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ORIGINAL ARTICLE

The Prognostic Significance of Glucose Transporter-1 Protein in Malignant Pleural Mesothelioma

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Abstract

Introduction: Malignant pleural mesothelioma (MPM) is a rare condition with a poor survival rate. This study was designed to determine the prognostic importance of glucose transporter-1 (GLUT-1) expression in operated patients with pleural mesothelioma.

Methods: Patients operated with a diagnosis of pleural mesothelioma between January 2005 and September 2014 were retrospectively analyzed in terms of age, gender, diagnosis method, maximum standardized uptake value in positron emission tomography, operation, pathology, GLUT-1 expression in the specimen, morbidity, and mortality.

Results: One hundred and twenty-nine patients were diagnosed as MPM. 75 (54 male and 21 female) of these patients underwent therapeutic operations. The mean age was 63 (range 41–89). Extrapleural pneumonectomy was performed in 27, pleurectomy/decortication in 25, and radical pleurectomy in 23 patients. The pathological diagnosis was epithelial in 67 and biphasic in 8 patients. All the patients were referred for adjuvant chemoradiotherapy and 69% completed the intended trimodality treatment. In 61 (81.3%) of the operated patients, the parietal pleura material was positive for GLUT-1. The morbidity was seen in 16 of the operated patients. The average survival time was 23.7 months after surgery. The average survival time was 24.5 months in patients with GLUT-1 expression <10% in extent, and 15.6 months in rest of the patients (p=0.001).

Discussion and Conclusion: MPM has a poor prognosis even after surgery. However, lower expression of GLUT-1 was associated with significantly longer survival in our study. The survival time was found to be better if the GLUT-1 extent was <10%. Larger studies are needed to prove the prognostic significance of GLUT-1.

Keywords: Glucose transporter-1 protein; malignant pleural mesothelioma; surgical therapy.

Malignant pleural mesothelioma (MPM) is a rare neoplasm originating from the mesothelial cells and has a poor survival rate. It was first described by Wagner et al.,[1] in 1960 with relation to asbestos exposure. Benign lesions of mesothelium are challenges to distinguish from malignant lesions of mesothelium, particularly in small biopsy specimens. Immunohistochemical markers are used to determine the malignant versus benign mesothelial proliferations[2].

Malignant cells require an energy supply like glucose to proliferate and multiply. Glucose uptake is controlled by glucose transporters (GLUTs). GLUT-1 is an energy-independent passive carrier system for transporting glucose. GLUT-1 cannot be detected in benign lesions of pleura[3,4]. In contrast, GLUT-1 is expressed in various malignancies such as MPM, thus bringing to mind the handiness and the importance of immunohistochemical markers such as GLUT-1 in concretizing the diagnosis and determining the prognosis of MPM[5].

Surgery, chemotherapy, and radiotherapy are used in the treatment of MPM. However, there is still no standard treatment modality. GLUT-1 is a member of the facilitative fam-

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ily of glucose transporters, and it is shown that this indicator is positive in 100% of malignant mesotheliomas, and it is expressed in 0% of reactive mesothelium[5]. This study was designed to determine the prognostic importance of GLUT-1 expression in operated patients with MPM. Thus, the hypothesis of this study is to clarify if there is a connection between the survival of MPM patients and GLUT-1 expression in MPM cells.

Materials and Methods

Patient Selection

Patients who underwent therapeutic operations with a diagnosis of pleural mesothelioma between January 2005 and September 2014 were added to the study. All the patients underwent computed tomography (CT) scan, fiberoptic bronchoscopy, and positron emission tomography (PET/CT). Patients were diagnosed either with pleural cytology or videothoracoscopic pleural biopsy. Patients with epithelial or biphasic mesothelioma were operated. Exclusion criteria for the operation were medically inoperable patients, sarcomatoid pathology, metastatic mesotheliomas, and disease extending to other cavities and patients that refused the operation. Plus patients who underwent neoadjuvant treatment were not included in the study as the therapy may affect GLUT-1 expression. Extrapleural pneumonectomy (EPP), pleurectomy/decortication (P/D), and radical pleurectomy (RP) were undertaken in patients according to the spread of the disease. EPP was performed in patients which the disease has spread to lung parenchyma. Patients with only pleural invasion were treated with P/D, whereas patients with macroscopic involvement of the diaphragm or the pericardium were treated with RP. The 7th MPM staging system was used[6]. The scientific research committee of our institution approved the study (No:239) and informed consent was obtained from all the patients.

Immunohistochemistry Examination

The pathology slides were stained by overnight incubation with primary antibodies against GLUT-1 (SPM498) (cat.# Ms-10637-R7, LabVision Thermo Fisher Scientific, Cheshire, UK). Appropriate positive and negative controls (red blood cells for GLUT-1) were used for the antibody. The extent of GLUT-1 staining was evaluated on a sliding scale of 0 to 4+ to represent the percentage of positive cells among mesothelial cells (0→<1%, 1+→1–10%, 2+→11–50%, 3+→51–80%, 4+→>80%). These were the percentages of the cells that showed cytoplasmic and/or membranous staining. The intensity was then scored as 1 = weak, 2 = moderate, and 3 = strong. Immunohistochemical staining was scored by the pathology department as well as an independent pathologist (Dr. AE).

Statistical Analysis

Data were retrospectively analyzed in terms of age, gender, diagnosis method, maximum standardized uptake value (SUVmax) in PET/CT, operation, definite pathology, GLUT-1 expression in the specimen, morbidity, and mortality. SPSS (Statistical Package for Social Sciences) for Windows version 22.0 was utilized for the statistical analysis. Kaplan–Meier test was performed for the survival analysis and Wilcoxon log-rank test for the comparison of the study groups. $P<0.05$ was considered to be statistically significant, and the distribution of data was addressed with a confidence interval (CI) of 95%.

Results

One hundred and twenty-nine mesothelioma patients were diagnosed as MPM. Seventy-five of these patients underwent therapeutic operations. 54 patients were male and 21 patients were female. The mean age was 63 (range 41–89). In 35 of the patients, mesothelioma was on the right side whereas 40 patients had mesothelioma in the left hemithorax. Seventy-two patients were diagnosed with pleural biopsy and 3 with pleural fluid cytology. The average of SUVmax in PET/CT was 4.9 (4.7 and 5.3 in patients that showed no GLUT-1 expression and in patients that showed GLUT-1 expression, respectively) ($p<0.05$). EPP was performed in 27, P/D in 25, and RP in 23 patients. There was no significant statistical difference according to the type of operation ($p=0.06$). All the patients were referred for adjuvant chemoradiotherapy, and 69% completed the intended trimodality (chemoradiotherapy) treatment. Seven patients were in stage IA, 13 in IB, 22 in II, 24 in III, and 9 in IV (Table 1). Morbidity was seen in 16 (21.3%) of the operated patients (Table 2). The per-operative

Table 1. TNM stages of the patients

		n
T		
	T1a	7
	T1b	15
	T2	23
	T3	21
	T4	9
N		
	N0	61
	N1	5
	N2	9
	N3	0
M		
	M0	75
	M1	0
Stage		
	IA	7
	IB	13
	II	22
	III	24
	IV	9

Table 2. Complications

Empyema	1	Dyspnea	6
Chylothorax	2	Pneumonia	1
Wound infection	3	Rethoracotomy	3*

*Two of the rethoracotomies were due to diaphragm herniation and one was due to hemorrhage.

cardiopulmonary arrest was seen in one patient.

The definite pathological diagnosis was epithelial in 67 and biphasic in 8 patients. The parietal pleura material was positive for GLUT-1 in 61 (81.3%) of the operated patients. fifty-eight of these GLUT-1 positive patients had a diagnosis of epithelial mesothelioma, whereas 3 had a diagnosis of biphasic mesothelioma. The sensitivity of GLUT-1 in MPM was 47.3% in our study.

The average overall survival time was 23.7 months after surgery. This ratio was found at 21.8 months in patients who underwent surgery, and who also showed GLUT-1 expression in the pathology specimen. Thirty-four patients had weak intensity of GLUT-1, 18 had moderate and 9 had strong. The average survival time was 15.6 months in patients with GLUT-1 expression > 10% in extent (Figs. 1 and 2). This ratio was found at 24.5 months in patients showing <10% GLUT-1 expression in extent (p=0.001) (Figs. 3 and 4). The survival of the patients according to the extent and intensity of GLUT-1 expression in the pathology specimen is summarized in Table 3.

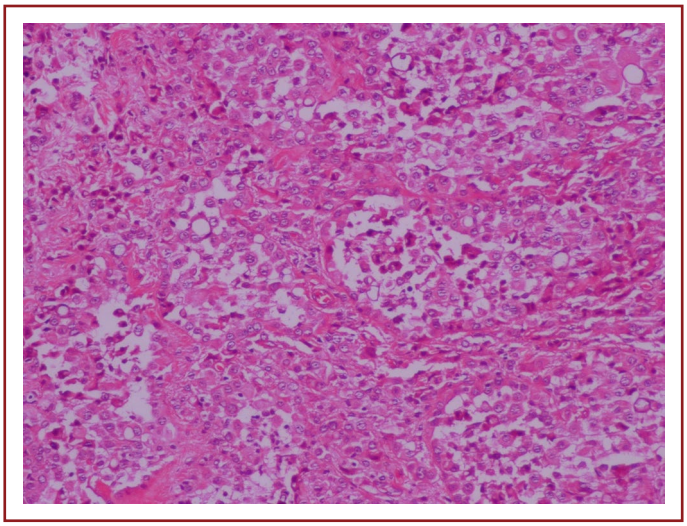

Figure 1. Pleural malign mesothelioma, HE, ×100.

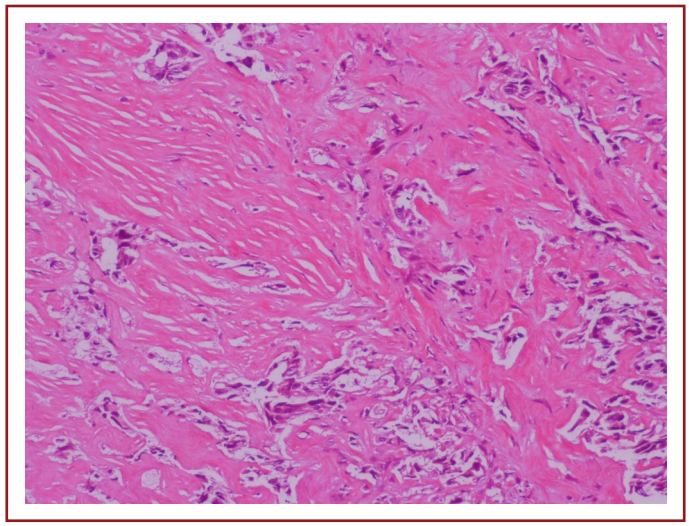

Figure 3. Pleural malign mesothelioma, HE, ×40.

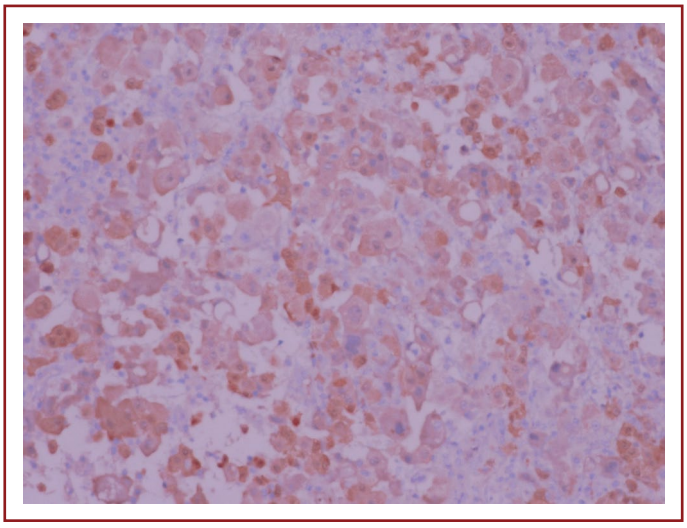

Figure 2. Same case as above, widespread and intense positivity with GLUT antibody (GLUT – IHC, ×100).

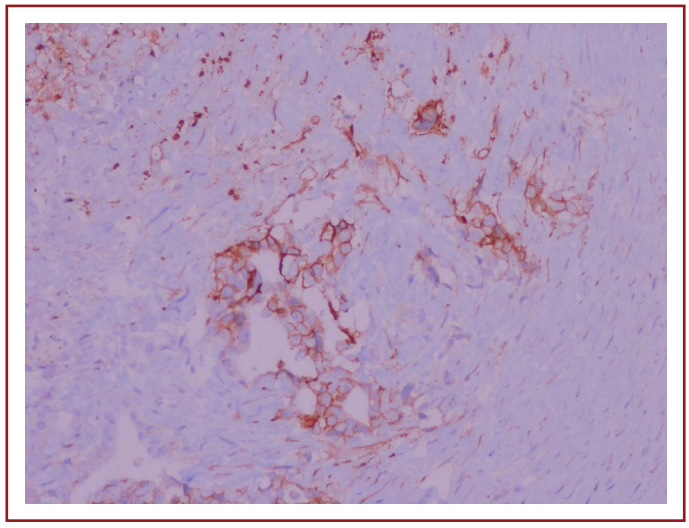

Figure 4. Same case as above, focal and moderately intense positivity with GLUT antibody (GLUT – IHC, ×100).

Table 3. Survival time in patients that showed GLUT-1 expression

		Intensity			Survival time (months)
		Weak	Moderate	Strong	
Extent	n	34	18	9	
<1%	27	27	0	0	24.8
1–10%	15	7	6	2	24.2
11–50%	7	0	5	2	14.3
51–80%	10	0	5	5	17.1
>80%	2	0	2	0	13.0
Survival time (months)		24.0	19.2	18.4	21.8

Extent: The percentage of GLUT-1 expression in the whole pathology section, Intensity: The intensity of GLUT-1 expression.

Discussion

It is important to remember that there are many diseases to be differentiated when making a pathological diagnosis and that the tissue to be differentiated varies in terms of histological type. Epithelioid types must be differentiated from lung adenocarcinoma for pleural mesothelioma,[7] ovarian serous papillary adenocarcinoma, or peritoneal serous carcinoma for peritoneal mesothelioma[8]. Immunohistochemical staining techniques are useful in accurate diagnosis of MPM. In epithelioid mesothelioma, calretinin, WT1, thrombomodulin, mesothelin, and D2-40 can be applied as a mesothelial cell marker. CEA, TTF-1, napsin A, and surfactant apoprotein are used as markers for lung adenocarcinoma[9].

GLUT-1 is expressed in normal tissues, as well as in many carcinomas including MPM. It has been suggested to be a marker for numerous malignancies and hypothesized that the increased expression of GLUT-1 helps to carry on energy supplies in malignant tumor cells to survive[5]. The increased expression of GLUT-1 has been correlated with advanced grade and higher proliferation in malignant neoplasms[10]. Grade and proliferation rates reflect the tumor's aggressiveness and directly affect the survival rate.

Kato et al.[4] described GLUT-1 immunoreactivity in pleural mesothelioma and demonstrated 100% sensitivity and 100% specificity (when the differential diagnosis was mesothelioma versus reactive mesothelium) in samples from 48 pleural mesotheliomas and 40 reactive mesothelial proliferations obtained at a Japanese referral cancer center. Lagana et al.[11] reported that the sensitivity of GLUT-1 in the diagnosis of MPM was 50% and 54% in thoracic and abdominal disease, respectively. Monaco et al.[12] recently looked at pleural and peritoneal mesotheliomas and compared GLUT-1 immunohistochemistry to p16 deletion by fluorescence in situ hybridization. They investigated 68 mesothelioma and 70 benign cases and reported a sensitivity of 40% and specificity of 93% for GLUT-1 immunohistochemistry. The staining occurred at a much lower rate in peritoneal (29%) than for their pleural cases (56%). This emphasizes the importance of GLUT-1 in mesothelioma of the pleura. The sensitivity of GLUT-1 in MPM was similar in our study.

There is no standard treatment for MPM. However, surgery, chemotherapy, and radiotherapy can be used in the trimodality treatment. Surgery still seems to be the indispensable option. A study from the SEER database showed that in comparison to no treatment, surgery alone was associated with significant improvement in survival (adjusted hazard ratio [adj HR] 0.64 [0.61–0.67]), but not radiation (adj HR 1.15 [1.08–1.23]). Surgery and radiation combined had similar survival as surgery alone (adj HR 0.69 [0.64–0.76]) [13]. These differences were described to be meaningful in a disease that has a very quick evolution and extremely short survival rate. Similar results were reported in the literature[14]. The average survival time was also similar in our group after surgery.

We found no report in the literature that showed the correlation between GLUT-1 and survival in MPM. However, in patients with pancreatic cancer, Lu et al.[15] reported the median overall survival time for the GLUT-1 positive group was 12.3 months compared with 22.2 months for the GLUT-1 negative group. In another study determining the prognostic factors of gastric adenocarcinoma, the median survival period was 14 months (95 % confidence interval [CI]: 9.2–18.8 months) for GLUT-1-positive patients and 55 months (95 % CI: 25.8–84.2; p=0.01) for GLUT-1-negative patients[16]. In our study, survival was worse in patients with GLUT-1 expression in the pathology specimen than GLUT-1 negative patients. Plus, as GLUT-1 expression rate increased, the survival ratio decreased. We found that the average survival time was significantly higher in patients with GLUT-1 expression <10% in extent than in the rest of the patients. The best survival seems to be in patients with weak intensity low GLUT-1 expression. The worst survival is the opposite of this with strong intensity high GLUT-1 expression.

The data of MPM survival according to the type of operation is still controversial in the literature. In a study, it is concluded that the patients who had P/D operations had better survival than those who underwent EPP[17].

Regarding long-term oncological outcomes, initial analysis of the IASLC reported a survival advantage in patients undergoing EPP compared to P/D[18]. The reasons of this difference may be because of the difference in stages and selection bias. In most studies, P/D was usually chosen for earlier stages and EPP for more advanced stages. However, we believe that it is difficult to give a clear recommendation for the best surgical approach and the surgery type must be selected according to the patient. In our study, there was no significant difference according to operation types. This may be the result of more advanced staged cases in our study group. The surgery for MPM is accepted as a debulking surgery advanced patients in our study group were operated for cytoreductive surgery.

Intrapleural chemotherapy can deliver high doses of drug locally with less toxicity than corresponding systemic therapy. Furthermore, when combined with hyperthermia, there is an increase in local drug absorption and cytotoxic effect. It is mentioned in the literature that surgery plus hyperthermic intrathoracic chemotherapy (HITHOC) is a feasible and safe option in the treatment of MPM patients with survival benefits[19,20]. We did not use HITHOC in our study group. However, a study concerning the benefit of HITHOC according to the GLUT-1 expression in MPM patients could provide more information about the treatment of this disease.

In patients with MPM, SUVmax in PET/CT is generally directive. One of the earliest studies on this subject was by Schneider et al.[21] They found that all primary malignant mesothelioma patients in the study accumulated F18-fluorodeoxyglucose (FDG), and the mean SUVmax was 7.6 (range, 3.33–14.85; n=9). Elboga et al.[22] further reported that PET-CT is a useful imaging modality in the differential diagnosis of malignant and benign pleural lesions. In their study, they found out that in malignant lesions the delayed SUV increases, while in benign lesions the delayed SUV decreases. In another study, the SUVmax of patients before treatment was 5.95±2.93 and increased to 6.38±3.19 after the treatment[23]. In our study, the average SUVmax was found lower in patients that showed no GLUT-1 expression than in patients that showed GLUT-1 expression. Abakay et al.[24] reported that a level of SUVmax>5 is associated with a 4.34 times poorer prognosis in MPM. In patients with increased SUVmax, survival is worse than in patients with less FDG uptake. This outcome seems to be consistent with GLUT-1 expression as both PET/CT and GLUT-1 show the glucose use of the tumor cell.

Conclusion

MPM is a difficult disease to manage with a median overall survival ranging between 9 and 17 months, regardless of stage[25]. The disease has a poor prognosis and a short survival rate even after surgery. In our study, the survival was worse in patients who showed GLUT-1 expression. Furthermore, in GLUT-1 positive patients, lower expression of GLUT-1 was associated with significantly longer survival. The survival time was found to be better if the GLUT-1 extent was <10%. This immunohistochemical marker seems to have prognostic importance in MPM. Larger studies are needed to prove the prognostic significance of GLUT-1.

Ethics Committee Approval: The University of Health Sciences Istanbul Sureyyapasa Chest Diseases and Thoracic Surgery Research and Training Hospital Scientific Research Committee approved the study (No:239, Date: 24.12.2021).

Peer-review: Externally peer-reviewed.

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