



Relationships between expression of glucose transporter protein-1 and hypoxia inducible factor-1 α , prognosis and ^{18}F -FDG uptake in laryngeal and hypopharyngeal carcinomas

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Contributions: (I) Conception and design: LF Shen, SH Zhou; (II) Administrative support: LF Shen; (III) Provision of study materials or patients: SH Zhou; (IV) Collection and assembly of data: LF Shen, Q Yu; (V) Data analysis and interpretation: LF Shen, Q Yu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: We investigated the relationships between glucose transporter protein-1 (GLUT-1) and hypoxia inducible factor-1 α (HIF-1 α) expression, 2-deoxy-2- ^{18}F -fluoro-D-glucose (^{18}F -FDG) uptake and prognosis in laryngeal and hypopharyngeal carcinomas patients.

Methods: Levels of GLUT-1 and HIF-1 α proteins were examined by immunohistochemistry in 55 patients with laryngeal and hypopharyngeal carcinomas. All patients underwent ^{18}F -FDG positron emission tomography-computed tomography (PET/CT) before surgery.

Results: Levels of GLUT-1 and HIF-1 α in laryngeal and hypopharyngeal carcinomas were significantly higher than in vocal cord polyps. GLUT-1 expression was correlated with HIF-1 α expression ($r=0.571$, $P<0.001$) and SUV_{max} ($r=0.495$, $P<0.001$). HIF-1 α expression was not correlated with SUV_{max} ($P=0.199$). HIF-1 α expression was correlated with tumor size ($r=0.351$, $P=0.009$). Multivariate analysis demonstrated that treatment method ($P=0.025$), tumor size ($P=0.008$), GLUT-1 expression ($P=0.032$), and HIF-1 α expression ($P=0.032$) were correlated with overall survival (OS).

Conclusions: Treatment method, tumor size, GLUT-1 and HIF-1 α levels were correlated with prognosis in laryngeal and hypopharyngeal carcinomas patients.

Keywords: Laryngeal carcinoma; hypopharyngeal carcinoma; 2-deoxy-2- ^{18}F -fluoro-D-glucose (^{18}F -FDG); hypoxia inducible factor-1 α (HIF-1 α); glucose transporter protein-1 (GLUT-1)

Submitted Nov 21, 2019. Accepted for publication Jan 16, 2020.

doi: 10.21037/tcr.2020.02.50

View this article at: <http://dx.doi.org/10.21037/tcr.2020.02.50>

Introduction

Head and neck squamous cell carcinoma (HNSCC) is a common malignant tumor, its morbidity ranks sixth among all malignant tumors, and, worldwide, the number of new cases exceeds 500,000 each year (1). Although some new functional surgeries have used recently and patient quality of life has improved greatly, the 5-year survival rate for some HNSCC patients (laryngeal and hypopharyngeal carcinoma patients) has not improved significantly in the last 40 years (2). The poor survival associated with the

advanced stage at diagnosis for the majority of cases and the lack of individual treatment. Thus, understanding the molecular biology of laryngeal and hypopharyngeal carcinoma is important for early diagnosis and treatment, and may eventually provide new therapeutic targets for laryngeal and hypopharyngeal carcinoma.

Warburg and colleagues found that, compared with normal tissue under aerobic conditions, the glucose consumption and lactic acid production of tumor tissues were increased. Indeed, the metabolism of malignant

tumors uses aerobic glycolysis, which is now called the Warburg effect (3). GLUT is an important energy transporter that mediates the Warburg effect. The glucose transporter is a protein that mediates the transmembrane transport of glucose, which is a major reason for the increased glucose metabolism seen in malignant tumor cells. GLUT-1 is a representative protein of the GLUT family and is widely expressed in cells of many body tissues. GLUT-1 is overexpressed in many malignant tumors to meet the energy needs of malignant tumor cells, including head and neck, lung, brain, breast, cervical, bladder, colorectal, esophageal, gastric, hepatocellular, ovarian, renal cell, pancreatic, thyroid, penile, and uterine cancers (4-6). GLUT-1 overexpression has been correlated with various tumor characteristics, including enhanced invasive potential, proliferative activity, decreased patient survival (7-10), tumor differentiation (11), and tumor stage (12). Our previous study found that GLUT-1 overexpression was associated with lymph node metastasis, progression, and poor prognosis in head and neck cancer (13), and the expression of GLUT-1 may be an independent predictor of survival in laryngeal carcinomas (14). However, the relationships between the expression of GLUT-1, clinicopathological features and prognosis in laryngeal and hypopharyngeal carcinomas have rarely been examined.

Hypoxia is a common phenomenon in solid tumors and is associated with poor prognosis in several types of cancer, including laryngeal squamous cell carcinoma and ovarian, breast, gallbladder, and pancreatic cancers (15). GLUT-1 has been considered a possible intrinsic marker of hypoxia in malignant tumors, and GLUT-1 is one of the downstream genes of HIF-1. HIF-1 is an important hypoxia-inducible factor (16). HIF regulates several aspects of tumorigenesis, including tumor angiogenesis, cell proliferation, metabolism, metastasis, differentiation, and the response to radiotherapy, HIF is an important regulatory factor of the malignant phenotype (17,18). Many studies have shown that overexpression of HIF-1 α played a role in tumor invasion, metastasis, angiogenesis, and resistance to chemotherapy (19), and was correlated with tumor stage and differentiation (20), as well as decreased disease-free survival and OS (21). Our previous work and other studies showed that the expression of HIF-1 α was associated with lymph node metastasis, T stage, prognosis, and the radiation resistance of laryngeal squamous cell carcinomas (14,22). Thus, the expression of HIF-1 α may be a predictor of laryngeal and hypopharyngeal carcinoma prognosis.

The Warburg effect has been demonstrated by the clinical application of positron emission tomography-computed tomography (PET/CT), typically with the marker ^{18}F -FDG, an analog of glucose. PET/CT has been used widely for early diagnosis of malignant tumors, evaluation of treatments, and monitoring of malignant tumor recurrence, metastasis, and residue after treatment. The ^{18}F -FDG uptake mechanism is not entirely clear, but recently, more studies have focused on the effects of GLUT-1 and HIF-1 α on the regulation of tumor cell ^{18}F -FDG uptake, but the results have been controversial. Some researchers have found that SUV_{max} was associated with prognosis, recurrence, and metastasis in some malignant tumors (23,24). A meta-analysis of 674 patients with HNSCC found that pretreatment ^{18}F -FDG-PET SUV_{max} or SUV_{mean} was associated with a poor prognosis in patients with head and neck cancer (25). However, whether ^{18}F -FDG SUV is a reliable prognostic factor in head and neck cancer remains controversial, Kitajima *et al.* found that the primary tumor SUV_{max} of laryngeal carcinoma was not associated with prognosis, but the nodal SUV_{max} was significantly associated with prognosis of laryngeal carcinoma (26). Some studies, including our previous study, found that ^{18}F -FDG PET/CT SUV_{max} in laryngeal and oral squamous cell carcinoma was associated with the expression of GLUT-1 and HIF-1 α (27,28). Yamada found that ^{18}F -FDG uptake in oral squamous cell carcinoma at an early stage was correlated with the expression of GLUT-1 and HIF-1 α , but in later-stage tumors, ^{18}F -FDG was not correlate with the expression of GLUT-1 or HIF-1 α (28). Also, pretreatment ^{18}F -FDG SUV_{max} in patients with laryngeal cancer was associated with survival, and may be a prognostic factor in these patients (27).

In this study, we explored relationships between the expression of GLUT-1 and HIF-1 α , SUV_{max} , clinicopathological factors, and prognosis in patients with laryngeal and hypopharyngeal carcinomas. Specifically, we analyzed correlations between GLUT-1 and HIF-1 α expression and SUV_{max} .

Methods

Ethics statement

The studies have been approved by the appropriate institutional committee and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments

or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Clinical data

This study involved 55 patients in whom laryngeal or hypopharyngeal carcinoma was confirmed histopathologically at our hospital between September 2010 and September 2016. All patients underwent ^{18}F -FDG PET/CT before operations (including biopsy surgery). None had received any previous chemotherapeutic or radiotherapeutic treatment. All patients were at their first tumor, they had full clinical data available. Additionally, 20 paraffin wax specimens of vocal cord polyps were selected randomly as the control group.

The institutional review board of The First Affiliated Hospital, College of Medicine, Zhejiang University (Hangzhou, Zhejiang, China) approved the present study. Informed consent was obtained from all participating patients.

PET/CT

^{18}F -FDG was synthesized at the PET Center, The First Affiliated Hospital, College of Medicine, Zhejiang University. The patients fasted for 4–6 h before the ^{18}F -FDG injection. Serum levels of glucose were monitored immediately before the ^{18}F -FDG injection (≤ 120 mg/dL). ^{18}F -FDG (5.5–7.4 MBq/kg) was administered intravenously. PET/CT scans were performed 1 h after ^{18}F -FDG injection with a combined scanner (Biograph Sensation 16; Siemens Medical, Erlangen, Germany). PET/CT data acquisition was performed as described previously (27). The ^{18}F -FDG accumulation was analyzed semiquantitatively by calculating the standardized uptake value (SUV) in regions of interest (ROIs) placed over suspected lesions. SUV_{max} was calculated based on the amount of injected ^{18}F -FDG and the body weight: $\text{SUV}_{\text{max}} = \text{maximum pixel value within the ROI (MBq/kg)} / [\text{injected dose (MBq)} / \text{body weight (kg)}]$.

In addition, 12 cases diagnosed with other lesions of the throat (8 cases of chronic inflammation of the throat, 1 of papilloma, 1 of laryngeal leukemia, 1 of vocal cord polyp, and 1 of piriform granulation) on preoperative PET/CT data were included in the study. The SUV_{max} of these lesions were also calculated. Receiver operating characteristic (ROC) curve analysis was used to define the optimal cut-off

SUV_{max} value to distinguish laryngeal and hypopharyngeal carcinomas from these non-tumor lesions.

Immunohistochemical staining

The expression of GLUT-1 and HIF-1 was detected by immunohistochemistry in 55 cases of laryngeal and hypopharyngeal carcinoma, and 20 cases of vocal cord polyps. Paraffin wax blocks of formalin-fixed biopsies specimens were obtained from the predominant lesions in each subject. Serial sections (4 μm) subjected to immunohistological staining were fixed with 3% H_2O_2 to block endogenous peroxidase activity, and treated with antigen retrieval solution for 15 min. The sections were incubated with primary monoclonal anti-GLUT-1 (dilution, 1:100; catalog no., ab14683; Abcam, Cambridge, UK) or monoclonal anti-HIF-1 α (dilution, 1:200; catalog no., ab51608; Abcam) antibody for 30 min at 36–38 $^{\circ}\text{C}$, followed by incubation with a secondary antibody (K5007, Dako) for 15 min at 20–25 $^{\circ}\text{C}$. The final reaction product was developed by exposure to 0.03% diaminobenzidine, and the nuclei were counterstained with hematoxylin.

Evaluation of immunohistochemistry

Immunohistochemical analyses for GLUT-1 and HIF-1 expression were performed independently by two experienced physicians who were unaware of the patients' data. Protein analysis was performed in 10 random high-magnification fields. The staining intensity was classified as 0, 1, 2, or 3 points for no staining, weak, moderate, and strong intensity, respectively. Moreover, the percentage of positive cells was rated as follows: 1 point, 0–25% positive cells, 2 points, 26–50% positive cells, 3 points, 51–75% positive cells, and 4 points, >75% positive cells. The expression levels of GLUT-1 and HIF-1 were assessed semi-quantitatively using the product of these scores (intensity \times %positive): 0–5 points = negative (–) and 6–12 points = positive (+).

Follow-up

Survival data for patients were obtained by telephone. Survival was determined from the date of surgery until the death of patients. A follow-up examination was performed every month during the first year, every 3 months during the second year, and every 6 months during the third to

Table 1 Patient characteristics

Patient characteristics	Number
Age	
>60 years	35
<60 years	20
Tumor location	
Laryngeal carcinoma	
Supraglottic carcinoma	7
Glottis carcinoma	12
Subglottic carcinoma	1
Hypopharyngeal carcinoma	
Pyriform sinus carcinoma	25
Posterior pharyngeal wall carcinoma	4
Postcricoid area carcinoma	6
Tumor differentiation	
Well	19
Moderately/poorly	36
Tumor size	
≤4 cm	32
>4 cm	23
Lymph node metastasis	
Present	39
Absent	16
Treatment method	
With radiotherapy	39
Without radiotherapy	16
Tumor staging	
I	2
II	8
III	6
IV	39

fifth years. In addition to routine physical examinations, patients underwent laryngoscopy, cervical CT or magnetic resonance imaging (MRI), or whole body PET/CT.

Statistical analysis

Statistical analyses were performed using the SPSS software

(ver. 22.0; SPSS, Inc., Chicago, IL, USA). Categorical variables were assessed by χ^2 or Fisher's exact tests. Correlation analyses were performed using Spearman's rank analysis. Survival curves were calculated using the Kaplan-Meier method and compared with the results of the log-rank test. The Cox proportional hazards regression model was used for multivariate analysis. P values <0.05 were considered to indicate statistical significance.

Results

Patient characteristics

Of the 55 patients with laryngeal and hypopharyngeal carcinoma (20 with laryngeal carcinoma, 35 with hypopharyngeal carcinoma), all patients had squamous cell carcinoma. Their mean age was 63.4 years (range, 43–88 years). The clinical stage was classified according to the National Comprehensive Cancer Network (NCCN) guidelines. Patients were divided into two groups: 10 early stage (I–II) and 45 late stage (III–IV) cases. In a further stratification, laryngeal carcinoma patients were divided into early-stage (I–II stage, 9 cases) and late stage (III–IV stage, 11 cases) cases. In hypopharyngeal carcinoma patients, there was only one early stage patient (II); thus, in the stratification, patients with hypopharyngeal carcinoma were divided stage II–III (5 cases), and stage IV (30 cases) groups. The other clinicopathological parameters of the patients are shown in *Table 1*.

The follow-up time was 1–44 months (median: 13.7 months). We lost track of one patient during the observation period and 36 were alive at the last follow-up (March 2017). The mean survival was 27.5±3.0 months (*Figure 1*).

Correlations between clinicopathological parameters, ¹⁸F-FDG accumulation, and OS

Of the 55 patients with laryngeal and hypopharyngeal carcinoma, the OS of patients receiving radiotherapy was 32.6±3.3 versus 17.4±3.8 months for the patients without radiotherapy. Kaplan-Meier curve analysis showed that patients receiving radiotherapy had a significantly longer OS than those without radiotherapy (log-rank test, P=0.004; *Figure 2*).

The OS of patients with laryngeal and hypopharyngeal carcinoma with a tumor >4 cm was 14.5±1.7 months versus 33.4±3.6 months for the patients with tumors <4 cm.

Kaplan-Meier curve analysis showed that patients with a tumor size >4 cm had a significantly shorter OS than those with tumors <4 cm (log-rank test, $P=0.002$; *Figure 2*).

However, age ($P=0.929$), clinical stage ($P=0.249$), lymph node metastasis ($P=0.924$), and tumor differentiation ($P=0.875$) showed no correlation with survival in laryngeal and hypopharyngeal carcinoma patients.

In a further stratified analysis, we found that of the 20 laryngeal carcinoma patients, those receiving radiotherapy had a significantly longer OS than those

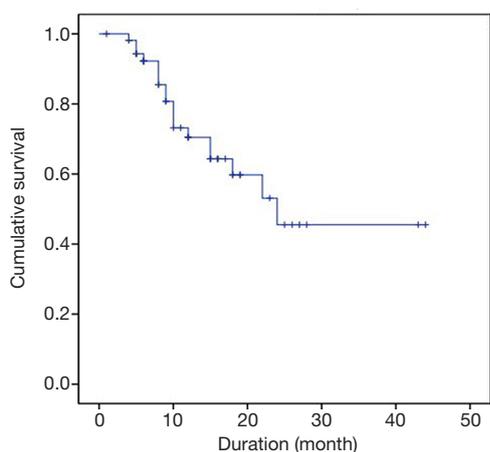


Figure 1 The survival of 55 patients with laryngeal and hypopharyngeal carcinoma.

without radiotherapy (log-rank test, $P=0.022$; *Figure 3*). However, age ($P=0.161$), clinical stage ($P=0.250$), tumor location ($P=0.500$), lymph node metastasis ($P=0.491$), tumor differentiation ($P=0.191$), and tumor size ($P=0.815$) showed no relationship with survival in laryngeal carcinoma patients.

In a stratified analysis of the 35 hypopharyngeal carcinoma patients, the patients receiving radiotherapy had a significantly longer OS than those without radiotherapy (log-rank test, $P=0.039$; *Figure 3*), and patients with a tumor >4 cm had a significantly shorter OS than those with a tumor <4 cm (log-rank test, $P=0.007$; *Figure 3*). However, age ($P=0.676$), clinical stage ($P=0.120$), tumor location ($P=0.166$), lymph node metastasis ($P=0.887$), and tumor differentiation ($P=0.603$) showed no relationship with OS in hypopharyngeal carcinoma patients.

The sensitivity and specificity for the detection of laryngeal or hypopharyngeal carcinoma at different cut-off values of SUV_{max} were determined according to a ROC curve analysis (*Figure 4*). A cut-off SUV_{max} value of 4.985 showed the highest Youden's index, of 0.838, which was associated with optimal sensitivity (90.9%) and specificity (92.9%). The area under the ROC curve was 0.951 ± 0.029 ($P < 0.001$). According to the cut-off value, the 55 patients with laryngeal and hypopharyngeal carcinoma were divided into two groups: high and low SUV_{max} groups. However, the OS of laryngeal and hypopharyngeal carcinoma patients with $SUV_{max} > 4.985$ was not significantly shorter than those

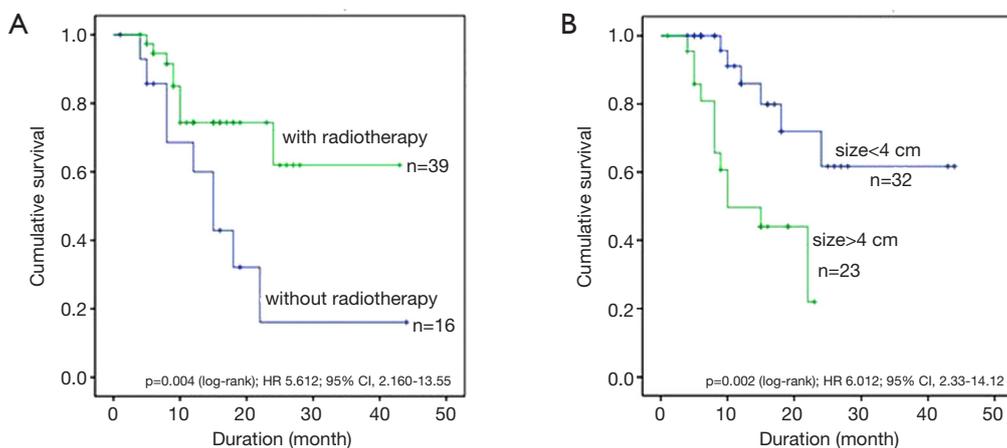


Figure 2 The survival analysis in patients with laryngeal and hypopharyngeal carcinoma. (A) the survival analysis in patients with radiotherapy group and patients without radiotherapy group with laryngeal and hypopharyngeal carcinoma; (B) the survival analysis in patients with tumor size larger than 4 cm group and patients with tumor size smaller than 4 cm group with laryngeal and hypopharyngeal carcinoma.

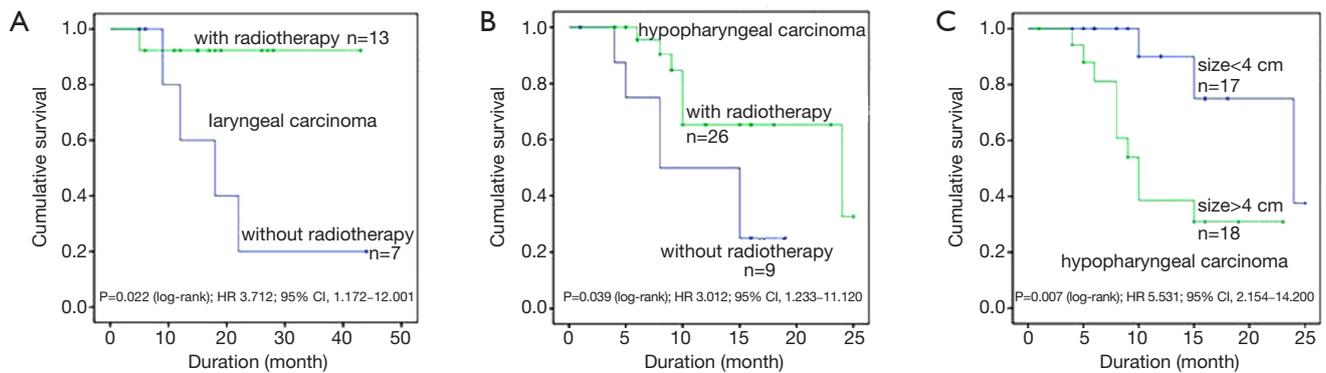


Figure 3 The stratified survival analysis in patients with laryngeal or hypopharyngeal carcinoma. (A) The stratified survival analysis in patients with radiotherapy group and patients without radiotherapy group with laryngeal carcinoma. (B) the stratified survival analysis in patients with radiotherapy group and patients without radiotherapy group with hypopharyngeal carcinoma; (C) the survival analysis in patients with tumor size larger than 4cm group and patients with tumor size smaller than 4cm group with hypopharyngeal carcinoma.

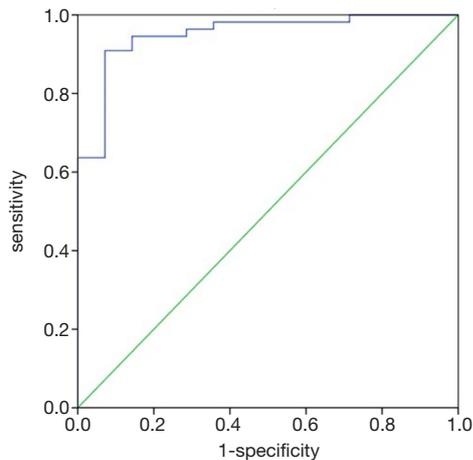


Figure 4 Receiver operator characteristic curve for distinguishing laryngeal or hypopharyngeal carcinoma from non-tumor lesions.

with $SUV_{max} < 4.985$ ($P=0.306$).

Prognostic significance of GLUT-1 and HIF-1 α overexpression

The positive rate of GLUT-1 in laryngeal and hypopharyngeal carcinoma was 49.1% (27/55), and that of HIF-1 α was 56.4% (31/55). GLUT-1 and HIF-1 α were negative expressed in vocal cord polyps, so GLUT-1 and HIF-1 α expression levels were significantly higher than in vocal cord polyps ($P<0.05$; *Figure 5*).

According to the expression of GLUT-1, the 55 laryngeal and hypopharyngeal carcinoma patients were divided into

negative ($n=28$) and positive groups ($n=27$). However, the OS was not significantly different between the two groups ($P=0.919$).

According to the expression of HIF-1 α , the 55 laryngeal and hypopharyngeal carcinoma patients were divided into negative ($n=24$) and positive groups ($n=31$). Again, the OS was not significantly different between the two groups ($P=0.083$).

Multivariate analysis demonstrated that treatment method (HR, 3.786; 95% CI, 1.185–12.095; $P=0.025$), tumor size (HR, 4.785; 95% CI, 1.495–15.152; $P=0.008$), GLUT-1 expression (HR, 4.282; 95% CI, 1.137–16.125; $P=0.032$), and HIF-1 α expression (HR, 4.592; 95% CI, 1.574–15.455; $P=0.032$) were correlated with OS in patients with laryngeal and hypopharyngeal carcinoma, however, tumor differentiation and SUVmax were not correlated with OS in patients with laryngeal and hypopharyngeal carcinoma. Further stratified analyses showed that GLUT-1 and HIF-1 α expression in laryngeal carcinoma patients did not correlate with survival ($P=0.914$ and 0.154 , respectively). According to the expression of HIF-1 α , patients with hypopharyngeal carcinoma were divided into negative ($n=21$) and positive groups ($n=14$). The survival of the negative group was 22.7 ± 1.6 months and that of the positive group was 11.8 ± 1.9 months; there was a significant difference between the survival of the two groups ($P<0.001$; *Figure 6*). However, GLUT-1 expression in hypopharyngeal carcinomas did not correlate with patient survival ($P=0.291$). A multivariate analysis demonstrated that tumor size (HR, 11.405; 95% CI, 1.181–110.107; $P=0.035$) and HIF-1 α expression (HR, 10.704; 95% CI, 1.313–87.224; $P=0.027$)

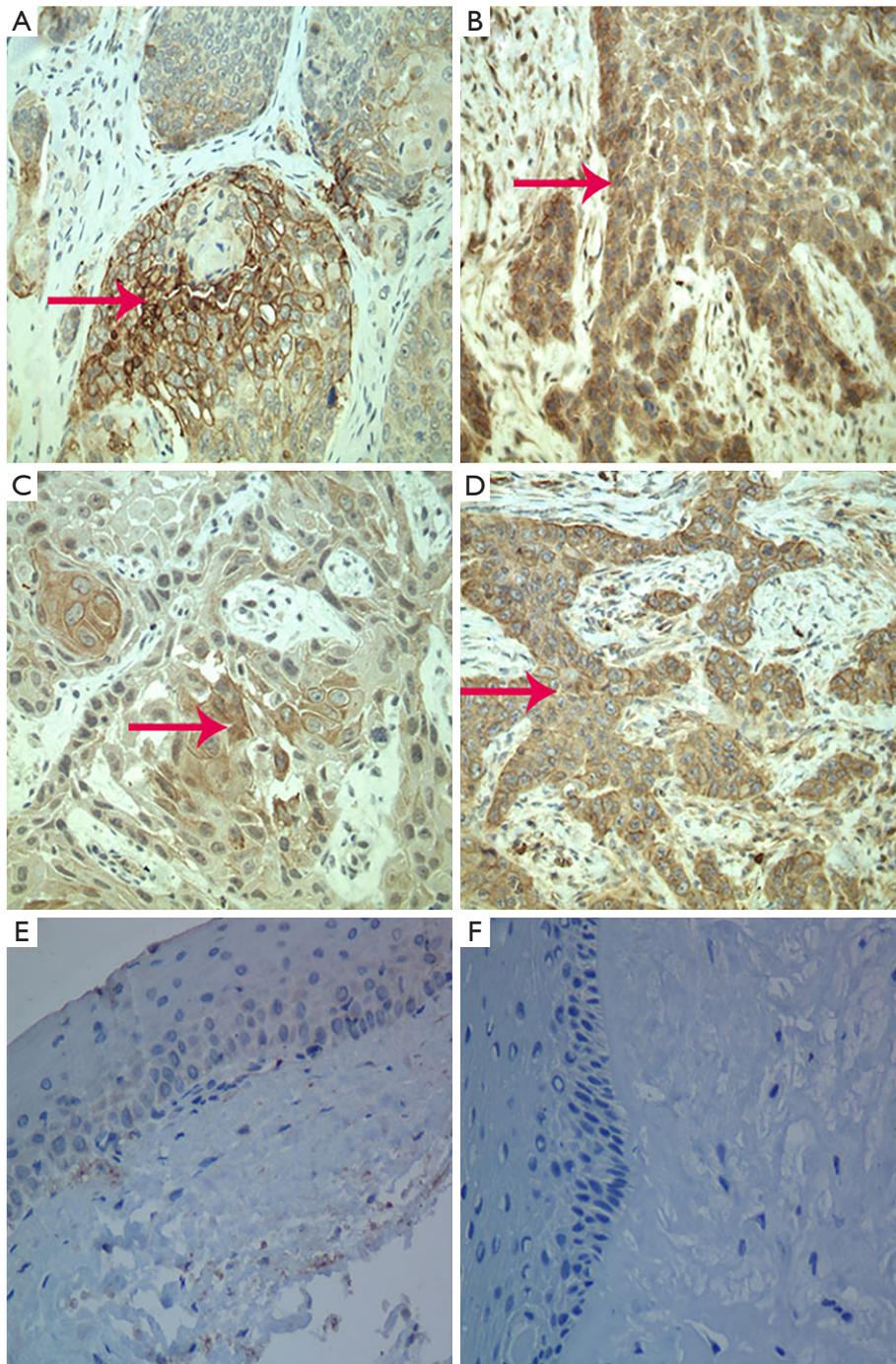


Figure 5 Glut-1 and HIF-1 α protein were positive expressed in the laryngeal squamous cell carcinoma and hypopharyngeal squamous cell carcinoma by immunostaining, and were negative expression in vocal cord polyps. Glut-1 was mainly diffused on the cell membrane of the tumor cells, HIF-1 α was diffused in the cytoplasm, in the graphs blue area represented the nuclei, brown area represented the target genes. (A) Positive expression of Glut-1 in laryngeal carcinoma (arrow); (B) positive expression of Glut-1 in hypopharyngeal carcinoma (arrow); (C) positive expression of HIF-1 α in laryngeal carcinoma (arrow); (D) positive expression of HIF-1 α in hypopharyngeal carcinoma (arrow); (E) negative expression of Glut-1 in vocal cord polyps. (F) negative expression of HIF-1 α in vocal cord polyps (magnification, $\times 400$). HIF-1 α , hypoxia inducible factor-1 α ; Glut-1, glucose transporter protein-1.

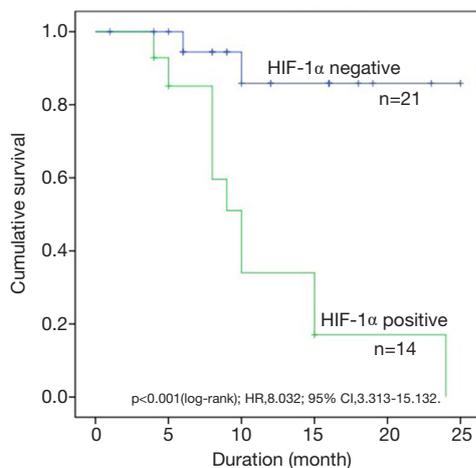


Figure 6 The survival analysis in HIF-1 α negative group and HIF-1 α positive group with hypopharyngeal carcinoma. HIF-1 α , hypoxia inducible factor-1 α .

correlated with the OS of patients with hypopharyngeal carcinoma, however, treatment method and tumor size were not correlated with OS of the patients with hypopharyngeal carcinoma.

Relationship between GLUT-1 and HIF-1 α expression, 18 F-FDG accumulation, and clinicopathological parameters

SUV_{max} and GLUT-1 expression in laryngeal and hypopharyngeal carcinoma were not correlate with age, tumor size, clinical stage, tumor differentiation, treatment method, or lymph node metastasis ($P > 0.05$). HIF-1 α expression was not correlate with age, clinical stage, tumor differentiation, treatment method, or lymph node metastasis in laryngeal and hypopharyngeal carcinoma patients ($P > 0.05$), but was correlated with tumor size ($r = 0.351$, $P = 0.009$). HIF-1 α expression was correlated with GLUT-1 expression ($r = 0.571$, $P < 0.001$) and GLUT-1 expression was correlated with SUV_{max} ($r = 0.495$, $P < 0.001$). However, HIF-1 α expression was not correlate with SUV_{max} ($P = 0.199$).

Further stratified analysis revealed that SUV_{max}, GLUT-1, and HIF-1 α expression in laryngeal carcinoma were not correlate with age, tumor location, tumor size, clinical stage, tumor differentiation, therapeutic method, or lymph node metastasis ($P > 0.05$). In laryngeal carcinoma, HIF-1 α expression was correlated with GLUT-1 expression ($r = 0.642$, $P = 0.018$). However, neither GLUT-1 nor HIF-1 α expression was correlated with SUV_{max} ($P = 0.193$ and 0.187 , respectively).

In hypopharyngeal carcinoma, SUV_{max} was correlated with tumor size ($r = 0.380$, $P = 0.028$) and GLUT-1 expression ($r = 0.649$, $P = 0.001$), but not with HIF-1 α expression ($P = 0.363$). SUV_{max} was not correlate with age, tumor location, clinical stage, tumor differentiation, treatment method, or lymph node metastasis ($P > 0.05$). HIF-1 α expression was correlated with tumor size ($r = 0.560$, $P = 0.001$) and GLUT-1 expression ($r = 0.459$, $P = 0.009$), but not with age, tumor location, clinical stage, tumor differentiation, treatment method, or lymph node metastasis ($P > 0.05$). GLUT-1 expression did not correlate with age, tumor location, tumor size, clinical stage, tumor differentiation, treatment method, or lymph node metastasis ($P > 0.05$).

Discussion

Relationships between the expression of GLUT-1 and HIF-1 α , clinicopathological features, and prognosis in patients with malignant tumors remain controversial. In this study, expression of HIF-1 α was correlated with tumor size. However, neither HIF-1 α nor GLUT-1 expression was correlated with age, stage, differentiation, treatment method, or lymph node metastasis in patients with laryngeal and hypopharyngeal carcinomas. HIF-1 α expression was correlated with GLUT-1 expression in laryngeal and hypopharyngeal carcinomas. Univariate analyses showed that the treatment method and tumor size were correlated with survival in laryngeal and hypopharyngeal carcinoma. Multivariate analysis showed that the treatment method, tumor size, and expression of HIF-1 α and GLUT-1 in laryngeal and hypopharyngeal carcinoma patients were correlated with OS. Further stratification analysis showed that treatment method of laryngeal or hypopharyngeal carcinoma was associated with survival, and HIF-1 α expression in hypopharyngeal carcinomas was associated with survival. So, we hypothesis that inhibition of Glut-1 and HIF-1 α expression may improve the prognosis of patients with laryngeal and hypopharyngeal carcinoma, although this requires further studies.

Some studies of ours and other authors had the controversial or similar results. In our previous study, we found that positive expression of HIF-1 α was correlated with OS in patients with laryngeal carcinomas ($P = 0.018$); however, expression of GLUT-1 was not correlated with OS (27). In another study, we found that expression of GLUT-1 was correlated with clinical stage ($P = 0.037$) and tumor-node-metastasis (TNM) classification ($P = 0.02$),

but not with survival rate (29). Iwasaki *et al.* found that the expression of HIF-1 α and GLUT-1 were significantly correlated with tumor stage and differentiation in cervical cancer, but the expression of HIF-1 α was not correlated with the expression of GLUT-1, and the expression of HIF-1 α and GLUT-1 were not correlated with disease-free survival or tumor size (20). Lu *et al.* found that in pancreatic cancer, GLUT-1 expression was correlated with poor prognosis, tumor volume, clinical stage, lymph node metastasis, SUV_{max}, and Ki-67 value (30). Wigerup *et al.* found that HIF-1 overexpression was correlated with poor prognosis and relapse in cancer patients (31). Other studies also found that GLUT-1 and HIF-1 α expression were correlated with total survival rate or disease-free survival in patients with papillary thyroid carcinoma (32), pancreatic adenocarcinoma (8), pancreatic neuroendocrine tumors (21), epithelial ovarian cancer (33), and osteosarcoma (34). However, other studies have found that GLUT-1 and HIF-1 α expression were not correlated with tumor prognosis or clinical stage; different papers have reported different results, even for the same types of tumor (35-38). Fujino *et al.* found that high expression of GLUT-1 in pancreatic endocrine carcinoma was associated with lymph node metastasis (21). Schlößer *et al.* found that GLUT-1 expression in gastric cancer was associated with T stage (37). Kobayashi *et al.* found that in esophageal squamous cell carcinoma, GLUT-1 expression was correlated with tumor stage (12). However, de Andrade Barreto *et al.* found that the expression of HIF-1 α in esophageal cancer was not correlated with patient clinicopathological features (39). Davis-Yadley *et al.* found that GLUT-1 expression was not correlated with tumor differentiation in pancreatic cancer (8). A meta-analysis of 486 patients with osteosarcoma revealed that HIF-1 overexpression was correlated with poor prognosis; OS in patients with high expression of HIF-1 was shorter than in patients with lower expression (40). A meta-analysis of 2,077 patients with colorectal cancer found that GLUT-1 was not associated with OS or disease-free survival, but subgroup analysis showed that in rectal cancer, GLUT-1 expression was associated with disease-free survival (41). In different tumors and with different investigators, the relationships between the expression of GLUT-1 and HIF-1 α and the prognosis of patients are different. This may be the result of differences in tumor type, clinical stage, and methods for the detection and evaluation of GLUT-1 and HIF-1 α expression.

In recent years, many authors have studied the relationship between ¹⁸F-FDG uptake in malignant tumors

and the prognosis of patients, but the results have been controversial. In this study, we sought to find the correlation between ¹⁸F-FDG uptake and the prognosis of the patients, and to guide individual treatment based on the preoperative ¹⁸F-FDG uptake. However, we found that the preoperative SUV_{max} of patients with laryngeal and hypopharyngeal carcinoma were not correlated with clinicopathological factors and prognosis. In our previous study, we found that shorter OS in patients with laryngeal cancer was correlated with higher SUV_{max} (SUV_{max}>11.2; P=0.043), but SUV_{max} was not correlated with the pathological type, TNM stage, tumor differentiation, or tumor location (27). Other studies found that ¹⁸F-FDG SUV_{max} was correlated with tumor differentiation and tumor stage in bone and soft tissue sarcomas (42), head and neck squamous cell carcinomas (11), esophageal squamous cell cancer (12), and anal cancer (43). Deantonio *et al.* found that SUV_{max} was not correlated with treatment method or survival rate in patients with anal cancer (43). In the study of Nguyen *et al.*, disease-free survival in non-small cell lung cancer was correlated with SUV_{max} (7), Ki-67 (25%), tumor size (3 cm), and tumor differentiation. There was a correlation between any two of GLUT-1, Ki-67, and SUV_{max}, but disease-free survival was not correlated with gender, tumor stage, or lymph node metastasis (44). These differences in relationships between SUV_{max} and prognosis in patients with malignant tumors may be due to differences in treatment, the range of SUV cut-off values, and the heterogeneity of tumors (45-47). SUV may also be an underestimate of ¹⁸F-FDG uptake when the tumor size is <20 mm, due to the partial volume effect (48). Furthermore, certain factors affect FDG uptake, including hypoxia, cell density, and expression of glycolysis-associated proteins (49,50).

The ¹⁸F-FDG uptake mechanism is not entirely clear, but recently, more studies have focused on the effects of GLUT-1 and HIF-1 α on the regulation of tumor cell ¹⁸F-FDG uptake. This study found that GLUT-1 expression correlated with SUV_{max} in patients with laryngeal and hypopharyngeal carcinoma, but HIF-1 α did not. However, our previous study indicated that ¹⁸F-FDG SUV_{max} was associated with GLUT-1 and HIF-1 expression in laryngeal carcinoma patients (27). This discrepancy may be due to the sample size, the different patients and the different methods for the detection and evaluation of GLUT-1 and HIF-1 α expression. Other studies found that GLUT-1 expression was correlated with ¹⁸F-FDG uptake in bone and soft tissue sarcomas (42), thymic epithelial tumors (51), esophageal squamous cell cancer (12), malignant melanoma (52),

and diffuse large B-cell lymphoma (53). Mees *et al.* found that ^{18}F -FDG uptake in an HT29 xenograft tumor was correlated with the expression of HIF-1 α (54). Yamada found that ^{18}F -FDG uptake in oral squamous cell carcinoma at an early stage was correlated with the expression of GLUT-1 and HIF-1 α , but in later-stage tumors, ^{18}F -FDG was not correlated with the expression of GLUT-1 or HIF-1 α (28). Jo found that in endometrial carcinoma, ^{18}F -FDG uptake was correlated with GLUT-1 expression, but not with HIF-1 α expression (55). Other studies found that SUV_{max} was not correlate with GLUT-1 expression in non-small cell lung cancer (56), head and neck squamous cell carcinomas (11), or central nervous system lymphomas (57). So, the relationship between ^{18}F -FDG uptake and GLUT-1 or HIF-1 α expression were not specific, and it need further research.

In summary, we found that the treatment method (with or without radiotherapy) and GLUT-1 and HIF-1 α expression were correlated with OS of patients with laryngeal and hypopharyngeal carcinoma. GLUT-1 and HIF-1 α may be indicators of tumor aggressiveness.

This study had several limitations. First, we used a retrospective design with a small sample size and a short follow-up time. Second, we did not use multiple indicators to assess ^{18}F -FDG accumulation in the laryngeal and hypopharyngeal carcinomas. Because the measurement of SUV_{max} is both relatively easy and observer-independent, it is used widely. SUV_{max} measures the highest pixel value within a region of interest, which might represent the metabolic activity of the most aggressive cells in a tumor (58). However, SUV_{max} may not reflect the biologic characteristics of the entire tumor. Metabolic tumor volume (MTV) seems to reflect the volume of high metabolic but does not estimate the degree of metabolic activity occurring above certain thresholds. Total lesion glycolysis (TLG) indexes both volume and metabolic activity; thus, TLG is a more comprehensive indicator that may better reflect the level of tumor metabolism (59). Some studies found that SUV_{max} of head and neck tumors was correlated with prognosis (60-62), however, others found that SUV_{max} of head and neck tumors was not correlated with the prognosis or treatment response (63,64). SUV_{max} does not reflect the biological characteristics of the whole tumor, so many authors have instead assessed MTV or TLG (65). Some studies found that the higher the MTV of non-small cell lung cancer, the shorter the survival of patients, but survival was not correlated with SUV (66). Park *et al.* also found that MTV was more predictive of survival rate than SUV_{max} (67).

Age, SUV_{max} , MTV, and TLG in oropharyngeal and hypopharyngeal cancer were correlated with disease-free survival (68). MTV and TLG in cervical cancer patients were associated with disease-free survival and OS, whereas SUV_{max} was not (69). It has also been found that ^{18}F -FDG PET/CT Deauville scores (DSs) of tumors, during or after treatment, were associated with prognosis, and that DS is a better predictive factor than SUV_{max} (70,71). Thus, we will assess the use of TLG and DS in a future study to quantify the uptake of ^{18}F -FDG in tumors.

Conclusions

The expression of GLUT-1 and HIF-1 α in laryngeal and hypopharyngeal carcinoma was significantly higher than that in vocal cord polyps. The expression of HIF-1 α was correlated with tumor size. GLUT-1 expression was correlated with HIF-1 α expression and SUV_{max} . Multivariate analysis showed that treatment method, tumor size, and GLUT-1 and HIF-1 α expression were correlated with the prognosis of patients with laryngeal and hypopharyngeal carcinoma. We hypothesis that inhibition of Glut-1 and HIF-1 α expression may improve the prognosis of patients with laryngeal and hypopharyngeal carcinoma, although this requires further studies. In the future, we will enroll more patients in our study, and take the prospective study to get the more accurate and reliable results.

Acknowledgments

We acknowledge the assistance of all those who participated in this project, especially the technologists in the Pathology department of the First Affiliated Hospital, College of Medicine, Zhejiang University.

Funding: This study was supported by the National Natural Science Foundation of China (No. 81172562 and 81372903).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2020.02.50>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved. The institutional review board of The First Affiliated Hospital, College of Medicine, Zhejiang University (Hangzhou, Zhejiang, China) approved the present study (2017-423). Informed consent was obtained from all participating patients

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Cite this article as: Shen LF, Zhou SH, Yu Q. Relationships between expression of glucose transporter protein-1 and hypoxia inducible factor-1 α , prognosis and ¹⁸F-FDG uptake in laryngeal and hypopharyngeal carcinomas. *Transl Cancer Res* 2020;9(4):2824-2837. doi: 10.21037/tcr.2020.02.50