and management for patients. Most studies have focused on single distant metastatic sites for ovarian cancer [5–8], but few have investigated the association between the patterns of distant metastases and prognosis of ovarian cancer. In addition, clinical prognostic factors for organ-specific distant metastases are rarely studied, primarily because such data are rarely recorded in population-based studies and metastatic sites such as bone and brain are in fact uncommon. Hjerpe et al. compared the survival of patients with lymph node metastases with pleural metastases only and also with other/multiple distant metastases for stage IV serous ovarian cancer [9]. However, they regarded multiple sites except lymph nodes and pleura as one category and did not further analyze the effects of site-specific distant metastases on survival.

The primary objective of this study was to investigate the relationship between site-specific patterns of distant metastases and overall survival of metastatic ovarian cancer using the surveillance, epidemiology, and end results (SEER) database. The secondary aim was to determine prognostic factors for organ-specific distant metastases.

## 2. Materials and methods

The National Cancer Institute's SEER database from years 2010–2014 was used in this study. Patients who were diagnosed before 2010 had no detailed information about site-specific metastases. All data were publicly available and exempt from Institutional Review Board review. Eligible women were older than 18 years old with histologically confirmed stage IV ovarian cancer. Tumor stage was based on the AJCC staging system in the SEER program and ovarian cancer patients with distant metastases were defined as having stage IV ovarian cancer. We excluded patients with ovarian cancer that was not the first malignancy or who lacked information about distant metastatic sites. Patients whose information of tumor grade, marital status, race and survival time was unavailable were also excluded. Patients with unknown surgery status were removed from the dataset. The original SEER database contains 29,074 ovarian cancer patients diagnosed from the years 2010 to 2014. We excluded 27,593 patients and finally obtained 1481 ovarian cancer patients for this study. The detailed exclusion criteria and reasons that we excluded them are shown in Table S1.

Variables that were analyzed in the dataset included age, histological subtype, tumor grade, marital status, race, treatments, sites of distant metastases, and the number of distant metastatic sites. Chemotherapy was classified as "yes" or "no/unknown" in the current database. The sites of distant metastases were classified as distant lymph nodes, liver, lung, bone, and brain. The SEER database includes the variables "Mets at Dx-Distant Lymph Nodes", "Mets at Dx-Liver", "Mets at Dx-Lung", "Mets at Dx-Bone" and "Mets at Dx-Brain" that identified the presence of distant metastatic involvement of the distant lymph nodes, liver, lung, bone and brain at time of diagnosis, respectively. The information about distant metastatic sites was obtained mainly from the medical records in the SEER program. The primary endpoint was overall survival in this study. We assessed the association between site-specific metastatic sites and overall survival. Furthermore, we explored prognostic factors for patients with distant lymph node metastases only, liver metastases only, and lung metastases only, respectively, because the sample size for these three distant metastases was relatively large.

Categorical variables were reported as counts (percentage). Independent predictors for overall survival were identified using univariate and multivariate Cox proportional hazard models. Variables that were statistically significant in the univariate Cox analysis were fitted in the multivariate Cox proportional hazard model. Survival times between different groups of patients were compared using Kaplan-Meier

analysis and log-rank tests. A two-tailed  $p$  value  $<0.05$  was considered statistically significant in all analyses. Statistical analyses were performed using SAS Version 9.4 (SAS Institute Inc., Cary, North Carolina), and figures were drawn using the R package *ggplot2* [10].

## 3. Results

### 3.1. Characteristics of study patients

A total of 1481 patients were included in the analysis according to the criteria described above. The demographic and clinicopathological characteristics of study patients are summarized in Table 1; 826 patients (55.77%) were  $<65$  years old, 748 (50.51%) had been married, 1212 (81.84%) were White and 1014 (68.47%) had serous ovarian cancer. In addition, detailed demographic and clinical characteristics by metastatic sites and the number of metastatic sites for study patients are shown in Tables S2 and S3, respectively.

### 3.2. Distribution of distant metastatic sites

A total of 1819 distant metastatic sites were identified in the 1481 patients. The most common sites were liver (682, 37.49%), followed by distant lymph nodes (534, 29.36%), lung (517, 28.42%), bone (68, 3.74%) and brain (18, 0.99%). Most patients (1195, 80.69%) had a single site of distant metastases, followed by two sites (240, 16.21%), three sites (40, 2.70%) and four sites (6, 0.41%). Detailed distributions of distant metastatic sites are shown in Table 2.

### 3.3. Treatment

Overall, 1264 patients (85.35%) underwent surgery, in which cytoreductive surgery (858, 67.88%) was the main surgery type, followed by unilateral or bilateral salpingo-oophorectomy with omentectomy (220, 17.41%). Most patients (1245, 84.06%) received chemotherapy; the remaining 236 patients (15.94%) either did not receive chemotherapy or their chemotherapy status was unknown. In patients who underwent surgery, most of them (1105, 87.42%) received chemotherapy, while 77 patients (5.20%) had neither surgery nor chemotherapy.

### 3.4. The impact of site-specific distant metastases on overall survival

The median survival time for patients with a single site and multiple sites of distant metastases was 30 and 22 months, respectively ( $p = 0.0021$ ; Fig. 1B). For patients with a single site of distant metastases, the median survival time was 30, 26, 7, 11, and 41 months for patients

**Table 1**  
Clinical Characteristics of the 1481 patients with stage IV ovarian cancer.

Variable	Level	N (%)
Age (years)	$<65$	826 (55.77)
	$\geq 65$	655 (44.23)
Histology	Serous	1014 (68.47)
	Non-serous	467 (31.53)
Grade	G1/G2	150 (10.13)
	G3/G4	1331 (89.87)
	Marital status	Married
Race	Never married	283 (19.11)
	Other <sup>a</sup>	450 (30.38)
	White	1212 (81.84)
Surgery	Black	139 (9.39)
	Other <sup>b</sup>	130 (8.78)
	Yes	1264 (85.35)
Chemotherapy	No	217 (14.65)
	Yes	1245 (84.06)
	No/Unknown	236 (15.94)

<sup>a</sup> Other includes divorced, separated, widowed and unmarried or domestic partner.

<sup>b</sup> Other includes American Indian, AK Native and Asian/Pacific Islander.

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