Role of Survivin in Glioma Progression: A Clinico-Pathological Study

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Abstract

Object: Gliomas are among the most aggressive of all human malignancies. Glioblastoma multiforme is the most malignant histopathological subtype. Survivin is one of the inhibitors of apoptosis. It is over-expressed in many human cancers. We performed clinical and pathological study aimed to clarify its role in glioma progression.

Methods: This study included 34 glioma patients. Clinical evaluation including age, sex, clinical presentation and location of the tumor, was done. Sections from glioma specimens were stained with H&E, classified and graded according to WHO classification, (2000) and then immunostained to detect Survivin protein expression.

Results: The study included 34 glioma cases. Survivin was expressed to a variable extent in most groups of gliomas (in 21/24, 1/4, 1/1 and 5/5 cases of astrocytomas, oligodendrogliomas, mixed oligoastrocytoma and ependymomas respectively). Survivin expression showed gradual up-regulation with increasing grade of astrocytomas from pilocytic astrocytomas (66.7%) → diffuse astrocytomas (77.8%) → anaplastic astrocytomas (100%) → glioblastoma multiforme (100%). This study showed that there is a strong correlation between the distribution and staining intensity of Survivin protein expression and the tumor grade (P< value< 0.01 and < 0.00 respectively). Also there is a strong correlation between Survivin protein expression as evidenced by immunoreactivity score (IRS) and tumor grade and proliferative activity (P value< 0.00 & <0.002 respectively).

Conclusion: Survivin plays an important role in the initiation of gliomas and their progression towards higher grades.

Introduction

Gliomas/glial tumors are primary brain tumors arising from glial cells, which form the supporting tissue of the nervous system. They account for about half of primary intracranial tumors [1]. About half of all childhood brain tumors are astrocytomas[2]. In adults, gliomas are the most common malignancy of the central nervous system [3]. The most frequent types of glioma are astrocytic (mainly astrocytomas and glioblastoma multiforme) [4]. In Egypt, brain tumors are particularly common, comprising 16.5% of tumors below the age of 20 years [5].

The clinical behavior of gliomas is variable according to type and grade of it. Nearly two thirds of gliomas are highly malignant lesions that account for a disproportionate share of brain tumor-related morbidity and mortality. Despite recent advances, two-year survival for glioblastoma with optimal therapy is less than 30%. Even among patients with low grade gliomas that confer a relatively good prognosis, treatment is almost never curative [6].

Survivin has been identified as an important member of the inhibitor of apoptosis protein (IAP) family [7]. It is over-expressed in many human cancers [8]. It has been shown that Survivin is highly expressed in gliomas and its high expression correlates with more aggressive behavior, decreased response to chemotherapeutic agents, and shortened survival times. Manipulation of Survivin regulation and expression may lead to the development of new immunotherapy and gene therapy strategies for the treatment of cancer [9].

Hoshino et al.[10,11] found that the proliferative activity is a useful predicting factor for both low and high grade gliomas, whereas Onda et al.,[12] found that the proliferative potential of diffusely infiltrating astrocytomas correlates with histological grade.

In this study, we aimed to emphasize the role of Survivin in glioma and to study the correlation between Survivin expression and tumor grade and proliferative activity as indicators for prognostic outcome.

Patients and methods:

This study was conducted to 34 glioma patients admitted to Sohag University Hospital during the period from 2005 to 2007. Clinical data including: age, sex of the patients, and location of tumors were reviewed for the 34 patients.

The specimens were formalin fixed and paraffin embedded. Five-micron tissue sections prepared and stained with hematoxylin and eosin (H&E). Sections were examined and each tumor typed and graded according to WHO classification (2000).

Reagents used in immunohistochemical study were concentrated rabbit polyclonal antibody for Survivin (Catalog # RB-9245-po, LabVision Corporation, Fremont, USA), and Universal Staining Kit (Catalog # TA-015-HP, LabVision Corporation, Fremont, USA), coated slides (Pre-cleaned Superfrost®)/Plus-Fisherbrand USA). The antibody was used at a dilution of 1:100 and its incubation period was two hours in a humid chamber at room temperature. The steps are the same as illustrated by the manufacturer.

Positive and negative control:

Sections from colon cancer known to express Survivin were used as positive control[3]. The negative

control slides were stained in parallel, but with omission of the primary antibody.

Evaluation of the immunostaining findings for Survivin:

Survivin was identified as brown cytoplasmic staining. The distribution and intensity of immunostaining were assessed at X40 & X100 magnifications, and semi-quantitative analysis was done using X200 & X400 magnifications. The staining distribution was expressed as negative if staining in <1% cells (0), focal (+1) and diffuse (+2) modified from Xie et al., (2006). The immunoreactivity score (IRS) was done for each case. It is equal to the extent of staining multiplied by its intensity [39]. The mitotic figures were counted/10 HPF for each case in the most active area.

Statistical analysis

Results were statistically analyzed by ANOVA (Analysis of Variance) test and Pearson's Correlation Coefficient using Statistical Package for Social Sciences (SPSS) for Windows.

Results

Clinicopathological characteristics:

The 34 specimens included 24 (70.6%) astrocytomas, 4 (11.8%) oligodendrogliomas, 5 (14.7%) ependymomas and one case (2.9%) mixed oligoastrocytoma (table 1). The 24 astrocytomas included 3 (12.5%) pilocytic astrocytoma, 9 (37.5%) diffuse fibrillary astrocytomas, 3 (12.5%) anaplastic astrocytomas, and 9 (37.5%) glioblastoma multiforms (table 2). Their age ranges, sex distribution and topographic sites of the studied tumors were illustrated in tables (1-4).

Immunohistochemical findings:

Survivin was expressed in tumor tissue, weakly expressed in the nearby brain tissue in a case of glioblastoma multiforme. Survivin was also weakly expressed in inflammatory cells and vascular endothelial cells in some cases.

Positive cases showed brown cytoplasmic Survivin staining, but only one case of diffuse fibrillary astrocytoma showed nuclear expression. Survivin immunoreactivity was variably expressed in glioma groups. Tables (5&6) illustrate Survivin distribution and staining intensity of the 34 studied cases.

Tables (7&8) illustrate Survivin immunoreactivity in astrocytic tumors according to their grades. There is a significant statistical difference in Survivin distribution ($P < 0.01$) and staining intensity ($P < 0.00$) and tumor grade. Table (9) showed a statistically significant relation between tumor grade and IRS ($P < 0.01$), and table (10) showed a statistically significant relation between the IRS and number of mitosis /10HPF in each tumor ($P < 0.01$).

Table (1): Types, age and sex gliomas

Histological types	No	%	Age		Sex	
			Mean	Range	Male	Female
Astrocytomas	24	70.6	43	2m-70y	16 (66.7%)	8 (33.3%)
Oligodendrogliomas	4	11.8	43	39y- 46y	2 (50%)	2 (50%)
Mixed oligoastrocytomas	1	2.9	40	40y	1 (100%)	0 (0%)
Ependymomas	5	14.7	26	4y- 55y	1 (20%)	4 (80%)
Total	34	100	40.3	2 m-70y	58.8%	41.2%

No = number, M = month, Y = year

Table (2): Types, age and sex of astrocytomas

Histological types	No	%	Age		Sex	
			Mean	Range	Male	Female
Pilocytic astrocytomas	3	12.5	20.7	12-38y	2 (66.7%)	1 (33.3%)
Diffuse astrocytomas	9	37.5	34	2m-50y	3 (33.3%)	6 (66.7%)
Anaplastic astrocytomas	3	12.5	50.3	47-57y	3 (100%)	0 (0%)
Glioblastoma multiforme	9	37.5	56.6	28-70y	7 (77.8%)	2 (22.2%)

Table (3): Histological classification of the studied 34 cases in relation to site

Histological types	No.	Sites			
		Cerebral hemispheres	Posterior fossa	Spinal cord	Thalamus
Astrocytomas	24	21	3	-	-
Oligodendrogliomas	4	3	-	-	1
Mixed oligoastrocytomas	1	1	-	-	-
Ependymomas	5	4	-	1	-
Total	34	29(85.3%)	3 (8.8%)	1(2.9%)	1 (2.9%)

Table (4): Topographic distribution of the studied astrocytic tumors

Sites	Pilocytic astrocytomas		Diffuse astrocytomas		Anaplastic astrocytomas		Glioblastoma multiforme		Total	
	No	%	No	%	No	%	No	%	No	%
Parietal	1	33.3	5	55.6	2	66.7	4	44.4	12	50
Frontal	-		2	22.2	1	33.3	5	55.6	8	33.3
Fronto-parietal	-		1	11.1	-	-	-	-	1	4.2

Table (5): Survivin expression in the studied gliomas

Type of glioma	Positive cases	Distribution of Survivin staining			Intensity of Survivin staining		
		None	Focal	Diffuse	0	+1	+2
Astrocytoma	21/24(87.5%)	3	12	9	3	13	8
Oligodendroglioma	1/4(25%)	3	1	0	3	1	0
Mixed oligoastrocytoma	1/1 (100%)	0	1	0	0	1	0
Ependymoma	5/5 (100%)	0	3	2	0	2	3
Total	28/34 (82.4)	6	17	11	6	17	11

Table (6): Survivin expression in astrocytic tumors

Types of astrocytoma	Positive cases No/%	Distribution of Survivin staining			Intensity of Survivin staining		
		None	Focal	Diffuse	0	+1	+2
Pilocytic astrocytoma	2/3 (66.7%)	1	2	0	1	2	0
Diffuse astrocytoma	7/9 (77.8%)	2	5	2	2	6	1
Anaplastic astrocytoma	3/3 (100%)	0	1	2	0	2	1
Glioblastoma multiforme	9/9 (100%)	0	4	5	0	3	6
Total	21/24 (87.5%)	3	12	9	3	13	8

Table (7): The relationship between tumor grade and Survivin expression distribution

Grade of the tumor	Positive cases	Distribution of survivin staining		
		None	Focal	Diffuse
Low grade tumors (I & II)	9/12 (75%)	3	7	2
High grade tumors (III &IV)	12/12 (100%)	0	5	7
Total	21/24 (87.5%)	3	12	9

ANOVA test is used $P < 0.01$

Table (8): The relationship between tumor grade and the intensity of Survivin expression

Tumor grade	Positive cases	Intensity of Survivin staining		
		None 0	Weak +1	Strong +2
Low grade tumors (grade-I & II)	9/12 (75%)	3	8	1
High grade tumors (grade-III & IV)	12/12 (100%)	0	5	7
Total	21/24 (87.5%)	3	13	8

ANOVA test is used $P < 0.00$

Table (9): The relationship between tumor grade and the immunoreactivity score (IRS):

Histological type			Immunoreactivity score (IRS)					P value
			0	1	2	3	4	
	No	Grade	No	No	No	No	No	
(a) Astrocytomas:	24		3	11	3	0	7	0.01
(1) Pilocytic astrocytoma	3	1	1	2	0	0	0	
(2) Diffuse astrocytoma	9	2	2	5	1	0	1	
(3)Anaplastic astrocytoma	3	3	0	1	1	0	1	
(4) Glioblastoma multiforme	9	4	0	3	1	0	5	
(b) Oligodendrogliomas	4	2	3	1	0	0	0	
(c) Mixed oligoastrocytoma	1	2	0	1	0	0	0	
(d) Ependymomas	5		0	0	3	0	2	
(1) Well differentiated	1	1	0	0	1	0	0	
(2) Poorly differentiated	4	2	0	0	2	0	2	
Total	34		6	13	6	0	9	

The test used is Pearson correlation.

Table (10): The relationship between the IRS and the number of mitosis/10HPF

Histological type	Immunoreactivity score (IRS)/number of cases	Number of mitosis/10 H.P.F	P value
(a) Astrocytomas:			P < 0.002 (significant) The test used is Pearson correlation.
(1) Pilocytic astrocytoma	0/1	0	
	1/2	0	
(2) Diffuse astrocytoma	0/2	0	
	1/5	0	
	2/1	0	
	4/1	0	
(3) Anaplastic astrocytoma	1/1	2	
	2/1	4	
	4/1	7	
(4) Glioblastoma multiforme.			
Case No. 1	1	0	
Case No. 2	1	2	
Case No. 3	1	0	
Case No. 4	2	0	
Case No. 5	4	1	
Case No. 6	4	5	
Case No. 7	4	4	
Case No. 8	4	0	
Case No. 9	4	9	
(b) Oligodendrogliomas.	0/3	0	
	1/1	0	
(c) Mixed oligoastrocytoma.	1/1	0	
(d) Ependymomas	2/3	0	
	4/2	0	

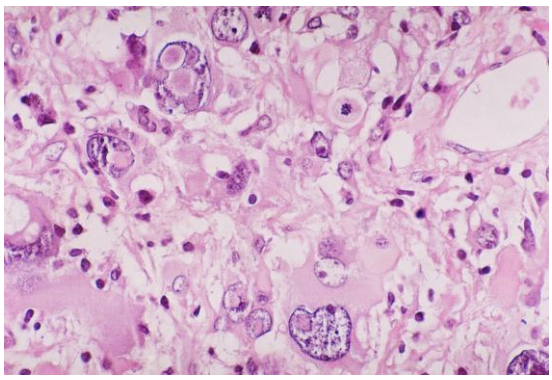

Figure (1): Giant cell glioblastoma showing with mitosis (arrow) (H&E X400)

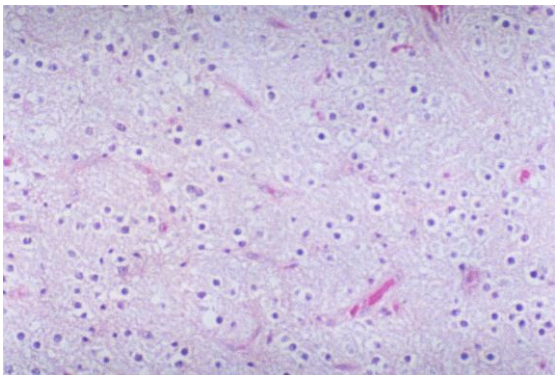

Figure (2): Oligodendroglioma showing cells with clear cytoplasm and rounded nuclei (H&E X200)

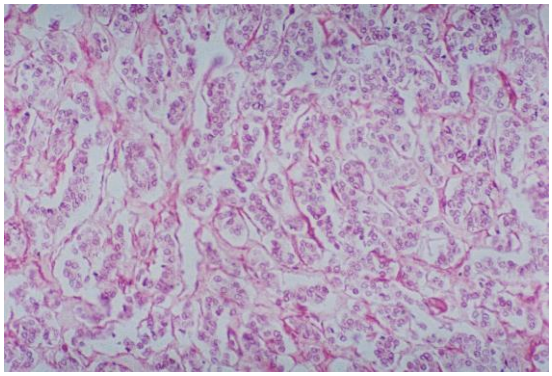

Figure (3): Ependymoma forming papillae (H & E X200)

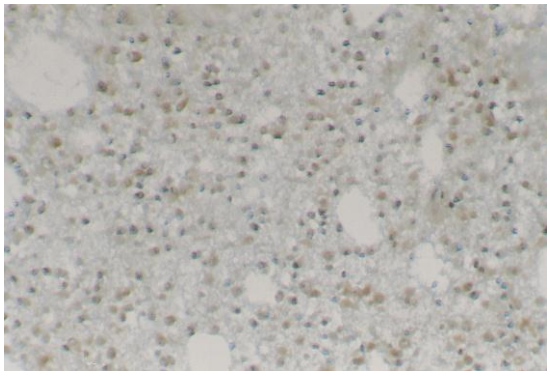

Figure (4): Pilocytic astrocytoma showing weak Survivin expression (X200)

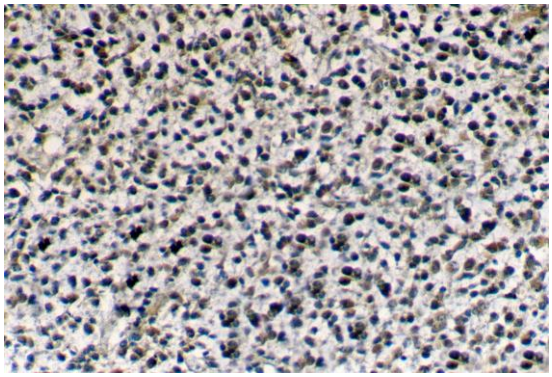

Figure (5): Anaplastic astrocytoma showing strong Survivin immunoreactivity (X200)

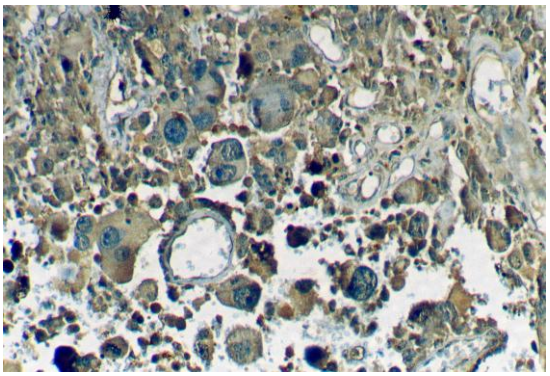

Figure (6): Glioblastoma multiforme showing weak Survivin expression (X400)

Discussion:

Gliomas are among the most aggressive of all human malignancies. Glioblastoma multiforme is the most malignant histopathologic subtype. It carries the worst prognosis, with median survival 9 to 10 month, despite aggressive surgery, radiation, and chemotherapy [14].

Gliomas remain one of the human tumors most refractory to treatment, despite continuing advances in radiotherapy, chemotherapy, and surgical techniques [15,16].

The ability of gliomas to avoid apoptotic death, both spontaneous and treatment-related, may permit progression to more aggressive phenotypes and may explain why gliomas, even at their earliest stages, are so resistant to conventional chemotherapy and radiation [17,18].

Because long term cure of glioma patients presently is elusive, understanding Survivin protein expression is fundamental to developing better therapies for these tumors, the most difficult human tumors of all [19].

We found that Survivin is not only expressed in tumor tissue, but also weakly expressed in the nearby brain tissue in a case of glioblastoma multiforme. Survivin protein was expressed weakly in inflammatory cells and vascular endothelial cells in some cases. These findings are in concordance with Das et al.,[20], Fangusaro et al.,[21], Yagihashi et al.,[22] and Fukuda and Pelus[23] who found that Survivin may show a low expression in a subset of adult normal differentiated tissues. The role of Survivin in normal cells has remained uncertain[24].

In this study Survivin protein expression was almost always cytoplasmic except in one case which showed nuclear expression. Survivin has both nuclear and cytoplasmic targets which appear to serve different functions[25]. Two forms of Survivin antibodies, which recognize predominantly nuclear and cytoplasmic forms of Survivin are commercially available [26].

Nuclear Survivin has been suggested to play an important role in chromosomal segregation during mitosis[27,28], while cytoplasmic Survivin has been characterized as antiapoptotic [29]. The two forms have some overlapping activity [30] and this may explain the single case of nuclear expression in this study.

In our study Survivin was found to be expressed in most gliomas (28/34, 82.4%). These results are in agreement with Sasaki et al.,[31], Chakravarti et al.,[19], and Kleinschmidt-DeMasters et al., [32].

Astrocytic tumors showed positive Survivin immunoreactivity in 87.5% of cases; 66.7% of pilocytic astrocytoma, 77.8% of diffuse astrocytoma, 100% of anaplastic astrocytoma, and 100% for glioblastoma multiforme.

In concordance with Sasaki et al.,[31], who found that the intensity and degree of Survivin protein expression showed an increase with tumor grade toward glioblastomas. We found gradual Survivin expression with increasing tumor grade from pilocytic astrocytoma → diffuse astrocytoma → anaplastic astrocytoma → glioblastoma multiforme. These findings suggest the role of Survivin in both the formation of low grade astrocytoma and the progression toward glioblastoma.

One of the four cases of oligodendroglioma showed positive

Survivin which is focal and mild. The rest of cases were not reactive. These findings are in keeping with that of Sasaki et al., [31] who studied six cases of oligodendroglioma and all were negative for Survivin except for mini-gemistocytes. In contrast Kleinschmidt-DeMasters et al.,[32] found that oligodendrogliomas grade-II and anaplastic oligodendrogliomas showed strong and diffuse staining for Survivin.

In agreement with Sasaki et al.,[31] who studied six cases of ependymoma and all were positive with various degrees. Our results showed that the five studied ependymomas were Survivin positive.

Cunningham et al.,[33] found that the histological grade is a useful parameter in distinguishing the behavior of the tumor. In the present study a highly significant relationship was found between tumor grade and Survivin IRS. So Survivin can be used for prediction of tumor behavior.

The mitotic activity and the histological grade are clinically useful in distinguishing the biologic behavior of tumors [34]. The relative radio-sensitivity of proliferating cells compared with non-proliferating cells has long been known. Highly proliferating tumors are associated with shorter postoperative progression-free intervals and with higher intrinsic radio-responsiveness, although not necessarily higher radio-curability [35].

In our study mitosis was evaluated and used as a simple indication for proliferative activity of tumor cells. A high significant correlation between the mitotic count/10HPF and the Survivin IRS was found. So Survivin expression could be used as a predictive factor for the biologic behavior of the tumor.

Our results are consistent with those of Hoshino et al.,[10,11] who found that the proliferative activity is a useful predicting factor for both low and high grade gliomas. Also, Montine et al., [36] found that the proliferative activity in astrocytomas strongly predict survival. Coons et al.,[37] and Heegaard et al.,[38] found that the higher proliferative activity in oligodendrogliomas has been correlated with shorter survival, and they suggest that the proliferative activity can be used as a predictive factor for glial tumors.

Conclusion

As Survivin is positive in most cases of gliomas, so it may be involved in their tumorigenesis. Up-regulation of Survivin expression with higher grades of astrocytomas, and with increased proliferative activity, suggest its role in the transition of astrocytomas to higher grades by preventing apoptosis, and accelerating cell growth and proliferation.

Recommendations:

Studying the expression of Survivin on a large number of cases and follow up of patients to emphasize the relation between Survivin expression and the prognosis are recommended.

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دور السرفيفين فى تطور الأورام الدبقية: دراسة اكلينيكية باثولوجية

ايمان محمد صلاح الدين محمد[1]، هالة صلاح الدين محمد[2]، هويدا اسماعيل حسن[3]، محمد أحمد عبد العال[4]

اقسام الباثولوجيا طب سوهاج[2،1] واسيوط [3] وقسم جراحة المخ والاعصاب طب سوهاج[4]

الموضوع: تعتبر الأورام الدبقية من أكثر الأورام الخبيثة عدوانية في الجنس البشري. كما أن الورم الدبقي الااسفنجي متعدد الأشكال هو المجموعة الاكثرخبثا من الناحية الهستوباثولوجية. ويعد السرفيفين واحدا من محبطي موت الخلايا المبرمج كما أن تعبيره يزيد كثيرا في الكثير من سرطانات الانسان. وقد اجرينا دراسة اكلينيكية باثولوجية الهدف منها توضيح دور السرفيفين في تطور الأورام الدبقية.

لطرق المستخدمة: وقد اشتملت هذه الدراسة على أربعة وثلاثين مريضا وقد شمل التقييم الاكلينيكي، السن والنوع وطريقة تقديم المرض لنفسه ومكان الورم.وقد تمت صباغة قطاعات من عينات الورم الدبقي بواسطة الهيماتوكسلين والايوسين وصنفت الأورام وتم تحديد درجتها طبقا لتصنيف تصنيف منظمة الصحة العالمية لعام 2000 ميلادية وصبغت بعدها لتحديد تعبير بروتين السرفيفين.

النتائج: وقد اشتمل التصنيف الهستوباثولوجى على 34 عينة للأورام الدبقية كالات كالاتى: 24 حالة أورام خلايا نجمية، 4 حالات أورام الخلية الدبقية العصبية الناقصة، حالة واحدة ورم مختلط من الخلايا النجمية والخلية الدبقية العصبية الناقصة، 5 حالات لأورام البطانة العصبية. و قد ضمت حالات أورام الخلايا النجمية والتى بلغ عددها 24 حالة 3 حالات ورم شعريو9 حالات ورم دبقي منتشر و3 حالات ورم دبقي متحول و9 حالات ورم دبقي اسفنجي متعدد الأشكال.

وقد وجد تعبير السرفيفين في معظم مجموعات الأورام الدبقية بدرجات متفاوتة. (24/21 ،4/1، 1/1، 5/5 لكل من الورم الدبقي الشعري، الورم الدبقي المنتشر، الورم الدبقي المتحول، الورم الدبقي الإسفنجي الأولي متعدد الأشكال علي التوالي). و بالنسبة لأنواع أورام الخلية النجمية المختلفة نجد ان تعبير السرفيفين يُظهر زيادة مضطردة مع زيادة درجة ورم الخلية النجمية من الورم الدبقي (66.7 %) الشعري ← الورم الدبقي المنتشر (77.8 %) ← الورم الدبقي المتحول (100 %) ← الورم الدبقي الإسفنجي الأولي متعدد الأشكال (100%).

وقد وجدنا في هذه الدراسة أن هناك علاقة قوية بين توزيع تعبير وكثافة صبغة بروتين السرفيفين ودرجة الورم ($P< 0.01\& < 0.00$) علي التوالي . وقد وجدنا ايضا علاقة قوية بين تعبير بروتين السرفيفين موضحا بمعدل التفاعل المناعي ودرجة الورم ودرجة تكاثره ($P < 0.00 \& <0.002$)علي التوالي.

الاستنتاج: يلعب السرفيفين دورا هاما في بدء تكون الأورام الدبقية وكذلك تطورها للمراحل الاعلى.