

Case series

Isolated distant lymph node metastases in ovarian cancer. Should a new substage be created?

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ABSTRACT

Objective: To evaluate the prognostic significance of isolated distant lymph node metastases in comparison to other metastatic sites and stage IIIC disease.

Methods: The National Cancer Data Base was accessed and patients diagnosed between 2004 and 2014 with stage IV or IIIC epithelial ovarian cancer who met criteria for pathological staging were identified. Overall survival (OS) was calculated with Kaplan-Meier curves and compared with the log-rank test. A Cox model was constructed to control for confounders.

Results: A total of 33,561 patients met the inclusion criteria; 582 (1.7%) had stage IV only due to distant lymph node metastases (stage IV-LN), 8130 (24.2%) had stage IV with other sites of distant metastases (stage IV-other) and 24,849 (75.4%) had stage IIIC disease. The median OS for patients with stage IV-LN was 42.41 months (95% CI: 37.59, 47.23) compared to 30.23 months (95% CI: 29.30, 31.16) for those with stage IV-other ($p < .001$) and 45.57 (95% CI: 44.86, 46.28) for those with stage IIIC disease ($p = .54$). On multivariate analysis, patients with stage IV-other had a worse survival (HR: 1.41, 95% CI: 1.27, 1.57) compared to those with stage IV-LN. There was no statistically significant difference in survival between patients with stage IV-LN and stage IIIC disease (HR: 1.00, CI: 0.90, 1.11, $p = .99$).

Conclusions: Isolated distant LN metastases is associated with better survival compared to stage IV disease due to other metastatic sites and comparable to patients with stage IIIC disease.

1. Introduction

Epithelial ovarian cancer (EOC) accounts for approximately 14,000 deaths annually in the United States (Morgan Jr et al., 2016). The main pattern of dissemination is direct intra-abdominal tumor cell seeding while lymphatic and hematogenous spread represent secondary routes (Kleppe et al., 2015).

The FIGO staging system was introduced to adequately reflect disease burden, outline patient prognosis and guide treatment decisions (Mutch and Prat, 2014). Approximately 12–21% of patients with ovarian cancer will be diagnosed with FIGO stage IV based on the presence of pathologically confirmed extra-peritoneal metastases (Ataseven et al., 2016a,b). The most common metastatic sites are malignant pleural effusion, parenchymal liver metastases, abdominal wall lesions and involvement of extra-abdominal lymph nodes such as supraclavicular, inguinal and mediastinal lymph nodes (Ataseven et al., 2016a,b).

In an effort to better reflect disease burden in the recently revised FIGO staging system, the IVA and IVB substages were introduced (Mutch and Prat, 2014). More specifically stage IVA includes patients with malignant pleural effusions while stage IVB includes patients with hepatic and splenic parenchymal metastases or metastases to extra-abdominal organs such as inguinal lymph nodes and lymph nodes outside the abdominal cavity (Mutch and Prat, 2014). However, subsequent studies have failed to demonstrate a prognostic significance of this classification (Ataseven et al., 2016a,b; Tajik et al., 2018; Toptas et al., 2016). In addition, recent evidence suggests that patients with stage IV with distant lymph nodes as the only distant metastatic site may in fact have a better prognosis than other stage IV patients (Deng et al., 2018; Hjerpe et al., 2018; Nasioudis et al., 2017). Since isolated distant lymph node metastasis is uncommon for patients with ovarian cancer, the majority of evidence for this clinical scenario is derived from large databases (Deng et al., 2018; Hjerpe et al., 2018; Nasioudis et al., 2017).

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The aim of the present study was to evaluate the prognostic significance of isolated distant lymph node metastases in comparison to other metastatic sites and stage IIIC disease using a large multi-institutional database that covers approximately 70% of all newly diagnosed malignancies in the United States.

2. Materials and methods

A cohort of patients diagnosed between 2004 and 2014 with a stage III or stage IV malignant epithelial ovarian tumor (histology codes corresponding to serous, mucinous, endometrioid or clear cell histology as grouped by International Agency on Research for Cancer) was selected from the National Cancer Data Base (NCDB). Patients who did not meet criteria for pathologic staging and cases with less than one month of follow-up were excluded from the present study. The NCDB, established jointly by the American Cancer Society and Commission on Cancer of the American College of Surgeons, is a hospital-based database capturing approximately 70% of all malignancies diagnosed in the United States (Bilimoria et al., 2008). Patient data are prospectively collected from participating commission-accredited cancer programs and are frequently audited to ensure their high-quality. All data are de-identified and available for research purposes. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytical or statistical methodology employed, or the conclusions drawn from these data. The present study was deemed exempt from the Institutional Board Review.

Based on the information available at the collaborative staging schema fields, three groups of patients were identified: patients with stage IV disease due to isolated distant lymph node metastasis, in the absence of metastases to other distant sites (stage IV-LN), patients with stage IV disease due to other distant metastatic sites (excluding distant lymph nodes) (stage IV-other) and patients with stage IIIC disease. Based on collaborative schema, iliac, para-aortic, lateral sacral and retroperitoneal lymph nodes are considered as regional while other lymph nodes are coded as distant. The discrimination between stage IVA (pleural effusion with positive cytology) from IVB was not feasible based on the available coding schema. Demographic, clinico-pathological, and treatment variables were extracted from the de-identified NCDB dataset. Patient race was recoded into White, and non-White. Age was grouped into < 65 and ≥ 65 years. The presence of medical comorbidities was assessed using the Charlson-Deyo Comorbidity index (a clinical comorbidity index designed for use with medical records that takes into account the severity of comorbid condition).

The frequency of distribution of categorical variables was compared with the chi-square test and continuous variables with Mann-Whitney U test. Overall survival was defined as the months elapsed from cancer diagnosis to the date of death or last-follow up. The median OS for each group was estimated following generation of Kaplan-Meier curves and compared with the log-rank test. A Cox model was constructed to control for variables associated with overall survival. All statistical analysis was performed with the SPSS v.24 statistical package (IBM Corp. Armonk, NY) and the alpha level of statistical significance was set at 0.05.

3. Results

A total of 33,561 patients met the inclusion criteria; 582 (1.7%) patients had stage IV disease only due to distant lymph node metastasis, 8130 (24.2%) patients had stage IV disease with other sites of distant metastases and 24,849 (75.4%) patients had stage IIIC disease. Demographic and clinico-pathological characteristics are summarized in Table 1. Compared to patients with stage IV-LN, those with stage IV-other were older, they were more likely to have comorbidities, and government issued insurance while they were less likely to receive surgery or chemotherapy. Patients with stage IIIC were more likely to receive tumor direct surgery compared to stage IV-LN.

According to the reverse Kaplan-Meier method, the median follow-up for patients with stage IV-LN, stage IV-other and stage IIIC disease was 74.18, 76.22 and 72.15 months respectively. Following the generation of Kaplan-Meier curves, the median OS for patients with stage IV-LN was 42.41 months (95% CI: 37.59, 47.23) compared to 30.23 months (95% CI: 29.30, 31.16) for those with stage IV-other ($p < .001$, Fig. 1) and 45.24 months (95% CI: 44.53, 45.95) for those with stage IIIC ($p = .54$, Fig. 2). After excluding patients who did not undergo cancer-directed surgery at any point in their care to avoid the inherited bias of the effect of surgical cytoreduction, the median OS for patients with stage IV-LN ($n = 505$) was 47.57 months (95% CI: 42.64, 52.50) compared to 33.41 months (95% CI: 32.35, 34.48) for those with stage IV-other ($n = 6825$) ($p < .001$) and 45.57 (95% CI: 44.86, 46.28) for patients with stage IIIC ($n = 24,534$) ($p = .46$). Based on available information, the rate of optimal cytoreduction for patients with stage IV-LN was 81.6% (129/158) compared to 81.8% (1412/1727) and 86.4% (6804/7872) for those with stage IV-other and stage IIIC disease respectively, $p < .001$. In patients who had optimal cytoreduction, those with stage IV-LN had better OS (median 63.41 months) compared to patients with stage IV-other (median 40.15 months, $p < .001$), while overall survival was not statistically different between stage IV-LN and stage IIIC (median 53.22, $p = .08$) (Supplemental Fig. 1).

After controlling for patient age, race, the type of insurance, the type of reporting facility (academic vs non-academic), the presence of co-morbidities, tumor histology (serous vs non-serous), the receipt of chemotherapy, and the performance of cancer directed surgery, patients with stage IV-other had worse survival (HR: 1.41, 95% CI: 1.27, 1.57, $p < .001$) compared to those with stage IV-LN. There was no statistically significant difference in survival between patients with stage IV-LN and stage IIIC disease (HR: 1.00, CI: 0.90, 1.11, $p = .99$).

4. Discussion

Similar to previous reports, in this large cohort of patients with advanced stage EOC derived from a multi-institutional hospital-based database, those with isolated distant LN metastases had better survival compared to those with stage IV disease due to other sites of metastases and similar survival to patients with stage IIIC disease.

Following the publication of the revised FIGO ovarian cancer staging schema multiple studies have failed to demonstrate a prognostic significance of the new stage IV subclassification. In a retrospective study Rosendahl et al. (2016) detected no survival difference between patients with stage IVA ($n = 149$) and stage IVB ($n = 613$) disease (both groups had 13%, 5-year overall survival). Similarly, Ataseven et al. (2016a,b) prospectively compared the survival of patients with stage IVA ($n = 102$) and stage IVB ($n = 138$) disease and did not find any statistically significant difference (median OS was 25 and 28 months respectively). Moreover, a previous analysis of the Surveillance, Epidemiology, and End Results (SEER) dataset, Nasioudis et al. (2017) demonstrated that patients with inguinal lymph node metastases (previously considered as stage III disease) had actually better outcomes than other stage IV patients and comparable to those of patients with stage III disease. However, in that study, information on the administration of chemotherapy was lacking. Similar to our results, in an analysis of the Swedish Cancer Registry that included patients diagnosed between 2009 and 2014 with stage IV serous carcinoma of the ovary fallopian tube or peritoneum, the median overall survival (OS) of those with non-regional lymph node metastases ($n = 51$) was 41.4 months compared to 25.2 and 26.8 months for patients with pleural involvement ($n = 195$) and other or multiple metastatic sites ($n = 187$) (Hjerpe et al., 2018). In that cohort, among patients with distant lymph nodes, there was a trend towards longer survival for patients who had primary cytoreductive surgery compared to those who had neoadjuvant chemotherapy followed by interval cytoreductive surgery, however it was not statistically significant (Hjerpe et al., 2018). In a recent analysis of 2436 patients with stage IV EOC derived

Table 1
Clinicopathological characteristics based on disease stage.

	Group 1	Group 2	Group 3	p-value
	Stage IV (distant LNs)	Stage IV (other distant metastasis)	Stage IIIC	
Age (median, years)	61	64	62	< 0.001
Age				< 0.001
< 65 years	347 (59.6%)	4244 (52.2%)	14,060 (56.6%)	
≥ 65 years	235 (40.4%)	3886 (47.8%)	10,789 (43.4%)	
Race				< 0.001
White	512 (88%)	7099 (87.3%)	22,165 (89.2%)	
Other/unknown	70 (12%)	1031 (12.7%)	2684 (10.8%)	
Comorbidities				< 0.001
Yes	95 (16.3%)	1657 (20.4%)	4488 (18.1%)	
No	487 (83.7%)	6473 (79.6%)	20,361 (81.9%)	
Insurance				< 0.001
Private	307 (52.7%)	3557 (43.8%)	12,200 (49.1%)	
Government	246 (42.3%)	4126 (50.8%)	11,514 (46.3%)	
Uninsured/Unknown	29 (5%)	447 (5.5%)	1135 (4.6%)	
Median Income				0.001
< 38,000\$	72 (12.5%)	1298 (16.4%)	3553 (14.6%)	
38,000\$–47,999\$	126 (21.9%)	1807 (22.8%)	5546 (22.7%)	
48,000\$–62,999\$	157 (27.3%)	2157 (27.2%)	6661 (27.3%)	
63,000\$	220 (38.3%)	2670 (33.7%)	8656 (35.4%)	
Type of reporting facility*				< 0.001
Academic	272 (48.9%)	3314 (41.9%)	10,822 (45%)	
Non-academic	284 (51.1%)	4604 (58.1%)	13,232 (55%)	
Histology				0.078
Serous	529 (90.9%)	7230 (88.9%)	22,297 (89.7%)	
Non-serous	53 (9.1%)	900 (11.1%)	2552 (10.3%)	
Surgery				< 0.001
Yes	518 (89%)	7129 (87.7%)	24,763 (99.6%)	
No/Unknown	64 (11%)	1001 (12.3%)	86 (0.3%)	
Chemotherapy				< 0.001
Yes	506 (86.9%)	6797 (83.6%)	21,549 (86.7%)	
No/Unknown	76 (13.1%)	1333 (16.4%)	3300 (13.3%)	

* Missing for 1033 patients

from the Netherlands Tumor Registry, the survival of patients with only extra-abdominal lymph node metastasis (12% of cohort) was superior to other stage IV patients (HR: 0.77, 95% CI 0.62, 0.95) (Timmermans et al., 2018). In another retrospective study, Suh et al. also

demonstrated that patients with stage IV disease due to metastases to the supraclavicular LNs had better overall survival compared to other stage IVB disease (Suh et al., 2013). In our cohort when examining only patients who had optimal cytoreduction, OS in patients with stage IV-

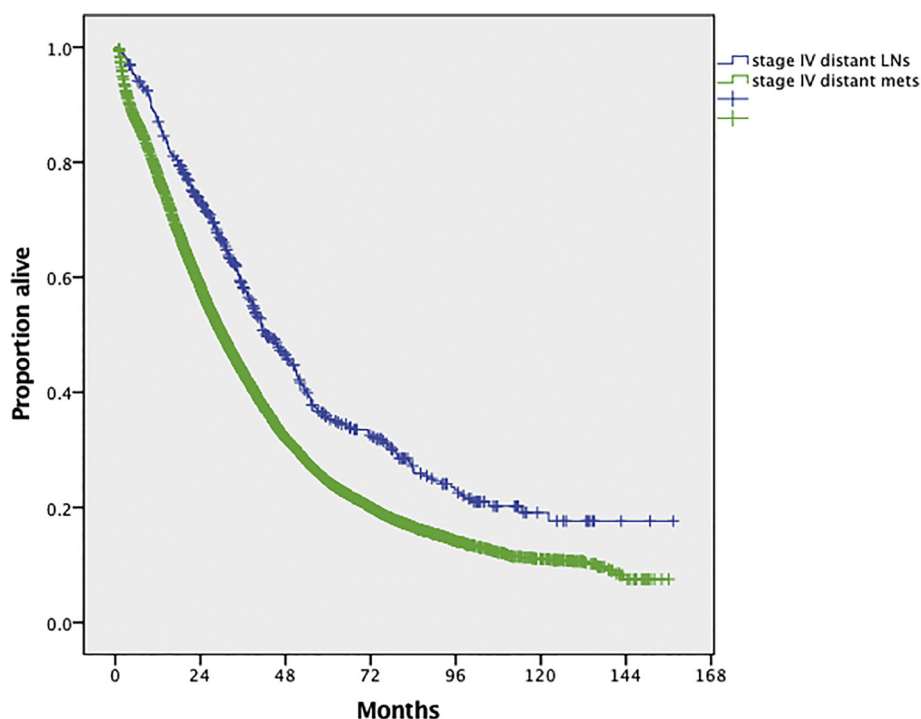


Fig. 1. Overall survival between stage IV due to distant lymph node metastases and stage IV due to other metastatic sites, $p < .001$ from log-rank.

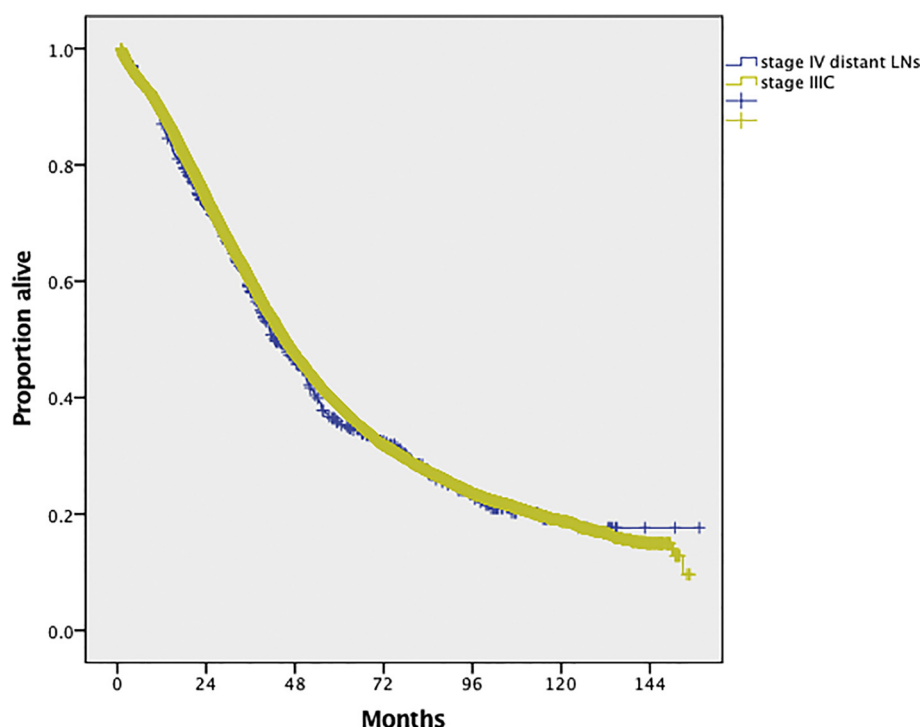


Fig. 2. Overall survival between stage IV due to distant lymph node metastases and stage IIIC, $p = .54$ from log-rank.

LN was better than those with stage IV-other and comparable to stage IIIC possibly reflecting an underlying difference in tumor biology. Ovarian cancer with isolated distant lymph node metastases may exhibit a less aggressive behavior compared to other forms of metastases. Studying tumor molecular profile based on site and route of metastases might aid in identifying biological explanation for tumor behavior, explain the associated survival outcomes and guide surveillance and treatment options.

Assignment to stage IVB disease can have significant implications in the management of patients with advanced stage cancer because physicians tend to administer neoadjuvant chemotherapy in stage IV disease without exploring the potential feasibility of cytoreductive surgery in this group since currently the surgical management of these patients is controversial. With the advancement of surgical techniques, the removal of the distant lymph nodes has become more feasible. Reports of transdiaphragmatic resection of cardiophrenic LNs and mediastinal LNs resections have been published, however the impact of thoracic cytoreduction has not been fully elucidated (Nasser et al., 2017). It should be mentioned that when we compared the survival of patients with stage IIIA1 disease ($n = 2649$) to those with stage IV-LN and gross intraperitoneal disease limited to the ovaries or pelvis (T1 or T2) ($n = 110$) the latter had worse overall survival (median 92.78 vs 54.37 months, $p = .037$).

Certain limitations of the present study should be noted. While all patients met criteria for pathologic staging, due to the absence of central pathology review, possible staging misclassifications cannot be excluded. In addition, we were not able to discriminate between IVA and IVB substages. Moreover, information on the exact location of the distant lymph nodes is not available, the present study relies on the accurate designation of regional and distant lymph nodes. As such coding misclassifications cannot be verified and may have affected the results of the analysis. Lastly, data on tumor relapse or cause of death were not available, thus evaluating progression-free and cancer-specific survival was not possible.

Our study adds to the growing body of literature suggesting that the new stage IV classification may not adequately reflect the prognosis of patients with epithelial ovarian cancer. The creation of a new substage

that includes patients with isolated distant lymph node metastasis or grouping them with stage IIIC should be evaluated in the next revision of the FIGO staging schema.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jgore.2019.03.008>.

Conflicts of interest

Nothing to declare.

Contributions

DN: conception, statistical analysis, critical analysis, drafting/final editing.

EK: critical analysis, drafting/final editing.

AH: critical analysis, drafting/final editing.

RJ: critical analysis, drafting/final editing.

RB: critical analysis, drafting/final editing.

MM: critical analysis, drafting, final editing.

NA: supervision, critical analysis, drafting, final editing.

References

- Ataseven, B., Chiva, L.M., Harter, P., Gonzalez-Martin, A., du Bois, A., 2016a. FIGO stage IV epithelial ovarian, fallopian tube and peritoneal cancer revisited. *Gynecol. Oncol.* 142 (3), 597–607 (Sep.).
- Ataseven, B., Harter, P., Grimm, C., et al., 2016b. The revised 2014 FIGO staging system for epithelial ovarian cancer: Is a subclassification into FIGO stage IVA and IVB justified? *Gynecol. Oncol.* 142 (2), 243–247 (Aug.).
- Bilimoria, K.Y., Stewart, A.K., Winchester, D.P., et al., 2008 Mar. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. *Ann. Surg. Oncol.* 15 (3), 683–690.
- Deng, K., Yang, C., Tan, Q., et al., 2018 Sep. Sites of distant metastases and overall survival in ovarian cancer: a study of 1481 patients. *Gynecol. Oncol.* 150 (3), 460–465 (Jul. 9).
- Hjerpe, E., Staf, C., Dahm-Kähler, P., et al., 2018. Lymph node metastases as only qualifier for stage IV serous ovarian cancer confers longer survival than other sites of distant disease - a Swedish Gynecologic Cancer Group (SweGCG) study. *Acta Oncol.* 57 (3), 331–337 (Mar.).
- Kleppe, M., Kraima, A.C., Kruitwagen, R.F., et al., 2015. Understanding lymphatic drainage pathways of the ovaries to predict sites for sentinel nodes in ovarian cancer. *Int.*

- J. Gynecol. Cancer 25 (8), 1405–1414 (Oct.).
- Morgan Jr., R.J., Armstrong, D.K., Alvarez, R.D., et al., 2016. NCCN clinical practice guidelines in oncology. J. Natl. Compr. Cancer Netw. 14 (9), 1134–1163 (Sep.).
- Mutch, D.G., Prat, J., 2014. FIGO staging for ovarian, fallopian tube and peritoneal cancer. Gynecol Oncol. 133 (3) (401–4 Jun.).
- Nasioudis, D., Chapman-Davis, E., Frey, M.K., et al., 2017. Should epithelial ovarian carcinoma metastatic to the inguinal lymph nodes be assigned stage IVB? Gynecol. Oncol. 147 (1), 81–84 (Oct.).
- Nasser, S., Kyrgiou, M., Krell, J., et al., 2017. A review of thoracic and mediastinal cytoreductive techniques in advanced ovarian cancer: extending the boundaries. Ann. Surg. Oncol. 24 (12), 3700–3705 (Nov.).
- Rosendahl, M., Høgdall, C.K., Mosgaard, B.J., 2016. Restaging and survival analysis of 4036 ovarian cancer patients according to the 2013 FIGO classification for ovarian, fallopian tube, and primary peritoneal cancer. Int. J. Gynecol. Cancer 26 (4), 680–687 (May).
- Suh, D.H., Kim, T.H., Kim, J.W., et al., 2013. Improvements to the FIGO staging for ovarian cancer: reconsideration of lymphatic spread and intraoperative tumor rupture. J. Gynecol. Oncol. 24 (4), 352–358 (Oct.).
- Tajik, P., van de Vrie, R., Zafarmand, M.H., et al., 2018. The FIGO stage IVA versus IVB of ovarian cancer: prognostic value and predictive value for neoadjuvant chemotherapy. Int. J. Gynecol. Cancer 28 (3), 453–458 (Mar.).
- Timmermans, M., Sonke, G., Van de Vijver, K., et al., 2018. Treatment of FIGO stage IV ovarian cancer should be tailored to the localization of metastases; results from a population-based study in the Netherlands. In: Poster presentation at the Biennial Meeting of the International Gynecologic Cancer Society, Kyoto, Japan, (September).
- Toptas, T., Pestereli, E., Erol, O., Bozkurt, S., Erdogan, G., Simsek, T., 2016. Validation of revised FIGO staging classification for cancer of the ovary, fallopian tube, and peritoneum based on a single histological type. Int. J. Gynecol. Cancer 26 (6), 1012–1019 (Jul.).