

# Hypoxia with <sup>18</sup>F-fluoroerythronitroimidazole integrated positron emission tomography and computed tomography (<sup>18</sup>F-FETNIM PET/CT) in locoregionally advanced head and neck cancer

## Hypoxia changes during chemoradiotherapy and impact on clinical outcome

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### Abstract

Hypoxia is a well-recognized biological characteristic to therapy resistance and negative prognostic factor in patients with head and neck squamous cell carcinoma (HNSCC). This study aims to investigate the changes of hypoxia measured by <sup>18</sup>F-fluoroerythronitroimidazole (FETNIM) uptake on integrated positron emission tomography and computed tomography (PET/CT) during chemoradiotherapy and its prognostic value of clinical outcome in locoregionally advanced HNSCC.

Thirty-two patients with locoregionally advanced HNSCC who received definitive treatment with concurrent chemoradiotherapy underwent FETNIM PET/CT scans before and after 5 weeks of treatment. The intensity of hypoxia using the maximum standardized uptake value (SUVmax) was evaluated both on primary lesion and metastatic lymph node (MLN). The pre-SUVmax and mid-SUVmax were defined as SUVmax on pre- and mid-FETNIM PET/CT. The local control (LC), regional control (RC), distant metastatic-free survival (DMFS), and overall survival (OS) were collected in patient follow-ups.

Mid-SUVmax decreased significantly both in the primary tumor ( $t=8.083, P<.001$ ) and MLN ( $t=6.808, P<.001$ ) compared to pre-SUVmax. With a median follow-up of 54 months, the 5-year LC, RC, DMFS, and OS rates were 55%, 66.7%, 64.7%, and 55%, respectively, for all of the patients. On univariate analysis, patients with high pre-SUVmax in primary tumor had significantly worse LC (56.3% vs 87.5%,  $P=.046$ ) and OS (43.8% vs 87.5%,  $P=.023$ ) than other patients. Patients with high mid-SUVmax had significantly worse DMFS (50% vs 84.6%,  $P=.049$ ) and OS (33.3% vs 73.1%,  $P=.028$ ) than other patients. The tumor grade and mid-SUVmax were the significant predictors of OS on multivariate analysis.

In this study, hypoxia in tumor significantly decreased during chemoradiotherapy. The persistent hypoxia predicted poor OS. The data provided evidence that FETNIM PET/CT could be used dynamically for selecting appropriate patients and optimal timing of hypoxia-adapted therapeutic regimens.

**Abbreviations:** <sup>18</sup>F-FETNIM = 18-labeled fluoroerythronitroimidazole, DMFS = distant metastatic-free survival, HNSCC = head and neck squamous cell carcinoma, LC = local control, MLN = metastatic lymph node, OS = overall survival, PET/CT = integrated positron emission tomography and computed tomography, RC = regional control, SUVmax = maximum standardized uptake value.

**Keywords:** clinical outcome, FETNIM, head and neck cancer, hypoxia imaging, PET/CT

Editor: Chinnadurai Mani.

The study has been presented at the 54<sup>TH</sup> Annual Meeting of the American Society for Radiation Oncology (ASTRO) in an ORAL Scientific Session, Boston, Massachusetts, USA. October 31, 2012.

This work was supported by the Science Technology Program of Jinan (201805051) and the Key Research Development Program of Shandong Province (2019GGX101057).

The authors report no conflicts of interest.

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How to cite this article: Hu M, Xie P, Lee NY, Li M, Ho F, Lian M, Zhao S, Yang G, Fu Z, Zheng J, Ma L, Yu J. Hypoxia with 18F-fluoroerythronitroimidazole integrated positron emission tomography and computed tomography (18F-FETNIM PET/CT) in loco-regionally advanced head and neck cancer. *Medicine* 2019;98:40(e17067).

Received: 27 May 2019 / Received in final form: 8 August 2019 / Accepted: 12 August 2019

<http://dx.doi.org/10.1097/MD.00000000000017067>

## 1. Introduction

Similar to other tumor sites, hypoxia is a well-recognized biological characteristic to chemotherapy and radiotherapy resistance, and regarded as a negative prognostic factor for outcome in patients with head and neck cancer (HNC).<sup>[1,2]</sup> Given its importance, efforts have been focused on hypoxic modification such as normobaric oxygen or carbogen breathing, hyperbaric oxygen, and hypoxic radiosensitizers for decades.<sup>[3–5]</sup> Unfortunately, studies have been inconclusive with varying results. A phase III trial using a hypoxia cytotoxin, tirapazamine, in addition to chemoradiation did not show any benefit in overcoming hypoxia when compared to chemoradiation alone.<sup>[4]</sup> Because no measurement of hypoxia was undertaken in the study, 1 big question is that an unselected group of patients that contained both hypoxic versus nonhypoxic tumors be treated by hypoxic modifications. Recent studies have highlighted on dose escalation to the hypoxia subvolume defined based on imaging data acquired before the start of therapy. However, it is suggested that boosting dose only based on one set of pretreatment information might be inappropriate because of the dynamic change of hypoxia during the therapy.<sup>[6]</sup> Selecting suitable patients and optimal timing will be the most rational choice for individual and personalized treatment strategies of overcoming hypoxia, which could improve outcomes and avoid unnecessary toxicity. Therefore, it has become increasingly important to establish the changes of tumor hypoxia during the treatment and its prognostic value on clinical outcome.

A great challenge for hypoxia-targeting therapy is to detect accurately the oxygen level and fluctuating intratumor for each individual patient. Studies have focused on positron emission tomography (PET) or integrated PET and computed tomography (CT) (PET/CT) imaging, which plays an important role in diagnosis, staging, treatment response, and prognosis of various tumors in clinical.<sup>[7–10]</sup> As a noninvasion tool, PET/CT-based hypoxic tracer has been becoming an ideal method to map tumor hypoxia information with adequate anatomical resolution and location, quantification, and repetition in 3 dimensions. The hypoxia tracers including fluoromisonidazole (FMISO), fluoroazomycin-arabinofuranoside (FAZA), and 2-nitroimidazole3-fluoro-2-(4-((2-nitro-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-1-ol (HX4), <sup>18</sup>F-labeled, have been proposed for detecting changes of hypoxia in patients with HNC.<sup>[11–14]</sup> FMISO is the most widely used in studies. However, the main drawback of FMISO is poor image quality because of low tumor-to-background ratio,<sup>[15]</sup> which may limit the applicability in clinical. <sup>18</sup>F-labeled fluoroerythronitroimidazole (FETNIM) is a derivative of nitroimidazole, which is more hydrophilic compared to FMISO.<sup>[16]</sup> The biodistribution of FETNIM can be expected more rapidly cleared from well-oxygenated tissues, resulting in a higher tumor-to-background ratio.<sup>[17]</sup> A comparative study between FETNIM and FMISO have shown advantages of the FETNIM consisting of lower and more favorable background signal in normal tissues than FMISO.<sup>[18]</sup> Published data indicated that FETNIM PET/CT is a very promising approach for detecting the presence and distribution of tumor hypoxia.<sup>[19–21]</sup>

To identify the patients who may especially benefit from tailored hypoxia-targeting therapy with optimal timing, it is essential to define the prognostic value of hypoxia changes. Hypoxia change have been detected before the start of therapy or at early time points (before 3 weeks) only for evaluating the possibility and feasibility of increasing the dose to stable hypoxic subvolumes.<sup>[13,22]</sup> In the late phase (after 4 weeks) of treatment,

the studies showed that both the intensity and the volume of tumor hypoxia remarkably decreased in a high proportion of patients.<sup>[12,14,23,24]</sup> However, few results indicated the effects of hypoxia change on the clinical outcome. The purpose of this study was to investigate the change of hypoxia during concurrent chemoradiotherapy (CCRT) using FETNIM PET/CT imaging in patients with loco-regionally advanced head and neck squamous cell carcinoma (HNSCC). Furthermore, we evaluated the prognostic value of hypoxia changes, both in primary tumor and metastatic lymph node (MLN).

## 2. Methods

### 2.1. Patients

Patients with newly diagnosed HNC with biopsy-proven squamous cell carcinomas were enrolled between September 2006 and July 2012 in Shandong Cancer Hospital and Institute. Before any therapy was performed, all patients received standard pre-treatment evaluations. Whenever necessary, SPECT and additional FDG PET/CT scan were taken. Staging was done by the standard of the American Joint Committee on Cancer version 7. Inclusion criteria included age from 18 to 70 years, WHO performance status 0–1, locoregionally advanced (T1-4, N1-3, M0). The exclusion criteria were previous radiotherapy in the head and neck region, previous history of malignant disease, and pregnancy. Thirty-two patients who were to receive concurrent chemoradiotherapy with curative intent were eligible in the study. Patient and tumor characteristics were summarized in Table 1.

**Table 1**  
Patient and tumor characteristics.

Patient and/tumor data	Number	%
Age, y		
<60	24	75
≥60	8	25
Sex		
Male	24	75
Female	8	25
Smoking		
Yes	24	75
No	8	25
WHO performance status		
0	27	84.4
1	5	15.6
Primary site		
oropharynx	5	15.6
Hypopharynx	11	34.4
larynx	13	40.6
Oral cavity	3	9.4
Clinical T stage		
1	3	9.4
2	13	40.6
3	10	31.3
4	6	18.7
Clinical N stage		
1	13	40.6
2	19	59.4
3	0	0
Grade		
I	5	15.6
II	25	78.1
III	2	6.3

Patients' written informed consent was obtained and the Research Ethics Committee and the Administration of Radioactive Substances Advisory Committee of Shandong Provisional Government approved this study.

## 2.2. FETNIM PET/CT imaging and analysis

With no fasting required, all patients underwent two FETNIM PET/CT scans: the first scan was performed before treatment (pre-FETNIM PET/CT), and the second one was performed after a mean dose of 50 Gy during the course of their CCRT (mid-FETNIM PET/CT). Details of the FETNIM prepared procedure, CT scan, PET scan, data reconstruction, and images transformation have been published previously.<sup>[21,24]</sup>

Images were qualitatively analyzed by 2 experienced nuclear medicine physicians. The frame on CT images of PET/CT was used to define the whole primary tumor and MLNs. Hypoxia was examined both as a dichotomous with semiquantitative measurement. The maximum standardized uptake value (SUVmax) was determined as PET index, which was measured on primary lesion and MLN by placing regions of interest. Because of the heterogeneity of tumor tissue, a maximum area of  $3 \times 3$  pixels ( $7.04 \times 7.04$  mm) inside each tumor region was determined, with an automated system to represent the highest radioactivity concentration in the tumor. The SUVmax was calculated as the activity concentration/injected dose/body weight). The pre-SUVmax was defined as SUVmax on pre-FETNIM PET/CT, and the mid-SUVmax was defined as SUVmax on mid-FETNIM PET/CT. In cases with multiple MLNs, 1 representative node that showed the highest FETNIM uptake was selected for evaluation.

## 2.3. Treatment and follow-up

All patients were treated with standard chemoradiotherapy. Patients underwent intensity-modulated radiotherapy in 35 to 37 fractions, 5 fractions a week with a daily dose of 1.8 Gy to 2 Gy, plus 2 to 3 cycles of cisplatin ( $70\text{--}100\text{ mg/m}^2$  intravenously within 3 days every 3 weeks). Patients who had failure after the primary treatment received salvage treatment, including chemotherapy alone, irradiation or re-irradiation with or without chemotherapy, salvage surgery, or best supportive care for patients with a low performance status.

After treatment, patients were evaluated every 2 to 3 months during the first 2 years, and every 4 to 6 months thereafter. At each follow-up visit, a routine physical examination and imaging were performed. Survival was defined as the interval from the beginning of diagnostic on study date until death from any cause or until the date of last follow-up for living patients. Five-year local control (LC), regional control (RC), distant metastases-free survival (DMFS), and overall survival (OS) rates were calculated.

## 2.4. Statistical analysis

Statistical analyses were performed using SPSS version 13.0 statistical software (SPSS Inc, Chicago, IL). The independent *t* test determined the difference of pre-SUVmax between primary tumor and MLN. Receiver operator characteristic (ROC) curves were determined to assess the optimal cutoff value of pre-SUVmax for predicting survival. The paired *t* test for determining the difference of hypoxia change was performed during radiotherapy. LC, RC, DMFS, and OS were calculated with the Kaplan-Meier method, and differences between the 2 groups

in survival curves were analyzed by the log-rank test. Multivariate analysis was performed to identify the prognostic factors influencing OS using Cox proportional hazards regression model. All of the tests were 2-tailed, and  $P < .05$  was considered to be statistically significant.

## 3. Results

### 3.1. Pretreatment FETNIM PET/CT findings

Tumor hypoxia patterns were heterogeneous among the patients. Pre-SUVmax ranged from 1.1 to 3.9 ( $2.313 \pm 0.7210$ ; median, 2.15) in the primary tumor, and from 0.9 to 4.1 ( $1.972 \pm 0.6962$ ; median, 1.75) in MLN. Pre-SUVmax of primary tumor was higher than that in MLN ( $t = 1.951$ ,  $P = .060$ ). Additionally, hypoxia presence remarkably differs from primary tumor and MLN in the same patient. Figure 1B showed highly focally increased and visually detectable uptake in the primary tumor (red arrow), whereas no uptake was detected in any MLNs (blue arrow). Contrarily, Figure 2A showed highly increased uptake in MLN (red arrow), versus FETNIM uptake in primary tumor similar to that of background (blue arrow).

The ability of pre-SUVmax for primary tumor and MLN to predict prognosis were respectively depicted by ROC curve. Areas under the curve (AUC) are 0.749 and 0.706, respectively. Figure 3 shows the ROC curve of pre-SUVmax for primary tumor and MLN. The best cutoff values were 2.15 and 1.65, respectively. Based on the cutoff values, 16 (50%) patients revealed enhanced FETNIM uptake on PET/CT scan in the primary tumor, and 18 (56.25%) showed detectable FETNIM distribution in MLN before any treatment.

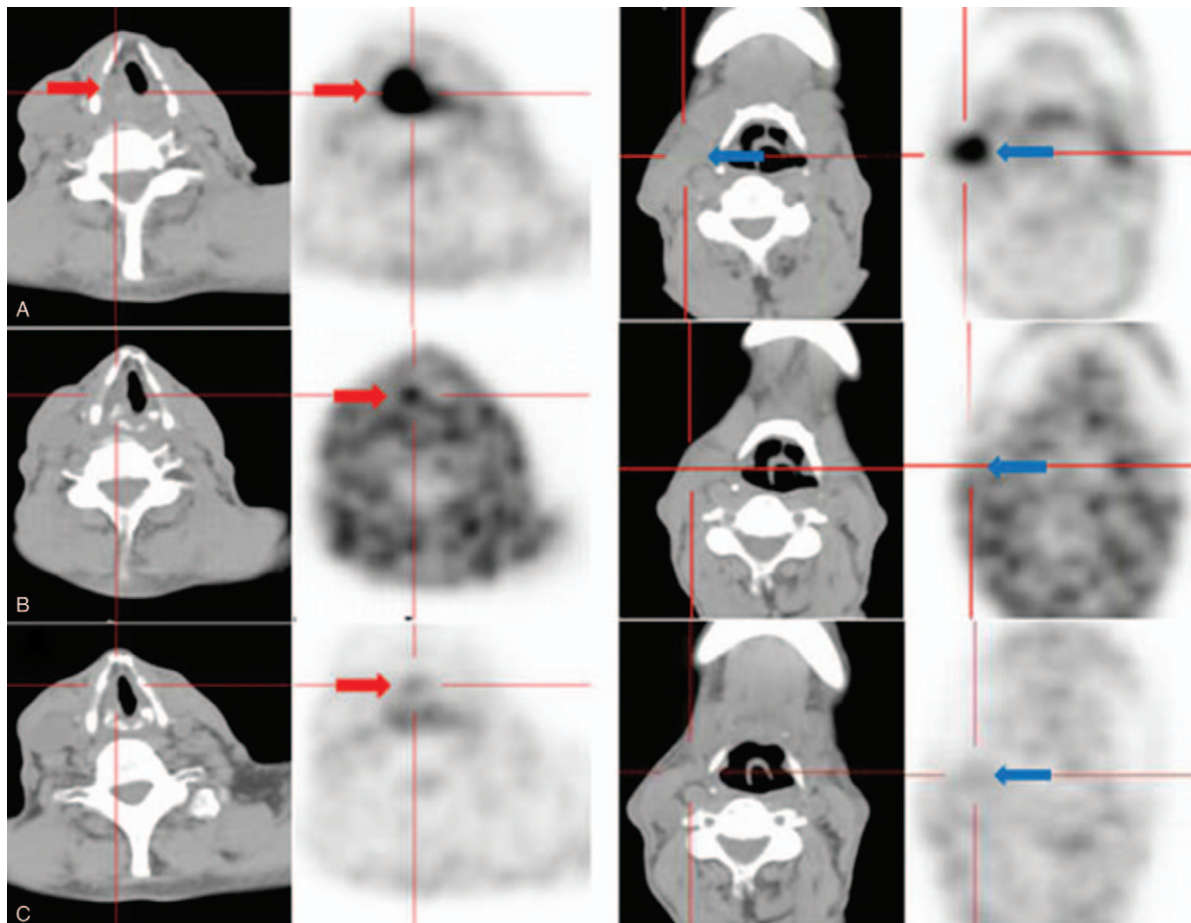
### 3.2. Mid-treatment FETNIM PET/CT findings

After 5 weeks of chemoradiation, mid-SUVmax ranged from 0.8 to 2.6 ( $1.381 \pm 0.4461$ , median, 1.35) in the primary tumor, and from 0.7 to 2.4 ( $1.309 \pm 0.3796$ , median, 1.3) in MLN. The magnitude of tumor hypoxia varied during the course of chemoradiation. The changes of FETNIM uptake on primary lesions and MLNs were shown in Figure 4. During treatment, mid-SUVmax decreased significantly both in the primary tumor ( $t = 8.083$ ,  $P < .001$ ) and MLN ( $t = 6.808$ ,  $P < .001$ ) compared to pre-SUVmax. There were 7 patients who had detectable FETNIM distribution before treatment, 2 patients (cut-off: 2.15) in primary tumor, and 5 (cut-off: 1.65) in MLN. There was no new hypoxic or increased SUVmax disease observed in either primary tumor or MLN after 5 weeks of treatment. Figure 1C showed that FETNIM uptake in primary tumor was similar to that of background (red arrow), and remained undetected in MLN (blue arrow) after 5 weeks therapy. Figure 2B showed persistent FETNIM uptake in MLN (red arrow), but undetected in primary tumor (blue arrow) after 5 weeks therapy.

### 3.3. Patient outcome analysis

Of all patients, 9 had local failure, 6 had regional failure, 7 developed distant metastases, and 10 died with a median follow-up of 54 (11–120) months. The 5-year LC, RC, DMFS, and OS rates were 55%, 66.7%, 64.7%, and 55% for all of the patients. Patients having tumors with high primary pre-SUVmax had significantly worse LC (56.3% vs 87.5%,  $P = .046$ ) and OS (43.8% vs 87.5%,  $P = .023$ ) than other patients, as shown in





**Figure 1.** A patient with hypopharyngeal cancer. (A) Pre-FDG PET/CT: primary tumor (red arrow), lymph node metastasis (blue arrow). (B) Pre- $^{18}\text{F}$ -fluoroerythronitroimidazole integrated positron emission tomography and computed tomography (FETNIM PET/CT): highly focally increased and visually detectable uptake in primary tumor (red arrow), but FETNIM uptake in lymph node metastasis similar to that of background (blue arrow). (C) Mid-FETNIM PET/CT: FETNIM uptake in primary tumor similar to that of background (red arrow), remain undetectable in lymph node metastasis (blue arrow).

Figure 5A and B. Patients having tumors with high mid-SUVmax had significantly worse DMFS (50% vs 84.6%,  $P = .049$ ) and OS (33.3% vs 73.1%,  $P = .028$ ) than other patients, as shown in Figure 5C and D.

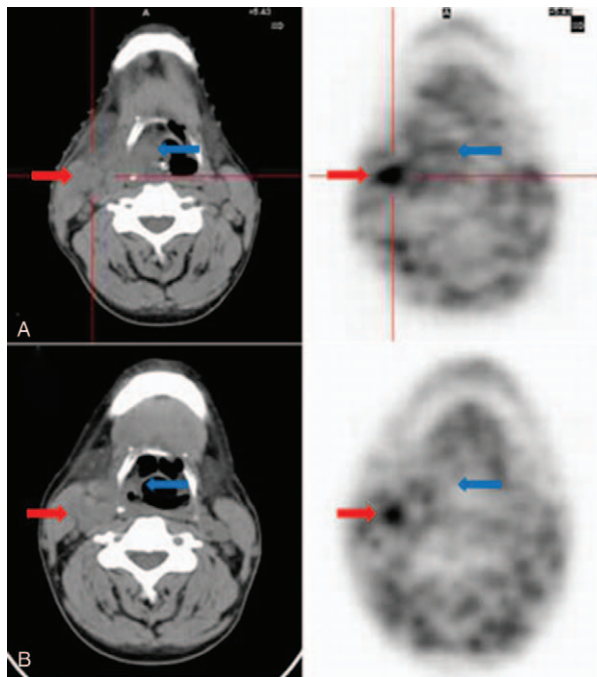
A Cox proportional hazards multivariate model of outcome was constructed to evaluate the pre-SUVmax of primary tumor, pre-SUVmax of MLN, age, sex, smoking, T stage, N stage, tumor grade, tumor site, and mid-SUVmax as predictors of OS. (If mid-SUVmax of either primary or MLN was no less than its cut-off, we defined these patients in high mid-SUVmax group.) The results indicated that only tumor grade (HR: 8.711;  $P = .022$ ) and mid-SUVmax (HR: 4.865;  $P = .043$ ) were the significant predictors of OS in our patient population, as shown in Table 2.

#### 4. Discussion

PET/CT with hypoxia tracer imaging is a reliable noninvasive method to quantify tumor hypoxia repeatedly and personally. To date, there is no standardized parameter and threshold to define tumor hypoxia on PET/CT images. In the present study, we evaluated the intensity of hypoxia using the SUVmax as the hypoxia discriminator at 2 hours after injection  $^{18}\text{F}$ -FETNIM, which predicted the OS in patients with non-small cell lung

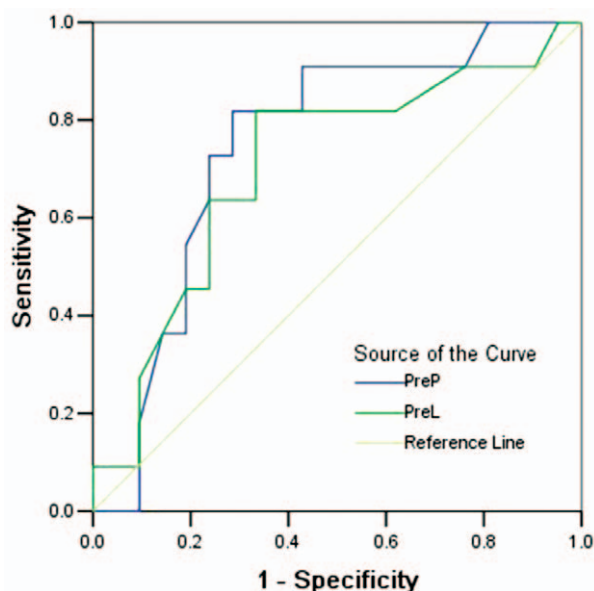
cancer in our previous study.<sup>[21]</sup> We separately define the thresholds of SUVmax in primary tumor and MLN to quantify the hypoxia owing to the heterogeneity of hypoxia. Because hypoxia is associated with a poor prognosis in HNSCC, the threshold was analyzed based on 5-year OS. The present study has indicated that FETNIM PET/CT is a promising biomarker to stratify patients at increased risk from OS, who would benefit from more aggressive treatment strategies.

Hypoxia heterogeneous is an important characteristic in tumor. The distribution of hypoxia differs from patient to patient, tumor to tumor, even spatial-temporal dynamics difference intratumor. In the present study, pre-treatment FETNIM PET/CT has showed the hypoxia intensity remarkably differs among individuals. To compare the difference of hypoxia between primary tumor and MLN, patients with N+ were enrolled in the study. The pre-SUVmax of primary tumor was higher than MLN. However, there was no significant difference to be found ( $P = .06$ ), which may be generated from limited sample. As far as the same patient was concerned, the intense hypoxia in primary tumor was not in accordance with MLN. In the present study, hypoxia was observed in primary tumors in some patients but not in MLN (Fig. 1), whereas it was reversed in other patients (Fig. 2). This is in agreement with the results



**Figure 2.** Another patient with hypopharyngeal cancer. (A) Pre-<sup>18</sup>F-fluoroerythronitroimidazole integrated positron emission tomography and computed tomography (FETNIM PET/CT): highly increased and visually detectable uptake in a lymph node metastasis (red arrow), contrarily, FETNIM uptake in primary tumor similar to that of background (blue arrow). (B) Mid-FETNIM PET/CT: persistent FETNIM uptake in the lymph node metastasis (red arrow), remain undetectable in primary tumor (blue arrow).

previously published. Mortensen et al<sup>[13]</sup> showed in 9 of 30 patients that there was no correlation between the hypoxia of the primary tumor and a lymph node on FAZA PET/CT imaging. Lee et al<sup>[25]</sup> reported on FMISO PET/CT, 7 of 20 patients were



**Figure 3.** The receiver operator characteristic curves of SUVmax for predicting survival.

positive only in lymph nodes but negative in primary, and 2 of 20 patients were positive only in primary tumor but negative in lymph nodes. These findings indicated that hypoxia in the primary tumor cannot represent the oxygenation status of the lymph node.<sup>[13]</sup> The advantage of FETNIM PET/CT is to identify the hypoxia individual tumor or patients. The heterogeneity of hypoxia in primary tumor and lymph node may be caused by variations in structure, local microenvironmental factors, and other factors within the primary disease and its draining lymph nodes.<sup>[26]</sup> It seems to be appropriate to escalate radiation dose for hypoxic areas, not only in primary tumor but also in lymph nodes, to make sure that all hypoxic cells are targeted.

Hypoxia in tumor is well known to be a dynamic process, especially during the course of chemoradiotherapy. In the present study, repeated FETNIM PET/CT scan was performed at the later treatment time points. As expected, the SUVmax decreased significantly after 5 weeks of chemoradiotherapy in both primary tumor and MLN compared to pretreatment baselines. We observed hypoxia disappearance in the majority of patients. On mid-treatment FETNIM PET/CT scans, 2 of 32 primary tumors had detectable hypoxia, and 5 of 32 patients had persistent detectable abnormal uptake in MLN. No lesion had increased uptake of FETNIM or new hypoxia area. Even without hypoxia-targeting therapy, resolution of hypoxia at the later treatment time points (4–6 weeks) has been described in previous FMISO PET/CT studies. Lee et al<sup>[25]</sup> found 16 of 18 patients had complete resolution of the hypoxia tracer uptake on FMISO PET/CT imaging after 4 weeks of RT plus chemotherapy in patients with HNC. The results of Wiedenmann et al<sup>[11]</sup> showed that the number of patients with hypoxic lesions decreased to 3 of 11, and the intensity of hypoxia, the ratio of the maximum SUV in the tumor to the mean SUV in contralateral neck musculature (TBRmax) on FMISO PET/CT, significantly decreased from 1.94 (pretreatment) to 1.27 ( $P=.003$ ) in week 5 of chemoradiotherapy. Zips et al<sup>[23]</sup> found that 10 of 24 patients remained hypoxic with a very small hypoxic subvolume at 50 to 60Gy of chemoradiotherapy. At the late phase during treatment, marked reduction in the level and the extent of hypoxia is caused by tumor shrinking significantly and reoxygenation occurs during fractionated radiotherapy over time, which could alter distribution of hypoxia and sensitivity to treatment.<sup>[11,23,25]</sup> It seems difficult to define the subvolume with little residual hypoxia area to boost the radiation dose. Therefore, at the late phase of the treatment, trying to escalate the dose of hypoxic subvolumes may be unfeasible. The study suggested that it may be an optimal timing for other hypoxia modification strategies including delivering the hypoxia-sensitize drugs, increasing oxygen level and supply.

Preclinical evidence has shown that treatment-induced reoxygenation may directly affect therapeutic response and prognosis.<sup>[27]</sup> In the present study, with a relatively long period of a median follow-up of 54 months, patients having tumors with high primary pre-SUVmax had significantly worse LC and OS than other patients only on univariate analysis, as evidenced by their lack of significance on multivariate analysis. The tumor grade and residual hypoxia after 5-week chemoradiotherapy have predictive value for 5-year OS both on univariate and multivariate analysis. The findings indicated that the persistent hypoxia at the later phase of treatment is even more important than pretreatment hypoxia in tumor. The present study emphasized that it is necessary to monitor hypoxia change and its effect on clinical outcome during treatment. The data of the

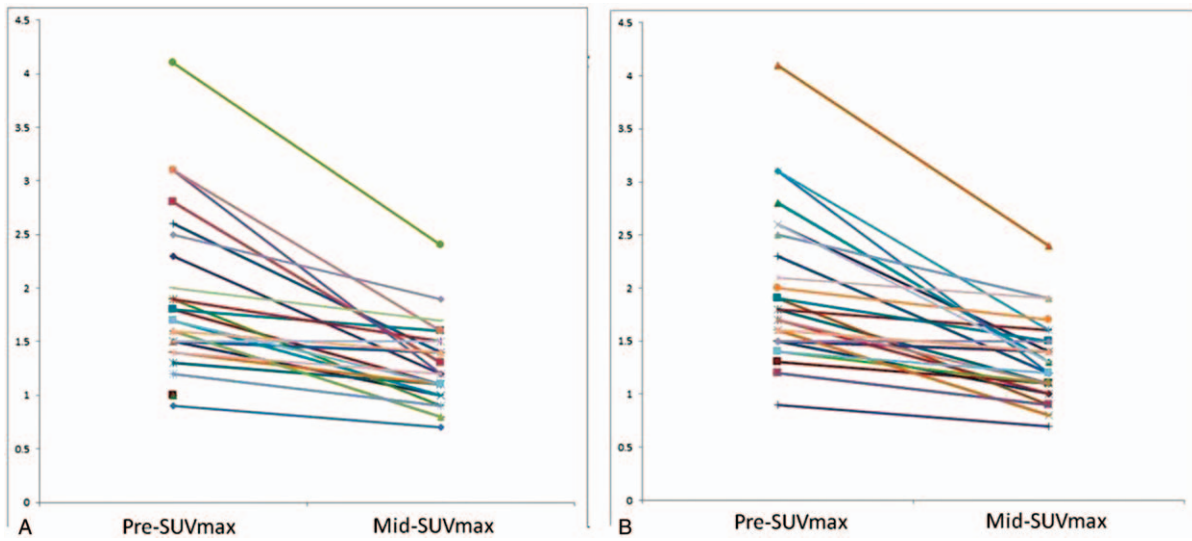


Figure 4. Changes of fluoroerythronitroimidazole uptake before and mid-treatment on primary lesions (A) and lymph nodes (B).

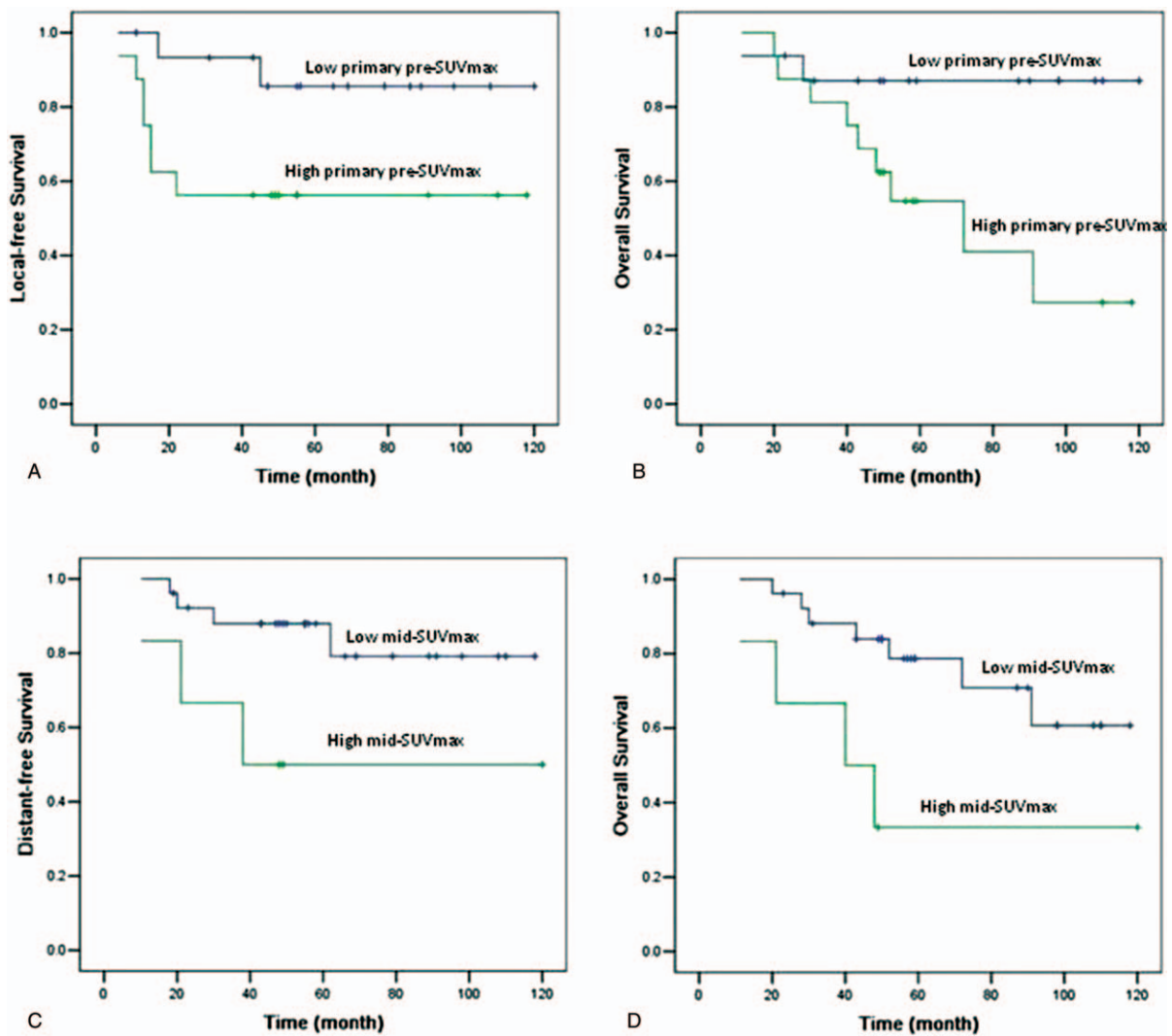


Figure 5. Survival identified by SUVmax. (A) Pre-SUVmax for local control. (B) Pre-SUVmax for overall survival (OS). (C) Mid-SUVmax for distant metastatic-free survival. (D) Mid-SUVmax for OS.



**Table 2**  
Results of multivariate analysis.

	Wald	HR	P
Grade	5.237	8.711	.022
Mid-SUVmax	4.112	4.865	.043

HR = hazard ratio.

prognostic value of the hypoxia change from repeated hypoxia PET imaging have been sparse with varying results. Zips et al<sup>[23]</sup> performed serial FMISO PET/CT imaging at 4 time points during treatment: baseline, 8 to 10 Gy, 18 to 20 Gy, 50 to 60 Gy. They only analyzed the hypoxia correlations with local control. The first and fourth PET/CT image parameters were only significantly associated with local recurrence on univariate Cox analysis. The hypoxic volumes of the second and third images were predictors of local recurrence on both uni- and multivariate Cox analysis. Wiedenmann et al<sup>[11]</sup> assessed tumor hypoxia in weeks 0, 2, and 5 of chemoradiotherapy by FMISO PET/CT, which showed a significant lower local control probability for more hypoxic than less hypoxic tumors in week 0 and 2. They only provided with the results on Kaplan-Meier analysis. Lee et al<sup>[25]</sup> did not observe treatment failure in 2 patients who showed evidence of residual tumor hypoxia on FMISO PET/CT imaging after 40 Gy of RT plus chemotherapy regimen. But they did not analyze the prognostic value of hypoxia change based on statistical analysis. The time point of repetitive hypoxic imaging, hypoxic parameter, threshold of defining tumor hypoxia, and follow-up period were different in the previous studies with small samples, which may explain the large variation in the results. The predictive value of hypoxia change should be evaluated in further studies.

## 5. Conclusions

In this study, the findings provide important information of hypoxia heterogeneity in primary tumor and MLN. FETNIM-uptake significantly decreased at later phase of chemoradiotherapy. Our data also have shown that persistent hypoxia during treatment predicted poor OS. This study provides evidence that FETNIM PET/CT is a reliable dynamic scan to select appropriate patients and optimal timing in hypoxia-adapted therapeutic regimens, which contribute to precise targeting hypoxia.

### 5.1. Limitations

The present study has several limitations. The major limitation is that the low number of persistent hypoxia patients at later phase of the treatment may have led to the deviation of the results. Although we enrolled the patients with strict criterion suitable for concurrent chemoradiotherapy including N+, PS 0-1, and age from 18 to 70 years, the patient cohort was homogenous with primary site, stage, and grade. Additionally, we evaluated the hypoxia change only at intensity level but not at spatial extent and selected 1 parameter as the hypoxia discriminator.

## Author contributions

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**Funding acquisition:** Man Hu.

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**Supervision:** Jinming Yu.

**Validation:** Man Hu.

**Visualization:** Min Li.

**Writing – original draft:** Man Hu.

**Writing – review & editing:** Nancy Y. Lee, Felix Ho, Ming Lian.

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