

# 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

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**Abstract.** Ovarian cancer represents an aggressive gynecological malignancy with a high capacity for dissemination. Once the tumor cells go beyond the pelvic area, upper abdominal involvement, including hepatic, diaphragmatic or even splenic, is frequently seen. The aim of the present study was to determine the impact on survival of parenchymatous versus peritoneal splenic metastases versus splenic hilum lymph node involvement at the time of primary cytoreduction for advanced-stage epithelial ovarian cancer. Sixty-six patients with a mean age of 54.12 years (range=25-80 years) were submitted to splenectomy in the context of primary cytoreduction at the Dan Setlacec Center of Gastrointestinal Disease and Liver Transplantation, Fundeni Clinical Institute, between January 2002 and May 2014. Although complete macroscopic resection was attempted in all cases, an R0 resection was achieved only in 57 out of the 66 cases. Histopathological studies confirmed the presence of serous subtype in 61 cases, while in the other five cases, the mucinous subtype was found. When studying the specimens of splenectomy, capsular invasion was found in 35 cases (53%), parenchymatous involvement was present in 19 (28.7%), and hilar involvement was present in 12 (18.1%). The overall morbidity rate was 30%, while the 30-

day postoperative mortality rate was 7%. The median overall survival for cases with peritoneal seeding was 58.4 months, while that for patients with parenchymatous involvement was 24.5 months ( $p=0.0126$ ); patients diagnosed with hilar involvement had a median overall survival of 40.6 months ( $p=0.362$ ). In conclusion, the presence of parenchymatous splenic metastases at primary cytoreduction for advanced-stage ovarian cancer is associated with significantly poorer survival when compared to hilar or peritoneal seeding.

Epithelial ovarian cancer (EOC) remains a lethal malignant disease which is best controlled by an aggressive surgical approach (1-4). While in cases with pelvically confined disease the benefits of complete cytoreduction have been widely demonstrated, recent studies tried to demonstrate if the presence of upper abdominal dissemination is the distinctive sign of a more biologically aggressive disease or if improved survival can also be obtained in these cases if an R0 resection is achieved (5-7). Based on the fact that large studies have demonstrated the benefit of hepatectomy in cases presenting upper abdominal liver-confined tumor burden and the differences in terms of survival for patients with peritoneal *versus* parenchymatous liver lesions (8-10), we determined if a similar difference in terms of overall survival is also present in regard to splenic lesions.

## Materials and Methods

After obtaining Ethics Committee approval (No. 183/2015), we retrospectively reviewed data of patients submitted to primary cytoreduction for advanced-stage ovarian cancer at the Dan Setlacec Center of Gastrointestinal Disease and Liver Transplantation, Fundeni Clinical Institute. Inclusion criterion was confirmation by histopathological studies of the presence of EOC with splenic

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Table I. The main preoperative characteristics including American Society of Anesthesiologists (ASA) score and International Federation of Obstetrics and Gynecology (FIGO) stage.

Preoperative characteristic	No. of cases
ASA score	
I-II	43
III-IV	23
FIGO stage	
IIIC	47
IV	19
Ascites	
Yes	41
No	25
Upper abdomen parenchimatous organ tumor burden limited to the spleen	
Yes	55
No	11

involvement. Cases in which splenectomy was performed due to intraoperative trauma which could not be controlled in a conservative manner were formally excluded. The final cohort included 66 cases with synchronous splenic lesions at the time of primary cytoreduction for advanced EOC.

Preoperative, intraoperative and postoperative data were collected retrospectively. The information included age at diagnosis of EOC, American Society of Anesthesiologists (ASA) score, neoadjuvant treatment, International Federation of Obstetrics and Gynecology (FIGO) stage, associated resections at the moment of primary cytoreduction, type of resection, histopathological subtype, degree of differentiation, type of splenic involvement (capsular, lymphatic or parenchymatous), postoperative complications according to the Dindo-Clavien scale and overall survival. Dates of death were obtained from the National Register of Population.

The differences between different subgroups were analyzed by the log-rank test and considered significant if  $p < 0.05$ . Kaplan–Meier survival curves were also used. Statistics and graphics were performed using SigmaPlot program, version 12 ([http:// www.alfasoft.com/en](http://www.alfasoft.com/en)).

## Results

Sixty-six patients with a mean age of 54.12 years (range=25-80 years) were considered eligible for the study. At diagnosis of EOC, the FIGO stage was IIIC or more in all cases, and in 11 patients, non-splenic parenchymatous visceral involvement, such as of the liver or pancreas, was noted. The median preoperative CA125 value was 711.5 U/ml (range=47-2100 U/ml). The main preoperative characteristics including ASA score, FIGO stage are summarized in Table I.

At primary cytoreduction, an R0 resection was attempted in all cases; however, it was achievable only in 57, in the other nine cases, tumor involvement of unresectable organs was diagnosed intraoperatively. The main intraoperative

Table II. Intraoperative characteristics of the study group.

Characteristic	No. of cases
Associated visceral resection	
Omentectomy	49
Peritonectomy	53
Colo-rectal resection	37
Appendectomy	14
Diaphragmatic resection	9
Cholecystectomy	10
Gastric resection	9
Urinary bladder resection	2
Atypical hepatectomy	1
Distal pancreatectomy	3
Ileal resection	1
Type of resection	
R0	57
R1	3
R2	6

Table III. Histopathological characteristics of the splenectomy specimens.

Characteristic	No. of cases
Histopathological sub-type	
Serous	61
Mucinous	5
Differentiation grade	
G1	14
G2	24
G3	28
Type of splenic involvement	
Capsular	35
Hilar	12
Parenchimatous	19

characteristics, including associated visceral resections, association of hyperthermic intraperitoneal chemotherapy, type of resection and postoperative results of the histopathological studies are shown in Table II.

Histopathological studies confirmed the presence of serous EOC in 61 cases, while in the other five cases, the mucinous subtype of EOC was found. When studying the specimens of splenectomy, capsular invasion was found in 35 cases (53%), parenchymatous (hematogenous) involvement was present in 19 cases (28.7%), while hilar involvement was present in 12 (18.1%). The main histopathological characteristics and the types of splenic involvement are shown in Table III.

The median duration of hospitalization was 12 days (range=4-63 days). The main postoperative complications were pancreatic fistulas (four cases), abdominal abscess (four

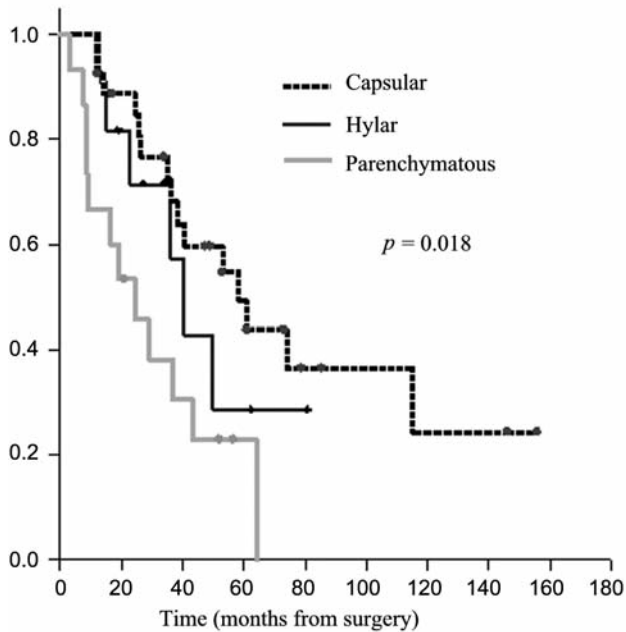


Figure 1. The influence on overall survival of patients with peritoneal versus those with parenchymatous splenic involvement.

cases, two of which necessitated percutaneous drainage, while the other two necessitated re-operation), pleural effusion (three cases, all needing pleural drainage), broncho-pneumonia (three cases), and neurological disorders (three cases). Re-operation was needed in four cases: two with abdominal abscesses, one with uncontrolled pancreatic fistula and one with hemoperitoneum. Postoperative complications classified according to the Clavien-Dindo scale (11) are shown in Table IV.

The overall morbidity rate was 30%, while the 30-day postoperative mortality rate was 7%. Early postoperative death occurred in five cases: two due to abdominal abscesses (with pancreatic origin and anastomotic enteral leakage, respectively), one due to broncho-pneumonia and acute respiratory failure, one due to a cerebral ischemic stroke which developed on the sixth postoperative day, and one from metabolic acidosis and multiple organ failure in an elderly patient with preoperative cardiac and respiratory dysfunction.

These results were compared to a control group including 272 patients with advanced-stage EOC submitted to primary cytoreductive surgery in the same period of time at the same Center in whom splenectomy was not needed. When studying the postoperative complications of the two groups, no significant difference was found: while in cases requiring splenectomy the overall morbidity rate was 30% and the 30-day mortality rate was 7%, in the control group

Table IV. Postoperative complications according to the Clavien-Dindo scale (11).

Type of complication (Clavien-Dindo scale)	No. of cases
Grade I	3
Grade II	6
Grade III	4
Grade IV	2
Grade V	5

in which splenectomy was not performed, complications occurred in 27% of cases and the postoperative mortality rate was 5%.

When comparing the postoperative outcomes between the cases presenting capsular *versus* parenchymatous or hilar invasion, a significantly improved survival was obtained for patients with peritoneal seeding. The median overall survival for cases with peritoneal seeding was 58.4 months, while that for those with parenchymatous involvement was 24.5 months ( $p=0.0126$ ); patients diagnosed with hilar involvement experienced an overall survival of 40.6 months. When studying the impact of hilar *versus* parenchymatous and respectively capsular lesions no significant modification in terms of survival were observed ( $p=0.362$  and respectively  $p=0.457$ ). (Figure 1, Table V).

**Discussion**

Ovarian cancer is still a significant global health problem, being responsible for a high number of deaths among women worldwide annually (1, 2). The main patterns of spread are via the peritoneal route, inducing diffuse surface involvement of the abdominal viscera, the hematogenous route giving rise to parenchymatous visceral metastases, and in a lower proportion of patients, the lymphatic route. Once tumor dissemination goes beyond the pelvic area, upper abdominal involvement is frequently seen. In these cases, at primary cytoreduction, associated visceral resection, such as peritoneal diaphragmatic stripping, full-thickness diaphragmatic resection, splenectomy, and minor or even major hepatectomy have been proposed in order to achieve an R0 resection (2-4).

Although the efficacy of complete cytoreduction has been widely accepted and demonstrated by large series of cases, the benefits of extended resection in the upper abdomen was from the outset a matter of debate (3-6). Some authors considered that the presence of an upper abdomen tumor burden reflects a tumor with a more aggressive biological behavior which is secondarily associated with poorer outcome. However, in time, due to the formation of multidisciplinary teams involving visceral

surgeons, hepato-bilio-pancreatic surgeons and gynecological oncologists, upper abdominal resections have become more frequent in order to obtain complete resection and have been proven to improve overall survival. Since postoperative outcomes are strongly related to the operative technique and to the postoperative management, and only in a low proportion to aggressive biological tumor behavior, upper abdominal resections have been widely used as a basic component of the therapeutic armamentarium against advanced-stage EOC (5-7, 12-16). Therefore, the preferred therapeutic option for patients with advanced-stage EOC with upper abdominal tumor burden remains an aggressive surgical approach followed by taxane- and platinum-based chemotherapy.

In one of the largest studies which focused on the importance of associated visceral resections at primary cytoreductive surgery, Eisenkop *et al.* included 203 cases and demonstrated that other therapeutic procedures such as diaphragmatic or bowel resection, or extended lymph node removal can be safely performed with no significant modification of the morbidity rate in order to achieve an R0 resection (16).

Parenchymatous liver metastases are usually associated with a poorer outcome, being considered as an inclusion criteria for FIGO stage IV ovarian cancer (8-10). Although it can be considered that parenchymatous involvement is indicative of poor prognosis, both hepatic and splenic metastases, a difference between the outcomes associated with the two hematogenous visceral involvements has been suggested. While in cases diagnosed with splenic metastases an R0 resection is easily achieved by complete resection of the involved organ, in cases presenting liver metastases, microscopic residual tumors might be still present in the remnant liver after complete macroscopic resection (10).

Splenic parenchymatous involvement is not a common condition, being reported in up to 41% of cases submitted to primary cytoreduction for advanced-stage EOC (16-19). Due to the limited number of cases presenting splenic involvement and to the various models of involvement (peritoneal, parenchymatous or even lymphatic seeding), initial studies reported conflicting results, failing to demonstrate if the presence of splenic involvement is itself a poor prognosis factor (17, 20, 21).

When estimating the risks and benefits of splenectomy as part of primary cytoreductive surgery, there are also only few studies focusing on this issue. In the study conducted by Eisenkop *et al.*, 404 patients with advanced-stage EOC were included; at primary cytoreduction, complete resection was achieved in 356 patients, 49 of them also requiring splenectomy in order to provide R0 resection. Postoperative morbidity was non-significantly higher in the subgroup of patients submitted to splenectomy; however, in this

subgroup, a higher number of pancreatic leaks was seen (6.1%), all of them being managed conservatively. When estimating the long-term results, patients in whom splenectomy was required had a median overall survival of 56.4 months and an estimated 5-year overall survival of 48%, comparable with the cases in whom splenectomy had not been performed; in the latter subgroup, the median overall survival was 76.8 months, while the estimated 5-year overall survival was 58% ( $p=0.4$ ) (15).

In cases presenting liver metastases, the benefit of surgery has been widely demonstrated; different outcomes in terms of survival have been recorded for cases presenting parenchymatous *versus* peritoneal seeding (12-14). These aspects led to the hypothesis that similar outcomes might also be associated with splenic metastases and encouraged surgeons to perform similar studies regarding the spleen and the various patterns of spread. In our present study, the proportion of patients with parenchymatous splenic metastases was 28.7% at the time of primary cytoreduction, similar to that reported by other authors. In the study conducted by Tanner *et al.*, overall incidence of parenchymatous splenic metastases of 21% was reported, while in a data review conducted by the same authors, an aggregate rate of hematogenous splenic involvement of 18% was provided (10).

In our cohort, a significant difference in terms of overall survival was also obtained for cases presenting parenchymatous involvement when compared to other patterns of spread (24.5 months *versus* 40.6 months for cases with hilar involvement and 58.4 months for cases with peritoneal seeding). These findings are in concordance with other literature data; for example, in a similar study conducted by Tanner *et al.* patients with parenchymatous splenic metastases had an overall survival rate of 28.5 months *versus* 51.2 months for cases with peritoneal seeding ( $p=0.004$ ) (10). In the same study, other prognostic factors which significantly impacted on disease-free survival and overall survival were age, preoperative albumin level, FIGO stage (III *versus* IV), serous histology, the presence of bulky upper abdominal disease, and administration of intraperitoneal chemotherapy. In multivariate analysis, only age, preoperative albumin, residual disease, FIGO stage IV, and the presence of parenchymatous splenic involvement were independently associated with overall survival (10).

In another similar study conducted by Ayhan *et al.*, a decrease of overall survival of 12 months was observed between patients with parenchymatous compared with those with peritoneal seeding, however, this was not statistically significant (20).

Contrarily to these results, in Magtibay *et al.*'s study involving patients submitted to splenectomy as part of primary and secondary cytoreductive surgery, no difference in terms of survival was reported between cases with parenchymatous *versus* those with peritoneal seeding. The



study included 112 patients who underwent splenectomy for advanced-stage EOC; in 66 cases, splenic involvement was found at primary cytoreduction, while in the other 46 cases, splenectomy was performed for recurrent EOC. The overall median survival for the primary cytoreduction group was 21.6 months, with an estimated 2-year survival of 46.2%, while the overall median survival in the secondary cytoreduction group was 20.3 months, with an estimated 2-year survival of 42.3%. Neither at the time of primary nor secondary cytoreduction did the presence of parenchymatous splenic involvement have any significant impact on overall survival ( $p=0.96$  and  $p=0.25$ , respectively). However, this might be explained by the small number of patients diagnosed with parenchymatous involvement (seven cases in the primary cytoreduction group and 11 cases in the secondary cytoreduction group, respectively) (22).

The current series demonstrate that splenectomy can be safely performed as part of primary cytoreduction. Although a morbidity rate of 30% and a mortality rate of 7% were encountered, these were not solely the result of complications related to splenectomy. Almost half of them seemed to be related to other performed surgeries, such as enteral resection, full-thickness diaphragmatic resection or to the preoperative associated co-morbidities, such as cardiac or respiratory disorders. Although a more significant benefit in terms of survival was achieved in patients with peritoneal or hilar involvement, cases retrospectively diagnosed with parenchymatous involvement also experienced a benefit in terms of survival.

## Conclusion

The presence of parenchymatous splenic metastases at primary cytoreduction for advanced-stage EOC seems to be an independent prognostic factor associated with poor prognosis when compared to the other types of splenic involvement, such as hilar or peritoneal seeding. However, splenectomy can be safely performed, with acceptable rates of postoperative morbidity and may bring survival benefit by increasing the rate of complete R0 resection.

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