Original Research

The prognostic significance and immuno-expression of survivin, mutant p_{53} and bcl-2 in 92 cases of epithelial ovarian cancer

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Summary

Background: Survivin is a member of the inhibitors of apoptosis protein family, commonly detected in human cancers and fetal tissue, with the ability to regulate programmed cell death and cell division. Aim of this study is to investigate the immuno-expression of survivin and its correlation with other anti-apoptotic markers (mutant p_{53} and bcl-2) in human ovarian cancer and assess the prognostic significance and possible therapeutic role of this protein in the future. *Materials and Methods:* Ninety-two cases of primary epithelial ovarian cancer over a 10-year period were included in the study. Sixty-six cases were diagnosed with serous ovarian cancer and twenty-six with endometrioid. All cases were fixed in formalin and paraffin-embedded standard techniques and processed by an immunostain method, in order to assess the survivin-positive cases and their prevalence in nucleus or cytoplasm. *Results:* Survivin cytoplasmic immuno-expression is associated with more advanced stage and grade of the ovarian disease. Nuclear survivin was more pronounced in tumors with better prognosis. Mutant p_{53} and bcl-2 were also positively co-expressed and associated with poor survival rate in all cases of serous ovarian carcinoma. Neither survivin nor bcl-2 were expressed in any case of endometrioid ovarian cancer. *Conclusion:* Survivin can play a key role as a potential future tumor marker to determine prognosis and predict response to various therapies.

Key words: Survivin; p_{53}; Bcl-2; Prognosis; Ovary; Cancer.

Introduction

Survivin is a 16.5 kDa multifunctional protein and member of the inhibitors of apoptosis protein (IAP) family [1-8]. Functionally, survivin has the ability to regulate programmed cell death and cell division [9-13]. It is commonly detected in most human cancers and fetal tissue, but not in normal differentiated adult tissues [14-18]. Overexpression of survivin has been an important diagnostic tumor marker associated with poor prognosis and aggressiveness [19].

Apoptosis is regulated mainly via an effect on caspase-9, which is activated via intrinsic and extrinsic pathways. Survivin possesses a single BIR domain but lacks the RING finger domain which is present in some other IAP members [20, 21]. The BIR domain contains amino acid residues and has an anti-apoptotic role [22].

The intrinsic pathway consists on the association between survivin and XIAP which is another member of the IAPs [23, 24]. The complex promotes stability and synergistically inhibition of caspase-9, which is a promoter of apoptosis [25]. The extrinsic pathway is activated by binding to and suppressing SMAC. SMAC is a promoter of apoptosis by complexing with specific IAPs. When survivin attaches to SMAC, it reduces the antagonism of SMAC for IAPs [26, 27]. Therefore, the free IAP can then interact with caspases and block apoptosis [28-31].

There is also evidence that survivin has a key role in cellular division promoting mitosis. It is well known the interaction between survivin and the microtubules of the mitotic spindle apparatus during the G2/M phase of cell cycle [32, 33]. Alternatively, survivin may accomplish this by association with aurora B and INCENP, formulating the chromosomal passenger complex [34]. Disruption of this interaction results in increased caspase-3 activity with loss of the anti-apoptotic role of survivin [35-43].

Our aim is to investigate the distribution pattern of survivin immuno-expression in human ovarian cancer and its correlation with other anti-apoptotic markers (mutant p_{53} and bcl-2) and evaluate the prognostic significance and possible therapeutic role that this protein may play in the future.

Materials and Methods

Ninety-two cases of primary epithelial ovarian cancer were included in our study. All patients were admitted in the 2nd Department of Obstetrics & Gynaecology, Aretaieio University Hospital of Athens, during a 10-year period (2001-2010). Sixty-six cases were diagnosed postoperatively with serous ovarian carcinomas and twenty-six

with endometrioid ovarian carcinomas. The average patient age was 60 years (27-88 years) and the tumor size was between 8-10cm. The localization was unilateral in seventy-four cases without any prevalence between the right and the left ovary. All patients gave informed consent according to Ethics-approved protocols and the research was granted permission by the Aretaieio Hospital Research and Ethics Committee (n.18-05/2013).

Tumor tissues were initially fixed in formalin and paraffin-embedded following the standard processes for histopathology evaluation. Additional sections from archival retrieved paraffin-embedded tumors were obtained in order to assess the immuno-expression of survivin, mutant p_{53} and bcl-2. In particular, a semi-automatic immuno-histochemistry method (IHC) was used with polyclonal survivin (1:80), monoclonal bcl-2 (1:160) and monoclonal p_{53} (1:120) in accordance to the manufacturer guidance.

The evaluation of the immunostain was performed using a semi-quantitative method by two observers and was recorded as 0-3+. It was considered as negative (-) when < 10% of cells were positive for immunostain, positive (1+) when > 10% of the cells were positive, and strongly positive (2+) when > 30% of the cells showed immunoreaction. The location of the stain in the cytoplasm or in the nucleus was recorded separately.

Statistical analysis: Statistical analysis of the Fisher's exact test or Chi-square test (x^2) was used to assess the survivin-positive cases according to clinic-pathological, surgical and biological characteristics. In order to measure the significance of our result we converted the values from Chi-square to a p-value, in order to understand whether our result can reject the null hypothesis or not. A small p-value typically < 0.05 indicates a strong evidence against the null hypothesis. The software package used was IBM SPPS v15.

Results

The immuno-expression of survivin was evaluated separately in the nucleus and/or the cytoplasm and the findings were correlated with grade and stage of the disease and compared with the other anti-apoptotic markers mutant p_{53} and bcl-2.

In the study were included sixty-six cases of serous ovarian carcinomas (group A) and twenty-six cases of endometrioid ovarian carcinomas (group B). All cases were classified according FIGO ovarian cancer classification.

Survivin in group A was expressed in 12 cases of Grade 1 (75%), of which 11 were classified as stage I and 1 as stage II. From these 11 cases of stage I, survivin was distributed in the nucleus in 8 cases (73%) (Figure 1). The remaining cases of positive survivin immunoreaction of stage I (27%) and the only one case of stage II (100%) showed cytoplasmic location. Stain intensity was high for the one single case of stage II. Furthermore, survivin was detected in 20 cases of Grade II (69%), of which 17 were marked as stage I and 3 as stage II. From these 17 cases of stage I, survivin

was expressed in the nucleus in only 2 cases (12%). In the rest 15 cases it was present mainly in the cytoplasm (82%), while in 1 case (6%) was identified in both nucleus and cytoplasm. Cytoplasmic expression was also confirmed in all 3 cases of stage II (100%).
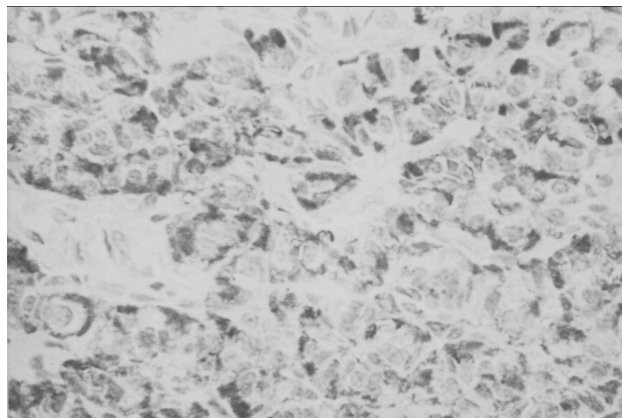

Figure 1. — Nuclear immuno-expression of survivin in serous ovarian cancer (immunostain $\times$ 120)

The expression of survivin was significantly raised in all cases of Grade 3. In particular, it was detected in 18 cases (86%). From those 18 cases, 11 were classified as stage I and 7 as stage II. Nuclear survivin distribution was observed in a single case (9%) of stage I. In the rest of the cases, cytoplasmic localization was more pronounced, in 91% of stage I and 100% of stage II. Stain positivity was also marked high in this group with 50% of the patients of stage II scoring 2+ and the rest scoring 3+ on a three-tiered immunostain system (Figure 2). They also studied the expression of the other anti-apoptotic markers bcl-2 and mutant p_{53} in accordance with grade and stage of the disease.
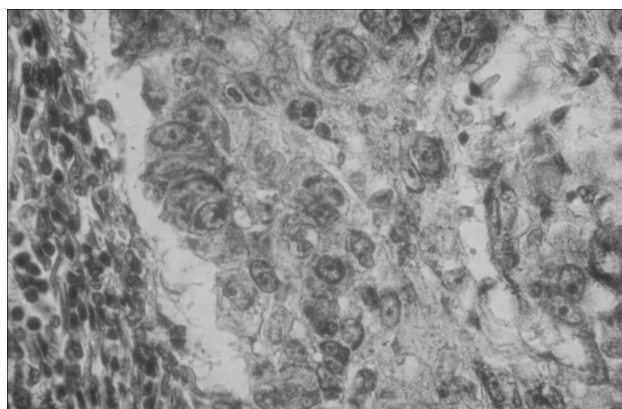

Figure 2. — Cytoplasmic immuno-expression of survivin in serous ovarian cancer (immunostain $\times$ 200)

Among the 16 cases of Grade 1, bcl-2 and mutant p_{53} were only identified in one case each (6%). In this single

Table 1. — *Pearson correlation coefficient in serous ovarian cancer.*

		GRADE	STAGE	NUCLEAR SURVIVIN	CELLULARSURVIVIN	p_{53}	BCL-2	SURVIVIN
AGE	Pearson Correlation	-0.038	0.082	-0.072	0.285*	-0.073	0.294*	0.309*
	Sig. (2-tailed)	0.761	0.511	0.566	0.02	0.56	0.016	0.012
	N	66	66	66	66	66	66	66
GRADE	Pearson Correlation	1	0.283*	-0.408**	0.538**	0.633**	0.359**	0.429**
	Sig. (2-tailed)		0.021	0.001	0	0	0.003	0
	N	66	66	66	66	66	66	66
STAGE	Pearson Correlation	0.283*	1	-0.401**	0.447**	0.212	0.379**	0.350**
	Sig. (2-tailed)	0.021		0.001	0	0.088	0.002	0.004
	N	66	66	66	66	66	66	66
p53	Pearson Correlation	0.633**	0.212	-0.387**	0.382**	1	0.326**	0.287*
	Sig. (2-tailed)	0	0.088	0.001	0.002		0.008	0.019
	N	66	66	66	66	66	66	66
BCL-2	Pearson Correlation	0.359**	0.379**	-0.292*	0.634**	0.326**	1	0.601**
	Sig. (2-tailed)	0.003	0.002	0.017	0	0.008		0
	N	66	66	66	66	66	66	66

case the disease was of stage II and co-expression with cellular survivin was noticed only with bcl-2.

Bcl-2 and mutant p_{53} were positively expressed in six cases each (21%) of those characterized as Grade 2, 4 cases of stage I and 2 cases of stage II. Co-expression of cellular survivin with bcl-2 was noticed in 5 out of 6 cases, while the co-expression of cellular survivin with mutant p_{53} was identified in 4 out of 6 cases.

The prevalence of these anti-apoptotic markers instead was higher in all cases of Grade 3 of the disease. In particular, bcl-2 was expressed in 10 cases (48%) and mutant p_{53} in 18 cases (86%). 50% of the cases were stage I and the rest was stage II. Cellular survivin was co-expressed simultaneously with bcl-2 in all 10 cases and with mutant p_{53} in 15 cases (Figure 3).

Survivin and bcl-2 were not expressed in any of the twenty-six cases included in the group B of patients, who were diagnosed with endometrioid ovarian cancer.

However, the mutant p_{53} was positively identified in both Grade 2 and 3 of the disease, but not in any of the cases of Grade 1. In particular, it was found in 2 cases of Grade 2 (40%) and in 6 cases of Grade 3 (75%). All cases were classified as stage I (Figure 4).

For statistical analysis the chi-square test was used and a significant correlation of survivin immuno-expression with both grade ($p < 0.0001$) and stage ($p = 0.002$) observed in all the cases of serous ovarian carcinoma. Moreover, the distribution of survivin in the nucleus and cytoplasm was more indicative for the grade ($p = 0.002$ and $p < 0.0001$) and less for the stage ($p = 0.021$ and $p = 0.016$). It is remarkable that the immuno-expression of cytoplasmic survivin was in linear equation with both grade and stage ($p < 0.0001$), but nuclear immuno-expression was in reverse correlation ($p = 0.001$) with grade and stage.

The presence of mutant p_{53} was highly depending to the grade ($p < 0.0001$) and less to the stage ($p = 0.045$). On the other hand, bcl-2 was correlated to the stage ($p = 0.008$) and less to the grade ($p = 0.012$) (Table 1). In all cases of endometrioid ovarian cancer, the mutant p_{53}, which was the only marker expressed in our study, showed a statistical significant correlation only with the tumor grade ($p = 0.0003$), but not with the stage ($p = 0.0725$) of the disease (Table 2).

Discussion

A significant survivin immuno-expression has been demonstrated in ovarian carcinomas [44, 45]. The percentage of survivin-positive cases varies from 75% in serous ovarian carcinomas of grade 1 to more than 85% in those with grade 3, same as with the study of Ferrandina *et al.* [46] which was based on 110 cases. In particular, survivin was expressed up to 100% in clinical cases of stage II and grade 3 of the disease.

In This study a significant correlation between nuclear and cytoplasmic localization of survivin was observed. In fact, high nuclear survivin immuno-expression was observed in the early stages of the disease, a fact that proposes a better chance of performing tumor cytoreduction, which also represents one of the major factors of response to chemotherapy and favorable prognosis. In contrast, cytoplasmic survivin immuno-expression was associated with more advanced stage and grade of the disease and therefore signifies a poor prognosis.

The percentage of nuclear survivin drops from 73 to 12% in ovarian carcinomas of grade 3, where the correspondent percentage of cytoplasmic survivin rises from 27 to 90%. However, Cohen *et al.* [47] showed in their study a correlation between nuclear survivin expression and poor prognostic markers. Ferrandina *et al.* [46] failed to find any relationship between cytoplasmic and nuclear survivin positivity rate with any of the parameters examined. The survivin staining status did not seem to be helpful in the prognosis of ovarian cancer in their study, which is a contradictory finding comparing to our study [47-49]. Yoshida *et*
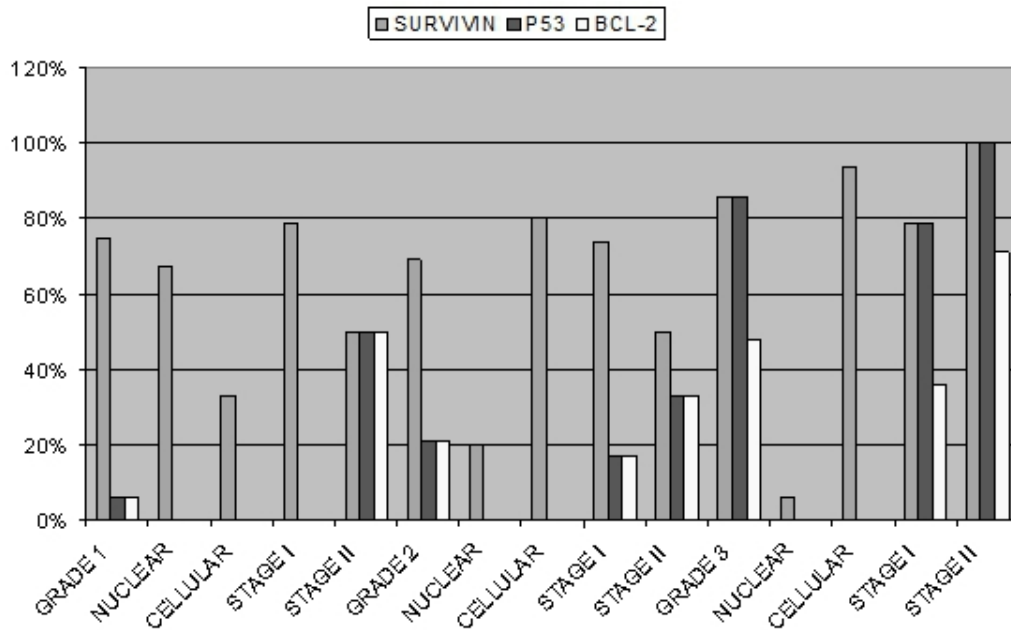
Figure 3. — Expression of survivin, p$_{53}$ and bcl-2 according to grade and stage in serous ovarian cancer.
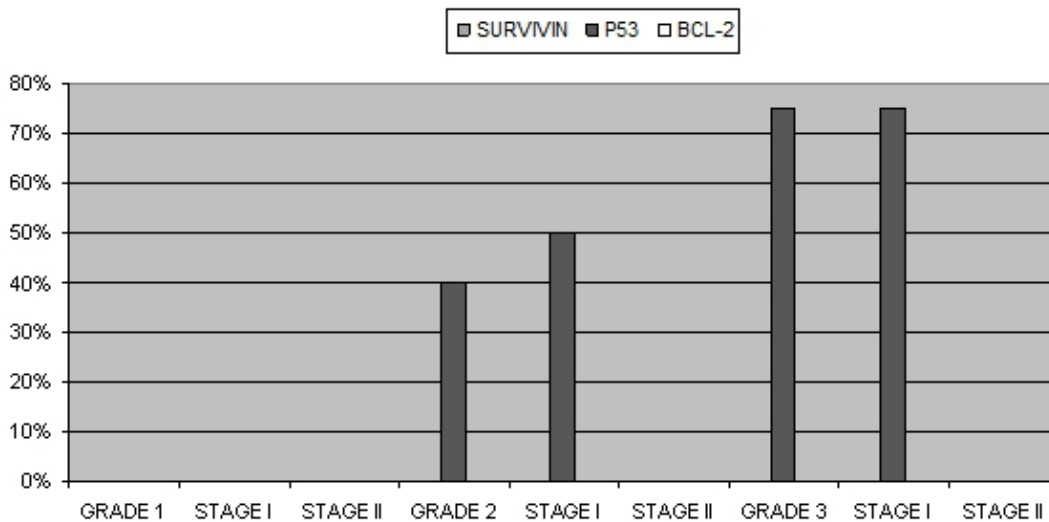

Figure 4. — Expression of survivin, p53 and bcl-2 according to grade and stage in endometrioid ovarian cancer.

al. [50], as well as Takai *et al.* [51] showed a significantly shorter disease-free survival period with a marked association with histological grade and stage when survivin was predominantly nuclear. Furthermore, in our study a significant correlation was observed in serous ovarian carcinomas between the other anti-apoptotic markers bcl-2 and mutant *p53* with grade and stage of the disease. Both have been identified sporadically in early stages, but their immuno-expression has been more pronounced in poorly differentiated stages reaching almost 86% for mutant *p53* and 48% for bcl-2. This finding is in contrast to a previous study of Neil *et al.* [52] where the mutant *p53* was a good prognos-

tic factor as it was found only in early stages of the ovarian carcinomas. Moreover, co-expression of these markers with survivin was identified in almost all cases especially in those of advanced disease. We noticed that co-expression of survivin with bcl-2 was in all 10 cases of grade 3 which we included in our study, where co-expression of survivin and mutant *p53* was detected in 15 out of 18 cases respectively. Same results to us were confirmed in other studies, including Mano *et al.* [53] who showed significantly poorer survival rate in patients with stage III-IV ovarian serous carcinomas expressing bcl-2 [54, 55]. Ferrandina *et al.* [46] also showed a high percentage of co-expression of survivin with

Table 2. — *Pearson correlation coefficient in endometrioid ovarian cancer.*

		GRADE
	Pearson Correlation	0.9993
P_{53}	Sig. (2-tailed)	0.0245
	N	26

both bcl-2 and mutant p_{53}. Finally, we failed to identify any expression of survivin or bcl-2 in any of the endometrioid cases included to our study. Instead, Cohen *et al.* [47] has managed to identify survivin in both cases of endometrioid carcinoma same as Ferrandina *et al.* [46] where survivin was expressed up to 91%. The only marker expressed in our study was the mutant p_{53}, which was found gradually more prominent when the disease was advanced. In particular, it was detectable in six cases out of eight of grade 3, but it was undetectable in all cases of grade 1.

Conclusion

Survivin has emerged as a useful and unique predictive tumor marker because it has the potential to trigger apoptosis and cell division [56-58]. There seems to be a strong correlation between tumor progression and resistance to chemotherapy with both survivin and mutant p_{53} expression and less with bcl-2 [59-61]. The immunohistochemical assessment of nuclear and cytoplasmic variant of survivin seems to be a helpful tool in regard of prognostic characterization of ovarian carcinoma, where the cytoplasmic form is associated with an unfavorable prognosis. Therefore, blocking survivin function by various molecular or immunotherapeutic agents in clinical trials in the future is emerging as a promising therapeutic strategy in cancer [62-67].

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

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