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Increased Expression of the GLUT-1 Gene is Associated With Worse Overall Survival in Resected Pancreatic Adenocarcinoma

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Abstract

Objectives—There is currently no reliable method to predict the risk of relapse after curative resection of early-stage pancreatic adenocarcinoma. Increased glucose metabolism observed on 18F-fluorodeoxyglucose positron emission tomography (PET) by malignant cells, the Warburg effect, is a well-known characteristic of the malignant phenotype. We investigated the role of glucose transporter type 1 (GLUT-1) gene expression, a glucose cell plasma membrane transporter, in early-stage pancreatic cancer.

Methods—Associations between GLUT-1 gene expression with PET maximum standardized uptake values (SUVmax) and histologic grade were investigated in early-stage pancreatic adenocarcinoma patients. Multivariate analysis was conducted to determine predictors of prognosis. Cox proportional hazards model was used for survival analysis.

Results—Sixty-three patients had GLUT-1 gene analysis performed, and 50 patients had both GLUT-1 analysis and PET scan. Patients with high GLUT-1 gene expression had a decreased overall survival by univariate analysis using Cox proportional hazards model (HR=2.82, $p=0.001$) and remained significant on multivariate analysis (HR=2.54, $p=0.03$). There was no correlation of GLUT-1 gene expression with histologic grade or PET SUVmax.

Conclusion—Increased GLUT-1 gene expression was associated with a decreased overall survival in pancreatic adenocarcinoma. This supports increased GLUT-1 gene expression as a potential prognostic marker in resected pancreatic adenocarcinoma.

Keywords

GLUT-1; pancreatic cancer; prognosis; overall survival; FDG-PET

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

INTRODUCTION

Increased glucose metabolism is a well-known characteristic of malignant cells. This phenomenon, known as the Warburg effect, takes advantage of the physiologic preferential use of glycolysis over oxidative phosphorylation used by malignant cells for their energetic needs [1,2]. Enhanced glucose uptake in tumors is reflected by the overexpression of glucose transporter proteins. Glucose transporters, such as glucose protein type 1 (GLUT-1), mediate the first rate-limiting step in glucose transport and allow the energy-independent transfer of glucose down its concentration gradient [3]. Although GLUT-1 is normally expressed in erythrocytes, endothelial cells, germinal centers of reactive lymph nodes, and several other additional sites, it is also expressed by pancreatic cancer cells [4, 5]. It is composed of 12 hydrophobic alpha-helical domains, with its gene belonging to the solute carrier 2A family, also known as *SLC2A* [3]. It is expressed in various malignancies, including pancreatic cancer.

The metabolic consequences of increased glucose transport remain unclear, but the overexpression seen in several human solid tumors has been associated with enhanced tumor aggressiveness and poor survival. GLUT-1 expression has been demonstrated to be associated with pancreatic cancer invasiveness and increasing histologic grade. However, only a few prognostic studies on GLUT-1 expression with pancreatic cancer have been performed to date and were conducted using just immunohistochemistry [6, 7].

Positron emission tomography (PET) is a non-invasive means of utilizing this knowledge of increased glucose metabolism of cells by detecting 2-fluorodeoxyglucose (FDG), a glucose analog that is preferentially taken up by tumor cells. PET imaging has been successfully used as a diagnostic and prognostic marker for multiple malignancies, including malignant melanoma, esophageal cancer, lung cancer, and breast cancer [8–14]. We have previously found that FDG uptake, as quantified by standardized uptake values (SUV), correlates with overall survival and recurrence-free survival in patients with stage I and II pancreatic cancer [15]. Recent studies have also shown that FDG uptake correlates with a greater immunohistochemical expression of GLUT-1 in pancreatic cancer cells [16].

Additionally, majority of these studies have not focused on early-stage I and II pancreatic adenocarcinomas where treatment is more likely to be successful and patients have a better chance of survival after diagnosis. Pancreatic cancer is the fourth leading cause of cancer-related death in the United States [17]. Only 8.7% of patients are diagnosed at a local stage, confined to the primary site, with an estimated 5-year survival of 24.1% [18]. This is in comparison to the 5-year survival rate of 9% and 2% for those with either regional spread to lymph nodes or distant metastasis, respectively [18]. In addition, American Joint Commission on Cancer (AJCC) staging for early-stage (stage I and II) cancer is not informative of long-term outcomes for most patients outside of stage Ia cancer, and there is currently no reliable method to predict the risk of relapse after curative resection of early-stage pancreatic adenocarcinoma. Therefore, identification of prognostic biomarker(s) is an area of unmet need in the management of pancreatic cancer. In this work, we investigated the role of the expression of the GLUT-1 gene in early-stage pancreatic cancer.

PATIENTS AND METHODS

Patients

Following Institutional Board Review approval, a database of pancreatic cancer patients was created by the Gastrointestinal Oncology Department at the Moffitt Cancer Center by performing a retrospective chart review of patients operated on from 1987 to present. Data collected included patient demographics, surgical procedure details, pathological tumor stage and histopathologic features, PET SUV measurements, peri-operative events, and complications. The diagnosis of pancreatic cancer was confirmed by pathological analysis of a surgical specimen in patients with resectable disease. Chart reviews were performed solely by experienced clinicians and recorded on standardized abstraction forms. Data were entered into a Microsoft Access database by a data analyst, and ambiguities in any data points were discussed, researched, and corrected. We queried this database for patients who had undergone operations at Moffitt between February 2004 and December 2010, focusing on those patients who had PET scans or were available for review as part of the pre-operative staging work-up. This study focused on patients who met criteria for stage I and II pancreatic ductal adenocarcinoma according to the AJCC TNM staging guidelines [20], and treatment of patients was according to National Comprehensive Cancer Network guidelines [21].

Tissues

Samples for mRNA analyses using Affymetrix chips were obtained from primary pancreatic cancer samples from 63 patients who had surgical resection for histologically verified pancreatic ductal adenocarcinoma. These samples were obtained from Moffitt's Total Cancer Care (TCC™) biorepository, a comprehensive clinical database with a large tumor bio-bank of >20,000 samples, as well as patient clinical data, where custom Affymetrix global GeneChip gene expression is analyzed. Patients prospectively provided written informed consent to participate in the IRB-approved TCC™ protocol. Clinicopathological findings were obtained from surgical records and included age, gender, tumor type, histological classification, level of lymph node metastasis, presence or absence of lymphatic and vascular invasion, date of diagnosis, date of death or last contact, and disease stage. For this study, the database was queried according to our inclusion criteria: diagnosis of pancreatic adenocarcinoma, no preoperative therapy, potentially curative radical resection, follow-up data available, and satisfactory tissue preservation. Patients with other pancreatic malignancies such as intraductal papillary mucinous adenocarcinoma, acinar cell carcinoma, and malignant endocrine tumors were excluded. All tumor specimens were reclassified on hematoxylin and eosin-stained slides, and histologic type and tumor grade were reassessed by a pathologist. Histologic grade was defined by the American College of Pathology as follows [22]: grade 1 = well differentiated (>95% of tumor composed of glands); grade 2 = moderately differentiated (50% to 95% of tumor composed of glands); and grade 3 = poorly differentiated (49% or less of tumor composed of glands). Overall survival was defined as time elapsed from surgery to death of patients with pancreatic cancer or last contact, which would be date of last follow-up visit. Disease-free survival was defined as time elapsed from surgery with curative intent to appearance of local disease recurrence, evidence of metastatic

lesions detected by computed tomography, or death from any cause without documentation of a cancer-related event.

18F-FDG PET protocol and analysis

For FDG-PET scans in patients with pancreatic cancer who are scheduled for resective surgery at our institution, non-diabetic patients are asked to fast for at least 4 hours and diabetic patients are asked to fast for at least 6 hours before scanning. Blood glucose concentrations are measured to ensure that glucose levels do not exceed 200 mg/dL before intravenous injection of FDG. There is then about a 90-minute interval between administration of 10 mCi FDG intravenously and the acquisition of the emission images to ensure adequate biodistribution of FDG. The average scan time is 3 minutes per bed, with there being 7 or 8 beds total. The normal slice thickness is 3.75 mm. We performed our FDG studies with a dedicated PET/CT scanner, the GE-Discovery DVCT-PET/CT (GE Medical Systems, Milwaukee, WI), which has a 70-cm aperture, 15-cm axial field of view, a 64-slice CT scanner, and a LYSO crystal-based PET scanner. This scanner includes a BGO block detector system and has a crystal size of 4.7 mm transaxially, 6.3 mm axially, and 30 mm radially. The axial sampling interval is 3.27 mm. PET images are reviewed by a board-certified nuclear medicine physician, and tumors are defined as having positive FDG uptake if the radioactivity of the tumor is higher than that of the surrounding tissue in visual analyses. Images are then assessed semi-quantitatively by measuring and calculating the maximum primary tumor standardized uptake value (SUVmax) normalized to lean body mass.

Statistical analysis

Using a comprehensive pancreatic adenocarcinoma database, we identified 63 patients with early-stage pancreatic adenocarcinoma (stage I and II) and performed a retrospective analysis of GLUT-1 gene expression and the association with prognosis of pancreatic adenocarcinoma. Overall survival was calculated from the date of surgery until the date of death or last contact. Cox proportional hazards model with the log-rank test was used for survival analysis. High (low) expression of the GLUT-1 gene is defined as expression values above (below) the median. Univariate analysis was performed as well as multivariate analysis to compare the role of GLUT-1 gene expression to other prognostic factors such as gender, age at diagnosis, grade, and pathological stage. GLUT-1 gene expression was also analyzed with respect to histologic grade and PET SUVmax by one-way ANOVA and Pearson correlation analysis, respectively. All statistical tests performed were two-sided and declared at the 5% significance level. Statistical analyses were performed with R software [23].

RESULTS

Patient demographics

We identified 63 patients (52.4% male) with an average age of 66 years who underwent pancreatic resection for histologically proven stage I and II pancreatic adenocarcinoma. There were 12 patients who were stage IB, 17 patients were stage IIA, and 34 patients were

stage IIB. All patients had curative surgical resection with adjuvant chemotherapy and chemoradiation therapy.

Association between GLUT-1 gene expression and patient survival

High expression levels (expression values above the median) of the GLUT-1 gene were associated with decreased overall survival in patients with pancreatic adenocarcinoma by univariate analysis using Cox proportional hazards model (hazard ratio (HR)=2.82, $p=0.001$, 95% CI=1.49–5.35) (Figure 1). Multivariate analysis further showed that the GLUT-1 gene is an independent prognostic factor, even after adjusting for gender, age at diagnosis, grade, and pathological stage (HR=2.54, $p=0.03$; 95% CI=1.11–5.81).

Association between GLUT-1 and FDG-PET

In a subset of 50 patients who had both analyses for GLUT-1 expression and SUVmax measurements, the correlation between these two parameters was investigated. No correlation was found between the two variables when using two separate probes for gene analysis ($p=0.1828$, $p=0.1716$) (Figure 2).

Association between GLUT-1 and histologic grade

All patients underwent resection of their pancreatic tumors, and their tissues were available for histologic evaluation. None of the patients chosen for this study underwent neoadjuvant chemotherapy or radiation. GLUT-1 gene expression was evaluated with histologic grade, and no significant correlation was found using two separate probes for gene analysis ($p=0.6946$, $p=0.5845$) (Figure 3).

DISCUSSION

We examined the prognostic values of GLUT-1 gene expression and FDG-PET uptake in stage I and II pancreatic cancer patients in conjunction with histologic grade. Increased GLUT-1 gene expression was found to be associated with decreased overall survival in patients with curative resection of early-stage pancreatic adenocarcinoma. We have also found that GLUT-1 gene expression is independent of histologic grade and PET SUVmax in patients with resected pancreatic adenocarcinoma.

To our knowledge, ours is the first study to evaluate the biologic significance of GLUT-1 gene expression with prognosis in patients with early stage I and II pancreatic adenocarcinomas, where treatment is likely to have a larger impact with improved chances of survival. Previous studies have investigated GLUT-1 expression and its association with various malignancies. A close relationship has been shown between GLUT-1 expression and either a worse prognosis or more poorly differentiated tumor in squamous cell carcinoma of the head and neck, non-small cell lung cancer, colorectal cancer, gastric cancer, endometrial and breast cancers, bladder cancer, and renal cell carcinoma [24–30]. There is also evidence suggesting that GLUT-1 may be a marker of malignant transformation due to its expression in most malignant mesotheliomas but not in benign reactive mesothelial lesion [31]. In pancreatic cancer, there is conflicting evidence as studies have shown either a poorer prognosis with increased GLUT-1 expression in invasive pancreatic adenocarcinoma without

regard to staging [32,33], whereas others have demonstrated no prognostic value at all [34]. We demonstrated that increased GLUT-1 gene expression is independently associated with decreased overall survival in patients with stage I and II pancreatic adenocarcinoma. Increased GLUT-1 expression is also associated with pancreatic cancer invasiveness, where forced overexpression of GLUT-1 induced increased matrix metalloproteinase-2 (MMP-2) expression and activity, along with cellular invasiveness, while GLUT-1 silencing created reductions in MMP-2 expression and activity, cellular invasiveness, and metastatic potential in vivo [6]. GLUT-1 expression has also been found to be related to histological grade and tumor size of ductal adenocarcinomas, with progressive increases in GLUT-1 expression from low- to high-grade adenocarcinomas; however, these results did not reach statistical significance with regard to overall survival [7]. All stages of tumors were evaluated as well, with significant GLUT-1 expression in all stages but stage IV (autopsy cases, 0/2), likely due to the limited stage IV cases available in this study. There was no statistically significant difference between the groups [7]. Another study evaluating all stages of tumor demonstrated higher GLUT-1 expression significantly correlated with advanced tumor stage (III and IV) [33]. These findings support the concept that increased GLUT-1 expression results in a more aggressive phenotype with decreased survival. In our analysis, we found that GLUT-1 gene expression actually did not have any association with histologic grade. Our findings suggest that GLUT-1 gene expression may act independently of histologic grade. Future additional studies are warranted for further investigation.

The mechanisms behind increased glucose transport expression and malignancy are controversial. It is known that increased glucose transport in malignant cells is associated with increased expression of GLUTs. This has been demonstrated in the cellular transformation of rat fibroblast cells by *ras* and *src* oncogenes, along with the Fujinami sarcoma virus, resulting in increased GLUT-1 expression and subsequently glucose transport [35]. Additional research in mouse fibroblasts demonstrated that this occurs through activation of enhancer elements within the GLUT-1 promoter by both *ras* and *src* [36]. A promoter and two enhancers act as the regulatory elements of the GLUT-1 gene, which have consensus sequences for the binding of various transcription factors such as serum-responsive element, cAMP-responsive element, and AP-1-binding sites [37]. In pancreatic cancer, 90–95% of cases are caused by a mutation in the *KRAS2* oncogene, which is the single most common genetic mutation in pancreatic cancer [38]. *KRAS2* is a member of the *ras* family of guanosine triphosphate (GTP) binding proteins that mediate a range of cellular functions through a signaling cascade. They are involved in cellular survival, proliferation, differentiation, and senescence as well as apoptosis. *Ras* is activated when GTP is bound and inactivated when GTP hydrolysis occurs to create guanosine diphosphate (GDP). In pancreatic cancer, mutations impair the intrinsic GTPase activity of the *KRAS2* gene product, resulting in a protein that is constitutively active in signal transduction [39]. This mutation has been found mainly on codon 12, with mutations also occasionally occurring on codon 13 or 61 [38]. These mutations are one of the earliest genetic abnormalities in the time sequence leading to pancreatic cancer and to the creation of a premalignant precursor, such as a pancreatic intraepithelial neoplasia. One study evaluated the molecular consequences of silencing mutant *K-ras* in pancreatic cancer cells through RNA interference (RNAi). Cell lines Panc-1 and MiaPaca-2 both showed reduced proliferation after *K-ras*

RNAi, and only MiaPaca-2 cells showed increased apoptosis. Both cell lines also showed alterations of GLUT-1 levels, with Panc-1 cells demonstrating decreased transcription and protein expression of GLUT-1 and MiaPaca-2 cells showing increased protein expression from events occurring post-transcriptionally since the amount of GLUT-1 transcript did not change after K-*ras* RNAi treatment [39]. These results further support an interconnection between GLUT-1 expression and *ras*, and it appears that both early mutations in pancreatic cancer progression and GLUT-1 promoter enhancement are linked by *ras* activation. Whether this is due to direct pathway involvement in GLUT-1 upregulation remains inconclusive but is a potential area of research for future investigation. On the contrary, it has also been postulated that increased GLUT-1 protein levels in transformed cells may be indirectly caused by low intracellular glucose levels secondary to rapid glucose consumption, leading to an upregulation of glucose transporters [1]. Regardless of the true mechanism, it is known that increased glucose transporters contribute to tumor growth, but the exact progression behind tumor development remains debatable.

Glucose inhibitors are under investigation as adjuvants in pancreatic cancer treatment. Inhibition of glucose transport by cytochalasin-B has increased gemcitabine-induced apoptosis in hepatoma cells. Another study revealed that GLUT-1 inhibition chemosensitized head and neck cancer cells to cisplatin [40,41]. Apigenin, a flavonoid drug, exhibits antiproliferative properties in pancreatic cancer by decreasing glucose uptake and downregulating GLUT-1 in human pancreatic cancer cells [42]. Given that gemcitabine is the mainstay of treatment in pancreatic cancer and its resistance remains a serious clinical challenge to treatment, a recent study showed that targeting the Warburg effect with a novel GLUT inhibitor, CG-5, in combination with gemcitabine caused greater suppression of Panc-1 xenograft tumor growth in vivo than either drug alone [43]. This occurs via CG-5 restoring the sensitivity of drug-resistant Panc-1 cells to gemcitabine by abrogating the effect of gemcitabine by targeting the upregulation of gemcitabine-induced expression of ribonucleotide reductase M2 catalytic subunits to overcome drug resistance. If this approach proves effective in future clinical studies, then inhibitors of glucose transport may be useful as adjuvants to cancer treatment.

We acknowledge the limitations of our study as related to the inherent bias associated with a retrospective single institution review. Additionally, a limiting factor was the small sample size of our cohort at 63 patients, which could explain the lack of statistical significance of some of our results. Our PET scans were also performed over a long period of time from 2004 to 2010. In an effort to account for this long time interval, each PET scan was re-reviewed by the same radiologist. There are several strengths to this study, including the comprehensive pathologic review of all tissue specimens, all patients were treated without neoadjuvant therapy, and our patient's information was kept in a well-maintained database. Our patients had also been treated at our institution in a consistent manner.

In conclusion, we have demonstrated that increased GLUT-1 gene expression is associated with a worse overall survival in patients with curative resection of stage I and II pancreatic adenocarcinoma. Our findings also indicate that there is no association between GLUT-1 gene expression with histologic grade and FDG-PET SUVmax values. Our data support the notion that GLUT-1 gene expression acts independently of histologic grade and PET

SUVmax in patients with resected pancreatic adenocarcinoma. Our results support further investigation of GLUT-1 as a potential prognostic marker for resected pancreatic adenocarcinoma. A future direction should evaluate the potential mechanism by which GLUT-1 gene expression is induced and the function of increased GLUT-1 gene expression in pancreatic adenocarcinoma cells.

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References

1. Warburg O. On the origin of cancer cells. *Science*. 1956; 123:309–314. [PubMed: 13298683]
2. Higashi K, Clavo AC, Wahl RL. Does FDG uptake measure proliferative activity of human cancer cells? In vitro comparison with DNA flow cytometry and tritiated thymidine uptake. *J Nucl Med*. 1993; 34:414–419. [PubMed: 8441032]
3. Macheda M, Rogers S, Best J. Molecular and cellular regulation of glucose transporter (GLUT) proteins in cancer. *J Cell Physiol*. 2005; 202:654–662. [PubMed: 15389572]
4. Cornford EM, Hyman S, Swartz BE. The human brain GLUT1 glucose transporter: ultrastructural localization to the blood-brain barrier endothelia. *J Cereb Blood Flow Metab*. 1994; 14:106–112. [PubMed: 8263045]
5. Kayano T, Burant CF, Fukumoto H, et al. Human facilitative glucose transporters. Isolation, functional characterization, and gene localization of cDNAs encoding an isoform (GLUT5) expressed in small intestine, kidney, muscle, and adipose tissue and an unusual glucose transporter pseudogene-like sequence (GLUT6). *J Biol Chem*. 1990; 265:13276–13282. [PubMed: 1695905]
6. Ito H, Duxbury M, Zinner MJ, et al. Glucose transporter-1 gene expression is associated with pancreatic cancer invasiveness and MMP-2 activity. *Surgery*. 2004; 136:548–556. [PubMed: 15349101]
7. Basturk O, Singh R, Kaygusuz E, et al. GLUT-1 Expression in Pancreatic Neoplasia. *Pancreas*. 2011; 40:187–192. [PubMed: 21206329]
8. MacManus MP, Seymour JF, Hicks RJ. Overview of early response assessment in lymphoma with FDG-PET. *Cancer Imaging*. 2007; 7:10–18. [PubMed: 17766210]
9. Dickson MA, Okuno SH, Keohan ML, et al. Phase II study of the HSP90-inhibitor BIIB021 in gastrointestinal stromal tumors. *Ann Oncol*. 2013; 24:252–257. [PubMed: 22898035]
10. Baudy AR, Dogan T, Flores-Mercado JE, et al. FDG-PET is a good biomarker of both early response and acquired resistance in BRAFV600 mutant melanomas treated with vemurafenib and the MEK inhibitor GDC-0973. *EJNMMI Res*. 2012; 2:22. [PubMed: 22651703]
11. Suzuki H, Kato K, Fujimoto Y, et al. (18)F-FDG-PET/CT predicts survival in hypopharyngeal squamous cell carcinoma. *Ann Nucl Med*. 2013; 27:297–302. [PubMed: 23337965]
12. zum Buschenfelde CM, Herrmann K, Schuster T, et al. (18)F-FDG PET-guided salvage neoadjuvant radiochemotherapy of adenocarcinoma of the esophagogastric junction: the MUNICON II trial. *J Nucl Med*. 2011; 52:1189–1196. [PubMed: 21764790]
13. Lam WW, Loke KS, Loi HY, et al. Pancreatic metastasis detected by F-18 FDG PET/CT in a patient with breast cancer. *Clin Nucl Med*. 2011; 36:479–480. [PubMed: 21552032]
14. Fischer B, Lassen U, Mortensen J, et al. Preoperative staging of lung cancer with combined PET-CT. *N Engl J Med*. 2009; 361:32–39. [PubMed: 19571281]
15. Pimiento J, Boutrid H, Weber J, et al. Low 18f-fluorodeoxyglucose uptake on positron emission tomography as a prognostic factor for stage I and II pancreatic cancer. *ASCO Meeting Abstracts*. 2012; 30:159.

16. Reske SN, Grillenberger KG, Glatting G, et al. Overexpression of glucose transporter 1 and increased FDG uptake in pancreatic carcinoma. *J Nucl Med*. 1997; 38:1344–1348. [PubMed: 9293784]
17. American Cancer Society. Cancer Facts & Figures 2014. Atlanta: American Cancer Society; 2014. [Accessed March, 29th, 2014]
18. Howlader, N.; Noone, AM.; Krapcho, M., et al. SEER Cancer Statistics Review, 1975–2010. National Cancer Institute; Bethesda, MD: Apr. 2013 http://seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER web site [Accessed March, 29th, 2014]
19. Helm J, Centeno BA, Coppola D, et al. Histologic characteristics enhance predictive value of American Joint Committee on Cancer staging in resectable pancreas cancer. *Cancer*. 2009; 115:4080–4089. [PubMed: 19626671]
20. American Joint Committee on Cancer. AJCC Cancer Staging Manual. 7. New York, NY: Springer; 2010. Exocrine and Endocrine Pancreas; p. 241–246.
21. Tempe MA, Arnoletti JP, Behrman SW, et al. Pancreatic Adenocarcinoma, version 2.2012: featured updates to the NCCN Guidelines. *J Natl Compr Cancer Netw*. 2012; 10:703–713.
22. Compton CC, Henson DE. Protocol for the Examination of Specimens From Patients With Carcinoma of the Exocrine Pancreas: a basis for checklists. Cancer Committee, College of American Pathologists. *Arch Pathol Lab Med*. 1997; 121:1129–36. [PubMed: 9372738]
23. R Foundation for Statistical Computing. [Accessed March 29th, 2014] R: A language and environment for statistical computing. 2003. Website:<http://www.R-project.org/>
24. Kunkel M, Reichert T, Benz P, et al. Overexpression of Glut-1 and Increased Glucose Metabolism in Tumors are Associated with a Poor Prognosis in Patients with Oral Squamous Cell Carcinoma. *Cancer*. 2003; 97:1015–1024. [PubMed: 12569601]
25. Younes M, Brown RW, Stephenson M, et al. Overexpression of Glut1 and Glut3 in stage I non small cell lung carcinoma is associated with poor survival. *Cancer*. 1997; 80:1046–1051. [PubMed: 9305704]
26. Haber RS, Rathan A, Weiser KR, et al. GLUT1 glucose transporter expression in colorectal carcinoma: a marker for poor prognosis. *Cancer*. 1998; 83:34–40. [PubMed: 9655290]
27. Kawamura T, Kusakabe T, Sugino T, et al. Expression of glucose transporter-1 in human gastric carcinoma. *Cancer*. 2001; 92:634–641. [PubMed: 11505409]
28. Krzeslak A, Wojcik-Krowiranda K, Forma E, et al. Expression of GLUT1 and GLUT3 glucose transporters in endometrial and breast cancers. *Pathol Oncol Res*. 2012; 18:721–728. [PubMed: 22270867]
29. Younes M, Juarez D, Lechago LV, et al. GLUT 1 expression in transitional cell carcinoma of the urinary bladder is associated with poor patient survival. *Anticancer Res*. 2001; 21:575–578. [PubMed: 11299807]
30. Lidgrn A, Bergh A, Grankvist K, et al. Glucose transporter-1 expression in renal cell carcinoma and its correlation with hypoxia inducible factor-1 α . *BJU Int*. 2008; 101:480–484. [PubMed: 17922867]
31. Kato Y, Tsuta K, Seki K, et al. Immunohistochemical detection of GLUT-1 can discriminate between reactive mesothelium and malignant mesothelioma. *Mod Pathol*. 2007; 20:215–220. [PubMed: 17192790]
32. Pizzi S, Porzionato A, Pasquali C, et al. Glucose transporter-1 expression and prognostic significance in pancreatic carcinogenesis. *Histol Histopathol*. 2009; 24:175–185. [PubMed: 19085834]
33. Sun HC, Qiu ZJ, Liu J, et al. Expression of hypoxia-inducible factor-1 α and associated proteins in pancreatic ductal adenocarcinoma and their impact on prognosis. *Int J Oncol*. 2007; 30:1359–1367. [PubMed: 17487356]
34. Lyshchik A, Higashi T, Hara T, et al. Expression of glucose transporter-1, hexokinase-II, proliferating cell nuclear antigen and survival of patients with pancreatic cancer. *Cancer Invest*. 2007; 25:154–162. [PubMed: 17530485]

35. Flier JS, Mueckler MM, Usher P, Lodish HF. Elevated levels of glucose transport and transporter messenger RNA are induced by ras or src oncogenes. *Science*. 1987; 235:1492–1495. [PubMed: 3103217]
36. Chen C, Pore N, Behrooz A, et al. Regulation of glut-1 mRNA by hypoxia inducible factor-1. *J Biol Chem*. 2001; 276:9519–9525. [PubMed: 11120745]
37. Kozlovsky N, Rudich A, Potashnik R, et al. Transcriptional Activation of the *Glut1* Gene in Response to Oxidative Stress in L6 Myotubes. *J Biol Chem*. 1997; 272:33367–33372. [PubMed: 9407130]
38. Maitra A, Hruban RH. Pancreatic Cancer. *Annu Rev Pathol*. 2008; 3:157–188. [PubMed: 18039136]
39. Hingorani SR, Tuveson DA. Ras redux: rethinking how and where Ras acts. *Curr Opin Genet Dev*. 2003; 13:6–13. [PubMed: 12573429]
40. Haberkorn U, Bellemann ME, Brix G, et al. Apoptosis and changes in glucose transport early after treatment of Morris hepatoma with gemcitabine. *Eur J Nucl Med*. 2001; 28:418–425. [PubMed: 11357491]
41. Wang YD, Li SJ, Liao JX. Inhibition of glucose transporter 1 (GLUT1) chemosensitized head and neck cancer cells to cisplatin. *Technol Cancer Res Treat*. 2013; 12:525–35. [PubMed: 23617290]
42. Melstrom LG, Salabat MR, Ding XZ, et al. Apigenin inhibits the GLUT-1 glucose transporter and the phosphoinositide 3-kinase/Akt pathway in human pancreatic cancer cells. *Pancreas*. 2008; 37:426–31. [PubMed: 18953257]
43. Lai IL, Chou CC, Lai PT, et al. Targeting the Warburg effect with a novel glucose transporter inhibitor to overcome gemcitabine resistance in pancreatic cancer cells. *Carcinogenesis*. 2014; 35:2203–2213. [PubMed: 24879635]

Figure 1. Overall survival

Patients with high GLUT-1 gene expression had significantly decreased overall survival.

Figure 2. FDG PET SUVmax

There was no statistical correlation found between GLUT-1 gene expression and SUVmax.

Figure 3. Histologic Grade

There was no statistical correlation found between GLUT-1 gene expression and histologic grade.