VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2019, vol. 90, no. 10, 582–588

ISSN 0017–0011

DOI: 10.5603/GP.2019.0102

GLUT1 expression is a supportive mean in predicting prognosis and survival estimates of endometrial carcinoma

Mohamad Nidal Khabaz[1], Imtiaz Ahmad Qureshi[1], Jaudah Ahmad Al-Maghrabi[2, 3]

[1]Department of Pathology, Rabigh Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[2]Department of Pathology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[3]King Faisal Specialist Hospital & Research Center, Jeddah, Saudi Arabia

ABSTRACT

Objectives: This study will investigate the phenotype of Glucose transporter 1 (GLUT1) in endometrial cancer and the association of its expression with tumor's clinicopathological factors.

Material and methods: Standard immunohistochemistry (IHC) staining protocol was utilized to identify the location and expression pattern of GLUT1 in a panel of 71 endometrial carcinomas compared to 30 normal tissues using tissue microarrays.

Results: High scores of GLUT1 staining are more frequent in cancer cases, it was recognized in 64 (90%) endometrial cancers and 12 (40%) control cases. Tissue histotype (cancer versus non-cancerous) was associated with IHC staining of GLUT1 ($p = 0.000$). Significant association between strong GLUT1 staining of malignant epithelial cells and stage of tumor ($p = 0.000$) was observed, advanced disease stages were more prevalent with high GLUT1 staining in malignant epithelial cells. There is also a significant association between high scores of GLUT1 staining and location of expression in transformed epithelium, cytoplasmic and membranous ($p = 0.000$), 100% of cases with cytoplasmic and membranous expression showed high GLUT1 staining scores. **Considerable varied survival models were observed with positive GLUT1 neoplasm regarding diagnosis, grade, stage, differentiation, and recurrence** (p-values 0.000, 0.000, 0.000, 0.002, and 0.000 respectively). Survival estimates are considerably healthier in positive GLUT1 staining cases of endometrial carcinoma, which have low grade, low stage and no recurrence.

Conclusions: GLUT1 expression has been found upregulated in endometrial carcinoma. IHC staining of GLUT1 can be a supportive mean in predicting prognosis and survival estimates of endometrial carcinoma with specific clinical factors.

Key words: GLUT1; immunohistochemistry; endometrial carcinoma

Ginekologia Polska 2019; 90, 10: 582–588

INTRODUCTION

Endometrial cancer (EC) is the second most frequent malignant neoplasm of the female reproductive system in USA [1]. **In Saudi Arabia, uterine corpus tumors are the most frequent cancer of female genital system [2]**. More than 400 cases of endometrial cancer were registered in 2015, which represented about 6.4 % of all recently confirmed cancer cases of all sites [2]. The mean age was 61 years (22–99). The most common morphological type is endometrioid adenocarcinoma not otherwise specified (NOS) accounts for 63.8 percent, and less commonly adenocarcinoma (NOS) 11.9%, carcinoma (NOS) 3.2%, serous cystadenocarcinoma 3.2%, papillary serous cystadenocarcinoma 3.0% and others [2]. Diagnosis and management of endometrial neoplasms depend greatly on patients' clinicopathological factors [patient age, tumor size and histological type as well as Fédération Internationale de Gynécologie Obstétrique (FIGO) grade as prognostic signs]. Yet, these clinical factors are not adequate to predict disease's outcomes due to endometrial tumors heterogeneity [3]. Regardless of significant improvements in cancer management and the good prognosis of endometrial tumors, about 15% of all endometrial tumors recur, of which up to 90% of recurrent tumors happen within 3 years [4]. The recurrent disease prognosis is poor; the median survival barely surpasses twelve months. At present, the total number of patients with recurrent endometrial tumor arises [5].

Corresponding author:
Jaudah Ahmad Al-Maghrabi
King A Bdulaziz University, Faculties Street, Alsulaimaniya, 21589 Jeddah, King Faisal Specialist Hospital & Research Center, Jeddah, Saudi Arabia
e-mail: jalmgrabi@kau.edu.sa

So, it is a pleading demand to find better diagnostic and prognostic markers and chemotherapeutic agents to facilitate clinical tasks for effective diagnosis, prognosis and treatment of endometrial carcinoma. Concentrated experimental works have been constructed to acquire new markers so as to support disease diagnosis and prognosis, improve patients' risk stratification and advance clinical management [6]. The majority of these biomarkers has not been satisfactorily specific or sensitive; this lead to a big interest in distinguishing biomarkers of transformed cells and tumor micro-environment which could have prognostic or predictive values of response to particular medications that could lead to proper therapy.

Glucose transporter 1 (GLUT1) is upregulated in a wide spectrum of human malignancies and its expression is absent in most types of normal epithelial cells. The expression of GLUT1 appears to be a potential marker for malignant transformation [7–8]. GLUT1 has been considered to have a significant role in the development of different neoplasms once overexpressed. Many recent studies associated GLUT1 expression with increased malignant potential, invasiveness, diagnosis, prognosis and survival in different neoplasms, including prostate, breast, colorectal, ovarian, lung, hepatic, pancreatic, esophageal and cervical carcinomas [8–10]. However, in endometrial cancer, many studies attempted to find similar association and prove that GLUT1 phenotype could be utilized as a diagnostic and prognostic tissue marker, but the findings were inconsistent and need further confirmation [11–22]. Therefore, this manuscript will describe the immunohistochemistry phenotype of GLUT1 in a panel of endometrial carcinomas compared to normal tissues, and analyse its relationship with clinicopathological features, to determine its clinical value and its role in endometrial cancer. Furthermore, this study will evaluate a GLUT1 expression as a diagnostic marker and predictor of survival in patients with endometrial carcinoma.

Objectives

This study will investigate the phenotype of Glucose transporter 1 (GLUT1) in endometrial cancer and the association of its expression with tumor's clinicopathological factors.

MATERIAL AND METHODS

Two groups of tissue samples were included in this study; the first group is 71 specimens related to patients with histologically confirmed endometrial carcinomas. The second group is 30 tissue samples from curetted patients for noncancerous conditions (4 endometrial polyps, 16 proliferative endometrium, and 10 secretory endometrium), as a control. The mean age of second group individuals was 36 (ranged 22–50). All ethical rules and regulations adapted by author institution have been followed.

This study will utilize GLUT1 monoclonal antibody using immunohistochemistry staining standard protocol to identify the location and expression pattern of GLUT1, which will be graded with respect to the estimated fraction of malignant cells with positive and relative intense stain.

All recruited tissue specimens were paraffin-embedded tissue blocks and were collected along with their clinicopathological data from the Department of Pathology (Tab. 1). All paraffin blocks were cut (4 μm thickness), Hematoxylin-and-Eosin (H&E) stained and reevaluated for diagnosis and grading confirmation by two pathologists. Later, tissue microarray (TMA) was built using all paraffin-embedded specimens of both groups (carcinomas and controls) in the same way as was stated by Al-Maghrabi et al. [23]. Next, TMA Blocks were cut into 4 μm slices, placed on coated slides and used later in immunohistochemistry (IHC) to detect GLUT1 using BenchMark autostainer (Ventana, Arizona, USA), anti-GLUT1 polyclonal antibody and UltraView Universal diaminobenzidine (DAB) Detection Kit (Ventana Medical Systems, USA). A slide with trisaminomethane (tris) buffer instead of anti- GLUT1 polyclonal antibody were included as a negative control in every staining procedure performed as well as positive tissue control of colorectal carcinoma as indicated by the manufacturer.

Two pathologists analyzed the quality of GLUT1 expression and approximated the percentage of positive neoplastic cells. The estimations of GLUT1 positive cells were determined by semi-quantitative procedure in 3 microscopic fields using 40 × lenses. All cases with brown color in less than 5% of neoplastic cells were counted negatively stained. Grades of 0, 1, 2, and 3 were assigned for negative, weak, modest and strong stain respectively. These scores are displayed in this report as high (2 and 3), and low (0 and 1). The lowest grade recorded by any pathologist was taken into account if a disparity occurred.

Statistical Analysis

The data were analysed by using version 21 of International Business Machines-Statistical Package for the Social Sciences (IBM-SPSS). All results were displayed as incidences and percentages. The relationship between clinical factors of ECs and GLUT1 immunoexpression was investigated by Fisher and chi-square tests. Assessment of survival distributions for several GLUT1 IHC staining scores were calculated by using a Log Rank test. The significance level was considered at $p < 0.05$.

RESULTS

Clinicopathological factors of all ECs cases with the expression of GLUT1 was presented in Table 1. Transformed epithelium of sixty four endometrial cancer cases (90.1%) showed high scores GLUT1 IHC staining, and 7 (9.9%) sam-

Table 1. Distribution of various clinicopathological variables with Glucose transporter 1 (GLUT1) immunostaining in transformed endometrial cells

		Gut 1 in Epithelial cells				p-value
		Low		High		
		n	[%]	n	[%]	
Group	**Control**	18	60.0	12	40.0	**0.000**
	Endometrial Cancer	7	9.9	64	90.1	
GLUT1 staining location	**Negative**	3	100	0	0.0	0.0001
	Cytoplasmic	4	40.0	6	60.0	
	Cytoplasmic and membranous	0	0.0	58	100.0	
Diagnosis	**Clear cell carcinoma**	0	0.0	1	100.0	0.695
	Endometrioid adenocarcinoma	7	11.9	52	88.1	
	MMMT	0	0.0	2	100.0	
	Serous carcinoma	0	0.0	9	100.0	
Grade	**I**	5	12.5	35	87.5	0.999
	II	2	8.7	21	91.3	
	III	0	0.0	6	100.0	
	Ungraded	0	0.0	2	100.0	
Stage	**I**	6	15.4	33	84.6	**0.000**
	II	0	0.0	5	100.0	
	III	0	0.0	9	100.0	
	IV	0	0.0	3	100.0	
	Unstaged	1	6.7	14	93.3	
Differentiation	**M**	2	10.0	18	90.0	0.884
	NA	0	0.0	2	100.0	
	P	0	0.0	8	100.0	
	W	5	12.2	36	87.8	
Recurrence	**No**	6	10.7	50	89.3	0.999
	Yes	1	6.7	14	93.3	
Alive	**No**	0	0.0	17	100.0	0.185
	Yes	7	13.0	47	87.0	

GLUT1 — Glucose transporter 1

ples revealed negative or weak staining. High scores of GLUT1 IHC staining in stromal cells of ECs were found in the total of only 21 out of 71 cases of ECs. High scores of GLUT1 staining were found more frequently in cancer cases, it was recognized in 64 (90%) endometrial cancers compared to 12 (40%) control cases. Staining of the normal endometrial epithelium, if present, was much lower than observed in tumor cells from the same patient.

Biologic behavior tissue type (cancer versus non-cancerous) was obviously associated with GLUT1 immunohistochemistry staining ($p = 0.000$). Significant association between strong GLUT1 staining of malignant epithelial cells and stage of tumor ($p = 0.000$) was observed, advanced disease stages were more prevalent with high GLUT1 staining in malignant epithelial cells. There is also a significant association between high GLUT1 staining scores and cytoplasmic and membranous expression locations in malignant epithelium ($p = 0.000$), 100 percent of cases (58) with cytoplasmic and membranous expression showed high GLUT1 staining scores. The remaining cases were 3 negative and ten cases revealed cytoplasmic staining only of which 60% were of strong staining.

Most positive GLUT1 cases showed a brown color in greater than 50% of the transformed cells (Fig. 1 A, B, C and D). Substantial variability was identified in GLUT1 staining, for instance, some neoplasms exhibited positive stain in selected glands or cells and others showed identical stain in all glandular or cellular parts. No significant associations were analysed between GLUT1 immunostaining and neoplasm diagnosis, grade, recurrence and alive/deceased status.

The log rank test was used to compare survival distributions among cases of low and high GLUT1 staining scores. Table 2 defines the average survival times of tumor patients with different clinical risk factors varied for

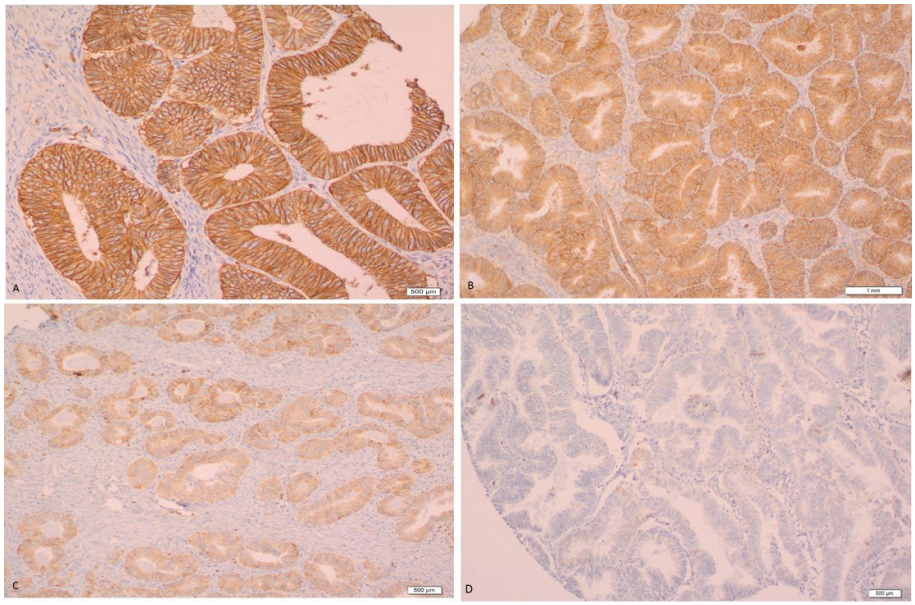

Figure 1. Glucose transporter 1 (GLUT1) immunostaining pattern in endometrial cancer; A — strong staining in endometrial tissue; B — moderate staining in endometrial cancer; C — weak staining in endometrial cancer; D — negative staining in endometrial cancer

Table 2. Comparison of survival distribution patterns by various clinicopathological variables in positive Glucose transporter 1 (GLUT1) immunostained endometrial cancers

		n	No. of Events	Mean	S.E	p-value[a]
Grade	**I**	40	4	105.016	7.000	0.000
	II	21	6	95.970	13.932	
	III	6	5	20.154	7.048	
	Ungraded	2	1	11.187	5.401	
Stage	**I**	38	2	108.154	6.788	0.000
	II	5	1	59.644	12.330	
	III	8	7	26.801	14.952	
	IV	3	3	22.198	14.932	
	Unstaged	15	3	97.449	10.617	
Differentiation	**W**	41	4	106.066	6.523	0.002
	M	18	6	87.111	16.245	
	P	8	5	45.745	15.734	
	NA	2	1	11.187	5.401	
Recurrence	**No**	55	7	102.797	6.065	0.000
	Yes	14	9	45.930	14.736	
Diagnosis	**Endometrioid adenocarcinoma**	59	8	114.965	7.348	0.000
	MMMT	2	1	11.187	5.401	
	Serous carcinoma	8	7	25.741	6.823	

a — Log-Rank test adjusted for GLUT1 immunostaining

GLUT1 staining. Considerable varied survival models were observed with neoplasm diagnosis, grade, stage, differentiation and recurrence (p-values 0.000, 0.000, 0.000, 0.002, and 0.000 respectively). Survival estimates are considerably healthier in positive GLUT1 staining cases of endometrial carcinoma, which have endometrioid adenocarcinoma type, low grade, low stage, well differentiation or no recurrence. On the other hand, positive neoplasms with high grade, high stage, poor differentiation or recurrence displayed poorer survival estimations. Kaplan Meier survival curves

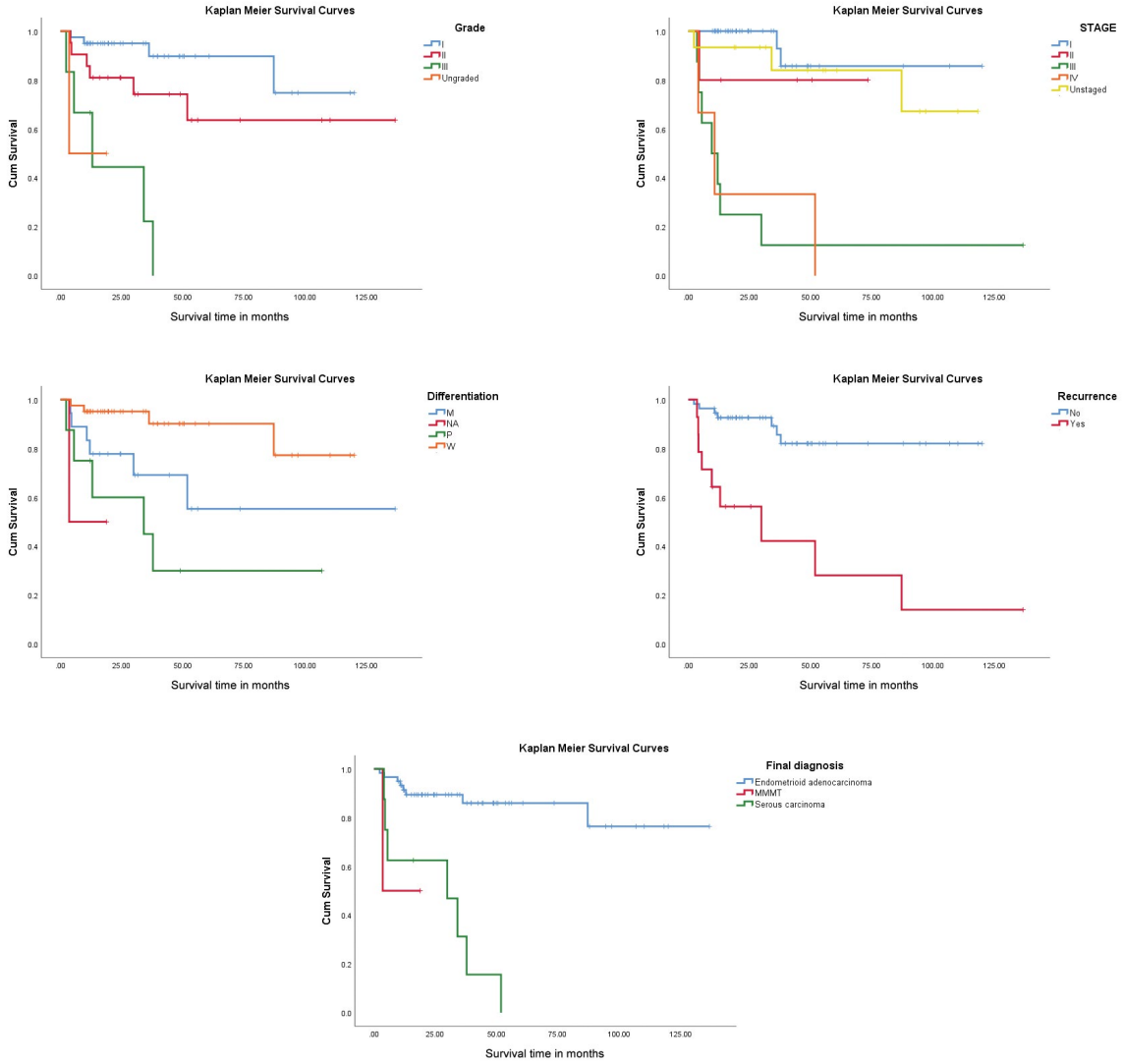

Figure 2. Kaplan Meier Survival Curves by various clinicopathological variables with Glucose transporter 1 (GLUT1) immunostaining in endometrial cancer

exhibited significant improved survival experience in cases of endometrioid adenocarcinoma type, low grade, low stage well differentiation or no recurrence (Fig. 2).

DISCUSSION

Glucose transporters have become one of the core subjects in cancer biology since it has been found that neoplastic cells show higher glucose metabolism in comparison with normal tissue. The resultant big growth in glucose necessity indicates a demand for a consistent rise in the transportation of glucose through the cell membrane. The greater part of tumors show increased expression of GLUT1 that has been existed in relevant normal counterpart tissues in non-cancerous states. Furthermore, because of the need for power to serve unrestrained proliferation, neoplastic cell frequently expresses GLUT1 that would not be expressed in the cells in ordinary circumstances [24–25]. The level and membranous location of GLUT1 expression could be an appropriate biomarker of glucose metabolism that might be assessed easily and economically as part of the histologic assessment practice of neoplasms [19]. Since increased expression of GLUT1 is already known in many neoplasms, its relationship with prognostic parameters has been studied [8–10]. The earliest and the most striking study on this subject to date is the one that was conducted on colon cancer. In addition to indicating GLUT1 as a good marker to determine aggressive biological behavior of colorectal carcinomas, it also showed a direct correlation between lymph node metastases and GLUT1 expression [26].

In endometrial neoplasms, nevertheless, many studies [11–22] tried to find a comparable association and verify that the IHC GLUT1 phenotype could be utilized as a diagnostic and prognostic tissue marker, but the findings were inconsistent (Tab. 3). In agreement with the majority of literature data, our

Table 3. Correlation between high level of Glucose transporter 1 (GLUT1) immunoreactivity and clinicopathological parameters of endometrial cancer in the current study compared to studies of the literature

Previous studies	GLUT1 in endometrial cancer	GLUT1 in control group	GLUT1 staining location	Grade	Stage	Recurr-ence	Alive/ Deceased status	Survival
The current study	90% p = 0.0001	40%	CM p = 0.0001	NS	0.000	NS	NS	p = 0.005
Nemejcova et al. 2017 [11]	90%	33%	M					
Anagnostou et al. 2017 [20]	63%		M	NS				
Al-Sharaky et al. 2016 [12]	98.5% p = 0.008	88.9%	CM	p = 0.003	p = 0.004			
Canpolat et al. 2016 [13]	95%	31.9%	M	p = 0.007	NS			NS
Ma et al. 2015 [14]	70% p < 0.05	14%	N	p < 0.05	p < 0.05			
Sadlecki et al. 2014 [15]	100%		CM	NS	NS	NS		NS
Xiong et al. 2010 [16]	71%	0%	M					
Wahl et al. 2010 [22]	53%	0%	M					
Ashton-Sager et al. 2006 [17]	90%	17%	M					
Goldman et al. 2006 [21]	present	present	C	p < 0.002				
Sebastiani et al. 2004 [18]	43%		M					NS
Wang et al. 2000 [19]	100%	0%	M					

GLUT1 — Glucose transporter 1; C — cytoplasmic; M — membranous; CM — cytoplasmic and membranous; N — nuclear; NS — not significant

results were capable statically to show increased cytoplasmic and/or membranous expression of GLUT1 in ECs compared to normal endometrium [11–22]. Decreased GLUT1 expression in normal endometrium as well as its weak expression in non-cancerous lesions and overexpression in endometrial cancer suggests that this molecule might be involved in endometrial carcinogenesis as the findings of this study and others [12, 14] showed significant association with tumor stage. On the other hand, some studies including the present one could not demonstrate any significant relationship between GLUT1 expression and other prognostic parameters of ECs [11, 15–20, 22]. While, few studies found that the association between GLUT1 phenotype and clinical data, i.e. increasing grade and stage, is statistically significant [12, 14]. Goldman et al. (2006) [21] and later Canpolat et al. (2016) [13] reported that among clinical characteristics, only grade was found to be significantly correlated to GLUT1 expression. According to Xiong et al. [16], the expression of GLUT1 can be used to distinguish between benign endometrial lesions and endometrial cancer but has no prognostic value in women with this malignancy. This is opposite to the present investigation which showed significant differences in the expression of GLUT1 associated with clinical stage or prognosis in endometrial cancer patients.

The present investigation showed that the impact of GLUT1 phenotype on the survival estimates of endometrial cancer was modified significantly by some clinical factors, including the type of tumor, grade, stage and recurrence. This finding is in line with the recent analyses of numerous studies which have reported paradoxical evidence of the relationship between GLUT1 expression and prognosis in solid human tumors [8, 27].

The differences between the previous studies and the current one could be clarified by method sensitivity, people's difference, and variations in the size of samples. The present report and previous similar ones which evaluated the diagnostic and prognostic power of GLUT1 immunoreactivity in endometrial malignancy had weak points such as the relatively small sample size involved in these studies and the semi-quantitative interpretation of immunostaining. However, greater inclusive studies are undoubtedly of great value for estimating the diagnostic and prognostic values of GLUT1 immunoreactivity in endometrial malignancy.

CONCLUSIONS

Our results showed increased expression of GLUT1 in endometrial tumors. IHC staining of GLUT1 can be a supportive mean in predicting prognosis and survival estimates of endometrial tumors with specific clinical factors.

Financial disclosure

This project was funded by the Deanship of Scientific Research (DSR) at King Abdulaziz University (KAU), Jeddah, under grant number (G: 190-828-1439). The authors acknowledge with thanks DSR for technical and financial support. The authors acknowledge with thanks Dr Nadeem Butt for completing statistical analysis.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018; 68(1): 7–30, doi: 10.3322/caac.21442, indexed in Pubmed: 29313949.
2. Alrawaji AI, Al-Shahrani ZS, Alzahrani W, et al. Cancer Incidence Report Saudi Arabia 2015, Saudi Cancer Registry 2018. https://nhic.gov.sa/eServices/Pages/TumorRegistration.aspx.
3. Piulats JM, Guerra E, Gil-Martín M, et al. Molecular approaches for classifying endometrial carcinoma. Gynecol Oncol. 2017; 145(1): 200–207, doi: 10.1016/j.ygyno.2016.12.015, indexed in Pubmed: 28040204.
4. Sohaib SA, Houghton SL, Meroni R, et al. Recurrent endometrial cancer: patterns of recurrent disease and assessment of prognosis. Clin Radiol. 2007; 62(1): 28–34; discussion 35, doi: 10.1016/j.crad.2006.06.015, indexed in Pubmed: 17145260.
5. Odagiri T, Watari H, Hosaka M, et al. Multivariate survival analysis of the patients with recurrent endometrial cancer. J Gynecol Oncol. 2011; 22(1): 3–8, doi: 10.3802/jgo.2011.22.1.3, indexed in Pubmed: 21607089.
6. Żyła MM, Wilczyński JR, Kostrzewa M, et al. The significance of markers in the diagnosis of endometrial cancer. Prz Menopauzalny. 2016; 15(3): 176–185, doi: 10.5114/pm.2016.63500, indexed in Pubmed: 27980530.
7. Noguchi Y, Saito A, Miyagi Y, et al. Suppression of facilitative glucose transporter 1 mRNA can suppress tumor growth. Cancer Letters. 2000; 154(2): 175–182, doi: 10.1016/s0304-3835(00)00392-x.
8. Wang Ji, Ye C, Chen C, et al. Glucose transporter GLUT1 expression and clinical outcome in solid tumors: a systematic review and meta-analysis. Oncotarget. 2017; 8(10): 16875–16886, doi: 10.18632/oncotarget.15171, indexed in Pubmed: 28187435.
9. Yu M, Yongzhi H, Chen S, et al. The prognostic value of GLUT1 in cancers: a systematic review and meta-analysis. Oncotarget. 2017; 8(26): 43356–43367, doi: 10.18632/oncotarget.17445, indexed in Pubmed: 28498810.
10. Zhang Bo, Xie Z, Li B. The clinicopathologic impacts and prognostic significance of GLUT1 expression in patients with lung cancer: A meta-analysis. Gene. 2019; 689: 76–83, doi: 10.1016/j.gene.2018.12.006, indexed in Pubmed: 30552981.
11. Němejcová K, Rosmusová J, Bártů M, et al. Expression of Glut-1 in Normal Endometrium and Endometrial Lesions: Analysis of 336 Cases. Int J Surg Pathol. 2017; 25(5): 389–396, doi: 10.1177/1066896916683510, indexed in Pubmed: 28381136.
12. Al-Sharaky DR, Abdou AG, Wahed MM, et al. HIF-1α and GLUT-1 Expression in Atypical Endometrial Hyperplasia, Type I and II Endometrial Carcinoma: A Potential Role in Pathogenesis. J Clin Diagn Res. 2016; 10(5): EC20–EC27, doi: 10.7860/JCDR/2016/19576.7805, indexed in Pubmed: 27437226.
13. Canpolat T, Ersöz C, Uğuz A, et al. GLUT-1 Expression in Proliferative Endometrium, Endometrial Hyperplasia, Endometrial Adenocarcinoma and the Relationship Between GLUT-1 Expression and Prognostic Parameters in Endometrial Adenocarcinoma. Turk Patoloji Derg. 2016; 32(3): 141–147, doi: 10.5146/tjpath.2015.01352, indexed in Pubmed: 27562387.
14. Ma X, Hui Y, Lin Li, et al. Clinical significance of COX-2, GLUT-1 and VEGF expressions in endometrial cancer tissues. Pak J Med Sci. 2015; 31(2): 280–284, doi: 10.12669/pjms.312.6604, indexed in Pubmed: 26101475.
15. Sadlecki P, Bodnar M, Grabiec M, et al. The role of Hypoxia-inducible factor-1 α , glucose transporter-1, (GLUT-1) and carbon anhydrase IX in endometrial cancer patients. Biomed Res Int. 2014; 2014: 616850, doi: 10.1155/2014/616850, indexed in Pubmed: 24745019.
16. Xiong Y, Xiong YY, Zhou YF. Expression and significance of beta-catenin, Glut-1 and PTEN in proliferative endometrium, endometrial intraepithelial neoplasia and endometrioid adenocarcinoma. Eur J Gynaecol Oncol. 2010; 31(2): 160–164, indexed in Pubmed: 20527231.
17. Ashton-Sager A, Paulino AFG, Afify AM. GLUT-1 is preferentially expressed in atypical endometrial hyperplasia and endometrial adenocarcinoma. Appl Immunohistochem Mol Morphol. 2006; 14(2): 187–192, doi: 10.1097/01.pai.0000162003.43334.c7, indexed in Pubmed: 16785788.
18. Sebastiani V, Visca P, Botti C, et al. Fatty acid synthase is a marker of increased risk of recurrence in endometrial carcinoma. Gynecol Oncol. 2004; 92(1): 101–105, doi: 10.1016/j.ygyno.2003.10.027, indexed in Pubmed: 14751145.
19. Wang BY, Kalir T, Sabo E, et al. Immunohistochemical staining of GLUT1 in benign, hyperplastic, and malignant endometrial epithelia. Cancer. 2000; 88(12): 2774–2781, indexed in Pubmed: 10870060.
20. Anagnostou E, Miliaras D, Meditskou S, et al. Immunohistochemical investigation of metabolic markers fatty acid synthase (FASN) and glucose transporter 1 (GLUT1) in normal endometrium, endometrial hyperplasia, and endometrial malignancy. Hippokratia. 2017; 21(4): 169–174, indexed in Pubmed: 30944506.
21. Goldman NA, Katz EB, Glenn AS, et al. GLUT1 and GLUT8 in endometrium and endometrial adenocarcinoma. Mod Pathol. 2006; 19(11): 1429–1436, doi: 10.1038/modpathol.3800656, indexed in Pubmed: 16892013.
22. Wahl H, Daudi S, Kshirsagar M, et al. Expression of metabolically targeted biomarkers in endometrial carcinoma. Gynecol Oncol. 2010; 116(1): 21–27, doi: 10.1016/j.ygyno.2009.10.040, indexed in Pubmed: 19878980.
23. Al-Maghrabi J, Emam E, Gomaa W, et al. c-MET immunostaining in colorectal carcinoma is associated with local disease recurrence. BMC Cancer. 2015; 15: 676, doi: 10.1186/s12885-015-1662-6, indexed in Pubmed: 26459369.
24. Warburg O. On the Origin of Cancer Cells. Science. 1956; 123(3191): 309–314, doi: 10.1126/science.123.3191.309.
25. Liberti MV, Locasale JW, Liberti MV, et al. The Warburg Effect: How Does it Benefit Cancer Cells? Trends Biochem Sci. 2016; 41(3): 211–218, doi: 10.1016/j.tibs.2015.12.001, indexed in Pubmed: 26778478.
26. Haber RS, Rathan A, Weiser KR, et al. GLUT1 glucose transporter expression in colorectal carcinoma: a marker for poor prognosis. Cancer. 1998; 83(1): 34–40, doi: 10.1002/(sici)1097-0142(19980701)83:1<34::aid-cncr5>3.0.co;2-e, indexed in Pubmed: 9655290.
27. Zhao ZX, Lu LW, Qiu J, et al. Glucose transporter-1 as an independent prognostic marker for cancer: a meta-analysis. Oncotarget. 2018; 9(2): 2728–2738, doi: 10.18632/oncotarget.18964, indexed in Pubmed: 29416806.