What is the Effect of Splenic Involvement Sites in Advanced Ovarian, Tubal and Peritoneal Epithelial Cancer on Overall Survival?

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Abstract

Purpose: In this study, we evaluated the significance of parenchymal, hilar, and capsular involvement of the spleen with regard to the overall survival of patients who required a splenectomy during cytoreduction procedures for primary or recurrent cancer.

Methods: This study includes data from 287 patients who underwent a splenectomy during optimal cytoreduction in epithelial ovarian, tubal, and peritoneal cancers. Spleen involvement regions were divided into four main groups, and the groups were classified as capsule, hilus, capsule + hilus, and other region involvement (paranchyma ± other(s) involvement site). The overall survivals of these four groups were compared.

Results: The mean age of the study group was 57.9 years, and the mean follow-up period of the patients was 43.2 months. The splenic involvement site was most frequently observed as hilus + capsule (42.2% n:121). Splenic parenchymal involvement was present in 27.9% (n: 80) of the patients. The overall survival for patients was 42 months. In the subgroup analysis, the worst overall survival was found in the group with capsule involvement at 33 months.

Conclusion: While parenchymal involvement of the spleen was considered to be stage IV according to FIGO staging, we could not detect low overall survival in patients with parenchymal involvement in our study. Our study, which has the largest number in the literature examining the relationship between splenic involvement and overall survival, can provide a remarkable perspective on the relationship between parenchymal involvement of the spleen and prognosis.

Introduction

Ovarian cancers constitute 3.4% of cancers in females and are the second most frequently observed gynecological cancer in developing countries and third in developed countries [1]. In the GLOBOCAN 2018 data, 295,414 new cases and 184,799 deaths were reported each year for ovarian cancer [1]. Generally, ovarian cancer is diagnosed at an advanced stage (stage III or IV) and has a poor overall prognosis.

The majority of primary ovarian malignancies are derived from epithelial cells, and serous carcinoma is the most common type of epithelial ovarian cancer (EOC) with a similar histology and clinical behavior to fallopian tube and peritoneal carcinomas.

A complete surgical staging of EOC is important for treatment and prognosis. There is a widespread acceptance that postoperative tumor residual mass is the most relevant prognostic factor in advanced ovarian cancer and this independent from all other clinically (age) and tumor specific factors (tumor histology and grade) [2]. The advantages of survival in the case of complete resection are so impressive that, considering the comorbidities and risk factors of individual patients, it is indisputable that a patient with complete tumor removal should refuse cytoreductive surgery if technically feasible [3]. To achieve optimal surgical results with improved survival in advanced stage of disease, surgical techniques include

apart from pelvic surgery with en block intestinal resections, including diaphragmatic stripping, splenectomy, distal pancreatectomy or liver capsule resection [4, 5]. In LION study (large prospective randomized trial) by Harter et al published in 2017 reported that systematic pelvic and para-aortic lymphadenectomy did not improve neither overall nor progression free survival in advanced ovarian cancer [6].

EOC, fallopian tube, and peritoneal carcinomas are staged surgically according to the International Federation of Gynecology and Obstetrics (FIGO) tumor, node, and metastasis (TNM) classification system. According to this classification, capsular involvement without parenchymal involvement of the spleen is stage IIIC while parenchymal involvement of the spleen is indicated as stage IV [7].

In this study, we compared the overall survivals of individuals with capsule, hilus, and parenchyma involvement of the spleen in epithelial ovarian, tubal, and peritoneal cancers who underwent a splenectomy. We wanted to investigate the question, does the parenchymal involvement of the spleen actually have a worse overall survival than other regional involvements? To our knowledge, this is the largest report in the literature to evaluate these possible relationships.

Materials And Methods

This retrospective, single institution, case control study was carried out at the Obstetrics and Gynecology Department of Baskent University in Ankara, Turkey. We evaluated 287 of 350 patients that met the inclusion criteria. In our study of patients who underwent cytoreductive surgery between 2006 and 2019, optimal debulking with residual tumor volume <1 cm was applied to all patients. Thirty-seven of 63 patients were excluded from the study because their primary was not EOC, fallopian tube, or peritoneal carcinomas. 26 patients were excluded from the study because of splenectomy due to surgical trauma. Data were obtained from hospital records.

Splenectomy was included in the primary cytoreductive surgery of 176 patients while 111 patients had splenectomy in secondary and tertiary surgery in the event of relapse. All patients had splenic involvement, and involvement of the three anatomical sites of the spleen (parenchyma, hilus, and capsule) was noted in the pathology reports for each patient. Spleen involvement regions were divided into four main groups, and the groups were classified as capsule, hilus, capsule + hilus, and other region involvement (Table 1).

Statistical evaluation of the data obtained in our study was performed using the SPSS version 22 software. The Kolmogorov–Smirnov test was used to evaluate distribution, and the Kruskal–Wallis test was used when the parametric test assumptions could not be fulfilled. Categorical variables were compared using the Chi-square test or Fisher’s exact test, as appropriate. Overall survival (OS) was defined as the time from the date of surgery to the date of death. The Kaplan–Meier method was used to estimate survival curves, and differences in survival were analyzed using the log-rank test. Differences were considered statistically significant at a p value < 0.05. P-values < 0.05 were considered significant.

Results

The study included 287 splenectomized patients. A splenectomy was performed in 61.3% of the patients (n:176) during the primary cytoreduction. 38.7% of the patients (n: 111) underwent a splenectomy during secondary or tertiary cytoreductive surgery due to relapse. The age of the patients ranged from 27 to 83 years old, with a mean age of 57.9 years, and the mean follow-up period for the patients was 43.2 months (1-165 months). In the group where a splenectomy was performed as a part of primary cytoreduction, the mean patient age was 59.6, and the mean follow-up period was 46.8 months while the mean patient age in the group in which splenectomy was applied as a part of secondary or tertiary cytoreduction was 55.1, and the mean patient follow-up period was 37.5 months. 67 patients needed intensive care in the postoperative period and mean intensive care stay was one day (1-69 days). The duration of the hospital stay was 15.8 days with a minimum of three and a maximum of 96 days.

According to pathologic reports, two-thirds of patients underwent a splenectomy due to ovarian cancer, 58 patients due to primary peritoneal cancer, and nine patients due to tubal cancer. Also, serous histology was detected in 263 (91.6%) of the patients (Table 1). The splenic involvement site was most frequently observed as hilus + capsule (42.2% n:121). Splenic parenchymal involvement was present in 27.9% (n: 80) of the patients. When the tumor origin sites were compared with splenic involvement regions, there was no difference between the groups.

When the spleen involvement sites in the primary cytoreduction group and the secondary-tertiary cytoreduction group were compared, it was determined that the capsule and hilus involvement group was statistically significantly higher in primary cytoreduction than the secondary-tertiary cytoreduction (p:0.007). In addition, the others group, which included parenchymal splenic involvement, was found to be statistically significantly higher in secondary-tertiary cytoreduction than primary cytoreduction (p:0.006).

When the splenectomy involvement site was evaluated as capsule, hilus, capsule and hilus, or others groups, the overall survival of patients with only capsule involvement was 32 ± 2.75 months [95% confidence interval (CI) = 26.5– 37.4 months]. The overall survival of the patients with only hilus involvement was 42 ± 5.7 months (95% CI = 30.8–53.2 months]. The overall survival of the patients with hilus andcapsule involvement was 40 ± 7.6 months (95% CI = 25.0–54.9 months], and the overall survival of the patients with other involvement sites were 50 ± 5.7 months (95% CI = 38.8–61.1months]. The overall survival for all patients was $42 \pm 3,1$ months (95% CI = 35.7-48.2 months] (Table 3) This difference was not significant when both groups were compared (Fig 1). Furthermore, patients who underwent a splenectomy during primary cytoreduction had a statistically significantly longer overall survival than patients who underwent secondary-tertiary cytoreduction (47 months' vs 40 months' p: 0.042).

Discussion

According to the results of our study, in patients with advanced ovarian, tubal and peritoneal epithelial cancer, involvement of the hilus and capsule was found to be the most common sites of the splenic involvement. It was observed that the effects of involvement of different parts of the spleen on the overall survival were different. The treatment of ovarian cancer depends on multifactorial features that include the stage of the disease, performance status of the patient and tumor features and some other clinical factors. Also, the complete resection of all macroscopic disease at primary debulking surgery has been shown to be the single most important independent prognostic factor in advanced disease [8]. For this reason, the surgical management for optimal treatment of ovarian cancer shifted in recent years from surgical resection of pelvic organs to a major surgery involving the upper abdomen. Brislow et al. showed that a 10% increase in cytoreduction resulted in a 5.5% increase in the patient's survival in their meta-analysis report [9].

In patients with clinically significant upper abdominal disease, splenectomy can be accepted as part of primary or secondary cytoreductive surgery [10]. Although we did not conduct research on surgical methods in our study, we would like to state that in the last years, minimally invasive surgical techniques have been increasingly used in surgical and gynecological oncology practice. For selected patients, laparoscopic splenectomy can be a feasible and safe approach in recurrent ovarian cancer patients with isolated spleen metastasis. Less blood loss, less bleeding, decreased morbidity, more rapid recovery and shorter interval to the initiation of adjuvant therapy can be listed as the advantages of this surgical method [11, 12].

In the study by Magtibay et al., splenic metastasis was detected in 46% of patients with ovarian cancer. In addition, they indicated the most common involvement of the spleen region as hilus (65%), capsule (52%), and parenchyma involvement (16%), respectively [10]. In the study by Tanner et al. of ovarian, tubal, and peritoneal cancer patients, the most common spleen involvement site was indicated as capsule, hilum, and parenchyma, respectively [13]. In addition, the most common spleen involvement site was reported as capsule in a study consisting of a similar patient group by Yasin et al. [14]. In the study by Bacalbasa et al. which only included patients with ovarian cancer, splenic involvement area was shown as capsule in the first frequency and parenchyma in the second frequency [15]. In our study, parenchymal involvement of the spleen was not the most frequent occurrence, similar to the literature. When spleen involvement sites were evaluated, it was observed that hilus involvement was the most common when there was a single involvement site, and, if multiple involvement regions existed, the togetherness of hilus and capsule together was the most frequent.

Parenchymal involvement of the spleen is considered stage 4, according to the ovarian cancer FIGO staging system. However, Magtibay et al. reported that patients with disease that directly involved the splenic parenchyma did not appear to have a more unfavorable prognosis compared to patients with disease involving only the splenic hilum or capsule [10]. They added that parenchymal splenic disease did not affect overall survival when compared to that of patients exhibiting only hilar or capsular disease involvement. On the other hand, Bacalbasa et al. reported that the presence of parenchymal splenic metastases is associated with significantly poorer survival when compared to hilar or peritoneal seeding

in ovarian cancer [15]. Tanner et al. reported similar results, and they reported that parenchymal splenic involvement is an independent risk factor for poor prognosis in patients with advanced ovarian, fallopian tube, and primary peritoneal cancer [13]. Contrarily, Yasin et al. reported in their study that advanced ovarian, tubal, and peritoneal epithelial cancer patients with hilus involvement have a lower overall survival [14]. In our study, there was no statistically significant difference between spleen involvement sites and overall survival. However, the worst survival in our study was found in those with only capsule involvement although this was not statistically significant.

The strengths of our study are high number of cases, the surgical and histopathological evaluation performed in a single tertiary cancer center by the same team and the long patient's follow-up period.

There are many factors affecting prognosis in ovarian cancer such as tumor histology, stage, BRCA mutation, angiogenic phenotype. We could not evaluate the effects of each of these prognostic factors separately in overall survivals that we compared in our study. This is the important limitation of our study. It is not a routine practice to look at the BRCA mutation in patients with ovarian cancer in our country, and the use of PARP inhibitors is not yet approved in our country. Therefore, although the number of patients with BRCA mutation positive and using PARP inhibitors has increased in recent years, it is still limited. On the other hand, the retrospective design and low number of patients with only parenchymal metastases can be considered as the weaknesses of the study.

In the future, studies involving large numbers of patients are needed to examine the relationship of splenic involvement sites with survival and other prognostic factors in advanced ovarian, tubal and peritoneal epithelial cancer.

In conclusion, this study had the largest number of patients in the literature in an examination of the relationship between spleen involvement and overall survival. When the subgroups were evaluated in this study, although it was not statistically significant, the worst overall survival was found in the group with capsule involvement of the spleen.

While parenchymal involvement of the spleen is considered to be stage IV according to FIGO staging, failure to detect low overall survival in patients with parenchymal involvement in our study will provide a remarkable perspective on the relationship between parenchymal involvement and prognosis.

Declarations

Funding This study was not supported by any funding.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Ethical approval All procedures performed in this study were in accordance with the institutional ethical standards and the 1964 Declaration of Helsinki and its later amendments or comparable ethical

standards. Ethical approval was not obtained from the participants included in this study because of the retrospective nature of the study.

Informed consent Informed consent was not obtained from the participants included in this study because of the retrospective nature of the study.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018 Nov;68(6):394-424. doi: 10.3322/caac.21492.
2. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). *Cancer*. 2009 Mar 15;115(6):1234-44. doi: 10.1002/cncr.24149.
3. du Bois A, Quinn M, Thigpen T, Vermorken J, Avall-Lundqvist E, Bookman M, et al. 2004 consensus statements on the management of ovarian cancer: final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIg OCCC 2004). *Ann Oncol*. 2005;16 Suppl 8:viii7-viii12. doi: 10.1093/annonc/mdi961.
4. Eisenkop SM, Spirtos NM, Lin WC. Splenectomy in the context of primary cytoreductive operations for advanced epithelial ovarian cancer. *Gynecol Oncol*. 2006 ;100(2):344-8. doi: 10.1016/j.ygyno.2005.08.036.
5. Eisenhauer EL, Abu-Rustum NR, Sonoda Y, Levine DA, Poyner EA, Aghajanian C, et al. The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients

- with stages IIIC-IV epithelial ovarian cancer. *Gynecol Oncol.* 2006;103(3):1083-90. doi: 10.1016/j.ygyno.2006.06.028.
6. Harter P, Sehouli J, Lorusso D, Reuss A, Vergote I, Marth C et al. LION: Lymphadenectomy in ovarian neoplasms—A prospective randomized AGO study group led gynecologic cancer intergroup trial. *Journal of Clinical Oncology.* 2017;35(15_suppl):5500 doi: 10.1200/JCO.2017.35.15_suppl.5500
 7. Mutch DG, Prat J. 2014 FIGO staging for ovarian, fallopian tube and peritoneal cancer. *Gynecol Oncol.* 2014 ;133(3):401-4. doi: 10.1016/j.ygyno.2014.04.013.
 8. Vergote I, du Bois A, Amant F, Heitz F, Leunen K, Harter P. Neoadjuvant chemotherapy in advanced ovarian cancer: On what do we agree and disagree? *Gynecol Oncol.* 2013 ;128(1):6-11. doi: 10.1016/j.ygyno.2012.09.013.
 9. Bristow RE, Puri I, Chi DS. Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis. *Gynecol Oncol.* 2009 ;112(1):265-74. doi: 10.1016/j.ygyno.2008.08.033.
 10. Magtibay PM, Adams PB, Silverman MB, Cha SS, Podratz KC. Splenectomy as part of cytoreductive surgery in ovarian cancer. *Gynecol Oncol.* 2006 ;102(2):369-74. doi: 10.1016/j.ygyno.2006.03.028.
 11. Gallotta V, Nero C, Lodoli C, Chiantera V, Pacelli F, Fagotti A. Laparoscopic Splenectomy for Secondary Cytoreduction in Ovarian Cancer Patients with Localized Spleen Recurrence: Feasibility and Technique. *J Minim Invasive Gynecol.* 2016;23(3):425-8. doi: 10.1016/j.jmig.2016.01.001.
 12. Gallotta V, Fagotti A, Fanfani F, Ferrandina G, Nero C, Costantini B. Laparoscopic surgical management of localized recurrent ovarian cancer: a single-institution experience. *Surg Endosc.* 2014 ;28(6):1808-15. doi: 10.1007/s00464-013-3390-9.
 13. Tanner EJ, Long KC, Feffer JB, Leitao MM Jr, Abu-Rustum NR, Barakat RR et al. Parenchymal splenic metastasis is an independent negative predictor of overall survival in advanced ovarian, fallopian tube, and primary peritoneal cancer. *Gynecologic Oncology*, 2013; 128(1), 28-33.
doi:10.1016/j.ygyno.2012.09.019
 14. Durmuş Y, İşçi Bostancı E, Duru Çöteli AS, Kayıkçioğlu F, Boran N. Metastasis patterns of the spleen and association with survival outcomes in advanced ovarian-tubal-peritoneal epithelial cancer. *Arch Gynecol Obstet.* 2019 ;300(5):1367-1375. doi: 10.1007/s00404-019-05300-y.
 15. Bacalbasa N, Balescu I, Dima S, Brasoveanu V, Popescu I. Hematogenous Splenic Metastases as an Independent Negative Prognosis Factor at the Moment of Primary Cytoreduction in Advanced Stage Epithelial Ovarian Cancer—A Single Center Experience. *Anticancer Res.* 2015;35(10):5649-54.

Tables

Table 1 Clinical, Pathological and Surgical Characteristics of the Study Group, Total Number Percentage

Mean age at diagnosis ± SD	57.9±11.4	
Mean follow-up time ± SD	43.2 ±34.5	
	n	%
Organ of origin		
Ovary	218	76
Ovary and Endometrium	2	0.7
Peritoneum	58	20.2
Tube	9	3.1
Histology		
Serous	262	91.3
Non-serous	24	8.4
Splenectomy		
Primary cytoreduction	176	61.3
Secondary-tertiary cytoreduction	111	38.7
Splenic involvement site		
Hilus	60	20.9
Capsule	26	9.1
Hilus+ Capsule	121	42.2
Others	80	27.8
Parenchymal	4	1.4
Parenchymal+ Hilus+ Capsule	38	13.2
Parenchymal+ Hilus	32	11.1
Parenchymal+ Capsule	6	2.1

Table 2 Rates of Splenic Involvement Site Groups in the Primary Cytoreduction Group and the Secondary Tertiary Cytoreduction Group

	Hilus (n/%)	Capsule (n/%)	Hilus+Capsule (n/%)	Others (n/%)
Primary cytoreduction	33(55%)	16 (61.5%)	88 (72.3 %)	39 (48.8%)
Secondary-tertiary cytoreduction	27 (45%)	10 (38.5%)	33 (27.3%)	41(51.2%)

Table 3

Median Survival Time According to Spleen Involvement Sites

Splenic involvement site	Estimate (months)	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Capsule	32	2.8	27	37
Hilus	42	5.7	31	53
Hilus+Capsule	40	7.6	25	55
Others	50	5.7	39	61
Overall	42	3.2	36	48

Figures

Figure 1

Graphical Presentation of Kaplan–Meier Analyses of Splenic Involvement Site and Overall Survival (p:0.145)