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Tumor Hypoxia Detected by ^{18}F-fluoromisonidazole Positron Emission Tomography (FMISO PET) as a Prognostic Indicator of Radiotherapy (RT)

IZUMI TACHIBANA[1], YASUMASA NISHIMURA[1], KOHEI HANAOKA[2], MASAHIRO INADA[1], KOHEI FUKUDA[1], HITOSHI TATEBE[1], KAZUKI ISHIKAWA[1], KIYOSHI NAKAMATSU[1], SHUICHI KANAMORI[1] and MAKOTO HOSONO[2]

[1]*Department of Radiation Oncology, and* [2]*Institute of Advanced Clinical Medicine, Kindai University of Medicine, Osakasayama, Japan*

Abstract. *Background/Aim: ^{18}F-misonidazole positron emission tomography (FMISO PET)/computed tomography (CT) obtained before and during radiotherapy (RT) was analyzed as to whether it could predict clinical outcome. Patients and Methods: Twenty-two patients were included. FMISO PET/ CT was performed twice before RT and at a dose of approximately 20 Gy/10 fractions. FMISO maximum standardized uptake values (SUV_{max}), the tumor-to-muscle ratios (T/M), and hypoxic volume (HV) in gross target volumes were measured. Results: Of the 22 tumors, 18 had hypoxic areas (SUV_{max} ≥1.60) before RT. SUV_{max}, T/M, and HV on the first PET/CT were significantly correlated with initial tumor response, although the values during RT were not related to the response. The overall survival and loco-regional control rates of patients below cut-off values were significantly better than those above the cut-off values. Conclusion: Tumor hypoxia detected by FMISO PET/CT before RT may predict clinical outcome.*

Hypoxic tumor cells are considered radioresistant and/or chemoresistant. In addition, hypoxia leads to metastasis with high frequency. Therefore, tumor hypoxia has been regarded as a poor prognostic factor in several cancers (1). ^{18}F-fluoromisonidazole positron emission tomography (FMISO PET) has been investigated as a non-invasive method of determining tumor hypoxia (2). Thus far, there are few reports that have revealed a correlation between FMISO PET and clinical results mainly in head and neck (H&N) cancer (3-6). Rajendran *et al*. reported that pretherapy FMISO PET uptake showed a strong trend to be an independent prognostic measure in the study of 73 patients with locally advanced H&N cancer (3). Kikuchi *et al*. analyzed clinical results of 17 patients with H&N cancers, and demonstrated that the disease specific survival of patients with high maximum standardized uptake values (SUV_{max}) of FMISO was significantly lower than those with low FMISO uptake (4). Similarly, Dirix *et al*. reported that H&N cancers with tumor to blood ratio (T/B) ≥1.45 before radiotherapy (RT) or with T/B ≥1.17 at 30 Gy of RT exhibited poor disease-free survival rates (5). Eschmann *et al*. compared FMISO uptake with tumor response and local recurrence for 26 patients with H&N cancers and 14 patients with non-small lung cancer. They reported that all H&N cancers with SUV_{max} >2.0 or tumor-to-muscle ratios (T/M) >1.6 recurred after therapy (6). For non-small lung cancer, all tumors with T/M>2.0 showed poor response to treatment (6). Thus, the most predictive hypoxic indicator still remains to be determined.

Over the past 15 years, positron emission tomography/ computed tomography (PET/CT) has grown and provided more accurate identification of the anatomical site than PET alone (7). Most of these studies, excluding Kikuchi's and Dirix's reports, used FMISO PET alone instead of PET/CT (4, 5).

In our previous report on FMISO PET/CT, we determined that the appropriate timing of FMISO examination was 180 minutes after injection of FMISO (8). Furthermore, the threshold of hypoxia was defined as 1.60 SUV_{max} in our F-MISO PET/CT system based on SUV_{max} of normal muscles (8). We continued the clinical trial of F-MISO PET/CT for several tumors. In the present study, we analyzed whether F-MISO PET/CT could predict clinical outcome of RT.

Correspondence to: Dr. Izumi Tachibana, Department of Radiation Oncology, Kindai University of Medicine, 377-2, Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan. Tel: +81 723660221 (ext. 3132), Fax: +81 723682388, e-mail: izu917@med.kindai.ac.jp

Key Words: Tumor hypoxia, ^{18}F-misonidazole, PET/CT, radiotherapy, reoxygenation.

Table I. *Patients and tumor characteristics.*

No.	Age/ Gender	Primary site	Stage/ Histology	Tumor length	RT dose	Chemotherapy regimen	1st SUV_{max}	1st HV (cc)	1st T/M	Response
1	65/M	Esophagus	T3 N0 M0/Sq	37 mm	60Gy/30fr	CDDP, 5-FU	1.73	0.1	1.24	CR
2	65/M	Esophagus	T4b N1 M0/Sq	70 mm	50Gy/25fr**	CDDP, 5-FU	2.00	0.2	1.80	non-CR
3	43/F	Esophagus	T3 N3 M0/Sq	80 mm	60Gy/30fr	CDDP, 5-FU	2.06	8.7	1.81	non-CR
4	62/M	Esophagus	T4b N2 M0/Sq	75 mm	50Gy/25fr**	CDDP, 5-FU	2.49	0.6	1.79	non-CR
5	72/M	Esophagus	T3 N1 M0/Sq	30 mm	60Gy/30fr	CDDP, 5-FU	3.06	75.6	2.66	non-CR
6	73/M	Esophagus	T3 N2 M0/Sq	28 mm	50Gy/25fr **	CDDP, 5-FU	3.12	6.7	2.38	non-CR
7	72/F	Anal canal	T2 N0 M0/Sq	45 mm	59.4Gy/33fr	5-FU, MMC	2.44	7.6	1.77	CR
8	56/M	Anal canal	T4 N1 M0/Ad	45 mm	45Gy/25fr**	5-FU, MMC	2.60	65.8	1.81	non-CR
9	48/M	Nasopharynx	T1 N2 M0/Sq	22 mm	70Gy/35fr	CDDP	1.34	0.0	1.06	CR
10	72/M	Nasopharynx	T1 N2b M0/Sq	16 mm	70Gy/35fr	CDDP	1.35	0.0	1.08	CR
11	64/M	Nasopharynx	T4 N2 M0/Sq	36 mm	70Gy/35fr	CDDP	1.38	0.0	1.29	CR
12	36/M	Nasopharynx	T4 N1 M0/Sq	42 mm	70Gy/35fr	CDDP	1.71	0.1	1.61	CR
13	49/M	Nasopharynx	T2 N1 M0/Sq	35 mm	70Gy/35fr	CDDP	1.90	0.1	1.30	CR
14	46/M	Nasopharynx	T3 N2c M0/Sq	35 mm	70Gy/35fr	CDDP	2.06	0.3	1.86	CR
15	55/M	Nasopharynx	T3 N2 M0/Sq	35 mm	70Gy/35fr	CDDP	2.43	0.5	1.74	non-CR
16	57/M	Lung	T4 N3 M0/Sq	68 mm	60Gy/30fr	CDDP, VNR,Nim	1.60	0.0	1.95	non-CR
17	67/M	Lung	T3 N1 M0/Sq	41 mm	45Gy/25fr**	CBDCA, TXL	1.80	0.1	1.48	non-CR
18	75/M	Maxilla sinus	T4a N1 M0/Sq	65 mm	42Gy/21fr*	CDDP, 5-FU	2.10	2.7	1.93	non-CR
19	60/F	Uterine body	recurrence/Ad	48 mm	64.4Gy/35fr	None	2.72	42.3	1.84	non-CR
20	64/M	Pancreas	T4 N0 M0/Ad	45 mm	50.4Gy/28fr	S-1	1.83	0.1	1.34	non-CR
21	67/M	Supra glottis	T2 N0 M0/Sq	22 mm	72.8Gy/56fr	None	1.36	0.0	1.39	CR
22	62/M	Oropharynx	T3 N0 M0/Aq	42 mm	70Gy/35fr	CDDP, Cet	5.72	18.5	4.14	non-CR

*RT was terminated due to severe acute toxicities. **Preoperative chemoradiation therapy. Ad: Adenocarcinoma; Sq; squamous cell carcinoma; CDDP: cisplatin; 5-FU: fluorouracil; MMC: mitomycin C; VNR: vinorelbine; Nim: nimotuzumab; CBDCA: carboplatin; TXL: taxol; Cet: cetsuximab; CR: complete response.

Patients and Methods

Patients. Between November 2009 and April 2015, 22 patients scheduled for RT for primary or recurrent tumors were enrolled in this prospective study. Eligible patients had histologically proven gross tumor volume, with performance status (PS) level of 0-1 and age from 20 to 80 (8). Patient and tumor characteristics are summarized in Table I. Twenty-two patients included 10 with H&N cancer, nine with gastrointestinal cancer, two with non-small cell lung cancer, and one with uterine body cancer. The initial tumor response was evaluated by CT, MRI, and clinical examination 1-2 months after the end of treatment according to the RECIST criteria (version 1.1) (9). In addition, histological response was evaluated for five tumors resected after preoperative chemo-radiotherapy (CRT). The study protocol was approved by the ethical committee of Kindai University of Medicine. All patients signed informed consent on FMISO PET/CT examination before entering the study.

FMISO protocol and analysis. The detailed method of PET/CT examination and FMISO synthesis were written in our previous report (8). Briefly, FMISO PET/CT was performed twice before RT and during fractionated RT at approximately 20 Gy/10 fractions. Patients were injected intravenously with 7.4 MBq/kg of F-MISO. In this report, we analyzed PET/CT at 180 min after administration of FMISO because pictures at 180 min after administration of FMISO were revealed to be of higher contrast than those at 100 min in the first ten patients (8). FMISO value of equal to or higher than 1.60 SUV was regarded as indicating hypoxia based on our previous study (8).

Data were analyzed and processed with a Siemens e.soft workstation to measure SUV (8). As hypoxic indicators, FMISO SUV_{max}, T/M ratio, and hypoxic volume (HV) in gross target volumes were measured. The highest SUV_{max} of the primary tumor and metastatic lymph nodes was used for analysis. T/M ratio was the SUV_{max} of the tumor divided by the SUV_{max} of muscle. HV means hypoxic volume that is tumor volume with FMISO SUVmax equal to or greater than 1.60. Initial tumor response was evaluated 1-2 months after RT, and it was categorized into CR (complete response) or non-CR, including partial response, no response, and progressive disease.

Radiation therapy and chemotherapy. For all 22 patients, FMISO PET/CT within two weeks before the start of RT was performed, but this information was not used for the treatment planning. Seventeen of all patients were treated as definitive RT of planned total dose of 50.4-72.8 Gy/28-56 fractions (median 70 Gy), although one patient terminated RT at 42 Gy due to severe acute toxicity caused by chemotherapy. The remaining five patients, three with esophageal, one with lung, and one with anal canal cancer were treated with preoperative CRT of 45-50 Gy/25 fractions, and curative resection could be done following CRT for all these patients. Except for two patients, the remaining twenty patients

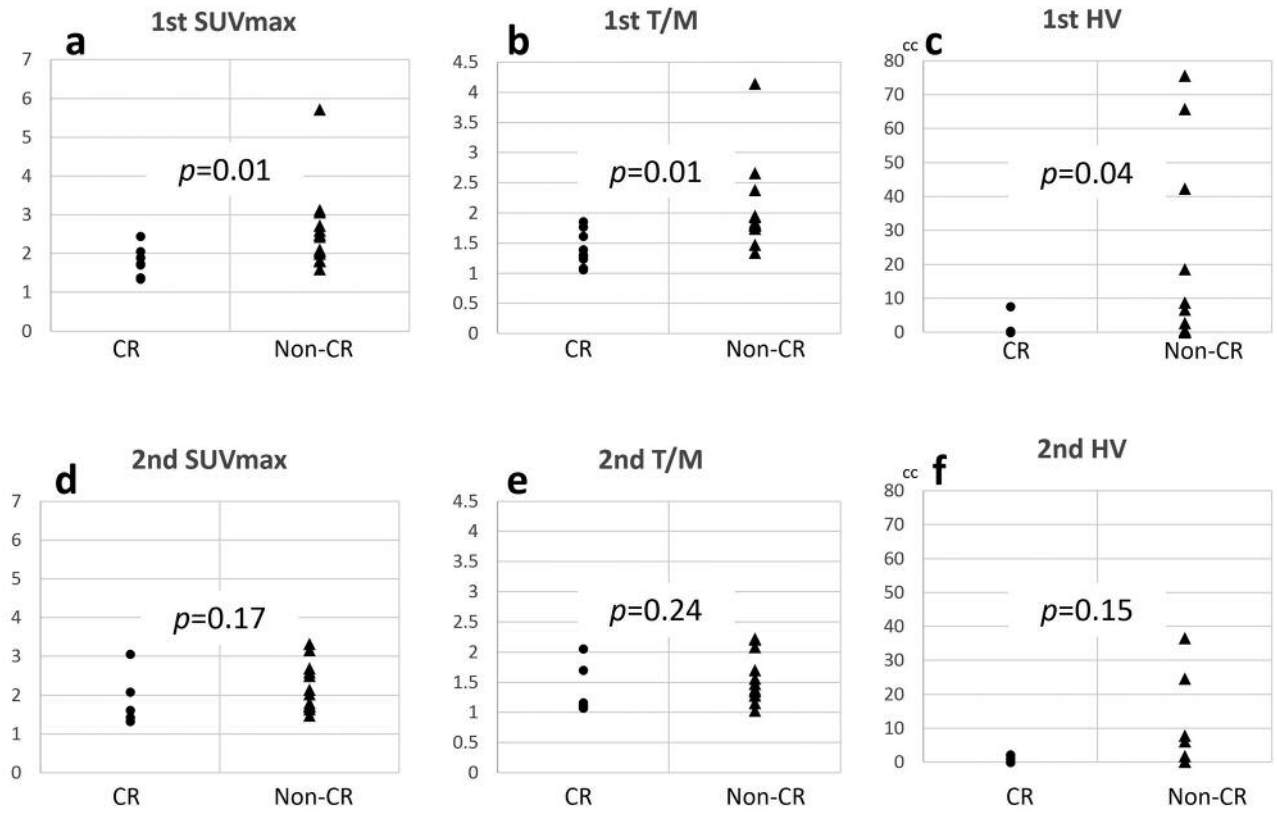

Figure 1. *Differences in hypoxic indicators at the 1st and 2nd FMISO PET examinations between the CR (n=9) and the non-CR groups (n=13). a: SUV_{max} at 1st FMISO examination. b: T/M ratio at 1st FMISO examination. c: HV at 1st FMISO examination. d: SUV_{max} at 2nd FMISO examination. e: T/M ratio at 2nd FMISO examination. f: HV at 2nd FMISO examination.*

were treated with concurrent CRT. The regimens of chemotherapy are summarized in Table I. Furthermore, one patient with supraglottic cancer was treated with accelerated hyperfractionated radiotherapy.

Follow-up and statistical analysis. The probability of survival and loco-regional control rate were estimated using the Kaplan-Meier method with significance assessed by the log-rank test. Survival was calculated from the first date of RT. Overall survival considered deaths due to any cause. Loco-regional control rate considered any recurrences in the primary site or regional lymph nodes as an event. Loco-regional control and distant progression was evaluated every 3-4 months for more than 5 years by clinical examination and CT scan with or without neck and pelvis MRI. Clinical outcome of all surviving patients was analyzed in March 2017; the median follow-up time for surviving patients was 47 months (range=20-80 months).

Differences in SUV_{max}, T/M ratio, and HV between CR and non-CR groups were analyzed by the unpaired student's *t*-test. A *p*-value of less than 0.05 was considered significant. The receiver operating characteristic (ROC) curve was used for finding the cut-off values of SUV_{max}, T/M ratio, and HV for predictor of prognosis (10).

Results

Eighteen of the 22 tumors had hypoxia (SUV_{max} ≥1.6) before RT, but the remaining three nasopharyngeal tumors and one supraglottic tumor did not exhibit any hypoxic areas. For 17 of the 22 patients, FMISO PET/CT was performed twice before and during fractionated RT. For the remaining five patients, secondary FMISO PET examinations were omitted due to acute renal failure for one patient and absence of hypoxic areas at the 1st FMISO PET examination for four patients. Except for one nasopharyngeal tumor, 16 of the 17 tumors showed a decrease in SUV_{max}, T/M ratio, or HV at the 2nd FMISO PET examination indicating reoxygenation. In terms of initial tumor response, nine tumors demonstrated CR and 13 tumors did not.

Figure 1 shows the differences in hypoxic indicators at the 1st and 2nd FMISO PET examinations between the CR (n=9) and the non-CR groups (n=13). SUV_{max}, T/M ratio, and HV at the 1st examination were significantly higher in the non-CR group than in the CR group. The mean±standard deviation

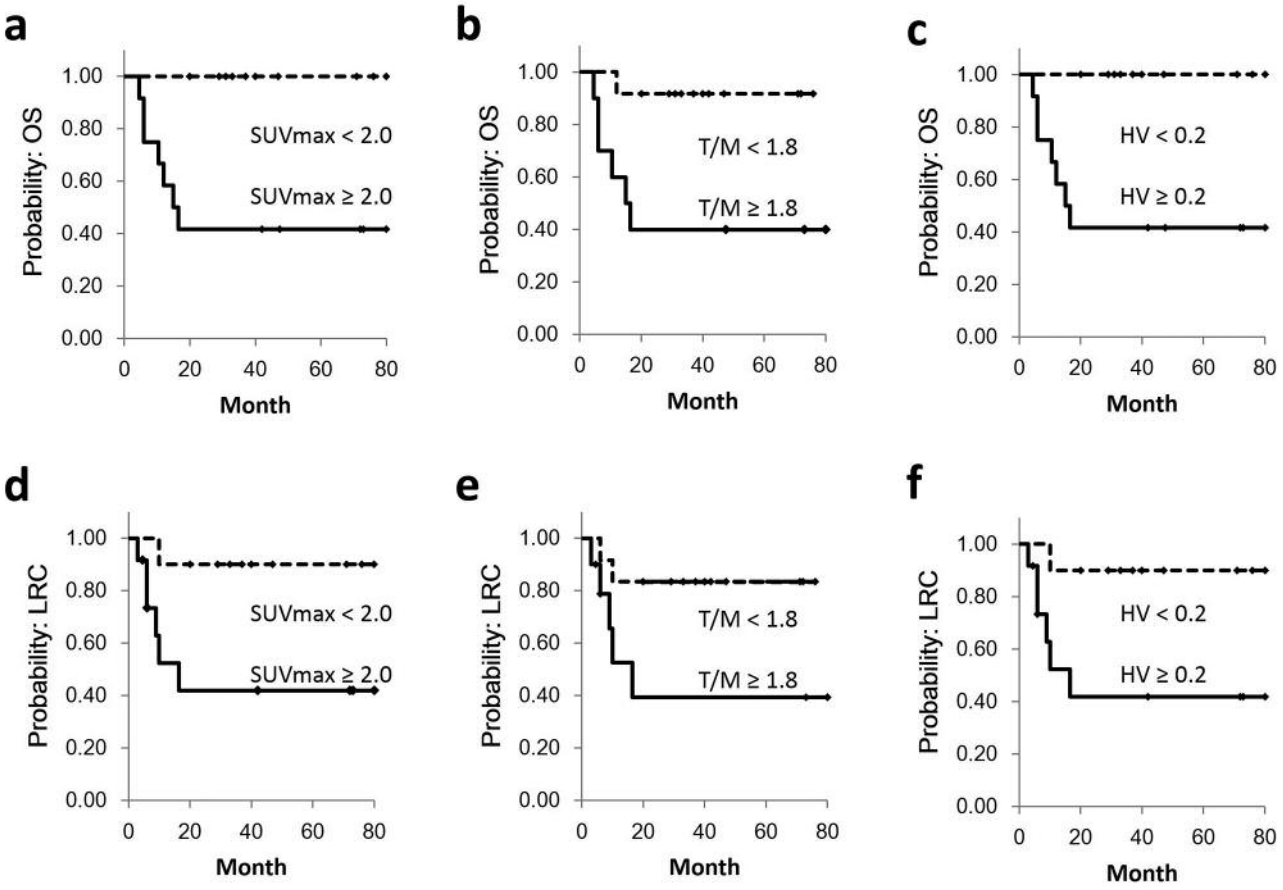

Figure 2. *The receiver operating characteristic (ROC) curve was shown for finding cut-off values of SUV_{max}, T/M ratio, and HV for predictors of prognosis. a: ROC curves at 1st F-MISO PET/CT. b: ROC curves at 2nd F-MISO PET/CT examination. The AUC at 1st FMISO was greater than that at 2nd FMISO. TPF: True positive fraction; FPF: false positive fraction.*

(SD) of SUV_{max} at the 1st FMISO PET for the non-CR group and CR-group were 2.4±1.0 and 1.7±0.4 (p=0.01), respectively. Similarly, the mean±SD of the T/M ratio and HV at the 1st FMISO PET in the non-CR group and CR group was 1.8±0.7 and 1.3±0.3 (p=0.01), and 2.7±25.6 and 0.1±2.4 (p=0.04), respectively. On the other hand, no significant differences in hypoxic indicators on the 2nd F-MISO PET were observed between the CR group and the non-CR group.

Based on the initial tumor response (CR *versus* non-CR), we analyzed the ROC curve to determine a cut-off value. The ROC curves for each hypoxic indicator at 1st FMISO PET/CT and 2nd FMISO PET/CT are demonstrated. Each area under the curve (AUC) of the 1st FMISO is greater than that of the 2nd FMISO (Figure 2). Therefore, hypoxic indicators of the 1st FMISO PET seem to be more suitable as prognostic factors. There were no significant differences in AUC among SUV_{max}, T/M ratio, or HV on the 1st F-MISO PET/CT. The point on the curve closest to the (0, 1) point was determined as the best cut-off value. The cut-off values determined by the ROC analysis were 2.0 for SUV_{max}, 1.8 for T/M, and 0.2 for HV.

Using the cut-off values of hypoxic indicators, overall survival rate (OS) for patients with SUV_{max} <2.0 was significantly better than that for patients with SUV_{max} ≥2.0 (p=0.005) (Figure 3a). Moreover, the OS of patients with T/M <1.8 was significantly better than that of patients with T/M ≥1.8 (p=0.009) (Figure 3b). Similarly, the OS of patients with HV <0.2 was significantly better than that of patients with HV ≥0.2 (p=0.005) (Figure 3c). In terms of loco-regional control rate (LRC), significant differences for all parameters were observed (Figure 3d-f). The LRC for tumors with under the cut-off values were better than those with above the cut-off values (for SUV_{max}, T/M ratio, HV; p=0.022, 0.045, 0.022, respectively).

Case report. A representative case was a 62-year-old male with oropharynx cancer (T3N0M0) (Figure 4a-f). The SUV_{max}, T/M, and HV before RT were 5.72, 4.14, and 18.5,

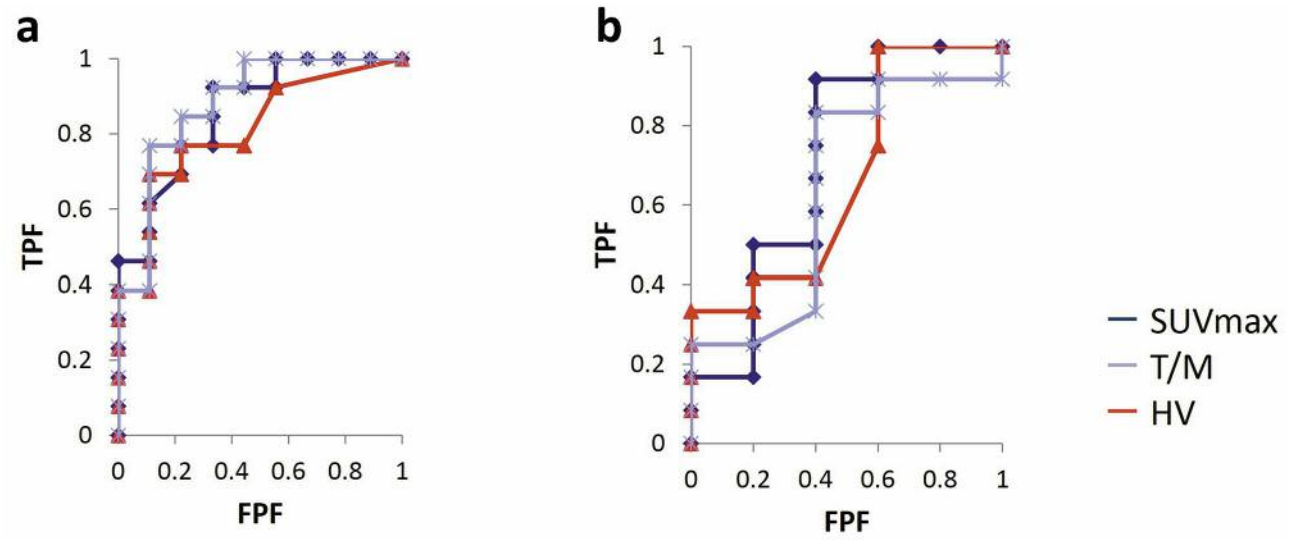

Figure 3. *The overall survival rates and loco-regional control rates according to hypoxic indicators in the 1st FMISO study. Hypoxic indicators were divided below or above the cut-off values. Overall survival rates for a: SUV_{max}, b: T/M ratio, and c: HV. Similarly, loco-regional control rates for d: SUV_{max}, e: T/M ratio, and f: HV.*

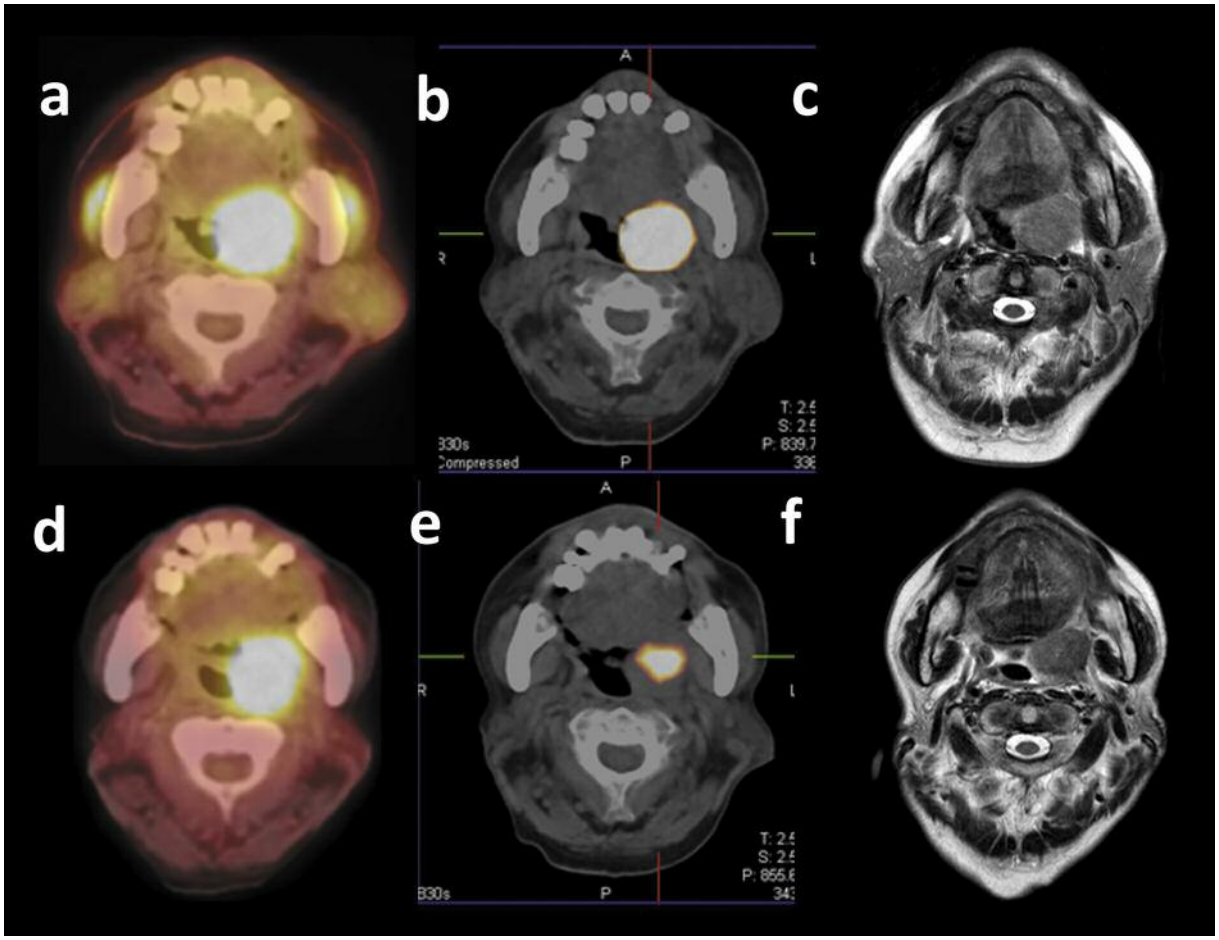

Figure 4. *Case1: A 62-year-old male with oropharynx cancer (T3N0M0) with strong FMISO accumulation at the first examination. a: FDG PET/CT before RT. b: FMISO PET/CT before RT. c: MRI before RT. d: FDG PET/CT after RT. e: FMISO PET/CT during RT. f: MRI after RT.*

respectively. The SUV_{max} of this tumor was the highest among all 22 tumors. At 20 Gy/10 fractions, all parameters of this patient decreased to 2.59, 1.70, and 1.8, respectively. This patient was treated with CRT of 70 Gy/35 fractions. As concurrent chemotherapy, cisplatin (CDDP, 80 mg/m^2) was given at 1 course, but severe leukopenia was noted. Thereafter, cetuximab (250 mg/m^2) was given weekly instead of CDDP. This tumor exhibited no tumor regression on MRI obtained one month after RT (Figure 4f), and retained high accumulation of FDG-PET/CT at 1.5 months after CRT (Figure 4d). Although salvage operation was performed for this patient after CRT, re-recurrence was noted soon after operation. This patient deceased 3 months after CRT.

Discussion

In the present study, we evaluated the relationship between three hypoxic indicators, SUV_{max} of FMISO, T/M ratio, and HV, and clinical outcomes of RT. In addition, the cut-off values of hypoxic indicators of FMISO PET as prognostic factors were determined. There were significant differences for hypoxic indicators between the CR group and non-CR group at 1st FMISO PET/CT. However, the difference between the two groups disappeared at 2nd FMISO PET/CT. After approximately 20 Gy of fractionated RT, all hypoxic indicators tended to decrease, probably due to reoxygenation, and the differences between the CR group and non-CR group at 1st FMISO PET/CT disappeared. Furthermore, the AUC on the ROC curve at 1st F-MISO PET was greater than that at 2nd F-MISO PET. Thus, hypoxic indicators before RT, not during RT, could predict initial tumor response.

Based on the ROC curve, the cut-off values were determined to be 2.0 for SUV_{max}, 1.8 for T/M, and 0.2 for HV. Using these cut-off values, assessment for OS and LRC was performed (Figure 3). There was a significant difference between patients with under and above the cut-off values for the three indicators. These cut-off values were useful as prognostic indicators for both OS and LRC. As shown in Figure 3, the prognostic values of the three hypoxic indicators were similar to each other. Clinically, SUV_{max} of FMISO may be the simplest indicator because its calculation is easy and influence from other parameters is omitted.

Rajendran reported that the tumor-to-blood ratios of FMISO (T/B ≥1.5) and hypoxic volume before RT were strong independent predictors in 73 patients with H&N cancers (3). This report included the largest number of patients to our knowledge. It concluded, similar with the present study, that high accumulation of FMISO PET and large hypoxic area before RT suggest poor prognosis. Limitations of our study were that several cancers with limited numbers of patients were included. In addition, treatment protocols were not the same for all patients. Thus, there are limitations for analysis of treatment effects and overall survival rate.

In addition to the prognostic value, FMISO PET/CT may be useful for radiation planning. We are now able to treat cancers using higher accuracy radiation therapy and advanced intensity modulated radiation therapy (IMRT) as dose painting. Using simultaneous integrated boost, dose escalation to severely hypoxic areas can be done, theoretically. Although some reports demonstrated dose painting RT plans up to a maximum tumor dose of 84-105 Gy using FMISO PET/CT (11), no clinical trials for dose escalation to hypoxic areas have been reported. A report on FMISO PET/CT in patients with H&N cancers revealed that hypoxia location were quite reproducible during 2 days (12). However, another report demonstrated that variability in spatial uptake can occur between repeat F-MISO PET scans (13). Thus, the reproducibility of tumor hypoxia remains still unclear. Moreover, one reason for not performing such clinical trials is reoxygenation of hypoxic areas during fractionated RT. In the present study, the mean SUV_{max} of the non-CR group decreased after fractionated RT indicating reoxygenation. Another limitation is that usual PET imaging is of insufficient spatial resolution. Therefore, dose escalation to hypoxic subvolumes of a tumor in FMISO PET/CT images obtained before RT seems inappropriate at present (14).

As dose escalation to markedly hypoxic sub-volume may be insufficient, change of treatment strategy should be considered. For case 1, a tumor with severe hypoxia, surgical resection may be better than definitive CRT. Furthermore, for these tumors, hypoxic cell sensitizers may be effective. For example, the radiosensitizer Nimorazole is currently standard therapy in head and neck cancer patients eligible for radiotherapy in Denmark (15). Moreover, doranidazole (PR-350), which is a hypoxic cell sensitizer, was reported to improve long term survival in patients with pancreatic cancer (16).

In conclusion, hypoxic indicators of FMISO PET/ CT obtained before RT can predict clinical outcome of RT. The cut-off values of hypoxic indicators were SUV_{max}: 2.0, T/M: 1.8, and HV:0.2.

Conflicts of Interest

None.

Acknowledgements

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