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Original Article

Evaluation of the Expression Intensity of Glucose Transporter-1 Marker and its Diagnostic Value in Differentiating Between Borderline and Malignant Ovarian Epithelial Tumors

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Abstract

Background: Ovarian cancer ranks second among gynecological cancers worldwide. This study aimed to compare the glucose transporter-1 (GLUT-1) expression in benign, borderline, and malignant ovarian epithelial tumors and evaluate GLUT-1 expression as a diagnostic tool for distinguishing tumors in the ovary.

Materials and Methods: This descriptive-analytical cross-sectional study analyzed 69 pathological samples of patients diagnosed with ovarian epithelial tumors who underwent oophorectomy. Immunohistochemical staining was performed using GLUT-1 antibody. The intensity of cell membrane staining and the proportion of positive neoplastic cells were graded to score immunostaining. Chi-square/Fisher's exact test was used to analyze the data. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), and staining accuracy for GLUT-1 in distinguishing borderline from invasive tumors were calculated by standard methods ($P<0.05$).

Results: In all benign tumors, GLUT-1 staining was negative. In addition, weak staining intensity was observed in 38.5% of borderline tumors, and 96% of invasive tumors had strong staining intensity ($P<0.001$). Strong GLUT-1 staining was found in 94.7% of Papillary Serous Carcinoma, 9/1% of Borderline Serous tumors, 100% of Brenner tumors, and clear cell carcinoma. The results demonstrated a high diagnostic value of GLUT-1 expression intensity in differentiating between borderline and malignant ovarian epithelial tumors (Accuracy: 97.10, Sensitivity: 96%, Specificity: 97.73).

Conclusion: Overall, GLUT-1 expression could help distinguish benign from borderline, especially borderline from malignant ovarian epithelial tumors. Thus, it seems that it provides useful prognostic information, particularly for the borderline category.

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

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Introduction

Ovarian cancer is the fifth leading cause of mortality in women globally and the second most common gynecological cancer after uterine cancer (1). Epithelial tumors, germ cell tumors, and stromal tumors are the three types of cells that make up the ovaries and can grow into different cancers (2). Most ovarian tumors are epithelial cell tumors. According to the World Health Organization (WHO) guidelines, ovarian epithelial tumors begin on the outer surface of the ovaries and are classed as benign, borderline, or malignant (1). It is difficult to separate borderline from invasive cancers until they have grown in size and stage (3).

Borderline ovarian tumors (BOTs) are mild to moderately abnormal epithelial cells that proliferate more than benign tumors but not as much as malignant counterparts (4). According to a recent study, the preoperative diagnosis of BOTs is only 69% accurate. (5). Considering that BOTs lack normal morphological markers, gynecologic oncologists typically struggle to detect them before surgery, especially non-serious ones (6). Many patients with BOTs display symptoms similar to invasive tumors, including the presence of solid components and ascites on ultrasound imaging, a certain extent of cellular proliferation, and nuclear atypia in the absence of infiltrative growth and/or apparent stromal invasion (7). However, unlike invasive tumors, BOTs are more common in young women who want to keep their

fertility and have a good prognosis even with conservative treatment (8).

The diagnosis of an ovarian lesion is difficult; nonetheless, it is critical in the preoperative environment to plan appropriate treatment operations and influence patient management. The growth of cancer cells is an energy-related process that is aided by enhanced glucose metabolism (9), indicating that a similar increase in glucose transporter protein uptake is necessary.

Glucose transporter-1 (GLUT-1), a facilitative cell surface glucose transport protein, is a member of the GLUT family (10). It is physiologically expressed and immunohistochemically detectable in erythrocytes, endothelial cells, placenta, and blood-tissue barriers (11). Glut-1 is a useful marker in pathology, and its expression is utilized to distinguish self-limiting infantile hemangiomas from other vascular diseases (12). GLUT-1 is mainly undetectable by immunohistochemistry on normal epithelial tissues and benign epithelial tumors but is expressed in a variety of malignancies (1). Thus, the expression of GLUT-1 appears to be a potential marker of malignant transformation. Further, its expression in thymic epithelial malignancies was previously measured by the percentage of positive cells, intensity of immunostaining, or a score integrating both of these variables (13).

Many studies have been conducted to differentiate benign tumors from malignant or invasive tumors (14-16). However, no study has so far evaluated GLUT1 expression in differentiating the ovarian borderlines (low malignant) from invasive tissues. Accordingly, this study attempted to compare the expression of GLUT-1 in benign, borderline, and malignant ovarian epithelial tumors. We evaluated the use of GLUT-1 as a diagnostic tool in distinguishing between morphologically dubious borderline and malignant changes in the ovary.

Materials and Methods

This descriptive-analytical cross-sectional study was performed at the Department of Pathology of Motahari Hospital, a public teaching medical center in Iran, from 2020 to 2021. Sixty-nine pathological samples of patients diagnosed with ovarian epithelial tumors who underwent oophorectomy were included in the study. The information about these patients was obtained by searching the computer system. The patients who had undergone chemotherapy or radiotherapy before the surgery were excluded from the study. Patients' age, histological type of tumor, and degree of malignancy were recorded, and GLUT-1 transporters were detected by immunohistochemistry using the labeled streptavidin-biotin procedure. The prepared glass slides were removed from the archive, and diagnosis and re-grading were performed after re-examining. If the slides were not of good quality or were broken, new sections were made from the existing paraffin blocks, and hematoxylin and eosin were stained.

Then, the appropriate block for each case was selected for immunohistochemical staining. Four-micron sections were selected from selected blocks, and immunohistochemical staining was performed, in which paraffin was removed first. The tissue with paraffin was transferred to the slides, and after sticking to the slide, we had to remove paraffin from the slide, which required washing the tissue. The slides were washed twice for five minutes with xylene, then soaked in 50%, 75%, 95%, and 100% alcohol for five minutes, and finally, they were washed with a buffer. An appropriate amount of diluted GLUT 1 antibody was added dropwise to all areas fixed on the slide.

Afterwise, the tissue was incubated with the antibody for about 10-20 minutes. Then, the slides were cooled down with TBS and washed for five minutes. In addition, the coloring pattern and color intensity of each case were examined, and the slides were divided into grades 0-4 based on staining intensity. The grading method represented 0, 1, 2, and 3 for no, low, moderate, and severe staining, respectively. The percentage of positively stained cells was classified as 0: < 10%, 1: 10-50%, and 2: > 50%. The final intensity score was calculated by multiplying the staining intensity score by the staining percentage score. All cases were subsequently classified into four expression groups according to the final scores (0, 1, 2, and 3 for negative (-), weak (+), moderate (++), and strong (+++), respectively). For determining the diagnostic value of the GLUT-1 biomarker in distinguishing between morphologically dubious borderline and malignant changes of the ovary, the intensities of 0, 1, and 2 were considered negative, while 3 was considered positive.

The mean, standard deviation (SD), and frequency (percentage) were reported for continuous variables The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), and staining accuracy for GLUT-1 in distinguishing benign and borderline from invasive tumors were calculated by standard methods. Chi-square/Fisher's exact test was employed to test the association between the histologic types and grades of ovarian epithelial tumors with GLUT-1 immunoreactivity. Statistical analysis was performed using the SPSS statistical package; in all statistical analyses, $P < 0.05$ was considered significant. One-way ANOVA was used to compare the age of patients between the three ovarian tumor categories.

Results

The present study included 68 patients. Overall, 23, 21, and 25 patients had benign tumors (10 mucinous cyst adenoma, 11 benign serous cyst, and 2 seromucinous tumors), borderline tumors (10 borderline mucinous tumors and 11 borderline serous tumors), and invasive

cancer (19 papillary serous carcinoma, 2 brenner tumor, and 4 clear cell carcinoma), respectively. The mean age of patients with malignant cancer, borderline tumors, and invasive cancer was 43.52 ± 16.99, 48.14 ± 13.53, and 51.36 ± 12.11 years, respectively. No significant difference was observed between the age of these three groups ($P = 0.172$). Table 1 compares the mean age of understudy groups.

Table 2 provides GLUT-1 staining intensity in different histological grades of ovarian epithelial tumors. Complete loss of GLUT-1 expression was observed in 15 (100%) cases of benign epithelial tumors. In contrast, only 8 (61.5%) benign cases showed weak staining intensity. In the case of borderline tumors, 6 (38.5%) had weak staining intensity, while 14 (93.3%) and 1 (4%) tumors represented moderate and strong staining intensity, respectively. In the invasive tumors, 1 (7.6%) presented moderate staining intensity, whereas 24 (96%) demonstrated strong staining intensity. A statistically significant relation was observed between the intensity of GLUT-1 immunoreactivity and different grades of ovarian epithelial tumors ($P < 0.001$).

Table 3 compares GLUT-1 staining intensity according to different histological types of ovarian epithelial malignant tumors. The majority (94.7%) of papillary serous carcinoma has shown strong staining intensity (Figures 1 and 2), while none of the mucinous tumors represented this type of staining intensity. On the other hand, 55.6% and 44.4% of mucinous tumors demonstrated moderate and weak GLUT-1 staining, respectively (Figure 3). In the case of mucinous cyst adenoma, 2 (20%) were weakly stained, and 8 (80%) indicated a negative staining pattern. In benign serous cysts, 5 (45.5%) and 6 (54.5%) had negative and weak GLUT-1 staining, respectively (Figure 4). Furthermore, borderline serous tumors presented 1 (9.1%) weak, 9 (81.8%) moderate, and

Table 1. Comparison of Mean Age of Understudy Groups

Variable	Groups	Number	Mean	Standard Deviation	Statistics F (2,66)	*P* Value
Age (y)	Benign group	23	43.52	16.99	1.81	0.172
	Borderline group	21	48.14	13.53		
	Invasive group	25	51.36	12.11		

Table 2. Intensity of GLUT-1 Immunoreactivity in Different Grades of Ovarian Epithelial Tumors (n = 69)

Lesion Number		Score of Intensity				Fisher's Exact Statistics	*P* Value
		0	+1	+2	+3		
Benign	23	15 (%100)	8 (61.5)	0	0	98.78	<0.001
Borderline	21	-	6 (38.5)	14 (93.3)	1 (4)		
Invasive	25	-	-	1 (6.7)	24 (96)		

Note. GLUT-1: Glucose transporter-1.
Significant association of different grades with an intensity score (P < 0.05). The score of intensity (Additive Quick Score) = Intensity of staining + Proportion of staining. 0: Negative staining, 1: Weak staining, 2: Moderate staining, and 3: Strong staining.

Table 3. Intensity of GLUT-1 Immunoreactivity in Different Histologic Types of Ovarian Epithelial Tumors (n = 69)

	Lesion	Score of Intensity				Fisher's Exact Statistics	*P* value
		0	+1	+2	+3		
Histologic types	Papillary Serous Carcinoma	0	0	1 (5.3)	18 (94.7)	95.13	<0.001
	Borderline Mucinous Tumor	0	4 (44.4)	6 (55.6)	0		
	Mucinous Cyst Adenoma	8 (80%)	2 (20%)	0	0		
	Benign Serous Cyst	5 (45.5)	6 (54.5)	0	0		
	Borderline Serous tumor	0	1 (9.1)	9 (81.8)	1 (9.1)		
	Brenner tumor	0	0	0	2 (100%)		
	Seromucinous Cyst	2 (100%)	-	-	-		
	Clear Cell Carcinoma	-	-		4 (100%)		

Note. GLUT-1: Glucose transporter-1.
Significant association of tumour lesion with the intensity score (P < 0.05). The score of intensity (Additive Quick Score) = Intensity of staining + Proportion of staining. 0: Negative staining, 1: Weak staining, 2: Moderate staining, and 3: Strong staining.

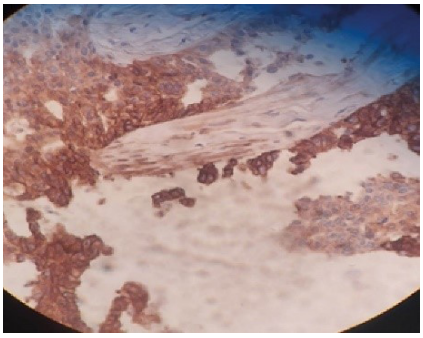

Figure 1. Malignant Papillary Serous Tumor With Staining Pattern GLUT-1 Marker With Strong (3) Intensity at 10x Magnification. *Note.* GLUT-1: Glucose transporter-1

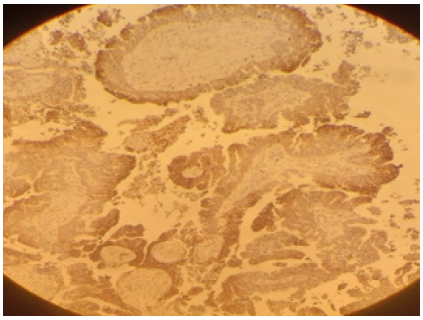

Figure 2. Malignant Papillary Serous Tumor With Staining Pattern GLUT-1 Marker With Strong (3) Intensity at 40x Magnification. *Note.* GLUT-1: Glucose transporter-1

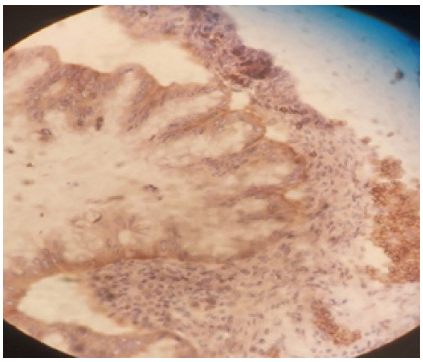

Figure 3. Borderline Mucinous Tumor With Staining Pattern GLUT-1 Marker With Weak (1) Intensity at 40x Magnification *Note.* GLUT-1: Glucose transporter-1

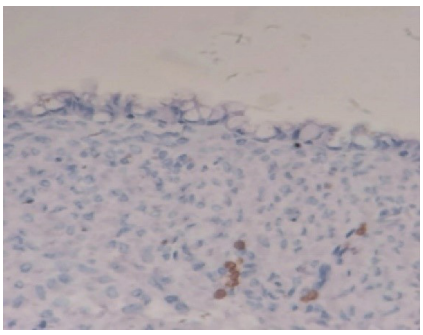

Figure 4. Benign Serous Tumor With Staining Pattern of GLUT-1 Marker With Negative (0) Intensity at 40x Magnification. *Note.* GLUT-1: Glucose transporter-1

1 (9.1%) strong GLUT-1 staining, respectively (Figure 5). Only strong GLUT-1 staining was shown (100%) in both the Brenner tumor and clear cell carcinoma (Figure 6). In contrast, seromucinous cyst represented negative GLUT-1 staining (100%). None of the papillary serous carcinoma, mucinous tumor borderline, serous tumor, Brenner tumor, and clear cell carcinoma cases showed negative staining for GLUT-1 ($P < 0.001$).

Table 4 presents the association between GLUT-1 marker results and grades of ovarian epithelial tumors and the diagnostic value of GLUT-1 expression compared with pathological findings.

Sixty-seven of 69 patients were correctly categorized (Accuracy = 97.10%) with sensitivity and specificity of 96% and 97.73 %, respectively. Positive GLUT-1 expression (score = 3) was observed in 1 and 24 patients with benign and borderline and invasive ovarian epithelial tumors, respectively. Based on the results, 96% of patients with positive GLUT-1 expression truly had invasive ovarian epithelial tumors (PPV = 96%). In addition, 97.73% of patients with a negative GLUT-1 expression truly had benign and borderline ovarian epithelial tumors (NPV = 97.73%). Based on the clinical findings, the association between GLUT-1 marker results and grades of ovarian epithelial tumors in histological findings was statistically significant (Pearson chi-square = 60.61, $P < 0.001$).

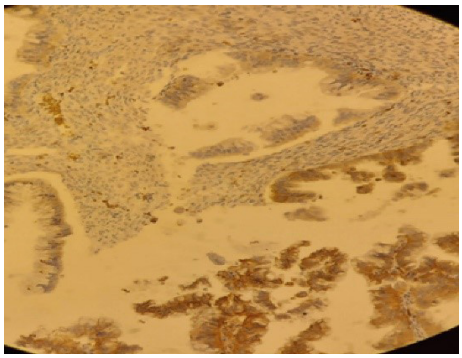

Figure 5. Borderline Serous Tumor With Staining Pattern GLUT-1 Marker With Moderate (2) Intensity at 40x Magnification. *Note.* GLUT-1: Glucose transporter-1

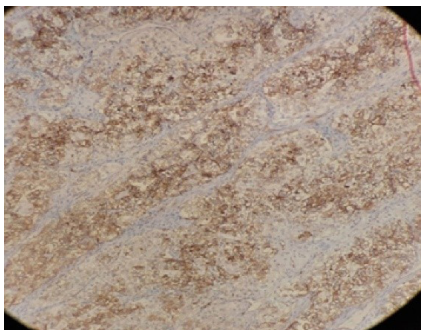

Figure 6. Malignant Clear Cell Tumor With Staining Pattern GLUT-1 Marker With Strong (3) Intensity at 40x Magnification. *Note.* GLUT-1: Glucose transporter-1

Table 4. Diagnostic Value of GLUT-1 Marker Differentiating Between Benign and Borderline and Invasive Ovarian Epithelial Tumors

		GLUT-1		*P* Value*	Sensitivity	Specificity	PPV	NPV
		Negative (0, +1, +2)	Positive (+3)					
Ovarian epithelial tumors	Benign and Borderline	43 (97.7)	1 (4.00)	<0.001	96%	97.73	96%	97.73
	Invasive	1 (2.30)	24 (96.00)					

Note. GLUT-1: Glucose transporter-1; PPV: Positive predictive value; NPV: Negative predictive value.
*Pearson chi-square = 60.61.

Discussion

Histological differentiation of borderline from malignant ovarian epithelial tumors can be challenging because they often exhibit similar behaviors to invasive carcinomas (17). Researchers have emphasized diagnostic biomarkers to differentiate between tumors (18). To our knowledge, this study is the first of its kind that compared GLUT-1 expression in benign, borderline, and malignant ovarian epithelial tumors and distinguished borderline from invasive tumors.

The findings of this study demonstrated that there was no significant difference in the mean age of the patients with benign, borderline, and malignant tumors. In addition, Abdul Hamid et al reported no significant difference between the median age for the study groups with phyllodes tumors (19). In line with other studies (1,20), our results represented a strong relationship between GLUT-1 expression and ovarian epithelial tumors. On the other hand, Xiong et al (21) reported that GLUT-1 expression can be utilized to distinguish between benign endometrial lesions and endometrial cancer; however, it has little predictive significance in women who have this cancer, which is contrary to the findings of this study.

Furthermore, the results showed that the majority (94.7%) of the malignant epithelial tumors, including papillary serous carcinoma (18/19), showed strong GLUT-1 staining, indicating the usefulness of this marker in assisting diagnosis. Additionally, only one case of borderline serous tumors had strong GLUT-1 staining (1/11), and GLUT-1 staining was negative among 11 benign serous cysts. This finding is almost the same with those of Ullah et al and Khabaz et al (1,22); the only difference is that both of these studies indicated that benign tumors had positive GLUT-1 staining, but the majority of benign tumors were negative in our study. Accordingly, patients with positive GLUT-1 expression tend to have a poorer prognosis than those with negative GLUT-1 expression, suggesting the biomarker's predictive relevance. In agreement with this statement, Szablewski reported that the overexpression of GLUT-1 was strongly related to poor survival in patients with various malignancies (23).

In this study, moderate staining intensity for GLUT-1 was found in most borderline mucinous (5/9) and serous (9/11) tumors, and strong staining was in malignant papillary serous carcinoma (18/19). The difference in architecture and proliferative activity between both tumors is due to the stratified papillary structure of its tumor cells, which is accompanied by fewer vascular channels. None of the borderline and invasive cases showed negative (0) staining. These findings align with a study conducted by Nagib et al (24) in which weak to moderate GLUT-1 expression was reported in most borderline cases. Furthermore, Cantuaria et al (25) demonstrated weak and moderate positivity in most borderline cases. On the contrary, in a study by Ruby et al, moderate to strong GLUT-1 expression (score = 2 or 3) was only observed in malignant tumors (20).

Moreover, twenty-four (95%) malignant epithelial tumors stained positively with anti-GLUT-1 among 25 cases in the present study. In positive cases, staining had strong intensity and was more extensive than in borderline tumors, and immunoexpression was observed in the majority of cell membranes. These findings conform to the results of Yan et al, representing moderate to strong GLUT-1 staining intensity in 96% of invasive cases (26).

Likewise, Cai et al (9) concluded that staining was absolutely negative in normal ovarian tissue, whereas GLUT-1 and P63 expression were greater in borderline tumors and adenocarcinoma cysts. These results are consistent with the findings of our study both in terms of the high sensitivity (95%) of GLUT-1 marker expression in distinguishing malignant tumors from borderline or benign tumors and the negative staining of benign ovarian tumors with GLUT-1 marker expression. Conversely, Ruby et al reported that GLUT-1 is not overly sensitive in determining whether a tumor is borderline or invasive (20).

According to the obtained results of the present investigation, GLUT-1 expression progresses slowly through all stages of ovarian tumors (benign, borderline, and malignant). Elbasateeny et al confirmed this result and showed that GLUT-1 expression in ovarian cancers is progressively stained (27). This finding suggests that the degree of GLUT-1 expression is closely linked to the histopathological grade of the malignant transformation of ovarian epithelial tumors, implying that they have an increased need for glucose metabolism. The weak points of this study are the relatively small sample size and the semi-quantitative interpretation of immunostaining. However, studies with large sample sizes are undoubtedly of great value for estimating the diagnostic and prognostic

values of GLUT-1 immunoreactivity in ovarian epithelial malignancy.

Conclusion

In general, it was revealed that GLUT-1 is involved in glucose uptake by ovarian epithelial tumor cells, leading to increased growth and biological aggressiveness. Our findings support GLUT-1 as a diagnostic tool to distinguish borderline from malignant ovarian tumors and suggest its association with different grades of ovarian epithelial tumors. Moreover, its relatively strong expression in serous tumors as compared to mucinous represents its association with the histological characteristics of the tumors. As a result, the predictive significance of GLUT-1 overexpression could be used to identify patients with a poor prognosis who would benefit from the future therapeutic targeting of overexpressed markers.

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Authors' Contribution

Siamak Naji Hadadi and Hale Ayatollahi: Conceptualization, original draft writing, investigation, and formal analysis; Masoumeh Noushyar and Siamak Naji Hadadi: Conceptualization, supervision, and project administration; Masoumeh Noushyar : project administration; Masoumeh Noushyar and Hale Ayatollahi: Investigation; Masoumeh Noushyar and Siamak Naji Hadadi: Writing, including reviewing and editing and investigation.

Competing Interests

The authors declare that they have no conflict of interests.

Ethical Approval

This study was conducted under the Declaration of Helsinki and approved by the Ethics Committee of Urmia University of Medical Sciences (with code: IR.UMSU.REC.1400.332).

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