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Is there any difference in lateralization in epithelial ovarian cancer cases?

Gorker Sel[1]✉, Anıl T Cakır[2], Muge Harma[3], Mehmet I Harma[4]

Introduction: **Whether there is a right or left lateralization difference in cancer involvement in double-sided organs has become a topic of interest in recent years. In addition, the density of cancer metastasis to the right or left lymph nodes has become a subject of inquisition. Our aim in this study is to retrospectively investigate differences in right- or left-sided ovarian cancer incidence.** ***Materials and methods:*** **In the Gynaecological Oncology Clinic of Zonguldak Bülent Ecevit University, 96 patients with epithelial ovarian cancer who were followed up between 2008 and 2017 were retrospectively noted as having right or left ovarian involvement or a tumour mass with right or left overgrowth.** ***Results and discussion:*** **A prominence of left ovarian involvement was observed in our study results. Especially when patients in the first stage of cancer, FIGO stage 1A, were examined, it was obvious that epithelial ovarian cancer tends to commence in the left ovary rather than the right ovary.** ***Conclusion:*** **There is a need for prospective studies with multidisciplinary studies including immunohistopathology to investigate hypotheses such as hormonal susceptibility, which can be postulated as an explanation for the higher frequency of left vs right ovary involvement in EOC.**

INTRODUCTION

Whether or not there is a right or left lateralization difference in cancer involvement in bilateral organs has become a topic of interest in recent years. For instance, skin cancer (1), lung (2), kidney (3) and testicular (4) cancers were dominantly observed on the right side, whereas breast cancer dominated on the left side of the body (5). Whether or not cancer metastasis is lateralized to the right or left lymph node has also been investigated in various studies in the current literature, which means that not only the cancer but also the metastases to the right or left side of the body are worth investigating (6-9). In this study, our aim is to retrospectively identify right or left ovarian involvement for all stages of epithelial ovarian cancer (EOC). Additionally, we aim to investigate the starting side, right or left, of the EOC.

MATERIALS AND METHODS

In the Zonguldak Bülent Ecevit University, Gynaecological Oncology Clinic, data on 96 EOC patients who were followed up between January 2008 and December 2017 were retrospectively screened. The patients' cancer stages were noted. Differentiating right or left lateralization in cases where only one ovary was involved in the pathology report, such as stage 1A, was the most reliable means of determining tumour origin. Because the tumour involves only one ovary, it was easy to determine whether the tumour was on the right or on the left side of the body. This could be performed without error by consulting the surgical records, pathology reports and preoperative imaging reports.

In stages other than stage 1A EOC, cancer lateralization was noted as having either right or left predominance; whether the pathology and surgical data were reported as right or left ovarian involvement was clear and unsuspicious. This also depends on the size and degree of capsule invasion of the tumour, as discussed below. When two ovaries were involved, such as in stage 1B, simultaneous right and left ovarian involvement was noted provided that the tumour size was similar on the two sides. For example, a maximum tumour diameter of 10 cm in the right ovary and minimal involvement in the left ovary was interpreted as tumour lateralization of the right side. However, a tumour in the right ovary of 5–6 cm diameter and a similar sized one in the left ovary of 3–4 cm diameter was interpreted as coexistence of the tumour on both sides, and the side on which the tumour initiated could not be identified.

The FIGO 2014 criteria were used in EOC staging. The standard surgical procedure included a median laparotomy incision, examination of intraperitoneal organs, ascites or peritoneal lavage aspiration for cytology, biopsy from suspicious sites from peritoneal examination, total hysterectomy and salpingo-oophorectomy, omentectomy, appendectomy and pelvic para-aortic lymphadenectomy, as shown on figure 1 and figure 2, serous and mucinous cancer of ovary, respectively. Our study was approved by the ethics committee for clinical studies with the protocol number of 2018-102-28/03, approval no: 2018-07-20 of Bülent Ecevit University, Zonguldak, Turkey on 28th of March 2018.

[1]Assistant Professor Dr.; Obstetrics and Gynaecology Department of Zonguldak Bülent Ecevit University, Turkey. Telephone number: 00903722612573; E-mail address: gorkersel@gmail.com, Orcid: 0000-0001-8653-5687; [2]Obstetrics and Gynaecology Department of Zonguldak Bülent Ecevit University, Bülent Ecevit Üniversitesi Kadın Hastalıklarıve Doğum Anabilim Dalı, Zonguldak; Email: dranilturhan@hotmail.com, Telephone number: 00903722612567, Orcid: 0000-0001-7976-4123; [3]Obstetrics and Gynaecology Department of Zonguldak Bülent Ecevit University, Bülent Ecevit Üniversitesi Kadın Hastalıklarıve Doğum Anabilim Dalı, Zonguldak, Email: Obgyn.info@gmail.com, Telephone number: 00903722612567, Orcid: 0000-0002-4327-674X, [4]Obstetrics and Gynaecology Department of Zonguldak Bülent Ecevit University, Bülent Ecevit Üniversitesi Kadın Hastalıklarıve Doğum Anabilim Dalı, Zonguldak, Email: gtd.contact@gmail.com, Telephone number: 00903722612567, Orcid: 0000-0002-9734-5253;

✉*Corresponding author*: Zonguldak Bülent Ecevit Universitesi, Tıp Fakultesi Hastanesi, Zonguldak Kozlu, 67100, Turkey. Telephone number: 00903722612573; E-mail address: gorkersel@gmail.com

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Table 1 Distribution of right and left ovarian involvement according to EOC stage

Stage Of EOC	Right Ovary		Left Ovary		Both Ovaries		Total No. of patients In the row
	No. of patients	Percentage In the row (%)	No. of patients	Percentage In the row (%)	No. of patients	Percentage In the row (%)	
1a	13	41.93	**18**	**58.06**	0	0	31
1b	0	0	0	0	3	100	3
1c	3	27.27	**6**	**54.54**	2	18.18	11
2a	0	0	**4**	**100**	0	0	4
2b	2	50	2	50	0	0	4
2c	0	0	0	0	**1**	**100**	1
3a	2	50	3	50	0	0	5
3b	1	33.33	**2**	**66.66**	0	0	3
3c	4	14.81	4	14.81	**19**	**70.37**	27
4	0	0	0	0	6	100	6
Total	25	26.04	**40**	**41.66**	31	32.29	96

Figure 1 Serous cancer of the ovary, macroscopic pathological image; **Figure 2** Mucinous cancer of the ovary, macroscopic pathological image

RESULTS AND DISCUSSION

Of the 96 patients with EOC diagnosed at all stages, 65 showed marked lateralization of ovarian cancer to the right or left side. In 65 patients, lateralization was discriminated as follows: 25 (38.46%) patients showed only right ovarian involvement and 40 (61.54%), only left ovarian EOC when compared with the contralateral ovary.

When all stages were evaluated in terms of lateralization of EOC, including both ovaries involvement, cancer involvement in the left ovary was more frequent than in the right ovary (59.67% versus 39.06%, respectively). However, this statistical insignificance could attributable to the insufficient total number of EOC patients. Therefore, this left ovary involvement tendency could not be established as a general rule of EOC.

In addition, we investigated the data on stage 1A patients according to the FIGO 2014 classification. At this stage, the tumour is observed in only one of the ovaries. In total, 30 patients were classified as stage 1A EOC. Thirteen (41.93%) of them had right and 18 (58.06%) of them had left ovary involvement only. Also at this stage, we observed that left ovary involvement of EOC was more frequent than right ovary involvement (58.06% versus 41.93%, respectively). Again, this difference was not statistically significant ($p > 0.05$ for the χ^2 test), that could be attributable to the insufficient number of patients; therefore, left ovary predominance could not be concluded for this stage.

Table 1 shows all of the numbers and percentages of EOC cases according to their involvement side and stage. In all stages in which right and left ovarian involvement could be distinguished as discussed above, the percentage of left ovary involvement was higher than that of right ovary involvement.

We observed a general trend toward higher left ovary involvement EOC, albeit not statistically significant. Particularly, when we investigated patients in an early stage of EOC, FIGO stage 1A, it could be postulated that EOC had a stronger tendency to start in the left ovary than in the right ovary. However, the difference between the percentages of right (41.93%) and left (58.06%) was not statistically significant ($p > 0.05$ for the $\chi 2$ test). Previous studies on ovarian cancer lateralization have reported a higher prevalence of right vs left ovary involvement (10), but our study found a different result in this regard. Moreover, our study has an advantage over previous studies, since we have expressed the importance of the stage 1A patient distribution and conducted a sub-group analysis on them, though previous laterality studies did not take this into account.

When 96 patients from all stages of EOC were evaluated, 31 (32.29%) patients had cancer in both right and left ovaries, 25 (26.04%) had cancer in the right ovary alone and 40 (41.66%), in the left ovary alone. In some cases of EOC, it is difficult to determine the ovary in which the cancer originated, and the possibility of error in interpreting a retrospective file scan must be taken into consideration. For this reason, we assigned importance to reporting the data on stage 1A EOC patients, as previously mentioned. As seen in Table 1, 58.06% of the 31 patients with Stage 1A EOC had left ovarian involvement. We believe these data to be more reliable in terms of lateralization. In an analysis of data involving all stages of cancer, a case could be classified incorrectly as having right or left ovary predominance, according to the size of the

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mass. However, when only cases in Stage 1A are examined, it is more certain that the cancer is limited to one or the other ovary, and the interpretation error that could occur when scanning patient files would be prevented.

In a lateralization study by Börekçi et al., they found right-sided asymmetry in lymph node involvement in gynaecologic cancers and hypothesised that cellular immunity prevents cancer metastasis more effectively on the left vs the right side (7). Lateralization studies on breast cancer have also shown that left-sided involvement is prominent, in agreement with our results (11). Furthermore, when the analysis was restricted to cases of unilateral breast cancer, like in our study on stage 1A patients, a predominance of cancer involvement of the left side was again observed (11, 12). This left-sided predominance of breast cancer was hypothetically linked to the hormonal sensitivity of the glandular structures in the left breast (12). This difference in hormonal sensitivity between the right and left sides could also be an explanation for our data: a difference in hormone receptor expression or the response to oestrogen between the right and left ovaries comes to mind. This hypothesis deserves further investigation in future studies. Also BRCA 1 and BRCA 2 mutations may have a role in tumour laterality in breast and ovarian cancer, since these two gene mutations create a significantly increased risk for developing those cancers at the same time (13).

Our study has some limitations. First, as mentioned above, the sample size was insufficient. Therefore, our results do not allow us to make a statistically meaningful statement. In addition, the retrospective nature of the study may have resulted in interpretation errors during data collection. We endeavoured to minimize this disadvantage by conducting a subgroup analysis of Stage 1A patients. It would be prudent to investigate whether there is a pathologically significant difference or an immunohistochemically difference between right and left ovary EOC; this can be further investigated prospectively with a larger number of patients.

CONCLUSION

It is a matter of debate whether a difference exists between the left and right sides of bilateral organs in terms of cancer initiation. In our study, left side involvement was more prominent than right side involvement in EOC patients. However, in terms of statistical significance, we believe that more patients need to be studied. There is also a need for prospective studies with more cases and multidisciplinary studies including immunohistopathology to investigate hypotheses such as hormonal susceptibility, which can be postulated as an explanation for the higher frequency of left vs right ovary involvement in EOC.

Learning Points

Frequency of left and right ovarian involvement in EOC. Possible attributable reasons for left ovarian prominence in EOC.

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