Prognostic effects of the metabolic tumor volume and total lesion glycolysis in patients with advanced squamous cell carcinoma of head and neck

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Background: To investigate the prognostic significance of quantitative parameters obtained from pre-treatment ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) scan on patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

Methods: Fifty patients with previously untreated, biopsy-proven, stage III–IV SCCHN who received induction chemotherapy (indCT) followed by local treatment (surgery, radiotherapy or both) were enrolled. We analyzed prognostic effects of the maximum standardized uptake value (SUVmax) of the primary tumor, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) along with clinicopathological variables on treatment outcomes.

Results: After a median follow-up of 44 months, locoregional recurrence and distant metastasis were observed in 13 and 3 patients, respectively. The SUVmax of the primary tumor and all analyzed clinicopathological characteristics had no correlation with treatment outcome. Both MTV and TLG were significant predictors for overall survival (OS) and locoregional progression-free survival (LRPFS) by both univariate and multivariate analyses, the 3-year rates of OS and LRPFS for patients with pre-treatment MTV < *vs.* ≥85 were 78.8% *vs.* 33.9% (P=0.0200) and 80.2% *vs.* 47.6% (P=0.0235). Similar results were obtained for the pre-treatment TLG (< *vs.* ≥620 were 78.8% *vs.* 34.6% for OS, P=0.0125; and were 80.9% *vs.* 43.1% for LRPFS, P=0.0106).

Conclusions: The pretreatment MTV and TLG are independent predictors for OS and LRPFS in patients with advanced SCCHN.

Keywords: Squamous cell carcinoma (SCC); head and neck (HN); positron emission tomography (PET); metabolic tumor volume (MTV); total lesion glycolysis (TLG)

Introduction

Head and neck cancer is the sixth most common malignancy worldwide and accounts for the fourth in man in Taiwan (1). These tumors are almost always histopathologically identical (>90% are squamous cell carcinoma) but their clinical behaviors and prognosis are quite heterogenous. Many studies tried to identify the high-risk clinicopathological features to predict the prognostic outcome, such as anatomic site, tumor size and extent of invasion, neck lymph node stage, poor pathologic characteristics (margin

status, angiolymphatic invasion, perineural invasion and extracapsular extension, etc.), but these factors could not fully predict the patients' prognosis (2,3).

[18]F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) scan is a functional image reflecting the tumor activity based on glucose metabolism. The FDG-PET has become the essential initial staging tool for head and neck cancers. Allal *et al.* used cut-off value as 5.5 for the SUVmax of the primary tumor (> and ≤5.5) and reported that the high pre-treatment standardized uptake value was associated with worse disease-free survival (DFS) (3-year DFS was 42% *vs.* 79%, P=0.005) and worse local control (3-year local control was 55% *vs.* 86%, P=0.01) for head and neck cancer treated by radiotherapy with or without chemotherapy (4). As the evolution of clinical investigations for FDG-PET quantitative parameters, the most widely used parameter is the maximum standardized uptake value (SUVmax) of the tumor, which has been demonstrated to predict survival in head and neck cancers (4-7). Liao *et al.* reported that the pre-treatment SUVmax of the primary tumor was significantly associated with local control (5-year local control rate for cutoff value of 19.3 was 55% *vs.* 88%, P=0.0135) and could be one component in predicting overall survival (OS) when combination with other prognosticators (such as tumor invasion depth, nodal SUVmax and presence of pathologic lymph node metastases) in oral cavity squamous cell carcinoma treated with surgery and neck dissection (5,6). Lin *et al.* also demonstrated that the pre-treatment SUVmax of the primary tumor was significantly associated with the primary tumor relapse-free survival in oropharyngeal and hypopharyngeal cancer treated with radiotherapy (SUVmax of the primary tumor >11 had inferior 2-year primary tumor relapse-free survival, 41% *vs.* 75%, P=0.003) (7). However, no definite threshold of the SUVmax of the primary tumor has been validated and it begs a question that whether a single pixel value within tumor mass, like SUVmax, is a good prognostic factor representing the whole lesion.

Recently, the volume-based parameters, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are theoretically better parameters estimating the metabolic tumor burden and have been demonstrated as better prognostic predictors than the SUVmax (8-12). Systemic review by Castelli (a total of 2,928 patients in 45 studies) reported that the MTV was well correlated with OS and DFS, with a higher predictive value than the SUVmax in head and neck cancer (13). Another systemic review by Pak (13 studies with a total of 1,180 patients) showed both

the high volumetric parameters of the MTV and the TLG were associated with increased adverse events (progression or recurrence) and decreased OS [combined HR for adverse events was 3.06 (2.33–4.01, P<0.00001) with MTV and 3.10 (2.27–4.24, P<0.00001)] with TLG; the pooled HR for OS was 3.51 (2.62–4.72, P<0.00001) with MTV and 3.14 (2.24–4.40, P<0.00001) with TLG (14). However, the enrolled patients in these studies had various kinds of primary tumor sites, all stage diseases with distinct prognosis, and treated with inconsistent treatment modalities.

Recent study published by Yu showed that the reduction percentage between the pre- and post-treatment MTV and TLG (42% reduction in MTV and 55% reduction in TLG) were correlated with event-free survival for head and neck cancer patients treated with induction chemotherapy (IndCT) with TPF regimen (Taxotere, Cisplatin and Fluorouracil) (15). The aim of this study is to explore the prognostic significance of the pre-treatment FDG-PET parameters on patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) who received IndCT followed by local therapy (surgery, radiotherapy or both).

Methods

Patients

From September 2010 to July 2013, a total of 50 patients with previously untreated, biopsy-proven SCCHN and stage III/IV diseases were enrolled to this retrospective study. The patient characteristics were described as *Table 1*. The median age at diagnosis was 52 years old (range, 35 to 77 years) and 92% of patients were male. Most patients (98%) belong to stage IV diseases. The numbers of the primary tumor origin were 13 in the oral cavity, 19 in the oropharynx and 18 in the hypopharynx, respectively.

Treatments

All patients received IndCT first with weekly CDFLEM regimen, consisting of cisplatin 60 mg/m², day 1, docetaxel 50 mg/m², day 8, 5-fluorouracil 2,500 mg/m² plus leucovorin 250 mg/m², day 15, and epirubicin 30 mg/m² plus methotrexate 30 mg/m², day 22, repeated every 4 weeks for 3–4 cycles. Local therapy after IndCT included surgery, radiotherapy (RT), concurrent chemoradiotherapy (CCRT), or cetuximab-radiotherapy (Bio-RT). The surgery is strongly recommended for oral cavity cancer patients,

Table 1 Patient characteristics and their relationship with the ^{18}F -FDG-PET parameters

Variable	N	%	SUVmax of the primary tumor					MTV					TLG				
			Low (<22)		High (≥22)		P	Low (<85)		High (≥85)		P	Low (<620)		High (≥620)		P
			n	%	n	%		n	%	n	%		n	%	n	%	
Sex							0.9999					0.5843					0.9999
Women	4	8.0	4	9.3	0	0.0		2	5.9	2	12.5		3	8.6	1	6.7	
Men	46	92.0	39	90.7	7	100.0		32	94.1	14	87.5		32	91.4	14	93.3	
Age							0.9999					0.7635					0.9999
<50	21	42.0	18	41.9	3	42.9		15	44.1	6	37.5		15	42.9	6	40.0	
≥50	29	58.0	25	58.1	4	57.1		19	55.9	10	62.5		20	57.1	9	60.0	
Performance status							0.6181					0.0017					0.0180
0	4	8.0	4	9.3	0	0.0		0	0.0	4	25.0		1	2.9	3	20.0	
1	38	76.0	33	76.7	5	71.4		26	76.5	12	75.0		26	74.3	12	80.0	
2	8	16.0	6	14.0	2	28.6		8	23.5	0	0.0		8	22.9	0	0.0	
Differentiation							0.9999					0.7872					0.9493
Well differentiation	2	4.0	2	4.7	0	0.0		2	5.9	0	0.0		2	5.7	0	0.0	
Moderate differentiation	24	48.0	20	46.5	4	57.1		16	47.1	8	50.0		17	48.6	7	46.7	
Poorly differentiation	20	40.0	17	39.5	3	42.9		14	41.2	6	37.5		13	37.1	7	46.7	
Unknown	4	8.0	4	9.3	0	0.0		2	5.9	2	12.5		3	8.6	1	6.7	
Primary site							0.3977					0.2031					0.0875
Oral cavity	13	26.0	10	23.3	3	42.9		7	20.6	6	37.5		8	22.9	5	33.3	
Oropharynx	19	38.0	16	37.2	3	42.9		12	35.3	7	43.8		11	31.4	8	53.3	
Hypopharynx	18	36.0	17	39.5	1	14.3		15	44.1	3	18.8		16	45.7	2	13.3	
Clinical T stage							0.4717					0.2127					0.2610
T1	1	2.0	1	2.3	0	0.0		0	0.0	1	6.3		0	0.0	1	6.7	
T2	8	16.0	8	18.6	0	0.0		7	20.6	1	6.3		7	20.0	1	6.7	
T3	13	26.0	10	23.3	3	42.9		10	29.4	3	18.8		10	28.6	3	20.0	
T4	28	56.0	24	55.8	4	57.1		17	50.0	11	68.8		18	51.4	10	66.7	
Clinical N stage							0.9999					0.0728					0.9999
N0	2	4.0	2	4.7	0	0.0		2	5.9	0	0.0		2	5.7	0	0.0	
N1	3	6.0	3	7.0	0	0.0		2	5.9	1	6.3		2	5.7	1	6.7	
N2	42	84.0	35	81.4	7	100.0		30	88.2	12	75.0		29	82.9	13	86.7	
N3	3	6.0	3	7.0	0	0.0		0	0.0	3	18.8		2	5.7	1	6.7	
Clinical stage							0.9999					0.9999					0.9999
Stage III	1	2.0	1	2.3	0	0.0		1	2.9	0	0.0		1	2.9	0	0.0	
Stage IV	49	98.0	42	97.7	7	100.0		33	97.1	16	100.0		34	97.1	15	100.0	

SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; ECOG, Eastern Cooperative Oncology Group.

but alternative local therapy would be selected if they refused surgery. CCRT is indicated for patients who had no response to IndCT and RT alone for those who responded to IndCT. Bio-RT is indicated for non-oral cavity cancer patients who had age ≥70 years, poor renal function and hearing impairment.

Seven of 13 patients with oral cavity cancer received surgery after IndCT. Two of them also received postoperative adjuvant RT due to pathologic risk features (one ypT4aN0, margin <1 mm; and one ypT1N2b, margin involved) and the remaining 5 patients did not receive postoperative adjuvant therapy [3 pathological complete response, 1 pathological stage T2N0, 1 refusal (ypT4aN0, margin 2 mm)].

Other patients with oropharynx (n=19) and hypopharynx (n=18) cancer and 6 oral cavity cancer patients received non-surgical local therapy modality, including intensity-modulated radiotherapy (IMRT) alone (n=24), Bio-RT (n=17), and CCRT (n=2), respectively. We used IMRT technique with conventional fractionation of a total 70 Gy (2.0 Gy daily fraction, five days per week) to the gross tumor volume region shown in pre-treatment CT scan or MRI (before IndCT). The drug of Bio-RT consisted of cetuximab, loading dose 400 mg/m^2 day 1 and then 250 mg/m^2 once per week. The concurrent chemotherapy during IMRT was weekly cisplatin 30 mg/m^2.

^{18}F-FDG-PET scan protocol

The pre-treatment FDG-PET scan was usually performed within 1 week prior to the start of the IndCT (median 5 days). All patients were asked to fast for a minimum of six hours (except for water) before the FDG-PET study. Their serum glucose levels were checked to ensure the readings were lower than 200 mg/dL before administration of the radiotracer. PET/CT images were acquired about 1 hour after intravenous injection of 3.7 MBq/kg body weight of F-^{18}FDG.

The imaging was performed using a whole body GEMINI TF 16-slice PET/CT scanner (Philips Healthcare, Cleveland, OH, USA). CT images were obtained without injection of contrast medium using the following settings: 120 kVp, 50 mA, 5 mm slice thickness, and 5 mm intervals. PET images were performed from the head to the upper thigh, and then were reconstructed using vendor supplied ASTONISH time-of-flight iterative reconstruction (Philips Healthcare, Andover, MA). Attenuation correction was performed based on the CT

data. The reconstructed spatial resolution was 5 mm in the centre of the field of view. The image voxel size was 4 mm × 4 mm × 4 mm for the PET images and 1.17 mm × 1.17 mm × 1.5 mm for the CT images.

Images analysis

PET images were retrospectively interpreted by two experienced nuclear medicine physicians by Philips Extended Brilliance Workspace Nuclear Medicine version 2.0. Tumor tracking was used to draw regions of interest. For semiquantitative analysis of FDG uptake, regions of interest were defined on the target lesions (primary tumor and metastatic neck lymph nodes) on the trans-axial PET images. The SUV was calculated for quantitative analysis of tumor FDG uptake, as follows:

SUV = tissue activity concentration (kBq/mL)/injected activity (kBq)/body weight (kg) with injected activity decay-corrected from the delay between injection and image acquisition.

Measurement of tumor volume

All tumor volume design was performed in the workstation SYNTEGRA (Phillips Medical Systems). The MTV was measured from attenuation-corrected FDG-PET images. The boundaries of the primary tumor and metastatic regional lymph nodes were drawn in the axial, coronal, and sagittal FDG-PET/CT images. To define the volume boundaries of the interest target, an SUV of 2.5 was assigned and the voxels with SUV intensity ≥2.5 were incorporated into the MTV (10,16). This volume was automatically determined within the region of interests by the review software. The average SUV (SUVmean) and maximum SUV (SUVmax) for the region with SUV ≥2.5 was also determined.

The TLG was calculated as SUVmean × MTV (10). The TLG values were divided into the TLG of primary tumor (primary TLG), TLG of the metastatic neck nodes (nodal TLG), and total tumor TLG (sum of the primary TLG plus nodal TLG), respectively.

Determination of the cut-off values for PET parameters

The receiver operating characteristic (ROC) curve and area under curve (AUC) were used to find the best cut-off values of the SUVmax of the primary tumor, the MTV and the TLG. The total tumor TLG was used as one

of the quantitative FDG-PET parameters in our study. We obtained cut-off values as 22 for the SUVmax of the primary tumor (≥ and <22), 85 for the MTV (≥ and <85) and 620 for the TLG (≥ and <620), respectively for further survival analysis.

Follow-up and statistical analysis

Patients received post-treatment regular follow-up (physical examinations, routine complete blood cell count, serologic biochemistry data of liver and kidney, and fiberscope) monthly for 3–6 months, at 3-month intervals for 3 years, and every 4–6 months thereafter. The computed tomography of head and neck was performed every 3–6 months for 3 years and annually thereafter. Locoregional failure was defined as biopsy-proven recurrence or progression of disease on serial image studies after completion of radiotherapy.

OS was defined as the time between the start day of IndCT and death or last follow-up visit. Locoregional progression-free survival (LRPFS) and distant metastasis failure-free survival (DMFFS) were calculated from the start day of IndCT to the date of locoregional recurrence and distant metastasis, respectively. Survival curves were analyzed by Kaplan-Meier method and a log-rank test was used to compare the difference between the subgroups.

The univariate Cox proportional hazards regression model was adjusted by age (< or ≥50 years old), sex, Eastern Cooperative Oncology Group performance status (ECOG PS 0 *vs.* 1–2), primary tumor site (oral cavity *vs.* oropharynx *vs.* hypopharynx), T-stage (T1–3 *vs.* T4), N-stage (N0–1 *vs.* N2–3) and different quantitative FDG-PET parameters (SUVmax of the primary tumor, MTV and TLG). Cox proportional hazard model was used in multivariate analysis to identify independent prognostic factors. All statistical analyses were performed in SAS version 9.3 and a 2-sided $P<0.05$ was considered statistically significant.

Results

Treatment outcomes

After a median follow-up of 44 months (range, 7 to 69 months) for living patients, 11 patients experienced locoregional recurrence alone, 1 distant metastasis alone, and 2 failures in both sites. The median duration was 9 months (range, 7 to 25 months) from treatment to locoregional failure and 7 months (range, 7 to 40 months) from treatment

to distant metastasis, respectively. So far, there were 16 deaths. The causes of death were 11 uncontrolled tumors, 3 non-cancer related, 1 complication-related and 1 unknown, respectively. The 3-year and 5-year OS rates were 66.7% and 63.8%, respectively. The 3-year and 5-year LRPFS rates were both 70.4%. The 3-year and 5-year DMFFS rates were 95.8% and 92.3%, respectively.

^{18}F-FDG-PET parameters

The patient characteristics and their relationship with the ^{18}F-FDG-PET parameters (SUVmax of primary tumor, MTV and TLG) were also described on *Table 1*. The median SUVmax of primary tumor for entire cohort was 15.5 (range, 4.8–55.7). Seven patients (14%) had primary tumor SUVmax ≥22, and all of them were clinical T3–4 tumor. The median MTV was 55.2 (range, 6.3–324.9). Sixteen patients (32%) had MTV ≥85, and most of them had clinical T4 (11/16, 68.8%) and clinical N2 (12/16, 75.0%) diseases. Fifteen patients (30%) had TLG ≥620, and the majority was clinical T4 (10/15, 66.7%) and clinical N2 (13/15, 86.7%) diseases. All of these patients who had higher value of PET-parameters had clinical stage IV disease.

Univariate analysis

The MTV and the TLG were the significant predictors for OS (P=0.0272 and 0.0185, respectively) and LRPFS (P=0.0346 and 0.0185, respectively) by univariate analysis (*Tables 2,3*). The other clinicopathological factors, such as sex, age, PS, primary site, T-stage, N-stage or the SUVmax of the primary tumor revealed no significant effects on both OS and LRPFS. No significant predictors were found in DMFFS.

The 3-year rates of OS and LRPFS for patients with pre-treatment MTV < *vs.* ≥85 were 78.8% *vs.* 33.9% (P=0.0200, *Figure 1A*) and 80.2% *vs.* 47.6% (P=0.0235, *Figure 1B*). The corresponding rates for patients with pre-treatment TLG < *vs.* ≥620 were 78.8% *vs.* 34.6% (P=0.0125, *Figure 2A*) and 80.9% *vs.* 43.1% (P=0.0106, *Figure 2B*).

Multivariate analysis

Multivariate analysis showed that the MTV and TLG were independent factors in predicting OS (P=0.0272 and 0.0185, respectively) and LRPFS (P=0.0346 and 0.0185, respectively). Again, all clinicopathological factors were not

Table 2 Univariate and multivariate analysis for overall survival

Variable	Interpretation	Univariate analysis			Multivariate analysis		
		HR	95% CI	P	HR	95% CI	P
SUVmax of primary tumor	High (≥22) vs. low (<22)	1.494	(0.426–5.245)	0.5310	–	–	–
Metabolic tumor volume	High (≥85) vs. low (<85)	3.060	(1.134–8.255)	0.0272	3.060	(1.134–8.255)	0.0272
Total lesion glycolysis	High (≥620) vs. low (<620)	3.286	(1.221–8.846)	0.0185	3.286	(1.221–8.846)	0.0185
Age	≥50 vs. <50	1.133	(0.421–3.048)	0.8041	–	–	–
Sex	Men vs. women	0.717	(0.163–3.161)	0.6605	–	–	–
Performance status (ECOG)	1–2 vs. 0	1.429	(0.324–6.294)	0.6370	–	–	–
Primary site	Oropharynx vs. oral cavity	1.495	(0.488–4.584)	0.4815	–	–	–
	Hypopharynx vs. oral cavity	0.504	(0.120–2.110)	0.3482	–	–	–
T-stage	T4 vs. T1–3	0.969	(0.360–2.605)	0.9501	–	–	–
N-stage	N2–3 vs. N0–1	1.906	(0.252–14.437)	0.5325	–	–	–

ECOG, Eastern Cooperative Oncology Group.

Table 3 Univariate and multivariate analysis for locoregional progression-free survival

Variable	Interpretation	Univariate analysis			Multivariate analysis		
		HR	95% CI	P	HR	95% CI	P
SUVmax of primary tumor	High (≥22) vs. low (<22)	1.241	(0.275–5.599)	0.7791	–	–	–
Metabolic tumor volume	High (≥85) vs. low (<85)	3.284	(1.090–9.896)	0.0346	3.284	(1.090–9.896)	0.0346
Total lesion glycolysis	High (≥620) vs. low (<620)	3.790	(1.250–11.488)	0.0185	3.790	(1.250–11.488)	0.0185
Age	≥50 vs. <50	1.384	(0.452–4.240)	0.5694	–	–	–
Sex	Men vs. women	1.096	(0.142–8.445)	0.9297	–	–	–
Performance status (ECOG)	1–2 vs. 0	–	–	–	–	–	–
Primary site	Oropharynx vs. oral cavity	0.582	(0.130–2.604)	0.4793	–	–	–
	Hypopharynx vs. oral cavity	1.166	(0.329–4.136)	0.8117	–	–	–
T Stage	T4 vs. T1–3	2.528	(0.695–9.201)	0.1593	–	–	–
N stage	N2–3 vs. N0–1	1.657	(0.215–12.756)	0.6276	–	–	–

ECOG, Eastern Cooperative Oncology Group.

independent prognostic factors in terms of OS (*Table 2*) and LRPFS (*Table 3*).

Discussion

FDG-PET/CT image is now widely used as a routine pre-treatment staging work-up for many cancer types. In addition, it can provide more information for radiation oncologists in delineation of the target volumes. Recently, quantitative parameters of FDG-PET were also found to

be a new kind of prognostic factor in various malignancies, including SCCHN (3,13,14,17,18).

Prior studies demonstrated that the SUVmax of the primary tumor was a significant prognostic factor for OS, DFS and local relapse-free survival in head and neck cancer (5-7,14). However, reports from other investigators could not support this finding (4,8-10,16). Results of the current study revealed that the SUVmax of the primary tumor did not correlate with OS and LRPFS. Although previous study showed nodal SUVmax was another significant prognostic
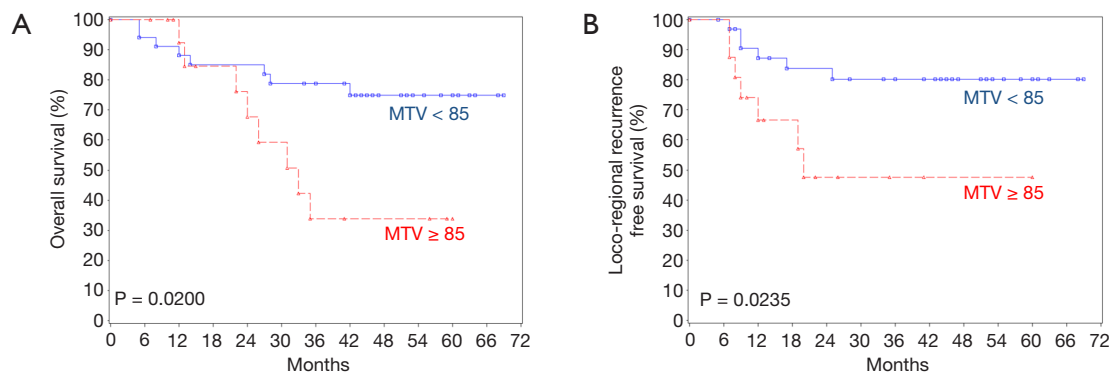
Figure 1 Overall survival (A) and Locoregional progression-free survival (B) according to the different metabolic tumor volume (MTV).
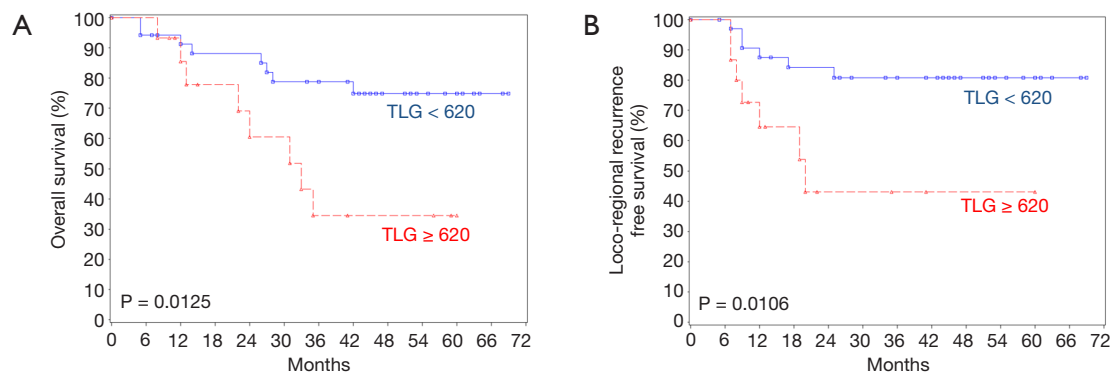

Figure 2 Overall survival (A) and Locoregional progression-free survival (B) according to the different total lesion glycolysis (TLG).

factor for patients with oral cavity cancer treated by surgery (6), we did not use this parameter in our study because not all patients has detectable lymphadenopathies in the PET/CT image.

Recently, more and more studies demonstrated that MTV was a better prognostic predictor than the SUVmax of the primary tumor in OS, DFS and LRPFS (3,8-10,14,16,19). A review article by Castelli *et al.* showed that the MTV was well correlated to OS and DFS and had a higher predictive value than the SUVmax of the primary tumor (13). Another review article by Pak *et al.* also concluded that the MTV had significant predictive value in OS by pooled hazard ratio of 3.51 (2.62–4.72, P<0.00001) (14). Our study showed similar results that the MTV was a significant predictor in terms of OS and LRPFS by both univariate and multivariate analyses.

In our study, a higher proportion of patients with MTV ≥85 had clinical N2 disease (P=0.0728), which was correlated with clinical finding of increased tumor burden. Although most of our enrolled patients were T3–4 (92%),

the MTV was not correlated with clinical T stage. The possible reason is the reflection of metabolic tumor burden by MTV instead of tumor size or invasion extent.

The new parameter of the TLG that reflects MTV plus FDG-uptake intensity of all lesions has been shown as a more significant predictor for treatment outcome in many malignancies. Several studies reported that the TLG was an important prognostic factor in predicting OS and DFS for head and neck cancer patients (14,17,18). A systematic review and meta-analysis by Pak *et al.* showed the TLG was a good predictor in OS by pooled hazard ratio of 3.14 (2.24–4.40, P<0.00001) (14). Our data support these findings. Besides, our study showed patients who had higher value of TLG had clinical T4 and N2 diseases. Although no significant difference was observed in TLG between clinical T and N stage, it was reasonable that more advanced disease represented more aggressive tumor behavior, which resulted in higher tumor metabolism.

The disadvantages of previous published literatures included (1) early to locally advanced diseases were all

enrolled, which was a confounding factor due to its distinct prognosis, (2) various kinds of cancer sites were enrolled, which represented a much more heterogenous tumor behaviors, (3) inconsistent treatment modalities, which cause difficult judgment of treatment outcomes, and (4) shorter follow-up duration and could not well reflect the real impact of different FDG-PET quantitative parameters.

In our study, the primary local therapy for patients with oral cavity cancer is surgery. However, due to good tumor response of chemotherapy, some patients refused surgery and local RT became an alternative treatment options. For patients with oropharyngeal or hypopharyngeal cancer, organ preservation treatment with IndCT followed by RT/CCRT/Bio-RT.

The strength of this study is a uniform IndCT regimen followed by local therapy and adequate follow-up time compared with previous studies. Our results illustrate that the pretreatment MTV and TLG are two important independent prognostic factors for patients with advanced SCCHN patients. These findings should be verified by larger-scale prospective studies in the future.

Acknowledgments

Footnote

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 study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board in our institution (IRB TCVGH No: CE17010A). Informed consent was taken from all individual participants.

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