The spread pattern of right and left epithelial ovarian cancers

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Summary

Objective: No attention has been paid in the past to the spread pattern of right and left epithelial carcinomas of the ovaries. We aimed to investigate the incidence, spread pattern and distribution of lymph node metastasis in epithelial ovarian cancer (EOC), comparing right versus left EOC of any stage, where the contralateral ovary is apparently and histologically tumor-free. *Methods:* Out of a total of 442 patients with EOC, 318 (72%) patients in the study had bilateral and 124 (28%) patients had unilateral ovarian cancer. The study enrolled 60 (48%) patients with right and 64 patients with left ovarian involvement (52%) where the contralateral ovary was tumor-free. Groups Right and Left were compared in terms of age, the tumor status of the lymph nodes, surgical stage, histology, grade, tumor extension out of the ovaries, omental tumor involvement and also omental and nodal involvement together. *Results:* The comparisons of the variables between Groups Right and Left did not show significant differences except for metastasis patterns in the left iliac lymph nodes and omentum ($p < 0.05$). Independent of age and histological type of the tumor, women with left-side EOC showed a significantly higher incidence of metastasis in the left iliac lymph nodes (OR: 7.04, 95% CI, 1.36-36.44) and omentum (OR: 2.87, 95% CI, 1.03-8.01), when compared to right-side EOC ($p < 0.05$). *Conclusion:* In this cohort of patients, we found that left-side unilateral EOC was more likely to metastasize to the left iliac lymph nodes and omentum than the right side where the contralateral ovary was tumor-free. This might be due to the difference in lymphatic drainage on the right and left side and/or the influence of peritoneal fluid movements. This suggestion needs to be supported by further studies.

Key words: Epithelial ovarian cancer; Ovarian cancer metastasis; Right and left side cancer; Unilateral ovarian cancer.

Introduction

Epithelial ovarian cancer (EOC) is the leading cause of death from gynecological malignancies. Although ovarian carcinoma indicates a difficult therapeutic management, it appears that patients with this disease expect further improvement in terms of survival, quality of life and perhaps future fertility. For this purpose, surgery and adjuvant treatment methods that are "minimum but enough" should be brought to light. While achieving maximum tumor reduction is an important principle in the surgical management of EOC, the extent to which the surgeon should go on to achieve that goal has not been sufficiently addressed. Thus, better understanding of tumorogenesis and spread patterns of EOC would contribute to management of the disease.

In the current study, we present the lymph node metastasis and spread pattern of unilateral EOC where the contralateral ovary is tumor-free. Our aim was to investigate whether right- side EOC has a different spread pattern when compared to left-side EOC where the contralateral ovary is apparently and histologically tumor-negative. To the best of our knowledge, no attention has been paid to the spread pattern of right- and left-side epithelial carcinomas of the ovaries in the literature.

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Material and Methods

Four hundred forty-two patients with EOC treated at Hacettepe University between January 1982 and January 2002 were retrospectively evaluated. Data was retrieved from hospital records and gynecological oncology files. Borderline malignancies, tumors other than primary EOCs, patients who had not undergone a systematic lymphadenectomy or who had received preoperative chemotherapy as well as EOCs with bilateral ovarian involvement were excluded from the study. The cases where tumor status of region or staging was not clearly defined in the files were also excluded from the study.

All the patients underwent staging laparotomy, including peritoneal fluid sampling, peritoneal biopsy, extended total hysterectomy and bilateral salpingo-oophorectomy, systematic pelvic and paraaortic lymphadenectomy, omentectomy and bowel resection if needed. Pelvic lymphadenectomy was accomplished by completely skeletonizing the external iliac vessels and removing all the nodes around the vessels. The common iliac and obturator nodes were dissected using blunt and sharp dissection, and all tissues above the obturator nerve were removed. The paraaortic area was exposed just above the bifurcation. The retroperitoneal space and the lymph nodes at the bifurcation of the aorta anterior to the vena cava and below the renal vessels on the right and left sides were dissected. Infracolic omentectomy was performed in addition to routine staging. Surgeries were undertaken by the same surgical team in all patients. All the specimens were evaluated by the same pathology group.

Retroperitoneal lymph node regions were classified as paraaortic, iliac and obturator. Lymph nodes in the pelvis were evaluated as right and left. Histology of the tumors was evaluated as mucinous, serous and others. The tumor grade was evaluated as grade 1 and grade 2, 3 in both groups due to the sample size.

The patients enrolled in the current study had right or left ovarian involvement with a tumor-free contralateral ovary. Groups Right and Left were compared in terms of age, the tumor status of lymph nodes, surgical stage, histology, grade, tumor extension of the ovaries, omental tumor involvement and also omental and nodal involvement together.

Statistical Analysis

Statistical analysis was carried out by using the Statistical Package for Social Sciences (SPSS Inc., Chicago, Illinois, USA), version 14.0. Significance was defined as $p < 0.05$. Data are presented as mean ± standard deviation (SD). Continuous variables were analyzed and compared using the Student's t-test. Differences between categorical variables were analyzed using the chi-square test and Fisher's exact test. The independence of significant factors ($p < 0.05$) was determined by the logistic regression method and estimated risks were calculated.

Results

The mean age of the participants was 52.7 years. Of a total of 442 patients with EOC, there were 318 (72%) patients with bilateral and 124 (28%) patients with unilateral ovarian cancer. The current study enrolled 60 (48%) patients with right and 64 patients with left ovarian involvement (52%) where the contralateral ovary was tumor-free.

Of these 124 patients, there were 76 (64%) patients with early stage (I-II) disease and, 43 (36%) patients with advanced stage (III-IV) disease. The disease was confined to the ovary in 70 (59%) patients, while extension out of the ovary was observed in 49 (41%) patients.

The most frequent histological types of EOC were mucinous and serous with percentages of 40% and 35%, respectively. Tumor grading was available in only 42% (n = 52) of patients, and 46% (n = 24) of these were found to be grade 1 and 54% (n = 28) grade 2 or 3. There were 22 (18%) patients with retroperitoneal lymph node involvement. Omental metastasis, however, was found in 26 (21%) of the patients. Omentum and lymph node involvement together was observed in 11 (9%) patients. Distribution of lymph node metastasis in the regions described in the Methods section is shown in Table 1.

There were no significant differences between Groups Right and Left in terms of age, tumor confinement in or extension out of the ovaries, or for early or advanced staged tumors. Metastasis to the paraaortic, pelvic, right iliac, right and left obturator lymph nodes did not differ between right and left groups.

Histological types of the tumors showed no significant difference when the right and left ovarian cancers with were compared. The comparison of the histological types of tumors that were only confined to the right or left ovary showed no significant differences.

Comparisons of the variables between right and left groups did not show significant differences except for metastasis patterns to the left iliac lymph nodes and omentum. Group Left showed a significantly higher incidence of metastasis to the left iliac lymph nodes and omentum when compared with the right group ($p < 0.05$). Right iliac lymph node metastasis and paraaortic lymph node metastasis were also more frequent in left EOCs compared to right EOCs, even though the data are not statistically significant ($p = 0.06$).

The incidence of pelvic and paraaortic lymph node metastasis, omental involvement and the statistical results of comparisons of Groups Right and Left are summarized in Table 1.

The localization side of the unilateral EOC on the right or left affects omental and left iliac lymph node metastasis, independent of age and histological type (serous, mucinous and others) of the tumor ($p < 0.05$). Estimated risks of omentum and left iliac lymph node metastasis for patients with unilateral EOC on the left side compared to the right side were calculated as the odds ratios 2.87 (95% CI, 1.03-8.01) and 7.04 (95% CI, 1.36-36.44), respectively.

Table 1. — *Comparisons of the spread patern of the right and left epithelial ovarian cancers*.

Variables	Total (n = 124)	Tumor status of ovaries, Tumor-positive/stated regions (%) Right tumor positive, left tumor-free (Group Right, n = 60)	Left tumor positive, Right tumor free (Group Left, n = 64)	*p*
Mean age (range)	52.7	52.6 (26-75)	52.7 (21-87)	ns
Stage	119			ns
Early (I-II)	76	42/58 (72)	34/61 (56)	
Advanced (III-IV)	43	16/58 (28)	27/61 (44)	
Histology*	124			ns
Mucinous	50	21/50 (42)	29/50 (58)	
Serous	43	21/43 (49)	22/43 (51)	
Others	31	18/31 (58)	13/31 (42)	
Grade	52			ns
Grade 1	24	14/29 (48)	10/23 (44)	
Grade 2,3	28	15/29 (52)	13/23 (56)	
Regions tumor-positive				
Confined to over	70	37/58 (64)	33/61 (52)	ns
Histology*				ns
Mucinous	38	16	22	
Serous	23	14	9	
Others	9	7	2	
Extension out of ovary	49	21/58 (36)	28/61 (46)	
Histology*				
Mucinous	12	5	7	ns
Serous	24	10	14	
Others	13	6	7	
Lymph node (LN)	22	8/49 (16)	14/46 (30)	ns
Paraaortic LN	11	3/44 (7)	8/38 (21)	ns
Pelvic LN	19	7/49 (14)	12/46 (26)	ns
Right iliac LN	13	4/49 (8)	9/45 (20)	ns
Right obturator LN	8	3/49 (6)	5/44 (11)	ns
Left iliac LN	11	2/48 (4)	9/45 (20)	< 0.05
Left obturator LN	8	3/49 (6)	5/44 (11)	ns
Omentum	26	7/50 (14)	19/58 (33)	< 0.05
Histology*				ns
Mucinous	8	2	6	
Serous	13	3	10	
Others	5	2	3	
Omentum (+)/LN (+)	11	3/49 (6)	8/46 (17)	ns

*Comparison for mucinous and for serous; LN: lymph node; ns: non significant.

Discussion

This study showed that EOCs originating from the left ovary more frequently metastasized to the omentum and left iliac lymph nodes compared to right ovary EOCs. Moreover, the left-side tumors had a tendency to be in advanced stage and with paraaortic lymph node metastasis even though relevant data is not statistically significant. Overall, there was a tumor-free ovary in 28% of the EOCs and the incidence of right and left tumors was similar.

Laterality of ovarian cancers has been evaluated in a few studies but to our knowledge there is no study which has aimed to compare the spread pattern of EOCs originating from the left and right sides. Some authors have evaluated the data as a part of their study without pursuing the goal of comparison, but the number of patients cited is very small and does not allow us to comment [1-3]. Regarding laterality of the metastatic lymph nodes, Onda *et al*. reported a higher frequency of ipsilateral lymph node metastasis; there was, however, no difference in the laterality of the metastatic lymph nodes. Additionally, contralateral pelvic and paraaortic metastasis has been reported in a case at clinical Stage I left ovarian cancer without ipsilateral nodal metastasis [4].

In the cohort of the current study, one-third of the patients had advanced stage disease despite a tumor-free ovary. Cass *et al*. [5] performed lymphadenectomy in 96 cases at clinical Stage I unilateral EOC and reported that even when retroperitoneal lymph nodes were positive, histologically cancer-free contralateral ovaries were found in 11 cases. Wu *et al*. [6] noted a high incidence of lymph node involvement in ovarian cancer (EOC and germ cells evaluated together) where the primary tumor site was the left ovary. In 38 cases in which the primary cancer originated in the left ovary, 17 (44.7%) were found to have positive pelvic nodes, whereas in 25 cases with primary cancer arising in the right ovary, only two (8%) had metastasis of the ipsilateral pelvic nodes [6]. The result of our study was similar in terms of lymph node metastasis. On the other hand, Morice *et al*. [7] reported a higher incidence of left ovarian cancer compared with the right side; 69 left versus 46 right involvements were found in a total of 276 patients with EOC. Considering the data in the current study, it remains unclear whether left-side ovarian cancer occurs more frequently than right-side. Although left and right unilateral ovarian tumors had similar nodal involvement (25% vs 28%), it was also found that when paraaortic nodes were involved, the left paraaortic chain above the level of the inferior mesenteric artery was the most frequently involved site (70 patients, 63%). Both reports made no inference about the reason for the lymphatic site involvement.

Ovarian cancer remains in the abdomen for a long time. It spreads in the abdomen, however, relatively quickly. Tumor cell migration is helped by the negative pressure in the subdiaphragmatic space. The influence of peritoneal fluid movement and the areas of peritoneal fluid stagnation could encourage the implantation of malignant cells [8]. Implantation may not be the only way that ovarian cancer appears over the abdominal surface. The lymphatic spread of ovarian cancer, and the frequency and primary sites of metastasis in the areas of drainage remain the subject of ongoing and future studies. The extent of intra-abdominal spread varies widely in advanced stages of ovarian cancer. This raises the question of the varying anatomical and biological status of these tumors. For example, omental metastasis as the sole abdominal finding was found in 48% of Stage III patients but in only 10% of Stage IV patients [9]. The authors suggested that Stage IV is probably not a progression of Stage III, but that it has a completely different mode of spread to begin with.

Direct lymphatic spread from the ovary occurs through the efferent lymph channels to the regional nodes. It is believed that the major path of lymphatic spread appears along the ovarian vessels. On the right, this path leads first to the paraaortic nodes at the level of the inferior pole of the kidney, and on the left to the area of renal hilus [10]. However, lymphatic spread may also occur directly from the ovarian hilus to the interiliac lymphatics through broad ligament folds. These nodes are the junction of a number of anastomoses with the other regional and paraaortic nodes [11].

Venous drainage asymmetry can be considered as one of the possible explanations of the more frequent occurrence of metastasis from left ovarian tumors. The right common iliac vein, which is shorter than the left, is nearly vertical in its direction. The left common iliac vein is longer than the right one and has a more oblique course [12]. The left gonadal veins are longer than the right ones. The right gonadal vein opens into the inferior vena cava at an acute angle. However, the left gonadal vein opens into the left renal vein at a right angle [13]. The lymphatic vessels run alongside all these veins. Not to be considered more than a suggestion, variations in the length of lymphatics and the angle of opening out of the lymphatics on each side may be causing tumor cells to stay in the left for a long time, allowing them to survive at that location.

In summary, the literature lacks satisfactory cases in that describe the distribution, frequency and comparison of right and left unilateral EOCs. In this cohort of patients we found that left-side EOC was more likely to metastasize to the left iliac lymph nodes and omentum than right-side EOC where the contralateral ovary was tumor-free. Right iliac lymph node metastasis and paraaortic lymph node metastasis were also more frequent in left EOC than on the right side, although relevant data is not statistically significant. This might be due to the difference of lymphatic drainage on the right and left sides and/or the influence of peritoneal fluid movements. This suggestion needs to be supported by new studies, however and it should be considered carefully in both minimally invasive and fertility-sparing surgery when the tumor is in the left ovary.

References

[1] Benedetti-Panici P., Greggi S., Maneschi F., Scambia G., Amoroso M., Rabitti C. *et al*.: "Anatomical and pathological study of retroperitoneal nodes in epithelial ovarian cancer". *Gynecol Oncol*., 1993, *51,* 150.

[2] Onda T., Yoshikawa H., Yokota H., Yasugi T., Taketani Y.: "Assessment of metastases to aortic and pelvic lymph nodes in epithelial ovarian carcinoma. A proposal for essential sites for lymph node biopsy". *Cancer,* 1996, *78,* 803.

[3] Tsumura N., Sakuragi N., Hareyama H., Satoh C., Oikawa M., Yamada H. *et al*.: "Distribution patern and risk factors of pelvic and para-aortic lymph node metastasis in epithelial ovarian carcinoma". *Int*. *J*. *Cancer,* 1998, *79,* 526.

[4] Walter A.J., Magrina J.F.: "Contralateral pelvic and aortic lymph node metastasis in clinical Stage I epithelial ovarian cancer". *Gynecol*. *Oncol*., 1999, *74,* 128.

[5] Cass I., Li A.J., Runowicz C.D., Fields A.L., Goldberg G.L., Leuchter R.S. *et al*.: "Patern of lymph node metastases in clinically unilateral Stage I invasive epithelial ovarian carcinomas". *Gynecol*. *Oncol*., 2001, *80,* 56.

[6] Wu P.C., Lang J.H., Huang R.L., Qu J.Y., Wang H., Tang M.Y. *et al*.: "Lymph node metastaz ve retroperitoneal lymphadenectomy in ovarian cancer". *Baillieres Clin*. *Obstet*. *Gynaecol*., 1989, *3,* 143.

[7] Morice P., Joulie F., Camatte S., Atallah D., Rouzier R., Pautier P. *et al*.: "Lymph node involvement in epithelial ovarian cancer: analysis of 276 pelvic and paraaortic lymphadenectomies and surgical implications". *J*. *Am*. *Coll*. *Surg*., 2003, *197,* 198.

[8] Meyers M.A.: "Distribution of intra-abdominal malignant seeding: dependency on dynamics of flow of ascitic fluid". *Am*. *J*. *Roentgenol*. *Radium*. *Ther. Nucl*. *Med*., 1973, *119,* 198.

[9] Pickel H., Lahousen M., Stettner H., Girardi F.: "The spread of ovarian cancer". *Baillieres Clin*. *Obstet*. *Gynaecol*., 1989, *3,* 3.

[10] Averette H.E., Lovecchio J.L., Townsend P.A., Sevin B.U., Girtanner R.E.: "Retroperitoneal lymphatic involvement by ovarian carcinoma". In: Bender H.G., Beck L. (eds.) Carcinoma of the Ovary. Cancer Campaign, vol. 7. Stuttgart, New York, Gustav Fischer Verlag, 1983, 101.

[11] Plentl A.A., Friedman E.A.: "Lymphatic system of female genitalia". In: Friedman E.A. (ed.) Major Problems in Obstetrics and Gynecology, Philadelphia, Saunders 1971, 168.

[12] Pick T.P., Howden R.: "Gray's Anatomy". 15th edition, New York, Bounty Books, 1977, 617.

[13] Wishahi M.M.: "Detailed anatomy of the internal spermatic vein and the ovarian vein. Human cadaver study and operative spermatic venography: clinical aspects". *J*. *Urol*., 1991, *145,* 780.

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