**Table 3.** Multivariate analyses for locoregional progression-free survival and overall survival

| Factors | *N* | LRPFS | | OAS | |
|---|---|---|---|---|---|
| | | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Gender | | | | | |
| Male | 116 | 0.572 (0.309–1.060) | 0.758 | 0.663 (0.365–1.202) | 0.1758 |
| Female | 38 | | | | |
| Age | | | | | |
| <61 | 75 | 0.988 (0.581–1.678) | 0.9640 | 0.772 (0.484–1.232) | 0.2784 |
| ≥61 | 79 | | | | |
| Site | | | | | |
| Oral cavity | 87 | 1.375 (0.781–2.418) | 0.2697 | 1.597 (0.968–2.634) | 0.0666 |
| Others | 67 | | | | |
| pTstage | | | | | |
| pT0-2 | 88 | 0.688 (0.399–1.187) | 0.1786 | 0.705 (0.435–1.145) | 0.1582 |
| pT3-4 | 66 | | | | |
| pNstage | | | | | |
| pN0-2a | 36 | 0.352 (0.165–0.751) | 0.0069 | 0.475 (0.262–0.860) | 0.0141 |
| pN2b-3 | 118 | | | | |
| Differentiation | | | | | |
| Poorly | 15 | 2.720 (1.249–5.921) | 0.0117 | 3.905 (2.075–7.348) | <0.0001 |
| Others | 139 | | | | |
| Major risks | | | | | |
| High | 113 | 1.982 (1.026–3.820) | 0.0418 | 1.792 (1.016–3.163) | 0.044 |
| Intermediate | 41 | | | | |

HR, hazard ratio; CI, confidence intervals.

**Table 4.** Patterns of failures

| Site | *n* | | *n* |
|---|---|---|---|
| Local only | 14 (16%) | Local recurrence | 31 |
| Local and nodal | 12 (14%) | In-field | 9 |
| Local and distant | 4 (5%) | Out-of-field | 22 |
| Local, nodal and distant | 1 (1%) | | |
| Nodal only | 28 (33%) | | |
| Nodal and distant | 3 (4%) | Regional recurrence | 44 |
| Distant only | 23 (27%) | In-field | 28 |
| Total | 85 | Out-of-field | 16 |

**Table 5.** Acute and late toxicities of grade 3 or greater

| | Gr3 | Gr4 | Gr5 |
|---|---|---|---|
| Acute | | | |
| Skin | 1 | 0 | 0 |
| Mucous membrane | 7 | 0 | 0 |
| Infection | 4 | 0 | 1 |
| Late | | | |
| Bone | 3 | 0 | 0 |
| Skin | 2 | 0 | 0 |
| Pharynx and esophagus | 1 | 0 | 0 |

patient developed Grade 5 acute toxicity due to DIC caused by infection.

Late toxicity of Grade 3 or greater developed in six patients only (3.8%). There were three patients with osteonecrosis of the jaw bone, two with skin necrosis and 1 with a Grade 3 pharyngeal stricture.

## DISCUSSION

Locally advanced HNSCC patients have poor prognoses. Fletcher et al. first reported on the benefits of PORT in 1970 (9). Since the 1970s, many reports have shown that PORT improved locoregional control (LRC) over that of historical control groups or surgery alone (1–3,10–12). In addition,

several risk features and prognostic factors regarding combined treatment with surgery and PORT such as surgical margins, ECE, T stage, N stage or the interval between surgery and PORT have also been described (13–18).

A multi-institutional, prospective, randomized trial was also undertaken in patients with advanced HNSCC to investigate the validity of using pathologic risk features and determine the need for, and dose of PORT (5). In that phase III trial, patients were categorized into low-, intermediate- and high-risk groups according to pathological features. Study designs were no PORT for the low-risk group ($n = 31$), 57.6 Gy for 6.5 weeks for the intermediate-risk group ($n = 31$), and by random assignment, 63 Gy for 5 weeks ($n = 76$) or 7 weeks ($n = 75$) for the high-risk group. Intermediate-risk patients (i.e. 1 adverse feature other than ECE) who received 57.6 Gy PORT had 5-year actuarial LRC and survival rates of 94 and 66%, respectively. In contrast, high-risk patients with ECE or more than one other adverse feature had 5-year actuarial LRC and survival rates of 68 and 42%, respectively.

Although several prospective randomized trials established evidence of the need for, and dose of PORT in patients with advanced HNSCC, the relatively high rates of severe toxicities are still problematic. Peters reported that a total of 17 (7.1%) patients sustained one or more moderate-to-severe late complications (Grade 3–4 on the modified RTOG scale) (4). The most frequent complication was pharyngo-esophageal stricture, followed by bone exposure or necrosis, fistula and severe neck fibrosis/edema. In addition, a dose–response relationship was identified when complications were analyzed in terms of the maximum target dose delivered. Ang et al. reported that 5 (16%) and 25 (33%) patients in the 57.6 Gy/6.5 week and 63 Gy/7 week groups, respectively, developed one or more Grade 3–4 late morbidities (5). The head and neck regions are important for a number of processes including respiration, chewing and swallowing. Therefore, adverse events have a direct impact on the quality of life. The rate of adverse events should be reduced while maintaining the therapeutic effects of the treatment to improve the outcome of advanced HNSCC patients.

In our institute, we treated advanced HNSCC with surgery and PORT according to pathological risk features. To reduce adverse events, we adopted LF-PORT with a focus on moderate- to high-risk regions. For this kind of treatment it is essential to have mutual trust and good communication between head and neck surgeons and radiation oncologists. For these purposes, we have conferences among head and neck surgeons and radiation oncologists once a week to discuss about treatment strategies for HNSCC patients.

In the present study, the rates of acute and late toxicities were quite low. Acute toxicities of Grade 3 or greater developed in 13 patients (8.4%), and late toxicities of Grade 3 or greater developed in six patients only (3.8%). Regarding the therapeutic effect, the 3-year rates of OAS and PFS were 53.8 and 42.1%, respectively. The 3-year rates of PFS in the high-risk group (i.e. close/positive margins and/or ECE) and intermediate-risk group were 34.7 and 62.8%, respectively ($P < 0.01$). The 3-year rates of LRPFS in the high- and intermediate-risk groups were 52.0 and 71.2%, respectively ($P = 0.10$). We think that the results of efficacy in intermediate-risk patients were comparable with those of other groups; therefore, it is reasonable to apply LF-PORT. However, the results of efficacy in the high-risk group were worse than those in the intermediate-risk group and historical controls (Table 6).

In 2004, two randomized trials, EORTC and RTOG, reported that adjuvant CRT was shown to be more efficient than adjuvant RT alone for both disease control and/or survival in selected high-risk locally advanced HNSCC patients (6,7) In a systematic review with meta-analysis of four RCTs including EORTC and RTOG trials (6,7,19,20), pooling trials confirmed the benefit of adjuvant CRT in LRC and OAS (19)

In the present study, there was no significant difference in the 3-year rates of OAS between the adjuvant RT and CRT groups (56.1 vs. 47.5%, $P = 0.11$). In addition, there was no significant improvement in the 3-year rates of OAS between RT and CRT even in high-risk patients (52.5 vs. 42.3%, $P = 0.10$). However, there were several selection biases to decide whether we strongly recommended patients to receive CRT depending on their general condition even though they had major risks.

In order to improve outcomes, we noted the pattern of recurrences. Initially, the most frequent recurrent pattern was only regional recurrence in 28 patients, and the total number of patients who had regional recurrence with or without other site recurrences was 44 (29%). Of these patients, 16 (36%) were located out-of-field. Sixty-nine percent of patients who had out-of-field regional recurrence had ECE lesions. Therefore, we need to be careful when shrinking the regional radiation field especially in patients with ECE. In other words, it is appropriate to apply an entire neck irradiation field in high-risk patients. In addition, of the 28 in-field regional recurrences, 20 patients (71%) had ECE, which suggests that a higher dose may be necessary to control ECE lesions. Peters et al. reported that there was better LRC with doses of 63 Gy than at lower doses in a subset of patients with ECE (4). On the other hand, we observed 31 local recurrences with or without other site recurrences, of which local recurrences without other sites were 14. Of 31 local recurrences, 22 were located out-of-field. We believe that it is reasonable to include the primary tumor bed in the radiation field if patients have high-risk features such as ECE, even if they do not have close/positive surgical margins.

We evaluated the efficacy of our LF-PORT with the aim of reducing morbidity by minimizing the radiation field. LF-PORT is a promising strategy for patients who have intermediate risk features without close/positive surgical margins and/or ECE because of the comparative tumor control rate and low adverse effects. However, the present study used retrospective analysis in a single institution. Therefore, it is important to evaluate the efficacy of LF-PORT in an intermediate risk group in a prospective clinical study.

We need to adopt a whole neck irradiation field including the primary tumor bed in high-risk patients who have surgical close/positive margins and/or ECE. For such high-risk

**Table 6.** Results of the treatment outcome for HNSCC patients treated with surgery and PORT with or without chemotherapy

| Author, year | Treatment | Risk category | No. of patients | Close/ positive margin (%) | ECE (%) | LRC or LRR (%) | PFS or DFS (%) (years) | OAS (%) (years) |
|---|---|---|---|---|---|---|---|---|
| Huang (1992) (10) | no RT | | 71 | 19 | 15 | 31 (5 years LRC) | NA | 41 (3) |
| | RT | | 54 | | | 59 (5 years LRC) | NA | 72 (3) |
| Ang (2001) (5) | RT | Low risk | 31 | 14 | 75 | 90 (5 years LRC) | NA | 83 (5) |
| | | Intermediate | 31 | | | 94 (5 years LRC) | NA | 66 (5) |
| | | High | 151 | | | 68 (5 years LRC) | NA | 42 (5) |
| Langendijk (2005) (18) | RT | Class I | 234 | 35 | 51 | 92 (5 years LRC) | 65 (5) | 67 (5) |
| | | Class II | 336 | | | 78 (5 years LRC) | 47 (5) | 50 (5) |
| | | Class III | 231 | | | 58 (5 years LRC) | 32 (5) | 36 (5) |
| Bernier (2004) (6) | RT | | 167 | 26 | 53 | 31 (5 years LRR) | 36 (5) | 40 (5) |
| | CRT | | 167 | 31 | 61 | 18 (5 years LRR) | 47 (5) | 53 (5) |
| Cooper (2004) (7) | RT | | 210 | 19 | 81 (including multiple LN) | 33 (3 years LRR) | 36 (3) | 47 (3) |
| | CRT | | 206 | 17 | 83 (including multiple LN) | 22 (3 years LRR) | 47 (3) | 56 (3) |
| Present | RT/CRT | Intermediate | 41 | 0 | 0 | 71.2 (5 years LRC) | 62.8 (5) | 58.8 (5) |
| | | High | 113 | 29 | 81 | 46 (5 years LRPFS) | 29.5 (5) | 39 (5) |
| | | All | 154 | 21 | 59 | 58.3 (5y LRPFS) | 38.1 (5) | 44.5 (5) |

LRR, locoregional recurrence; PFS, progression-free survival; DFS, disease-free survival; CRT, chemoradiotherapy.

patients, depending on their risk factors, a higher dose or in some cases, chemotherapy may be needed.

## Conflict of interest statement

None declared.

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# Locoregional Control After Intensity-modulated Radiotherapy for Nasopharyngeal Carcinoma with an Anatomy-based Target Definition

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**Objective:** The objective of the study was to evaluate locoregional control after intensity-modulated radiotherapy for nasopharyngeal cancer using a target definition along with anatomical boundaries.

**Methods:** Forty patients with biopsy-proven squamous cell or non-keratinizing carcinoma of the nasopharynx who underwent intensity-modulated radiotherapy between April 2006 and November 2009 were reviewed. There were 10 females and 30 males with a median age of 48 years (range, 17–74 years). More than half of the patients had T3/4 ($n = 21$) and/or N2/3 ($n = 24$) disease. Intensity-modulated radiotherapy was administered as 70 Gy/33 fractions with or without concomitant chemotherapy. The clinical target volume was contoured along with muscular fascia or periosteum, and the prescribed radiotherapy dose was determined for each anatomical compartment and lymph node level in the head and neck.

**Results:** One local recurrence was observed at Meckel's cave on the periphery of the high-risk clinical target volume receiving a total dose of <63 Gy. Otherwise, six locoregional failures were observed within irradiated volume receiving 70 Gy. Local and nodal control rates at 3 years were 91 and 89%, respectively. Adverse events were acceptable, and 25 (81%) of 31 patients who were alive without recurrence at 2 years had xerostomia of ≤Grade 1. The overall survival rate at 3 years was 87%.

**Conclusions:** Target definition along with anatomically defined boundaries was feasible without compromise of the therapeutic ratio. It is worth testing this method further to minimize the unnecessary irradiated volume and to standardize the target definition in intensity-modulated radiotherapy for nasopharyngeal cancer.

*Key words: nasopharyngeal cancer – intensity-modulated radiotherapy – anatomical compartment – patterns of spread*

## INTRODUCTION

Intensity-modulated radiotherapy (IMRT) is one of the most prominent therapeutic advances in the last decade for patients with nasopharyngeal cancer (NPC) with local and nodal control rates exceeding 90% (1–5). In IMRT, meticulous delineation of the clinical target volume (CTV) with special attention to the patterns of spread is extremely important. In general, spread of NPC follows anatomic compartments that are bounded by anatomic barriers (e.g. muscular fascia or periosteum) (6). Recent high-resolution computed tomography (CT) and magnetic resonance imaging (MRI) images have yielded exquisite anatomical information that can clearly depict whether the gross tumor volume (GTV) penetrates these anatomic barriers. Involvement of NPC in one anatomical compartment correlates with contiguous spread to the adjacent compartments (7,8). However, definition of clinical and subclinical target volumes had been largely derived from the experience of two-/three-dimensional radiotherapy, and the method for target delineation by using modern radiographic and fiberscopic images had not been fully addressed. Excellent locoregional tumor control rates had been reported from experienced centers in IMRT to the CTV using GTV plus 5–10 mm uniform expansion with individual modification due to proximity of critical organs (1–4,9). On the other hand, Lee et al. reported that centralized review and feed back were required to diminish major deviation of target specification from 31 to 12% in their multicenter study using the same CTV definition (5). A similar result was observed in another multicenter study that 32% of patients had major deviations for tumor volume contouring (10). Major deviations from the treatment protocol may deteriorate locoregional tumor control (10,11). In principle, anatomical boundaries were selected as cut planes in curative surgery for head and neck cancer in order to achieve margin-free resection without unnecessary sacrifice of normal tissues. Anatomically defined planes such as muscular fascia and periosteum are theoretically unchangeable lines on CT images for IMRT planning, and it should then be appropriate landmarks to determine the boundary of CTV and non-cancerous normal tissues to reduce unnecessary irradiated volume. We attempted to determine the CTV in accordance with anatomical compartments of the head and neck area since the start of IMRT at our institution, and preliminary results of local and regional tumor control are described in this report.

## PATIENTS AND METHODS

### Patient Population

From April 2006 to November 2009, 41 patients with biopsy-proven squamous cell or non-keratinizing carcinoma of the nasopharynx without evidence of distant organ metastasis underwent IMRT at our institution. All patients underwent CT and MRI of the head and neck as part of the pretreatment evaluation. Diseases were re-staged according to the American Joint Committee on Cancer (AJCC) Staging Manual (seventh edition) (12). One patient died because of an unidentified accident immediately after completion of treatment and excluded from this analysis, and the remaining 40 patients were the subjects of this study.

### Contouring of the Clinical Target Volume Around the Primary Disease

All patients underwent CT simulation with 3 mm slice thickness after immobilization in the supine position using thermoplastic masks. CT images with and without contrast enhancement were always obtained during simulation, and registration of MRI at the treatment position with planning CT images was routinely used in patients with T3/4 diseases. We considered that head and neck fiberscopy findings were more important than CT/MRI information in the determination of mucosal extent of GTV at the primary site (GTVp). Tumor invasion to adjacent anatomical compartments, such as parapharyngeal, masticator, perivertebral spaces, pterygopalatine fossa, occipital (clivus), temporal (petrous apex) and/or sphenoid bones, was evaluated with CT and MRI. A high-risk CTV was defined as follows: (i) pharyngeal and sinonasal mucosal space within 2 cm from the margin of the mucosal irregularity, unless it was in close proximity to the chiasma and optic nerve, (ii) entire ipsilateral parapharyngeal space and/or infratemporal fossa (medial and lateral pterygoid muscles), only when gross tumor invasion to these structures was observed in CT/MRI, (iii) individual cranial bones, pterygopalatine fossa and/or perivertebral space within a volume of GTVp + 1 cm expansion, only when gross tumor invasion to these structures was observed and (iv) Meckel's cave was included in the high-risk CTV when there was clinical and/or radiographic evidence of tumor penetration through the foramen lacerum and/or foramen ovale. Margins of these high-risk CTVs were defined at the fascia or periosteum of each anatomical compartment.

The intermediate-risk CTV was contoured at the anatomical compartments without gross tumor invasion but abutting to the GTVp as follows: (i) entire parapharyngeal space, (ii) entire medial and lateral pterygoid muscles only when GTVp attached to the inner fascia of these muscles, (iii) entire volume of the sphenoid bone invaded by the tumor and outside of the volume of GTVp +1 cm, (iv) temporal and occipital bone and/or pterygopalatine fossa within GTVp +2 cm and outside of GTVp +1 cm, if tumors invaded these structures and (v) ipsilateral Meckel's cave when GTVp invaded foramen lacerum and/or masticator space. Schematic figures illustrating the above concept are shown in Figure 1.

### Contouring of the Clinical Target Volume at the Neck Nodes

Lymph node stations in the neck were designated as Levels I–V, supraclavicular and retropharyngeal nodes according to the AJCC Staging Manual (seventh edition). A high-risk CTV was defined as the entire level containing gross nodal disease

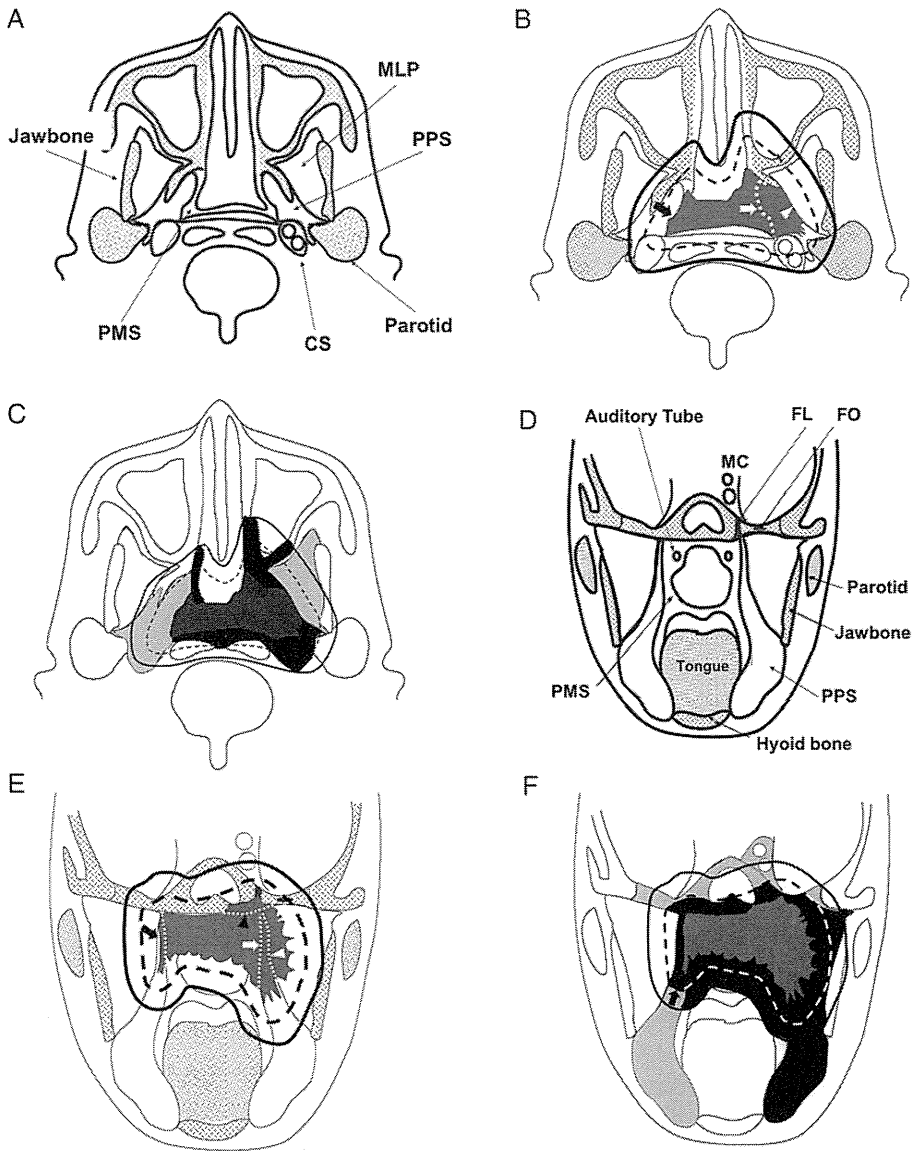


**Figure 1.** An example of the anatomical boundary-based target definitions: (A) normal anatomy in the axial plane, (B) gross tumor volume (GTV, solid black area) extends beyond the mucosal space (white arrow) but not penetrating the inner fascia of the masticator space (arrowhead), and confined within the mucosal space on the contralateral side (black arrow), solid and dotted lines represent uniform expansion of GTV +2 and 1 cm, respectively, (C) high- and intermediate-risk clinical target volume (CTV) receiving 70 Gy (black area) and 60 Gy/33 fractions (light gray area), respectively. Another example is shown in (D–F); (D) normal anatomy in the coronal plane, (E) GTV invades ipsilateral parapharyngeal space (white arrow), infratemporal fossa (white arrowhead) and skull base (black arrowhead). The GTV also shows minimal invasion to the contralateral parapharyngeal space but not attached to pterygoid muscles (black arrow). (F) Definition of CTV. Limitation of the high-risk CTV in the contralateral parapharyngeal within GTV +1 cm (dotted line) is a vital option to reduce radiotherapy (RT) dose to the oral cavity and pharyngeal mucosal space when parapharyngeal invasion is not extensive (black arrow). PMS, pharyngeal mucosal space; PPS, parapharyngeal space; CS, carotid sheath; MLP, medial and lateral pterygoid muscles; FL, foramen lacerum; FO, foramen ovale; MC, Meckel's cave.

(GTVn), which was determined by neck lymph nodes of $\geq$1 cm in smallest dimension, any equivocal retropharyngeal lymph nodes (15), or which had central necrosis on CT/MRI. In the case of nodal disease that had nodes of $\geq$3 cm in diameter, or when extracapsular spread was suggested on CT/MRI, the volume within the uniform three-dimensional expansion of gross nodal disease +1 cm was also defined as high-risk CTV. An intermediate-risk CTV was defined as lymph node levels that were adjacent to the high-risk CTV with radiological evidence of extracapsular extension. A low-risk CTV encompassed all Levels II–V and supraclavicular nodes, and retropharyngeal nodal stations above the level of the hyoid bone and that was outside of the high- or intermediate-risk CTV. Level Ib was defined as low-risk CTV when GTVp infiltrated the ipsilateral nasal cavity. All GTVs were contoured according to the physical and radiographic findings before induction chemotherapy for patients who underwent this chemotherapy as described in the next section.

### Dose Prescription and Treatment Techniques

The step-and-shoot technique with a 10 mm-wide multi-leaf collimator using a fixed nine beam arrangement of 6 million volt X-rays was used during this study period. PTV encompassed CTV with a 5 mm margin. Total RT doses to the PTV of high, intermediate and low risks were 70, 60 and 54 Gy, respectively. A simultaneous integrated boost using 33 fractions over 6.5 weeks was used, and the entire PTV was treated with extended-field IMRT. On treatment planning CT, dose distribution in each slice was meticulously evaluated, and the plans were optimized to eliminate hot spots receiving a total RT dose of $\geq$77 Gy. In principle, the IMRT plan was approved when $>$95% volume (D95) of the PTV received $>$95% of the prescribed dose. A part of the PTV within 3 mm beneath the skin surface was eliminated in this evaluation. The total RT dose to the chiasma and at least the unilateral optic nerve was always restricted to $<$60 Gy because none of the patients had clinical and radiographic signs of optic nerve invasion of the tumor at presentation. Otherwise, the dose constraint to the planning organs at risk volume was determined according to the Radiation Therapy Oncology Group 0225 Study protocol (5).

According to the previous trials (13,14), concomitant followed by adjuvant platinum-based chemotherapy was done in clinically fit patients with Stage III/IV disease. Those who had Stage I/II keratinizing squamous cell carcinoma also received concomitant chemotherapy because of poor expectation of local control in patients with this histology (16). For competent patients with N2/3 disease and/or T4 disease attaching to the optic chiasma, three courses of induction chemotherapy with docetaxel, cisplatin and S-1 were done (17). Dental examinations and placement of a percutaneous gastrostomy tube (PEG) were routinely done before the start of IMRT. Changes in the body contours were monitored at least weekly during the IMRT with megavoltage CT generated by the linac in all patients, with the intention of revising plans according to the estimated changes of dose distribution in the target volume and critical organs. In fact, revisions were made in four patients. IMRT plans were made using Xio version 4.5.0 (Elekta, Stockholm, Sweden) for the first five patients, and Pinnacle 3 (Philips, Amsterdam, the Netherlands) for the rest.

### Outcome Measures and Statistical Considerations

Patients were monitored at least twice a week during IMRT. Follow-up visits were requested monthly within 2 years after completion of RT, at least once per 3 months during the third year, and once per 6 months thereafter. Radiological examinations including CT and/or MRI of the head and neck were performed at least twice within 6 months immediately after treatment, and at regular intervals of 6–12 months thereafter. Time-to-event analyses from the start of RT were made using the Kaplan–Meier estimates according to the data fixed on 1 November 2012. Biopsy-proven recurrence of the primary tumor or radiographic evidence of regrowth of neck adenopathy was considered as events for calculating the local and nodal control rates, respectively. Radiographic evidence of development of distant failure was determined as an event for calculating distant failure rates. Patterns of recurrences were classified according to the definition by Chao et al. (18). Patients who died without these events were censored at the time of last follow-up examination. Death from any cause was defined as an event in calculating overall survival. Also, recurrence at any site or death from any cause was used in estimating progression-free survival. Statistical significance was evaluated using the log-rank test. Adverse events were estimated according to the National Cancer Institute Common Terminology Criteria of Adverse Events version 4.0. All patients provided written informed consent. This retrospective analysis was approved by our institutional ethics committee.

## RESULTS

### Patients

One patient was lost to follow-up at 23 months with radiological evidence of nodal recurrence. The median follow-up period for other surviving patients was 45 months (25–62 months). The characteristics of patients are listed in Table 1. High-risk CTV within the mucosal space was confined within posterior one-third of the nasal cavity in all but one patient, while it was within the pharyngeal mucosal space above the level of inferior border of the second cervical vertebra (C2) in all but two patients. In patients with T4 disease, the entire ipsilateral medial and lateral pterygoid muscles were included in high-risk CTV in three patients, and otherwise, it was confined to the sphenoid and temporal bones, basiocciput, Meckel's cave, perivertebral, retropharyngeal and sinonasal/pharyngeal mucosal spaces. Concomitant chemotherapy was performed in 38 (95%) patients, and 20 (53%) of these 38 patients also received induction chemotherapy. The overall treatment time of RT ranged from 46 to 57 days (median, 50 days).

### Tumor Control and Survival Outcomes

There were seven locoregional tumor persistence or recurrences as listed in Table 2. The local and nodal control rates at 3 years were 91% (95% confidence interval, 82–100%) and 89% (79–99%), respectively. The locoregional control rate at 3 years was 83% (71–96%). A review of IMRT dose distributions revealed that six of the seven locoregional failures were 'in-field', and one local recurrence at the Meckel's cave was 'marginal' according to the definition by Chao et al. This marginal recurrence occurred in patients who had T3 disease deeply invading the ipsilateral foramen lacerum. Although the site of recurrence was defined as high-risk CTV, the administered total dose was $<$63 Gy aiming at dose reduction to the adjacent temporal lobe of the brain. Local control rates in patients with T1/2 and T3/4 disease were 95% (95% CI 85–100%) and 90% (77–100%), respectively, at 3 years ($P = 0.744$). The distant failure rate at 3 years was 24% (8–40%). The Kaplan–Meier estimates of locoregional and

**Table 1.** Characteristics of patients

| Characteristics | Number of patients | % |
|---|---|---|
| Gender | | |
| Male | 30 | 75 |
| Female | 10 | 25 |
| Age, median (range), years | 48 (17–74) | |
| Histology | | |
| Keratinizing SCC | 3 | 8 |
| SCC, NOS | 1 | 3 |
| Non-keratinizing carcinoma | | |
| Differentiated | 13 | 33 |
| Undifferentiated | 23 | 58 |
| T classification | | |
| T1 | 12 | 30 |
| T2 | 7 | 18 |
| T3 | 7 | 18 |
| T4 | 14 | 35 |
| N classification | | |
| N0 | 2 | 5 |
| N1 | 14 | 35 |
| N2 | 19 | 48 |
| N3a | 1 | 3 |
| N3b | 4 | 10 |
| Stage | | |
| I | 1 | 3 |
| II | 6 | 15 |
| III | 14 | 35 |
| IVA | 14 | 35 |
| IVB | 5 | 13 |
| Zubrod performance status | | |
| 0 | 1 | 3 |
| 1 | 35 | 88 |
| 2 | 4 | 10 |
| Tumor location | | |
| Lateral wall | 19 | 48 |
| Posterosuperior wall | 10 | 25 |
| Superior wall | 7 | 18 |
| Posterior wall | 4 | 10 |

SCC NOS, squamous cell carcinoma, not otherwise specified.

distant failure rates are shown in Figure 2. Progression-free and overall survival rates at 3 years were 61% (45–76%) and 87% (76–98%), respectively (Fig. 3). Locoregional control, distant failure and overall survival rates at 3 years for patients with Stage I–III disease ($n = 21$) were 81% (95% CI, 64–98%), 17% (0–34%) and 90% (77–100%), respectively, whereas these rates were 89% (74–100%), 27% (8–46%) and 83% (65–100%), respectively, for 19 patients with Stage IV disease. Overall and progression-free survival rates at 3 years for 20 patients who received induction chemotherapy were 89 and 63%, and it was 85 and 59% for the rest, respectively ($P > 0.500$).

### Adverse Events

Grade 3 dermatitis and symptomatic mucositis due to IMRT were observed in 5 (12%) and 25 (63%) patients, respectively. All surviving patients maintained their normalcy of diet and were not PEG dependent at 1 year after completion of IMRT. The median value of mean IMRT doses to the parotid gland on the side receiving lower dose was 33 Gy (19–49 Gy). The mean total IMRT dose to the spared cochlea was <55 Gy in all patients. The type and frequency of late adverse events for 37 patients who were alive at 2 years are listed in Table 3. One patient experienced Grade 3 neck induration at 4 years after IMRT (1 year after completion of salvage chemotherapy for bone metastasis). He died subsequently with radiological evidence of lung metastasis. Of 31 patients who were alive and disease-free at 24 months, hearing loss of Grade 3 was observed in 4 (13%) patients. Twenty-five (81%) of these 31 patients experienced sense of recovery of their mouth dryness and were able to intake a normal solid diet (xerostomia of ≤Grade 1) at 2 years (Fig. 4). One patient whose T4 disease collapsed at 4 months after completion of IMRT developed a deep ulcer at the parapahryngeal and masticator spaces (Grade 3 pharyngeal necrosis). Osteonecrosis of the ipsilateral mandible and temporal lobe necrosis were observed subsequently. She died of pneumonia without evidence of tumor recurrence at 35 months. Otherwise, no Grade 2 or worse adverse events were observed at the time of last follow-up.

## DISCUSSION

Although excellent locoregional control after IMRT had been reported from certain centers that had abundant experience of two-to-three-dimensional RT for NPC, wide prevalence of these results in the medical community is indispensable. Assuming that inter-observer variation of the target definition is categorized as a systematic error, larger margins would be required to determine the planning target volume than accountable by random errors (19). Therefore, meticulous target definition based on the detailed estimation of extent of tumor and precise knowledge of patterns of tumor spread is indispensable. Pharyngeal and sinonasal mucosal spaces within GTVp +2 cm margins were determined as high-risk CTV during this study period because of our belief of the aggressive nature of NPC with regard to lymphovascular invasion. However, this should be done with extreme caution. It should be noted that GTVp at the mucosal space was determined by direct fiberscopy findings because GTVp definition based on imaging alone was likely

**Table 2.** Patterns of locoregional failure

| Patient age/gender | TN classification | Histology | Site of recurrence | Time to event (months) | Salvage treatment | Final status (months) |
|---|---|---|---|---|---|---|
| 49M | T2N2 | SCC NOS | Local, in-field | 0 | None | 11 DOD |
| 54M | T3N1 | Non-kerat. differentiated | Local, in-field | 21 | Re-RT | 45 AWD |
| 49M | T3N1 | Non-kerat. differentiated | Local, marginal | 36 | Re-RT | 43 AWD |
| 53F | T2N3a | Non-kerat. undifferentiated | Nodal, in-field | 0 | None | 12 DOD |
| 34M | T1N2 | Non-kerat. undifferentiated | Nodal, in-field | 10 | Re-RT | 23 AWD |
| 47F | T2N1 | Non-kerat. differentiated | Nodal, in-field | 28 | Re-RT | 54 NED |
| 45M | T4N1 | Keratinizing | Nodal, in-field | 34 | Chemotherapy | 38 AWD |

M, male; F, female; Non-kerat, non-keratinizing; Re-RT, reirradiation; DOD, died of index cancer; AWD, alive with disease; NED, no evidence of disease; in-field, within irradiated volume receiving 70 Gy/33 fractions; marginal, at the margin of irradiated volume receiving 70 Gy/33fractions according to the definition by Chao et al. (18).

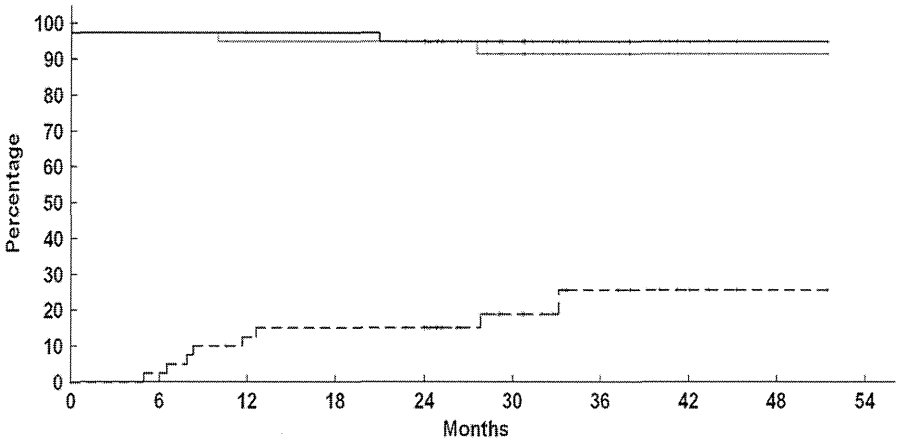


**Figure 2.** Kaplan–Meier estimates of local control (thick solid), nodal control (thin solid) and distant failure rates (dotted line).

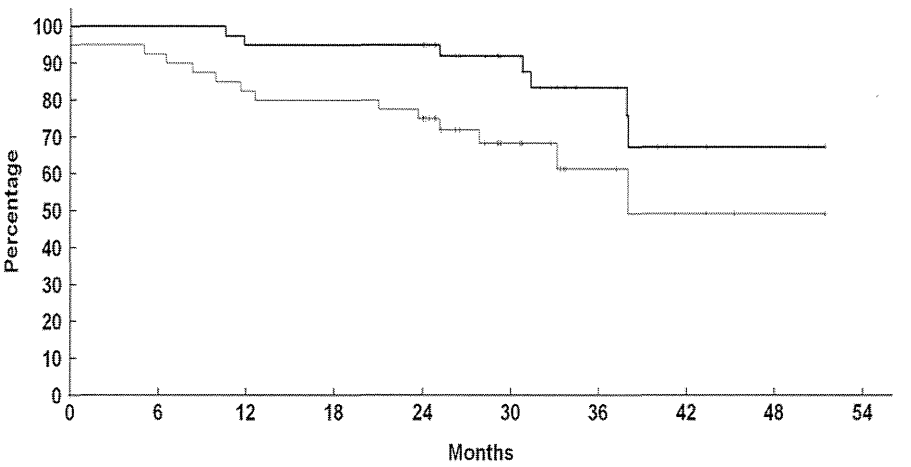


**Figure 3.** Kaplan–Meier estimates of overall (thick) and progression-free (thin line) survival rates.

to overestimate the real GTVp (6,20). Correct depiction of this mucosal GTVp for the planning CT is an extremely important process, because any regulation defining a GTV–CTV margin is meaningless without this effort. In our experience, high-risk CTV was confined within posterior one-third of the nasal cavity, and oropharyngeal mucosal space above the level of lower border of C2 with few exceptions. Therefore, the reason must be clearly recorded when high-risk CTV larger than these limits is defined. In other words, adding 2 cm margin to the GTV that was determined with imaging alone should not be done to avoid an unacceptably huge high-risk CTV.

**Table 3.** Type and frequency of late adverse events for 37 patients who were alive at 2 years

| Adverse effect | Grade | | | |
|---|---|---|---|---|
| | 0/1 | 2 | 3 | NA[a] |
| Skin/soft tissue | 35 | 1 | 1 | 0 |
| Pharyngeal mucositis/necrosis | 36 | 0 | 1 | 0 |
| Salivary gland | 27 | 7 | 0 | 3 |
| Esophagus | 34 | 0 | 0 | 3 |
| Larynx | 34 | 2 | 0 | 1 |
| Central nervous system | 33 | 0 | 1 | 3 |
| Bone | 36 | 0 | 1 | 0 |
| Joint | 36 | 0 | 1 | 0 |
| Hearing impaired (at least unilateral) | 23 | 10 | 4 | 0 |
| Other | 37 | 0 | 0 | 0 |
| Worst overall | | | | |
| Number of patients | 20 | 10 | 5 | 2[b] |
| Percentage of total patients | 54 | 27 | 14 | 5 |

[a]NA, not assessable because of aggravation of general conditions due to disease recurrence.
[b]Number of patients who did not experience ≥Grade 2 late adverse events other than NA items.

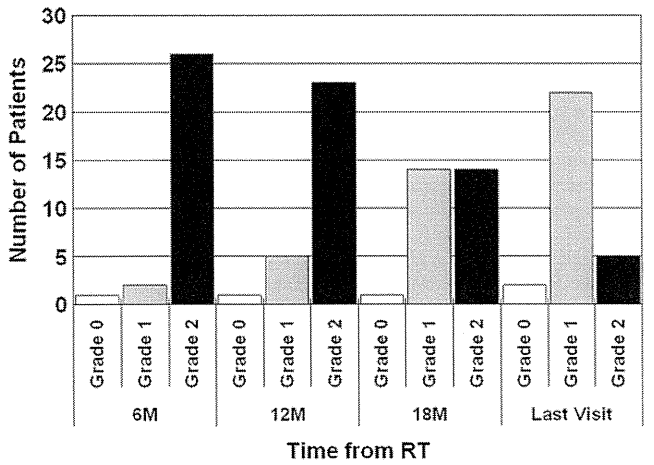


**Figure 4.** Frequency of Grade 0–2 xerostomia at 6, 12 and 18 months (M) after completion of RT and last follow-up visit.

NPC has a high propensity of parapharyngeal space invasion (8). The parapharyngeal space that was judged as free from tumor invasion was not encompassed within the CTV in this study period. However, no marginal recurrence was observed within the parapharyngeal space in this series of patients. If possibility of tumor invasion could not be completely denied, definition of the high-risk CTV within the parapharyngeal space by expansion of GTVp +1 cm as shown in Figure 1 was thought to be an appropriate option based on the results of previous reports (1,2,4,5,9). In general, most of the patients with NPC had nodal metastasis with radiological signs of extracapsular spread, which required extensive coverage of the ipsilateral parapharyngeal space. Therefore, to determine the entire ipsilateral parapharyngeal space as the high-risk CTV was considered justifiable when the patient had gross tumor invasion to this space on MRI. As noted by Grégoire et al., muscular fascias are strong barriers against muscle infiltration. When the fascia has been disrupted, the whole muscle is at risk (21). Based on this concept, the high-risk CTV encompassed the entire pterygoid muscles in three patients with T4 disease.

Adverse influence of variation in treatment planning was suggested in one patient who experienced marginal recurrence at Meckel's cave. Consequently, our method should be continuously fine-tuned according to the accumulation of clinical experiences. Otherwise, all locoregional failures were 'in-field', which could not be ascribable to inadequacy of our target definition. This single institutional study with a limited number of patients could not demonstrate the appropriateness of our target definition for all patterns of spread. Lin et al. (22) addressed a possibility to reduce IMRT target volume compared with that as defined in two- to three-dimensional radiotherapy era without deterioration of tumor control. Local and nodal control rates exceeded 95% at 3 years and no isolated recurrence was observed at reduced CTV in the posterior maxillary sinus, posterior clivus and/or posterior nasal cavity in 323 NPC patients (75% had T2/3 disease). In our study, three of the seven locoregional recurrences occurred at >2 years post IMRT. Therefore, longer follow-up is required to compare matured results among various definitions of the CTV and chemoradiotherapy procedures.

Lee et al. (5) reported that 46 of 68 (68%) patients experienced Grade 3 or worse acute gastrointestinal toxicities. Wolden et al. (2) showed that, in 74 patients (46% had N2/3 disease), the average mean dose to the parotid was 35.2 Gy and the mean dose was limited to ≤26 Gy in 30 of 84 parotid glands (35.7%). Grade 2 xerostomia was observed in 32% at 12 months, and the incidence of Grade 3 hearing loss was 15%. Ng et al. (9) showed that an average mean parotid dose was ~40 Gy in 193 NPC patients, 90% of them had N2/3 disease. All of these data were comparable that observed in this study. Nevertheless, our resources to conduct IMRT during this preliminary period were considered as one of the reasons for adverse events, which should be improved along with the advancement of technologies to spare normal tissues more efficiently. No firm conclusion could be made regarding the effect of chemotherapy because of heterogeneous background of patients. Needless to say, it is impossible to evaluate the risks and benefits of additional chemotherapy without adequate CTV definition.

Possibility of this method to reduce inter-observer variation was not supported by any evidence in this report. Nevertheless, a clear definition must be established before wide prevalence of IMRT for NPC. Although there were difference in the background of patients, local control rates for patients who had T3/4 disease were relatively poor in previous reports (2,4,9). In our

study, similar local control rates exceeding 90% at 3 years, which compared favorably with other series, were observed in patients with T1/2 and T3/4 tumors. Therefore, it is conceivable that the significance of our anatomical boundary-based target definition is worth testing further for patients with advanced disease, especially in the new departments intending to implement nasopharynx IMRT into their practice.

## CONCLUSION

An anatomical boundary-based definition of the CTV instead of simple three-dimensional expansion of the GTV was feasible without compromising locoregional tumor control and adverse events on the premise that meticulous estimation of extent of the tumor was done with fiberscopic and modern radiographic examinations. This method has a possibility to standardize the target definition as experienced in surgical oncology, and to facilitate reduction of inter-observer variation in multicenter studies. Further study of this procedure is needed in accordance with accumulating experiences and advancing resources in IMRT.

## Conflict of interest statement

None declared.

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Clinical Investigation: Head and Neck Cancer

# [$^{18}$F]fluoromisonidazole and a New PET System With Semiconductor Detectors and a Depth of Interaction System for Intensity Modulated Radiation Therapy for Nasopharyngeal Cancer

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**Summary**

The impact of a New PET system using an $^{18}$F-labeled fluoromisonidazole (FMISO)-guided intensity modulated radiation therapy plan was investigated by comparing the plan with a state-of-the-art PET/CT system in nasopharyngeal cancer (NPC) patients. New PET was found to be useful for accurate dose escalation in FMISO-guided IMRT for patients with NPC.

**Purpose:** The impact of a new type of positron emission tomography (New PET) with semiconductor detectors using $^{18}$F-labeled fluoromisonidazole (FMISO)-guided intensity modulated radiation therapy (IMRT) was compared with a state-of-the-art PET/computed tomography (PET/CT) system 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 (GTVh) was determined using each PET ($_{\mathrm{NewPET}}$GTVh and $_{\mathrm{PET/CT}}$GTVh, respectively). Dose escalation IMRT plans prescribing 84 Gy to each GTVh were carried out.

**Results:** The threshold of the T/M ratio was 1.35 for New PET and 1.23 for PET/CT. The mean volume of $_{\mathrm{NewPET}}$GTVh was significantly smaller than that of $_{\mathrm{PET/CT}}$GTVh (1.5 ± 1.6 cc vs 4.7 ± 4.6 cc, respectively; $P = .0020$). 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 1 PET/CT-guided plan, because the threshold dose to the brainstem was exceeded.

**Conclusions:** New PET was found to be useful for accurate dose escalation in FMISO-guided IMRT for patients with NPC. © 2013 Elsevier Inc.

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Conflict of interest: 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.

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## Introduction

Hypoxia is well known as an important factor relating to radioresistance (1). In head-and-neck cancer, 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 noninvasive 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 of the usefulness of FMISO-PET in 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 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-deoxyglucose (FDG)-PET images (14).

In this study, we established the threshold of FMISO normal uptake by using New PET and a state-of-the-art whole-body PET-computed tomography (PET-CT) system with lutetium oxyorthosilicate scintillation detectors and extended field of view (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 differences 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 chemoradiation therapy for local control in patients with NPC.

## Methods and Materials

### Patient characteristics

Our institutional review board approved the protocol for this study in 2007. Between April 2008 and March 2011, 40 patients with newly diagnosed head-and-neck cancer and brain tumors 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 otolaryngologists 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 12 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 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 (range, 40-78 years) in patients examined with New PET and 67.5 years (range, 56-83 years) 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). Briefly, the New PET system is equipped with small semiconductor detectors and a depth of interaction 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 FMISO was injected intravenously 4 h before scanning. Details of the performances of these 2 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.

### Thresholds of the nasopharynx-to-muscle ratio and the tumor-to-muscle ratios

FMISO-PET images were registered to image analysis software (Vox-Base, J-MAC System, Sapporo, Japan). In the control group, the maximum 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 a radius of 1 cm was placed in the left lateral, left medial, right medial, and right lateral positions of the posterior cervical muscle, and the average SUVmax of these ROIs was calculated. The nasopharyngeal SUVmax divided by the average of the SUVmax of the posterior cervical muscle ROI 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 we confirmed the normal distribution, we calculated the upper threshold of the normal N/M ratio as the average + 1.96 × standard deviation (SD), 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.

### Definition of the hypoxic region in NPC and comparison of hypoxic volumes by the 2 systems

In the NPC group, all patients underwent CT (Somatom Sensation; Siemens) with individualized head, neck, and

shoulder immobilization masks. Images from the CT scans with 2-mm slices were obtained for each patient. CT images and FMISO-PET images obtained by each PET scan were coregistered to make fusion images, using 3-dimensional radiation therapy planning software (Pinnacle3 version 80m; Philips Radiation Oncology Systems, Fitchburg, WI). The gross tumor volume (GTV) was determined on the CT image, and other available images (ie, 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.

## 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.

Clinical target volume 1 (CTV1) was defined as the volume containing the GTV and any microscopic disease at risk. CTV2 and CTV3 were at high-risk and low-risk volumes, respectively. A margin of 3 mm was added to each CTV and defined as planning target volumes (PTV1, PTV2, and PTV3). 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 procedures 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 2-sided Wilcoxon signed-rank test was used to compare DVH parameters between plans. A significance *P* value of .05 was used.

# Results

## Thresholds of the N/M ratios of New PET and PET/CT

The averages ± SD of the N/M ratios in the control group examined with New PET and PET/CT were 1.151 ± 0.103 and 1.054 ± 0.086, respectively. The distribution was approved to be normal by the *W* test ($P = .3902$ and $P = .9993$, respectively). The upper thresholds of the N/M ratio were 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.

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

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

*Abbreviations:* $D_{95}$ = minimal dose to 95% of the volume; Dmax = maximal point dose of the volume; Dmean = mean dose of the volume; FMISO = [$_{18}$F]fluoromisonidazole; GTVh = hypoxic volume in the gross tumor volume; IMRT = intensity modulated radiation therapy; OAR = organ at risk; PTV = planning target volume; $V_{77Gy}$ = percentage of the volume receiving ≥77 Gy.

## 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 10 patients were the materials used

**Table 2** Characteristics of patients in the NPC group

| Patient | Age (y) | 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 | + |

*Abbreviations:* FMISO = [$_{18}$F]fluoromisonidazole; NPC = nasopharyngeal cancer

**Table 3** Treatment, local relapse, and deaths of 10 NPC patients who received radical treatment and were followed for more than 1 y

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

*Abbreviations:* CRT = chemoradiation therapy; FMISO = [$_{18}$F] fluoromisonidazole; fr = fraction; NPC = nasopharyngeal cancer; RT = radiation therapy.

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

Ten patients in the NPC group received radical treatment and were followed for more than 1 year with a median follow-up period of 23.1 months, ranging from 14.8-30.8 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.

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

In the 10 NPC patients receiving both types of PET examination and having abnormal uptake, the mean SUVmax in $_{NewPET}$GTVh was 2.55 ± 0.71 and the mean SUVmax in $_{PET/CT}$GTVh was 2.38 ± 0.62 ($P$=.1934; Wilcoxon signed-rank test). Four patients received New PET first, and 6 patients received PET/CT first. The mean SUVmax in the first PET scanning was 2.38 ± 0.81, and the mean SUVmax in the later PET scanning was 2.41 ± 0.71 ($P$=.4316).

The mean volumes of $_{NewPET}$GTVh and $_{PET/CT}$GTVh were 1.5 ± 1.6 cc and 4.7 ± 4.6 cc, respectively ($P$=.0020) (Fig. 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 1 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 ($P$=.0020).

## Dose escalation IMRT simulation planning

DVHs of the GTVh, PTV, and OARs 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 1 patient by 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 ≥80.5 Gy ($V_{80.5Gy}$) of the PTV ($P$=.0391), the $V_{84Gy}$ of PTV ($P$=.0137), the mean dose to the right parotid gland ($P$=.0488), $V_{30Gy}$ to the right parotid gland ($P$=.0156), $V_{30Gy}$ of the left parotid gland ($P$=.0159), and the maximum dose to the brainstem ($P$=.0273) were significantly lower using $_{NewPET}$GTVh than $_{PET/CT}$GTVh in the IMRT plan.

## Discussion

Hypoxic imaging has been recently developed, and FMISO, Cu(II)-diacetyl-bis($N^4$-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 use of FMISO as the standard in pretreatment examination as well as for image guidance in radiation therapy planning (7). If the resolution of PET scanners can be improved, the advantage of FMISO-PET, which has extensive preclinical and clinical experience, would be reappraised.

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

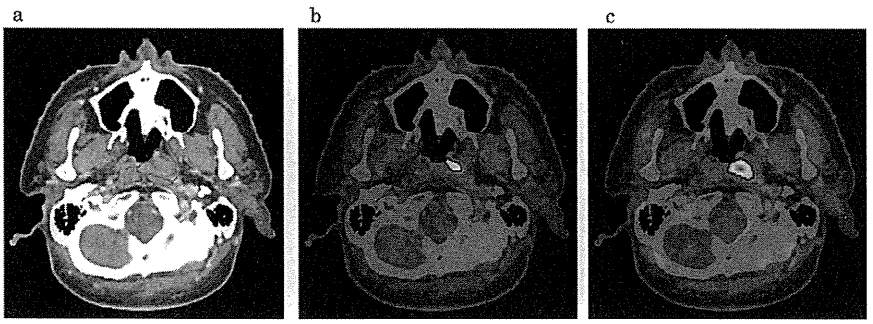


**Fig. 1.** Example of delineation in a NPC patient. (a) CT image: pink line indicates the GTV. (b) Semiconductor PET image fused to CT image; black line indicates hypoxic volume in the GTV ($_{NewPET}$GTVh). (c) Scintillator PET image fused to a CT image; brown line indicates hypoxic volume in the GTV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

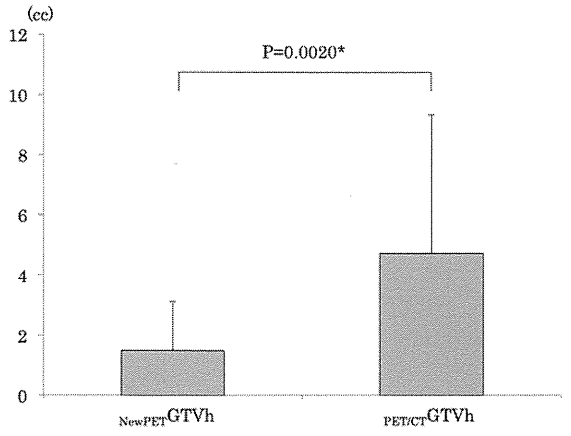


**Fig. 2.** Comparison of average volume of GTVh for each PET scan. Error bars indicate SDs.

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 (18) in 1996, using scintillator PET (PC4096-15WB; Scanditronix). In the present study, the threshold 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 (18). 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 radiation therapy 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 (19) 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 chemoradiation therapy and only 1 relapse was observed in their series. 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 New PET was smaller than that 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 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 New PET, we extended the emission scan time to 30 min, 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 analysis. The differences in GTVh may have been due to the difference of the scatter fraction and spatial resolution.

For head-and-neck cancers containing intratumoral hypoxia, the usefulness of dose escalation using hypoxic imaging has been investigated. Popple et al (3) 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. 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 OARs was significantly lower in the IMRT plan using New PET than in PET/CT. The reason is

**Table 4** DVH comparison between new PET-guided and PET/CT-guided IMRT

| Structure | Evaluation | New PET-guided IMRT average ± SD | PET/CT-guided IMRT average ± SD | *P* (Wilcoxon signed-rank test. *P<.05) |
|---|---|---|---|---|
| GTVh | $V_{84Gy}$ (%) | 96.1 ± 1.4 | 96.1 ± 1.2 | .3223 |
| PTV1 | Dmin (Gy) | 44.5 ± 10.7 | 44.4 ± 10.8 | .6250 |
| | $V_{65.1Gy}$ (%) | 98.9 ± 0.4 | 99.0 ± 0.5 | .2891 |
| | Dmax (Gy) | 87.4 ± 1.5 | 87.9 ± 1.4 | .2754 |
| | Dmean (Gy) | 74.8 ± 0.7 | 75.0 ± 0.7 | .0645 |
| | $V_{70Gy}$ (%) | 95.6 ± 0.7 | 95.9 ± 0.9 | .0957 |
| | $V_{77Gy}$ (%) | 10.4 ± 4.5 | 11.9 ± 5.1 | .3223 |
| | $V_{80.5Gy}$ (%) | 3.0 ± 1.6 | 4.2 ± 2.8 | .0391* |
| | $V_{84Gy}$ (%) | 1.1 ± 0.9 | 2.0 ± 2.0 | .0137* |
| Right parotid | Dmean (Gy) | 36.9 ± 8.0 | 37.7 ± 7.5 | .0488* |
| | $V_{30Gy}$ (%) | 50.1 ± 17.8 | 54.4 ± 17.4 | .0156* |
| Left parotid | Dmean (Gy) | 39.6 ± 5.1 | 39.9 ± 5.0 | .1934 |
| | $V_{30Gy}$ (%) | 57.3 ± 11.7 | 59.0 ± 12.6 | .0195* |
| Brainstem | Dmax (Gy) | 50.6 ± 4.2 | 53.2 ± 7.3 | .0273* |
| Spine | Dmax (Gy) | 44.3 ± 2.7 | 44.2 ± 2.4 | .6953 |
| Oral cavity | Dmean (Gy) | 45.3 ± 5.1 | 45.6 ± 5.1 | .2754 |
| Carotid artery | Dmax (Gy) | 80.6 ± 3.2 | 82.4 ± 4.6 | .0840 |

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

simply that $_{NewPET}$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 shortcomings of this study are 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.

## Conclusions

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 data from normal nasopharyngeal tissue, the dose for the hypoxic region was escalated sufficiently with a lower dose to OAR by 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 could 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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