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ORIGINAL RESEARCH

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Prognostic analysis of splenic parenchymal metastasis in patients with advanced ovarian cancer

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Abstract

Background: Splenic metastasis are typically associated with peritoneal seeding and multi-organ involvement in advanced ovarian cancer. Although splenic parenchymal lesions are classified as International Federation of Gynecology and Obstetrics (FIGO) stage IVB, they are usually surgically resectable. The aim of this study was to evaluate the patterns and prognostic significance of splenic parenchymal metastases in advanced ovarian cancer. **Methods**: We conducted a retrospective review of medical records of patients who underwent splenectomy as part of cytoreductive surgery for advanced ovarian cancer between 2007 and 2018. The patients were categorized into two groups based on the presence of parenchymal invasion or capsular/hilar invasion. Clinical characteristics, including histological invasion patterns, and survival outcomes were analyzed. **Results**: A total of 110 ovarian cancer patients underwent splenectomy: 55 (50%), 40 (36.4%) and 15 (13.6%) patients underwent splenectomy during primary debulking surgery, interval debulking surgery, and disease recurrence, respectively. The median age was fifty-five, and all patients had FIGO stage IIIB–IV disease. A total of 33 (30.1%) patients had splenic parenchymal invasion, and all lesions were accompanied by capsular or hilar metastasis without solitary parenchymal invasion. Among the patients with primary disease (n = 95), 43 (45.3%) had stage IV disease, including 33 (30.1%) with splenic parenchymal metastasis. There were no significant differences in progression-free survival (p = 0.698) and overall survival (p = 0.928) between patients with parenchymal invasion and those with capsular/hilar metastasis. **Conclusions**: Although splenic parenchymal metastasis shows widespread tumor dissemination, splenic parenchymal metastasis was consistently associated with capsular or hilar involvement, suggesting surgically treatable disease. The prognosis of splenic parenchymal metastasis was comparable to that of capsular or hilar invasion, warranting its consideration as FIGO stage IIIC disease.

Keywords

Advanced ovarian cancer; Splenectomy; Parenchymal invasion; FIGO stage

1. Introduction

Advanced ovarian cancer is an extremely aggressive disease that is often diagnosed at an advanced stage, with a considerable number of patients presenting with distant metastasis with poor prognosis [1]. Despite improvements in treatment, the survival rates for advanced ovarian cancer patients are still low. Standard treatment for advanced ovarian cancer typically involves surgery, chemotherapy and targeted therapy [1]. However, despite of these treatments, the survival rates for advanced ovarian cancer remain low. Recent research has focused on investigating alternative treatment options to improve survival rates for patients with advanced ovarian cancer. One such treatment choice is splenectomy, or surgical removal of the spleen, has been proposed as a potential treatment option for advanced ovarian cancer patients. In some cases, ovarian cancer can spread to the spleen, resulting in splenomegaly and other complications. Splenectomy may help to reduce the size of the spleen and improve treatment outcomes.

The incidence of splenic invasion in advanced ovarian cancer is generally low, ranging from approximately 2.3% to 7.1%, with an average of 5% [1]. There are several reasons for this finding. Firstly, the spleen, as a single organ, has immune functions that can eliminate cancer cells through lymphocytes. Secondly, the splenic capsule can function as a barrier to prevent cancer invasion due to its contractile property and barrier function. Thirdly, the tortuosity of the splenic vessels and the circulation of abdominal fluid can make it difficult for cancer cells to implant themselves [2, 3]. However, despite these reasons, invasion of the colon-splenic flexure along the gastro-colic ligament and splenic capsule is common, leading to splenectomy being performed in 31% of patients with

advanced ovarian cancer during cytoreductive surgery [4, 5]. In cases where splenic hilum invasion is suspected, distal pancreatectomy with splenectomy is performed for complete resection.

As mentioned above, splenic parenchymal invasions are uncommon, but approximately 3% of patients undergo splenectomy for complete cytoreductive surgery [4, 5]. Due to the limited number of cases with splenic metastasis, early studies have shown conflicting results due to various routes of tumor invasion, making it difficult to establish splenic invasion itself as a poor prognostic factor in patients with advanced ovarian cancer [6].

According to the current International Federation of Gynecology and Obstetrics (FIGO) staging system for ovarian cancer, stage IVB is defined as cancer that has spread beyond the pelvis to distant organs or structures, such as the liver, lungs or spleen. Therefore, when ovarian cancer metastasizes to the spleen, it is classified as stage IVB disease [7, 8], indicating widespread cancer dissemination with upper abdominal invasion [9]. During cytoreductive surgery, unlike hepatic metastasis, the entire spleen can be completely removed, and even with microscopic metastasis could be removed regardless of the pattern of splenic invasion. Therefore, we will discuss the clinical implications of splenic metastasis, including its impact on treatment options and patient outcomes. We will also examine the role of splenectomy in the management of advanced ovarian cancer with splenic metastasis and evaluate the pattern of splenic parenchymal metastasis and its prognostic value in patients with advanced ovarian cancer.

2. Patients and methods

2.1 Study design

This study is a retrospective analysis of patients with advanced ovarian cancer and splenic metastasis. We conducted a retrospective review of medical records of patients who underwent splenectomy as part of cytoreductive surgery for advanced ovarian cancer at Ajou University Hospital between 2007 and 2018. The median follow-up period of the patients was 38 months (range: 2–157 months).

2.2 Inclusion and exclusion criteria

Patients with histologically confirmed advanced ovarian cancer (FIGO stage III or IV) and splenic metastasis who underwent splenectomy during cytoreductive surgery were included in the study. Patients with incomplete medical records, inadequate follow-up data, or prior splenectomy were excluded.

2.3 Data collection

Data on patient demographics, clinical characteristics, treatment modalities, and outcomes were collected from medical records and FIGO staging was decided based on surgical and pathological findings. In this study, splenic metastasis was defined based on pre-operative radiological imaging using computed tomography (CT) and suspicious gross splenic invasion during cytoreductive surgery. The primary outcome of this study was the prognostic analysis of splenic parenchymal metastasis in patients with advanced ovarian cancer. Based on the pathological results, patients were divided into parenchymal invasion and capsular/hilar invasion groups.

2.4 Statistical analysis

Descriptive statistics were used to summarize patient characteristics and treatment modalities. Overall survival (OS) was calculated from the date of diagnosis to the date of death or last follow-up. Kaplan-Meier survival curves were used to estimate survival probabilities, and the log-rank test was used to compare survival between groups. All statistical analyses were performed using SPSS (Version 25, IBM Corp., Armonk, NY, USA), and significance was considered if p-value < 0.05.

3. Results

In this retrospective study, we analyzed the clinical characteristics, treatment modalities, and outcomes of patients with advanced ovarian cancer and splenic metastasis. A total of 110 ovarian cancer patients who underwent splenectomy at the Ajou University Hospital were included. The median follow-up period of the patients was 38 months (range: 2–157 months).

The median age of the patients was 55 years (range: 24–80), and all patients had FIGO stage IIIB–IV disease. Most of the patients had FIGO stage IIIC disease (65 (59.1%)), while the remaining patients had IVB (36 (32.7%)), IVA (7 (6.4%)), and IIIB (2 (1.8%)) disease. Among the 36 IVB patients, twenty-two had other IVB diagnostic factors simultaneously, such as cardio-phrenic lymph node metastasis (14 patients), diaphragm muscle metastasis (1 patient), umbilical metastasis (2 patients), chest wall metastasis (1 patient), liver parenchymal metastasis (3 patients), and right axillary metastasis (1 patient). All these lesions were removed during cytoreductive surgery. The histopathological subtypes were predominantly serous (102 (92.8%)) and non-serous (8 (7.2%)) epithelial ovarian cancers and among the serous patients, there were 4 cases of low-grade serous carcinoma included. All eight cases of non-serous epithelial ovarian cancer were recurrent.

Of the 110 patients, 55 (50%), 40 (36.4%) and 15 (13.6%) patients underwent splenectomy during primary cytoreductive surgery, interval debulking surgery, and disease recurrence, respectively. During the cytoreductive surgery, R0 resection was tried, except in twenty-two cases (20%) where R0 resection was not achieved owing to unresectable organ involvement seen during the surgery. Consequently, eighty-eight patients (80%) had no gross residual disease during surgery (Table 1). If the splenic metastasis disappeared following neoadjuvant chemotherapy in Interval Debulking Surgery (IDS) group, then splenectomy was not performed. In cases where no visible lesions were observed during gross examination during the surgery along with the results of post-chemotherapy computed tomography (CT), it was determined that the absence of lesions indicated a favorable response to the chemotherapy, and it was believed that microscopic residual tumors could be eliminated through adjuvant chemotherapy following surgery. Additionally, in such cases, additional splenectomy was not performed to minimize potential post-operative complications

associated with splenectomy and to reduce surgical time, facilitating faster postoperative recovery for the patients. In addition, the fact that all the surgeries were performed by the same surgeon, which also contributed to the consistency of the surgical procedures, which is important for achieving no residual disease in Primary Debulking Surgery (PDS) or IDS.

TABLE 1. Patients' characteristics (n = 110).

Patients' characteristics	n (%), median (range)
Age	
Median age	55 (24–80)
Histopathological subtypes	
Serous	102 (92.8%)
Non-serous	8 (7.2%)
Surgery type	
Primary debulking surgery (PDS)	55 (50.0%)
Interval debulking surgery (IDS)	40 (36.4%)
Recurrent disease surgery	15 (13.6%)
Initial FIGO stage	
IIIB	2 (1.8%)
IIIC	65 (59.1%)
IVA	7 (6.4%)
IVB	36 (32.7%)
Residual disease	
No gross residual disease (NGR)	88 (80.0%)
GR-1 (≤1 cm)	20 (18.2%)
GR-2 (>1 cm)	2 (1.8%)

Abbreviations: FIGO: International Federation of Gynecology and Obstetrics; GR-1: Gross residual disease ≤1 cm; GR-2: Gross residual disease >1 cm.

We evaluated the splenectomy specimens and pathological results and found that 33 (30.1%) patients had splenic parenchymal invasions, and all lesions were accompanied by capsular or hilar metastasis without solitary parenchymal invasion. The types of splenic involvement are summarized in Table 2. In sixteen cases (14.5%), there were suspected splenic tumor invasions intraoperatively and radiologically, but final pathological result showed no tumor invasion. These suspected lesions could be either an inflammatory changes, fibrosis or a residual scar of the post chemotherapy. Fifty-six patients (50.9%) showed capsular invasion, and five showed hilar invasion. As previously mentioned, thirty-three patients (30.1%) showed parenchymal invasion, but all lesions showed simultaneous capsular and hilar invasion.

Among patients with primary disease (n = 95), 43 (45.3%) had stage IV disease, including 33 (30.1%) with splenic parenchymal metastasis. In the subgroup analysis focusing on the parenchymal invasion group which are summarized in Table 3, the percentage refers to the proportion of patients with splenic parenchymal metastasis out of the total cohort of 110 patients, out of these thirty-three patients, 18 (54.5%), 9 (27.3%), and six patients (18.2%) underwent primary cytoreductive surgery, interval cytoreductive surgery, and surgery for recurrent disease, respectively. Twenty-seven patients (81.8%) showed hilar invasion, six showed capsular invasion, and none showed solitary parenchymal invasion.

TABLE 2. Types of splenic involvement.

Types of splenic involvement	n (%)
No tumor invasion	16 (14.5%)
Capsular invasion	56 (50.9%)
Hilar invasion	5 (4.5%)
Parenchymal invasion	33 (30.1%)

TABLE 3. Patients' characteristics of parenchymal invasion subgroup (n = 33).

Patients' characteristics	n (%), median (range)
Surgery type	
PDS	18 (54.5%)
IDS	9 (27.3%)
Recurrent disease surgery	6 (18.2%)
FIGO stage	
IVB	33 (100%)
Residual disease	
No gross residual disease (NGR)	24 (72.7%)
GR-1 (≤1 cm)	9 (27.3%)
GR-2 (>1 cm)	0
Parenchymal invasion route	
Hilar invasion	27 (81.8%)
Capsular invasion	6 (18.2%)
Solitary parenchymal invasion	0

Abbreviations: FIGO: International Federation of Gynecology and Obstetrics; PDS: Primary debulking surgery; IDS: Interval debulking surgery; GR-1: Gross residual disease ≤1 cm; GR-2: Gross residual disease >1 cm.

We also compared the postoperative outcomes between the non-parenchymal invasion group (capsular/hilar metastasis) and the parenchymal invasion group. There were no significant differences seen in progression-free survival (p = 0.698) or overall survival (p = 0.928) between patients with parenchymal invasion and those with capsular/hilar metastasis (Figs. 1,2).

4. Discussion

This study aims to evaluate the significance of splenic metastasis in patients with advanced ovarian cancer and to investigate whether the current FIGO staging system accurately reflects the disease burden in these patients.

Our findings suggest that splenic metastasis is a significant and relatively common manifestation of advanced ovarian cancer [8], and that it should be considered in the staging and treatment planning of these patients.

In most cases, ovarian cancer is commonly diagnosed at

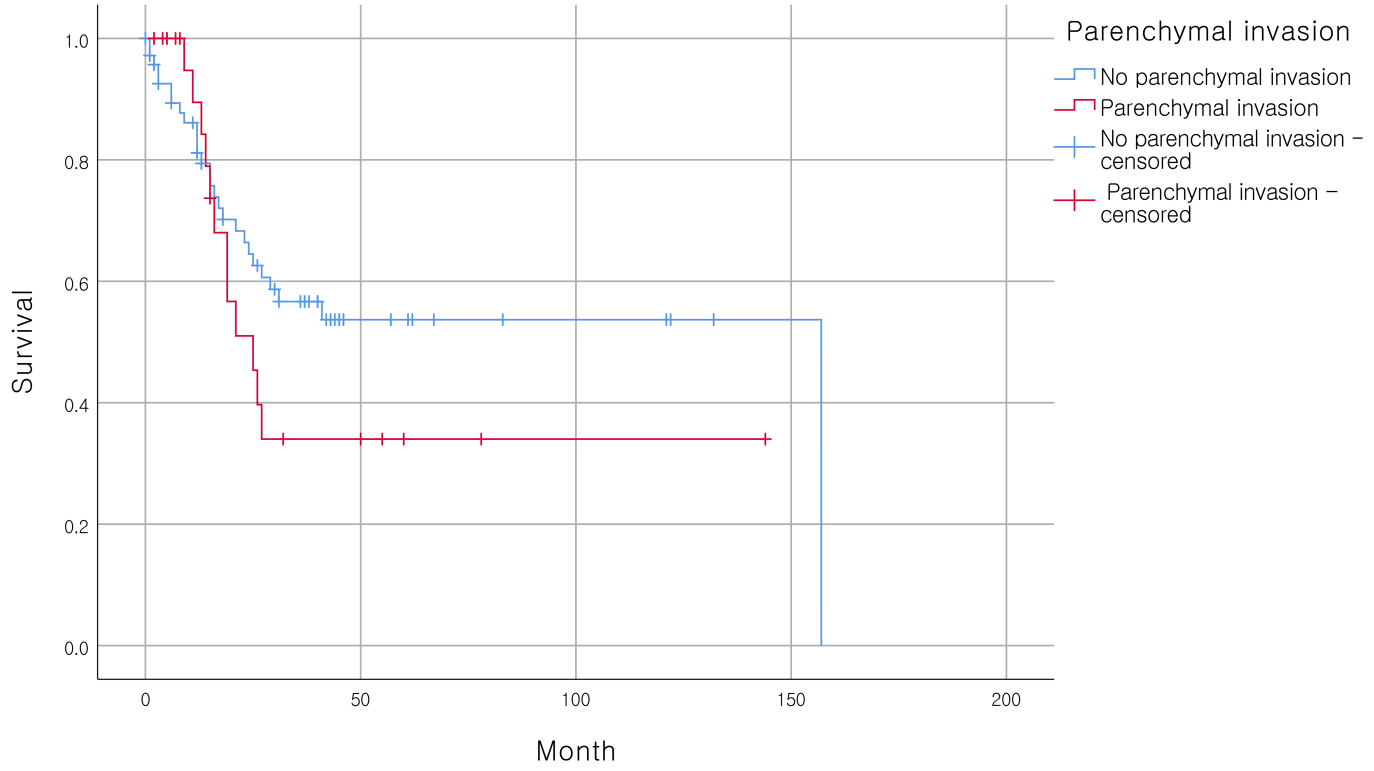

FIGURE 1. Influence on progression-free survival of patients with parenchymal versus non-parenchymal invasion (p = 0.698).

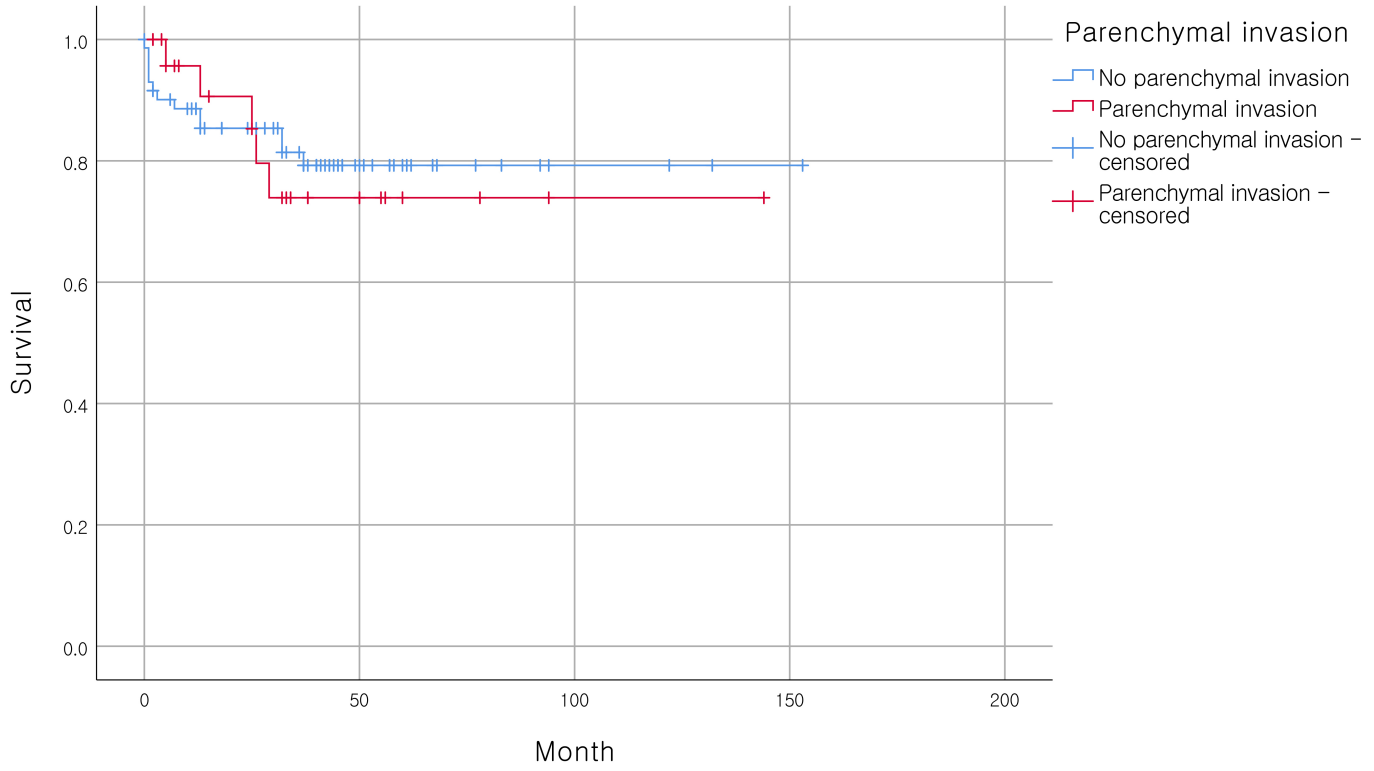

FIGURE 2. Influence on overall survival of patients with parenchymal versus non-parenchymal invasion (p = 0.928).

an advanced stage and is associated with high mortality rates, despite proper treatment. It is one of the most common diseases associated with mortality worldwide [8–11]. Although ovarian cancer is known to spread through lymphatic routes, the peritoneal and hematogenous spread can cause visceral parenchymal metastasis [1, 2]. However, hematogenous spread is very rare in ovarian cancer, in most cases, metastasis occurs through peritoneal spread. Therefore, splenic metastasis of ovarian cancer usually grows around the spleen (hilar and capsular invasion) and usually does not grow in the parenchyma. Parenchymal metastasis may represent a hematogenous spread of the disease, whereas capsular or hilar involvement represents peritoneal seeding [8]. Although splenic parenchymal metastasis reflects widespread tumor dissemination, all lesions are followed by hilar or capsular involvement and surgically treatable disease [8, 9].

As previously known, complete cytoreduction to reduce the resulting tumor burden is widely known as a very important prognostic factor of advanced ovarian cancer patients [12–14]. Once ovarian cancer has metastasized beyond the pelvis, upper abdominal invasion is common. In this case, by performing complete R0 resection, the diaphragm peritoneum, diaphragm muscle, and several organs, including the liver, gall bladder, and spleen, are removed [12–15]. Although complete R0 resection is known to be an important prognostic factor in advanced ovarian cancer patients, some researchers predict an aggressive tumor if ovarian cancer invades the upper abdomen [6, 14]. However, since upper abdominal surgery for R0 complete resection is increasing and is more common and safe, it is believed that the survival outcome of ovarian cancer will also improve.

As seen in the FIGO staging, liver parenchymal invasion is diagnosed with IVB disease [7, 8], but in the case of liver metastasis, the characteristic immune system and other characteristics of the spleen are absent [13, 15], as described in the Introduction. Thus, the microscopic residual tumor may remain, as the liver cannot be removed entirely, unlike with the spleen in splenectomy [15]. Thus, liver parenchymal metastasis should be considered different from splenic parenchymal metastasis.

This study had several limitations, including its retrospective design and potential for selection bias. Additionally, the small sample size limits the ability to draw definitive conclusions about the effectiveness of splenectomy in advanced ovarian cancer patients with splenic metastasis. Further studies with larger patient populations are needed to confirm the findings and decide the best treatment approach for patients with ovarian cancer and splenic metastasis.

Additionally, there is a limitation in accurately assessing whether there is a difference in tumor burden between the parenchymal invasion group and the capsular invasion or hilar invasion group. This distinction may have an impact on the poor prognosis seen in cases of spleen parenchymal invasion in stage IVB, potentially due to a higher initial disease burden.

However, we did not see any differences in survival among the several types of splenic metastasis, and the type of splenic involvement, including parenchymal, hilar and capsular invasion, did not appear as an independent poor prognostic factor.

5. Conclusions

In conclusion, our study suggests that splenic metastasis is one of the significant manifestations of advanced ovarian cancer, and that it should be considered in the staging and treatment planning of these patients. The current FIGO staging system may not accurately reflect the disease burden in patients with ovarian cancer with splenic metastasis, and a reclassification to stage IIIC might be possible. Although, the decision to perform splenectomy in these patients should be based on individual patient characteristics and the potential risks and benefits of the procedure, and further research is necessary to decide the optimal treatment approach for advanced ovarian cancer with splenic metastasis. Therefore, we suggest that the prognosis of splenic parenchymal metastasis was not inferior to that of capsular or hilar invasion; therefore, it might be considered as FIGO stage IIIC disease. Thus, safely performed splenectomy may increase the survival rate of advanced ovarian cancer patients by achieving R0 resection.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

SJC—contributed to study design and critical revision. JeK, JL—contributed to data analysis and manuscript writing. JHS, JuK—contributed to data acquisition and analysis. TWK—contributed study conception and critical revision. All authors approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Review Board of Ajou University Hospital (AJOUIRB-MDB-2022-116). As a retrospective study, the requirement for informed consent was waived by the IRB.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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