

Does GLUT-1 have a Role in Prognosis of Breast Carcinoma of Egyptian Patients?

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ABSTRACT

Introduction: Breast Cancer (BC) is the most common malignancy in females worldwide. It constitutes 38.8% of all malignant tumours among Egyptian females. Triple negative breast cancer has not confirmed therapeutic molecular target and has a poor prognosis, so identification of new biological key pathways might aid in finding targets of potential interest for therapeutic blockade. Glucose transporter 1 (GLUT-1) has important role in the transport of glucose in malignant cells and overexpressed in different types of human cancers but its expression in breast carcinoma tissues is controversial.

Aim: To evaluate the role of GLUT-1 in breast carcinoma in Egyptian patients.

Materials and Methods: Retrospective study included 79 Invasive Duct Carcinoma (IDC) specimens retrieved from the archival cases of Pathology Department, faculty of medicine, Menoufia University, Egypt, spanning the period between January, 2010 and December, 2017. All cases were stained for GLUT-1 antibody.

Results: Eighty percent of the studied IDC cases showed positive GLUT-1 expression, positive cases are divided into +1,

+2 and +3 and 55% of positive cases were +3. There was a highly statistical significant association between positive GLUT-1 expression and advanced nodal stage ($p=0.001$) and advanced T stage ($p=0.000$). Furthermore, there was a highly statistical significant association between positive GLUT-1 expression and poor degree of differentiation (Grade III) ($p=0.000$). Moreover, there was a statistical significant association between (+3) GLUT-1 positivity and advanced stage (III and IV) ($p=0.018$). Also, there is a trend of significance between GLUT-1 expression and hormonal status as 94.1% of triple negative cases showed positive GLUT-1 expression ($p=0.078$). There was no statistical association between GLUT-1 expression and overall survival and univariate survival analysis revealed the bad prognostic impact of negative hormonal status ($p=0.002$).

Conclusion: GLUT-1 is a poor prognostic marker in view of association between positive GLUT-1 expression and advanced nodal stage, advanced T stage, advanced stage grouping (III and IV) and poor degree of differentiation (Grade). Furthermore, inhibition of GLUT-1 might play a therapeutic role for triple negative breast cancer.

Keywords: Immunohistochemistry, Invasive duct carcinoma, Prognostic marker

INTRODUCTION

BC is the most common malignancy in females worldwide [1] and the leading cause of cancer death in women [2]. In Egypt, the most common cancer in female is breast cancer constituting 38.8% followed by non-Hodgkin's lymphoma (8.5%). Also, it is the second cause of cancer death in females after lung cancer [3,4].

Luminal A, Luminal B, human epidermal growth factor receptor 2 (HER2) overexpressing, basal-like, and normal-like are five distinct subtypes of breast cancer with different clinical outcomes [5].

The majority of Basal Like Breast Cancer (BLBCs) are characterised by the expression of basal cytokeratins (CKs) 5/6 and 17, Epidermal Growth Factor Receptor (EGFR), c-kit, and Vascular Endothelial Growth Factor (VEGF) and lack Estrogen Receptor (ER), Progesterone Receptor (PR), and HER2 protein overexpression [6,7].

The first step for glucose metabolism is the transport of glucose across the plasma membrane which is mediated by facilitative Glucose Transporter Proteins (GLUTs) that contain fourteen members [8,9]. GLUT-1, also named facilitates glucose transporter member 1 (SLC2A1) [10], is involved in glucose uptake in the basic state and is broadly expressed in the body tissues. GLUT-1 is elevated in almost all human cancers including brain, breast, head and neck, bladder, renal, colorectal, lung and ovarian cancers [9].

The aim of this study was to clarify the Immunohistochemical (IHC) expression of GLUT-1 and to examine any associations with pathological, clinical and survival data to help in assessing patient's prognosis using 79 breast carcinoma patients.

MATERIALS AND METHODS

This was a random retrospective study that included 79 specimens of breast invasive duct carcinoma retrieved from the archival cases of Pathology Department, Faculty of medicine, Menoufia University, Egypt, spanning the period between January 2010 and December 2017. The clinicopathological data were obtained from the patients' sheets and TNM staging system (2010) is used for staging of the tumour according to size into T1, T2, T3 and T4 and to nodal status into Nx, N0, N1, N2 and N3 [11].

Immunohistochemistry

Paraffin-embedded tissue sections (5 μ m) were deparaffinized in xylene and rehydrated. The sections were treated with 10 μ M citrate buffer, pH 6.0, at 96°C for 10-20 minutes followed by 10 mL Tris-EDTA for 10-20 minutes. Endogenous peroxidase was blocked with peroxidase-blocking reagent (cat. #TP-015-HD) (Lab Vision Cooperation 46360 Ferment Blvd. Ferment, CA 94538-6406, USA, California) using GLUT-1 rabbit polyclonal antibody, {Thermo Fisher Scientific Anatomical Pathology (Fremont, CA)} with a dilution of 1:200. A positive reaction was revealed using the streptavidin-biotin-peroxidase technique (cat. #TP-015-HD) (Lab Vision Cooperation 46360 Ferment Blvd. Ferment, CA 94538-6406, USA) with chromogen DAB. The sections were counterstained with Mayer's haematoxylin (Bio Genex, cat. No. 94583) for 30-60 seconds to stain nuclei then sections were washed in tap water for five minutes.

Red blood cells within tissue sections from a capillary haemangioma case were used as positive controls for GLUT-1. Also intravascular RBCs in the studied slides were used as internal control and negative controls were made by substituting the primary antibodies with non-immune serum.

Interpretation of Immunostaining Results of GLUT-1

Positivity for GLUT-1 was defined as detectable membranous staining in tumour cells. GLUT-1 immunostaining was quantified by grading the proportion of cells that were GLUT-positive. The grading system was as follows: absence of immunoreactive cells =negative; less than 10% of immunoreactive cells=1+; 10% to 50% of immunoreactive tumour cells=2+; and greater than 50% of immunoreactive cells=3+. For statistical analyses, each tissue section was classified as GLUT-1 positive or negative [12].

Overall Survival Data

By revising the patient’s files for breast carcinoma cases ranged from 2010 to 2017, overall survival time was available for all patients (100%).

STATISTICAL ANALYSIS

The statistical analysis was conducted using SPSS “Statistical Package for the Social Sciences” program for windows, version 20, SPSS Inc., Chicago, Illinois, USA. Mann-Whitney (U) and Kruskal-Wallis tests were used to compare nonparametric data and the chi-square was used to assess the association between the clinicopathological parameters and GLUT-1 expression. p-value ≤0.05 was considered to indicate statistical significance in all tests.

RESULTS

The clinicopathological characteristics of invasive duct carcinoma cases are shown in [Table/Fig-1].

Immunohistochemical Results of GLUT-1 in Normal Breast Tissue

Some normal and hyperplastic mammary epithelial cells in tumour-free areas were GLUT-1-positive; however, the intensity of staining in these cells was lower than in cancer cells. GLUT-1-positive normal mammary cells exhibited a diffuse cytoplasmic staining, unlike the cancer cells, and their cell membranes were GLUT-1 negative.

Immunohistochemical Results of GLUT-1 in insitu Ductal Carcinoma

Cells of in-situ ductal carcinoma present in the studied carcinoma cases showed membranous staining similar to that of cancer cells. Immunohistochemical results of GLUT-1 in the studied invasive duct carcinoma cases are shown in [Table/Fig-2,3]. The relationship of GLUT-1 expression in invasive duct carcinoma cases and the studied clinicopathological parameters are shown [Table/Fig-4,5]. There was a highly statistical significant association between positive GLUT-1 expression and advanced nodal stage (p=0.001) and advanced T stage (p=0.000). Furthermore, there was a highly statistical significant association between positive GLUT-1 expression and poor degree of differentiation (Grade) (p=0.000). Moreover, there was a statistical significant association between high GLUT-1 positivity (+3) and advanced stage grouping (III and IV) (p=0.018). Also, there is a trend of significance between GLUT-1 expression and hormonal status as 94.1% of triple negative cases showed positive GLUT-1 expression (p=0.078).

Overall Survival

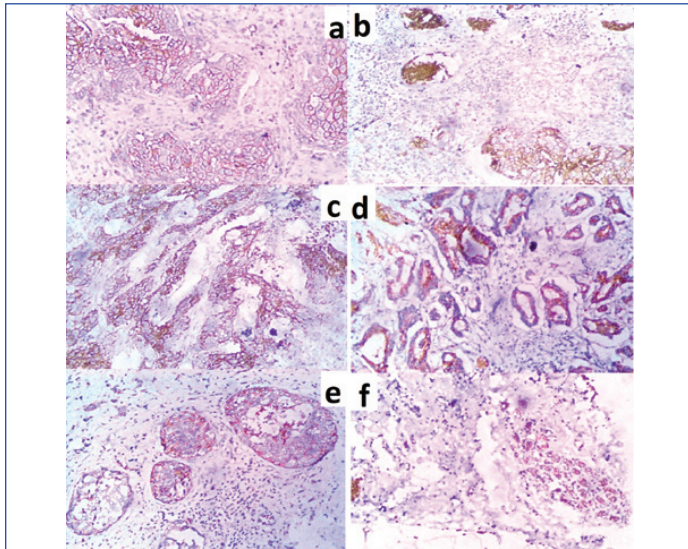
When revising the patients’ files for breast carcinoma overall survival time was available for all (100%) patients. The range of survival time

Variable	n (%)
Age (years)	
Mean±SD	48.152±12.136
Median	48
Range	27-83
Family history	
Positive	62 (78%)
Negative	17 (22%)
Menopausal status:	
Premenopausal	50 (63%)
Post menopausal	29 (37%)
T stage (75 cases)	
T1	11 (14%)
T2	39 (49%)
T3	10 (13%)
T4	15 (24%)
Nodal stage	
Nx	17 (22%)
N0	16 (20%)
N1	8 (10%)
N2	16 (20%)
N3	22 (28%)
Multicentricity	
Present	11 (14%)
Absent	68 (86%)
Vascular invasion	
Present	7 (9%)
Absent	72 (91%)
Perineural invasion	
Present	5 (6%)
Absent	74 (94%)
Stage grouping	
I	5 (6%)
II	14 (18%)
III	50 (63%)
IV	10 (13%)
Hormonal status	
ER+, PR+ and Her2 neu+	12 (15%)
ER-, PR- and Her2 neu+	8 (10%)
Triple negative	17 (22%)
ER+, PR+ and Her2 neu-	32 (40%)
ER+, PR- and Her2 neu-	6 (8%)
ER-, PR+ and Her2 neu+	0 (0%)
ER-, PR+ and Her2 neu-	0 (0%)
ER+, PR- and Her2 neu+	4 (5%)
Grade	
I	6 (8%)
II	22 (28%)
III	51 (64%)
Extracapsular nodal invasion	
Present	5 (6%)
Absent	74 (94%)
Metastasis	
Present	10 (13%)
Absent	69 (87%)

[Table/Fig-1]: Clinicopathological data of the studied invasive duct carcinoma cases. n: Number; SD: Standard deviation; M:F: Male to female

Variables	n (%)
GLUT-1 expression	
• Positive	63 (80%)
• Negative	16 (20%)
Positive GLUT-1 expression	
• +1	8 (10%)
• +2	28 (35%)
• +3	27 (55%)

[Table/Fig-2]: Immunohistochemical results of GLUT-1 in the studied invasive duct carcinoma cases.



[Table/Fig-3]: a) Positive membranous GLUT-1 expression in a case of invasive duct carcinoma (IDC) G III (IHC X 200); b) Positive membranous GLUT-1 expression in a case of IDC G III with positivity in intravascular RBCs as internal control (IHC X 100); c) Positive membranous GLUT-1 expression in a case of IDC G II (IHC X 200); d) Positive membranous GLUT-1 expression in a case of IDC G I (IHC X 200); e) Positive membranous GLUT-1 expression in Insitue ductal carcinoma (IHC X 200) and f) Positive cytoplasmic GLUT-1 expression in normal breast lobules (IHC X 100)

P value	Test	GLUT 1 expression		Variables
		Positive	Negative	
Age	58.8±14.1	55.1±13.4	U=0.254	0.604
Family history				
Positive	3 (17.6%)	14 (82.4%)	$\chi^2=0.091$	0.763
Negative	13 (21%)	49 (79%)		
Menopausal status				
Premenopausal	11 (22%)	39 (78%)	$\chi^2=0.257$	0.612
Post menopausal	5 (17.2%)	24 (82.8%)		
T stage (75 cases)				
T1	5 (45.5%)	6 (54.5%)	$\chi^2=5.605$	0.231
T2	7 (17.9%)	32 (82.1%)		
T3	1 (10%)	9 (90%)		
T4	2 (13.3%)	13 (86.7%)		
Nodal status				
Nx	3 (17.6%)	14 (82.4%)	$\chi^2=18.78$	0.001**
N0	9 (56.3%)	7 (43.8%)		
N1	2 (25%)	6 (75%)		
N2	0 (0%)	16 (100%)		
N3	2 (9.1%)	20 (90.9%)		
Multicentricity				
Present	1 (9.1%)	10 (90.9%)	$\chi^2=0.986$	0.321
Absent	15 (22.1%)	53 (77.9%)		
Vascular invasion				

Present	0 (0%)	7 (100%)	$\chi^2=1.951$	0.163
Absent	16 (22.1%)	56 (77.8%)		
Perineural invasion				
Present	0 (0%)	5 (100%)	$\chi^2=1.356$	0.244
Absent	16 (21.6%)	58 (78.4%)		
Stage grouping				
I	4 (80%)	1 (20%)	$\chi^2=20.128$	0.000**
II	6 (42.9%)	8 (57.1%)		
III	4 (8%)	46 (92%)		
IV	2 (20%)	8 (80%)		
Hormonal status				
ER+, PR+ and Her2 neu+	5 (71.7%)	7 (58.3%)	$\chi^2=9.904$	0.078
ER-, PR- and Her2 neu+	0 (0%)	8 (100%)		
Triple negative	1 (5.9%)	16 (94.1%)		
ER+, PR+ and Her2 neu-	7 (21.9%)	35 (78.1%)		
ER+, PR- and Her2 neu-	1 (16.7%)	5 (83.3%)		
ER+, PR- and Her2 neu+	2 (50%)	2 (50%)		
Grade				
I	5 (83.3%)	1 (16.7%)	$\chi^2=16.037$	0.000**
II	3 (13.6%)	19 (86.4%)		
III	8 (15.7%)	43 (84.3%)		
Extracapsular nodal invasion				
Present	0 (0%)	5 (100%)	$\chi^2=1.356$	0.244
Absent	16 (21.6%)	58 (78.4%)		
Metastasis				
Present	2 (20%)	8 (80%)	$\chi^2=0.000$	0.983
Absent	14 (20.3%)	55 (79.7%)		

[Table/Fig-4]: The relationship of GLUT-1 expression in invasive duct carcinoma cases and the studied clinicopathological parameters. n: Number; SD: Standard deviation; **: Highly-significant; χ^2 : Chi square; U: Mann-Whitney test; %: Percent

Variables	Positive GLUT-1 expression			Test	p-value
	+1	+2	+3		
Age	45.2±11.1	46.1±10.2	48.3±12.4	u=1.286	0.526
Family history					
Positive	8 (16.3%)	19 (38.8%)	22 (44.9%)	$\chi^2=4.094$	0.129
Negative	0 (0%)	9 (64.3%)	5 (35.7%)		
Menopausal status					
Premenopausal	5 (12.8%)	16 (41%)	18 (46.2%)	$\chi^2=0.530$	0.767
Post menopausal	3 (12.5%)	12 (50%)	9 (37.5%)		
T stage (75 cases)					
T1	3 (50%)	2 (33.3%)	1 (16.7%)	$\chi^2=22.403$	0.004**
T2	4 (12.5%)	18 (56.3%)	10 (31.3%)		
T3	0 (0%)	6 (66.7%)	3 (33.3%)		
T4	1 (7.7%)	1 (7.7%)	11 (84.6%)		
Nodal status					
Nx	0 (0%)	1 (7.1%)	13 (92.9%)	$\chi^2=32.588$	0.000**
N0	2 (28.6%)	5 (71.4%)	0 (0%)		
N1	3 (50%)	3 (50%)	0 (0%)		
N2	2 (12.5%)	10 (62.5%)	4 (25%)		
N3	1 (5%)	9 (45%)	10 (50%)		
Multicentricity					
Present	0 (0%)	3 (30%)	7 (70%)	$\chi^2=4.111$	0.128
Absent	8 (15.1%)	25 (47.2%)	20 (37.7%)		
Vascular invasion					

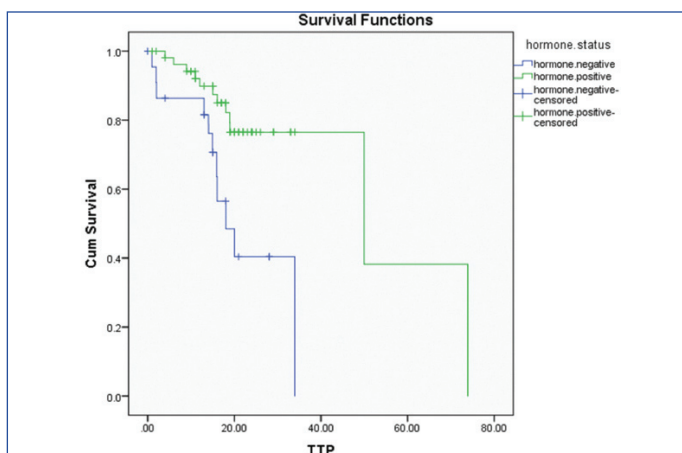
Present	0 (0%)	4 (57.1%)	3 (42.9%)	$\chi^2=1.286$	0.526
Absent	8 (14.3%)	24 (42.9%)	24 (42.9%)		
Perineural invasion					
Present	0 (0%)	3 (50%)	2 (40%)	$\chi^2=0.996$	0.608
Absent	8 (13.8%)	25 (43.1%)	25 (43.1%)		
Stage grouping					
I	1 (100%)	0 (0%)	0 (0%)	$\chi^2=15.249$	0.018*
II	2 (25%)	6 (75%)	0 (0%)		
III	5 (10.9%)	19 (41.3%)	22 (47.8%)		
IV	0 (0%)	3 (37.5%)	5 (62.5%)		
Hormonal status					
ER+, PR+ and Her2 neu+	1 (14.3%)	1 (14.3%)	5 (71.4%)	$\chi^2=7.551$	0.673
ER-, PR- and Her2 neu+	1 (12.5%)	3 (37.5%)	4 (50%)		
Triple negative	2 (12.5%)	7 (43.8%)	7 (43.8%)		
ER+, PR+ and Her2 neu-	3 (12%)	13 (52%)	9 (36%)		
ER+, PR- and Her2 neu-	0 (0%)	3 (60%)	2 (40%)		
ER+, PR- and Her2 neu+	1 (50%)	1 (50%)	0 (0%)		
Grade					
I	0 (0%)	1 (100%)	0 (0%)	$\chi^2=7.206$	0.125
II	4 (21.1%)	11 (57.9%)	4 (21.1%)		
III	4 (9.3%)	16 (37.2%)	23 (53.5%)		
Extracapsular nodal invasion					
Present	1 (20%)	2 (40%)	2 (40%)	$\chi^2=0.263$	0.877
Absent	7 (12.1%)	26 (44.8%)	25 (43.1%)		
Metastasis					
Present	0 (0%)	3 (37.5%)	5 (62.5%)	$\chi^2=2.088$	0.352
Absent	8 (14.5%)	25 (45.5%)	22 (40%)		

[Table/Fig-5]: The relationship of GLUT-1 positive expression in invasive duct carcinoma cases and the studied clinicopathological parameters. SD: Standard deviation; *: significant; **: highly significant; χ^2 : Chi square; U: Mann-Whitney test; %: Percent

Variables	Mean			Median			p-value
	Estimate	95% CI		Estimate	95% CI		
		Lower	Upper		Lower	Upper	
GLUT 1	-	-	-	-	-	-	0.01
Tumour size							
T1 and T2	44.57	30.83	56.30	49.97	7.72	92.21	0.79
T3 and T4	28.54	23.90	33.27	33.91	-	-	
Overall	41.62	28.46	54.78	49.91	22.85	77.09	
Nodal status							
Positive	39.65	26.89	52.42	33.97	11.46	56.48	0.19
Negative	26.77	24.02	29.53	-	-	-	
Overall	40.90	28.11	53.68	33.97	12.52	55.42	
Stage							
1 and 2	27.02	24.52	29.51	-	-	-	0.09
3 and 4	38.86	26.27	51.46	33.97	11.29	56.65	
Overall	40.90	28.11	53.68	33.97	12.52	55.42	
Hormonal status							
Negative	21.48	15.83	27.12	18.07	11.85	24.28	0.002**
Positive	50.60	35.82	65.37	49.97	6.71	93.23	
Overall	40.90	28.11	53.68	33.97	12.52	55.42	
Her 2 neu							

Positive	42.21	26.18	58.24	49.97	5.00	94.93	0.87
Negative	27.26	24.00	30.53	33.97	-	-	
Overall	40.90	28.11	53.68	33.97	12.52	55.42	
Grade							
1 and 2	21.00	19.39	22.61	-	-	-	0.61
3 and 4	40.67	27.81	53.52	33.97	12.46	55.48	
Overall	40.90	28.11	53.68	33.97	12.52	55.42	
Vascular invasion							
Present	22.82	20.72	24.91	-	-	-	0.40
Absent	40.28	27.54	53.02	33.97	12.36	55.58	
Overall	40.90	28.11	53.68	33.97	12.52	55.42	
Perineural invasion							
Present	22.02	18.83	225.21	-	-	-	0.74
Absent	40.79	27.92	53.66	33.97	12.47	55.47	
Overall	40.90	28.11	53.68	33.97	12.52	55.42	

[Table/Fig-6]: Univariate survival analysis for breast carcinoma cases. N.B: No descriptive statistics were computed for GLUT because all GLUT negative cases were censored to progression (No GLUT negative cases were progressed) **: Highly significant; CI: Confidence interval



[Table/Fig-7]: Kaplan-Meier overall survival for breast carcinoma patients with different hormonal status p<0.002 "highly significant".

was 1 to 105 months with 21.01±14.477 as mean±SD of months and a median of 20 months.

Univariate Survival Analysis for Breast Carcinoma Cases

Univariate survival analysis revealed the bad prognostic impact of negative hormonal status (p-value=0.002) on patient outcome [Table/Fig-6,7]:

DISCUSSION

Prevalence of GLUT-1 membranous expression in breast carcinoma cases was 71.8% [13] and range from 42% to 90% [14] and this was near the results in the present study as we found GLUT-1 expression in 80 % of the studied cases. Moreover, the present results were higher than that reported for the same antibody by Kang SS et al., (47%). These differences might have been related to differences in patient populations or tumour types.

Some normal and hyperplastic mammary epithelial cells in tumour-free areas were GLUT-1-positive; however, the intensity of staining in these cells was lower than in cancer cells. GLUT-1-positive normal mammary cells exhibited a diffuse cytoplasmic staining, unlike the cancer cells, and their cell membranes were GLUT-1 negative and this result agreed with Kuo SJ et al., [13]. However, this disagreed with Alo PL et al., who reported that 36% of typical/atypical hyperplastic breast tissue expressed GLUT-1 and normal adjacent tissues were positive in 31% of their cases [15].

Absence of membranous GLUT-1 expression in normal and hyperplastic breast tissue and its presence in in-situ ductal

carcinoma and ductal carcinoma cases might clarify that GLUT-1 might have a role in early transformation process [15,16].

In the present study there was a statistical significant association between GLUT-1 positivity and poor prognostic factors including advanced nodal stage, advanced T stage, poor degree of differentiation (Grade) and advanced stage grouping (III and IV). These results agreed with Alo PL et al., who found that GLUT-1 expression was increased in poorly differentiated breast carcinoma and associated with high proliferative activity, increased invasiveness, and aggressive behaviour [15]. Moreover these results agreed also with Kawamura T et al., who reported that overexpression of GLUT-1 has been described in various malignant tumours and was associated with enhanced tumour aggressiveness and poor outcome [17].

Also the present study agreed with other studies that reported that GLUT-1 was also a prognostic molecular biomarker for patients with colorectal cancer liver metastasis [18].

These results could be explained as GLUT-1 could promote cell proliferation, migration and invasion by regulating epidermal growth factor receptor and integrin signaling in triple-negative breast cancer cells. Also, GLUT-1 was one of number of proteins acting through the Hypoxia-Inducible Factor 1 (HIF-1) pathway, which allowed tumour cells to survive the harsh tumour microenvironment and lead to resistance to radiotherapy and chemotherapy and is associated with a more aggressive phenotype with an increased propensity for metastases [19].

Inhibition of GLUT-1 might be used as an effective method for curing chemo-resistant breast cancer patients. As blocking of GLUT-1 can effectively decrease intracellular glucose level and induce energy stress in malignant cells, which initiates the activation of Adenosine Monophosphate Activated Protein Kinase (AMPK). AMPK might induce phosphorylation of tuberous sclerosis complex that increases its ability to suppress mammalian target of rapamycin (mTOR) activity, that could enhance the breast cancer cells death probably through activating AMPK and inhibiting Motor [20].

Furthermore, there was a trend of significance between GLUT-1 expression and hormonal status as 94.1% of triple negative cases showed positive GLUT-1 expression. These results agreed with Kang SS et al., who found that GLUT-1 expression correlated with negative ER and negative PR cases [15].

In the present study there was no statistically significant association between GLUT-1 expression and overall survival as no descriptive statistics were computed for GLUT-1 because all GLUT-1 negative cases were censored to progression and these results agreed with Kuo SJ et al., who found that there was no correlation between GLUT-1 expression and either recurrence or survival rate [13].

However, these results disagreed with Kang SS and Chun YK who found that GLUT-1 expression correlated with poor disease free survival. These differences might have been related to differences in patient populations or tumour types.

LIMITATION

The small number of invasive duct carcinoma cases as they were 79 cases only.

CONCLUSION

GLUT-1 is a poor prognostic marker in view of association between positive GLUT-1 expression and advanced nodal stage, advanced T stage, advanced stage grouping (III and IV) and poor degree of differentiation (Grade). Furthermore, inhibition of GLUT-1 might play a therapeutic role for triple negative breast cancer.

REFERENCES

- [1] Siegel RL, Miller KD, Jemal A. Cancer Statistics 2017. *CA Cancer J Clin.* 2017;67:07-30.
- [2] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin.* 2015;65:87-108.
- [3] Ibrahim AS, Khaled HM, Mikhail NN, Baraka H, Kamel H. Cancer Incidence in Egypt: results of the National Population-Based Cancer Registry Program. *Journal of Cancer Epidemiology.* 2014;2014:437971.
- [4] El Bolkainy MN, Nohu MA, Farahat IG, El Bolkainy TN, Badawy OM. Breast cancer, in pathology of cancer. 5th edition. 2016. Chapter 18: 298-312.
- [5] Brenton JD, Carey LA, Ahmed AA, Caldas C. Molecular classification and molecular forecasting of breast cancer: ready for clinical application? *Lin Oncol.* 2005;23(29):7350-60.
- [6] Nielsen TO, Hsu FD, Jensen K, Cheang M, Karaca G, Hu Z, et al. Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. *Clin Cancer Res.* 2005;10(16):5367-74.
- [7] Linderholm BK, Hellborg H, Johansson U, Elmberger G, Skoog L, Lehtiö J, et al. Significantly higher levels of Vascular Endothelial Growth Factor (VEGF) and shorter survival times for patients with primary operable triple-negative breast cancer. *Ann Oncol.* 2009;20(10):1639-46.
- [8] Thorens B, Mueckler M. Glucose transporters in the 21st Century. *Am J Physiol Endocrinol Metab.* 2010;298:E141-45.
- [9] Macheda ML, Rogers S, Best JD. Molecular and cellular regulation of glucose transporter (GLUT) proteins in cancer. *J Cell Physiol.* 2005;202:654-62.
- [10] Wang Y, Yun Y, Wu B, Wen L, Wen M, Yang H, et al. FOXM1 promotes reprogramming of glucose metabolism in epithelial ovarian cancer cells via activation of GLUT1 and HK2 transcription. *Oncotarget.* 2016;7:47985-97.
- [11] Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, et al. *AJCC Cancer Staging Manual.* 7th ed. New York, NY: Springer-Verlag; 2010.
- [12] Kang SS, Chun YK, Hur MH, Lee HK, Kim YJ, Hong SR, et al. Clinical Significance of Glucose Transporter 1 (GLUT1) Expression in Human Breast Carcinoma. *Jpn J Cancer Res.* 2002;93:1123-28.
- [13] Kuo SJ, Wu YC, Chen CP, Tseng HS, Chen DR. Expression of glucose transporter-1 in Taiwanese patients with breast carcinoma-a preliminary report. *Kaohsiung J Med Sci.* 2006;22:339-45.
- [14] Brown RS, Goodman TM, Zasadny KR, Greenson JK, Wahl RL. Expression of hexokinase II and Glut-1 in untreated human breast cancer. *Nucl Med Biol.* 2002;29(4):443-53.
- [15] Alo PL, Visca P, Botti C, Galati GM, Sebastiani V, Andreano T, et al. Immunohistochemical expression of human erythrocyte glucose transporter and fatty acid synthase in infiltrating breast carcinomas and adjacent typical/atypical hyperplastic or normal breast tissue. *Am J Clin Pathol.* 2001;116(1):129-34.
- [16] Wellberg EA, Johnson S, Finlay-Schultz J, Lewis AS, Terrell KL, Sartorius CA, et al. The glucose transporter GLUT1 is required for ErbB2-induced mammary tumourigenesis. *Breast Cancer Research.* 2016;18:131.
- [17] Kawamura T, Kusakabe T, Sugino T, Watanabe K, Fukuda T, Nashimoto A, et al. Expression of glucose transporter-1 in human gastric carcinoma: association with tumour aggressiveness, metastasis, and patient survival. *Cancer.* 2001;92(3):634-41.
- [18] Goos JA, de Cuba EM, Coupe VM, Diosdado B, Delis-Van Diemen PM, et al. Glucose transporter 1 (SLC2A1) and vascular endothelial growth factor A (VEGFA) predict survival after resection of colorectal cancer liver metastasis. *Ann Surg.* 2016; 263:138-145.
- [19] Semenza GL. Hypoxia, clonal selection, and the role of HIF-1 in tumour progression. *Crit Rev Biochem Mol Biol.* 2000; 35(2), 71-103.
- [20] Fruman DA, Rommel C. PI3K and cancer: lessons, challenges and opportunities. *Nat Rev Drug Discov* 2014; 13:140-156.

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