Role of IGF-I in Primary Ovarian Cancer – A Study of the OVCAD European Consortium*

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Abstract. *Background/Aim: IGF-I (insulin growth factor 1) is crucially involved in cellular proliferation. Moreover, deregulation of IGF-I has been shown to be relevant in the carcinogenesis of various tumor entities. However, the impact of IGF-I in epithelial ovarian cancer (EOC) is unclear. In the present study, we investigated the predictive and prognostic role of circulatory IGF-I in primary EOC patients. Patients and Methods: In the FP6 European Project "OVCAD", 275 consecutive primary EOC patients were enrolled. Patients were eligible if radical cytoreductive surgery and platinum-based chemotherapy were performed. Plasma IGF-I was detected using ELISA. Results: Increased plasma IGF-I levels were more frequently found in well-differentiated epithelial ovarian carcinoma (p=0.0047). A weak correlation was observed between IGF-I levels and CA-125 in patients with serous EOC (p=0.04). No association between IGF-I expression and other clinico-pathological parameters was observed. Conclusion: IGF-I is overexpressed in patients with well-differentiated EOC. Further studies are warranted to elucidate the role of IGF-I in this sub-group of patients.*

Ovarian cancer is the leading cause of cancer-related death due to gynecological malignancies (1). Most patients are diagnosed with advanced-stage disease; despite extensive research there exists a lack of efficient biomarkers, diagnostic tools or specific symptoms to detect early-stage ovarian cancer. However, optimal treatment consists of radical cytoreductive surgery and platinum-based chemotherapy. The major prognostic factors for overall survival are no macroscopic residual tumor mass after cytoreductive surgery and response to platinum-based chemotherapy. Further known independent prognostic factors are age, performance status, grade and FIGO stage (2). Although 80% of patients initially respond well to platinum-based chemotherapy, most relapse and disease progresses, further developing resistance to chemotherapy eventually leading to death (3, 4).

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Abbreviations: IGF-I: Insulin growth factor 1, IGF-IR: insulin-like growth factor 1 receptor, EOC: epithelial ovarian cancer, OVCAD: Ovarian Cancer Diagnosis initiative, FP6: the Sixth Framework Programme (FP6) EU project "OVCAD", OS: overall survival, PFS: progression-free survival, FIGO: International Federation of Gynecology and Obstetrics, CI: confidence interval, HGSOC: high-grade serous ovarian cancer, LGSOC: low-grade serous ovarian cancer.

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IGF-I is a hormone crucially involved in the physiology of cell proliferation (5). IGF-I is coded on chromosome 12 and produced in the liver by stimulatation from the pituitary growth hormone (GH) (6, 7). It is also mentioned that the pituitary GH and the hepatic IGF-I are maybe involved in the maintenance of ovarian functions (6). Moreover, deregulation of IGF-I has been shown to be related to various tumors (8). A number of studies have demonstrated that the signaling pathways of the insulin-like growth factors (IGF) increase the risk for several types of epithelial neoplasms, for example of the breast, prostate and colorectum (9-11). IGF-I hormone has also been hypothesized to play a role in the development of ovarian cancer (12). Nevertheless there exist only few data on the role of IGF1 in ovarian cancer. The objective of the present study was to determine the expression of IGF-I in plasma and its correlation with clinical prognostic factors, *e.g.* histological grade and subtype, age, residual tumor mass, platinum resistance, BMI, volume of ascites, progression-free and overall survival in women with primary epithelial ovarian cancer.

Patients and Methods

Study population. Between February 2005 and December 2008, 275 patients between 18 and 85 years (median age=58 years) with primary advanced ovarian cancer were enrolled in the OVCAD project (www.ovcad.eu). All patients had been treated at five comprehensive centers for ovarian cancer management (Department of Gynecology at Charité – Medical University Berlin (Berlin, Germany), Department of Gynecologic Oncology, University Hospital Leuven (Leuven, Belgium), Department of Obstetrics and Gynecology, Medical University of Vienna (Vienna, Austria), Department of Gynecology, University Medical Center Hamburg-Eppendorf (Hamburg, Germany), and Department of Gynecology and Obstetrics, Innsbruck Medical University (Innsbruck, Austria). Inclusion criteria were age of 18 years or older, histologically confirmed ovarian cancer, FIGO (International Federation of Gynecology and Obstetrics) stage II to IV, cytoreductive surgery, platinum-based chemotherapy. Stage FIGO-I cases were excluded due to better clinical outcome. Ethical Committee approval was provided by the participating OVCAD partners (ML2524, HEK190504, EK366, EK260 EK207/2003). Before collection of tissue, plasma and ascites, written informed consent was obtained from the patients. Patient's characteristics are shown in Table I. For documentation, a systematic surgical and histopathological tumor documentation instrument was used (13).

Clinical definitions. Progression-free survival (PFS) was defined as the time after treatment and disease progression or death. Overall survival was defined as the time from diagnosis and the date of death or date of last contact. RECIST (Response Evaluation Criteria In Solid Tumors) criteria (version 1.1) and the GCIC (Gynecological Cancer Intergroup) were used for assessment of response (14, 15).

Patients whose disease recurred within 6 month after the last cycle of platinum-based chemotherapy were classified as "platinum-resistant", those whose disease recurred in ≥6 months were defined as "platinum-sensitive". Residual tumor mass after cytoreduction was defined as no macroscopical residual tumor mass, macroscopical tumor mass ≤0.5 cm, 0.5-1 cm, 1-2 cm and >2 cm. The body mass index (BMI) is expressed in kg/m^2 and is defined as the body mass divided by the square of the body height. We calculated the BMI for our patients preoperatively. Tumors were graded as G1 (well-differentiated/low-grade) G2 (moderately-differentiated/intermediate-grade) or G3 (poorly-differentiated/high-grade). Since the inclusion ended in December 2008, the old FIGO classification was used (16). The median follow-up was 37 months (range=1–69 month). The main data for all patients were updated and stored in a data system after the accuracy of the data were verified.

Laboratory analyses. All measurements were performed at the Department of Gynecology at Charité, Medical University Berlin. Plasma was collected using an EDTA collecting tube before or during surgery and prior to chemotherapy treatment. Within 30 min of collection, samples were centrifuged for 15 min at 1,000 x g, aliquoted and stored at –80˚C until further processing. Before measuring, samples were pre-treated to release IFG-I from binding proteins. IGF-I concentrations in plasma were measured using specific ELISAs (Human IGF-I Immunoassay, Quantikine, R&D systems, Catalog Number: DG100, SG100, PDG100) according to the manufacturer's instructions. In the current study, only IGF-I levels in plasma were calculated.

CA-125 Luminex. CA125 in plasma was presented in 237 patients and was determined by using the Luminex technique. Samples were analyzed following the instruction of the MILLIPLEX MAP Kit (Cancer Biomarker Panel, Cat: 48-020).

Statistical analyses. The clinical data were collected and registered in an online data base. The statistics was performed using the SPSS software. A two-tailed p-value <0.05 was considered statistically significant. As classical clinical prognostic factors, the following parameters were considered: FIGO-stage, age at first diagnosis, histological subtype, grading, presence of ascites, residual tumor mass after surgery, response to platinum based chemotherapy, overall survival and progression-free survival.

Correlations between IGF-I expression and age, volume of ascites and CA125 expression were evaluated using Spearman rank correlation. Associations between IGF-I expression and histology, FIGO stage, grading, residual tumor mass and response to platinum based chemotherapy were appropriated either by using Kruskall–Wallis H–test or Mann–Whitney *U*–test. Overall survival and progression-free survival rates and 95% confidence intervals (95% CI) were estimated according to Kaplan–Meier-method. Log-rank test statistics for analysis of the equality of survival distribution were performed. The cut-off value was defined using receiver operating characteristics curves (ROC), as the value with the maximal sum of sensitivity and specificity (17).

Results

Baseline characteristics. A total of 275 newly-diagnosed EOC were recruited for this study. The median BMI was 25 kg/m^2, with a range from 16 kg/m^2 to 40 kg/m^2. According to the former FIGO-classification 212 patients (77.1%) had FIGO III-stage, 48 (17.5 %) had FIGO IV-stage and 15 (5.4%) a FIGO II-stage ovarian cancer. Serous

Table I. *Patients' characteristics*.

	Median (Q_1-Q_3)	
Age (years)	58 (50-67)	
Overall survival (months)	25 (22-48)	
Follow-up (months)	37 (22-49)	
	N	%
Histology		
Serous	237	86.2
HGSOC	227	82.5
LGSOC	9	3.3
Endometrioid	13	4.7
Mixed	11	4
Undifferentiated	9	3.3
Mucinous	3	1.1
Clear cell carcinomas	2	0,7
FIGO Stage		
FIGO II	15	5.4
FIGO III	212	77.1
FIGO IV	48	17.5
Grading#		
Grade I	10	3.6
Grade II	64	23.3
Grade III	200	72.7
Volume of ascites		
No ascites	66	24
≤500ml	110	40
>500ml	100	36
Peritoneal carcinomatosis		
Yes	186	67.6
No	89	32.4
Residual tumor mass*		
None	188	68.4
≤0.5cm	25	9.1
>0.5 <1cm	23	8.4
>1cm	38	13.8
Response to platinum based chemotherapy§		
Platinum sensitive	204	74.5
Platinum resistant	70	25.5

Grading, residual tumor mass and response to adjuvant chemotherapy for one patient were not available.

histology was found in 237 patients (86%). Well-differentiated/low-grade carcinomas were found in 10 patients (3.6%), moderately-differentiated/intermediate-grade in 64 (23.3%) and poorly-differentiated/high-grade in 200 (72.7%) patients. Macroscopic cytoreduction rate was received by 188 patients (68.4%). All patients' characteristics are summarized in Table I and have been described in detail in previous studies (18, 19).

Clinical response and follow-up. The median follow-up time was 37 months with a range from 1 to 69 months. During this time we noted 134 (48.7%) death events, 129 (46.9%) were cancer related. One-hundred and forty-one (51.3%) of the patients were alive at the end of the study. Two-hundred and four patients (74.5%) were sensitive to platinum-based chemotherapy, whereas 70 patients (25.5%) were platinum-resistant (Table I).

IGF-1 and CA125 expression in plasma. The IGF-I expression in plasma was determined in all patients with EOC. Median plasma IGF-I expression was 18.45 mg/ml (interquartile range [IQR]=12.5-28.3). When we tested only the serous EOC the median of IGF-I levels was 18.6 (IQR=12.4-28.6).

The CA125 expression in plasma was determined in 237 patients. The median of the preoperative CA-125 plasma levels was 553 U/ml with a range from 7 to 37,820 U/ml.

Correlation of IGF-I expression and clinical prognostic factors of all patients with EOC. Increased plasma IGF-I levels were more frequently found in well-differentiated epithelial ovarian carcinoma (p=0.0047) than in G2/G3 EOC (Figure 1A). No statistical significance were observed by age at diagnosis (<55, ≥55 years) (p=0.32), volume of ascites (p=0.16) and no significance between CA125 expression and IGF-1 levels (p=0.05). Furthermore, there were no significant associations between IGF-I expression and histology (p=0.65), FIGO stage (p=0.49) and residual tumor mass (p=0.10). There was also no significant correlation with platinum response (p=0.61) (Table II).

Correlation of IGF-1 expression and clinical prognostic factors of patients with serous ovarian cancer. Due to low incidence we excluded the non-serous histology (n=38) for further analyses (Table II). There were no significant correlations between IGF-I expression and age, when stratified by age at diagnosis (<55, ≥55 years) (p=0.23) or with volume of ascites (p=0.18). When we only compared the sub-group of patients with serous ovarian cancer, there was no significant association between LGSOC and HGSOC and the IGF-I values observed (p=0.054) (Figure 1B). There is a weak-moderate negative correlation between CA125 and IGF-1, when only the serous ovarian cancers were analyzed (p=0.04), with a Spearman coefficient rho of -0.15. The higher the value of CA125, the lower was the plasma IGF-1 concentration. Furthermore, there were no significant associations between IGF-I expression and FIGO stage (p=0.94), residual tumor mass (p=0.12), BMI (p=0,37) and platinum response (p=0.45) (Table II).

Impact of overall survival and progression-free survival. Regarding the overall survival and using a cut-off value of 15 ng/ml for plasma IGF-I levels in all patients with EOC, no significant differences were observed. The area under the curve was 0.50, 95% confidence interval=0.41-0.5 with a

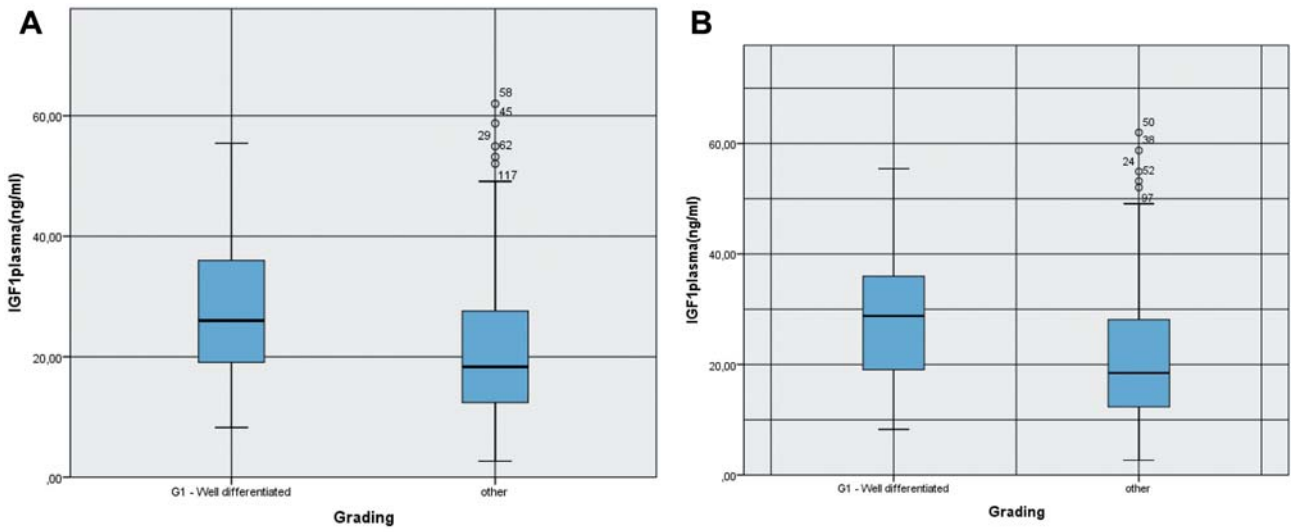

Figure 1. *A: Distribution of IGF-I in G1 and G2/3 patients with EOC. B: Distribution of IGF-I in G1 and G2/3 in patients with serous ovarian cancer.*

sensitivity of 70% and a specificity of 41%. When patients with low IGF-I levels were compared to patients with high IGF-I levels, no significant improvement in OS was found (p=0.18) (Figure 2A). A similar pattern could be observed in sub-group analyses by serous tumors (p=0.37). Regarding progression-free survival, plasma IGF-I concentration was also not a predictive factor in the univariate analysis when the whole collective of EOC was analyzed (p=0.17), nor for patients with serous ovarian cancer only (p=0.37) (Figures 2B and 3B).

We also performed a multivariate analysis that included age at primary diagnosis, FIGO stage, histology (serous *vs.* others), grade, volume of ascites, residual tumor mass, platinum response and recruiting center. In the Cox Regression analysis residual tumor mass (p=0.001, HR=2.55, 95%CI=1.49-4.36), response to platinum therapy (p<0.001, HR=10.84, 95%CI=6.4-18.34) and age at first diagnosis (p=0.006, HR=1.03, 95%CI=1.009-1.054) remained the only independent prognostic factors for OS. In the multivariate analysis with the same clinical parameters as for OS, except platinum response, only residual tumor mass and FIGO stages were independent predictive factors for progression-free survival (p=0.002, HR=1.77, 95%CI=1.24-2.53 and p=0.001, HR=5.76, 95% CI=1.9-17.3, respectively).

Discussion

Insulin-like growth factors are part of a complex system of at least four IGF-receptors, of three secreted ligands (insulin, insulin-like growth factor-1 and insulin-like growth factor-2) and six IGF-binding proteins (20). It has been shown that they both play a role in oncogenic transformation (21). The current analysis is based on a single biomarker in the IGF signaling axis. As far as we are aware of, current data suggest IGF-I and IGF-IR to be the most relevant members of the insulin-like-growth factors family for ovarian carcinogenesis (20). In our retrospective study we evaluated the relationship between IGF-I and clinically important prognostic factors of primary epithelial ovarian cancer. We did not observe any clear associations between IGF-I and EOC. We hypothesized that circulating IGF-I would be different in low- and high-grade EOC. It has been described that LGSOC is more responsive to IGF-I stimulation and IGF-IR inhibition compared with HGSOC cancer cell lines (22). In our study there was no statistical significance between IGF-I circulatory levels in patients with LGSOC. However, when we analyzed patients with ovarian cancer, we observed a weak correlation between well-differentiated tumors (in our case nine LGSOC and one low-grade endometrioid EOC) and plasma levels of IGF-I. A possible explanation of our results may be the small number of patients with low-grade ovarian cancer (n=10). High-grade and low-grade serous epithelial ovarian cancer evolved differently. Silva *et al*. first proposed the binary grading system for serous carcinoma suggesting a dualistic mechanism for the genesis of serous ovarian carcinomas (23). Binary grading system is adopted in many institutions (24, 25). Gershenson *et al*. showed relative chemoresistance in low-grade compared to high-grade ovarian cancers. Persistent or recurrent disease after primary chemotherapy was also associated with a shorter progression-free survival time (26). Relative chemoresistance was subsequently also observed in reports of patients with low-grade ovarian cancer treated with neoadjuvant chemotherapy

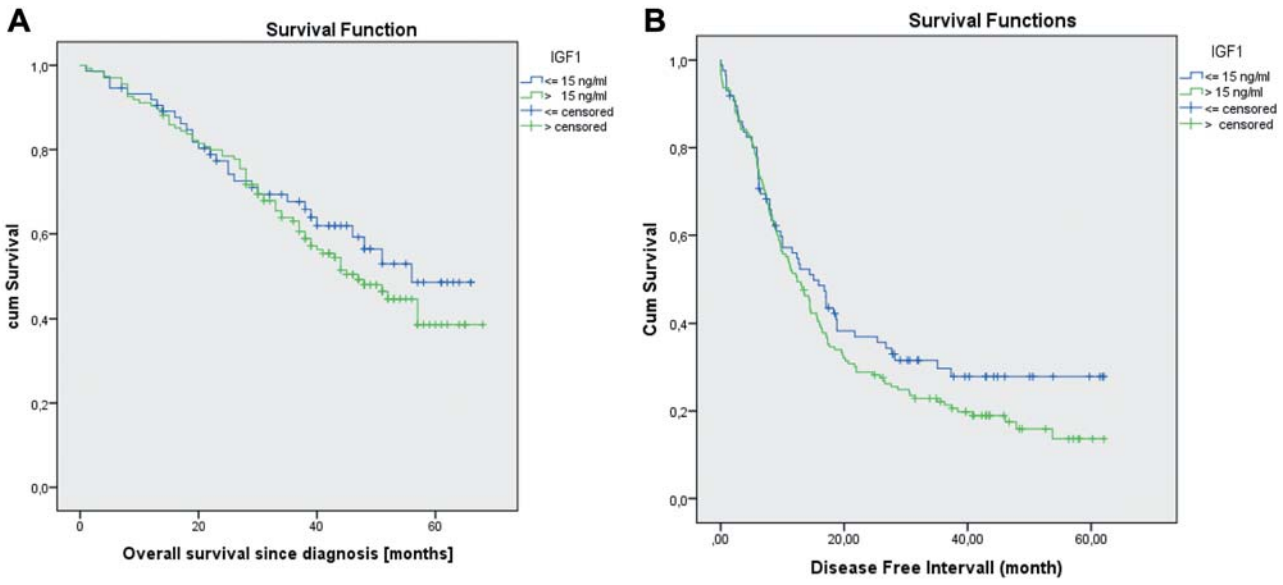

Figure 2. *A: Kaplan-Meier survival curve of IGF-I plasma levels of all patients with EOC did not differ significantly by using a cut-off of 15 ng/ml. Patients with low IGF-I levels had, in opposition to patients with high IGF-I levels, no significance in OS (HR: 1.31; 95%CI: 0.88-1.95, p=0.18). B: Kaplan-Meier curve: Progression-free survival according to IGF-I plasma levels in all patients with EOC (HR: 1.21; 95% CI: 0.88-1.65; p=0.17).*

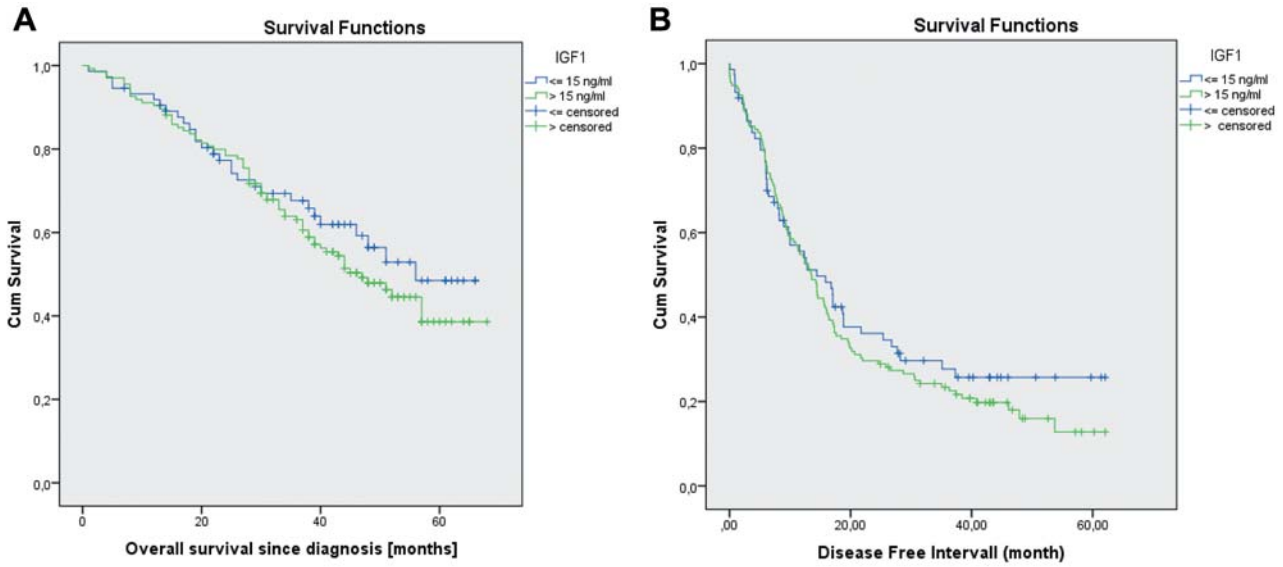

Figure 3. *A: Kaplan-Meier curve for OS according to IGF-I plasma levels of patients with serious EOC did not differ significantly by using a cut-off of 15 ng/ml (HR: 1.22; 95%CI: 0.79-1.88, p=0.37). B: Kaplan-Meier curve for PFS according to IGF-I plasma levels for patients with serious ovarian cancer. (HR: 1.16; 95%CI: 0.83-1.61, p=0.40).*

(27). Although low-grade and high-grade ovarian carcinomas which behave differently are treated according to the same protocol of cytoreductive surgery followed by platinum-based chemotherapy. Therefore, there is an urgent need for new therapy modalities for patients with low-grade ovarian cancer. Further studies in this sub-group of patients are necessary.

We also considered age-specific analyses stratified by age (<55 *vs*. ≥55 years). Three prospective studies have evaluated this association (28-30). Lukanova *et al*. found in a nested case-control study a direct association between IGF-I concentrations in serum and ovarian cancer risk in women younger than 55 years at cancer diagnosis. Similar results are

Table II. *Correlation with clinical prognostic factors.*

IGF-I parameters	All patients with EOC		Patients with serous EOC	
	Median, (IQR)	*p*-Value	Median, (IQR)	*p*-Value
FIGO Stage				
IIA – IIC	17.0 (11.9-19.2)	0,49	18.3 (12.9-25.1)	
IIIA – IV	19.0 (12.5-28.5)		19.0 (12.3-28.7)	
Grading				
Grade I	26.0 (18.8-38.2)	<0.022##	28.8 (18.6-40.4)	<0.054#
Grade II	15.7 (11.4-24.1)		15.5 (11.1-23.8)	
Grade III	19.1 (13.7-28.6)		19.21 (13.8-28.8)	
Grade I and II/ III		<0.047#		
Volume of ascites				
0	19.2 (11.8-31.2)	0.16##	21.0 (13.4-28.8)	0.18##
≤500 ml	20.9 (13.9-27.8)		20.9 (14.0-31.5)	
>500 ml	16.7 (11.9-26.8)		16.9 (11.5-27.1)	
Residual tumor mass				
No residual mass	21.0 (13.4-28.8)	0.10#	21.0 (13.4-28.8)	0.12#
≤0.5 cm	17.9 (15.3-28.4)		19.0 (14.1-28.4)	
>0,5<1 cm	15.7 (9.6-23.3)		14.9 (8.9-21.2)	
1-2 cm	19.1 (11.0-29.6)		26.1 (12.1-32.8)	
>2 cm	17.0 (11.5-26.3)		16.4 (11.2-30.5)	
Response to platinum based chemotherapy				
Platinum sensitive	19.0 (12.7-27.4)	0.61#	19.2 (13.3-28.3)	0.45#
Platinum resistant	17.8 (12.3-30.3)		17.56 (11.0-30.6)	
Age				
<55	21.1 (12.4-30.0)	0.32#	21.4 (12.4-31.1)	0.23#
≥55	17.2 (12.5-27.1)		18.1 (12.2-27.2)	
BMI				
<25	19.1 (12.0-30.4)	0.68#	18.6 (12.3-28.6)	0.89#
≥25	18.5 (13.0-25.7)		19.0 (13.1-28.6)	
	Spearman's rho		Spearman's rho	
BMI	0.01	0.92	<-0.00	0.97
Age	–0.05	0.42	–0.06	0.37
CA 125	–0.13	0.05	–0.15	0.04
Ascites volume	–0.06	0.37	–0.06	0.43

Grading, residual tumor mass and response to adjuvant chemotherapy for one patient was not available. #Mann-Whitney U test; ##Kruskal-Wallis test.

shown by Peeters *et al*. (n=56). This study also described an association between IGF-I concentration in serum and women younger than 55 years. Tworoger *et al*. controversially noted an association between plasma IGF-I and EOC among women diagnosed after 55 years. We enrolled a far larger number of patients, however, our study showed no correlation with age.

The impact of IGF-I in the pathophysiology of ovarian cancer is controversially discussed. In our study, a negative correlation between CA125 and IGF-I levels in plasma was observed in serous ovarian cancer (p=0.04). Similar results are shown by Bese *et al*. in the serum of patients with EOC (31). CA125 is a biomarker well-known to be increased mostly in serous and endometrioid EOC (32), and expressed to a lesser amount in other histological sub-types. CA125 is a so called gold-standard biomarker for monitoring response to platinum-based chemotherapy, especially in high-grade serous ovarian cancers. The correlation of CA125 and IGF-I in serous EOC only, most of them HGSOC, might underline once more the particularities in the tumor biology of HGSOC.

Suggesting that IGF-IR could be used as a potential therapeutic target for EOC treatment, *in vitro* studies have shown that blocking the signal of IGF-IR could inhibit the growth of ovarian cancer cells. IGF-I signaling is predominantly mediated by the IGF-IR (8). Tang *et al*. showed in a pre-clinical study that inhibition of IGF-IR by

antisense oligonucleotide can increase the sensitivity of ovarian cancer cells to cisplatin (33). Another study from Singh *et al*. also found that picropodophyllin, an IGF-IR inhibitor, could reverse the cisplatin-paclitaxel resistance (34). Our study failed to show any correlation between IGF-I expression in plasma and response to platinum-based chemotherapy.

Most published results suggesting a role of IGF-I in the pathogenesis of ovarian cancer were performed in tissue or serum. In our study IGF-I was determined in plasma of patients with primary EOC. So this might be one difference that could explain our results.

In the current study, the results showed no correlations with clinical and pathological prognostic factors for HGSOC patients. IGF-I circulatory levels seem to correlate with the presence of well-differentiated endometrioid and serous EOC. Nevertheless further studies including a larger number of well-differentiated EOC patients are needed.

Conflicts of Interest

The OVCAD project was funded by the European commission as FP6 Specific Targeted Research and Innovation Project with contract No. 018698. The Authors declare no conflicts of interest.

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