



GLUT-1 Expression in Proliferative Endometrium, Endometrial Hyperplasia, Endometrial Adenocarcinoma and the Relationship Between GLUT-1 Expression and Prognostic Parameters in Endometrial Adenocarcinoma

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ABSTRACT

Objective: Malignant cells show increased glucose uptake in in vitro and in vivo studies. This uptake is mediated by glucose transporter proteins. GLUT-1 is the most common transporter protein, and its expression is reported to be increase in many human cancers. The aim of this study is to determine the GLUT-1 overexpression in benign, hyperplastic, and malignant endometrial tissues, to evaluate the usefulness of GLUT-1 expression in endometrial hyperplasia, and to determine its role in the neoplastic progression to endometrioid type adenocarcinoma. We also aimed to analyze prognostic clinical parameters, predict prognosis, and survival.

Material and Method: We examined immunohistochemical expression of GLUT-1 in 91 cases of endometrial hyperplasia, 100 cases of endometrioid type adenocarcinoma, and 10 proliferative endometrial tissues. The percentage of positive cells and staining intensity were assessed in a semi quantitative fashion and scored (1+ to 3+).

Results: GLUT-1 immunoreactivity was not present in proliferative endometrium. Twenty-nine (31.9%) of 91 endometrial hyperplasia cases showed positive immunoreactivity, of which only six were cases of hyperplasia without atypia while 23 of them were cases with atypia. We found GLUT-1 positivity of 95% in endometrioid type adenocarcinoma. GLUT-1 overexpression was not significantly correlated with any of the clinicopathological parameters except histological grade in endometrioid adenocarcinoma; the survival was not found to be correlated with GLUT-1 expression.

Conclusion: GLUT-1 immunostaining may be useful in distinguishing hyperplasia without atypia from hyperplasia with atypia; GLUT-1 overexpression is a consistent feature of endometrioid adenocarcinoma. A correlation between GLUT -1 expression and tumor grade has been found, although other prognostic parameters and survival has no meaningful correlation.

Key Words: GLUT-1, Prognosis, Endometrial hyperplasia, Endometrioid adenocarcinoma

INTRODUCTION

Glucose is the basic energy source for the maintenance of human metabolism. In humans, glucose hemostasis is regulated by certain steps that are dependent on each other; glucose transport proteins (GLUT) are the major transport proteins regulating glucose entry into cells (1,2). There are 14 types of GLUT with different sensitivity to insulin stimulus, tissue distribution, and glucose affinity (2,3). GLUT-1 is the most well-known transport protein that is primarily found in erythrocytes, blood-brain barrier, liver and capillary endothelium (1-5).

Malignant cells need a higher glucose transporter gene expression due to their increased metabolic rates and glucose requirements. This expression and activity is

regulated by some oncogenes and growth factors (4,6-8). Increased GLUT-1 expression has been reported in many human cancers such as lung, gallbladder, gastric, head and neck, colorectal, ovarian, pancreatic, esophageal, breast, laryngeal and bladder carcinoma (4-7, 9-15). Some studies in the literature have shown GLUT-1 expression in endometrial hyperplasia and endometrial carcinoma; however, only a few studies have scrutinized the impact of GLUT-1 expression on prognostic parameters and survival (16-19).

In this study, we analyzed the expression of GLUT-1 in endometrial hyperplasia to determine its role in endometrioid type adenocarcinoma, in hyperplasia and its correlation with tumor's prognostic parameters and survival.

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MATERIAL and METHOD

This study was approved by Çukurova University Faculty of Medicine Department of Pathology. Paraffin-embedded tissue blocks of 91 previously diagnosed cases of endometrial hyperplasia (EH), and 100 previously diagnosed endometrioid type endometrial adenocarcinoma (ETEA) cases were included. These patients underwent total abdominal hysterectomy, with bilateral salpingoophorectomy and pelvic lymph node dissection and omentectomy after diagnosis of endometrial cancer based on specimens obtained from curettage. Information was present on survivals, stages and clinical data. Exclusion criteria included unknown survival information and stages. The control group consisted of incidental endometrial tissue samples with proliferative endometrium characteristics that belong to patients who underwent curettage or underwent to hysterectomy for leiomyoma. In all cancer patients, age, clinical stage, histologic grade, myometrial invasion (>50%), lymph node metastases, lymphovascular space invasion, cervical and ovarian involvement, and peritoneal cytology positivity were determined. Surgical procedure and detailed pathologic reports were obtained and recorded.

All ETEA cases were reviewed. Clinical stage was assessed based on the evaluation of the surgical specimens, radiological and physical examination findings belonging to patients by two independent pathologists according to International Federation of Gynecology and Obstetrics (FIGO) 2009 system (20). Since the statistical evaluation of a single case will not be meaningful, the only Stage 4 case was included in Stage 3 cases. Subjects with no myometrial invasion were labeled as the first group; those with the involvement of $\frac{1}{2}$ of superficial layer of myometrium as the second group; and those with the involvement of $\frac{1}{2}$ of deep layer of myometrium as the third group. The subjects were categorized into 2 groups based on the status of lymphovascular invasion, lymph node metastasis, cervical and adnexal involvement, and positive peritoneal cytology. In all cancer patients, overall survival was determined in months. Only, cases with proven death related to cancer were analyzed. The follow-up time was between 60 to 82 months.

EH cases were evaluated according to WHO 1994 classification at the time of their diagnosis. There was only one case diagnosed as "hyperplasia with simple atypia", and this single case was included in the group of cases with "hyperplasia with complex atypia". Hence, our hyperplasia cases were grouped as hyperplasia with or without atypia according to the latest, 2013 WHO classification (21). There were 51 EH cases without atypia and 40 EH cases with atypia.

Hematoxylin-Eosin stained preparations of the cases were examined in light microscope and suitable paraffin blocks were selected for each case. The immunohistochemical staining was performed on selected formalin fixed paraffin embedded tissues. Five μ m thick sections were taken from the paraffin blocks, and the immunohistochemical studies were performed on this sections using Mouse monoclonal antibody GLUT-1 (Cat RB-078-A1 Neo Markers and dilution 1:50) with positive and negative control blocks. Placental tissue was used as a positive control.

GLUT-1 expression was determined immunohistochemically and all H.E stained slides were evaluated using the light microscope at 20x magnification with Nikon (Eclipse 800) microscopes used by two independent pathologists who were blind to patients' clinical data. Only linear membranous staining was considered positive for GLUT-1 expression. The percentage of positive stained tumor cells in tissue samples were semi quantitatively determined (0-3). Staining in at least 1% to 10% of tumor cells was considered as positive staining with GLUT-1. 0: negative staining, 1: 1-10% positive staining, 2: 10-50% positive staining, 3: \geq 50% positive staining. The correlation between GLUT-1 staining score, ETEA, EH, and ETEA's histopathological prognostic parameters, FIGO grade, myometrial invasion, lymphovascular invasion, cervical involvement, adnexal involvement, lymph node metastasis, peritoneal cytology positivity and survival was statistically evaluated.

Statistical analysis was performed by using the SPSS (Version 17.0, SPSS Inc., Chicago, IL, USA) statistical software package. Normally distributed continuous variables were presented as mean \pm standard deviation (normality was assessed using Kolmogorov-Smirnov test or, when $n < 30$, Shapiro-Wilk's test); non-normally distributed continuous variables were presented as median. Relationship between tissue GLUT-1 expression and clinical parameters was analyzed using χ^2 method, and Student's t test. A p value of less than 0.05 was considered statistically significant.

RESULTS

The patient group was consisted of 91 EH cases diagnosed between the years 1985 and 2004, and 100 ETEA cases diagnosed between the years 1985 and 2003 at Çukurova University Faculty of Medicine Department of Pathology. The mean age of the ETEA cases was 57.81 ± 10.957 years, with the youngest patient being 28 and the oldest 79 years of age. The EH cases had a mean age of 49.31 ± 10.214 , with the youngest patient being 27 and the oldest 79 years of age. The mean age of the control group was 47.30 ± 2.830 years. Patients with hyperplasia without atypia had a mean age of 48.30 ± 10.497 years and those with atypia had a mean age of 50.9 ± 9.675 years ($p = 0.104$).

The study group of ETEA included 66 patients with stage I endometrioid carcinoma, 16 with stage II endometrioid carcinoma, 17 with stage III endometrioid carcinoma, and 1 patient with stage IV endometrioid carcinoma. Histological grade I (G1) was noted in 36 (36%) women, G2 in 44 (44%) women, and G3 in 20 (20%) women.

Among 91 EH cases, 51 (56%) had no atypia and 40 (44%) had atypia. While there was no GLUT-1 expression in 62 (68.1%) of the EH cases, 29 (31.9%) EH cases showed immunohistochemical GLUT-1 expression. GLUT-1 was not expressed more than 50% of cells in any of the cases. Of the GLUT-1 positive EH cases, 6 (20.7%) had complex hyperplasia without atypia, 23 (79.3%) had hyperplasia with atypia. There was a significant difference between

hyperplasia cases with and without atypia with respect to GLUT-1 expression ($p=0.0001$) (Figure 1,2).

A significant correlation was found between GLUT-1 expression and grade in ETEA cases ($p=0.007$). No statistically significant differences were observed between GLUT-1 expression and myometrial invasion ($p=0.667$), lymph node metastases ($p=0.776$), cervical involvement ($p=0.460$), adnexal involvement ($p=0.335$), vascular invasion ($p=0.775$) and positive peritoneal cytology ($p=0.570$). The correlation between GLUT-1 expression and prognostic parameters in ETEA was shown on (Table I).

While there was no GLUT-1 expression in 5 (5%) of ETEA cases, it was positive in 95 (95%) of ETEA cases (Figure 3,4). None of the tissue samples of the proliferative endometrium

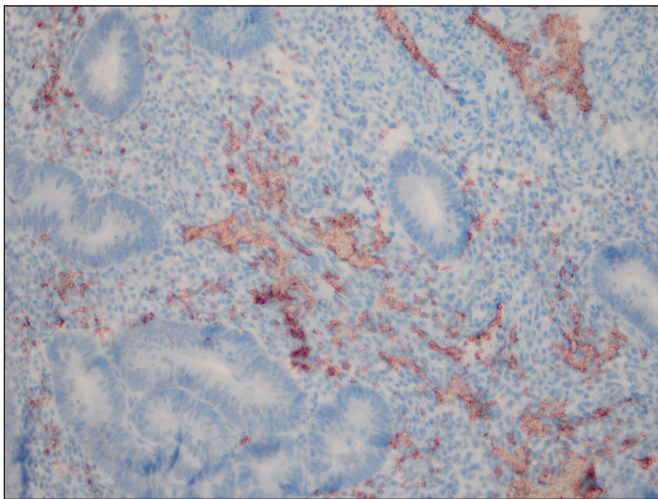


Figure 1: Immunohistochemically staining GLUT-1 in hyperplastic endometrium without atypia (GLUT-1; x200).

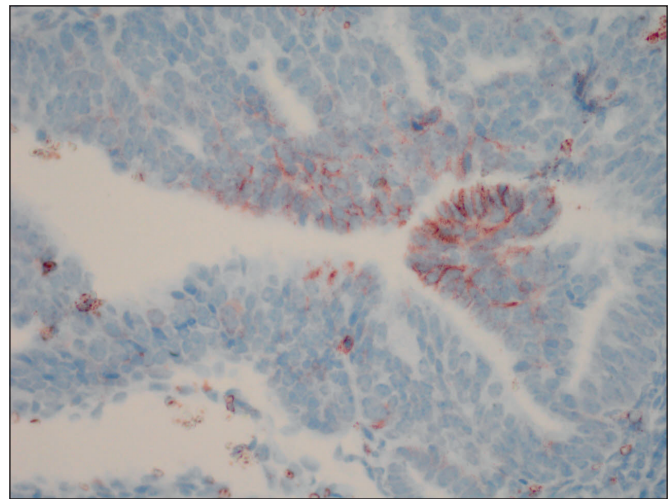


Figure 2: Immunohistochemically staining GLUT-1 in hyperplastic endometrium with atypia (GLUT-1; x400).

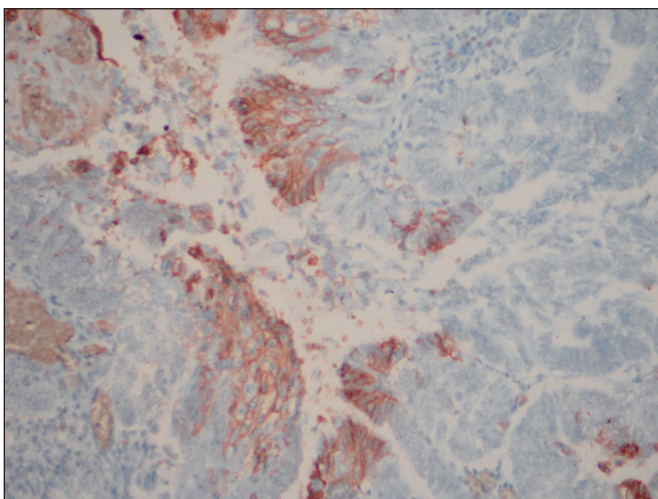


Figure 3: GLUT-1 staining in endometrioid type endometrial adenocarcinoma, Grade II (GLUT-1; x200).

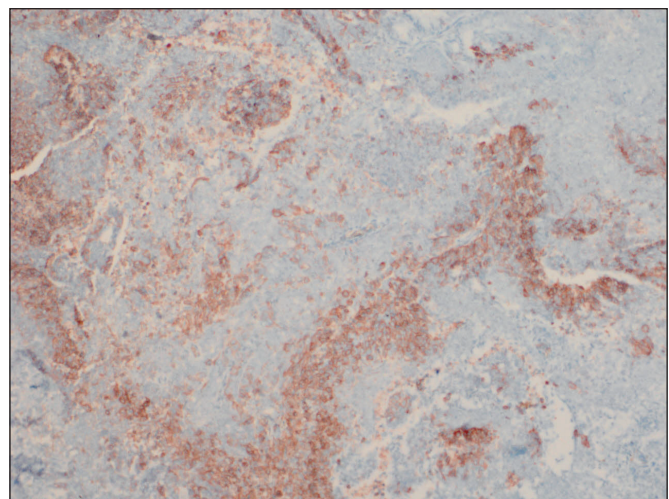


Figure 4: GLUT-1 staining in endometrioid type endometrial adenocarcinoma, Grade I (GLUT-1; x200).

in the control group showed GLUT-1 expression. The distribution of GLUT-1 expression among EH, ETEA, and control groups was shown on (Table II).

The correlation between GLUT-1 expression and survival was analyzed and the survival time was assessed. The patients' median overall survival when GLUT-1 was expressed in more than $\geq 50\%$ of cells was 60 months. The patients' median overall survival when GLUT-1 was expressed in less than $< 50\%$ of cells was 82 months. No statistically significant differences were observed between GLUT-1 expression and survival ($p=0.5$).

DISCUSSION

Endometrial cancer is the most common gynecological cancer in Europe and North America and the seventh most common cause of death worldwide; more than 80% of endometrial cancers are ETEA (22,23). To date, the pathogenesis of endometrial cancer remains unclear, and it is considered to represent a multi-step, multi-stage, multi-factor complex biological process involving a number of genetic variations (24,25). Molecular, endocrinological, and epidemiological alterations typical for epithelial tumors differ between the two mentioned types of epithelial cancers. In other words, a concrete aberration can be different for a type I and a type II tumor. Type I tumors are estrogen-

Table I: The prognostic parameters of endometrioid type endometrial adenocarcinoma cases and correlation between GLUT-1 expression and prognostic parameters.

			GLUT-1(-) n(%)	GLUT-1 $\leq 50\%$ n(%)	GLUT-1 $> 50\%$ n(%)	P value
Endometrial carcinoma Stage	1	66	5 (76%)	48 (72.7%)	13(19.7%)	0.525
	2	16	0	13 (81.3%)	3(18.8%)	
	3-4	18	0	13 (72.7%)	5(27.8%)	
Grade	I	36	3 (8.3%)	29 (80.6%)	4 (11.1%)	0.007
	II	44	2 (4.5%)	35 (79.5%)	7 (15.9%)	
	III	20	0 (0%)	10 (50%)	10 (50%)	
Myometrial invasion	(-)	5	0 (0%)	4 (80%)	1 (20 %)	0.667
	$\leq 50\%$	51	4 (7.8%)	38 (74.5%)	9 (17.6 %)	
	$> 50\%$	44	1 (2.3%)	32 (72.7%)		
Lymphovascular invasion	(-)	65	4 (6.2%)	47 (77.3%)	14 (21.5%)	0.744
	(+)	35	1 (2.9%)	27 (77.1%)	7 (20%)	
Cervical involvement	(-)	79	5 (6.3%)	57 (72.2%)	17 (21.5%)	0.460
	(+)	21	0 (0%)	17 (81%)	4 (19.0%)	
Ovarian involvement	(-)	89	5 (5.6%)	67 (75.3%)	17 (9.1%)	0.335
	(+)	11	0 (0)	7 (63.6%)	4 (36.4%)	
Lymph node metastases	(-)	90	5(5.6%)	67 (74.4%)	18 (20%)	0.766
	(+)	9	0(0%)	7 (77.8%)	2 (22.2%)	
Peritoneal cytology	(-)	67	2 (3%)	52 (77.6%)	13 (19.4%)	0.570
	(+)	9	0 (0%)	6 (66.7%)	3 (33.3%)	

Table II: GLUT-1 expression in endometrial hyperplasia, endometrioid type endometrial adenocarcinoma, and control groups.

	Expression (%)	Endometrial hyperplasia n=91	Endometrioid carcinoma n=100	Control n=10
GLUT-1 Expression	(-)	62 (69.1%)	5 (5%)	0
	1%-10%	10 (11.1%)	54 (54%)	0
	10%-50%	19 (20.8%)	20 (20%)	0
	$> 50\%$	0	21 (21%)	0

dependent, and associated with endometrial hyperplasia, whereas type II tumors are estrogen-independent and associated with endometrial atrophy. Type I tumors are the most common histological type and comprise low-grade adenocarcinomas (25, 26).

EH is the major preneoplastic lesion for type I tumors (27, 28). EH is the most common overdiagnosed condition that is surgically treated (29). WHO classification dated 1985 is the oldest and most widely used classification system and it separates endometrial proliferation into simple or complex hyperplasia on the basis of architectural features, and typical or atypical on the basis of cytological features that are originally defined by Kurman et al. in 1985. The classification system was based on both structural and cellular properties, and has been shown to be associated with intraobserver variation. Furthermore, it has been reported that cellular atypia rather than structural properties increases carcinoma risk (30, 31). In the latest WHO 2013 classification that replaced the WHO's 1994 classification, EHs were classified in a two-group system as hyperplasia without atypia and hyperplasia with atypia (21). Hyperplasia cases were also assessed according to WHO 2013 classification in our study. For diagnosing ETEA cases at an early stage, it is highly important to define EH cases and differentiate hyperplasia cases with atypia that constitute a high risk group from other hyperplasias, and distinguish well-differentiated ETEAs from other lesions in order to provide necessary appropriate treatments and to avoid over diagnosis. The main problem of the current and the previous classification systems is their subjectivity in the determination of atypia. Therefore, searching for adjunctive diagnostic methods, that would be helpful in addition to current morphological criteria to define hyperplasia with atypia gains increasing importance. It is a major unmet need to determine the presence of atypia by an objective criterion and to differentiate well-differentiated adenocarcinoma and hyperplasia especially in small endometrial biopsy and curettage samples. Although some cytometric, immunohistochemical, and molecular genetic alterations have been studied for use in the differential diagnosis, a method for routine practice that is more useful than light microscopic findings is yet to be found.

To date, many studies have indicated that malignant neoplasms have greater metabolic activity and variable glucose need compared to normal tissues. It has been shown that glucose utilization is increased in *in vivo* and *in vitro* conditions (1-4,16). This increase is the result of the increased expression of glucose transport proteins that mediate glucose entry into cells. GLUT-1 is a well-known

member of 14 glucose transfer proteins (4-19, 32). Since GLUT-1 protein is found in cellular membrane, its increased expression can immunohistochemically be detected in the form of membranous staining (5,12,16,19).

A number of studies have shown that GLUT-1 is overexpressed very early in preneoplastic and premalignant lesions including colonic adenoma, borderline ovarian tumors, cervical intraepithelial neoplasia, and prostatic intraepithelial neoplasia (9,10,33,34). Kalir et al. (10) showed that GLUT-1 expression predicted malignant progression in benign borderline and malignant tumors of ovary; they also reported that all of the invasive serous borderline implants were GLUT-1 positive whereas 3 noninvasive implants were GLUT-1 negative. It is quite difficult to differentiate this in routine H&E stained preparations. These studies support the notion that GLUT-1 may take part in carcinogenesis of colonic and ovarian carcinomas and may be useful in detecting preneoplastic lesions (9,10).

As far as we know, the study by Wang et al. (16) is the first to show GLUT-1 expression in EH and tumors. In that study, GLUT-1 expression was detected in all EHs with atypia and endometrial carcinomas. Studies in subsequent years have demonstrated varying rates of GLUT-1 expression in EH (71%, 58.3%, 58%) and ETEA (90%, 70.8 %, 71%) (17-19). Ma et al. in 2015 (35) found positive GLUT-1 expression in 25% of EH cases and 70% of tumors. Although GLUT-1 expression in that study was lower in EH cases compared to that found in our study, it was not specified whether hyperplasia cases had atypia or not. In our study, GLUT-1 expression rate was 79.3% in hyperplasia with atypia and 20.7% in hyperplasia without atypia. All of our tumor cases had GLUT-1 expression. Statistically, this finding seems to support the idea that GLUT-1 immunostaining could be useful as an additional marker distinguishing cases of hyperplasia with atypia from those without atypia. This distinction would be guiding to detect EH with atypia, which is a strong risk factor for endometrial carcinoma that is known to play an important role in the genesis of endometrial tumors, especially Type 1. GLUT-1 is highly expressed in endometrial cancer, which can be used to differentiate benign endometrium from atypically hyperplastic endometrium (17-19,35). Since increased expression of GLUT-1 is already known in many neoplasms, its relationship with prognostic parameters has been studied. The earliest and the most striking study on this subject to date is the one that was conducted on colon cancer. In addition to indicate GLUT-1 as a good marker to determine aggressive biological behavior of colorectal carcinomas, it also showed a direct correlation between

lymph node metastases and GLUT-1 expression (9). GLUT-1 positivity rate was found to be 74% in lung tumors. It was shown to be associated with poor differentiation and correlated to a larger tumor size and lymph node positivity (36). Kawamura et al. (37) demonstrated that GLUT-1 was correlated to the tumor's invasion depth, lymphatic spread, venous invasion, lymph node metastasis, liver metastasis, and stage of gastric carcinoma. In endometrial tumors, on the other hand, the correlation between GLUT-1 expression and clinical characteristics, i.e. increasing stage, decreasing degree of differentiation, and lymphatic metastasis, was significant ($P<0.05$) (35). Among ETEA's prognostic parameters, grade was found to be significantly correlated to GLUT-1 expression in our study. GLUT-1 expression was not significantly correlated to other prognostic factors (myometrial invasion, lymphovascular invasion, cervical and adnexal involvement, lymph node metastasis, positive peritoneal lavage fluid). In 2010 Xiong et al. (19) similarly failed to show a correlation between the prognostic parameters and GLUT-1 expression in endometrioid adenocarcinoma. In accordance with the literature data, our results suggest that GLUT-1 is a marker of early stages of endometrial neoplastic transformation (17-19,35,37).

Haber et al. reported that the mortality rate of colon carcinoma increased 2.4 folds in patients with a GLUT-1 expression of $\geq 50\%$ compared to ones with a GLUT-1 expression of $<50\%$ (9). Another study demonstrated that GLUT-1 expression was inversely proportional to survival in gallbladder carcinoma (38). Overexpression of GLUT-1 and increased glucose metabolism in tumors are associated with a poor prognosis in patients with oral squamous cell carcinoma, and GLUT-1 has been shown to be a significant negative biomarker of prognosis and overall survival (39). In our study, mean survival was 60 months in patients with a GLUT-1 expression of more than 50% versus 82 months in those with an expression of less than 50%. That is, as GLUT-1 expression increases, survival decreases, although this correlation was not significant.

In conclusion, the expression of GLUT-1 in EH with atypia and ETEA may play a role in the diagnosis, and may be helpful in distinguishing EH without atypia from EH with atypia. GLUT-1 may guide physicians in determining cases with atypia who are at high risk for cancer development. GLUT-1's position in this field can be determined by close clinical follow-up of cases that have both atypia and a high GLUT-1 expression rate. GLUT-1 plays a role at the early stage of endometrial carcinogenesis, and it may be used as a subsidiary parameter to show the correlation of prognostic parameters and histological grade in ETEA cases.

Our study or other previous studies could not demonstrate any significant relationship between GLUT-1 expression and other prognostic parameters and survival.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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