^{18}F-fluoromisonidazole (FMISO) and new PET system with semiconductor detectors and a depth of interaction (DOI) system for intensity-modulated radiation therapy (IMRT) for nasopharyngeal cancer

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Running title: FMISO and semiconductor PET for IMRT

Conflicts of Interest Notification

This study is from the “Future Drug Discovery and Medical Care Innovation Program,” which is a collaborative research project between Hokkaido University and Hitachi Co., Ltd.

Abstract

Purpose: The impact of a new type of positron emission tomography with semiconductor detectors (New PET) on an ^{18}F-fluoromisonidazole (FMISO)-guided intensity-modulated radiation therapy (IMRT) plan was investigated by comparing the plan with the use of a state-of-the-art PET/computed tomography system (PET/CT) in nasopharyngeal cancer (NPC) patients.

Methods and Materials: Twenty-four patients with non-NPC malignant tumors (control group) and 16 patients with NPC were subjected to FMISO-PET. The threshold of the tumor-to-muscle (T/M) ratio in each PET scan was calculated. The hypoxic volume within the gross tumor volume was determined using each PET ($_{NewPET}$GTVh and $_{PET/CT}$GTVh, respectively). Dose-escalation IMRT plans prescribing 84Gy to each GTVh were carried out.

Results: The threshold of the T/M ratio was calculated to be 1.35 for New PET and 1.23 for PET/CT. The mean volume of $_{NewPET}$GTVh was significantly smaller than that of $_{PET/CT}$GTVh (1.5±1.6cc vs. 4.7±4.6cc, respectively, P=0.0020). The dose-escalation IMRT plans using New PET were superior in dose distribution to those using PET/CT. Dose escalation was possible in all 10 New PET-guided plans but not in one PET/CT-guided plan, because the threshold dose to the brainstem was exceeded.

Conclusion: New PET was suggested to be useful for accurate dose escalation in FMISO-guided IMRT for patients with NPC.

Key words: radiotherapy, hypoxia, positron emission tomography, ^{18}F-fluoromisonidazole, semiconductor

Summary

The impact of a New PET on an FMISO-guided IMRT plan was investigated by comparing the plan with the use of a state-of-the-art PET/CT system in NPC patients. New PET was suggested to be useful for accurate dose escalation in FMISO-guided IMRT for patients with NPC.

Introduction

Hypoxia is well known as an important factor relating to radioresistance (1). In head and neck cancers, hypoxia has been shown to be associated with poor outcome (2). A recent simulation study showed that dose escalation to the hypoxic region would contribute to the tumor control probability (3). The development of a dose escalation technique using intensity-modulated radiation therapy (IMRT) or proton beam therapy is expected for use in treating patients with head and neck cancers, including nasopharyngeal cancer (NPC) (4, 5). Direct measurements using the Eppendorf electrode have been suggested as the gold standard for hypoxic measurement, but it is an invasive examination that is restricted to accessible tumors (6). A non-invasive approach to measuring the hypoxic region using positron emission tomography (PET) imaging has been developed and examined in previous studies (7).

^{18}F-fluoromisonidazole (FMISO) is one of the hypoxia tracers. Its binding to the molecules in viable hypoxic cells is known to be proportional to the level of hypoxia (8). PET using FMISO (FMISO-PET) has been expected to be usable for mapping of the hypoxic region in head and neck cancers (9). There have been several studies about the usefulness of FMISO-PET in the treatment planning for dose escalation in IMRT of

head and neck cancers (10-12).

The hypoxic region is likely to be small, and thus high spatial resolution is necessary for planning. We have shown that a prototype of a PET system with semiconductor detectors (New PET) has a spatial resolution of 2.3 mm, which is better than that of the conventional high-resolution whole-body PET system with bismuth germanium oxide (BGO) scintillation detectors (13). New PET was shown to be useful for delineating the uptake of NPC because of its sharper edge at the tumor boundary in ^{18}F-fluoro-deoxy-glucose (FDG) -PET images (14).

In this study, we established the threshold of FMISO normal uptake using New PET and a state-of-the-art whole-body PET-computed tomography (PET-CT) system with lutetium oxyorthosilicate (LSO) scintillation detectors and extended field of view (FOV) (TruePoint Biograph 64 with True V and high-resolution option, Asahi-Siemens, Tokyo, Japan) (PET/CT) and compared the hypoxic volumes visualized by New PET and PET/CT. We performed IMRT simulation planning for the dose escalation to the hypoxic region in NPC and compared the difference in dose volume histogram (DVH) between the plan using New PET and the plan using PET/CT. We also evaluated the predictive value of FMISO uptake before chemoradiotherapy for local control in patients with NPC.

Materials and methods

Patient characteristics

Our Institutional Review Board approved the protocol for this study in 2007. Between April 2008 and March 2011, 40 newly diagnosed head and neck cancer and brain tumor patients were subjected to FMISO-PET. The process used to select study patients is shown in a flowchart in Appendix 1. Sixteen patients among them had NPC (NPC group) and received FMISO-PET before any treatment. These patients received standard treatment, and were followed by radiation oncologists and oto-laryngologists in our hospital periodically. The status of local control and survival were investigated in this study. All patients in the NPC group received New PET, and twelve patients among them received both New PET and PET/CT.

Twenty-four patients with other tumors (10 brain tumors, 9 oral cancers, 4 thyroid cancers, and 1 laryngeal cancer) were defined as the control group in this study. The patients in the control group were examined with CT and magnetic resonance imaging (MRI) to prove that there was no abnormality in the nasopharynx or the posterior cervical muscle. In the control group, 14 patients were examined with New PET, and 14

patients were examined with PET/CT, and thus 4 were examined with both New PET and PET/CT. The median age was 64 years old (range: 40-78 y.o.) in patients examined with New PET and 67.5 years old (range: 56-83 y.o.) in patients examined with PET/CT. The number of males and females was 7 and 7, respectively, in patients examined with New PET, and 8 and 6, respectively, in patients examined with PET/CT.

Written informed consent for study participation was obtained from all patients before the FMISO-PET examination.

FMISO-PET scans

Details of the New PET system were described previously (13-15). In brief, the New PET system is equipped with small semiconductor detectors and a depth of interaction (DOI) system to obtain sufficient sensitivity and a higher spatial resolution.

FMISO-PET was performed with the New PET and with PET/CT. About 400 MBq of ^{18}F-FMISO was injected intravenously 4 hours before scanning. Details of the performances of these two scanners are listed in Appendix 2. In the patients who were subjected to both types of PET scan, the scan order was randomly determined and the scans were performed sequentially. We used dedicated fixation during PET scanning.

Threshold of the nasopharynx-to-muscle (N/M) ratio and the tumor-to-muscle (T/M) ratio

FMISO-PET images were registered to image analysis software (VOX-BASE, J-MAC SYSTEM, Sapporo). In the control group, the max value of standardized uptake value (SUVmax) in normal nasopharyngeal soft tissue was calculated using each PET scan image. Laterally displayed or fused CT images were used as the reference for localization. The region of interest (ROI) with radius 1 cm was placed in the left lateral, left medial, right medial, and right lateral position of posterior cervical muscle, and the average of SUV max of these ROIs was calculated. The nasopharyngeal SUVmax divided by the average of the SUVmax of the posterior cervical muscle ROIs was calculated and defined as the nasopharynx-to-muscle (N/M) ratio. The N/M ratio was calculated for both New PET and PET/CT. After confirming the normal distribution, we calculated the upper threshold of the normal N/M ratio as the average + 1.96 × standard deviation, which indicated the upper value of 95% confidence interval. Each upper threshold of the normal N/M ratio in New PET and PET/CT, respectively, was used as a threshold of the tumor-to-muscle (T/M) ratio in the patients with NPC.

The definition of the hypoxic region in nasopharyngeal cancer and the comparison of

hypoxic volume by the two systems

In the NPC group, all patients underwent CT (SOMATOM Sensation, Siemens) with individualized head, neck, and shoulder immobilization masks. Images from the CT scan with 2-mm slices were obtained for each patient. The CT images and FMISO PET images obtained by each PET scan were co-registered to make fusion images using three-dimensional radiation therapy planning software (Pinnacle3 v80m, Philips Radiation Oncology Systems, Fitchburg, WI). The gross tumor volume (GTV) was determined on the CT image, and other available images (i.e., magnetic resonance imaging or FDG-PET) were referenced. The hypoxic volume in GTV (GTVh) was determined as the volume that had a T/M ratio higher than the upper threshold using FMISO-PET. The hypoxic volumes in the GTV were named $_{NewPET}$GTVh and $_{PET/CT}$GTVh, respectively.

The dose-escalation IMRT simulation planning targeting the hypoxic volume

Ten NPC patients received both types of FMISO-PET examination and had abnormally high FMISO uptake. The dose-escalation IMRT simulation plans targeting the hypoxic volume were generated for these 10 patients. Pinnacle3 was used to make IMRT simulation plans.

The clinical target volume 1 (CTV1) was defined as the volume containing the GTV and any microscopic disease at risk. CTV 2 and CTV 3 were at high-risk and low-risk volume, respectively. A margin of 3 mm was added to each CTV and defined as the planning target volume (PTV1, PTV2, and PTV3, respectively). The prescription dose to the PTVs and the dose constraints to the organ at risk (OAR) are shown in Table 1. Eighty-four Gy was prescribed to the D95 of each GTVh in this simulation study. Hypoxia-based IMRT dose escalation plans were generated for 10 NPC patients who underwent standard-dose IMRT for their disease. We did not add the margin to expand the GTVh to the PTVh, in agreement with the procedure followed by Chao et al. (7) and Lee et al. (10).

Statistics

We used statistics software (JMP9, SAS Institute Inc. Cary, NC) to analyze the data. The W-test of Shapiro-Wilk was used to approve the normal distribution of the FMISO activity in the nasopharyngeal region in the control group. A two-sided Wilcoxon signed-rank test was used to compare the DVH parameters between plans. A significance P value of 0.05 was used.

Results

Threshold of the N/M ratio of New PET and PET/CT

The average ± standard deviation (SD) of the N/M ratio in the control group examined with New PET and PET/CT was 1.151 ± 0.103 and 1.054 ± 0.086, respectively. The distribution was approved to be normal by the W-test ($p=0.3902$ and $p=0.9993$, respectively). The upper threshold of the N/M ratio was calculated to be 1.35 with New PET and 1.23 with PET/CT. We also analyzed the 4 control cases on whom both types of PET were performed. The average of the N/M ratio and the upper threshold were 1.118 ± 0.042 and 1.20 with New PET, and 1.099 ± 0.044 and 1.18 with PET/CT, respectively.

Clinical Relevance in the NPC group

Thirteen of the 16 patients in the NPC group experienced abnormally high uptake of FMISO (Table 2).

Twelve patients in the NPC group received both types of PET examination, and the judgments regarding whether they had abnormally high uptake were fully consistent. Ten of the twelve patients receiving both types of PET examination had abnormally high uptake. The data for these ten patients were the materials used for the comparison

of New PET and PET/CT for simulation planning using FMISO-PET. All of the NPC patients received standard treatment with standard-dose radiation therapy (66-70Gy).

Ten patients in the NPC group received radical treatment and were followed for more than one year with a median follow-up period of 23.1 months, ranging from 14.8 to 30.8 months (Table 3). Three patients experienced local relapse at 9, 11, and 12 months after the first examination in our department. One patient died as a result of NPC at 30.8 months. All patients who experienced local failure had high uptake in FMISO before treatment. No patients who showed normal uptake of FMISO-PET experienced local relapse.

The SUVmax and the volume of $_{NewPET}$GTVh and $_{PET/CT}$GTVh

In the ten NPC patients receiving both types of PET examination and having abnormal uptake, the mean of SUVmax in $_{NewPET}$GTVh was 2.55 ± 0.71 and the mean of SUVmax in $_{PET/CT}$GTVh was 2.38 ± 0.62 (P=0.1934, Wilcoxon signed-rank test). Four patients received New PET first, and six patients received PET/CT first. The mean of SUVmax in the first PET scanning was 2.38 ± 0.81, and the mean of SUVmax in the later PET scanning was 2.41 ± 0.71(P=0.4316).

The mean volume of $_{NewPET}$GTVh and $_{PET/CT}$GTVh was 1.5 ± 1.6 cc and 4.7 ± 4.6 cc,

respectively (P=0.0020) (Figure 1). The GTVh was smaller with New PET for all 10 patients, irrespective of the order of the examinations. Figure 2 shows an example of both FMISO-PET images for one NPC patient. The mean fraction of $_{NewPET}$GTVh was 0.04 ± 0.04 of total GTV, and that of $_{PET/CT}$GTVh was 0.14 ± 0.12 (P=0.0020).

Dose-escalation IMRT simulation planning

DVH of the GTVh, PTV, and OAR are shown in Table 4. Dose escalation was possible in all 10 patients receiving both types of PET examination using $_{NewPET}$GTVh in IMRT plans, maintaining dose constraints for OAR. However, it was not possible in one patient using $_{PET/CT}$GTVh in the IMRT plan, because the threshold dose to the brainstem exceeded the dose constraint. The percentage of the volume receiving ≥ 80.5Gy ($V_{80.5Gy}$) of PTV (p=0.0391), V_{84Gy} of PTV (p=0.0137), mean dose of right parotid gland (p=0.0488), V_{30Gy} of right parotid gland (p=0.0156), V_{30Gy} of left parotid gland (p=0.0159), and the maximum dose to the brainstem (p=0.0273) were significantly lower using $_{NewPET}$GTVh than $_{PET/CT}$GTVh in the IMRT plan.

Discussion

Hypoxic imaging has been developed in recent years, and FMISO, Cu(II)-diacetyl-bis(N4-methylthiosemicarbazone) (Cu-ATSM), and ^{18}F-fluoroazomycin arabinoside (FAZA) have been investigated as hypoxic tracers (9). Among them, FMISO has been studied with the most extensive clinical experience. However, mainly because of the limited contrast between tumor and normal tissue, there has been skepticism about the usage of FMISO as the standard in pre-treatment examination as well as for image guidance in radiotherapy planning (7). If the resolution of PET scanners can be improved, the advantage of FMISO-PET, which has a large pre-clinical and clinical experience, would be reappraised.

We scanned the images at 4 hours after FMISO injection. Thorwarth et al. reported that blood pooling remained at 2 hours after FMISO injection, and good contrast was obtained at 4 hours after injection (16). Our FMISO study adopted 4 hours of delay before scanning and also showed good contrast (17).

We used the T/M ratio to evaluate FMISO uptake, because the T/M ratio was shown to correlate with the degree of hypoxia directly measured using an Eppendorf electrode (6). The threshold value of 1.24 was reported by Yeh, et al. in 1996 using scintillator PET (PC4096-15WB, Scanditronix) (18). In the present study, the thresholds of the T/M ratio of FMISO-PET were calculated to be 1.23 using PET/CT, which is very close to the

ratio reported previously by Yeh et al. However, it was 1.35 using New PET in the present study, suggesting that the threshold of the T/M ratio in FMISO-PET differs between New PET and PET/CT.

The present study showed that local relapse was observed only in NPC patients with a high uptake of FMISO. This may imply that higher uptake of FMISO before radiotherapy is related to radioresistance in patients with NPC, although the number of patients in the present study was too small to allow for such a conclusion. On the other hand, Lee et al. have reported that the effects of pretreatment FMISO uptake in patients with oropharyngeal cancers could not be assessed because the population they examined was too sensitive to chemoradiotherapy and only one relapse was observed in their series (19). Their findings do not contradict our findings and suggest the importance of selecting the disease to be examined in future studies. Reducing the entire dose of PTV while maintaining the dose gradient with a high dose to the hypoxic volume could be one strategy for dose-optimization focused on hypoxia.

The hypoxic volume defined by the New PET was smaller than defined by PET/CT. The spatial resolution after reconstruction and energy resolution of New PET was higher than that of PET/CT. On the other hand, the sensitivity per unit of time, defined as the detecting counts per second, of PET/CT was 1.8 times higher than that of the

New PET. Sensitivity is an important factor in the study of low-uptake radiopharmaceuticals such as FMISO. To compensate for the relatively low sensitivity per unit of time of the New PET, we extended the emission scan time to 30 minutes, which was 3 times longer than that of PET/CT. As a result, the total counts in the New PET were comparable to those in PET/CT, and they were sufficient for the analysis. The difference in the GTVh may have been due to the difference of the scatter fraction and spatial resolution.

For head and neck cancers containing intra-tumoral hypoxia, the usefulness of dose-escalation using hypoxic imaging has been investigated. Popple et al. reported that a modest boost dose (120%-150% of the primary dose) to the hypoxic subvolume increases tumor control probability using a Monte Carlo model (3). In the present study, we performed FMISO PET-guided IMRT simulations in 10 NPC patients. This is the first study that demonstrated the effect of the difference in PET scanners on dose escalation IMRT plans. The dose to OAR was significantly lower in the IMRT plan using New PET compared to the PET/CT. The reason is simply that the $_{NewPET}$GTVh was smaller than $_{PET/CT}$GTVh. Because a lower dose can be delivered to OAR and better quality of life can result, the effort to develop an accurate PET scanner is important for the innovation of radiation therapy.

The shortcoming of this study is the small number of patients included, and the absence of laboratory investigation or phantom study data. Although the local failure rate in this study seems relatively high, we could not draw any definite conclusion about the reason for this rate because of the small number of patients in this study. However, our results indicated the potential usefulness of FMISO-PET in radiation therapy and the need for caution when operating different PET scanners, such as in a multicenter clinical trial.

Conclusion

In conclusion, the difference in PET scanner used for examination affected the definition of hypoxic volume significantly. Using the threshold of abnormal uptake of FMISO, which was determined from the data on normal nasopharyngeal tissue, the dose for the hypoxic region was escalated sufficiently with a lower dose to OAR using New PET compared to using PET/CT, due to the smaller size of GTVh with New PET in an IMRT simulation plan. Development of a more precise and accurate PET scanner can be a breakthrough for accurate dose escalation in FMISO-guided IMRT for patients with NPC. Further investigations are required to confirm our findings.

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Legends

Figure 1. Example of delineation in a nasopharyngeal cancer patient. (a) CT image; the pink line indicates the gross tumor volume (GTV). (b) Semiconductor PET image fused to CT image; the black line indicates hypoxic volume in the GTV ($_{NewPET}$GTVh). (c) Scintillator PET image fused to a CT image; the brown line indicates hypoxic volume in the GTV ($_{PET/CT}$GTVh).

Figure 2. Comparison of average volume of hypoxic volume in gross tumor volume (GTVh) for each PET scan. Error bars indicate the standard deviation.

Appendix

Appendix 1. The process used to select study patients

Appendix 2. The performances and the condition of image acquisition and reconstruction in the scanners

Acknowledgement

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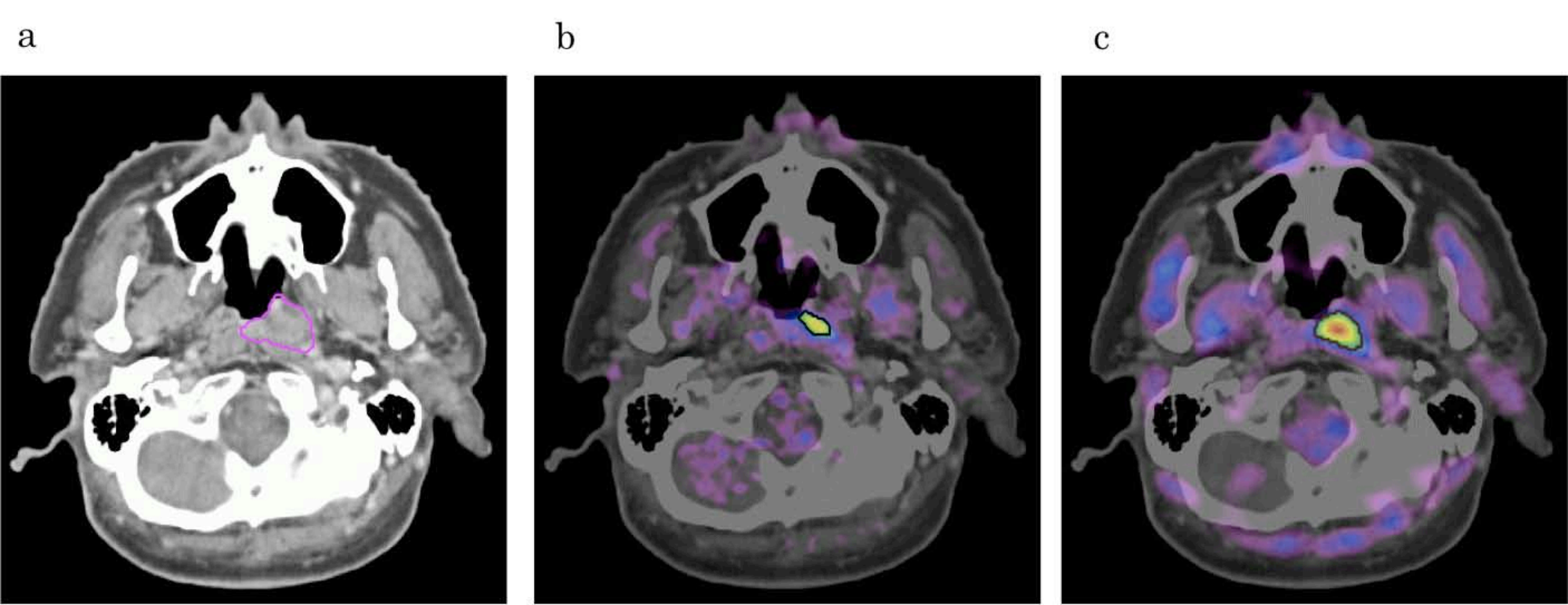
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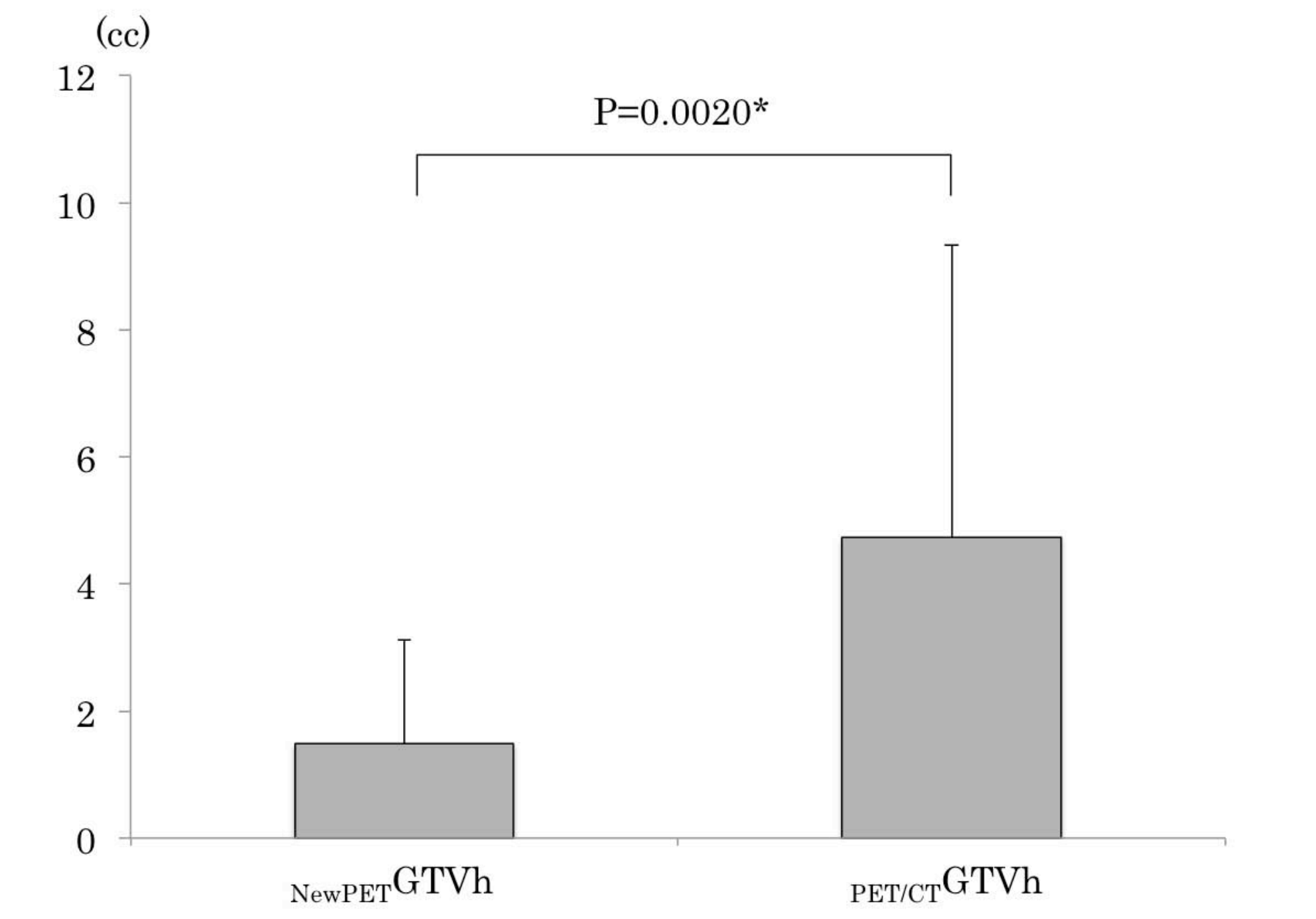
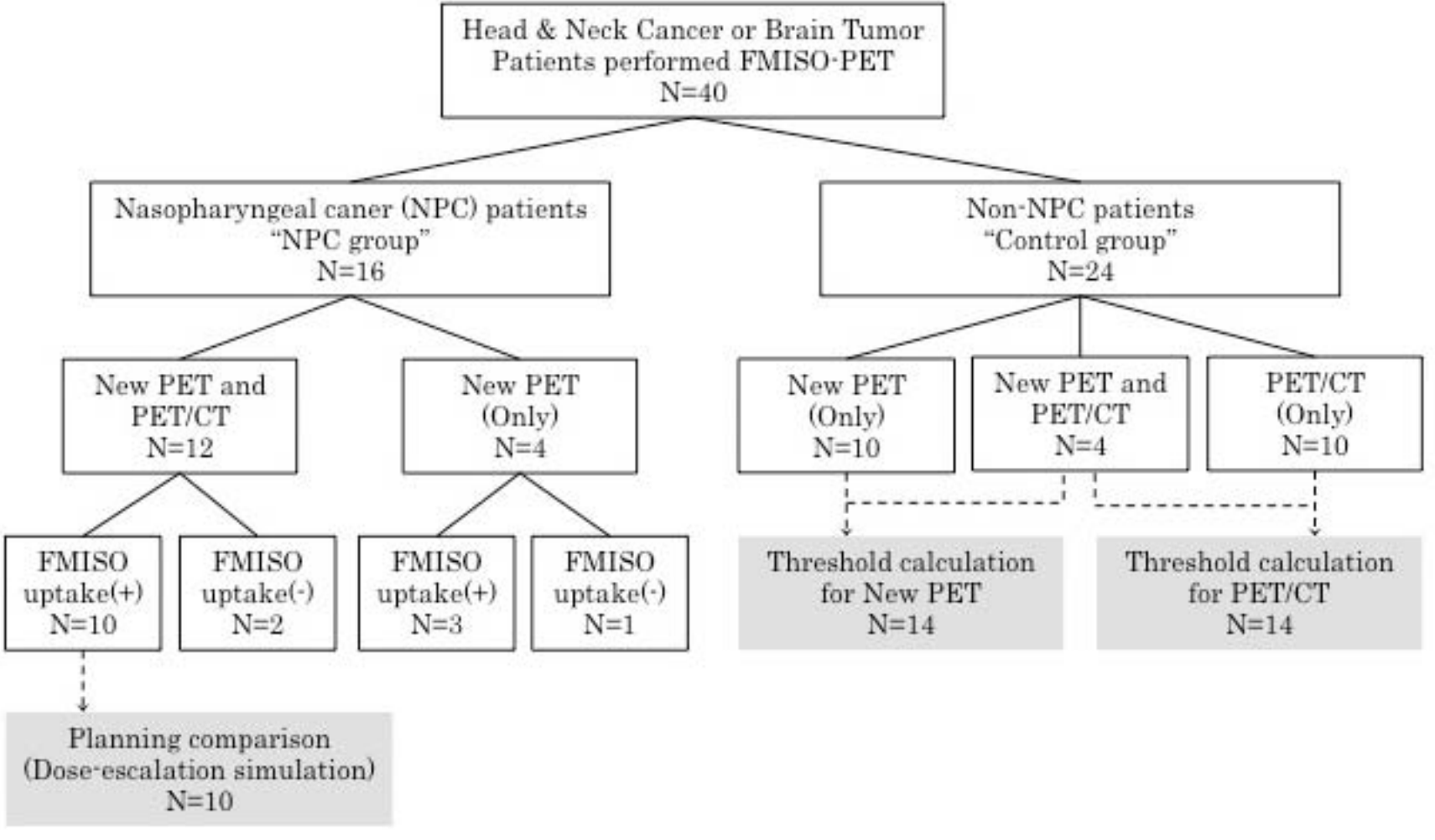


Abbreviations: $_{NewPET}$GTVh=GTVh defined by New PET, $_{PET/CT}$GTVh=GTVh defined by PET/CT


Head & Neck Cancer or Brain Tumor
Patients performed FMISO-PET
N=40
Nasopharyngeal caner (NPC) patients
"NPC group"
N=16
Non-NPC patients
"Control group"
N=24
New PET and
PET/CT
N=12
New PET
(Only)
N=4
New PET
(Only)
N=10
New PET and
PET/CT
N=4
PET/CT
(Only)
N=10
FMISO
uptake(+)
N=10
FMISO
uptake(-)
N=2
FMISO
uptake(+)
N=3
FMISO
uptake(-)
N=1
Threshold calculation
for New PET
N=14
Threshold calculation
for PET/CT
N=14
Planning comparison
(Dose-escalation simulation)
N=10

Appendix 2. The performances and the condition of image acquisition and reconstruction in the scanners

		New PET	PET/CT	Standard
Spatial resolution (Transaxial)	@1cm	2.3mm	4.6mm	NEMA NU-2 2001
	@10cm	4.8mm	5.3mm	NEMA NU-2 2001
Spatial resolution (axial)	@1cm	5.1mm	4.9mm	NEMA NU-2 2001
	@10cm	5.9mm	6.1mm	NEMA NU-2 2001
Sensitivity		4.2kcps/MBq@450keV	7.6kcps/MBq@435KeV	NEMA NU-2 2001
Scatter fraction(3D)		23%@450KeV	37.5%@425KeV	NEMA NU-2 1994
Energy resolution		4.1%	14.0%	
FOV(axial)		246mm	216mm	
Reconstraction method		MRP−PVC	True X	
Number of slice		87	109	
Reconstraction matrix		256x256	168x168	
Spatial resolution after reconstruction (Transaxial)	@1cm	2.5mm	6.5mm	
	@10cm	2.9mm	6.7mm	

FOV(transaxial)	310mm	300mm(2x zoom acqution)

Abbreviations: MRP-PVC=the new reconstruction based on Median root prior and maximum a prior reconstruction, NEMA=the National Electrical Manufacturers Association

Table 1. Prescriptions to the target volumes and constraints of OARs in FMISO-guided IMRT simulation plan

Prescription to the target volumes	
GTVh	D_{95}>84Gy
PTV1	D_{95}>70Gy, V_{77Gy}<20%, $V_{80.5Gy}$<5%
PTV2	D_{95}>63Gy
PTV3	D_{95}>56Gy
Constraints of OARs	
Brainstem	Dmax<54Gy
Spinal cord	Dmax<45Gy
Optic nerve	Dmax<54Gy
Parotid grand	V_{30Gy}≤50%, Dmean≤26Gy
Oral cavity	Dmean≤50Gy
Oropharynx and Hypopharynx	Dmean≤45Gy

Abbreviations: GTVh=hypoxic volume in GTV, D_{95}=minimal dose to 95% of the volume,

PTV=planning target volume, V_{77Gy}=percentage of the volume receiving ≥ 77Gy,

OAR=organ at risk, Dmax=maximal point dose of the volume, Dmean=mean dose of the volume

Table 2. Characteristics of patients in the nasopharyngeal cancer (NPC) group

Patient Number	Age	Sex	T Stage	N Stage	M Stage	FMISO uptake
1	61	male	2a	2	0	+
2	48	male	1	1	0	+
3	59	female	4	1	0	+
4	53	male	2b	1	0	+
5	45	female	2b	2	0	+
6	66	female	2a	0	0	+
7	40	male	3	1	0	+
8	77	male	2	2	0	-
9	50	female	2b	2	0	+
10	61	male	2b	2	0	-
11	73	male	4	1	1	+
12	62	female	4	3b	1	+
13	52	male	3	2	0	+
14	53	male	1	3b	1	-
15	57	male	3	2	0	+
16	66	male	3	0	0	+

Table 3. Treatment, Local relapse and Death of 10 nasopharyngeal cancer patients receiving radical treatment and followed for more than one year

Patient Number	FMISO uptake	Treatment	RT dose	follow up period (months)	Local relapse	Death
1	+	CRT	70Gy/35fr	30.8	+	+
2	+	CRT	70Gy/35fr	27.7	+	-
3	+	CRT	66Gy/33fr	27.0	-	-
4	+	CRT	70Gy/35fr	24.2	-	-
5	+	CRT	70Gy/35fr	23.6	+	-
6	+	CRT	70Gy/35fr	22.5	-	-
7	+	CRT	70Gy/35fr	19.7	-	-
8	-	RT	70Gy/35fr	18.5	-	-
9	+	CRT	70Gy/35fr	15.0	-	-
10	-	CRT	70Gy/35fr	14.8	-	-

Abbreviations: CRT=chemoradiation therapy, RT=radiation therapy

Table 4. DVH comparison between New PET and PET/CT guided IMRT

Structure	Evaluation	New PET guided IMRT (Average ± SD)	PET/CT guided IMRT (Average ± SD)	P= (Wilcoxon signed-rank test)
GTVh	V_{84Gy} (%)	96.1 ± 1.4	96.1 ± 1.2	0.3223
PTV1	Dmin(Gy)	44.5 ± 10.7	44.4 ± 10.8	0.6250
	$V_{65.1Gy}$ (%)	98.9 ± 0.4	99.0 ± 0.5	0.2891
	Dmax (Gy)	87.4 ± 1.5	87.9 ± 1.4	0.2754
	Dmean (Gy)	74.8 ± 0.7	75.0 ± 0.7	0.0645
	V_{70Gy} (%)	95.6 ± 0.7	95.9 ± 0.9	0.0957
	V_{77Gy} (%)	10.4 ± 4.5	11.9 ± 5.1	0.3223
	$V_{80.5Gy}$ (%)	3.0 ± 1.6	4.2 ± 2.8	0.0391*
	V_{84Gy} (%)	1.1 ± 0.9	2.0 ± 2.0	0.0137*
Right parotid	Dmean(Gy)	36.9 ± 8.0	37.7 ± 7.5	0.0488*
	V_{30Gy} (%)	50.1 ± 17.8	54.4 ± 17.4	0.0156*
Left parotid	Dmean (Gy)	39.6 ± 5.1	39.9 ± 5.0	0.1934
	V_{30Gy} (%)	57.3 ± 11.7	59.0 ± 12.6	0.0195*
Brainstem	Dmax (Gy)	50.6 ± 4.2	53.2 ± 7.3	0.0273*
Spine	Dmax (Gy)	44.3 ± 2.7	44.2 ± 2.4	0.6953
Oral cavity	Dmean(Gy)	45.3 ± 5.1	45.6 ± 5.1	0.2754
Carotid artery	Dmax (Gy)	80.6 ± 3.2	82.4 ± 4.6	0.0840

Abbreviations: DVH=dose volume histogram, PET=positron emission tomography, IMRT=intensity-modulated radiation therapy, SD=standard deviation, GTVh=hypoxic volume in gross tumor volume, V_{84Gy}=percentage of the volume receiving ≥ 84Gy, PTV=planning target volume, Dmin=minimal point dose of the volume, Dmax=maximal point dose of the volume, Dmean=mean dose of the volume