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Prognostic significance of MAPK, Topo IIα and E-cadherin immunoexpression in ovarian serous carcinomas

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Ovarian cancer accounts for only 3% of all cancers in women but is the most lethal gynaecologic malignancy. Low-grade and high-grade ovarian serous carcinomas (OSCs) represent two different diseases with different prognosis, approaches to detection and treatment. We assessed correlation between, MAPK, topoIIα, E-cadherin immunoexpression and clinicopathological features with overall survival (OS) in OSCs. The study included 81 patients undergoing surgery between January 1995 and December 2005.

Formalin fixed paraffin embedded tumour sections were reviewed and examined immunohistochemically using antibodies against MAPK, topoIIα and E-cadherin. The clinicopathological features included: age at surgery, stage according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO), tumour grade, residual disease and vascular invasion. Only ten patients (12.3%) were diagnosed in early FIGO stage of disease. According to morphological criteria, 13.6% of tumor samples were low-grade OSCs and 86.4% were high-grade OSCs. On uninominal analysis, residual disease ($p<0.001$), E-cadherin ($p<0.001$), vascular invasion ($p=0.002$), high-grade morphology ($p=0.025$) and FIGO stage III-IV ($p=0.010$) were related to significantly shorter OS. We found no significant association between, MAPK and topoIIα expression and OS. Multinominal analysis revealed that only residual disease ($p<0.001$) and negative E-cadherin immunoexpression were useful independent predictors of unfavourable clinical outcome and shorter OS.

Key words: serous ovarian carcinoma, MAPK, topoIIα, E-cadherin, survival analysis

Ovarian cancer is a complex neoplastic disease. It accounts for only 3% of all cancers in women but has one of the highest death-to-incidence ratios [1]. Owing to nonspecific symptomatology and the lack of reliable screening tests [2], the majority of patients are diagnosed in advanced clinical stages with a poor long-term outcome [3]. At the same time, new evidence has challenged the hypothesis that "ovarian" cancer arises from the ovary and has directed attention to the distal fallopian tube as an origination for high grade serous carcinomas [4-7]. So, the search for possible prognostic and predictive biomarkers and its potential use in clinical practice remains complex.

Low-grade and high-grade serous carcinomas are basically two different diseases, as indicated by differences in molecular changes, precursor lesions, ways of spread and response to chemotherapy [8, 9].

Low-grade serous carcinomas tend to have a normal karyotype and wild-type TP53 but frequent mutations in BRAF and KRAS genes, the upstream regulators of mitogen-activated protein kinase (MAPK) [10, 11]. MAPK is a serine/threonine protein kinase that responds to multiple extracellular stimuli such as environmental factors, growth factors, cytokines, insulin. RAS/RAF/MEK/MAPK signaling pathway is involved in multiple biological processes, including regulation of cell growth, proliferation, differentiation, apoptosis, angiogenesis, migration and invasion [12, 13]. The MAPK pathway components are known to participate in lung, mammary, colon, liver, gastric, pancreatic and prostatic tumorigenesis, as well as haematological malignancies [14]. Despite in vitro studies of the MAPK signaling pathway [15, 16], little is known about the MAPK immunoexpression in tissue samples of

ovarian cancer and its possible influence in tumor progression and disease outcome.

High-grade serous cancers represent the majority of OSC cases. They are genetically unstable with aggressive biological phenotype, primarily diagnosed as advanced disease. TP53 gene mutation is an early event in the pathogenesis of these tumors and is present in 96-100 % of high-grade cases [6, 7, 17, 18]. The loss of wild type p53 may result in unregulated or inappropriate expression of topoisomerase II alpha (topo IIα) [19, 20]. Topo IIα is a 170-kD ubiquitous ribozyme encoded by Topo IIα gene, localized at chromosome 17q21-22. It is a key enzyme that alters the instantaneous cleavage of double-stranded DNA and the chromosomal topological structure, facilitating subsequent double-strand break relegation. These enzymes play a crucial role in DNA metabolism, including DNA replication, transcription, repair and chromosome condensation/segregation [21, 22]. Topo IIα expression have been investigated in a variety of cancers, including laryngeal carcinomas, breast carcinomas and colorectal carcinomas [22-24], but just a few studies have examined the prognostic role of topoIIα immunoexpression in OSCs [25-29].

E-cadherin, a calcium-dependent transmembrane glycoprotein expressed in most epithelial tissue, constructs a tight junction which connects adjacent cells [30]. E-cadherin, was characterized as a potent tumor suppressor. Down-regulation of E-cadherin leads to mesenchymal morphology and increased cell migration and invasion as well as metastasis. Loss of the E-cadherin leads to activation of known oncogenic signaling pathways, including mitogen-activated protein kinase (MAPK) and rat sarcoma viral oncogene (Ras), as demonstrated by Soto et al, 2008 [31]. Contrary, re-introduction of E-cadherin in cell lines induces to reversal of poorly differentiated carcinoma phenotypes back to a well-differentiated, minimally invasive epithelioid phenotype with well developed cell-cell junctions [32].

Reduced expression of E-cadherin has been correlated with poor survival in various cancers including prostate, gastric, ovarian and inflammatory breast cancer [33-44]

In the current study, we analysed immunoexpression of MAPK, topoIIα and E-cadherin along with conventional clinicopathological factors, to demonstrate its possible prognostic relevance in ovarian serous cancer.

Patients and methods

Tumor samples were obtained from the primary surgery material prior to chemotherapy. Formalin-fixed, paraffin-embedded tumor tissue samples of 81 OSCs were retrieved from the archives of the Department of Pathology, Clinical Hospital Center Split and classified as low-grade or high-grade serous carcinomas according to WHO (2014) [45]. All patients were staged according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO) staging system [46]. Residual tumor size was provided by the primary surgeon and postoperative measurement by image analysis. Patients were classified according to residual tumour in two groups: optimal surgery (no visible postoperative residuals) and suboptimal surgery (visible residuals) [47].

All patients, exept three diagnosed as FIGO Ia, hystological grade 1, were threated with platinum-based chemotherapy. Survival time was calculated as the interval from the day of surgery to the last visit or death from the ovarian cancer-related cause until December 2010.

The Ethical committee for biomedical research of the Clinical Hospital Center Split and School of Medicine approved that this research are in compliance with the Helsinki Declaration (reference number 49-1/06).

Immunohistochemical staining and analysis. All procedures were performed according to the manufacturers' protocols, using the standard streptavidin-biotin-peroxidase technique. Paraffin 4 μm thick tissue sections were placed on silane-coated slides, deparaffinized in xylene, rehydrated in descending concentrations of alcohol and treated in a microwave oven (750 W and 110 °C, 3 times for 5 minutes in a citrate buffer), to facilitate antigen retrieval.

Immunostainings for topoIIα and E-cadherin were performed with monoclonal antibodies to human, topoIIα (DAKO, Glostrup, Denmark, mouse anti-human 7816, at a dilution of 1:75) and E-cadherin (DAKO, Denmark mouse anti-human, clone NCH-38, at a dilutions of 1:100). Immunostaining for MAPK was performed with rabbit polyclonal antibody, pTEpY, which specifically reacts with phosphorylated (active) MAPK (Promega, Madison, WI, V8031, at a dilution of 1:500). All slides were incubated with labeled streptavidin-biotin followed by diaminobenzidin chromogen (DAKO). Mayer's hematoxylin was used for counterstaining.

Staining was evaluated according to the number of cells showing positivity (as a percentage of positive cells) within representative areas of the tumor sample. Nuclear staining for topoIIα was considered as a positive result (Figure 1A, B). Positive reaction for MAPK was defined as discrete localization of the brown chromogen in the nucleus or cytoplasm (Figure 1C, D). Expression of E-cadherin was assessed using a semiquantitative scoring system, ranging from 0, 1+, 2+, and 3+ as follows:

- 0, no immunoreactivity
- 1+, incomplete or dot-like faintly membranous immunoreactivity
- 2+, complete circumferential membranous immunoreactivity of < 10% of tumour cells
- 3+, complete circumferential membranous immunoreactivity of ≥10% of tumour cells

For statistical analysis, based on reports in the published literature, cut-off levels were stratified at 10% for topoIIα [48] and 5% for MAPK [10]. After semiquantitative analysis, E-cadherin expression were summarised into two groups: E-cadherin positive (score 3+, cut off ≥ 10 %) (Figure 2) and E-cadherin negative (scores 0, 1+ and 2+), based on the results from meta-analysis published by Peng et al [49].

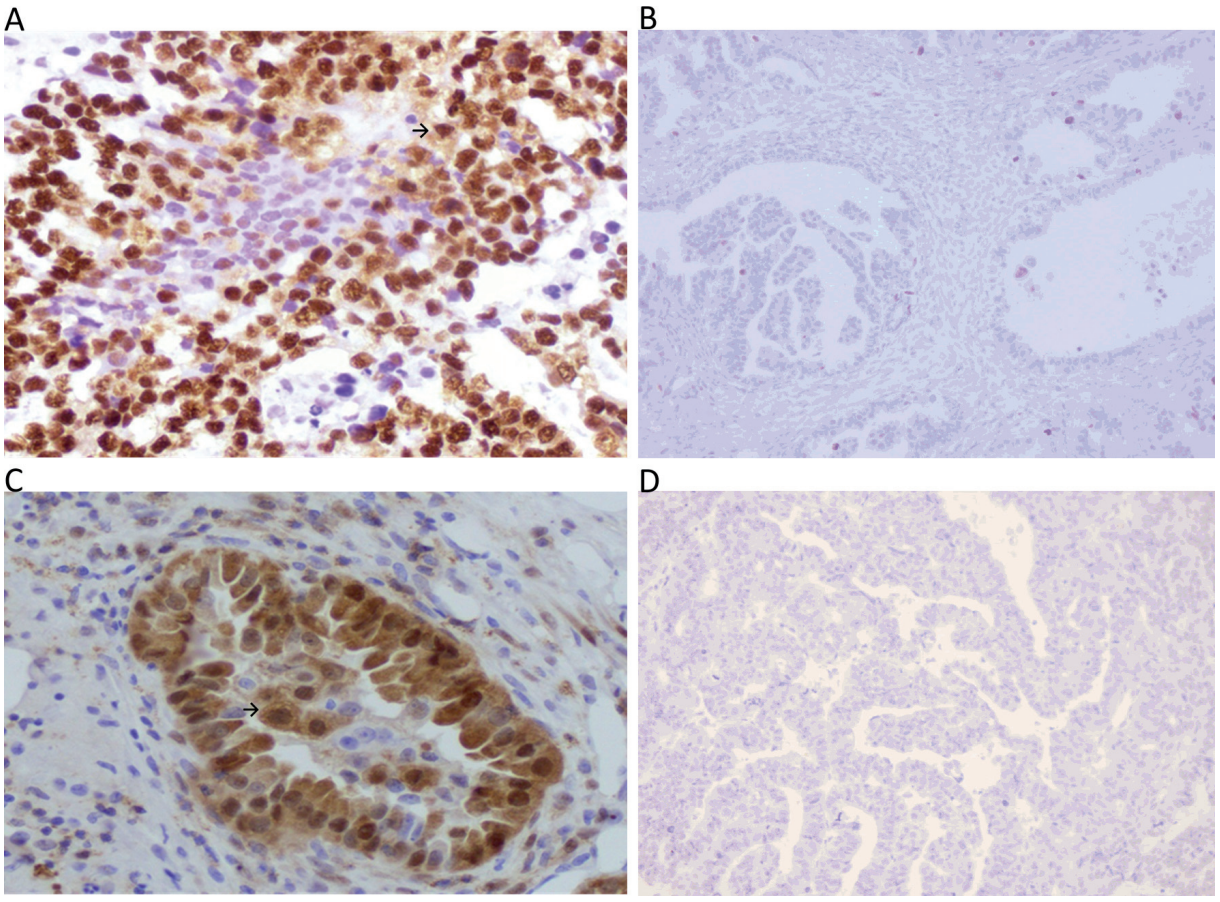

Figure 1. A) positive topoIIα immunoexpression in high grade ovarian serous carcinoma shown as brown nuclear immunoreaction, pointed by arrow (x400); B) negative topoIIα immunoexpression in high grade ovarian serous carcinoma (x400); C) positive MAPK immunoexpression in high grade ovarian serous carcinoma shown as brown nuclear and cytoplasmic immunoreaction, pointed by arrow (x400); D) negative MAPK immunoexpression in high grade ovarian serous carcinoma (x400).

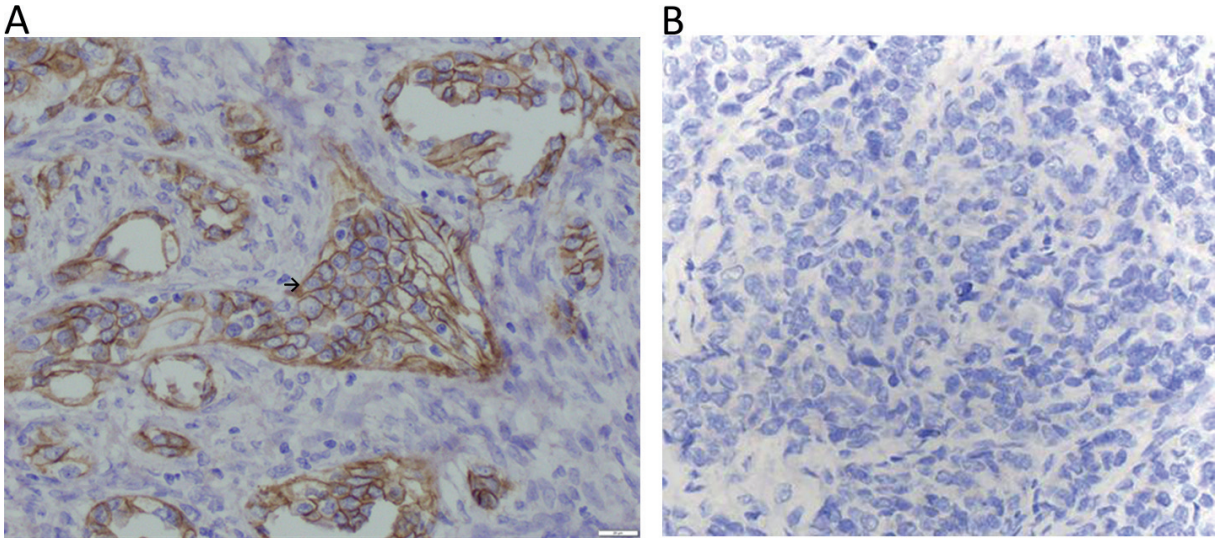

Figure 2. A) positive E-cadherin immunoexpression in high grade ovarian serous carcinoma shown as brown membranous immunoreaction, pointed by arrow (x400); B) negative E-cadherin immunoexpression in high grade ovarian serous carcinoma (x400).

Negative controls for all immunostainings were created by omission of the primary antibody. The evaluation of the immunohistochemical staining was performed independently by two authors with special interest in gynecological pathology.

Statistical analysis. Statistical analysis was carried out using the SPSS version 16.0 software package. All *p* values ≤ 0.05 were considered statistically significant. Survival time was analysed by the Kaplan- Meyer method. Log-rank test was used to assess differences among groups. Uninominal and multinominal Cox proportional hazard regression model was used to examine all factors found to be prognostic of overall survival.

Table 1.Clinicopathological variables of 81 patients with OSCs in relation to disease outcome.

VARIABLES		Alive n=21 (26%)	Deceased n=60 (74%)	TOTAL n=81
Age (years)		55 (40-71)	61.0 (37-89)	60.0 (37-89)
FIGO stage	I-II	10 (47.6)	0 (0)	10 (12.3)
	III-IV	11 (52.4)	60 (100)	71 (87.7)
Grade	low-	5 (45.5)	6 (54.5)	11 (13.6)
	high-	15 (21.4)	55 (78.6)	70 (86.4)
Vascular invasion	Yes	7 (33.3)	44 (73.3)	51 (63.0)
	No	14 (66.7)	16 (26.7)	30 (37.0)
Surgery	Optimal	13 (61.9)	6 (10.3)	19 (24.1)
	Suboptimal	8 (38.1)	52 (89.7)	60 (76.0)
MAPK	pos.	9 (42.9)	10 (16,7)	19 (23.5)
	neg.	12 (57.1)	50 (83.3)	62 (76.5)
topo IIα	pos.	15 (75.0)	46 (75.0)	61 (75.3)
	neg.	5 (25.0)	15 (25.0)	20 (24.7)
E-cadherin	pos.	18 (85.7)	28 (46.7)	46 (56.8)
	neg.	3 (14.1)	32 (53.3)	35 (43.2)

Results

The study included 81 patients undergoing surgery between January 1995 and December 2005. According to morphological criteria, 13.6% of tumor samples were low-grade OSCs and 86.4% were high-grade OSCs. During the follow-up period (until October 2010), 60 (74%) patients deceased from ovarian cancer-related causes. All deceased patients were diagnosed in advanced stage of disease and 55 (78,6%) of them had tumor sample of high-grade OSC. No visible postoperative residuals after initial surgery (optimal surgery) had only six deceased patients (10.3%) (Table 1).

Out of 81 cases, only ten patients (12.3%) were diagnosed in early FIGO stage (I-II) of disease. During the follow-up period, none of the patients diagnosed at the early FIGO clinical stage did not deceased while patients diagnosed in the advanced stage (III-IV) lived an average of 42 months (p = <0.001). Overall survival (OS) was 2,04 times shorter (51 vs 104 months) in patients with high-grade OSCs (p=0.033) and 2,05 times shorter (41 vs 84 months) if vascular invasion was present (p=0.004). Positive E-cadherin expression was associated with statistically better OS (p<0.001). Also, patients younger than 60 years had a better survival compared to older one (p = 0.042) (Table 2). No significant association was found between other variables included in this analysis.

Uninominal analysis was shown significant relationship between OS and optimal surgery (p<0.001), vascular invasion (p=0.002), grade (p=0.025), E-cadherin immunostaining (p<0.001) and FIGO stage (p=0.010). Cox multinominal analysis confirmed that only negative E-cadherin immunoexpression and optimal surgery were both associated with the shorter OS (p<0.001), (Table 3, Figure 3). We found no significant association between MAPK and topoIIα immunoexpression and OS.

Table 2. Log rank analysis of overall survival (OS) according to studied parameters in 81 patients with OSC.

Variables		OS (months)	SE	95% CI	Median	LR	*p*
MAPK	neg.	51	7	38-65	29	0.89	0.345
	pos.	51	10	30-71	21		
topo Iiα	neg.	61	13	35-86	37	0.14	0.707
	pos.	56	8	40-71	26		
E-cadherin	neg.	32	7	18-46	21	14.3	<0.001*
	pos.	76	10	56-97	52		
FIGO stage	I-II	158	0	158-158	158	16.7	<0.001*
	III-IV	43	6	31-55	24		
Grade	low-	104	20	65-144			
	high-	51	7	37-64	25	4.53	0.033*
Vascular invasion	no	84	12	60-107	48	8.44	0.004*
	yes	41	7	27-55	23		
Surgery	optimal	121	13	96-147	158	20	<0.001*
	suboptimal	33	4	25-41	21		
Age (years)	≤60	69	10	50-88	40	4.12	0.042*
	>60	43	9	26-61	19		

Discussion

A growing body of researches indicates that significant differences exist in the clinical and molecular characteristics of low- and high-grade ovarian serous carcinomas. Low-grade OSCs tends to behave in an indolent manner, most likely arises in a stepwise way. Therefore, only women with low-grade OSC (~ 10%) could benefit from the current screening approach to detect disease in early stage and thereby prolong survival. Despite this better starting point and less aggressive clinical course, the survival outcome is still controversial. It seems that women with low-grade OSC exhibit chemotherapy resistance and remain at high risk for recurrence and cancer-related death [50, 51]. According to Fader et al., patients with low-grade serous carcinoma and measurable residual disease had a similar adjusted hazard ratio for death as their high-grade serous carcinoma counterparts with measurable disease [52]. High-grade OSCs represents nearly 90% of all cases of OSCs and is characterized by more aggressive behaviour. Regardless of new treatments, long-term outcomes have not significantly changed in the past 30 years, with the five-year overall survival remaining between 20%– 40% [2, 53].

In our study, 13.6% of tumor samples were low-grade and 86.4% were high-grade OSCs. As we expected, patients with high-grade disease had worse clinicopathological features compared to those of low-grade: advanced FIGO stage, suboptimal cytoreduction, higher mitotic activity and vascular invasion, reflecting the aggressive phenotype of this group of tumors [54].

It seems that the most important prognostic indicator in patients with advanced stage ovarian cancer is the volume of residual disease after surgical debulking [55-57], in addition to tumor grade [58] and FIGO stage of disease [18, 59-67]. As surgical techniques have evolved, what represents optimal cytoreduction has shifted from less than 2 cm to less than 1 cm [68]. The current standard of care for patients with disseminated disease is maximal surgical cytoreduction. Some clinicians have proposed that the true goal of cytoreductive surgery should be to reduce tumor to "no grossly visible disease at the end of the operation" [69-71]. Reducing tumor burden to where no macroscopic tumor is left before chemotherapy is considered optimal cytoreduction [72]. According to our results, optimal cytoreduction was achieved in 63.6% patients with low-grade and only 17.1% patients with high-grade disease. Patients with optimal cytoreduction lived an average of 121 months unlike those with suboptimal cytoreduction that lived an average of 33 months. Optimal surgical cytoreduction was confirmed as independent predictor of favourable clinical outcome (p<0.001).

In addition, we were able to state that patients with high-grade OSCs had 2.04 times shorter OS as compared to those of low-grade (p=0.033). According to the Danish study on 4317 women with OSCs, binary grading system has proved as significant predictor of survival [73]. Although our univariate analysis confirmed the relationship between high-grade OSC and shorter overall survival, this association did not remain significant in multivariable analysis, probably due to small number of low-grade OSC samples.

Table 3. Multinominal Cox regression analysis Forward Stepwise (Wald) for overall survival (OS)

Variables		RR	95% CI	*P*
E-cadherin	neg. pos.	3.3	1.9-5.8	<0.001*
Surgery	optimal suboptimal	5.6	2.3-13.8	<0.001*

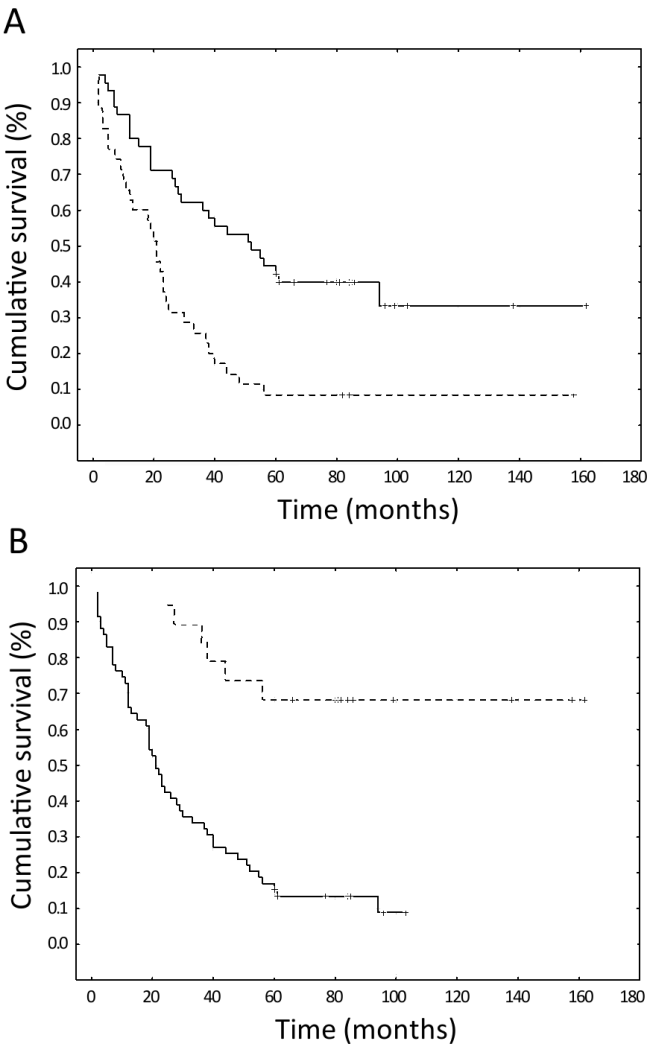

Figure 3. A) Overall survival of 81 patients with ovarian serous carcinoma, stratified by E-cadherin status. The continuous line represents positive E-cadherin expression; the dashed line represents negative E-cadherin expression; Kaplan-Meier analysis (p<0.001). B) Overall survival of 81 patients with ovarian serous carcinoma, stratified by residual tumour. The dashed line represents patients with optimal surgery (no visible postoperative residuals); the continuous line represents patients with suboptimal surgery (visible residuals); Kaplan-Meier analysis (p<0.001).

Also, during the follow-up period, none of the patients diagnosed at the early FIGO clinical stage did not deceased while patients diagnosed in the advanced stage lived an average of 42 months (p=<0.001). Our study is limited by its humble number of early stage patients.

As we have previously shown [54], there were significant differences in the immunoexpression of MAPK and topo IIα between low- and high-grade OSCs. It remains unclear whether these ones, along with E-cadherin, could be used as a prognostic tool.

The literature on MAPK immunoexpression and its prognostic value in OSCs is quite limited. Givant-Horwitz and coworkers presented the first evidence of in vivo involvement of MAPKs in the clinical course of ovarian cancer and the possible effect of chemotherapy on intracellular signalling in this disease [74]. As downstream signaling molecules, MAPK may also be involved in Aryl hydrocarbon receptor (AhR) signaling which plays an important role in inhibiting ovarian cancer cell growth [75, 76]. Correlation between MAPK expression and overall survival in serous ovarian carcinoma was analyzed by Hsu and coworkers [10]. They found that expression of active MAPK alone served as a good survival indicator in the 2-year follow-up but not in the 5-year follow-up. Unfortunately, we could not confirm that positive immunoexpression of MAPK was associated with longer overall survival.

Tumors overexpressing mutant forms of p53 protein theoretically do not have capacity to negatively regulate topo IIα transcriptional activity, so the tumors should possess a high level of topo IIα expression [77]. Immunohistochemical expression of topo IIα in ovarian carcinomas has been demonstrated in several studies [25-27, 48]. According to some authors, topoIIα labeling index (LI) increase with mitotic activity, tumor grade, FIGO stage and indicate poor prognosis [26, 27, 29, 75, 78]. Based on our results, topo IIα immunoexpression was significantly higher in the high-grade as compared to low-grade OSCs but we could not confirm that its immunoexpression was significantly related to overal survivall, with the cut-off level stratified at 10%. Study done by Schindlbeck et al. corresponds to our results [28].

Furthermore, we confirmed that E-cadherin expression is prognostic factor for patient survival. Multivariate analysis for overall survival showed that positive E-cadherin expression (p<0.001) is associated with longer OS. Our results are in agreement with some of the previously published [33-35, 37-39, 43].

Correlation between E-cadherin expression and clinical and pathological features and overall survival in serous ovarian carcinoma FIGO stage III and IV and various tumor grades was analyzed by Bačić and coworkers [43]. Negative expression of E-cadherin was shown to be significant independent predictor of poorer survival. Similarly, Daraï et al. analyzed the expression of E-cadherin in benign, borderline and malignant ovarian tumors [33]. In ovarian carcinoma, patients with negative E-cadherin staining presented with significantly shorter survival. These results suggested that alterations in E-cadherin and N-cadherin expression are differently involved in ovarian carcinogenesis and may have diagnostic and prognostic values. Moreover, Faleiro-Rodrigues and coworkers analyzed E-cadherin expression in 104 patients with various histological type of primary ovarian carcinomas, all FIGO stage and grade. In the multivariate analyses, negative E-cadherin and presence of residual tumor after cytoreductive surgery were independent prognostic factors for survival [34]. Also, Blechschmidt and coworkers analyzed expression of E-cadherin and his repressor Snail immunohistochemistry in primary cancers and their corresponding metastases in 48 patients with various histological type FIGO stage III and IV. They found that primary tumor and their metastases with reduced E-cadherin expression were significantly associated with shorter overall survival [37]. In the Korean study, conducted by Shim et al it was confirmed that reduced E-cadherin expression in 72 consecutive patients with different stages of serous ovarian cancer correlated with poor survival [38]. In line to previous studies, Ho and coworkers analyzed expression of E-cadherin immunohistochemicaly in 61 patients with advanced ovarian clear cell adenocarcinoma FIGO stage IIC-IV [39]. The expected 5-year OS rate with positive E-cadherin immunoexpression was significantly better than negative. The expected 5-year OS rate of those receiving paclitaxel-based chemotherapy was better than non-paclitaxel platinum-based chemotherapy for those with positive E-cadherin expression. The above benefit has not been confirmed in patients with negative E-cadherin expression. Paclitaxel-based chemotherapy and positive E-cadherin immunoexpression were two independent prognostic factors in OS for ovarian clear cell adenocarcinoma [39]. Recently, correlation between immunoexpression of E-cadherin and efficacy of first line platinum-based chemotherapy in 98 patients with advanced-stage high-grade serous ovarian carcinoma has been analysed [44]. Patients with positive E-cadherin expression presented a significantly better response to first line platinum-based chemotherapy and platinum sensitivity. This investigation confirmed that negative E-cadherin expression was associated with poorer OS.

Finally, meta-analysis of 9 studies and 915 patients, confirmed that reduced expression of E-cadherin positivity was associated with poor overall survival. Study population are concentrated in FIGO stages III and IV, therefore the conclusion may be more suitable for advanced ovarian cancer [49]. Also, there are negative results published making this field more complicated [49, 79, 80].

In conclusion, the high mortality rate is attributed to occult development for most ovarian serous cancers and available screening tests that focus on early stage disease will miss aggressive high grade OSC. So, our focus should be minimal volume of disease. According to our results, optimal surgical cytoreduction, defined as "no visible postoperative residuals", was proved as independent predictor of clinical outcome. Therefore, the role of surgery in the treatment of ovarian cancer is crucial in an effort to extend the sur-

vival. We also confirmed prognostic value of E-cadherin in early and advanced FIGO stages of serous ovarian cancers. Negative E-cadherin expression was shown to be significant, independent predictor of poorer OS. Although we could not confirm that immunoexpression of topo IIα and MAPK were associated with longer overall survival, they represent an important target and may be a valuable novel approach for cancer treatment.

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Supplementary Table 1. Distribution of genotypes and alleles of *Axin2* rs2240308 polymorphism

Number	First Author	Type of cancer	Frequencies distribution of genotypes					
			Case			Control		
			CC	CT	TT	CC	CT	TT
1	Rosales-Reynoso	Colorectal cancer	25	109	54	22	59	18
2	Aristizabal-Pachon	Breast cancer	20	58	24	44	55	3
3	Kim	HCC [a]	124	100	18	246	195	41
4	Liu	PTC [b]	27	24	2	17	29	4
5	Liu	Lung cancer	235	216	47	211	255	67
6	Ma	Prostate cancer	61	31	11	39	52	9
7	Mostowska	Ovarian cancer	67	115	46	71	146	65
8	Naghibalhossaini	Colorectal cancer	34	57	19	55	98	26
9	Pinarbasi	Prostate cancer	30	35	19	34	48	18
10	Gunes	Astrocytoma	39	45	16	32	52	16
11	Gunes	Lung cancer	45	47	8	32	52	16
12	Kanzaki	Lung cancer	81	71	8	42	52	15
13	Kanzaki	Colorectal cancer	54	44	15	42	52	15
14	Kanzaki	HNC [c]	25	29	9	42	52	15

[a] hepatocellular carcinoma (HCC)

[b] papillary thyroid carcinoma (PTC)

[c] head and neck cancer (HNC)

Supplementary Table 2. Sensitivity analysis of *Axin2* rs2240308 in dominant model

Study omitted	Cancer type	OR (95%CI)	*P* for heterogeneity	I^2
Rosales-Reynoso	colorectal cancer	0.81 (0.65-1.00)	0.003	60.1%
Aristizabal-Pachon	breast cancer	0.79 (0.70-0.89)	0.093	36.3%
Kim	hepatocellular carcinoma	0.84 (0.66-1.07)	0.000	65.8%
Liu	papillary thyroid carcinoma	0.87 (0.70-1.10)	0.000	65.6%
Liu	lung cancer	0.87 (0.67-1.11)	0.000	65.9%
Ma	prostate cancer	0.89 (0.71-1.11)	0.002	61.7%
Mostowska	ovarian cancer	0.86 (0.67-1.09)	0.000	67.1%
Naghibalhossaini	colorectal cancer	0.84 (0.66-1.07)	0.000	66.7%
Pinarbasi	prostate cancer	0.85 (0.67-1.07)	0.000	67.1%
Gunes	astrocytoma	0.86 (0.68-1.09)	0.000	67.0%
Gunes	lung cancer	0.87 (0.69-1.10)	0.000	65.6%
Kanzaki	lung cancer	0.87 (0.69-1.10)	0.000	65.7%
Kanzaki	colorectal cancer	0.87 (0.68-1.10)	0.000	66.7%
Kanzaki	head and neck cancer	0.84 (0.67-1.07)	0.000	67.0%