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RESEARCH

Weapons Ovarian Epithelial Tumors May Use in Immune Escape: An Immunohistochemical Correlational Study

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Abstract Investigate FasL and survivin expression in a series of primary ovarian surface epithelial tumors, correlate their expression with each other, and characterize the presence of CD3+ T-lymphocytes in studied tumors and determine whether their presence correlates with FasL or survivin expression in malignant cases. FasL and survivin expression was assessed in 54 ovarian epithelial tumors. The results were compared between different tumor types and grades. Correlation between both markers' expression in all studied tumors was done. Either marker's expression was compared to the mean CD3+ T-lymphocytes per HPF in the studied malignant tumors. Either FasL or survivin expression was significantly higher in malignant versus benign ovarian epithelial tumors ($p<0.001$ for both) and both markers were strongly correlated to each other ($r=0.877$ & $p<0.001$). Malignant tumors show significantly higher mean CD3+ T-lymphocytes than benign and borderline tumors. The mean CD3+ T-lymphocytes decrease significantly on increasing malignant tumor grade ($p=0.019$) and expression of both FasL and survivin ($r=-0.729$, -0.582, respectively & $p<0.001$ for both). The higher expression of FasL and survivin in malignant as compared to benign ovarian tumors suggest that they have a significant role in pathogenesis of ovarian carcinoma. Both markers are strongly correlated to each other and may contribute to immune escape of ovarian carcinoma as their higher expression is associated with decreased number of CD3+T-lymphocytes.

Keywords FasL · Survivin · CD3+ T-lymphocytes · Ovarian epithelial tumors · Immune escape

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Introduction

Tumor escape is a major obstacle to successful immunotherapy [1]. Despite compelling evidence that immunogenic tumors can be rejected by the immune system under optimum conditions, a large number of tumors continue to grow and evade immune mediated elimination [2]. During carcinogenesis, tumors develop multiple mechanisms to evade the host immune response. One of such mechanisms is upregulation of Fas ligand (FasL/CD95L) expression. FasL was first identified in 1993 as a 40 kDa type II transmembrane protein belonging to the tumor necrosis factor (TNF) family [3]. FasL interacts with its receptor, Fas (CD95/APO-1), and can trigger a cascade of subcellular events culminating in the apoptotic cell death of sensitive cells [4]. This interaction is thought to play an important role in promoting immune privilege in both normal and malignant tissues [5]. Therefore, it has been proposed that FasL-expressing tumor cells may induce Fas-mediated apoptosis in tumor infiltrating lymphocytes (TILs) [6, 7]. However, the role of FasL in tumor immune evasion and immune privilege is controversial [8, 9].

Several proteins that inhibit Fas-mediated apoptotic signaling have been identified, including the bcl −2 family and the inhibitor-of-apoptosis (IAP) family [10, 11]. Survivin, a member of the latter family, has been shown to block Fas-mediated apoptosis through direct inhibition of caspase-3 and −7, which act as terminal effectors in the apoptotic protease cascade [12, 13].

Survivin protein is commonly detected in fetal tissues but not in normal adult tissues, while being overexpressed in human cancer, thus suggesting the contribution of survivin gene reactivation in carcinogenesis [14]. Several studies have attempted to delineate the clinical role of survivin expression in epithelial ovarian cancer but no

definitive conclusions could be drawn probably because of the size and/or heterogeneity of the population series, incompleteness of clinical information as well as the use of different antibodies and methods of score of survivin expression [15–19].

Epithelial ovarian cancer accounts for the majority of ovarian malignancies. It is estimated to be the third most common malignancy of the female genital tract and the first leading cause of death from gynecological cancer in the US in 2008 [20]. The mechanisms by which ovarian tumor cells express FasL are not well defined, and whether survivin is involved in these pathways is unclear. So, the aims of this study were to 1) investigate the expression of FasL and survivin in a series of primary ovarian surface epithelial tumors, 2) correlate their expression with each other, and 3) characterize the presence of CD3+ T-lymphocytes in the studied tumors and determine whether their presence correlates with FasL or survivin expression in the malignant cases.

Materials and Methods

Materials

This retrospective study was performed on formalin fixed paraffin embedded blocks of routinely processed primary resection specimens of 32 ovarian carcinoma cases (cases with history of preoperative chemotherapy or radiotherapy were excluded), 12 borderline ovarian tumors, and 10 benign epithelial ovarian tumors.

Paraffin blocks of all cases were retrieved from files of the Pathology Department, Tanta Faculty of Medicine and used for preparation of hematoxylin and eosin (H&E)-stained tissue sections. The latter were examined to confirm the histological diagnosis to determine tumor type and grade malignant tumors included according to Lee et al., 2003 [21].

Methods

Immunohistochemistry

For immunohistochemistry, 3-μm sections were deparaffinised in xylene for 30 min and rehydrated with a graded alcohol series. Sections were then subjected to antigen retrieval in 10 mM citrate buffer, pH 6.0 (Lab Vision Catalogue # AP-9003) in a pressure cooker for 10 min followed by cooling at room temperature for 20 min and rinsing with phosphate-buffered saline (PBS) for 1 min. Endogenous peroxidase was blocked by immersion of the sections in 3% hydrogen peroxide solution for 10 min, then washing them in PBS. Immunohistochemical staining was performed using the Lab Vision's UltraVision Detection Kit (TP-015-HD) according to the manufacturer's protocol. Sections were incubated for 10 min with Ultra V block to prevent non-specific background staining. This was followed by rinsing the sections with PBS. Afterwards, an overnight incubation was done in a humidity chamber with rabbit polyclonal primary antibody against survivin (Lab Vision Catalogue # RB- 9245-R7, Ready to Use), FasL (Lab Vision Catalogue # RB-9029-R7, Ready to Use) and Anti-Human CD3 (Dako Code # A0452 at 1:100 dilution) followed by washing in PBS. Sections were then covered with 4–5 drops of UltraVision biotinylated goat anti-polyvalent secondary antibody, incubated at room temperature for 10 min, then washed in PBS, followed by incubation with streptavidin peroxidase solution for 10 min at room temperature, then rinsing with PBS. Sections were then covered for 15 min by adding one drop of 3-30-diamino-benzidine-tetrahydrochloride (DAB) chromogen mixed with 2 ml of DAB substrate. Finally, sections were counterstained with Mayer's haematoxylin, dehydrated in alcohol and mounted in distyrene, plasticizer, and xylene (DPX). Sections of colonic adenocarcinoma were used as positive controls for survivin, and sections of tonsil were used as positive controls for both FASL and CD3. Negative controls had primary antibody replaced by buffer.

Immunohistochemical Evaluation

Scoring of FasL and Survivin: Numbers of positively stained cells with each antibody (P) were scored as 0 (0%), 1 (< 10%), 2 (10–50%), or 3 (> 50%). Staining intensity (I) was graded semiquantitatively as 0 (none), 1 (weak), 2 (moderate), or 3 (intense). Then values of P x I (PI) with≥2 were regarded as positive [22].

Scoring of CD3 Protein Expression: Numbers of positively stained TILs were counted manually in 5 separate 400× high-power microscopic fields (HPFs) and the mean number of positively stained cells per HPF was calculated as reported by Zhang et al., 2010 [23].

Statistical Analysis

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) software for Windows, Version 18.0. The following tests were done: Chi-square test for comparing qualitative data; Kruskal-Wallis test for comparing marker expression between more than two different groups; Mann–Whitney test for comparing marker expression between two groups; Spearman's Rank Correlation Coefficient to assess if there is a correlation between FasL

and survivin expression in the studied tumors, and to assess if either of them has a relation with CD3+ TILs or tumor grade in studied malignant tumors. A probability value (p) of less than 0.05 was considered statistically significant.

Results

Histologic Findings

This study included 54 ovarian surface epithelial tumor cases, of which 18.52% (10 of 54) were benign, 22.22% (12 of 54) were borderline and 59.26% (32 of 54) were malignant. The malignant tumor group was subdivided into 37.50% (12 of 32) serous carcinoma, 31.25% (10 of 32) endometrioid carcinoma, 15.63% (5 of 32) clear cell and 15.63% (5 of 32) mucinous carcinomas. Also, the studied malignant tumors were categorized as grade I in 21.88% (7 of 32) of cases, grade II in 56.25% (18 of 32) of cases, and grade III in 21.88% (7 of 32) of cases.

FASL Expression in Studied Cases

Immunohistochemical analysis revealed that FasL expression was located mainly in the cytoplasm of ovarian tumor cells (Fig. 1a-d), an example of negative expression is shown in Fig. 1e. FasL positivity (PI value≥2) varied significantly among different studied groups ($p<0.001$). It was detected in 20% (2 of 10) of benign tumors, 41.67% (5 of 12) of borderline tumors, and 81.25% (26 of 32) of malignant tumors (Table 1). The total tendency of FasL expression (Table 2) was increased from benign to borderline to malignant tumors ($p<0.001$). The FasL expression in malignant and borderline tumors was significantly higher than in benign tumors ($p<0.001$, $p=0.03$ respectively). However on comparing its expression in malignant versus borderline tumors, the difference was not statistically significant ($p=0.15$). Within the malignant tumor group FasL positivity was detected in 75% (9 of 12) of serous carcinomas, 80% (8 of 10) of endometrioid carcinomas, 100% (5 of 5) of clear cell carcinomas, and 80% (4 of 5) mucinous carcinomas (Fig. 2). The total tendency of FasL expression varied among different malignant tumor subtypes (Table 3), however the difference didn't reach statistical significance ($p=0.577$). FasL expression correlation with malignant tumor grade was not statistically significant ($r=0.303$; $p=0.092$).

Survivin Expression in Studied Cases

Immunohistochemical analysis revealed that survivin expression was located mainly in the cytoplasm of ovarian tumor cells (Fig. 3a-d), an example of negative expression is shown in Fig. 3e. Survivin positivity (PI value≥2) varied significantly among different studied groups ($p<0.001$). It was detected in 20% (2 of 10) of benign tumors, 33.33% (4 of 12) of borderline tumors, and 78.13% (25 of 32) of malignant tumors (Table 1). The total tendency of survivin expression (Table 2) was increased from benign to

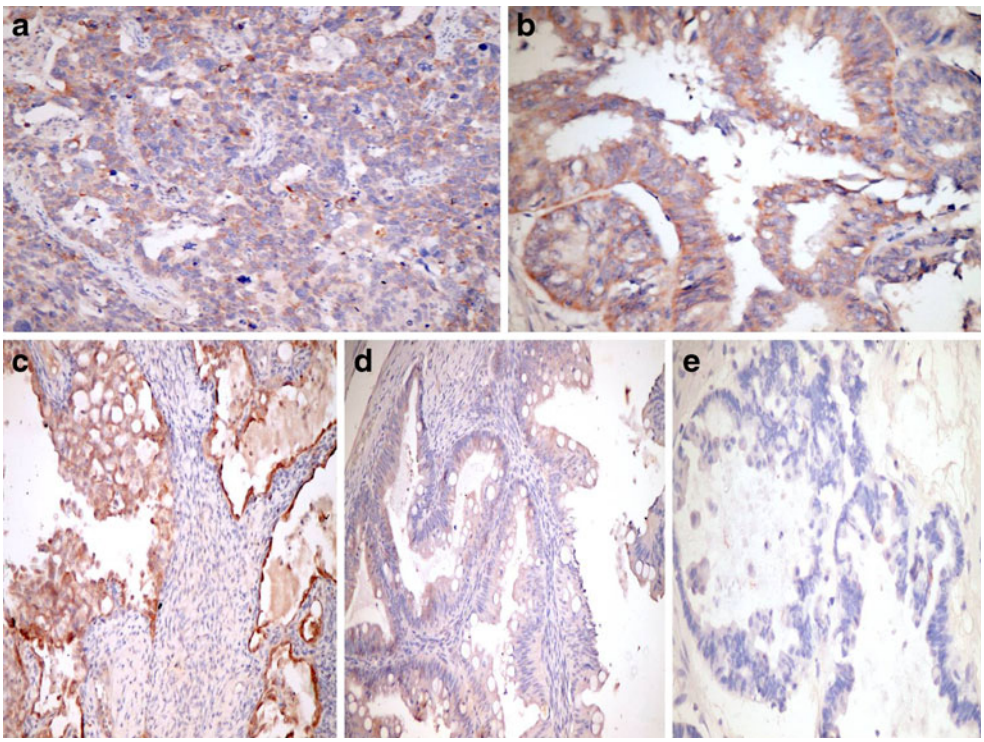


Fig. 1 FasL cytoplasmic positivity in serous (a), endometrioid (b), clear cell (c) carcinomas, borderline mucinous tumor (d), and negativity in a borderline serous tumor (e) [a, c & d immunoperoxidase X200; b & e immunoperoxidase X400]

Table 1 Distribution of FasL and survivin positivity in benign, borderline, and malignant ovarian tumors

		Groups						Chi-square	
		Benign		Borderline		Malignant		X^2	P-value
		N	%	N	%	N	%		
FasL	Negative	8	80.00	7	58.33	6	18.75	14.482	0.001[a]
	Positive	2	20.00	5	41.67	26	81.25		
Survivin	Negative	8	80.00	8	66.67	7	21.88	14.184	0.001[a]
	Positive	2	20.00	4	33.33	25	78.13		

[a]Significant

borderline to malignant tumors ($p<0.001$). Survivin expression in malignant tumors was significantly higher than that in borderline and benign tumors ($p<0.001$, $p=0.01$ respectively). However on comparing its expression in borderline versus benign tumors, the difference was not statistically significant ($p=0.07$). Within the malignant tumor group survivin positivity was detected in 66.67% (8 of 12) of serous carcinomas, 80% (8 of 10) of endometrioid carcinomas, 100% (5 of 5) of clear cell carcinomas, and 80% (4 of 5) mucinous carcinomas (Fig. 4). The total tendency of survivin expression varied among different malignant tumor subtypes (Table 3), however the difference didn't reach statistical significance ($p=0.099$). Survivin expression correlation with malignant tumor grade didn't reach statistical significance with $r=0.331$ & $p=0.064$.

Statistical Correlation Between FasL and Survivin Expression in the Studied Cases

The correlation between FasL and survivin expression was investigated using Spearman's rank correlation coefficient. A strong positive correlation between both proteins was identified in the studied cases with $r=0.877$ & $p<0.001$ (Fig. 5). Thus the total tendency of increasing FasL expression paralleled the total tendency of increasing survivin expression in the studied cases. An overlapping positivity of both markers was present in 57.4% (31 0f 54) of studied cases. Within the benign tumor cases, all (2 of 2) FasL positive cases were survivin positive as well. While in the borderline tumor group 4 of 5 survivin positive cases showed FasL positivity. In the malignant tumor group 25 of 26 survivin positive cases showed also FasL positivity.

Distribution of CD3+ TILs in Studied Tumors and Their Correlation to Fasl & Survivin in the Malignant Cases

CD3+ T-lymphocytes were observed in 96.857% (31 of 32) of malignant tumors, in 100% (12 of 12) of borderline tumors, and in 90% (9 of 10) of benign tumors. The positive immune reaction was highlighted by the brownish cytoplasmic staining (Figure 6a-d) and an example of absent CD3+TILs is shown in Fig. 6e. Table 2 shows that

Table 2 Comparative Expression of FasL, Survivin and CD3 among different studied tumor groups

		Groups			Kruskal-Wallis Test		Mann–Whitney Test (P-value)	
		Benign	Borderline	Malignant	*X*2	P-value		
FasL PI value	Median	0.00	1.00	2.00	13.92	<0.001[a]	P_1	0.03[a]
	IQR	1.25	2.00	1.75			P_2	0.00[a]
	Mean rank	12.30	25.63	32.95			P_3	0.15
Survivin PI value	Median	0.00	1.00	2.00	16.90	<0.001[a]	P_1	0.07
	IQR	1.25	1.00	2.00			P_2	0.00[a]
	Mean rank	13.00	21.58	34.25			P_3	0.01[a]
Mean CD3+TILs	Median	1.80	4.60	23.50	31.30	<0.001[a]	P_1	0.01[a]
	IQR	2.00	2.90	19.45			P_2	0.00[a]
	Mean rank	8.90	17.17	37.19			P_3	0.00[a]

IQR:- Interquartile Range

[a] Significant

P1: Benign vs. borderline

P2: Benign vs. malignant

P3: Borderline vs. malignant

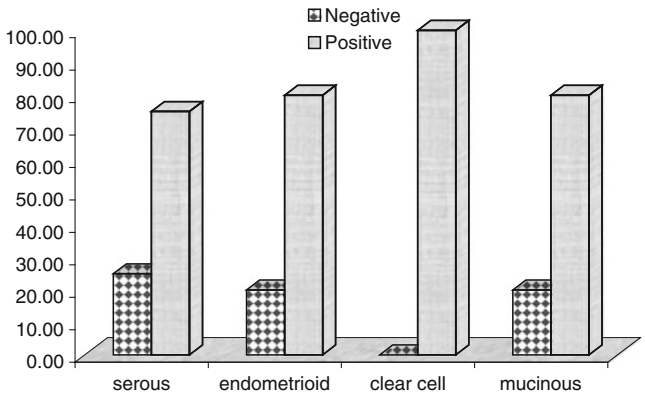


Fig. 2 Distribution of FasL positivity among different malignant tumor subtypes

the mean CD3+ TILs per HPF increased significantly ($p<0.001$) from benign to borderline to malignant tumors (Median=1.8, 4.6, 23.5 & IQR=2, 2.9, 19.45 respectively). The mean CD3+ TILs per HPF was significantly higher in malignant group when compared to borderline and benign groups ($p<0.001$ for both). Borderline group showed also significantly higher mean CD3+ TILs per HPF than benign group ($p=0.01$). Within the malignant tumor group, the variation in the mean CD3+ TILs per HPF was near significance ($p=0.056$) among different malignant tumor subtypes (Table 3). The higher grade of malignant tumors showed significantly ($p=0.019$) lower mean CD3+ TILs per HPF (Table 4).

Spearman's rank correlation coefficient was used to investigate the relationship between the mean CD3+ TILs per HPF and FasL or survivin expression in the studied malignant tumor cases. The mean CD3+ TILs per HPF within the malignant tumor group showed statistically significant inverse correlation with either FasL or survivin with $r=-0.729$, -0.582 respectively & $p<0.001$ for both (Fig. 7a, b). Thus, the mean CD3+ TILs per HPF was decreased on increasing FasL or survivin expression and vice versa.

Discussion

Interactions between the immune system and malignant cells play an important role in tumor genesis. Failure of the immune system to detect and reject transformed cells may lead to cancer development. Tumors use multiple mechanisms to escape from immune-mediated rejection. Many of these mechanisms are now known on cellular and molecular levels. Despite this knowledge, cancer immunotherapy is still not an established treatment in the clinic [24].

One such immune escape ways is that tumor cells use many mechanisms to acquire apoptosis resistance such as the overexpression of antiapoptotic molecules. The IAP family member survivin is expressed in a highly tumor-specific manner [25]. It is found in the vast majority of human tumors, but not in normal adult tissues [14]. It is likely that apoptosis resistance is not only relevant for tumor genesis and resistance to chemotherapy, but also influences immunosurveillance and immunotherapy. Tumor cells may not only resist destruction by the immune system passively, but may also kill TILs actively to suppress the anti-tumor immune response, a phenomenon called "tumor counterattack" [26–28]. The "weapon" tumors may use to delete CD95-sensitive immune cells is FasL/CD95L.

The mechanisms by which cancer cells express FasL are not well defined, and whether survivin is involved in these pathways is unclear. So this study aimed, in part, to investigate the expression of FasL and survivin in a series of primary

Table 3 Comparative expression of FasL, survivin and CD3 among different malignant tumor subtypes

		Median	Interquartile Range (IQR)	Mean rank	Kruskal Wallis Test	
					X^2	P-value
FasL PI value	serous	2.500	1.750	15.625	1.976	0.577
	endometrioid	2.000	1.250	14.700		
	clear cell	3.000	4.500	21.300		
	mucinous	2.000	3.500	17.400		
Survivin PI value	serous	2.000	1.750	12.500	6.280	0.099
	endometrioid	2.000	2.750	16.100		
	clear cell	4.000	5.000	24.000		
	mucinous	4.000	3.500	19.400		
Mean CD3+TILs	serous	18.800	17.750	14.958	7.577	0.056
	endometrioid	31.700	17.200	22.850		
	clear cell	13.400	18.500	10.200		
	mucinous	21.600	27.700	13.800		

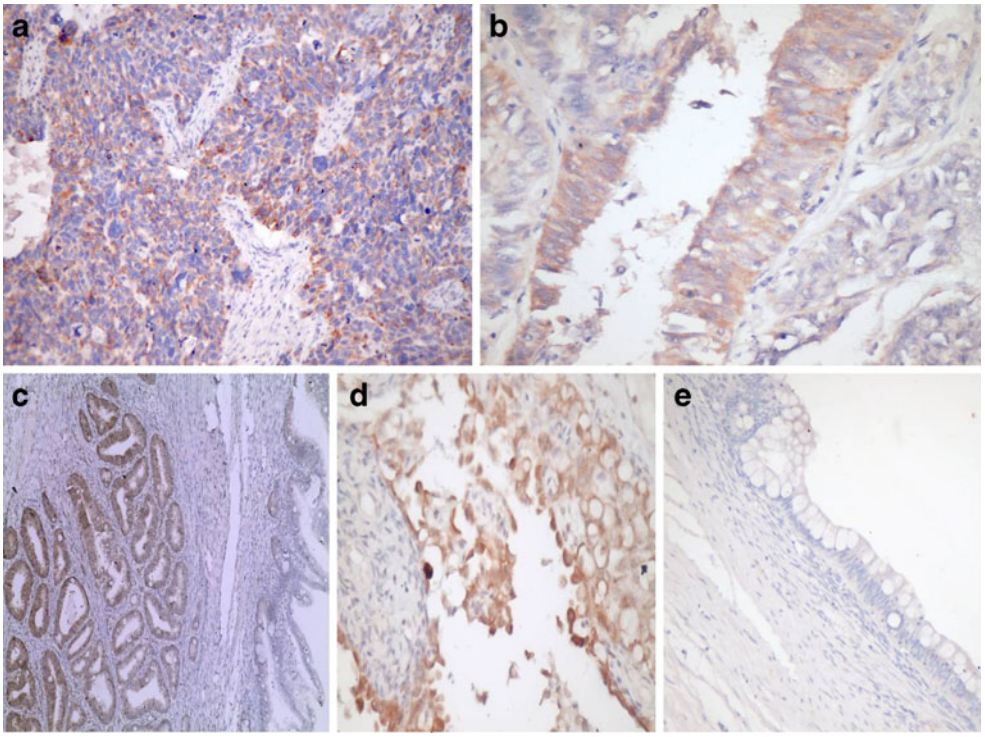


Fig. 3 Survivin cytoplasmic positivity in serous (a), endometrioid (b), mucinous (c), clear cell carcinomas (d), and negativity in a mucinous cystadenoma (e) [a & c immunoperoxidase X200; b, d & e immunoperoxidase X400]

ovarian surface epithelial tumors and correlate their expression with each other. This work shows that FasL or survivin positivity (PI value≥2) varies significantly among different studied groups ($p<0.001$ for both). Within the malignant ovarian tumor group 81.25, 78.13% are FasL or survivin positive respectively, while 41.67, 33.33% of borderline tumor group show FasL or survivin positivity respectively. Lastly, 20% only of benign tumor group are FasL or survivin positive. The total tendency of FasL or survivin expression increases from benign to borderline to malignant tumors ($p<0.001$ for both markers). The malignant tumor group shows significantly higher expression of both markers when compared to benign tumors ($p<0.001$ for both) and of FasL only when compared to borderline tumors ($p=0.01$). Besides, the borderline tumor group shows significantly higher FasL expression than benign tumors ($p=0.03$). However no statistical significance is detected on comparing malignant versus borderline tumors for FasL expression ($p=0.15$) and also on comparing survivin expression in borderline versus benign tumors ($p=0.07$).

These findings go with that of Ma et al. [29] who reported that the level of survivin or FasL expression in their study

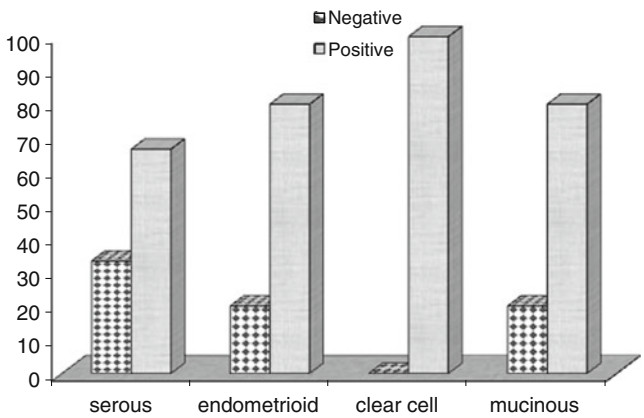
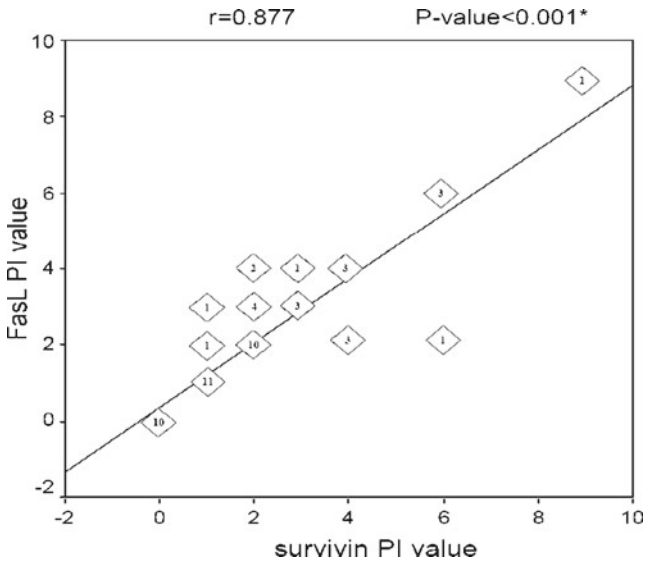


Fig. 4 Distribution of survivin positivity among different malignant tumor subtypes



* Significant

Fig. 5 Scatter graph showing correlation between FasL and survivin expression in individual studied tumors. The number of cases in each group is shown within each symbol

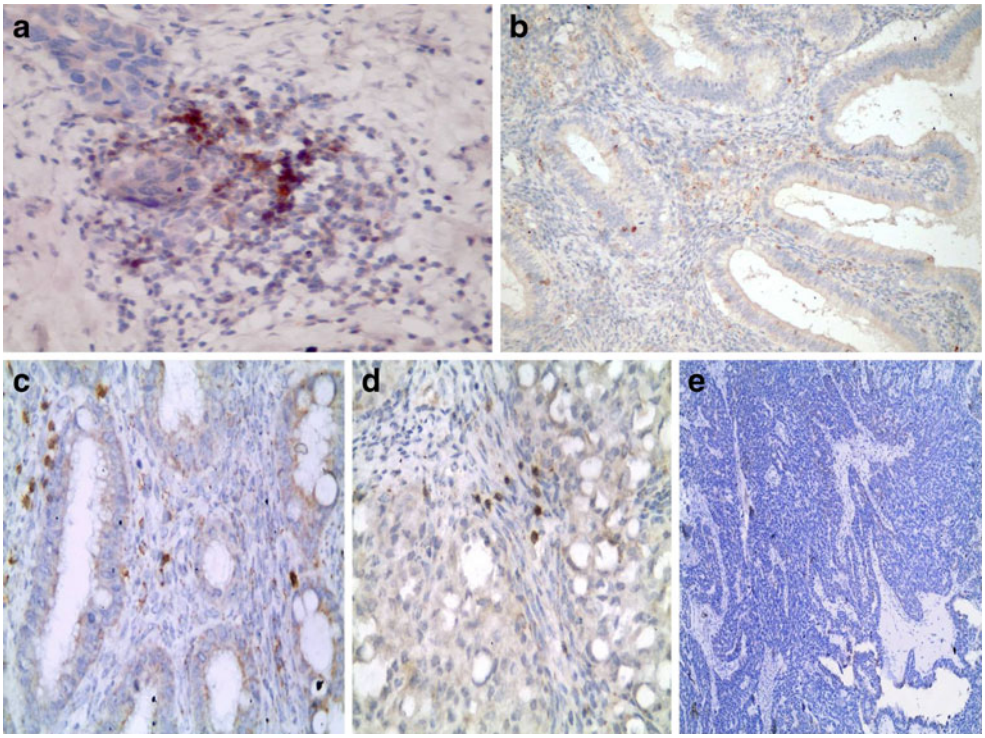


Fig. 6 CD3+ TILs are present in serous (a), endometrioid (b), mucinous (c), clear cell carcinomas (d), nearly absent in another case of serous carcinoma (e) [a, c & d immunoperoxidase X400; b & e immunoperoxidase X200]

was significantly higher in patients with ovarian carcinoma than in patients with benign ovarian tumors. Sui et al. [16] study showed significantly higher survivin expression in malignant or borderline tumors than in benign tumors and they suggested that survivin overexpression may play a pivotal role in the progression of ovarian tumors and may provide an important prognostic implication for epithelial ovarian carcinomas. Zaffaroni et al. [18] reported that ovarian cancers with cytoplasmic survivin expression showed clinical resistance to taxol/platinum-based therapeutic regimes, with a lower clinical or pathological complete remission rate. Munakata et al. [22] and Arts et al. [30] found that FasL immunostaining was more frequent in malignant ovarian tumors than benign and borderline tumors.

FasL expression at high levels in benign ovarian tumors was found by Zusman et al. [31] whereas Munakata et al. [22] found only 1 patient with some staining for FasL in a group of benign serous tumors. Twenty of 30 specimens of borderline tumors were positive for FasL in van Haaften-Day et al. study [32]. Ben-Hur et al. [33] concluded that the initial development of ovarian tumors is accompanied by high epithelial expression of Fas, FasL and bcl-2 proteins.

In contrast to others [17, 19, 29] this study doesn't show significant correlation of either FasL or survivin expression with malignant tumor grade. This was similar to Ferrandina et al. [34].

This work shows a positive correlation between FasL and survivin expression in the studied cases with $r=0.877$ & $p<0.001$. An overlapping positivity of both markers is present in 57.4% of the studied cases. All, 80, 96.15% of FasL positive benign, borderline, malignant tumors, respectively, are survivin positive as well.

Similarly Ma et al. [29] found that positive survivin expression was strongly correlated with FasL expression. These findings go also with that of Asanuma et al. [35] who found that survivin up-regulates FasL expression by augmenting gene transcription.

In the past decade, several investigators have recognized the immune system and, in particular, the presence of TILs as a valuable, clinically relevant prognostic marker and as an immunological basis for the development of novel therapeutic strategies in patients with epithelial cancers [36] such as adenocarcinomas of the lung [37], the colorectum [38] and the breast [39].

In the case of ovarian carcinomas, TILs have been characterized and further specified in functional terms in a

Table 4 Correlation between mean CD3+TIL per HPF and malignant tumor grade

Grade	Mean CD3+TIL		
	IQR	Median	Mean rank
I	6.8	30.6	25
II	19.70	18.3	15
III	17.2	14.6	11.85714
Kruskal Wallis Test	X^2	7.92	
	P-value	0.019[a]	

[a] Significant

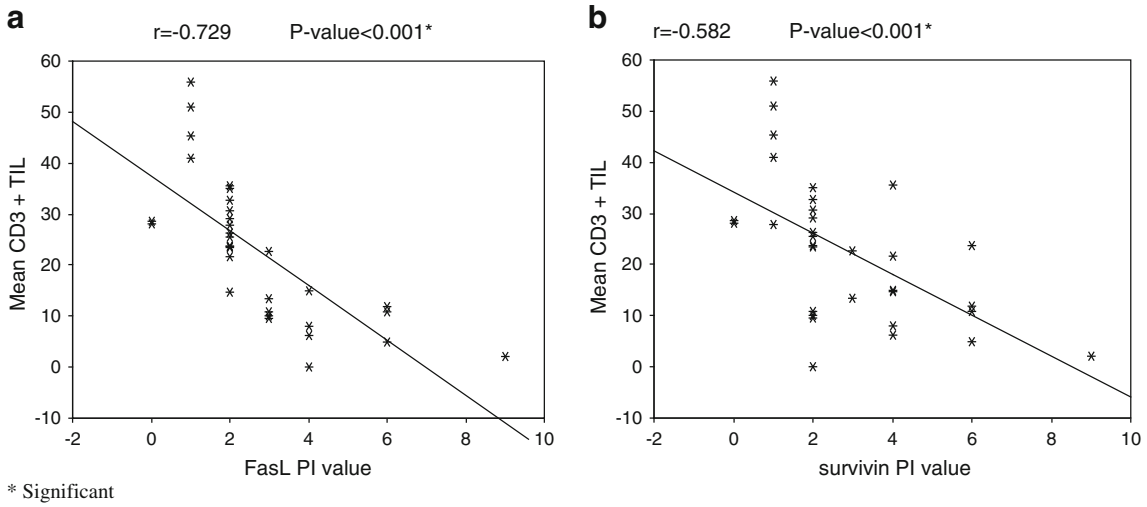


Fig. 7 Scatter graph showing correlation between Mean CD3+ TILs per HPF and FasL (a) or survivin (b) expression in the studied malignant tumors

variety of studies [40–47] and the general consensus is that the presence of T lymphocytes has a major impact on the progression and clinical course of the disease. In particular, it was shown that high numbers of CD3-positive T cells are indicative for improved survival [48].

CD3+ TILs are observed in 96.857, 100, and 90% of malignant, borderline, and benign tumors of this study, respectively. The mean CD3+ TILs per HPF increases significantly ($p<0.001$) from benign to borderline to malignant tumors (Median=1.8, 4.6, 23.5 & IQR=2, 2.9, 19.45 respectively).

This result is supported by the data of others [31, 49] who concluded that T cells play an important role in the pathophysiology of ovarian cancer. Similar findings have been obtained by Kabawat et al. [50] who attributed the higher ratio of lymphocytes in ovarian carcinomas to the better recognition of malignant tumors by the immune system. Alternative explanations may lie in the frequent occurrence of necrosis of malignant tumor cells with subsequent release of chemotactic factors as added by Helal et al. [49]. However, Kullander and Rausing [51] reported that T cells were sparsely represented in benign and malignant ovarian tumors. Accordingly, they concluded that immunogenic activity would be weak in ovarian cancer, a concept that contrasts with our findings and those of others [49].

This study shows that increasing malignant tumor grade is associated significantly with lower mean CD3+ TILs per HPF. This later finding may indicate that lack of tumor differentiation may influence the degree of immune response and may be associated with some mechanisms of tumor immune escape. However, few studies investigated the relationship between the amount of TIL and the histologic grade of ovarian carcinoma. In contrast to this study, Helal et al. [49] and Negus et al. [52] showed no correlation tumor infiltrating mononuclear cells and ovarian tumor grade, while Puccetti et al. found an association between the nuclear grading of the neoplastic cells and the local tumor specific T cell responses in renal cell carcinoma [53].

In this study Spearman's rank correlation coefficient is used to investigate the relationship between the mean CD3+ TILs per HPF and FasL or survivin expression in the studied malignant tumor cases. The mean CD3+ TILs per HPF within the malignant tumor group shows statistically significant inverse correlation with both FasL or survivin with $r=-0.729$, -0.582 respectively & $p<0.001$ for both. Thus, the mean CD3+ TILs per HPF is decreased on increasing FasL or survivin expression and vice versa.

These findings are similar to others [22, 35]. Asanuma et al. [35] suggested that survivin enables cancer cells to suppress attack by immune cells via inhibition of Fas-mediated apoptotic signaling, and also fight back via induction of FasL. Also Okada et al. [54] findings indicated that the FasL expressed in colorectal carcinoma cells may kill the Fas-positive immune effective TILs by means of a Fas-FasL system termed Fas counterattack.

In summary, this study shows that both FasL and survivin are expressed significantly higher in malignant ovarian epithelial tumors than benign tumors and are strongly correlated to each other. This suggests that they may have a significant role in the pathogenesis of ovarian carcinoma. CD3+ TILs show significantly higher numbers in malignant versus borderline and benign ovarian epithelial tumors and they significantly decrease with increasing malignant tumor grade and expression of FasL or survivin. This later finding suggests that FasL and survivin may contribute to the immune privilege of the tumor as survivin

may not only enables cancer cells to escape apoptosis, but may also induce FasL expression by cancer cells that acts as weapon to counterattack TILs. Thus FasL and survivin could be useful prognostic markers for ovarian carcinoma. However, deeper insight into the molecular mechanisms underlying tumor immune escape in larger scale studies are needed as they may finally lead to novel therapeutic approaches that can be used for the benefit of cancer patients.

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