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Prognostic Value and Therapeutic Implications of Pleural Carcinosis and Malignant Pleural Effusion in Advanced Epithelial Ovarian Cancer

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Abstract. *Aim: To demonstrate the prognostic value of pleural carcinosis/effusion in a cohort of patients with advanced epithelial ovarian cancer (EOC) and the associated therapeutic implications. Patients and Methods: Overall, data for 388 patients with EOC with confirmed malignant pleural effusion (MPE) or pleural carcinosis were retrospectively analyzed. Exclusion criteria were non-epithelial ovarian malignancies and presence of other comorbidities associated with pleural effusions. Results: The prognosis after the occurrence of MPE during the EOC in relapsed cases was poor with an overall survival of 9.9 months. In the multivariate analysis, the time point of the manifestation of the pleural effusion (p<0.001), platinum sensitivity (p=0.003), performance status (p=0.045) and presence of ascites (p=0.004) were significant prognostic factors for overall survival. Conclusion: Even in this less favorable collective, well-established EOC prognostic factors were associated with a significantly better overall survival. This suggests that the overall behavioral pattern of the disease has strong similarities in patients with and without pleural effusion or carcinosis and merits an equally high therapeutic effort.*

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Malignant pleural effusion (MPE) with or without associated pleural carcinosis signals a more advanced disease and an overall higher tumor burden in patients with epithelial ovarian cancer (EOC). These patients generally have a less favorable oncological outcome compared to those with earlier tumor stages and are also more challenging to manage surgically and conservatively due to the negative implications of the effusion on the cardiopulmonary functional capacity and the performance status of the patients (1, 2). Even though pleural carcinosis/effusion is defined as stage IVA disease, it represents a separate prognostic group since numerous prospective and retrospective studies have repeatedly demonstrated its more favorable prognosis compared to stage IVB disease due to intra-parenchymatous distant metastases such as of the liver, lungs and brain (3). This distinct oncological pattern has been reflected in the recent change in the International Federation of Gynecology and Obstetrics (FIGO) classification of ovarian cancer, where pleural effusion is not clustered together with hepatic or splenic parenchymal metastasis or metastasis to extra-abdominal organs but is classified as stage IVA when positive cytology of the pleural fluid is confirmed as opposed to stage IVB (4).

In an era of continuous striving for high surgical quality and expertise, with investment and extension of maximal surgical effort even in those patients with a higher disease burden (5), it is of paramount importance to evaluate the impact of MPE/pleural carcinosis on surgical outcome and success, and to assess the value of total macroscopic tumor clearance even for those patients who often are still denied cytoreductive surgery. The aim of the present study was to demonstrate the prognostic value of pleural carcinosis and MPE in a large cohort of patients with advanced EOC operated within a maximal-effort setting and the associated therapeutic implications.

Patients and Methods

Surgical procedures and data collection: We performed a retrospective analysis of patients with primary ovarian, tubal or peritoneal cancer who were operated within the time period of 01.01.2004 to 28.2.2011 at the Charite University Hospital of Berlin, Campus Virchow Klinikum. All patients who developed MPE or pleural carcinosis over the course of their disease were included in the study cohort. Their clinical history and outcome were captured within the SAP database (SAP-Enterprise Resource Planning, version 7.1; Copyright 2010 SAP AG) and identified by using following International Classification of Disease-10 Codes (6): C56.0 (for ovarian cancer), C57.0 for fallopian tube cancer and C57.8 for peritoneal cancer in combination with MPE or secondary pleural carcinosis (C78.2, C78.21 and C38.4). A confirmed diagnosis of pleural effusion or pleural carcinosis was accepted as cytologically confirmed, clearly demonstrated in the staging imaging or histologically confirmed. Not all patients with radiological pleural effusion had a cytological confirmation. Exclusion criteria were non-epithelial ovarian malignancies and the presence of other comorbidities that might potentially be associated with the development of pleural effusion such as concomitant cancer, or cardiopulmonary comorbidities.

The intraoperative tumor dissemination pattern, surgical and clinical outcome and type of surgical and systemic treatments were extracted from electronic and hard copy patient records and clinical trial registries. For every patient, the detailed tumor pattern was intraoperatively assessed based on the surgical procedures performed. Postoperatively, all surgical and histological findings were entered into a validated documentation system (Intraoperative Mapping of Ovarian Cancer) developed for ovarian neoplasms with special focus on the description of the tumor pattern, maximal tumor burden, and postoperative tumor residuals (6, 7). Patient informed consent was always obtained prior to surgery, sample collection and documentation.

Depending on their response to their last platinum-based chemotherapy, relapses were classified as platinum-sensitive if they occurred 6 months after the last cycle and -resistant if they occurred within 6 months. Patients were followed-up clinically at 3-monthly intervals for the first 3 years and then 6-monthly intervals for a further 2 years. Relapse was defined by appearance of new tumor spread intra-abdominally or new distant metastasis in imagining or progression of existing tumor focuses. Solitary CA125 increase was not sufficient to define relapse (8).

Statistical analysis. Statistical analysis was performed using SPSS software, version 20.0 (IBM, Armonk, NY, USA). The follow-up and survival times were calculated starting on the day of initial treatment, chemotherapy or surgery depending on what the patients received first, or the date of diagnosis for patients who received palliative treatment only. Survival over time was calculated using the Kaplan–Meier method. All parameters are expressed as the median with a range or mean and 95% confidence intervals (95% CI). Multivariate analysis was performed using the Cox-regression method. Continuous variables were tested for normality using the Shapiro–Wilk test and comparisons were made with Student's *t*-test for normally distributed data or with Mann–Whitney *U*-test for non-parametric variables. Categorical variables were compared with Fisher's exact test. Survival curves were compared with the log-rank test. Differences were considered significant for $p<0.05$.

Results

From a pool of 1,972 patients with EOC, we identified a subset of 388 women with a diagnosis of EOC combined with either pleural effusion or pleural carcinosis or both. From those, we retrospectively confirmed the presence of EOC and cytologically, radiologically or histologically confirmed MPE/carcinosis over the entire course of the disease in 141 patients. The incidence of MPE/carcinosis in our collective was 9.4% (Table I). The median patient age was 57.1 (range=22-81) years at the time of diagnosis. Overall, 90.7% had serous histology and 73% had high-grade EOC. The vast majority of the evaluated patients underwent cytoreductive surgery at initial diagnosis (136 out of 141; 96.5%), seven of these patients (5%) had received neoadjuvant chemotherapy and underwent interval debulking surgery, and only five out of 141 patients (3.5%) received primary chemotherapy and were not operated on at all.

Overall, 81 (59.5%) out of the 136 operated patients underwent surgery without macroscopic residual disease. A total of 56 (41.2%) patients underwent some type of diaphragmatic surgical intervention (stripping, or full-thickness resection), and seven (12.5%) underwent infrared coagulation at the diaphragm. Fourteen (66.7%) out of the 21 patients who underwent a full-thickness diaphragmatic resection had abnormal pleura at inspection and palpation, and only two (9.5%) had normal-appearing pleura. Fifty-five (40.4%) of all operated patients developed new postoperative pleural effusions; this percentage was much higher in the subset of patients who underwent diaphragmatic surgery (82.1%) (Table II).

All 136 surgical patients were able to receive adjuvant chemotherapy. All chemotherapy regimens were platinum-based.

In a median follow-up period of 36 (range: 7-163) months, 135 out of the 141 patients (95.7%) experienced at least one relapse, whereas 66 patients (46.8%) experienced 3-7 episodes of relapse. The median overall survival (OS) of the whole study population was 31.4 months (95% CI=25.24-37.58) and for patients with pleural effusion/carcinosis was 23,7 (95% CI=13.27-34.15) months.

Patients with FIGO stage IVA had a longer median OS in comparison to those with stage IVB disease: 24.15 months (95% CI=13.6-34.7) *versus* 14.28 months (95% CI=9.57-18.9) ($p=0.131$) (Figure 1).

Patients who were tumor-free after surgery had a significantly longer OS compared to those with macroscopic residual tumor at 23.65 (95% CI=16.04-31.26) compared to only 13.95 (95% CI=3.43-24.46, $p=0.270$) months, respectively, in those with stage IVA and 26.68 (95% CI=1.25-52.10) *versus* 11.87 (95% CI=5.68-18.06, $p=0.997$) months, respectively, in those with stage IVB disease.

The median time between primary diagnosis of EOC and formation of MPE/pleural carcinosis in this cohort was

Table I. *Characteristics of patients (n=141).*

Parameter		Value
Age at diagnosis	Median (range)	5.1 (18-81)
Diagnosis, n (%)	Ovarian cancer	126 (89.4)
	Tubal cancer	2 (1.4)
	Peritoneal cancer	13 (9.2)
FIGO stage at primary diagnosis, n (%)	I and II	8 (5.9)
	III	68 (50)
	IVA	41 (30.1)
	IVB	19 (14)
Histology, n (%)	Serous	107 (90.7)
	Mucinous	4 (3.4)
	Endometroid	3 (2.5)
	Mixed Müllerian tumor	3 (2.5)
	Transitional cell	1 (0.8)
Grading, n (%)	I	3 (2.5)
	II	30 (24.6)
	III	89 (73)
Lymph node involvement, n (%)	N0	24 (26.1)
	N1	68 (73.9)
Distant metastasis at diagnosis, n (%)	None	125 (88.7)
	Liver	6 (4.2)
	Spleen	4 (2.8)
	Extra-abdominal lymph nodes	4 (2.8)
	Lungs	3 (2.1)
	Abdominal wall	3 (2.1)
Distant metastasis over disease course, n (%)	Yes	72 (51.1)
	No	69 (48.9)
Ascites, n (%)	Yes	73 (79.3)
	No	19 (20.7)

FIGO: International Federation of Gynecology and Obstetrics.

Table II. *Procedures performed at the time of primary surgery and outcome.*

Parameter	n (%)
Primary surgery (n=136)	
Laparotomy	105 (74.5)
Two staged surgery	31 (22)
Macroscopic pleural carcinosis during intraoperative inspection and palpation at primary surgery	
Yes	14 (10.3)
No	2 (1.5)
Residual tumor after surgery	
Macroscopically tumor-free	81 (59.5)
<1 cm	36 (26.5)
<2 cm	6 (4.4)
>2 cm	13 (9.6)
Postoperative pleural effusion	
Yes	55 (40.4)
No	81 (59.6)
Diaphragmatic surgery (n=56)	
Type	
Diaphragmatic stripping	28 (50.0)
Full-thickness resection	21 (37.5)
Infrared coagulation	7 (12.5)
Postoperative pleural effusion	
Yes	46 (82.1)
No	10 (17.9)

approximately 25 months. The presence of MPE at primary diagnosis was significantly associated with poor progression-free survival of 21,4 months whereas the occurrence of MPE in relapsed cases significantly shortened the progression-free survival to 7.3 months ($p<0.0001$) (Figure 2). The vast majority of the affected patients (82.3%) were symptomatic with a poorer performance status due to the MPE/carcinosis. The most common symptom was shortness of breath, followed by fatigue and cough. Symptomatic patients from MPE/carcinosis at primary diagnosis had an OS of 8.8 months compared to 17.0 months in patients who were not symptomatic from MPE/carcinosis at primary diagnosis (95% CI=7.673-12.19 months; $p=0.007$).

In the multivariate analysis, four relevant prognostic factors for OS were identified. The time point of the manifestation of the MPE (primary *vs*. relapse: odds ratio (OR) of 2.378, 95% CI=1.465-3.858; $p<0.001$), platinum sensitivity (yes *vs*. no: OR=1.788, 95% CI=1.133-2.821; $p=0.003$), performance status (Eastern Cooperative Oncology Group performance status 0+1 *vs*. 2+3: OR=1.829, 95% CI=1.013-3.303; $p=0.045$) and presence of ascites (yes *vs*. no: OR=2.079, 95% CI=1.257-3.437; $p=0.004$) were significant prognostic factors for OS. Age of the patient at diagnosis of MPE and the level of serum cancer antigen-125 were not significantly associated with OS outcomes. The results are demonstrated in Table III and Figures 2 and 3.

Discussion

This is to our knowledge one of the largest systematic analyses evaluating the impact of MPE in patients with advanced EOC who undergo maximal-effort cytoreductive surgery within a specialized environment. The median survival of 23.7 months for those with FIGO IV disease were in concordance with an exploratory analysis of the AGO-OVAR group, which stated that macroscopically tumor-free resection at this stage is an important prognostic factor and the only factor amenable to improvement by therapy (3). Similar results were reported in the study by Eitan *et al*. from Memorial Sloan-Kettering, the median survival of patients with MPE was significantly reduced when comparing optimally cytoreduced stage IIIC cases with stage IV ones based solely on malignant effusion (9).

Generally, the prognosis after the occurrence of MPE during EOC in relapsed cases was poor in our cohort. Nevertheless, Porcel *et al*. reported survival advantage of patients with MPE and ovarian tumors as compared to patients with lung and breast cancer that developed MPE

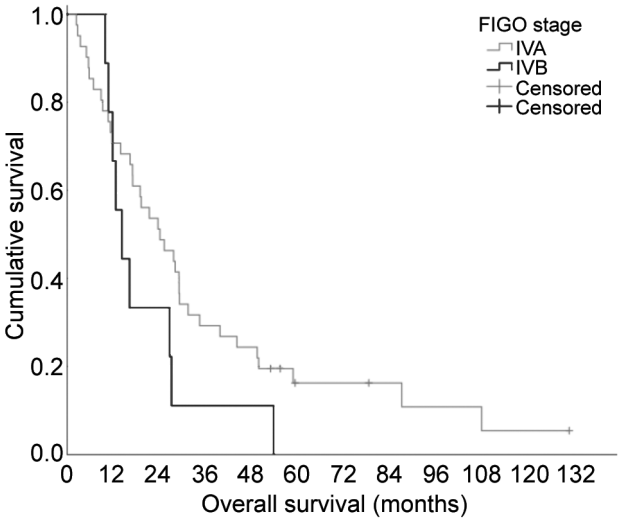

Figure 1. *Overall survival curves for patients with primary diagnosis of pleural carcinosis (p=0.131).*

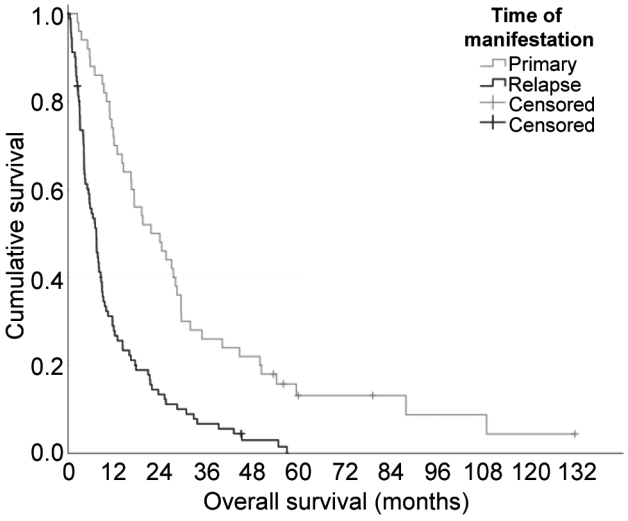

Figure 2. *Overall survival curves according to the time of manifestation (primary or relapse) of pleural effusion (p<0.001).*

(absolute differences of 41 and 20 months, respectively; $p<0.005$) (10).

However, we showed that even in this less favorable patient collective, the otherwise well-established prognostic factors of EOC such as platinum sensitivity, good performance status and absence of ascites were associated with a significantly better OS, suggesting that the overall behavioral pattern of the disease has strong similarities in patients with and without MPE and merits an approach with equally high therapeutic effort.

As an interesting observation, we demonstrated that almost 82.3% of the affected patients were highly symptomatic with respiratory symptoms, resulting in a poorer performance status due to their MPE or pleural carcinosis. In our cohort, most patients still underwent primary cytoreduction. However, this might still potentially have had significant implications on treatment decisions and the overall journey of the patient. We know from multiple prospective randomized trials (11-13) that upfront cytoreductive debulking surgery requires high patient resources and a good overall status to avoid surgical morbidity, therefore the presence of MPE, especially in symptomatic patients, can be a reason for many to follow the neoadjuvant route instead of performing primary cytoreduction (14, 15).

In a retrospective study by Winter *et al.*, data from 360 patients showed that patients with stage IV disease had a median OS comparable with that of those with stage III if they underwent ultraradical cytoreductive surgery (16). There is evidence that at the time of initial diagnosis, up to 70% of patients with FIGO stage IV disease had peritoneal involvement (17), which complicates complete cytoreduction. Again, in our study, we observed that patients

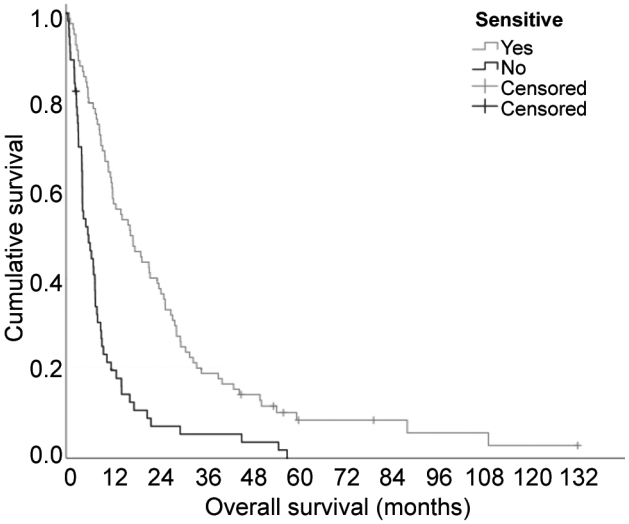

Figure 3. *Overall survival curves according to platinum sensitivity (p=0.003).*

with MPE and carcinosis still benefited from maximal-effort upfront cytoreduction. Moreover, despite the radicality of the surgery in those symptomatic and more challenging patients, all of them were able to proceed to adjuvant chemotherapy. This may indicate that the fear of radical upfront surgery among its many opponents, which is not necessarily justified in the hands of a specialized and dedicated team as demonstrated in similar analyses (18, 19) may compromise oncological outcome in patients with stage IVA EOC.

Table III. *Multivariate regression analysis of patients with pleural effusion/carcinosis.*

	Subgroup/comparison	Exp (B)	95% CI for Exp (B)	*p*-Value
Age at diagnosis		1.002	0.985-1.020	0.781
Appearance of MPE	Primary *vs*. relapse	2.378	1.465-3.858	<0.0001
Platinum sensitivity	No *vs*. yes	1.788	1.133-2.821	0.013
CA125 at diagnosis	100-1,000 U/ml	1.777	0.789-3.998	0.165
	>1,000 U/ml	1.984	0.855-4.606	0.111
ECOG performance status	2+3 *vs*. 0+1	1.829	1.013-3.303	0.045
Symptomatic pleural effusion	Yes *vs*. no	1.58	0.659-2.037	0.610
Ascites at diagnosis	Yes *vs*. no	2.079	1.257-3.437	0.004

MPE: Malignant pleural effusion; CA-125: cancer antigen 125; ECOG: Eastern Cooperative Oncology Group; Exp (B): exponential of the B-coefficient; 95% CI for 95% confidence interval.

Conclusion

Our results demonstrate that the presence of MPE does not exclude an optimal surgical outcome and, therefore, should not be used as a single stratification factor. Even in this less favorable patient collective, the otherwise well-established prognostic factors of EOC were associated with a significantly better OS, suggesting that the overall behavioral pattern of the disease has strong similarities in patients with and without MPE or pleural carcinosis and merits an equally high therapeutic effort.

Conflicts of Interest

The Authors have no competing interests to disclose.

Authors' Contributions

Sehouli J: Concept development, article review and editing. Nasser S: Literature review, data analysis and interpretation, and writing of article. Fotopoulou C: Data analysis and interpretation, and writing of article. Babayeva A: Data analysis and interpretation, and writing of article. Kaulich J: Data collection and article review. Olschewski J: Article review. Braicu E: Article review. Beteta C: Article review. Richter R: Statistical analysis and data analysis.

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