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# Does Glut-1 and Maspin Expression Have Prognostic Value in Uterine Cervical Carcinomas

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**Abstract**

**Aim:** Cervical cancer is the the most common gynecologic malignancy worldwide with approximately 750,000 new cases annually. The aim of this study was to pose the histopathologic and clinical features of cervical carcinoma, as well as, the immunohistochemical expression of glucose transporter 1 (GLUT-1) and maspin, and their association with clinicopathological parameters in these cases and whether this relationship is effective with prognosis and survival.

**Methods:** 114 patients were included in this study with the diagnosis of cervix carcinoma between 1992-2012. Tissue microaaray was performed and taken sections immunstained with GLUT-1 and maspin. The relationship is investigated between findings and prognostic factors, local recurrence, distant metastasis and survival.

**Results:** Tumor type, lymph node invasion, and lymphovascular invasion (LVI) and clinic parameters like recurrence and metastasis have not show statistically significant difference with the presence of GLUT-1 and maspin immunreactivity. However, the relationship between maspin expression and stage shows statistically significant difference ($p = 0.048$) indicating that the higher expression of maspin is correlated with lower stages.

**Conclusion:** In our study we observed that the presence of maspin expression and stage have shown statistically significant difference but we could not detect the same difference between GLUT-1 presence and stage. Also we did not find any correlation between GLUT-1 and maspin expression with the factors which are mentioned in the literature that affect prognosis and survival like stage, tumor type, lymph node status, LVI, involvement of parametrium.

**Keywords:** Carcinoma of the cervix, GLUT-1, maspin, immunohistochemistry

## Introduction

Cervical cancer (CC) is mostly occurred in less developed countries and is the most common gynecological malignancy with approximately 750,000 new cases annually worldwide (1-4). In United States (U.S.) CC death rate has reduced because of using routine screening programs. In 2000, with an estimated 12,800 new cases and 4,600 deaths, CC is the third most common gynecologic malignancy in the United States and a large percentage of women with advanced stage disease continues to die of local recurrence and metastatic disease (3-5). The frequent type of CC is squamous cell carcinoma (SCC) followed by adenocarcinomas (AC) and its subtypes, other epithelial tumors and mesenchymal tumors respectively (6).

Although a complex treatment protocol 40% relapse occurs in CC. In spite of numerous well-known prognostic factors like clinical stage, lymph node metastasis, tumor size and depth of invasion, we need better prognostic markers to reduce the risk of relapse, managing patients and determining treatment protocols. Therefore, to numerous studies in the literature have been made in cervical carcinomas about prognostic markers including hypoxia and angiogenesis, genetic amplifications, immunity and response to treatment. A portion of this study was found associated with prognosis but in some studies larger series are needed.

One of the markers studied in various tumors reported to be associated with hypoxia is the glucose transporter-1 (GLUT-1). Under physiological conditions, GLUT-1 shows strong expression in erythrocytes and blood-brain or blood-nerve barrier (7-9). GLUT-1 overexpression is available in a wide variety of solid tumors (7) and CC is one of this tumors (10). GLUT-1 overexpression contributes significantly to enhanced glucose found in solid tumors phenomenon and this is a feature utilized for diagnostic purposes (11-12). Studies show increased GLUT-1 mRNA existence various types of tumors such as stomach (13), colorectal (14), lungs (15), brain (16-17), head and neck (18), and pancreas (19). CC which has few studies needed large series and more number of studies. The other marker is maspin, a protease inhibitor which has been identified as type II tumor suppressor gene (20-23). Maspin aberrant gene expression have been reported in many tumors, such as breast, prostate and thyroid carcinoma (24-26). There are several publications on the effects on prognosis (27-33). However, there has been no studies published in the literature about the expression of maspin and it's relationship with prognosis in cervical cancer .

In the light of this information in the literature, this study intends to reveal the histopathological and clinical features as well as showing the expression of GLUT-1 and maspin and their relationship with clinicopathological parameters, prognosis and survival.

## Materials and Methods

114 patients who have diagnosed as cervical carcinoma in Dokuz Eylul University (DEU) Department of Medical Pathology between the years 1992 - 2012 between the years included in the study. Hematoxylin & eosin (H & E) stained slides belonging to cases was selected which demonstrates tumor from DEU Department of Pathology Preparation and Block Archive. Later an area 5 mm in diameter is marked that best reflects the characteristic of the tumor. Then, using quick ray system (Tissue-Tek® Quick- Ray™ 8018) tissue microarray (TMA) paraffin blocks performed. 4 micron thickness sections were taken from TMA blocks for immunohistochemical (IHC) staining.

The section taken placed into oven overnight. The following day sections were deparaffinized with xylene, rehydrated in descending series of alcohols and washed in

distilled water. Then sections were immersed in a solution of 0.3% H2O2 and they are boiled in PT module for 20 minutes at 95 degrees Celsius in buffer solution of EDTA (pH:7) and left to cool at room temperature. Ultra V block was applied and then appropriate primary antibody (Maspin- polyclonal rabbit antihuman MASPIN H-30: sc-22762, Santa Cruz, 1/50 dilution and Anti-GLUT-1- polyclonal rabbit antihuman GLUT-1, lot number 2043895, MILLIPORE, 1/50 dilution) was applied and the incubation was allowed for 1 hour providing the antibodies to bind. Then the sections were washed in Tris buffer solution followed by biotin/streptavidin application.Later diaminobenzidine (DAB) solution used as chromogen. Finally, slides were counterstained with Mayer's hematoxylin, dehydrated in an ascending alcohol series, and covered with a coverslip. Prostate tissue has been used as positive control for both maspin and GLUT-1. Cytoplasmic staining for maspin and membranous staining for GLUT-1 was considered positive in control tissues.

While evaluating all of the cases under microscope necrosis, stroma, normal epithelium and different areas of edge effects were ignored. . Cytoplasmic staining for maspin and membranous staining for GLUT-1 was considered positive. Negative or weak staining was considered as negative and moderate or strong staining was considered positive in all cases for both GLUT-1 and maspin (Figure 1) (34).

All data has been converted to statistical data to using Statistical Package For the Social Sciences (SPSS) 15.0. In the analysis, the normal distribution of data was checked by applying the Kolmogorov-Smirnov test. After that the chi-square test, Fisher's exact test, Kaplan-Meier analysis and regression analysis were used. Due to the lack of significance to create the model, multivariate analysis was not applied.

**Findings**

The ages of patients included to the study were between 27 and 80 (mean 52.32± 11.911). Material types of cases reached our department were classified as radical hysterectomy, bilateral salpingo-oophorectomy and lymph node dissection, biopsy, endocervical curettage, conization,and consultation of the biopsy of external center. The most common tumor is SCC (%87,7). Statistical analysis applied by grouping the patients to SCC and tumors types except SCC because the tumor types except SCC has small numbers. When cases evaluated by FIGO staging system, the most common stage was stage I (%64,1). Statistical analysis applied by grouping patients as stage I (tumor limited to the cervix) and other stage (stage II, stage III, stage IV) (not limited to cervical tumors) due to the small numbers of advanced stages. The number radical surgery material is 89 therefore other cases evaluated by clinical staging. The patients which does not have radical surgical material evaluated radiologically for ovary, endometrial, parametrial, vaginal and lymph node involvement.

Follow-up of the patients ranged from 1-192 months with average follow-up period 48.28 (±43,907) months. On survival analysis of patients, the 5-year survival rate is about 92%. Four (3.5%) patients died in the follow-up period and nine (7.9%) had distant metastases at the time of diagnosis consisting of lung, liver, mediastinum, scapula. In the follow-up period of 6 cases (5.3%) had local recurrence and 5 patients (4.4%) had distant metastases. 15 patients (%13,2) had endometrial, 4 patients (%3,5) had ovarial and 22 (%19,3 ) had parametrial involvement whereas 33 patients (%28,9) had metastatic lymph node (internal iliac, pevic and paraaortic).

GLUT-1 expression could be evaluated in 105 cases due to spilling up of the tissue in sectioning and

immunohistochemistry step. From this 105 (100%) patients 95 (90,47%) had verified FIGO stage data. 70 patients (73,7%) had tumor limited to cervix of the 95 (100%) case that we can analyze GLUT-1. 20 cases (%28.6) had no staining from this 70 (%100) cases. Statistically significant relationship was not observed between GLUT-1 and stage in Fisher's exact test (p=0.291).

We could evaluate GLUT-1 staining in 93 (88.6%) SCC cases and 25 (%26.9) of these had no staining. The 10 (%83.3) case from the 12 (%11,4) case with tumors except SCC stained positive with GLUT-1. There were no statistically significant relationship between tumor type and GLUT-1 expression (p=0.727).

There are 89 (84.8%) cases with no lymph node involvement and among these 89 (%100) cases 67 (%75.9) had positive staining. The 11 (%68.7) cases among 16 (%15.2) cases which had lymph node involvement had GLUT-1 positivity. A statistically significant relationship between GLUT-1 expression and LN involvement with was not observed (p=0.551).

No statistically significant relationship was observed between GLUT-1 positivity and parametrial, endometrial, ovarian involvement (p=0.269, p=0.108, p=0.570). Similarly, there is no statistical significance between GLUT-1 expression and clinical parameters like local recurrence, metastasis and death (p>0.05 ) .

GLUT-1 positive and negative patients had no significant relationship with Kaplan-Meier survival analysis (p= 0.222).

Maspin expression could be evaluated in 105 cases due to spilling up of the tissue in sectioning and immunohistochemistry step. From this 106 (100%) patients 95 (89,6%) had verified FIGO stage data. 71 (74.7%) of these 95 (%100) patients has tumor limited to cervix and 28 (%39.5) of these had no staining with maspin. 43 (%60.5) had positively staining with maspin. The number of patients which tumor does not limited to cervix 24 (%25.3) and 20 (%83.3) of these cases had positive staining. These findings showed correlation with maspin and stage (p=0.048). This indicates that tumors limited to cervix shows increased maspin expression than tumors not limited to cervix.

94 (88.7%) patients diagnosed as SCC from 106 (100%) patients we could evaluate maspin and 62 (%66.0) patients had positive staining with maspin while 32 (%34.0) had no staining. Number of cases which has tumors except SCC was 12 (%11.3) and 8 (%66.7) of these cases had positive staining. A statistically significant correlation was not observed between tumor type and the expression of maspin(p=1.000 ).

32 (%35.6) of the 90 (%84.9) patients which has no LN metastasis had no staining with maspin and 58 (%64.4) had positive staining. 4 (%25.0) patients had no staining among 16 (%100) patients which has LN metastasis and 12 (%75.0) showed maspin expression. A statistically significant association between involvement with LD maspin expression was not observed (p=0.569).

A statistically significant relationship between maspin expression and parametrial, endometrial and ovarian involvement was not observed (p=0.066, p=0.769, p=1.000). Likewise clinical parameters like local recurrence, metastasis and death showed no statistically significant relationship with maspin positivity (p >0.05).

Maspin positive and negative cases showed no significant relationship with survival in Kaplan-Meier survival analysis (p=0.419).

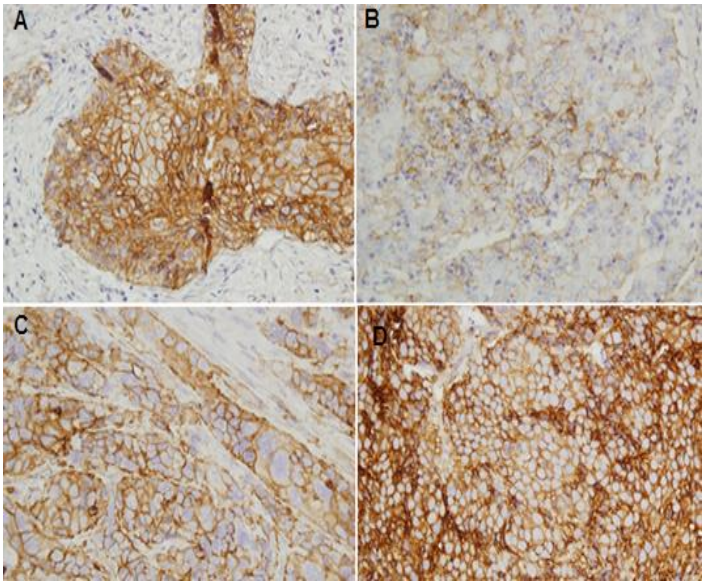


Figure 1: A) Image of GLUT-1 positive tumor and negative stromal area B) Weak GLUT-1 positive area accepted as negative C-D) GLUT-1 stained areas

**Discussion**

Cervical cancer (CC), is the most common gynecologic malignancy worldwide mostly in less developed countries with about 750,000 new cases occurring annually and ranks 13th among cancer-induced deaths in Turkey (1-4). SCC constitutes 75- 85% of CC (6). Although a complex treatment protocol, 40% of invasive CC relapses. Therefore new prognostic markers is needed to predict the outcome except well known ones like stage, LN involvement and metastasis. For this reason tumor-hypoxia is one of the issues that is being investigated.

Malignant tumors adapt to hypoxic conditions through a variety of molecules. Neovascularization associated with hypoxia stimulates invasiveness and metastatic capacity and glycolytic activity and the studies in the literature have shown that in many significant areas of tumor hypoxia (35).

Malignant tumor development is also an energy-dependent process, supported by an increase in glucose metabolism resulting in the increase of glucose transporter proteins in the cell membrane. GLUT-1 mediates glucose uptake, thus facilitating the anaerobic glycolysis. This protein is usually not detectable in normal epithelium and benign tumors, but in various tumors including the stomach, colorectal and lung cancers expression has been reported to be associated with poor prognosis (13-15). Ma X. et al reported that GLUT-1 positivity rates increase from normal to carcinoma group in endometrial tissues and similar to this study Canpolat T. et al reported that there was a significant difference between endometrial hyperplasia cases with and without atypia, and proliferative endometrium showed no staining while endometrial adenocarcinoma cases showed %95 positivity (36-37). In a study which includes 51 SCC, 20 normal cervical tissue and 20 CIN cases; most of the normal cervical tissue has shown GLUT-1 positivity in only basal epitelial layer and 5% case shas shown epitelial positivity. 48 (%94.1) of 51 SCC cases demonstrated GLUT-1 overexpression while 3 (%5.9) cases demonstrated minimal expression and in all cases tumor stroma has shown no expression. Staining intensity and the severity were detected increased significantly in all degree of the dysplasia and carcinoma compared with normal epithelium (38).

Regarded as the most important parameter stage and GLUT-1 relationship shows different results in different studies. In 2007, researchers was evaluated GLUT-1 immunoreactivity in 25 patients with head and neck SCC. No statistical significance was found GLUT-1 immunoreactivity and T stage (39). In gynocologic tissues, Sadlecki P. et al reported no relationship between endometial carcinomas and FIGO stage, histologic grade, lymph node and distant metastasis, myometrial invasion depth, cervical and adnexial involvement and recurrence however another study found that GLUT-1 was correlated with stage of clinical disease in epithelial ovarian carcinomas (40-41). When considering CC, Mayer A. et al demonstrated GLUT-1 expression is increased linearly

with FIGO stage and higher expression level of GLUT-1 is detected in stage II cases compared with stage I cases on CC in a different study (42-43). On the contrary Huang XQ et al reported that no significant association was observed between GLUT-1 expression and patient age, FIGO stage, histopathological grade, or tumor diameter (44). Our study was also focused on a gynecological malignancy, no statistically significant relationship between GLUT-1 expression and tumor stage was detected (p=0.291). This situation can be caused by the lack of advanced staged cases included to study. Different results can be obtained in larger and more homogeneous series of stage groups. Also, we did not observe a statistically significant correlation between distant metastases and GLUT-1 expression (p=0.186). In a study on rectal tumors in 2003,distant metastasis had no correlation with GLUT-1 expression either (35).

GLUT-1 expression was associated with lymph node metastasis in colorectal carcinoma and SCC of tongue (14, 45). Likewise in endometrial carcinomas positive expression rates of GLUT-1seen in the increase of the stage, decrease of the differantiation and lymphatic metastasis (36). But in our study, statistical significance was not observed between the GLUT-1 expression and LNI (p=0.551).

In oral SCC cases, it has shown that local recurrence ,which is an important indicator of treatment response, and GLUT-1 expression has a correlation (47). In contrast, the was no statistically significant relationship was found local recurrence in tongue carcinomas and GLUT-1 expression (45). Likewise, our study has not detected statistically significant relationship between the local recurrence and the GLUT-1 expression. But on the report published in 2014, it was told that GLUT-1 staining was much stronger in the radiation-resistant group than the radiation-sensitive group in cervix carcinomas (44).

There are publications indicating that GLUT-1 expression is a negative indicator when duration of life and death is taken into consideration (10,14). In pulmonary neuroendocrine carcinomas no correlation found between GLUT-1 score and survival in the univariate analysis as well as no association detected on progression-free survival time with the expression of GLUT-1 in CC (46, 44). In our study, there was no association between survival and GLUT-1 expression (p=0.570) .

Maspin, a protease inhibitor is also defined as type II tumor suppressor gene (21-24). The relationship between tumor and maspin reported in several publications with various results (34,48-50). Zheng H. et al reported that there are nuclear and cytoplasmic positivity diffusely distributed in varying levels in colorectal adenocarcinomas and statistical analysis indicates that there is an increase on maspin expression from non-tumoral mucosa towards tumor (48). In the study which includes 41 endometrioid endometrial carcinoma, 27 patients (66%) was observed of aberrant expression of maspin while normal endometrial glands had none (50). On contrast, Blandamura S et al found increasing levels of maspin expression from normal endometrial cells to endometrial adenocarcinoma (51).

In a research published in 2015, it is suggested that maspin gene can significantly inhibit human cervical SCC SiHa cell proliferation and effectively slow cancer growth (52). In 2001-2002, Xu C. et al observed that comparing to invasive SCC cases, cases of CIN 3 and MICA showed significantly stronger expression of maspin while other clinicopathologic parameters have not been evaluated (53). Similarly Liu Z. et al detected decreasing expression of maspin in normal cervical epitelium, CIN 3 and uterin SCC respectively (54).

Different results were obtained in studies of LN metastasis and tumor stage evaluation on different tumors. In a study

conducted in laryngeal carcinoma, no significant correlation was reported in the statistics between maspin expression and LN situation (55). Also no association was found between maspin expression and tumor stage or LN condition in primary non-small cell lung cancer likewise in colorectal carcinoma (53, 48, 57). Cao D et al. reported that tumor stage, LN status and perineural invasion had no asssosiation with the expression of maspin in the article published in 2007 on pancreatic ductal carcinomas (58). Li HW. et al found that FIGO stage I and III endometriod endometrial carcinoma cases showed more maspin expression compared to normal endometrium but they failed to show the same relationship between stage II and stage III (59). Tissue micro array was performed and maspin expression was evaluated in 340 cases of gastric biopsies and contrast to previous studies, this study suggested that there is a positive correlation between maspin expression and invasion depth, stage and LN involvement (60).

Thyroid papillary thyroid carcinoma (PTC) has been reported to be only positive lesion for maspin in a study of 63 cases including benign and malignant lesions and surrounding normal thyroid tissue as control tissue. In the same study a statistically significant correlation between maspin positive cases and clinicopathological parameters including tumor stage not detected (61). In cervical SCC cases, Liu Z. et al found no statistical significant difference between stage Ib and stage II as well as lymph node involvement (54). Similarly we did not find a statistically significant relationship between lymph node metastasis and the expression of maspin ($p=0.569$). However, we noticed that expression of maspin increases when tumor stage increases and this increase was statistically significant ($p=0.048$).

Local recurrence is one important factor in the evaluation of response to therapy, but there is not much publications associated with it. Nosaka K. et al. reported that maspin-positive status was significantly correlated with recurrence in the study on 46 cervical adenocarcinomas (62). On contrary, and similar to our study, Cho JH. et al. found no statistically significant correlation between the expression of maspin and local recurrence in their study on tongue carcinomas (63). Metastasis is another important factor in the evaluation of response to therapy. Zheng H et al detected negatively correlation in their study with maspin expression and liver metastasis in colorectal carcinoma (48). But we did not show a statistically significant relationship between metastasis and the expression of maspin ($p>0.05$). Similarly Tahany M et al. reported no statistically significant relationship although PTC patients with distant metastasis shows the loss of maspin expression (61).

Survival is an important indicator used to evaluate the prognosis varies among publications. Statistically significant difference was shown in univariate analysis between maspin expression and survival in breast cancer cases (64). In another study on breast cancer which used TMA, maspin overexpression is associated with increased death risk in patients with no LN involvement (65). Yu M et.al reported that, cumulative survival rates among gastric cancer were negatively correlated with the expression of maspin but it's mentioned that maspin is not an independent factor for prognosis (60). In contrast to these publications, Solomon L.A. et al reported that high maspin expression is associated with increased survival in ovarian carcinomas (66).In our study, no statistically significant difference was observed between survival and expression of maspin ($p>0.05$). Likewise, in tongue carcinomas no relationship was found between low or high maspin expression and survival (63). According to Kaplan-Meier analysis, Zheng H. et al detected no association between

maspin expression and survival of patients in colorectal neoplasia patients (48).

In conclusion GLUT-1 and maspin are thought to be important factors on prognosis and resistance to treatment in cervical carcinomas but we only found correlation with maspin and stage (p=0.048) which indicates that tumors limited to cervix shows increased maspin expression than tumors not limited to cervix. There is not many studies on maspin and how does it's expression effect on prognosis. Maspin evaluation shoud be performed on larger and more homogenous series to show the relationship between CC and prognosis.

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