Aus der Klinik für Gynäkologie der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Überexpression des Vaskulären Endothelialen Wachstumsfaktor Rezeptor 2 (VEGFR2) bei Langzeitüberlebenden eines fortgeschrittenen serösen Ovarialkarzinoms

Overexpression of Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) in Long-term Survivors of Advanced High-Grade Serous Ovarian Cancer

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Zusammenfassung

Ziel: Die Prognose für Patienten mit hochgradigem serösem Ovarialkarzinom (HGSOC) ist schlecht. Derzeit gibt es keine definierten Biomarker, die zwischen einer guten und einer schlechten Prognose unterscheiden könnten. In dieser Studie soll untersucht werden, ob es Unterschiede bei den Angiogenese-Biomarkern zwischen Langzeitüberlebenden und denen mit schlechter Prognose gibt, wobei Tumorproben aus einer großen Kohorte von Langzeitüberlebenden und passenden Kontrollen verwendet werden.

Methoden: Aus der Tumor Bank Ovarian Cancer wurden Tumorproben von 62 "Langzeitüberlebenden" und 62 passenden Kontrollen identifiziert. Alle Patienten wurden als HGSOC in fortgeschrittenen Stadien diagnostiziert [Federation International of Gynecology and Obstetrics (FIGO) Stadium III-IV]. Patienten, bei denen nach einer primären platinbasierten Chemotherapie für mindestens 5 Jahre (5+ Jahre) kein Rezidiv auftrat, wurden als „Langzeitüberlebende“ definiert, und Patienten, bei denen das erste Rezidiv zwischen 6 Monaten und 3 Jahren auftrat, wurden für die Kontrollen ausgewählt. Langzeit- und Kontrollkohorten wurden nach Alter und postoperativen Tumorresten verglichen. Eine pathologische Untersuchung wurde durchgeführt, um die hochgradige seröse Histologie nachzuweisen. Immunhistochemie wurde an Tumorproben durchgeführt, um die Expression des vaskulären endothelialen Wachstumsfaktors (VEGF) A und des VEGF-Rezeptors 2 (VEGFR2) zu bestimmen. Der Chi-Quadrat-Test oder der Fisher-Test wurde verwendet, um den Unterschied zwischen Langzeit- und Kontrollgruppen bei den Biomarkern festzustellen.

Ergebnisse: Die VEGFA-Expression korrelierte signifikant mit der VEGFR2-Expression ($p < 0{,}0001$, Spearman-Koeffizient 0,347). Obwohl die VEGFA-Expression nicht mit dem

progressionsfreien 5-Jahres-Überleben (PFS) (p = 0,075) zusammenhängt, wurde eine Überexpression von VEGFR2 bei Langzeitüberlebenden häufiger beobachtet (77,4%, 48/62) als bei Kontrollpersonen (51,6%, 30) / 62, p = 0,001). Der Unterschied in VEGFR2 blieb nach Anpassung des FIGO-Stadiums und der VEGFA-Expression signifikant (p = 0,005). In der gesamten Kohorte der analysierten Patienten wurde das höchste Expressionsniveau von VEGFR2 in einer Untergruppe von Patienten mit PFS über 10 Jahre (10+ Jahre) beobachtet (p = 0,001).

Schlussfolgerungen: Unsere Studie zeigte eine signifikante Korrelation zwischen VEGFR2-Überexpression und 5+ Jahre PFS bei HGSOC-Patienten, unabhängig von Alter, FIGO-Stadium, restlicher Tumormasse und VEGFA-Expression.

Abstract

Objective: The prognosis for high-grade serous ovarian cancer (HGSOC) patients is poor. There are no defined biomarkers to identify between good and poor prognosis at the present. This study is to analyze if there are differences in angiogenesis biomarkers between long-term survivors and poor survivors, using tumor samples from a large cohort of long-term survivors and matched controls.

Methods: Tumor samples of 62 “long-term survivors” and 62 matched controls were identified from the Tumor Bank Ovarian Cancer. All patients were diagnosed as HGSOC in advanced stages [Federation International of Gynecology and Obstetrics (FIGO) stage III-IV]. Patients with no relapse for at least 5 years (5_+ years) after primary platinum-based chemotherapy were defined as “long-term survivor”, and patients who had the first relapse occurred between 6 months and 3 years were selected for controls. Long-term and control cohorts were matched by age and post-surgical tumor residuals. A pathological review has been performed in order to prove the high-grade serous histology. Immunohistochemistry was performed on tumor samples to determine the expressions of vascular endothelial growth factor (VEGF) A and VEGF receptor 2 (VEGFR2). Chi-square test or Fisher’s test were used to access the difference in biomarkers between long-term and control groups.

Results: VEGFA expression was found to be significantly correlated with VEGFR2 expression ($p<0.0001$, Spearman coefficient 0.347). Although VEGFA expression was not related to 5_+ years progression-free survival (PFS) ($p=0.075$), VEGFR2 overexpression was seen more frequently in long-term survivors (77.4%, 48/62) than in controls (51.6%, 30/62, $p=0.001$). The difference in VEGFR2 remained significant after adjusting FIGO stage and VEGFA expression ($p=0.005$). Within the whole cohort of analyzed patients, the highest

expression level of VEGFR2 was seen in subgroup of patients with PFS longer than 10 years (10_+ years) (p=0.001).

Conclusion: Our study showed a significant correlation between VEGFR2 overexpression and 5_+ year PFS in HGSOC patients, independent of age, FIGO stage, residual tumor mass and VEGFA expression.

Introduction

Almost 70-80% of ovarian-cancer-associated death caused by high-grade serous ovarian cancer (HGSOC) [1-3]. Although the knowledge of this distinct subtype has been improved in past 10 years, the clinical outcome remains poor. The introduction of a taxane and platinum-combination chemotherapy has dramatically improved the outcomes 20 years ago. Recent phase III clinical trial also proved Olaparibmaintenance treatment significantly extended PFS for 13.6 months in BRCA1/2 mutated and platinum-sensitive patients with relapsed ovarian cancer, compared with placebo. However, comparing with other gynecological malignancies, the long-term survival for HGSOC has only been modestly improved, despite all the refinements to surgery and chemotherapy regimens [1] [4].

Treatment resistance is a crucial factor for the high mortality associated with HGSOC. Despite 80% of the patients will benefit from primary cytoreduction and respond well to platinum-based chemotherapy, almost all of them will experience multiple recurrences and eventually die from a disease that is resistant to platinum chemotherapy [1]. The mechanisms of recurrence are diverse in individuals, including the activation of AKT signaling, the loss of BRCA1 methylation, reversion of germline mutations in BRCA1/2, a shift to a higher stromal content and overexpression of the drug transporter ABCB1[1]. Particularly, some patients with established risk factors such as older age, advanced FIGO stage, serous histology type and tumor residual still achieved long-term survival after completion of chemotherapy. A recent clinical study analyzed 3582 women with epithelial ovarian cancer (EOC) to demonstrate that, nearly one-third of 10+ year survivors was initially diagnosed at advanced stages, including high-grade serous cancer [5]. Thus, a better understanding of particular characters of HGSOC long-term survivors is important to improving the prognosis. However, the factors leading to very good outcome are still not well

understood.

In this context, exploring biomarkers to characterize the long-term survivors after platinum therapy is urgently needed, in order to find more precise therapy to improve poor outcomes. Besides, including long-term survivors into standard treatment regimens may result in patients' overtreatment, whereas into clinical trials may lead to selection-biases and subsequently unreliable results.

Angiogenesis process forms new blood vessels to provide nutrients and oxygen for ovarian tumors to grow [6-8]. This process is considered to be mainly regulated through the vascular endothelial growth factor (VEGF) A and VEGF receptor 2 (VEGFA/VEGFR2) signaling pathway [9]. Several studies showed that ovarian cancer is a highly vascularized tumor with high levels of VEGF, which usually has been correlated with advanced stages and poor clinical outcome [10]. Bevacizumab, the first anti-VEGF therapy approved in OC, has been confirmed to improve the PFS without effect on overall survival. However, long-term survivors were rarely included in most studies on anti-VEGF/VEGFR therapies in primary OC, due to the mean follow-up time being less than 5 years. Thus, angiogenesis characteristics of HGSOC patients with very good prognosis are still unclear.

This study aimed to investigate the correlation between VEGFA/VEGFR2 expressions and long-term PFS, analyzing homogeneous samples from 124 advanced primary HGSOC patients.

Methods and materials

Sample collection

In total of 124 patients with primary advanced HGSOC (FIGO stage III-IV) were selected, including 62 “long-term survivors” and 62 controls. “Long-term survivors” were patients without relapse of the disease within 5 years since the completion of the primary chemotherapy (PFS 5+ years). Controls were defined as primary HGSOC patients in whom the disease recurred within 6 months to 3 years after the primary chemotherapy (PFS 0.5-3 years). The two cohorts were 1:1 matched by age at first diagnosis (up to 5 years younger or older) and macroscopic tumor residual after initial surgery (no residual vs. with residual).

The 124 patients were all treated from 1985 to 2013 in five European high-volume Gynecologic Oncology Centers: Charité Medical University of Berlin, Germany; University-Medical-Center Hamburg-Eppendorf, Germany; Medical University of Innsbruck, Austria; University Hospital Leuven, Belgium; University of Medicine and Pharmacy Iuliu Hatieganu Cluj-Napoca, Romania. Their tumor-tissue samples were collected from the Tumor Bank Ovarian Cancer Consortium (TOC-consortium, www.toc-network.de). All patients underwent cytoreduction and platinum-based chemotherapy following the standard procedure [21]. Staging was performed and defined in accordance with the FIGO-criteria for ovarian cancer (1987) [22]. Tissue samples of ovarian cancer and patients’ clinical data and follow-up information were prospectively collected during the primary cytoreduction within the TOC consortium. The diagnosis of HGSOC was confirmed by central histopathological review, which was also used to ensure the tissue quality and tumor content. Tumor grading was re-evaluated according to World Health Organization (WHO) pathological classification (2014). Tumor samples for the long-term group were retrieved from all 5 centers of TOC-consortium, while the samples in control were only available in Charité Medical University of Berlin.

The inclusion criteria were: 1) diagnosis of primary HGSOC, FIGO stage III-IV; 2) platinum-free survival > 6 months. 3) availability of formalin-fixed, paraffin-embedded ovarian cancer tissue samples 4) available clinico-pathological and follow-up information. Patients without chemotherapy-naïve tumor tissue for immunohistochemistry were all excluded.

PFS was defined as time interval from the end of first chemotherapy to first recurrence of disease. Overall survival (OS) was defined as time interval between diagnosis and patients' death or loss of follow-up. Response to treatment and diagnosis of recurrence was determined according to CA125 and imagistic or clinical evidence of relapse.

The study protocol was approved by each local Ethics Committees (Charité 2004-000034, Innsbruck AN2015-0237 354/4.7, Hamburg EK200313, Leuven MML1022, Cluj 39). The informed consents were given and signed by patients before the surgery and sample collection, regarding using their bio-specimens and clinical-pathological data for research purpose.

Immunohistochemical staining

Hematoxylin and eosin were used to stain sections of chemotherapy naïve ovarian carcinoma tissues. A trained pathologist (SD) marked representative tumor areas for tissue microarrays (TMAs). Consecutively TMAs were constructed as previously described [24]. Per tumor 4 tissue cores of 1.5 mm diameter were used and transferred into a recipient paraffin block. Slides were firstly deparaffinated and rehydrated in a series of descending alcoholic concentration.

Rabbit polyclonal antibodies directed against the VEGFA or VEGFR2 (Abcam, Cambridge, United Kingdom) were purchased for detecting VEGFA and VEGFR2 on tissue samples. For

antigen retrieval, slides were boiled in a pressure cooker for 5 minutes in 0.01 M sodium citrate buffer at pH 9.0 and then put in TBS-buffer for the same time. After blocking the endogenous peroxidase, slides were incubated with the primary antibody, diluted 1:250 for VEGFA and 1:500 for VEGFR2 in antibody diluents solution (Zytomed Systems, Berlin, Germany) for 30 minutes at room temperature. A Dako Real Detection System (Dako, Glostrup, Denmark) was used for visualization, according to a standard protocol provided by the manufacturer using DAB+ Chromogen. Counterstaining was carried out with Haemalaun (Dr Hollborn, Leipzig, Germany). Afterwards the tissue was dehydrated and cover-slipped with Vitroclud (Medizintechnik Langenbrinck, Emmerdingen, Germany).

One experienced pathologist (ETT) and one trained medical student (JG) assessed the immunohistochemical expressions for the two bio-markers. These two persons finished the evaluation separately without knowing any information regarding patient's characteristics and outcome. When they had different results on the same sample, a multi-headed microscope was used to confirm the expression level for both biomarkers. A semi-quantitative immunoreactivity score (IRS) was applied for calculating the immunoreactivity of VEGFA and VEGFR2, as published in previous studies [11, 16, 17, 25]. The IRS (range 0-12) was obtained by multiplying the scores of staining intensities (range 0-3) and staining proportions (range 0-4). The intensities scores were: 0, negative; 1, weak; 2, moderate; 3, strong. And for proportions, scores were calculated as: 0, no cells stained; 1, <10% of cells stained; 2, 11-50% of cells stained; 3, 51-80% of cells stained; 4, >80% of cells stained. Because no established cut-offs for VEGFA/VEGFR2 expression exists, a logistic regression model was then performed with different IRS to conclude a cutoff to dichotomize the expressions for VEGFA or VEGFR2. As a consequence, a IRS of 0-6 was defined as "low expression" and a IRS of 7-12 as "high expression", for both two bio-markers.

Statistical analyses

IBM SPSS Statistics 22.0 (SPSS, Inc., Chicago, IL) was used for statistical analyses. Categorical variables were presented as frequency with percentage. Continuous variables were summarized by means and standard deviations, or median and inter quartile range (IQR) where appropriate. The Shapiro-Wilk test was used to the normal distribution for continuous variables. When continuous variables were normally distributed, a Student t test would be used to examine the intra-group differences. When continuous variables were non-normally distributed, a Mann-Whitney U test would be performed instead. Difference between categorical variables were analyzed by Chi-square test or Fisher's exact where appropriate. Correlation test (Spearman coefficient, 2-tailed) were performed to analyze the correlation between expressions of VEGFA and VEGFR2. Multivariable-logistic regression model was used to evaluate the independent impact of VEGFA and VEGFR2. A two-tailed p value of <0.05 was considered as statistically significant.

Results

Patients' clinico-pathological information are presented in Table 1. No patients had experienced anti-VEGF/VEGFR therapy. There was no difference in FIGO stage between long-term and control patients (Table 1, Figure 1).

Expressions of VEGFA and VEGFR2

Stained VEGFA and VEGFR2 proteins were showed to be localized in the cytoplasm (Figure 2, a-b, e-f). For long-term group and control, the IRS distributions of both biomarkers were presented (Figure 2, c, d, g and h). VEGFR2 expression was significantly correlated with VEGFA expression ($p>0.0001$, Spearman coefficient 0.347). VEGFR2 overexpression ($VEGFR2_{high}$) was most frequently seen in long-term groups (77.4%, 48/62) than in the control (51.6%, 30/62, $p=0.001$), even after adjusting FIGO stage and VEGFA expression in multivariate analysis ($p=0.005$, Figure 3b, Table 2). Although more samples (49/62,79.0%) in long-term group were evaluated as VEGFA overexpression ($VEGFA_{high}$) than in control (40/62, 64.5%), the difference was not statistically significant ($p=0.073$, Figure 3a, Table 2). In addition, overexpression of both two markers were also more frequent in the long-term survivors (62.9% 39/62) than in control (42.0%, 26/62, $p=0.003$, Figure 3c).

VEGFA/VEGFR2 expressions of with-residual and no-residual patients

We investigated VEGFA and VEGFR2 expressions in patients with (n=28) or without residual (n=96). Among both with-residual and no-residual patients, $VEGFR2_{high}$ was more common in long-term samples than in control (no-residual, 75.0% vs 54.2%, $p=0.033$; and with-residual, 85.7% vs 28.6% $p=0.006$, Figure 3,d-g). However, the difference in $VEGFA_{high}$ was not statistically significant, among both no-residual and with-residual subgroups.

VEGFA and VEGFR2 expressions and PFS duration

To investigate the changes of biomarkers by PFS duration, we analyzed the VEGFA and VEGFR2 expression in 4 subgroups: PFS ≥ 120 moths (10+year), PFS=60-119 months (5-10 years), PFS= 13-36 months (1-3 years), and PFS= 6-12 months. There was still no difference in age, FIGO stage and tumor residual among the 4 subgroups. VEGFR2$_{high}$ was seen most frequently (91.3%) in PFS 10+years subgroup. The highest median IRS of 9 was also found in PFS 10+years patients, and the lowest score of 6 was in group of PFS 1-3 years ($p=0.001$). VEGFR2 expression stayed stable in patients with PFS of less than 3 years (no difference between 6-12months and 1-3 years groups, $P=0.211$). However, VEGFR2 expression significantly increased in groups of 5-10 years and 10+years ($p<0.001$). On the contrary, with a stable median IRS of 8 in all subgroups, VEGFA expression was found to be in no relation to PFS duration ($p=0.298$).

Discussion

In our study, we found VEGFR2 overexpression significantly associated with long-term PFS in primary HGSOC patients, independent of age, FIGO stage and tumor residual mass. The correlation between VEGFA expression and long-term survival was not significant, despite VEGFA and VEGFR2 expressions were positively correlated in our analyses.

VEGF has been considered as a promising target for anticancer therapeutics. The most common approaches to inhibit VEGF have been VEGFR-targeted or VEGFA-targeted molecules, which have been applied on both primary and recurrent ovarian cancers [19, 26-28]. Three phase III randomized trials showed a median extension of 4-6 months in PFS after anti-VEGFA (Bevacizumab) or anti-VEGFR treatments (Pazopanib) in primary ovarian cancers [26, 29, 30]. In GOG 0218 trial (NCT00262847), chemotherapy plus Bevacizumab failed to achieve significant improvement on the overall survival compared with chemotherapy alone. However, according to the median PFS of 15 months and the follow-up time of 3 years in these studies, long-term survivors with PFS of 5+ years were rarely included. In our study, VEGFR2 overexpression in long-term survivors of HGSOC was the first time reported. Nevertheless, this finding should be further verified in mechanism studies.

One of strengths in our study is the well-selected population. In previous reports, patients were not matched by established prognostic-factors such as stage, residual status and age. When including these factors into multivariate analyses, the case numbers for HGSOC patients were very small [15, 16, 20] [27, 28, 32]. And the prognostic value of VEGFA or VEGFR2 were much reduced, when adjusted by stage, grade, histology and residual status [11, 15-17]. In addition, earlier researches mostly analyzed a mix population of both platinum-resistant and platinum-sensitive patients [9-11, 16, 17, 19, 25, 31]. Due to the distinct biology

and different prognosis between platinum-resistant and platinum sensitive OC [1-2], in our study only platinum-sensitive patients were included, and all of them are diagnosed as HGSOC in advanced stages. Particularly, we only included patients with advanced stage to avoid bias, as those with early stage usually had much better prognosis [5]. And the influences of established prognostic factors (age and residual disease) were also eliminated through the matching process. Thus, we revealed an independent impact of VEGFR2 on good prognosis.

Besides appropriate patient-selection, long-term follow-up also should be stressed when evaluating the role of VEGFA/VEGFR2. One study demonstrated the correlation between VEGFA and response to chemotherapy was only found within 6 months after treatment. However, the correlation was not significant within 12 months after chemotherapy [18]. A randomized clinical trial showed a similar result that VEGFA inversely impacted on PFS according to the length of treatment [33]. High expression of VEGFA predicted shorter PFS in 2-year treated women but correlated with longer PFS in 5-years treated patients. Similar with these results, we also found that VEGFR2 expression increased significantly among long-term survivors, while remaining a stable level in patients with PFS of 6months-3years. According to our results, long-term follow-up should be considered when accessing the value of VEGFR2 in HGSOC patients.

We also included the present largest sample-size of long-term HGSOC survivors and matched controls, highlighted as another strength of this study. Since 5+ year PFS is rare in patients with advanced HGSOC, our 124 patients are the largest homogeneous population to investigate VEGFR2 and prolonged outcomes. Particularly, centers in our tumor bank consortium are all high-volume centers of ovarian cancer, providing high quality of the tumor debulking and standardized protocols of sample collection.

Similar to our findings, Zhang et al. reported a higher protein levels of VEGFR2 in control tissue compared with human squamous-cell carcinomas, and upregulated VEGFR2 expression when treating tumor-associated endothelial cells by anti-VEGFA monoclonal antibody bevacizumab [34]. The inhibition of tumor angiogenesis was mediated by blockage of VEGF that induced up-regulation of VEGFR2 through the JNK/c-Jun pathway and ubiquitin-proteasome system [34]. This finding might help to explain why VEGFR2 overexpression was significantly more frequent in long-term survivors in our study. The long-term values of anti-VEGFR or anti-VEGFR2 treatments for HGSOC patients may need further validation.

The overexpressed VEGFR2 in our “long-term survivors” might also result from the patient selection, which may include more patients with BRCA1/2 mutations that are strongly related to improved prognosis [35-37]. Our previous study demonstrated that HGSOC patients with somatic BRCA1/2 mutations had higher protein level of VEGF, and their prognosis were better [38]. BRCA mutation carriers were found with higher levels of VEGF mRNA ($p= 0.04$) than the non-carriers in a breast cancer study [39]. Further, an ovarian cancer study revealed an overexpressed VEGF-dependent gene signature (VDGs) in BRCA mutation carriers [40]. VEGF can be down-regulated by Caveolin-1, which can be inhibited by dysfunctional BRCA1 in HGSOC, resulting an increased expression of VEGF [41]. However, there were no available samples to analyze BRCA1/2 mutation in our study. BRCA1/2 mutation should be assessed together with VEGF expression in further investigation on HGSOC survivors.

VEGFR2 binds different members of the VEGF family and affect systems other than angiogenesis. VEGFC and VEGFD can also activate VEGFR2 to assemble lymphatic vessels and capillaries affecting not only primary tumor growth but also lymphatic vessel functionality and tumor cell metastatic spread [42-44]. In our study, VEGFR2 and VEGFA expression were significantly correlated, but only VEGFR2 overexpression has been found

in long-term survivors, indicating other mechanisms might also be involved in VEGFR2 activation. Nevertheless, we only tested VEGFA and VEGFR2 expression as they were major regulation markers of angiogenesis, which was one our limitations. Further investigation and validation on this signaling pathway are therefore needed.

The study has some limitations. The sample size was relatively small, and information of BRCA status and VEGFC/VEGFD staining were not available. Besides, patients experienced anti-VEGF/VEGFR treatments were not included in the study, and the control group were all from single center (Charité Medical University of Berlin).

In conclusion, VEGFR2 overexpression was found to independently correlate with long-term PFS for patient with primary advanced HGSOC. Further clinical trials and basic studies should investigate the long-term value of anti-VEGF therapies. However, our findings may still provide a new insight into understanding tumor pathogenesis of ovarian cancer patients with excellent prognosis.

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Table 1. Clinicopathological information for long-term survivors and control [45].

	N	control (N=62)	Long-term (N=62)	*P* value*
		Mean ± SD		
Age	124	56.6±10.0	57.1±10.2	0.841
		N (%)		
FIGO stage	124			0.260
III		53 (85.5)	57 (91.9)	
IV		9 (14.5)	5 (8.1)	
Tumor residual	124			1.0
No		48 (77.4)	48 (77.4)	
Yes		14 (22.6)	14 (22.6)	
Ascites	115			0.011
No		6 (10.7)	19 (32.2)	
≤500ml		28 (50.0)	27 (45.8)	
> 500ml		22 (39.3)	13 (22.0)	
CA125 before surgery	105			0.318
≤500 U/ml		21 (38.9)	22 (48.9)	
> 500 U/ml		33 (61.1)	33 (51.1)	
Lymph node metastasis	124			0.340
NX		4 (6.5)	9 (14.5)	
N0		17 (27.4)	16 (25.8)	
N1		41 (66.1)	37 (59.7)	
Neoadjuvant chemotherapy	108			0.558
No		55(98.2)	49(94.2)	
Yes		1 (1.8)	3 (5.8)	
Chemotherapy	124			0.001
Taxol+Carboplatin		56 (90.3)	40 (64.5)	
Carboplatin or Cisplatin		0 (0)	2 (3.2)	
Other platinum-based therapy		6 (9.7)	20 (32.3)	

Notes: In analysis of difference between two groups, Mann-Whitney U test was used for continuous variables and Chi-Square test was used for categorical variables. Significant difference: P<0.05. * Difference between control and long-term groups.

Table 2. Difference in VEGFA and VEGFR2 expressions between long-term survivors and control [45].

	N	control (N=62)	Long-term (N=62)	*P**	adjusted *P* [a]
		N (%)			
VEGF A	124				
Low		22 (35.5)	13 (21.0)	0.073	
High		40 (64.5)	49 (79.0)		
VEGF R2	124			0.001	0.005
Low		32 (48.4)	14 (22.6)		
High		30 (51.6)	48 (77.4)		
VEGFA+VEGFR2	124				
Both low		18 (29.0)	4 (6.5)	0.003	
Both high		26 (42.0)	39 (62.9)		
Other[b]		18 (29.0)	19 (30.6)		

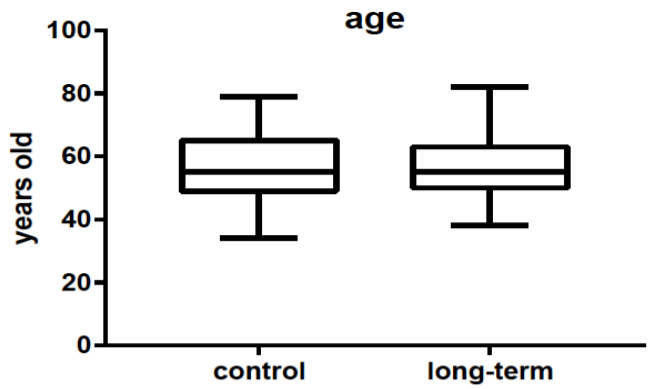
Notes: Chi-Square test was used for categorical variables. Significant difference: P<0.05.

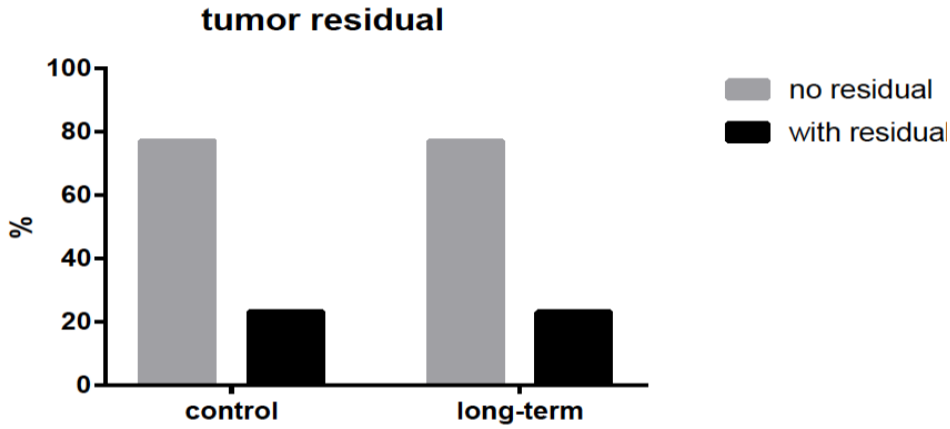
* Difference between control and long-term groups.

a. P-value adjusted by FIGO stage and VEGFA expression in logistic regression model.

b. Either $VEGFA_{high}$ or $VEGFR2_{high}$

Figure 1. No difference in age, tumor residual and FIGO stage between two groups [45].





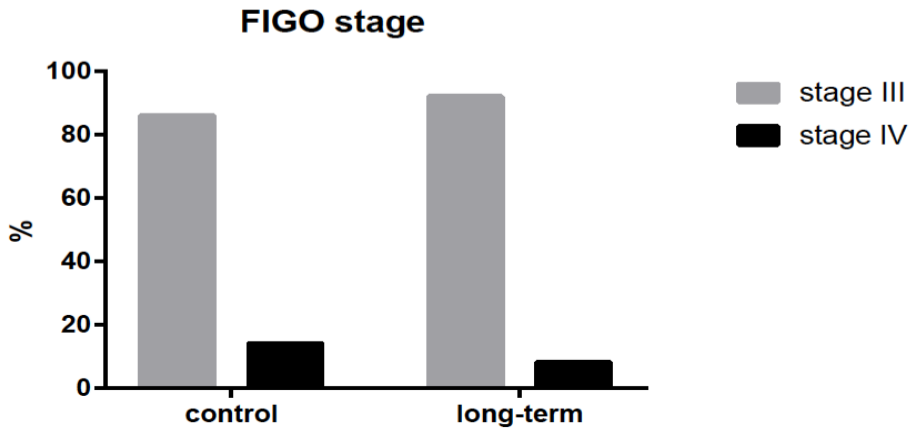


Figure 2. VEGFA and VEGFR2 expression by Immunohistochemistry: weak expressions of VEGFA (2a) and VEGFR2 (2e) in tumor cells; strong expressions of VEGFA (2b) and VEGFR2 (2f) in tumor cells with weak background staining in stroma cells; and IRS distribution of VEGFA (2c-2d) and VEGFR2 (2g-2h) expression in long-term and control groups [45].

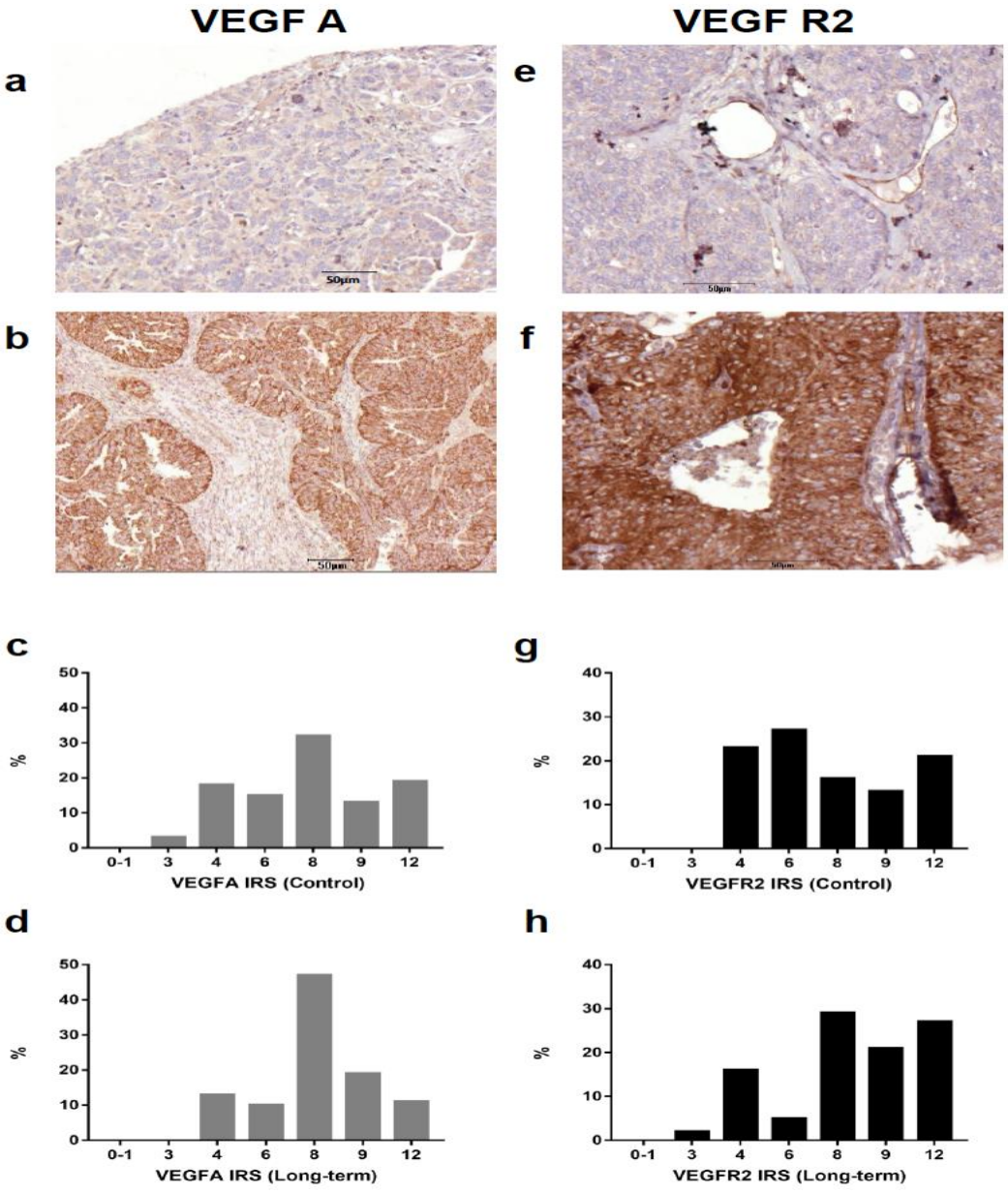


Figure 3. Difference in VEGFA and VEGFR2 expressions between long-term and the control groups: VEGFA (a) and VEGFR2 (b) expression and their co-expression (c) between two groups in all patients (n=124); difference in VEGFA (d) and VEGFR2 (e) expressions between two groups in no-residual patients (n=96); and difference in VEGFA (f) and VEGFR2 (g) expressions between two groups in with-residual patients (n=28) [45].

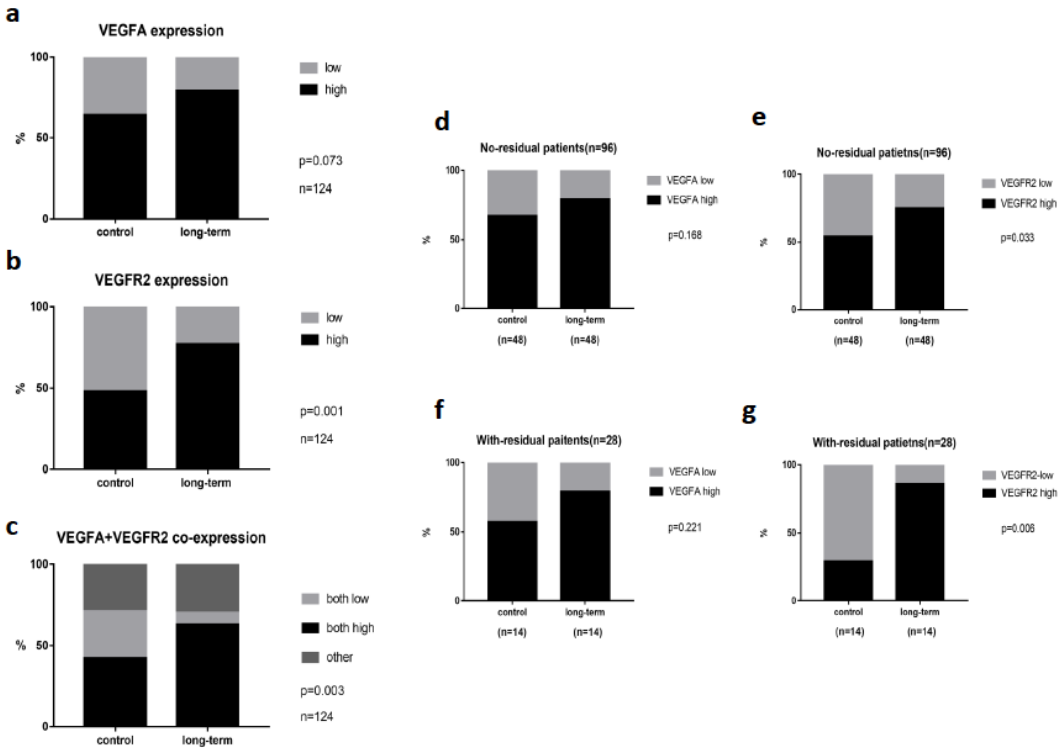
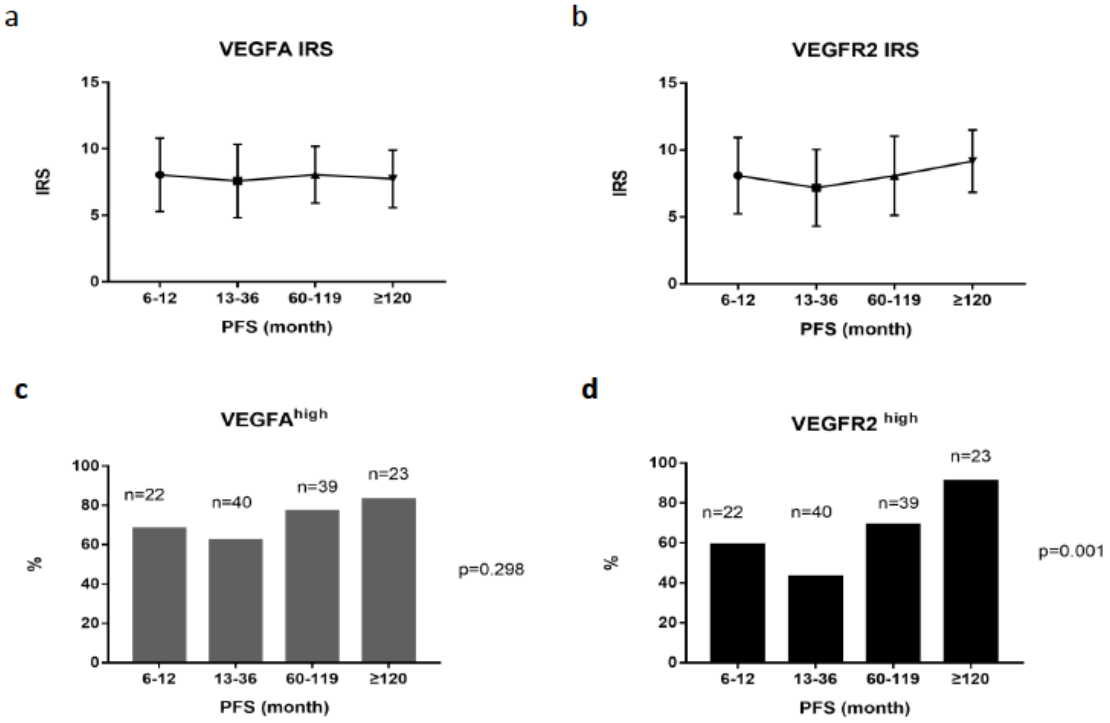


Figure 4. Correlation between VEGFA/VEGFR2 expressions and PFS: IRS of VEGFA (4a) and VEGFR2 (4b), and high expression of VEGFA (4c) and VEGFR2 (4d) in patients with subgroups according to PFS duration [45].



Eidesstattliche Versicherung

„Ich, Jun Guan, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Überexpression des Vaskulären Endothelialen Wachstumsfaktor Rezeptor 2 (VEGFR2) bei Langzeitüberlebenden eines fortgeschrittenen serösen Ovarialkarzinoms“[Overexpression of Vascular endothelial growth factor receptor 2 (VEGFR2) in long-term survivors of advanced high-grade serous ovarian cancer] selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum

Unterschrift

Anteilserklärung an den erfolgten Publikationen

Jun Guan hatte folgenden Anteil an den folgenden Publikationen:

Publikation: **Guan J,** Darb-Esfahani S, Richter R, Taube ET, Ruscito I, Mahner S, Woelber L, Prieske K, Concin N, Vergote I, Van Nieuwenhuysen E, Achimas-Cadariu P, Glajzer J, Woopen H, Stanske M, Kulbe H, Denkert C, Sehouli J, Braicu EI. Vascular endothelial growth factor receptor 2 (VEGFR2) correlates with long-term survival in patients with advanced high-grade serous ovarian cancer (HGSOC): a study from the Tumor Bank Ovarian Cancer (TOC) Consortium. J Cancer Res Clin Oncol. 2019 Apr;145(4):1063-1073. doi: 10.1007/s00432-019-02877-4. (Impact Factor: 3.3)

Beitrag im Einzelnen:

As the independent first author, my contribution in my project and dissertation contains:
- literature research;
- understanding of the current state of the art;
- development of the study concept/protocol;
- screening and matching patients;
- identifying potential prognostic bio-markers for experiment;
- exploring and establishing the protocol for immunohistochemistry of VEGFA/VEGFR2;
- performing all the experiments;
- primary evaluation of the expressions of VEGFA/VEGFR2;
- data analysis and its critical interpretation;
- creation of diagrams and figures;
- writing and revising the manuscript;
- communicating with all the co-authors and revising paper according to their suggestions;
- submitting article to journals till it was accepted and published.

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Unterschrift der Doktorandin

Journal Data Filtered By: **Selected JCR Year: 2017** Selected Editions: SCIE,SSCI
Selected Categories: **"ONCOLOGY"** Selected Category Scheme: WoS
Gesamtanzahl: 222 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	CA-A CANCER JOURNAL FOR CLINICIANS	28,839	244.585	0.066030
2	NATURE REVIEWS CANCER	50,407	42.784	0.079730
3	LANCET ONCOLOGY	44,961	36.418	0.136440
4	JOURNAL OF CLINICAL ONCOLOGY	156,474	26.303	0.285130
5	Nature Reviews Clinical Oncology	8,354	24.653	0.026110
6	Cancer Discovery	11,896	24.373	0.065350
7	CANCER CELL	35,217	22.844	0.096910
8	JAMA Oncology	5,707	20.871	0.027770
9	ANNALS OF ONCOLOGY	38,738	13.926	0.095780
10	JNCI-Journal of the National Cancer Institute	37,933	11.238	0.052550
11	Journal of Thoracic Oncology	15,010	10.336	0.033280
12	CLINICAL CANCER RESEARCH	81,859	10.199	0.132210
13	SEMINARS IN CANCER BIOLOGY	6,330	10.198	0.010740
14	LEUKEMIA	25,265	10.023	0.059580
15	NEURO-ONCOLOGY	10,930	9.384	0.030350
16	Cancer Immunology Research	4,361	9.188	0.021180
17	CANCER RESEARCH	139,291	9.130	0.130190
18	Journal for ImmunoTherapy of Cancer	1,675	8.374	0.007130
19	BIOCHIMICA ET BIOPHYSICA ACTA-REVIEWS ON CANCER	5,276	8.220	0.009300
20	Blood Cancer Journal	1,804	8.125	0.007660
21	CANCER TREATMENT REVIEWS	7,870	8.122	0.015820
22	Molecular Cancer	10,301	7.776	0.017280
23	INTERNATIONAL JOURNAL OF CANCER	51,800	7.360	0.071870
24	Journal of Hematology & Oncology	4,098	7.333	0.009750
25	EUROPEAN JOURNAL OF CANCER	29,883	7.191	0.050170
26	ONCOGENE	66,411	6.854	0.075960
27	CANCER	68,221	6.537	0.074740
28	CANCER LETTERS	29,311	6.491	0.042280
29	Journal of the National Comprehensive Cancer Network	5,143	6.471	0.017530
30	Advances in Cancer Research	2,343	6.422	0.003690
31	JOURNAL OF PATHOLOGY	16,156	6.253	0.024060

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
32	Therapeutic Advances in Medical Oncology	1,020	6.238	0.002650
33	JOURNAL OF EXPERIMENTAL & CLINICAL CANCER RESEARCH	5,661	6.217	0.008740
34	BREAST CANCER RESEARCH	11,022	6.142	0.020000
35	Pigment Cell & Melanoma Research	4,430	6.115	0.007840
36	Clinical Epigenetics	2,172	6.091	0.007720
37	CANCER AND METASTASIS REVIEWS	6,106	6.081	0.006870
38	BRITISH JOURNAL OF CANCER	46,723	5.922	0.065130
39	STEM CELLS	21,694	5.587	0.035680
40	INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS	46,595	5.554	0.055060
41	OncoImmunology	5,963	5.503	0.020500
42	MOLECULAR CANCER THERAPEUTICS	19,211	5.365	0.031690
43	ENDOCRINE-RELATED CANCER	7,114	5.331	0.012410
44	Cancers	3,897	5.326	0.008990
45	ONCOLOGIST	11,433	5.306	0.020480
46	Molecular Oncology	4,529	5.264	0.013160
47	CARCINOGENESIS	21,776	5.072	0.021960
48	Gastric Cancer	4,290	5.045	0.006460
49	NEOPLASIA	6,801	4.994	0.008860
50	SEMINARS IN ONCOLOGY	5,409	4.942	0.007270
52	CELLULAR ONCOLOGY	1,322	4.761	0.002020
53	Oncogenesis	1,348	4.722	0.004480
54	ORAL ONCOLOGY	8,949	4.636	0.013760
55	Cancer Biology & Medicine	816	4.607	0.002330
56	MOLECULAR CANCER RESEARCH	7,834	4.597	0.013490
57	JOURNAL OF ENVIRONMENTAL SCIENCE AND HEALTH PART C-ENVIRONMENTAL CARCINOGENESIS & ECOTOXICOLOGY REVIEWS	895	4.586	0.000810
58	CANCER EPIDEMIOLOGY BIOMARKERS & PREVENTION	19,976	4.554	0.029440
59	GYNECOLOGIC ONCOLOGY	23,652	4.540	0.034310
60	Journal of Oncology	1,573	4.528	0.002410
61	BONE MARROW TRANSPLANTATION	12,506	4.497	0.020810

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
62	CRITICAL REVIEWS IN ONCOLOGY HEMATOLOGY	6,956	4.495	0.012190
63	LUNG CANCER	11,340	4.486	0.019070
64	Frontiers in Oncology	6,599	4.416	0.024250
65	CANCER SCIENCE	11,994	4.372	0.016230
66	CANCER IMMUNOLOGY IMMUNOTHERAPY	7,509	4.225	0.012830
67	Clinical Lung Cancer	2,360	4.204	0.005450
68	PROSTATE CANCER AND PROSTATIC DISEASES	2,022	4.099	0.004890
69	CANCER GENE THERAPY	2,928	4.044	0.003610
70	SEMINARS IN RADIATION ONCOLOGY	2,480	4.027	0.003620
71	Cancer Prevention Research	5,348	4.021	0.011930
72	American Journal of Cancer Research	3,246	3.998	0.008250
73	Cancer Cell International	2,393	3.960	0.004960
74	Targeted Oncology	1,008	3.877	0.002560
75	CANCER CYTOPATHOLOGY	2,544	3.866	0.004380
76	Clinical Colorectal Cancer	1,264	3.861	0.002620
77	ANNALS OF SURGICAL ONCOLOGY	26,592	3.857	0.053440
78	MOLECULAR CARCINOGENESIS	5,244	3.851	0.007630
79	JOURNAL OF IMMUNOTHERAPY	3,093	3.826	0.004590
80	BIODRUGS	1,435	3.825	0.002460
81	Chinese Journal of Cancer	2,161	3.822	0.003960
82	Journal of Cancer Survivorship	2,225	3.713	0.007530
83	Cancer Management and Research	739	3.702	0.001970
84	Molecular Therapy-Oncolytics	254	3.690	0.000830
85	Chinese Journal of Cancer Research	1,128	3.689	0.002420
86	EJSO	7,996	3.688	0.014750
87	CURRENT OPINION IN ONCOLOGY	2,962	3.653	0.005630
88	BREAST CANCER RESEARCH AND TREATMENT	19,709	3.605	0.037840
89	CURRENT TREATMENT OPTIONS IN ONCOLOGY	1,242	3.562	0.002670
90	CANCER JOURNAL	2,899	3.519	0.005390
91	INVESTIGATIONAL NEW DRUGS	4,450	3.502	0.009350
92	Journal of Bone Oncology	280	3.500	0.000860

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
93	ACTA ONCOLOGICA	7,207	3.473	0.013060
94	CLINICAL & EXPERIMENTAL METASTASIS	3,506	3.455	0.004330
94	PSYCHO-ONCOLOGY	10,201	3.455	0.019830
96	INTERNATIONAL JOURNAL OF HYPERTHERMIA	3,350	3.440	0.004040
97	AMERICAN JOURNAL OF CLINICAL ONCOLOGY-CANCER CLINICAL TRIALS	4,247	3.424	0.005470
98	ONCOLOGY-NEW YORK	2,317	3.398	0.003800
99	UROLOGIC ONCOLOGY-SEMINARS AND ORIGINAL INVESTIGATIONS	4,787	3.397	0.013310
100	CANCER BIOLOGY & THERAPY	7,577	3.373	0.008280
101	GENES CHROMOSOMES & CANCER	5,116	3.362	0.006970
102	Journal of Geriatric Oncology	895	3.359	0.003320
103	Journal of Gynecologic Oncology	957	3.340	0.002260
104	INTERNATIONAL JOURNAL OF ONCOLOGY	15,493	3.333	0.022360
105	EXPERIMENTAL CELL RESEARCH	19,420	3.309	0.019610
106	BMC CANCER	24,272	3.288	0.053080
107	JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY	7,401	3.282	0.010800
108	Journal of Cancer	2,710	3.249	0.006580
109	Cancer Research and Treatment	1,873	3.230	0.004340
110	Cancer Medicine	3,123	3.202	0.011220
111	HEMATOLOGICAL ONCOLOGY	1,007	3.193	0.002060
112	Surgical Oncology Clinics of North America	1,139	3.178	0.002150
113	ONCOLOGY RESEARCH	1,573	3.143	0.001570
114	World Journal of Gastrointestinal Oncology	1,069	3.140	0.002520
115	MELANOMA RESEARCH	2,356	3.135	0.004620
116	Current Oncology Reports	1,650	3.122	0.003720
117	HEMATOLOGY-ONCOLOGY CLINICS OF NORTH AMERICA	2,277	3.098	0.004500
118	Translational Oncology	1,791	3.071	0.004510
119	American Journal of Translational Research	3,677	3.061	0.008470
120	JOURNAL OF NEURO-ONCOLOGY	10,858	3.060	0.017330
121	CLINICAL ONCOLOGY	3,372	3.055	0.005910
122	CANCER IMAGING	1,150	3.016	0.002250

The selected publication

Guan J, Darb-Esfahani S, Richter R, Taube ET, Ruscito I, Mahner S, Woelber L, Prieske K, Concin N, Vergote I, Van Nieuwenhuysen E, Achimas-Cadariu P, Glajzer J, Woopen H, Stanske M, Kulbe H, Denkert C, Sehouli J, Braicu EI. **Vascular endothelial growth factor receptor 2 (VEGFR2) correlates with long-term survival in patients with advanced high-grade serous ovarian cancer (HGSOC): a study from the Tumor Bank Ovarian Cancer (TOC) Consortium.** J Cancer Res Clin Oncol. 2019 Apr;145(4):1063-1073. (Impact Factor: 3.3)

https://doi.org/10.1007/s00432-019-02877-4

Curriculum Vitae

My Curriculum Vitae does not appear in the electronic version of my paper for reasons of data protection.

Complete List of Publications

1. **Guan J,** Darb-Esfahani S, Richter R, Taube ET, Ruscito I, Mahner S, Woelber L, Prieske K, Concin N, Vergote I, Van Nieuwenhuysen E, Achimas-Cadariu P, Glajzer J, Woopen H, Stanske M, Kulbe H, Denkert C, Sehouli J, Braicu EI. Vascular endothelial growth factor receptor 2 (VEGFR2) correlates with long-term survival in patients with advanced high-grade serous ovarian cancer (HGSOC): a study from the Tumor Bank Ovarian Cancer (TOC) Consortium. J Cancer Res Clin Oncol. 2019 Apr;145(4):1063-1073. doi: 10.1007/s00432-019-02877-4. (Impact Factor: 3.3)

2. **Guan J**, Xie L, Luo X, Yang B, Zhang H, Zhu Q, Chen X. Estrogen and progesterone double loss predicted poor survivals in. grade I-II endometrial endometrioid adenocarcinoma. J Gynecol Oncol. 2019 Jan;30(1):e13. doi: 10.3802/jgo.2019.30.e13.(Impact Factor:3.3)

3. Nassir M, **Guan J,** Luketina H, Siepmann T, Rohr I, Richter R, Castillo-Tong DC, Zeillinger R, Vergote I, Van Nieuwenhuysen E, Concin N, Marth C, Hall C, Mahner S, Woelber L, Sehouli J, Braicu EI. The role of HE-4 for prediction of recurrence in epithelial ovarian cancer patients-results from the OVCAD study. Tumour Biol. 2016 Mar;37(3):3009-16. doi: 10.1007/s13277-015-4031-9. (Impact Factor:3.6)

4. Zhang Y, Shi T, Yin S, Ma S, Shi D, **Guan J**, Xiang L, Liu Y, Ren Y, Tan D, Zang R. An improved nerve-sparing radical. hysterectomy technique for cervical cancer using the paravesico-vaginal space as a new surgical landmark. Oncotarget. 2017 Jul 5;8(52):90413-90420. doi: 10.18632/oncotarget.19011. (Impact Factor: 5.0)

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