Prognostic Significance of CA-125 in the Management of Patients with Recurrent Epithelial Ovarian Carcinoma Selected for Secondary Cytoreduction*

SVEN MAHNER[1**], LINN WOELBER[1**], SABINE JUNG[1], CHRISTINE ZU EULENBURG[2], MAIKE IHNEN[1], JOERG SCHWARZ[1], JALID SEHOULI[3] and FRITZ JAENICKE[1]

Departments of [1]Gynecology, and [2]Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Hamburg; [3]Department of Gynecology and Obstetrics, Charité Campus Virchow-Klinikum, University Medicine Berlin, Germany

Abstract. *Background: Despite radical surgical and chemotherapeutic treatment of ovarian cancer, the majority of patients develop recurrence and die due to progressive disease. Routine measurement of the tumor marker CA-125 is often used in the follow-up management. However, the role of preoperative CA-125 as a prognostic factor before secondary cytoreduction of relapsed ovarian cancer has not been determined. Patients and Methods: CA-125 serum concentration and relevant clinico-pathological variables were analyzed regarding their potential prognostic impact in patients selected for secondary cytoreduction of recurrent epithelial ovarian cancer. Results: In total, 48 patients underwent secondary cytoreduction at the University Medical Center Hamburg-Eppendorf between 1996 and 2004 and 36 patients were evaluable for serum CA-125 concentration. Median age was 60 years (range 30-78 years) and median relapse-free survival before secondary cytoreduction was 18 months. The median time to progression after secondary surgery was 22 months (range 1-100 months), and median overall survival was 26 months (range 1-100 months). Serum CA-125 at the time of secondary cytoreduction was elevated (>35 kU/L) in 30 of 36 patients (81%) with a median of 212 kU/L (range 6-3866 kU/L). Multivariate analysis did not reveal a prognostic significance for preoperative CA-125. The only independent prognostic factors of improved survival were progression-free interval before secondary cytoreduction (p=0.047) and minimal residual disease after secondary cytoreduction (p=0.024). Conclusion: Although most patients had elevated serum CA-125 at the time of secondary cytoreductive surgery, CA-125 had no prognostic relevance.*

Ovarian cancer accounts for the highest mortality of all gynecologic malignancies and is the fourth most frequent cancer in women (1). Despite radical surgery and adjuvant systemic chemotherapy, the majority of patients develop recurrent disease (2). Because of this high likelihood of disease recurrence, most women are closely monitored after completing initial treatment. The usual follow-up consists of history of typical symptoms such as abdominal pain, bloating, swelling or dyspepsia and clinical examination including a pelvic exam (3). Besides vaginal and abdominal ultrasound, radiological assessment should not regularly be performed during follow-up outside of clinical trials because results are often misleading due to scarring after radical primary surgery and small peritoneal deposits are often missed by computed tomography (CT) or magnetic resonance imaging (MRI) (4-6).

The serum marker cancer antigen (CA)-125 is a useful alternative method of monitoring disease progression in epithelial ovarian cancer. It was first described in 1981 by Robert Bast and colleagues as an antigen that is increased in the majority of patients with epithelial ovarian cancer (7) and was later shown to correlate with the course of the disease (8). The CA-125 molecule is a high molecular weight membrane glycoprotein that is not exclusively expressed on ovarian cancer tumor cells but also by a

*Presented at the 8th International Conference of Anticancer Research, 17-22 October 2008, Kos, Greece.

This work was presented in part at the 'VII. International Symposium of the North-Eastern German Society of Gynecologic Oncology(NOGGO)' during the 8th International Conference of Anticancer Research, 17-22 October 2008, Kos, Greece.

**Both authors contributed equally to this work.

Correspondence to: Dr. Sven Mahner, MD, Department of Gynecology, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany. Tel: +49 40741052510, Fax: +49 4074105 4355, e-mail: Sven.Mahner@gmx.de

Key Words: Ovarian cancer, progression, relapse, CA-125, survival.

number of other cell types including pleura, peritoneum and mullerian epithelia (9). A rising CA-125 during follow-up is increasingly accepted as an indicator of disease recurrence in patients with ovarian cancer (10, 11).

Although primary cytoreductive surgery is well accepted as the crucial step of initial management, the use of cytoreductive surgery in the setting of recurrent disease is less clearly defined. Most retrospective studies have demonstrated a benefit of secondary cytoreduction but to date, there is no data from randomized phase 3 trials available (12, 13). Moreover, prognostic or predictive markers regarding the outcome of surgery in relapsed ovarian cancer have yet to be defined. Therefore the current study was conducted to determine the role and prognostic significance of preoperative CA-125 in recurrent ovarian cancer before secondary cytoreduction.

Patients and Methods

Patients with relapsed epithelial ovarian carcinoma who presented for secondary surgery at the University Medical Center Hamburg-Eppendorf between 1996 and 2004 were included in this study. Patients who were considered to have recurrent disease that was resectable then underwent an attempted secondary cytoreduction. This was defined as a surgical exploration with the intent of resecting all visible tumor. The decision to attempt secondary cytoreduction was based on the results of clinical examination, previous therapies and performance status of the patient on an individual basis. Additional radiological examinations were performed if necessary, but besides vaginal ultrasound, no other routine test was performed. All cases were discussed at an interdisciplinary tumor board consisting of gynecological oncologists, medical oncologists, radiologists, pathologists and surgical oncologists if necessary. Patients who had ovarian carcinoma of low malignant potential (borderline tumors) and patients who underwent surgery solely for the correction of bowel obstruction were excluded from the present analysis. Clinicopathological factors were evaluated by reviewing medical charts and pathological records. Clinical outcome was followed from the date of surgery to the date of death or the date of last follow-up for patients who remained alive. Median follow up was 13 months (range 1-100 months). All patients gave written informed consent for tissue collection and review of their medical records according to the Investigational Review Board and Ethics Committee guidelines.

CA-125 was measured by a commercially available radioimmunoassay used throughout the study period.

Analysis of potential prognostic factors was performed with the log-rank test for categorical factors and the Cox proportional hazards model for continuous factors. Probability values less than 0.05 were regarded as statistically significant. All statistical analyses were conducted using SPSS software Version 15 (SPSS Inc., Chicago, IL, USA).

Results

A total of 48 patients were included in this study; detailed patient characteristics are listed in Table I. Twelve cases were not available for CA-125 assessment before surgery and were excluded from the tumor marker analysis. All patients underwent secondary cytoreduction defined as a surgical exploration with the intent to resect all visible disease. Median age was 60 years (range 30-78 years). Median relapse-free survival before secondary cytoreduction was 18 months (range 5-100 months) and the median time to progression after secondary surgery was 22 months (range 1-100 months). Median overall survival after secondary debulking was 26 months (range 1-100 months). Disease recurrence was located mainly at the intestine (Table II). A complete tumor resection of all visible disease was achieved in 33% of the patients. Overall, 44% of the patients had residual disease less than 5 mm in greatest diameter (Table I).

Serum CA-125 at time of relapse surgery was elevated (>35 kU/L) in 30 out of 36 patients (81%) with a median of 212 kU/L (range 6-3866).

Multivariate analysis of all relevant biological and surgical parameters did not reveal any prognostic significance for preoperative serum CA-125 concentration (Table III). The only independent prognostic factors of improved survival were the progression-free interval before secondary cytoreduction (p=0.047) and minimal disease after secondary cytoreduction (p=0.024).

Discussion

To determine the prognostic role of CA-125 in recurrent ovarian cancer before secondary cytoreduction, 48 patients with relapsed epithelial ovarian carcinoma who presented for surgery were analyzed. Secondary cytoreduction was defined as a surgical exploration with the intent to resect all visible disease. Complete tumor resection was achieved in 33% of the patients with a rate of 44% of patients that had residual disease of less than 5 mm in greatest diameter.

Although cytoreductive surgery is well established in the primary management of ovarian cancer, the use of cytoreductive surgery in the setting of recurrent disease is defined less clearly as there are no data from randomized phase 3 trials available. Retrospective analyses demonstrated that selected patients can benefit from surgical efforts in relapsed disease, but there is no consensus on appropriate criteria and parameters to select these patients. It is believed that secondary debulking yields a survival benefit mainly in platinum sensitive patients. The first study regarding the value of secondary cytoreduction was published more than 20 years ago by Berek *et al.* (14). More recently, the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO-OVAR) conducted a retrospective multicenter trial (AGO-DESKTOP I) to analyze patients with secondary cytoreduction and determine prognostic and predictive markers (12). They found that only complete resection was associated with prolonged survival and identified a criteria panel associated with complete cytoreduction, which is

Table I. *Patient characteristics (n=48).*

Age (years)	
Median	60
Range	30-78
FIGO-Stage at initial diagnosis	
I	4
II	5
III	32
IV	7
Grading	
1	3
2	3
3	32
Not determined/unknown	10
Residual tumor after secondary surgery	
Microscopic	16
<0.5 cm	5
0.5-1 cm	2
1-2 cm	5
>2 cm	8
Not determined / unknown	12
Histological subtype	
Serous	33
Mucinous	4
Endometrioid	1
Clear cell	1
Undifferentiated	9
Ascites before surgery	
None	19
<500 mL	13
≥500 mL	7
Not determined/unknown	9

Table II. *Localization of recurrent disease at secondary surgery, multiple sites per patient possible (n=37).*

Localization	n	%
Small intestine	8	22%
Mesenterium	7	19%
Liver	6	16%
Transverse colon	6	16%
Pelvis	5	14%
Vaginal cuff	4	11%
Abdominal wall	4	11%
Pancreas	4	11%
Sigmoid colon	3	8%
Bladder	3	8%
Stomach	3	8%
Spleen	3	8%
Paraaortic lymph nodes	3	8%
Diaphragm	2	5%
Rectum	2	5%
Omentum minus	2	5%
Iliac lymph nodes	1	3%
Inguinal lymph nodes	1	3%
Skin	1	3%

currently being verified in a prospective trial (AGO-DESKTOP II). Patient recruitment has finished and final results of this trial are pending. Regarding the optimal result of secondary cytoreduction, other authors found different results: Chi *et al*. demonstrated in a large single center retrospective analysis at the Memorial Sloan-Kettering Cancer Center that patients with residual tumor up to 5 mm could benefit from secondary cytoreduction (15), confirming earlier results of a study by Jänicke *et al*. (13). In the current study, 5 mm was found to be the optimal cut-off for residual disease of patients who benefit from secondary cytoreduction (data on file).

A rising CA-125 during follow-up is increasingly accepted as a sign of recurrent disease in ovarian cancer (10). The Gynecologic Cancer Intergroup (GCIG) has therefore proposed a definition of disease progression on the basis of CA-125 serum concentrations (16). Patients with increased pre-treatment CA-125 concentrations that later normalize need to have CA-125 concentrations more than two times the upper limit of normal on two occasions at least one week apart for disease to be considered progressive; in patients with increased pre-treatment CA-125 concentrations that never normalized during treatment, CA-125 concentrations need to be more than two times the nadir value on two occasions at least one week apart; patients with normal pre-treatment CA-125 concentrations need to have CA-125 concentrations more than two times the upper limit of normal on two occasions at least one week apart. This definition is currently being incorporated into many clinical trials and has been validated by comparing disease progression defined by RECIST criteria (17) and GCIG criteria in a large randomized phase 3 trial (10).

In this study, it was observed that most patients with relapsed ovarian cancer also had an increased CA-125 (81%), a rate similar to the results of van der Burg *et al*. (18). However, a prognostic relevance of increased CA-125 was not observed in multivariate analysis (p=0.999, Table III). The only independent prognostic factors of improved survival in this cohort were the progression-free interval before secondary cytoreduction (p=0.047) and minimal residual disease after secondary cytoreduction (p=0.024), confirming previous results of other retrospective analyses (12). Although only CA-125 above the upper limit of normal (35 kU/L) has been considered suspicious of relapsed disease in this study as well as in most of the other trials, disease progression might already be predicted by increasing values within the normal range. A small study of 11 patients by Wilder *et al*. suggested that a progressive increase of serum CA-125 concentration within the normal range in three consecutive measurements was highly predictive of tumor recurrence (19). Another study

Table III. *Multivariate analysis to determine the impact on overall survival based on 33 patients (CA-125 missing in 12 patients, additional variables missing in 3 patients).*

Predictive factor	*p*-Value
Minimal residual disease after secondary cytoreduction	**0.024**
Minimal residual disease after primary cytoreduction	0.846
Progression-free interval before secondary cytoreduction (months)	**0.047**
Initial FIGO – stage (I *vs*. II *vs*. III *vs*. IV)	0.593
Age (below *vs*. above 60 years)	0.147
Histological subtype (serous *vs*. mucinous *vs*. others)	0.290
Grading (GI *vs*. GII *vs*. GIII)	0.590
Ascites (below *vs*. above 500 mL)	0.876
Preoperative CA – 125 (below *vs*. above 35 kU/L)	0.999
Locoregional *vs*. diffuse relapse	0.164
Second-line chemotherapy (platinum-based *vs*. non platinum-base)	0.464
Bowel resection (yes/no)	0.377
Diaphragmal resection (yes/no)	0.689
Upper abdominal resection (yes/no)	0.872
Lymphadenectomy (yes/no)	0.186

of 39 patients with marker-positive ovarian cancer demonstrated that an absolute increase of CA-125 serum concentration of 10 kU/L within the normal range or a relative increase of 100% compared to nadir concentration was highly predictive of recurrence (20). These criteria for relapsed ovarian cancer should be further evaluated in larger patient cohorts to improve selection of possible candidates for secondary cytoreduction, as early detection of more localized disease could potentially facilitate optimal resection. However, a survival benefit for early treatment of relapsed ovarian cancer based on CA-125 measurement has not been verified. The European Organization for Research and Treatment in Cancer (EORTC) randomized women with rising CA-125 following primary treatment to immediate second-line treatment or delayed until onset of symptoms or clinical recurrence. Patient recruitment was finished in 2008 and final results are expected at the ASCO annual meeting 2009.

Another possibility to improve patient selection and planning of surgical interventions could be the application of more sensitive radiological assessments such as PET/CT. Bristow *et al*. demonstrated in a study of 14 patients with rising CA-125 concentrations that PET/CT was able to detect localized recurrent disease while conventional imaging was negative or equivocal (21). Thus, a possible algorithm for future follow-up management of patients with epithelial ovarian cancer could consist of regular CA-125 measurement, taking serial increase within the normal range into account, followed by PET/CT in case of rising CA-125 concentrations to select patients for possible secondary cytoreduction. A prospective evaluation of this algorithm within a clinical trial is highly desirable. CA-125 alone, although elevated in more than 80% of the patients in this study, was not prognostically relevant in this setting.

Acknowledgements

We would like to thank Dr. Christian Utler and Professor Christoph Thomssen for their help with the design of the study protocol.

References

1 Cancer Facts and Figures. American Cancer Society 2007.

2 du Bois A, Luck HJ, Meier W, Adams HP, Mobus V, Costa S, Bauknecht T, Richter B, Warm M, Schroder W, Olbricht S, Nitz U, Jackisch C, Emons G, Wagner U, Kuhn W and Pfisterer J: A randomized clinical trial of cisplatin/paclitaxel *versus* carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst *95(17)*: 1320-1329, 2003.

3 Chan KK, Tam KF, Tse KY and Ngan HY: The role of regular physical examination in the detection of ovarian cancer recurrence. Gynecol Oncol *110(2)*: 158-161, 2008.

4 Fehm T, Heller F, Kramer S, Jager W and Gebauer G: Evaluation of CA125, physical and radiological findings in follow-up of ovarian cancer patients. Anticancer Res *25(3A)*: 1551-1554, 2005.

5 Ricke J, Sehouli J, Hach C, Hanninen EL, Lichtenegger W and Felix R: Prospective evaluation of contrast-enhanced MRI in the depiction of peritoneal spread in primary or recurrent ovarian cancer. Eur Radiol *13(5)*: 943-949, 2003.

6 Henrich W, Fotopoulou C, Fuchs I, Wolf C, Schmider A, Denkert C, Lichtenegger W and Sehouli J: Value of preoperative transvaginal sonography (TVS) in the description of tumor pattern in ovarian cancer patients: results of a prospective study. Anticancer Res *27(6C)*: 4289-4294, 2007.

7 Bast RC Jr, Feeney M, Lazarus H, Nadler LM, Colvin RB and Knapp RC: Reactivity of a monoclonal antibody with human ovarian carcinoma. J Clin Invest *68(5)*: 1331-1337, 1981.

8 Bast RC Jr, Klug TL, St John E, Jenison E, Niloff JM, Lazarus H, Berkowitz RS, Leavitt T, Griffiths CT, Parker L, Zurawski VR Jr and Knapp RC: A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. N Engl J Med *309(15)*: 883-887, 1983.

9 Kabawat SE, Bast RC Jr, Bhan AK, Welch WR, Knapp RC and Colvin RB: Tissue distribution of a coelomic-epithelium-related antigen recognized by the monoclonal antibody OC125. Int J Gynecol Pathol *2(3)*: 275-285, 1983.
10 Rustin GJ, Timmers P, Nelstrop A, Shreeves G, Bentzen SM, Baron B, Piccart MJ, Bertelsen K, Stuart G, Cassidy J and Eisenhauer E: Comparison of CA-125 and standard definitions of progression of ovarian cancer in the intergroup trial of cisplatin and paclitaxel *versus* cisplatin and cyclophosphamide. J Clin Oncol *24(1)*: 45-51, 2006.
11 Sehouli J, Akdogan Z, Heinze T, Konsgen D, Stengel D, Mustea A and Lichtenegger W: Preoperative determination of CASA (cancer-associated serum antigen) and CA-125 for the discrimination between benign and malignant pelvic tumor mass: a prospective study. Anticancer Res *23(2A)*: 1115-1118, 2003.
12 Harter P, Bois A, Hahmann M, Hasenburg A, Burges A, Loibl S, Gropp M, Huober J, Fink D, Schroder W, Muenstedt K, Schmalfeldt B, Emons G, Pfisterer J, Wollschlaeger K, Meerpohl HG, Breitbach GP, Tanner B and Sehouli J: Surgery in recurrent ovarian cancer: the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR trial. Ann Surg Oncol *13(12)*: 1702-1710, 2006.
13 Janicke F, Holscher M, Kuhn W, von Hugo R, Pache L, Siewert JR and Graeff H: Radical surgical procedure improves survival time in patients with recurrent ovarian cancer. Cancer *70(8)*: 2129-2136, 1992.
14 Berek JS, Hacker NF, Lagasse LD, Nieberg RK and Elashoff RM: Survival of patients following secondary cytoreductive surgery in ovarian cancer. Obstet Gynecol *61(2)*: 189-193, 1983.
15 Chi DS, McCaughty K, Diaz JP, Huh J, Schwabenbauer S, Hummer AJ, Venkatraman ES, Aghajanian C, Sonoda Y, Abu-Rustum NR and Barakat RR: Guidelines and selection criteria for secondary cytoreductive surgery in patients with recurrent, platinum-sensitive epithelial ovarian carcinoma. Cancer *106(9)*: 1933-1939, 2006.
16 Vergote I, Rustin GJ, Eisenhauer EA, Kristensen GB, Pujade-Lauraine E, Parmar MK, Friedlander M, Jakobsen A and Vermorken JB: Re: new guidelines to evaluate the response to treatment in solid tumors ovarian cancer. Gynecologic Cancer Intergroup. J Natl Cancer Inst *92(18)*: 1534-1535, 2000.
17 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst *92(3)*: 205-216, 2000.
18 van der Burg ME, Lammes FB and Verweij J: The role of CA-125 in the early diagnosis of progressive disease in ovarian cancer. Ann Oncol *1(4)*: 301-302, 1990.
19 Wilder JL, Pavlik E, Straughn JM, Kirby T, Higgins RV, DePriest PD, Ueland FR, Kryscio RJ, Whitley RJ and Nagell J: Clinical implications of a rising serum CA-125 within the normal range in patients with epithelial ovarian cancer: a preliminary investigation. Gynecol Oncol *89(2)*: 233-235, 2003.
20 Santillan A, Garg R, Zahurak ML, Gardner GJ, Giuntoli RL, 2nd, Armstrong DK and Bristow RE: Risk of epithelial ovarian cancer recurrence in patients with rising serum CA-125 levels within the normal range. J Clin Oncol *23(36)*: 9338-9343, 2005.
21 Bristow RE, Giuntoli RL 2nd, Pannu HK, Schulick RD, Fishman EK and Wahl RL: Combined PET/CT for detecting recurrent ovarian cancer limited to retroperitoneal lymph nodes. Gynecol Oncol *99(2)*: 294-300, 2005.
22 Mahner S: Pros and cons for CA-125 monitoring in the follow up management of ovarian cancer patients. Anticancer Res *28(5C)*: 3393, 2008.

Received January 6, 2009
Revised March 14, 2009
Accepted April 13, 2009