GLUCOSE TRANSPORTER-1 (GLUT-1) IMMUNOREACTIVITY IN BENIGN, BORDERLINE AND MALIGNANT OVARIAN EPITHELIAL TUMORS.

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ABSTRACT

OBJECTIVE: Recent study analyzed GLUT-1 expression in ovarian epithelial tumors by its immunohistochemical implication to distinguish benign, borderline and malignant tumors. **STUDY DESIGN**: An Analytical Cross-sectional study. **PLACE & DURATION:** Department of pathology, Basic medical sciences institute (BMSI), JPMC from July 2020 to December 2020. **METHODOLOGY:** Our study based on the analysis of ovarian tumor samples (irrespective of surgical procedure; except biopsies). Out of 408 cases of histopathologically proven ovarian tumors received in last five years, 72 cases were selected and analyzed further for morphological features, grading and results of immunostaining. Immunohistochemical staining was performed using Rabbit polyclonal antibody. The immunostaining was evaluated and scored by grading the intensity of cell membrane staining and proportion of positive neoplastic cells. Chi-square/fisher exact test (will be applied for values<5) was used to test the association between the intensity and the ovarian epithelial neoplasm, grade and type of lesions. **RESULTS**: We observed that majority (86.4%) of benign tumors were GLUT-1 negative, while none of GLUT-1 showed GLUT-1 negativity. Consequently, majority (77.8%) of borderline tumors revealed moderate GLUT-1 staining but none of them showed marked staining intensity. In contrast, most of malignant epithelial tumors (56.1%) displayed marked extensive GLUT-1 staining. **CONCLUSION:** We concluded that GLUT-1 is a useful marker to distinguish benign ovarian tumors from borderline and borderline from their malignant counterparts. Hence, GLUT-1 can be a useful adjunct to the histopathological diagnosis of ovarian epithelial tumors by serving as an objective parameter that can correlate with their biological behavior and possible clinical outcome.

KEYWORDS: Ovarian epithelial tumors, Immunohistochemical, GLUT-1, Benign, Borderline, Malignant

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INTRODUCTION

Ovarian cancer is the fifth most frequent cause of death from cancer in women in U.K. and ranks second among the gynaecological cancers, following uterine cancer.[1] According to Shaukat Khanum Collective Cancer Registry Report (1994-2011), ovarian cancer ranks second among malignancies in adult females (>18 yrs) in Pakistan, accounting for 5.7% of the total cancers in females.[2] According to the Karachi Cancer Registry, ovarian cancer found to be third most common malignancy diagnosed in women; moreover Karachi south and all urban population falls into a high risk region for ovarian cancer, which accounts to second highest incidence in Asia after urban Delhi.[3,4] Surface epithelial tumors originate from the surface epithelium of the ovary and classified as benign, borderline and malignant under the recommendation of WHO[5]; accounts for approximately 60% of all ovarian tumors and 90% of malignant ovarian ovarian tumors.[6]

It is important to separate borderline ovarian tumors from the invasive tumors because of their superior prognosis.[7] This distinction however, is not always easy on routine H&E stained tissue sections

because of controversy regarding the arbitrary diagnostic criteria and considerable interobserver variability.[8]

A major problem with the diagnosis of a serous borderline tumor is that the absence of stromal invasion is the only feature that distinguishes them from invasive low grade ovarian tumors. The papillae of LMP serous tumors can be deeply invaginated in the stroma leaving doubt on the presence of invasion.

A meticulous sampling is therefore necessary to carry out these important determinations. Despite the complete and accurate histological assessment, the identification of borderline tumors on routine H&E stained sections subjects to considerable interobserver variability as well as associated with difficulty in early invasive lesions. GLUT-1 is a transmembrane transport protein that facilitates glucose transport into cells, normally expressed in tissues which depend mainly on glucose metabolism.[9] GLUT-1 is largely undetectable by immunohistochemistry on normal epithelial tissues and benign epithelial tumors but is expressed in a significant proportion of a variety of human cancers[10] including hepatic, pancreatic, breast, esophageal, brain, renal, lung, cutaneous, colorectal, endometrium, ovarian and cervical carcinoma.[11]

It was estimated that positive correlation exists between Glut-1 expression and tumor proliferation, malignant transformation and poor prognosis.[12,13]

In this study, we attempted to compare the expression of GLUT-1 in benign, borderline and malignant ovarian epithelial tumors; and evaluated the use of GLUT-1 as a diagnostic tool in distinguishing between morphologically dubious borderline and malignant changes of the ovary.

OBJECTIVE

This study is designed to evaluate GLUT-1 expression in ovarian tumors focusing on the association with the degree of neoplastic nature i.e, benign, borderline malignancy and overt malignancy. Furthermore, to assess the role of GLUT-1 as a diagnostic and histologic prognostic marker in those cases where differentiation between premalignant borderline and malignant changes in ovarian epithelial neoplasms poses difficulty.

MATERIALS AND METHODS

This is a cross-sectional study, performed at the department of pathology, BMSI, JPMC, from July 2020 to December 2020, based on the analysis of ovarian tumor samples (irrespective of surgical procedure; except biopsies). From the data of last five year period, total of 408 cases of ovarian tumors were found to be received in our centre, out of which 72 cases were selected and analyzed further for morphological features, grading and results of immunostaining. Immunostaining was performed on selected cases using polyclonal antibody against GLUT-1. For the purpose of this study, GLUT-1 expression was considered positive only if distinct membrane staining was present, and negative in which 100% of the cells were GLUT-1 negative. As expected, strong staining of RBC membrane was observed and served as an internal positive control while nonepithelial ovarian stromal cells served as an internal negative control. However, human colorectal carcinoma known to be positive for GLUT-1 used as positive control. As negative controls, adjacent sections were incubated in parallel with non-immune serum instead of the primary antibody.

The intensity of staining was graded as no staining (0), weak staining (1+), moderate staining (2+) and strong staining (3+). The extent of staining was estimated in percentage by counting positive tumor cell membranes, scored as follow: none (0%), weak (1+, less than 10%), moderate (2+, 10-50%) and intense (3+, greater than 50%). An additive quick score is then calculated as[14]

Score of intensity (Additive Quick Score) = Intensity of staining + Proportion of staining

1. 0 Score = Negative staining (0)
2. Score of 2 and 3 = Weak staining **(1+)**
3. Score of 4 and 5 = Moderate staining **(2+)**
4. Score of 6 = Strong staining **(3+)**

Chi-square/fisher exact test (will be applied for values<5) was used to test the association between the intensity and the ovarian epithelial neoplasm, grade and type of lesions. In all statistical analysis only p-value <0.05 was considered significant.

Inclusion criteria included all properly formalin fixed, paraffin-embedded surgical pathology specimen of ovarian tumors received in the department of pathology, BMSI, during the above mentioned time period. All Poorly fixed tissue, non-epithelial ovarian tumors and tumors metastizing to ovary were all excluded.

RESULTS AND OBSERVATIONS

Selected cases included 22 benign tumors (11 serous cystadenomas, 11 mucinous cystadenomas), 9 borderline tumors (7 serous, 2 mucinous), 41 adenocarcinomas (26 serous, 7 mucinous, 5 endometroid, 1 clear cell, 2 poorly/undifferentiated).

Table 1 shows the GLUT-1 staining intensity in different histological grades of ovarian epithelial tumors. Complete loss of GLUT-1 expression was observed in 86.4% (19/22) cases of benign epithelial tumors including 11 mucinous cystadenomas and 8 serous cystadenomas. While only 13.6% (3/22) cases of serous cystadenomas showed weak staining intensity, which was focal in nature and often seen in the apices of papillae. In case of borderline tumors, 77.8% (7/9) tumors showed moderate staining intensity while 22.2% (2/9) had weak staining intensity. Staining was focal and mostly obvious at papillary tufts.

39 out of 41 cases of malignant tumors stained positively for GLUT-1; and 56.1% (23/41) cases showed strong (3+) staining

intensity with extensive distribution, 31.7% (13/41) had also moderate GLUT-1 staining. It was observed that strong expression was found to be clustered far away from vascular stroma. Only 4.87% (2/41) of cases were non-staining for GLUT-1, which included 1 case of clear cell carcinoma and 1 case of undifferentiated tumor.

Table 2 compares GLUT-1staining intensity according to the different histological types of ovarian epithelial malignant tumors. Majority (69.23%) of serous cystadenocarcinomas has shown strong staining intensity while none of mucinous cystadenocarcinoma did so. 57.1% of mucinous cystadenocarcinomas showed moderate GLUT-1 staining and remaining 42.85% has shown weak staining intensity. In case of endometroid carcinomas, 80% (4/5) were strongly stained and 20% (1/5) has shown moderate staining pattern. None of the case of serous, mucinous and endometroid carcinoma has shown negative staining for GLUT-1.One case of poorly differentiated epithelial tumor has showed strong (3+) GLUT-1 staining.

TABLE I: INTENSITY OF GLUT-1 IMMUNOREACTIVITY IN DIFFERENT GRADES OF OVARIAN EPITHELIAL TUMORS (n=72)

Lesion	Total No. of cases	Score of Intensity				P-value
		0	1+	2+	3+	
Benign	22	19(86.4%)	3(13.6%)	0	0	0.001
Borderline	9	0	2(22.2%)	7 (77.8%)	0	
Malignant	41	2(4.9%)	3(7.3%)	13(31.7%)	23 (56.1%)	

Significant association of different grades with intensity score $p<0.05$

Score of intensity (Additive Quick Score) = Intensity of staining + Proportion of staining

0 = Negative staining**1** = Weak staining**2** = Moderate staining**3** = Strong staining

TABLE II: INTENSITY OF GLUT-1 IMMUNOREACTIVITYIN DIFFERENT HISTOLOGIC TYPES OF OVARIAN EPITHELIAL TUMORS (n=41)

Lesion	Total no. of cases	Intesity score				P-value
		0	1+	2+	3+	
Serous	26	0	0	8(30.8%)	18 (69.2%)	0.001
Mucinous	7	0	3 (42.85%)	4 (57.1%)	0	
Endometroid	5	0	0	1 (20.0%)	4 (80.0%)	
Clear Cell	1	1(100%)	0	0	0	
Poorly Differentiated	1	0	0	0	1(100%)	
Undifferentiated	1	1 (100%)	0	0	0	

Significant association of tumour lesion with intensity score $p<0.05$

Score of intensity (Additive Quick Score) = Intensity of staining + Proportion of staining

0 = Negative staining**1** = Weak staining**2** = Moderate staining**3** = Strong staining

DISCUSSION

As the prognosis, outcome and treatment strategy of ovarian tumors mainly depend upon their histological grade; researchers have been emphasized on the diagnostic as well as prognostic markers to differentiate between benign, premalignant borderline and malignant ovarian tumors. The present study has attempted to observe the role of GLUT-1 immunoexpression on full spectrum of ovarian epithelial tumors. Our study has revealed a strong association of GLUT-1 immunoreactivity with ovarian epithelial neoplasms. This is in close relation with various studies [15,16] reporting that GLUT-1 expression has been associated with neoplastic progression in the natural history of gall bladder & endometrial carcinoma respectively. In the current study, majority (86.36%) of the benign epithelial tumors including all mucinous (11/11) and most of serous (8/11) showed negative GLUT-1 staining. This finding is almost the same as reported by Kalir and Ozcan [15,16], the only difference being that the both the above studies have not shown even a single case of benign tumor (cystadenomas) to be positive; however we have found 13.63% (3/22) cases to be weakly but focally (1+) GLUT-1 positive. Keeping in view that we have also considered only membrane-specific reaction to be positive, just as taken by above mentioned authors, this difference could be due to the technical discrepancies i.e. use of computer assisted image analysis system for immunoscoring by other authors. Moderate (2+) staining intensity for GLUT-1 was observed in most (77.77%) of borderline tumors followed by weak staining (1+) in 22.22% of the cases. None of the borderline case showed negative (0) or marked staining (3+). Our findings are in accordance with different studies. A study done by Rudlowski et al[17] has observed weak to moderate GLUT-1 expression in all of their borderline cases; similarly Cantuaria et al[18] has found weak (1+) positivity in 60% and moderate (2+) positivity in 40% of borderline cases in his study. In a study of Kalir et al[15] , 80% of borderline tumors stained positively with GLUT-1, with weak to moderate staining intensity and focal distribution. We observed patchy and focal pattern of GLUT-1 expression in borderline tumors, frequently at the apices of papillary tufts. In addition, it was also noted that 85.7% (6/7) of the serous borderline tumors has shown moderate GLUT-1 staining and only 14.28% (1/7) showed weak (1+) staining; while 50% (1/2) of mucinous borderline tumors

showed moderate and 50% showed weak GLUT-1 staining. This is in close proximity to Lida et al[19] who found majority (54%) of serous borderline tumors to be moderately stained while majority (68%) of mucinous borderline tumors to be weakly GLUT-1 stained.

Out of 41 malignant epithelial tumors in our study, 39 (95.12%) stained positively with anti-GLUT1. In positive cases, staining was of moderate (in 31.7% of cases) to strong (in 56.1% of cases) intensity and was more extensive than in the borderline tumors i.e. in 70.7% of malignant cases, immunoexpression was seen in >50% of the cell membranes. These findings corresponds to those by Iida et al[19] , whose 26% of carcinomas had moderate and 54% had strong staining intensity. Kalir et al[15] has also found moderate to strong GLUT-1 staining intensity in 96% cases of ovarian carcinoma. Above explained figures has mentioned that GLUT-1 immunoreactivity progresses gradually through all stages of ovarian tumors i.e. benign, premalignant borderline to frank carcinoma; suggesting that the degree of expression of the GLUT-1 is in close association with histopathological grade of malignant transformation of ovarian epithelial tumors by supporting their increase need for glucose metabolism. Various studies done by Kalir[15], Cantuaria[18] and Iida[19] and has also shown the similar pattern of progressive GLUT-1 distribution among ovarian epithelial tumors. Two recent studies also showed almost similar results. A study by Elbasateeny[23] also found to be in concordance of our study, showed Glut-1 staining was absent in all benign ovarian tumors, and showed progressively more staining in invasive tumors as compared to borderline tumors. These differences in Glut-1 expression among the studied benign, borderline and malignant tumors were statistically highly significant. Similarly study by Yu & colleagues[24] found expression of GLUT-1 immunochemistry staining result to be different in ovarian benign, borderline and malignant tumors and their intensity as positively related with the malignancy and histological grade. It was also observed that expression of GLUT-1 differed among the histological types; and difference between serous and mucinous was significant. This difference of immunoexpression was more obvious among ovarian carcinomas rather than borderline counterparts therefore majority of studies have compared carcinomas of different histological types for GLUT-1 immunoreactivity. Iida et al[19] had observed that most (39%) of mucinous adenocarcinomas revealed moderate (2+) GLUT-1 positivity while most (76%) of serous adenocarcinomas appeared to be strongly (3+) positive. We observed the same pattern in our series, moderate (2+) GLUT-1 staining in most (57.14%) of mucinous adenocarcinomas and strong (3+) GLUT-1 staining in majority (69.23%) of serous adenocarcinomas. Cantuaria et al[18] have found similar pattern with slightly different frequencies in his study. They also observed 3+ score (> 50% of cell membranes) of GLUT-1 positivity in 36% of their serous and 12% of mucinous adenocarcinomas. None of our cases of mucinous adenocarcinoma were markedly (3+) positive, which is in concordance to study by Ozcan et al[16] who reported all his cases of mucinous adenocarcinoma to be moderately (2+) GLUT-1 positive. The reason of this distinct difference in GLUT-1 expression between serous and mucinous tumors is the different architecture and proliferative activity. The strong expression in serous type, particularly adenocarcinomas is considered to be related to its high proliferative ability, which leads to papillary stratified structure of its tumor cells accompanied by fewer vascular channels. Papillary architecture of tumor cells is believed to lead to more hypoxic microenvironment resulting in intense GLUT-1 expression in serous tumors. However, mucinous adenocarcinomas may face less oxygen-deprived cell environment because the back-to-back arrangement of nests of tumor cells is accompanied by fine vascular stroma even when the adenocarcinoma nests are very crowded[19]. The same speculation was supported by Yasuda[20] who found strong expression of GLUT-1 in thyroid papillary carcinomas as compared to follicular carcinomas. Our finding in which GLUT-1 is mostly strongly expressed in tumor cells distal from stroma particularly at perinecrotic areas could also be explained by induction of hypoxia-sensing pathway, one target of which is the GLUT1 gene, leading to enhanced expression of this protein.[15] A study by Ito et al[21] suggested that GLUT-1 also regulate MMP-2 protein which by means of increase degradation of basement membrane leads to early tumor invasion and metastasis. In addition, Cantuaria et al[22] already reported significantly shorter disease free survival rate in patients with GLUT-1 overexpression. Another utility of GLUT-1 found by Kalir[15] is its use as a marker to distinguish invasive from non-invasive serous borderline implants.

We thus concluded that GLUT-1 plays a leading role in glucose uptake by ovarian epithelial tumor cells, providing they increase growth and aggressive biological behavior. Our findings support the fact of potential relevance of GLUT-1 as a diagnostic tool and a meaningful protein target for the treatment of ovarian cancers in future.[23-26]

CONCLUSION

According to our study, surface epithelial tumors are the commonest among ovarian tumors in our population; with the mean age of 47 years for ovarian carcinomas. GLUT-1 was found to be an interesting biomarker as its progressive increase immunoexpression from benign to borderline to malignant ovarian neoplasms

suggests its association with different grades of ovarian epithelial tumors; moreover its relative strong expression in serous tumors as compared to mucinous shows its association with the histological characteristics of the tumors. Thus, on the basis of our observations we concluded that GLUT-1 immunoprofiling may assist in discrimination of benign from borderline and borderline from malignant ovarian tumors when overlapping morphological features create difficulty on routine staining. It also provides useful prognostic information particularly for borderline category; moreover the utility of GLUT-1 as a marker to distinguish invasive from non-invasive serous borderline implants could be recommended. Thus, prognostic implication of GLUT-1 overexpression could help in identification of patient with poor prognosis that may benefit from specific therapeutic targeting of the overexpressed marker in future.

RECOMMENDATIONS

Further studies based on large number of cases with complete follow-up data are recommended. However, use of immunohistochemistry to evaluate protein levels is only semi-quantitative; therefore molecular studies along with GLUT-1 immunoprofiling are recommended to identify genetic mutation in ovarian epithelial tumors, so malignant behavior of tumor can be ascertained as well as to predict their response to different treatment modalities.

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REFERENCES

1. Cancer Research UK: cancer incidence for common cancers 2010; Available from www.cancerresearchuk.org/ cancer-info/ cancerstats/ incidence/ common cancers/uk-cancer-incidence-statistics-for-common-cancers. Last updated 19/12/12.
2. Shaukat Khanum Memorial Cancer Hospital Registry: Collective Cancer Registry Report (1994-2011); Available at www.shaukatkhanum.org.pk/images/ skm_img/downloads/pdf/ccrr_1994_2011.pdf
3. Bhurgri Y, Shaheen S, Kayani N, Nazir K, Ahmed R, Ahmed U, Bashir I, Setna F, Bhurgri A, Hasan SH, Zaidi SMH. Incidence, trends and morphology of ovarian carcinoma in KarachI (1995-2002). Asian Pacific J Cancer Prev 2011; 12:1567-1571.
4. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB (2002). Cancer Incidence in Five Continents VIII, No.155. Lyon: IARC
5. Lee KR, Tavassoli FA, Prat J, Dietel M, Gersell DJ, Rutgers J. Tumors of the ovary and peritoneum In: Tavassoli FA, Devilee P, eds. World Health Organization classification of tumors. Pathology and Genetics. Tumours of the Breast and Female Genital Organs. Lyon: IARC Press 2003; pp.114 -115.
6. Chen VW, Rulz B, Kllleen JL, Cote TR, Wu XC, Correa CN. Pathology and Classification of Ovarian Tumors. Cancer 2003; 97(Suppl):2631-2642.
7. Lalwani N, Shanbhogue AKP, Vikram R, Nagar A, Jagirdar J, Prasad SR, 2010. Current update on borderline ovarian neoplasms. Am J Roentgenol 2010; 194:330-336.
8. Lodhi S, Najam S, Pervez S. DNA Ploidy Analysis of Borderline Epithelial Ovarian Tumors. J Pak Med Assoc 2000; 50:349-51.
9. Legan M, Tevzic S, Tolar A, Luzar B, Marolt VF. Glucose Transporter-1 (GLUT-1) Immunoreactivity in Benign, premalignant and malignant lesions of the gall bladder. Pathol Oncol Res 2011; 17(1):61-66
10. Younes M, Lechago LV, Somoano JR, Mosharaf M, Lechago J. Wide expression of the human erythrocyte glucose transporter GLUT-1 in human cancers. Cancer Res 1996; 56:1164–7.
11. Maria L Macheda , Suzanne Rogers, James D Best. Molecular and cellular regulation of glucose transporter (GLUT) proteins in cancer. J Cell Physiol 2005 Mar;202(3):654-62.
12. Semaan A, Munkarah AR, Arabi H, Bandyopadhyay S, Seward S, Kumar S, Qazi A. Hussein Y, Morris RT, Ali-Fehmi R. Expression of GLUT-1 in epithelial ovarian carcinoma: correlation with tumor cell proliferation, angiogenesis, survival and ability to predict optimal cytoreduction. Gynecologic oncology 2011; 121(1):181-186.
13. Cantuaria G, Fagotti A, Ferradina G, Magalhaes A, Nadji M, Angioli R, Penalver M, Mancuso S, Scambia G. GLUT-1 Expression in ovarian carcinoma: Association with survival and response to chemotherapy. Cancer 2001; 92:1144-50.
14. Kalantari M, Nazeran T , Tabrizi F V. Quick Score and H-Score Assessment

of P504s (AMACR) Expression in Renal Cell Carcinoma (RCC) and Relation with Histologic Grade. Iranian Journal of Pathology (2012) 7 (3), 157 – 164

15. Legan M, Tevzic S, Tolar A, Luzar B, Marolt VF. Glucose Transporter-1 (GLUT-1) Immunoreactivity in Benign, premalignant and malignant lesions of the gall bladder. Pathol Oncol Res 2011; 17(1):61-66.
16. Wang BY, Kalir T, Sabo E, Sherman DE, Cohen C, Burstein DE. Immunohistochemical staining of GLUT1 in benign, hyperplastic, and malignant endometrial epithelia. Cancer 2000; 88:2774–81.
17. 15. Kalir T, Wang B.Y., Goldfischer M, Haber R.S., Reder I, Demopoulus R, Cohen C.J., Burstein D.E., 2002. Immunohistochemical staining of GLUT1 in benign, borderline, and malignant ovarian epithelia. Cancer, 94: 1078–1082
18. Ozcan A, Deveci MS, Oztas E, Dede M, Yenen MC, Korgun ET, Gunhan O. Prognostic value of GLUT-1 expression in ovarian surface epithelial tumors: a morphometric study**.**Analytical and quantitative cytology and histology. Anal Quant Cytol Histol 2005; 27(4):181-6.
19. Rudlowski C, Moser M, Becker AJ, Rath W, Buttner R, Schroder W, Schurmann A, 2004. GLUT1 mRNA and protein expression in ovarian borderline tumors and cancer. Oncology, 66 (5), 404-10.
20. 18. Cantuaria G, Magalhaes A, Penalver M, Angioli R, Braunschweiger P, Gomez-Marin O, Kanhoush R, Fernandez-Gomez C, Nadji M., 2000. Expression of GLUT-1 Glucose transporter in borderline and malignant tumors of the ovary. Gynecologic Oncology, 79 (1), 33-7.
21. Iida T, Yasuda M, Miyazawa M, Fujita M, Osamura RY, Hirasawa T, Muramatsu T, Murakami M, Saito K, Mikami M., 2008. Hypoxic status in ovarian serous and mucinous tumors: relationship between histological characteristics and HIF-1alpha/GLUT-1 expression. Archives of Gynecology and Obstetrics. Arch Gynecol Obstet, 277(6), 539-46.
22. Yasuda M, Ogane N, Hayashi H, Kameda Y, Miyagi Y, Iida T, Mori Y, Tsukinoki K, Minematsu T, Osamura Y Glucose transporter-1 expression in the thyroid gland: clinicopathological significance for papillary carcinoma. Oncol Rep. 2005 Dec;14(6):1499-504.
23. Ito S, Fukusato T, Nemoto T, Sekihara H, Seyama Y, Kubota S. Coexpression of Glucose Transporter –1 and Matrix Metalloproteinase-2 in human Cancers. Journal of the National cancer institute 2002; 94(14): 1080-1091.
24. Cantuaria G, Magalhaes A, Penalver M, Angioli R, Braunschweiger P, Gomez-Marin O, Kanhoush R, Fernandez-Gomez C, Nadji M., 2000. Expression of GLUT-1 Glucose transporter in borderline and malignant tumors of the ovary. Gynecologic Oncology, 79 (1), 33-7.
25. Elbasateeny S, Abdelwahab M M, A.Ibrahem M, Harera I S. Immunohistochemical expression of GLUT-1 in epithelial ovarian tumors: correlation with the clinicopathological factors and tumor proliferative marker PCNA. Int. J. Adv. Res. 2017 5 (1), 789-800.
26. Yu X J, Song J C, Du J, Shi Y Q, Liu Y X, Shen Y. GLUT-1 and its regulating factor HIF-1α expression in epithelial ovarian tumors: GLUT-1 is associated with molecular typing and grade of epithelial ovarian cancer. Int J Clin Exp Pathol 2017;10(4):4479-4487.