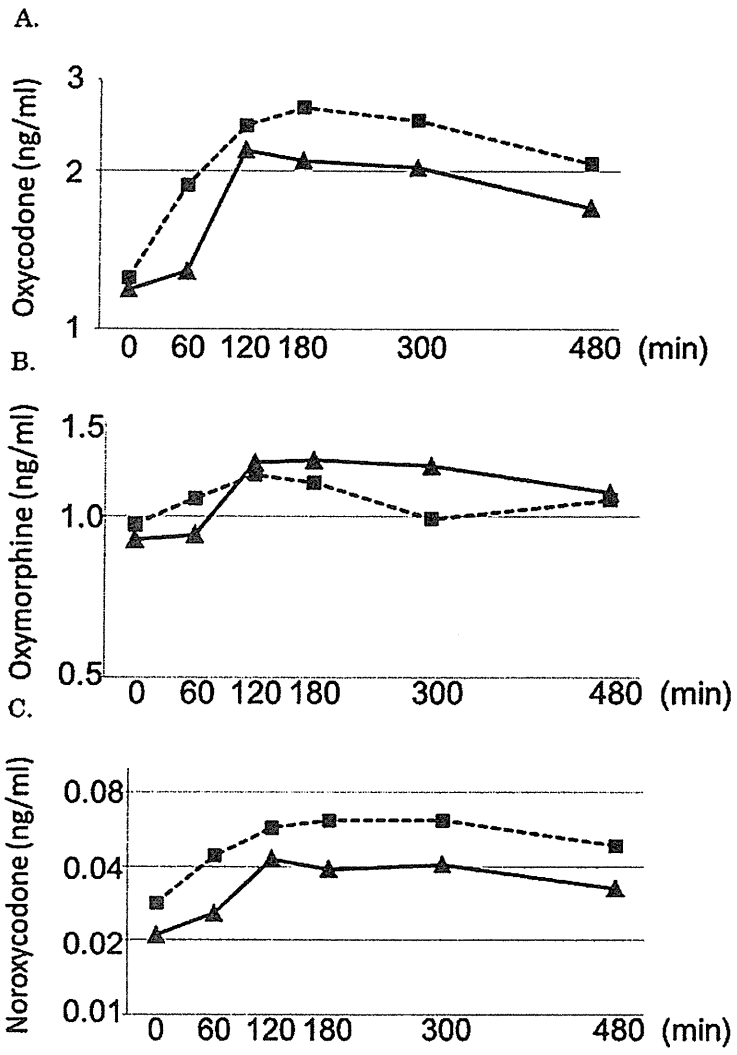


**Figure 2. Mean plasma concentration curves of oxycodone, noroxycodone, and oxymorphone in patients (n=6) who were administered with 10 mg of CR oxycodone every 12 hours alone (period A, triangles) or with aprepitant (period B, squares).** ▲ without aprepitant, ■ with aprepitant.
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throughout the study. Adverse events were evaluated using the CTCAE v4.0.

## Blood sampling

Blood samples for pharmacokinetic analysis were collected immediately before and 1, 2, 3, 5, and 8 hour after administration of oxycodone in periods A and B. An additional sample was collected to allow for analysis of trough concentration before administration of oxycodone in the morning on the following day of period B. After blood was collected in lithium heparin-containing tubes, plasma was separated within 30 min by centrifugation at 1,500×g for 10 min at 4°C and stored at −80°C until analysis. Plasma concentrations of oxycodone, noroxycodone, and oxymorphone were determined using a liquid chromatography tandem mass spectrometric method. The lower limit of quantification was 0.1 ng/ml.

## Pharmacokinetic analysis

Pharmacokinetic variables of oxycodone, noroxycodone, and oxymorphone were determined using the Pheoenix WinNonlin pharmacokinetic program (Pharsight, Mountain View, California). The Cmax and time to maximum concentration (Tmax) were observed directly from the data. The AUC with extrapolation to 8 hour ($AUC_{0-8}$) was calculated by the trapezoidal rule. The linear trapezoidal rule was used for successive increasing concentration values, and the logarithmic trapezoidal rule for decreasing concentration values. Metabolite-to-parent drug AUC ratios (AUCm/AUCp) were calculated to compare the relative abundance of each metabolite.

## Statistical Analysis

This study was designed in order to exclude a clinically significant higher exposure to oxycodone and its metabolites. The null hypothesis was that coadministration of aprepitant would not

**Table 3.** Pharmacokinetic parameter of oxycodone and its metabolites.

| | Oxycodone | | | Noroxycodone | Oxymorphone |
|---|---|---|---|---|---|
| | Cmax (ng/mL) | Tmax (hr) | $AUC_{0\rightarrow 8}$ (ng*hr/mL) | $AUC_{0\rightarrow 8}$ (ng*hr/mL) | $AUC_{0\rightarrow 8}$ (ng*hr/mL) |
| Number of patients | 20 | 20 | 20 | 20 | 15** |
| Without aprepitant | 2.28 | 2.67 | 882 | 718 | 14.9 |
| | (31.4%) | (57.7%) | (35.7%) | (45.2%) | (78.0%) |
| With aprepitant | 2.79 | 3.62 | 1102 | 616 | 20.7 |
| | (28.0%) | (32.1%) | (29.9%) | (51.6%) | (65.8%) |
| ratio | 1.22 | | 1.25 | 0.86 | 1.34 |
| | (1.11–1.34) | | (1.14–1.36) | (0.81–0.91) | (1.20–1.49) |
| p-value* | 0.0002 | 0.07 | 0.00004 | 0.00005 | 0.00004 |

Abbreviations: Cmax, peak plasma concentration; Tmax, time to peak plasma concentration; $AUC_{0\rightarrow 8}$, area under the time-concentration curve from 0 to 8 hours; ratio, the ratio of the geometric mean value of CR oxycodone with aprepitant to those without aprepitant.
Geometric mean (% coefficient variance).
Values were corrected for dose, assuming that all patients received 20 mg of oxycodone.
*Paired t-test for difference between logarithmic geometric means (two-sided).
**Five patients were excluded due to below lower limit of quantitation.
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increase the plasma concentration of oxycodone to a clinically meaningful degree, i.e., the ratio of the geometric mean $AUC_{0\rightarrow 8}$ for oxycodone between period A and period B would be <1.33. Package insert of oxycodone reports that the AUC of oxycodone in steady state was 216.2±97.4 ng.hr/ml [mean ± standard deviation, coefficient of variance (CV) was 45.1%] in patients with cancer pain (n = 32). We estimated that 20 subjects were needed to detect a 33% difference in the $AUC_{0\rightarrow 8}$ for oxycodone at a power of 80% and level of significance $p<0.05$ (two-sided). The calculations used the sample size procedures in NCSS PASS 11 software. Data are expressed as the geometric mean ± SD. Statistical significance of logarithmic geometric means in AUC and Cmax was analyzed using a paired Student's t-test, with a probability level of 0.05 used as the criterion of significance. Tmax was analyzed using a Wilcoxon signed-rank test. All statistical analyses were performed with NCSS 2007 (NCSS, LLC. Kaysville, UT).

## Results

### Patient population

Twenty one patients were assessed for eligibility and 20 patients were allocated to intervention from September 2010 to December 2012 (Figure 1). Their characteristics are listed in Table 1. There were 17 men and 3 women with Eastern Cooperative Oncology Group performance status 1 to 2. The predominant tumor types were pancreatic cancer and head and neck cancer, with all patients having stage IV disease. Each patient was administered regularly with the appropriate dose of oral CR oxycodone every 8

**Table 4.** Trough concentrations of oxycodone and its metabolites.

| | Oxycodone | | Noroxycodone | | Oxymorphone | |
|---|---|---|---|---|---|---|
| | N | (ng/mL) | N | (ng/mL) | N | (ng/mL) |
| Day 1 pre-dose | 20 | 1.29 | 20 | 1.28 | 14 | 0.0243 |
| Without aprepitant | | (53.1%) | | (46.2%) | | (72.7%) |
| Day 2 pre-dose | 20 | 1.22 | 20 | 1.23 | 14 | 0.0277 |
| Without aprepitant | | (49.3%) | | (47.8%) | | (68.8%) |
| Day 3 pre-dose | 19 | 2.00 | 19 | 0.97 | 17 | 0.0321 |
| With aprepitant | | (49.2%) | | (54.5%) | | (78.8%) |
| Ratio (D3 to D1) | 19 | 1.57 | 19 | 0.760 | 13 | 1.36 |
| p-value* | | 0.001 | | 0.00003 | | 0.02 |
| Ratio (D3 to D2) | 19 | 1.65 | 19 | 0.796 | 13 | 1.32 |
| p-value* | | 0.0001 | | 0.00001 | | 0.02 |

Abbreviations: N, number of patients; Ratio (D3 to D1), the ratio of the geometric mean trough concentration of CR oxycodone plus aprepitant on day 3 to those of CR oxycodone alone on day 1; Ratio (D3 to D2), the ratio of the geometric mean trough concentration of CR oxycodone plus aprepitant on day 3 to those of CR oxycodone alone on day 2.
Geometric mean (% coefficient variance).
Values were corrected for dose, assuming that all patients received 20 mg of oxycodone.
*Paired t-test for difference between logarithmic geometric means (two-sided).
doi:10.1371/journal.pone.0104215.t004

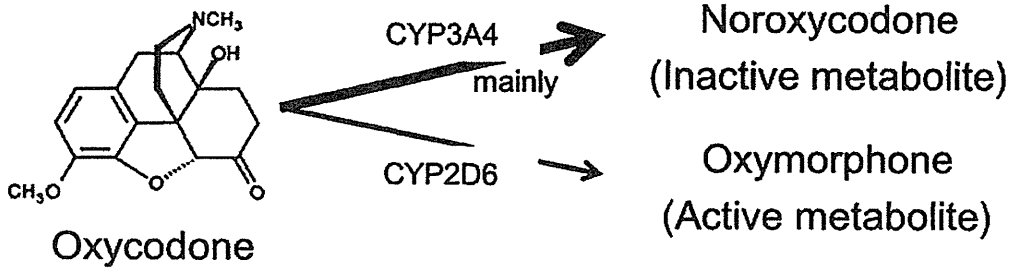


**Figure 3. Metabolic pathway of Oxycodone.**
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or 12 hours (Table 2). The median daily dosage of oxycodone was 20 mg (range, 10–60 mg) and the mean was 21.5 mg, with the median for each dosage being 10 mg (range, 5–20 mg) and the mean being 9.25 mg.

### Oxycodone and its metabolites pharmacokinetics

All 20 patients were assessed for pharmacokinetics of oxycodone and its metabolites with and without aprepitant administration. In five patients who were administered with 5 mg of oral CR oxycodone every 12 hours, the plasma oxymorphone concentration was below the limit of quantification. Table 3 and 4 summarize the pharmacokinetic parameters of oxycodone administered alone or with aprepitant. Figure 2 shows the geometric mean plasma concentrations of oxycodone and its metabolites in patients (n = 6) who were administered with 10 mg of CR oxycodone every 12 hours alone or with aprepitant. The ratio of the geometric mean $AUC_{0-8}$ and Cmax of CR oxycodone plus aprepitant [1,102 ng*hr/ml (CV 29.9%) and 2.79 ng/ml (CV 28.0%), respectively] to those of CR oxycodone alone [882 ng*hr/ml (CV 35.7%) and 2.28 ng/ml (CV 31.4%), respectively] was 1.25 (95% CI 1.14, 1.36; CV 21.8%; p = 0.00004) and 1.22 (95% CI 1.11, 1.34; CV 20.6%; p = 0.0002), respectively. The ratio of the geometric mean $AUC_{0-8}$ of noroxycodone and oxymorphone with aprepitant [616 ng*hr/ml (CV 51.6%) and 20.7 ng*hr/ml (CV 65.8%), respectively] to those without aprepitant [718 ng*hr/ml (CV 45.2%) and 14.9 ng*hr/ml (CV 78.0%), respectively] was 0.86 (95% CI 0.81, 0.91; p = 0.00005) and 1.34 (95% CI 1.20, 1.49; p = 0.00004), respectively. The plasma concentrations of oxycodone and its metabolites were affected significantly by presence or absence of aprepitant.

The trough concentration of oxycodone and its metabolite on day 1 were similar to those on day 2, because steady state was reached. However, these trough concentrations with aprepitant on day 3 were higher than those on day 1 and day 2. The ratio of the geometric mean trough concentration of CR oxycodone plus aprepitant on day 3 to those of CR oxycodone alone on day 2 was 1.65 in oxycodone (p = 0.0001), 0.796 in noroxycodone (p = 0.00001), and 1.32 in oxymorphone (p = 0.02), respectively.

In this study and clinical practice, there was no increased incidence in pharmacologic effect and side effects of oxycodone due to concomitant use of aprepitant.

## Discussion

The predominant metabolic pathway of oxycodone is CYP3A4-mediated N-demethylation to noroxycodone, while a minor proportion undergoes 3-O-demethylation to oxymorphone by CYP2D6 (Figure 3). This study demonstrated that inhibition of CYP3A4-mediated N-demethylation by aprepitant significantly increased the AUC of oxycodone by 25% and decreased the AUC of noroxycodone by 14%, while subsequently increasing the AUC of oxymorphone by 34% through alternating CYP2D6 pathway. We estimated in advance that a clinical meaningful significant level of interaction between oxycodone and aprepitant would be a 33% increase in the ratio of the geometric mean $AUC_{0\rightarrow\infty}$ under conditions where the CV was 45.1%. Essentially, the impact of aprepitant upon oxycodone was less than expected but the actual CV in the AUC of oxycodone was 30 and 35% in this study. Therefore, we consider that statistical significance was achieved as a result. In this study and clinical practice, there would be no increased incidence in pharmacologic effect and side effects of oxycodone due to concomitant use of aprepitant. We consider that a 25% increase (median 1.25; 95% CI 1.14, 1.36) in the ratio of the geometric mean $AUC_{0\rightarrow\infty}$ is a statistically significant effect, but that, due to its less extent than expected, at this time there is no need to change the CR oxycodone dose in clinical use of aprepitant in cancer patients, with adequate attention. With regard to oxymorphone which is an active metabolite, because oxymorphone is a potent opioid that has a 4 to 6 times lower μ-opioid receptor affinity and lower concentration than oxycodone [6] [14], an increase of oxymorphone would be unlikely to have a significant impact on the clinical relevance. However, because the recommended dose of aprepitant is 125-mg/80-mg regimen over 3 days, it is important to further investigate the possible effects of the 125-mg/80-mg aprepitant regimen on the pharmacokinetics of orally administered CR oxycodone in patients with cancer pain.

Aprepitant had no detectable inhibitory effect on the pharmacokinetics of intravenously administered docetaxel or vinorelbine [10] [11] but resulted in increased plasma concentration of orally administered dexamethasone or CR oxycodone [9]. It is expected that an orally-coadministered drug is affected to a greater extent by an inhibitory effect of intestinal CYP3A4 than intravenously-administered drug due to the higher intestinal concentration of aprepitant as compared to the plasma concentration. Therefore, we consider that this result for CR oxycodone may not be applicable to intravenously administered oxycodone. In this study, our patients received individual dose and schedule of CR oxycodone and combined with various anti-cancer agents according to standard treatment for their tumor types. Additionally, we didn't conducted placebo-controlled trial, because the primary endpoint in this study is not pharmacodynamics of oxycodone and its metabolites but pharmacokinetics. These are limitations of study, because this study was conducted in subjects whom continued to be administered CR oxycodone routinely for cancer pain. Further study to validate effects of aprepitant on the pharmacokinetics and pharmacodynamics of controlled-release oral oxycodone pharmacokinetic is expected.

The trough concentration of oxycodone and its metabolite on day 1 pre-dose were similar to those on day 2 pre-dose, despite these trough concentrations with aprepitant on day 3 were higher than those on day1 and day 2. This indicated that the trough concentrations of CR oxycodone alone at steady state were not observed inter-day variability (Table 4). Meanwhile, the ratio of the geometric mean $AUC_{0-8}$ and trough concentration of CR oxycodone plus aprepitant to those of CR oxycodone alone was 1.25 (range 0.98–1.96) and 1.65 (range 0.54–3.41), respectively, with wide inter-patient variability observed (Figures S1 and S2). A pharmacogenomics study showed that a CYP2D6 genotype had an impact on plasma concentrations of oxycodone and oxymorphone, and the metabolism of oxycodone [15]. First, we are now planning a further pharmacogenomics study. Secondly, we will analyze plasma concentrations of aprepitant and investigate the possible influence of aprepitant concentrations on the pharmacokinetics of orally administered CR oxycodone.

In conclusion, aprepitant increased the exposure of oxycodone by 25% due to inhibiting its CYP3A4-mediated N-demethylation. The clinical use of aprepitant in patients receiving multiple doses of CR oxycodone for cancer pain significantly altered plasma concentration levels, but would not appear to need modification of the CR oxycodone dose in clinical co-administration of aprepitant in cancer patients, with adequate attention.

## Supporting Information

**Figure S1 Individual value plot of $AUC_{0-8}$ of (A) oxycodone (n = 20), (B) noroxycodone (n = 20), and (C) oxymorphone (n = 15) in patients who were administered with CR oxycodone alone or with aprepitant.** Dose of CR oxycodone: circle (5 mg), triangle (10 mg), square (15 mg), and pentagon (20 mg).
(TIF)

**Figure S2 Individual value plot of trough concentration of (a) oxycodone (n = 19), (b) noroxycodone (n = 19), and (c) oxymorphone (n = 13) in patients who were administered with CR oxycodone alone or with aprepitant.** Dose of CR oxycodone: circle (5 mg), triangle (10 mg), square (15 mg), and pentagon (20 mg).
(TIF)

**Checklist S1 TREND Statement Checklist.**
(PDF)

**Protocol S1 Clinical Study Protocol (Japanese version).**
(PDF)

**Protocol S2 Clinical Study Protocol (English version).**
(DOCX)

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## Author Contributions

Conceived and designed the experiments: YF, NC, HM. Performed the experiments: YF, MT, NC, NK, TS, YI, TM, HM. Analyzed the data: YF, MT, YI, HM. Contributed reagents/materials/analysis tools: YF, MT, HM. Wrote the paper: YF, MT, NC, YI, HM.

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# Measuring quality of life in patients with head and neck cancer: Update of the EORTC QLQ-H&N Module, Phase III

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**ABSTRACT:** *Background.* The objective of this study was to pilot test an updated version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module (EORTC QLQ-H&N60).

*Methods.* Patients with head and neck cancer were asked to complete a list of 60 head and neck cancer-specific items comprising the updated EORTC head and neck module and the core questionnaire EORTC QLQ-C30. Debriefing interviews were conducted to identify any irrelevant items and confusing or upsetting wording.

*Results.* Interviews were performed with 330 patients from 17 countries, representing different head and neck cancer sites and treatments. Forty-one of the 60 items were retained according to the predefined EORTC criteria for module development, for another 2 items the wording was refined, and 17 items were removed.

*Conclusion.* The preliminary EORTC QLQ-H&N43 can now be used in academic research. Psychometrics will be tested in a larger field study.
 *Head Neck* 00: 000–000, 2014

**KEY WORDS:** head and neck neoplasms, larynx, pharynx, oral cavity, multimodal therapies, chemoradiation, quality of life

## INTRODUCTION

Over the past 30 years, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Group (QLG) has developed numerous self-reported questionnaires to assess quality of life (QOL) in oncology.[1] These tools generally use a modular approach, with a 30-item core questionnaire[2] and additional modules for different cancer sites or treatments covering specific symptoms, treatment side-effects, and functional problems. One of the first site-specific modules was the 37-item head and neck cancer module (EORTC QLQ-H&N37), published in 1992.[3] It was subsequently shortened into the QLQ-H&N35 and validated[4] and finally tested in a European field study.[5] Since that time, numerous researchers and clinicians have used the QLQ-

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H&N35, and it has been administered in at least 19 different languages in 26 countries,[6] 8 phase III trials, 10 phase II trials, 42 cohort studies, 2 case-control studies, and 72 cross-sectional studies.[6]

A recent systematic review demonstrated that the QLQ-H&N35 scales possessed robust psychometric characteristics and that it has achieved good acceptance by patients throughout the world.[6] It also revealed, however, that some methodological improvements had been suggested by the users of the QLQ-H&N35, for example, to reduce the relatively high percentage of missing values on the speech (7%) and sexuality (11.5%) scale, or to improve the internal consistency of the speech scale,[6] indicating a need for updating and revising the module. In addition, standard treatments of head and neck cancer have evolved during the past decades, now including induction or simultaneous concomitant chemotherapy and/or targeted therapies more frequently, and it was considered that the H&N35 did not sufficiently cover the side-effects of these treatments.[7,8]

As a consequence, the EORTC Quality of Life Group together with the EORTC Head and Neck Cancer Group including the principal investigator of the QLQ-H&N35 discussed whether or not to revise the QLQ-H&N35. On the one hand, it would be desirable to have a module sensitive to detect QOL issues of current therapy regimens. On the other hand, changing a well-established and widespread questionnaire has the disadvantage that comparisons between studies using different versions would be hindered. Moreover, investigators and clinicians may be in doubt about which version to use in new studies.

Therefore, it was decided to first systematically investigate whether an update of the QLQ-H&N35 was indeed really necessary. After a literature review identifying potentially relevant new issues, we conducted interviews with 137 patients and 96 health care professionals finding that 26 issues relevant for patients' QOL were not part of the current head and neck module,[9] for example, rash and neurological problems, yielding a list of 60 issues. This confirmed that an update of the QLQ-H&N35 would be useful, both from a clinical and a research point of view. This was agreed between the EORTC Quality of Life Group and the EORTC Head and Neck Cancer Group.

Consequently, the new issues were reformatted into items and the EORTC item bank[10] was consulted for consistency. The response format conforms with the EORTC recommendations ranging from 1 = not at all to 4 = very much. The resulting provisional updated module QLQ-H&N60 then needed pilot-testing with respect to understanding, comprehensiveness, and applicability (phase III according to the EORTC Module Development Guidelines),[11] which was the primary purpose of the current study. A secondary purpose was to condense/shorten the module as much as possible without compromising its validity and comprehensiveness.

## MATERIALS AND METHODS

### Translations

The items were translated from English into Danish, Dutch, French, German, Greek, Hebrew, Italian, Japanese, Mandarin, Norwegian, Polish, Portuguese, Spanish, and Swedish following a standardized forward-backward procedure.[11] After the translation report was approved by the Translation Unit of the EORTC Quality of Life Department, and after native speakers with a clinical background had checked the translation, data collection commenced.

### Data collection

Patients were enrolled from 21 collaborating hospitals via members of the EORTC QLG. Patients with head and neck cancer with disease affecting the following tumor sites were eligible: larynx, hypopharynx, nasopharynx, oropharynx, parotid gland, nose, and oral cavity. Exclusion criteria included thyroid and eye cancer, insufficient command of any of the languages that the H&N60 was translated into, and severe cognitive dysfunction. Patients could have had any of the following treatments: surgery alone, surgery with radiotherapy, surgery with (radio) chemotherapy, (radio) chemotherapy alone, radiation alone, and biological therapy with and without any other treatment. Patients could be on or off treatment.

The procedure for patient interviews followed the EORTC QLG Module Development Guidelines.[11] Eligible patients were approached and invited to participate in this study. They received information about this project and could ask the study personnel any questions about the study. Once they had provided written informed consent, they were asked to complete the core questionnaire QLQ-C30 and the updated provisional head and neck module QLQ-H&N60.

After the patient had completed the questionnaire, a brief structured interview was conducted asking if there were any questions that were difficult to understand or perceived as upsetting. If patients found an item difficult to understand or confusing, they were asked to indicate how they would word this question. The interview ended with gaining their opinions on which were the 15 most relevant items, any irrelevant items, and any important items that were not included yet, addressing the entire questionnaire. Questionnaire completion and interview were conducted within one single patient visit.

Data on age, sex, education, tumor site, stage of disease, treatment, and performance status was collected using a Case Report Form to be completed by the interviewer. Data entry was done manually in Leipzig, Germany.

The study protocol was approved by the local ethical committees according to the national requirements. Informed consent was obtained before administration of the provisional module and interviews. Questionnaires were mailed to Leipzig, with no personal identifiable information.

### Data analysis

Data analysis was performed in accordance with the EORTC QLG Module Development Guidelines.[11] To retain an item in the module, it should fulfil certain predefined criteria.

### Criterion 1, relevance

The item mean value is >1.5 (on a scale of 1–4).

### Criterion 2, relevance

More than 50% of the patients rate this item as 3 ("quite a bit") or 4 ("very much").

TABLE 1. Demographic characteristics of the sample ($n = 330$).

| Category | No. of patients | (%) |
|---|---|---|
| Sex | | |
| Female | 92 | (27.9) |
| Male | 232 | (70.3) |
| Unknown | 6 | (1.8) |
| Age, y | | |
| <50 | 39 | (11.8) |
| 50–59 | 96 | (29.1) |
| 60–69 | 115 | (34.9) |
| 70–79 | 61 | (18.5) |
| ≤80 | 15 | (4.6) |
| Unknown | 4 | (1.2) |
| School education | | |
| Compulsory school education or less | 133 | (40.3) |
| Post compulsory school education | 117 | (35.5) |
| University level | 77 | (23.3) |
| Not specified | 3 | (0.9) |
| Country | | |
| Chile | 9 | (2.7) |
| Denmark | 8 | (2.4) |
| France | 13 | (3.9) |
| Greece | 9 | (2.7) |
| Germany | 66 | (20.0) |
| Israel | 22 | (6.7) |
| Italy | 37 | (11.2) |
| Japan | 5 | (1.5) |
| Norway | 25 | (7.6) |
| Poland | 13 | (3.9) |
| Portugal | 20 | (6.1) |
| Spain | 15 | (4.6) |
| Sweden | 25 | (7.6) |
| Taiwan | 18 | (5.5) |
| The Netherlands | 19 | (5.8) |
| United Kingdom | 11 | (3.3) |
| United States | 15 | (4.6) |

### Criterion 3, neither floor nor ceiling effects

More than 10% of the patients rate this item with a score of 1 or 2; >10% rate this item as 3 or 4.

### Criterion 4, range

The responses to the item include the full range of the scale from 1 to 4.

### Criterion 5, not upsetting

Less than 5% of the patients find the item upsetting.

### Criterion 6, not difficult

Less than 5% of the patients find the item difficult to understand.

### Criterion 7, compliance

More than 95% of the patients complete the item.

### Criterion 8, priority

More than 10% of the patients rate the item as relevant.

The aim was to include items fulfilling 5 of the first 7 criteria or criterion 8. Additional items could be added if the particular issue was mentioned by at least 5 patients.

Also, items were added to scales according to a hypothesized scale structure and the internal consistency (Cronbach's Alpha) of this scale was calculated. This information was used as an additional "Criterion α" indicating that the item can meaningfully be combined with other items to form a multi-item scale (ie, Cronbach's Alpha is ≥0.70) and the Alpha decreases if the item is removed.

All these criteria were tabulated together with the results of the methodological review[6] and the results discussed with a multiprofessional expert group at the EORTC QLG Spring Meeting 2013. This group decided, based on the results, their clinical experience, and the results of the review,[6] whether to keep the item as is, to remove the item, or change the wording.

## RESULTS

### Sample

Between August 2011 and February 2013, a total of 333 patients were enrolled. Three patients were excluded because they had thyroid ($n = 1$) or eye cancer ($n = 2$), resulting in 330 eligible participants. Patients came from 21 institutions in 17 countries, distributed over Central Europe ($n = 66$), Southern Europe ($n = 81$), Northern Europe ($n = 58$), Eastern Europe ($n = 13$), Western Europe ($n = 43$), Asia ($n = 45$), Northern America ($n = 15$), and Southern America ($n = 9$). Seventy percent of the patients were men, and the average age was 61 years (range, 25–89 years). The most frequent tumor site was oral cavity ($n = 94$), followed by oropharynx ($n = 80$), and larynx ($n = 79$). Full demographic and clinical sample characteristics are shown in Tables 1 and 2.

### Module administration

The time needed to complete the H&N60 was less than 10 minutes in 30% of all cases, 41% needed 11 to 15 minutes, 18% needed 16 to 20 minutes, 8% needed 21 to 30 minutes, and 3% needed more than 30 minutes.

Sixty-eight percent completed the module on their own, 25% needed assistance from the interviewer, and 7% from relatives or friends.

### Preliminary module

Based on the predefined thresholds, 47 of the 60 items had a mean >1.5 and therefore fulfilled criterion 1, none had >50% responses of "quite a lot" or "very much" (criterion 2), 55 had neither floor nor ceiling effects (criterion 3), all had a range of 1 to 4 (criterion 4), 58 were not upsetting for more than 5% (criterion 5), 58 were not difficult to understand for more than 5% (criterion 6), and 56 were completed by >95% of the patients (criterion 7). Fifty-two items fulfilled at least 5 of these 7 criteria. Fifteen items were prioritized by >10% of the patients (criterion 8). All of the highly prioritized items fulfilled at least 5 of the first 7 criteria.

Considering these criteria and the preliminary scale structure, the expert group decided to retain 41 items as they were, to amend the wording of 2 items, and to remove 17 items. Details are shown in Table 3. The wording of item 46 was changed from "Have you had problems because of losing some teeth (as part of your

TABLE 2. Clinical characteristics of the sample ($n = 330$).

| Category | No. of patients | (%) |
|---|---|---|
| Tumor site | | |
| Larynx | 79 | (23.9) |
| Hypopharynx | 19 | (5.8) |
| Oropharynx | 80 | (24.2) |
| Nasopharynx | 18 | (5.5) |
| Oral cavity | 94 | (28.5) |
| Parotid gland | 6 | (1.8) |
| Nasal cavity and sinuses | 19 | (5.8) |
| Unknown primary | 5 | (1.5) |
| Other | 8 | (2.4) |
| Unknown | 2 | (0.6) |
| Karnofsky performance score | | |
| ≤50 | 7 | (2.1) |
| 60 | 36 | (10.9) |
| 70 | 60 | (18.2) |
| 80 | 66 | (20.0) |
| 90 | 105 | (31.8) |
| 100 | 54 | (16.4) |
| Unknown | 2 | (0.6) |
| Recurrent disease | | |
| No | 279 | (84.6) |
| Yes | 47 | (14.2) |
| Unknown | 4 | (1.2) |
| Tumor stage (UICC 2005) | | |
| I | 41 | (12.4) |
| II | 55 | (16.7) |
| III | 62 | (18.8) |
| IV | 148 | (44.9) |
| Unknown | 24 | (7.3) |
| Treatment | | |
| OP alone | 58 | (17.6) |
| RT alone | 35 | (10.6) |
| CT alone | 6 | (1.8) |
| RCT without OP | 67 | (20.3) |
| OP + RCT | 77 | (23.3) |
| OP + CT | 3 | (0.9) |
| OP + RT | 78 | (23.6) |
| Other | 3 | (0.9) |
| Unknown | 2 | (0.6) |
| Targeted therapy | | |
| No | 295 | (89.4) |
| Yes | 32 | (9.7) |
| Unknown | 3 | (0.9) |
| Stage of treatment | | |
| Before treatment | 11 | (3.3) |
| During treatment | 132 | (40.0) |
| <6 mo after end of treatment | 49 | (14.9) |
| ≥6 mo after end of treatment | 63 | (19.1) |
| ≥12 mo after end of treatment | 71 | (21.5) |
| Unknown | 4 | (1.2) |

Abbreviations: UICC, Union for International Cancer Control; OP, surgery; RT, radiotherapy; CT, chemotherapy; RCT, radio-chemotherapy.

treatment)?" into "Have you had problems because of losing some teeth?" and item 71 from "Have you been hoarse?" into "Have you had problems with hoarseness?"

There were 44 additional items suggested by patients. The most frequently mentioned issues were doctor-patient-relationship (4×), mental well-being (3×), and information about the disease or treatment (2×). However, none was mentioned 5 times or more. In addition, these issues are covered by the QLQ-C30 and the EORTC information module.[12] Therefore, no new items were added to the questionnaire and the resulting preliminary module contains 43 items.

## DISCUSSION

The EORTC QLQ-H&N43 is an updated and revised version of the EORTC QLQ-H&N35, measuring QOL in patients with head and neck malignancies excluding eye and thyroid cancers. Patients representing different tumor sites, tumor stages, treatment options, and treatment phases were included in this update to ensure that the module is applicable in a broad variety of clinical studies.

Traditionally, the EORTC H&N module has followed the concept of targeting a heterogeneous group of patients. This is in contrast to other EORTC QOL modules. For example, the modules for patients with gynecological malignancies were developed separately for cervical,[13] endometrial,[14] and ovarian cancer,[15] and a module for vulval cancer is currently under development. That approach has certain advantages. For example, the module can be shorter as the variety and number of QOL issues relevant to the patients is smaller because the disease and the treatment-specific side effects are similar. Shorter questionnaires are usually preferred by clinicians and researchers. However, as many clinical trials in head and neck oncology enroll patients with different tumor sites, it was decided after discussion within the EORTC Quality of Life Group and the EORTC Head and Neck Cancer Group to continue with the previous concept of having one single module for all types of head and neck malignancies (except eye and thyroid cancer, which are specific entities with their own profile of QOL experience). This ensures that within one trial one module can be used instead of needing to include two or more different modules. As a consequence, the module is somewhat longer than other EORTC questionnaires. Compared to the previous version, QLQ-H&N35, it contains additional questions regarding skin problems, a typical symptom after targeted therapy,[16] neurological side-effects, and shoulder problems, whereas some issues that can be assessed more reliably by other means were removed (for example, weight or pain medication). However, the QLQ-H&N43 contains many scales of the QLQ-H&N35, thus, data from studies using the 2 different versions of the EORTC head and neck module will be comparable to some extent. We also tried to harmonize the QLQ-H&N43 with the newly developed EORTC oral health module OH-17.[17] However, although there are some overlapping issues across both modules, they do not focus on the same QOL areas. The OH-17 targets oral health issues in a variety of cancer diagnoses whereas the head and neck module is for head and neck cancer only.

The patients in our sample can be considered representative of a wider head and neck cancer population. The male/female ratio, as well as the distribution of tumor sites, mirrors the incidence data of head and neck malignancies. The educational level is probably skewed to a higher educational level than the general head and neck cancer population, although we can state that participants

TABLE 3. Results of patient interviews.

| | | | | | crit α | | crit 1 | | crit 2 | | crit 3 | | crit 4 | | crit 5 | | crit 6 | | crit 7 | | | | crit 8 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| item Nr | wording | hypothesized scale | α of hypothesized scale | α if item removed | decreased α if item removed? | mean | mean > 1.5? | proportion of scores 3/4 | scores 3/4 >50%? | proportion of scores 1/2 | neither floor nor ceiling | range | range | % upsetting | <5% upsetting | % difficult | <5% difficult | proportion complete | >95% complete? | sum crit 1 to 7 | min. 5 of crit 1 to 7? | proportion relevant | >= 10% relevant | Decision |
| q 31 | Have you had a swelling in your neck? | LY | n.a. | n.a. | 1 | 1.7 | 1 | 0.20 | 0 | 0.79 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 1.00 | 1 | 6 | 1 | 0.08 | 0 | keep |
| q 32 | Have you had problems with wound healing? | WOU | 0.45 | n.a. | 0 | 1.4 | 0 | 0.14 | 0 | 0.84 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.98 | 1 | 5 | 1 | 0.04 | 0 | keep |
| q 33 | Have you had skin problems (e.g. itchy, dry)? | SKIN | 0.82 | 0.75 | 1 | 1.8 | 1 | 0.23 | 0 | 0.77 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.99 | 1 | 6 | 1 | 0.08 | 0 | keep |
| q 34 | Has dryness of your skin bothered you? | SKIN | 0.82 | 0.74 | 1 | 1.6 | 1 | 0.15 | 0 | 0.82 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.98 | 1 | 6 | 1 | 0.06 | 0 | remove |
| q 35 | Have you had tingling or numbness in your hands or feet? | NEU | 0.48 | n.a. | 0 | 1.5 | 1 | 0.14 | 0 | 0.86 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 1.00 | 1 | 6 | 1 | 0.04 | 0 | keep |
| q 36 | Have you felt dizzy? | NEU | 0.48 | n.a. | 0 | 1.5 | 0 | 0.11 | 0 | 0.88 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.99 | 1 | 5 | 1 | 0.02 | 0 | remove |
| q 37 | Have you had a rash? | SKIN | 0.82 | 0.82 | 1 | 1.3 | 0 | 0.07 | 0 | 0.91 | 0 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.98 | 1 | 4 | 0 | 0.03 | 0 | keep |
| q 38 | Have you had problems with hearing because of your treatment? | HEAR | n.a. | n.a. | 1 | 1.5 | 0 | 0.15 | 0 | 0.84 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.99 | 1 | 5 | 1 | 0.05 | 0 | remove |
| q 39 | Has your skin colour changed? | SKIN | 0.82 | 0.81 | 1 | 1.4 | 0 | 0.11 | 0 | 0.88 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.99 | 1 | 5 | 1 | 0.04 | 0 | keep |
| q 40 | Have you been bothered by itchy skin? | SKIN | 0.82 | 0.78 | 1 | 1.5 | 0 | 0.11 | 0 | 0.88 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.99 | 1 | 5 | 1 | 0.03 | 0 | remove |
| q 41 | Have you had trouble speaking clearly? | SP | 0.84 | 0.78 | 1 | 2.2 | 1 | 0.35 | 0 | 0.64 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.99 | 1 | 6 | 1 | 0.12 | 1 | keep |
| q 42 | Have you had trouble talking in a noisy environment? | SP | 0.84 | 0.80 | 1 | 2.1 | 1 | 0.33 | 0 | 0.66 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.98 | 1 | 6 | 1 | 0.07 | 0 | keep |
| q 43 | Has it been difficult to raise your arm or to move it sideways? | SHO | 0.84 | n.a. | 1 | 1.6 | 1 | 0.19 | 0 | 0.79 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.99 | 1 | 6 | 1 | 0.07 | 0 | keep |
| q 44 | Have you had pain in your shoulder? | SHO | 0.84 | n.a. | 1 | 1.7 | 1 | 0.19 | 0 | 0.81 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 1.00 | 1 | 6 | 1 | 0.04 | 0 | keep |
| q 45 | Have you had problems with transferred tissue (your flap | WOU | 0.45 | n.a. | 0 | 1.3 | 0 | 0.07 | 0 | 0.84 | 0 | 1–4 | 1 | 0.00 | 1 | 0.08 | 0 | 0.91 | 0 | 2 | 0 | 0.02 | 0 | remove |

TABLE 3. *Continued*

| | | | | | crit α | | crit 1 | | crit 2 | | crit 3 | | crit 4 | | crit 5 | | crit 6 | | crit 7 | | | crit 8 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| item Nr | wording | hypothesized scale | α of hypothesized scale | α if item removed | decreased α if item removed? | mean | mean > 1.5? | proportion of scores 3/4 | scores 3/4 >50%? | proportion of scores 1/2 | neither floor nor ceiling | range | range | % upsetting | <5% upsetting | % difficult | <5% difficult | proportion complete | >95% complete? | sum crit 1 to 7 | min. 5 of crit 1 to 7? | proportion relevant | >= 10% relevant | Decision |
| | put in at your operation)? | | | | | | | | | | | | | | | | | | | | | | | |
| q 46 | Have you had problems because of losing some teeth (as part of your treatment)? | TE | 0.78 | 0.73 | 1 | 1.8 | 1 | 0.24 | 0 | 0.73 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.98 | 1 | 6 | 1 | 0.07 | 0 | change |
| q 47 | Have you had trouble chewing? | TE | 0.78 | 0.70 | 1 | 2.2 | 1 | 0.37 | 0 | 0.61 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.98 | 1 | 6 | 1 | 0.15 | 1 | keep |
| q 48 | Have you felt uncomfortable about being physically intimate? | PC | 0.82 | 0.79 | 1 | 1.7 | 1 | 0.18 | 0 | 0.76 | 1 | 1–4 | 1 | 0.03 | 1 | 0.05 | 0 | 0.94 | 0 | 4 | 0 | 0.04 | 0 | remove |
| q 49 | Have you felt less physically attractive as a result of your disease or treatment? | BI | 0.87 | 0.84 | 1 | 1.8 | 1 | 0.24 | 0 | 0.74 | 1 | 1–4 | 1 | 0.02 | 1 | 0.02 | 1 | 0.98 | 1 | 6 | 1 | 0.05 | 0 | keep |
| q 50 | Have you felt dissatisfied with your body? | BI | 0.87 | 0.84 | 1 | 1.7 | 1 | 0.18 | 0 | 0.80 | 1 | 1–4 | 1 | 0.01 | 1 | 0.02 | 1 | 0.98 | 1 | 6 | 1 | 0.06 | 0 | keep |
| q 51 | Have you felt less feminine/masculine as a result of your illness or treatment? | BI | 0.87 | 0.85 | 1 | 1.5 | 0 | 0.14 | 0 | 0.83 | 1 | 1–4 | 1 | 0.01 | 1 | 0.02 | 1 | 0.97 | 1 | 5 | 1 | 0.05 | 0 | remove |
| q 52 | Have you been worried about your return to work? | ANX | 0.77 | 0.83 | 0 | 1.6 | 1 | 0.17 | 0 | 0.78 | 1 | 1–4 | 1 | 0.00 | 1 | 0.03 | 1 | 0.95 | 1 | 6 | 1 | 0.04 | 0 | remove |
| q 53 | Have you been worried about the results of examinations and tests? | ANX | 0.77 | 0.60 | 1 | 2.2 | 1 | 0.34 | 0 | 0.65 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.99 | 1 | 6 | 1 | 0.12 | 1 | keep |
| q 54 | Have you been worried about your health in the future? | ANX | 0.77 | 0.58 | 1 | 2.4 | 1 | 0.41 | 0 | 0.59 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.99 | 1 | 6 | 1 | 0.16 | 1 | keep |
| q 55 | Have you felt less secure because your look has changed? | BI | 0.87 | 0.85 | 1 | 1.6 | 1 | 0.17 | 0 | 0.82 | 1 | 1–4 | 1 | 0.01 | 1 | 0.00 | 1 | 0.98 | 1 | 6 | 1 | 0.04 | 0 | remove |
| q 56 | Have you had pain in your mouth?* | PA | 0.85 | 0.76 | 1 | 1.9 | 1 | 0.28 | 0 | 0.72 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 1.00 | 1 | 6 | 1 | 0.15 | 1 | keep |

TABLE 3. *Continued*

| | | | | | crit α | | crit 1 | | crit 2 | | crit 3 | | crit 4 | | crit 5 | | crit 6 | | crit 7 | | | | crit 8 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| item Nr | wording | hypothesized scale | α of hypothesized scale | α if item removed | decreased α if item removed? | mean | mean > 1.5? | proportion of scores 3/4 | scores 3/4 >50%? | proportion of scores 1/2 | neither floor nor ceiling | range | range | % upsetting | <5% upsetting | % difficult | <5% difficult | proportion complete | >95% complete? | sum crit 1 to 7 | min. 5 of crit 1 to 7? | proportion relevant | >= 10% relevant | Decision |
| q 57 | Have you had pain in your jaw? * | PA | 0.85 | 0.82 | 1 | 1.6 | 1 | 0.20 | 0 | 0.79 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.99 | 1 | 6 | 1 | 0.07 | 0 | keep |
| q 58 | Have you had soreness in your mouth? * | PA | 0.85 | 0.77 | 1 | 1.9 | 1 | 0.24 | 0 | 0.74 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.98 | 1 | 6 | 1 | 0.11 | 1 | keep |
| q 59 | Have you had pain in your throat? * | PA | 0.85 | 0.86 | 0 | 1.9 | 1 | 0.26 | 0 | 0.73 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.99 | 1 | 6 | 1 | 0.12 | 1 | keep |
| q 60 | Have you had problems swallowing liquids? * | SW | 0.86 | 0.81 | 1 | 1.8 | 1 | 0.24 | 0 | 0.75 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.99 | 1 | 6 | 1 | 0.12 | 1 | keep |
| q 61 | Have you had problems swallowing pureed food? * | SW | 0.86 | 0.78 | 1 | 1.8 | 1 | 0.24 | 0 | 0.75 | 1 | 1–4 | 1 | 0.00 | 1 | 0.02 | 1 | 0.99 | 1 | 6 | 1 | 0.14 | 1 | keep |
| q 62 | Have you had problems swallowing solid food? * | SW | 0.86 | 0.82 | 1 | 2.3 | 1 | 0.41 | 0 | 0.58 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.99 | 1 | 6 | 1 | 0.20 | 1 | keep |
| q 63 | Have you choked when swallowing? * | SW | 0.86 | 0.88 | 0 | 1.7 | 1 | 0.18 | 0 | 0.81 | 1 | 1–4 | 1 | 0.00 | 1 | 0.02 | 1 | 0.99 | 1 | 6 | 1 | 0.11 | 1 | keep |
| q 64 | Have you had problems with your teeth? * | TE | 0.78 | 0.69 | 1 | 1.8 | 1 | 0.24 | 0 | 0.76 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.99 | 1 | 6 | 1 | 0.07 | 0 | keep |
| q 65 | Have you had problems opening your mouth wide? * | OM | n.a. | n.a. | 1 | 1.9 | 1 | 0.29 | 0 | 0.70 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.99 | 1 | 6 | 1 | 0.08 | 0 | keep |
| q 66 | Have you had a dry mouth? * | DR | 0.78 | n.a. | 1 | 2.4 | 1 | 0.46 | 0 | 0.53 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.99 | 1 | 6 | 1 | 0.16 | 1 | keep |
| q 67 | Have you had sticky saliva? * | DR | 0.78 | n.a. | 1 | 2.3 | 1 | 0.40 | 0 | 0.59 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.99 | 1 | 6 | 1 | 0.15 | 1 | keep |
| q 68 | Have you had problems with your sense of smell? * | SE | 0.69 | n.a. | 0 | 1.7 | 1 | 0.24 | 0 | 0.75 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.99 | 1 | 6 | 1 | 0.05 | 0 | keep |
| q 69 | Have you had problems with your sense of taste? * | SE | 0.69 | n.a. | 0 | 2.2 | 1 | 0.39 | 0 | 0.60 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.99 | 1 | 6 | 1 | 0.12 | 1 | keep |
| q 70 | Have you had problems with coughing? * | CO | n.a. | n.a. | 1 | 1.9 | 1 | 0.25 | 0 | 0.74 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 1.00 | 1 | 6 | 1 | 0.05 | 0 | keep |
| q 71 | Have you been hoarse? * | SP | 0.84 | 0.89 | 0 | 1.9 | 1 | 0.26 | 0 | 0.73 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.99 | 1 | 6 | 1 | 0.04 | 0 | change |
| q 72 | Have you felt ill? * | FI | n.a. | n.a. | 1 | 1.8 | 1 | 0.24 | 0 | 0.75 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.99 | 1 | 6 | 1 | 0.03 | 0 | remove |
| q 73 | Has your appearance bothered you? * | BI | 0.87 | 0.85 | 1 | 1.6 | 1 | 0.16 | 0 | 0.83 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.98 | 1 | 6 | 1 | 0.03 | 0 | keep |

TABLE 3. *Continued*

| | | | | | crit α | | crit 1 | | crit 2 | | crit 3 | | crit 4 | | crit 5 | | crit 6 | | crit 7 | | | crit 8 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| item Nr | wording | hypothesized scale | α of hypothesized scale | α if item removed | decreased α if item removed? | mean | mean > 1.5? | proportion of scores 3/4 | scores 3/4 >50%? | proportion of scores 1/2 | neither floor nor ceiling | range | range | % upsetting | <5% upsetting | % difficult | <5% difficult | proportion complete | >95% complete? | sum crit 1 to 7 | min. 5 of crit 1 to 7? | proportion relevant | >= 10% relevant | Decision |
| q 74 | Have you had problems eating? * | SO | 0.85 | 0.83 | 1 | 2.2 | 1 | 0.39 | 0 | 0.60 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.99 | 1 | 6 | 1 | 0.13 | 1 | keep |
| q 75 | Have you had problems eating in front of your family? * | SO | 0.85 | 0.81 | 1 | 1.6 | 1 | 0.18 | 0 | 0.80 | 1 | 1–4 | 1 | 0.00 | 1 | 0.02 | 1 | 0.98 | 1 | 6 | 1 | 0.06 | 0 | keep |
| q 76 | Have you had problems eating in front of other people? * | SO | 0.85 | 0.79 | 1 | 1.8 | 1 | 0.24 | 0 | 0.75 | 1 | 1–4 | 1 | 0.00 | 1 | 0.02 | 1 | 0.98 | 1 | 6 | 1 | 0.08 | 0 | keep |
| q 77 | Have you had problems enjoying your meals? * | SO | 0.85 | 0.82 | 1 | 2.1 | 1 | 0.33 | 0 | 0.66 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.98 | 1 | 6 | 1 | 0.11 | 0 | keep |
| q 78 | Have you had problems talking to other people? * | SP | 0.84 | 0.78 | 1 | 1.8 | 1 | 0.26 | 0 | 0.74 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.99 | 1 | 6 | 1 | 0.08 | 0 | keep |
| q 79 | Have you had problems talking on the telephone? * | SP | 0.84 | 0.77 | 1 | 1.9 | 1 | 0.27 | 0 | 0.72 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.98 | 1 | 6 | 1 | 0.09 | 0 | keep |
| q 80 | Have you had problems having social contact with your family or friends? * | SC | 0.71 | n.a. | 1 | 1.4 | 0 | 0.10 | 0 | 0.89 | 0 | 1–4 | 1 | 0.00 | 1 | 0.02 | 1 | 0.99 | 1 | 4 | 0 | 0.03 | 0 | remove |
| q 81 | Have you had problems going out in public? * | SC | 0.71 | n.a. | 1 | 1.5 | 0 | 0.14 | 0 | 0.84 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.98 | 1 | 5 | 1 | 0.04 | 0 | keep |
| q 82 | Have you had problems having close physical contact with family or friends? * | PC | 0.82 | 0.85 | 0 | 1.3 | 0 | 0.08 | 0 | 0.88 | 0 | 1–4 | 1 | 0.01 | 1 | 0.02 | 1 | 0.96 | 1 | 4 | 0 | 0.02 | 0 | remove |
| q 83 | Have you felt less interest in sex? * | PC | 0.82 | 0.69 | 1 | 2.0 | 1 | 0.29 | 0 | 0.63 | 1 | 1–4 | 1 | 0.06 | 0 | 0.04 | 1 | 0.92 | 0 | 4 | 0 | 0.05 | 0 | keep |
| q 84 | Have you felt less sexual enjoyment? * | PC | 0.82 | 0.70 | 1 | 1.9 | 1 | 0.25 | 0 | 0.64 | 1 | 1–4 | 1 | 0.06 | 0 | 0.04 | 1 | 0.88 | 0 | 4 | 0 | 0.03 | 0 | keep |
| q 85 | Have you used pain-killers? * | PK | n.a. | n.a. | 1 | 2.1 | 1 | 0.34 | 0 | 0.65 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.99 | 1 | 6 | 1 | 0.05 | 0 | remove |
| q 86 | Have you taken any nutritional supplements (excluding vitamins)? * | NU | n.a. | n.a. | 1 | 1.7 | 1 | 0.22 | 0 | 0.75 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.98 | 1 | 6 | 1 | 0.02 | 0 | remove |

TABLE 3. *Continued*

| | | | | | crit α | | crit 1 | | crit 2 | | crit 3 | | crit 4 | | crit 5 | | crit 6 | | crit 7 | | | crit 8 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| item Nr | wording | hypothesized scale | α of hypothesized scale | α if item removed | decreased α if item removed? | mean | mean > 1.5? | proportion of scores 3/4 | scores 3/4 >50%? | proportion of scores 1/2 | neither floor nor ceiling | range | range | % upsetting | <5% upsetting | % difficult | <5% difficult | proportion complete | >95% complete? | sum crit 1 to 7 | min. 5 of crit 1 to 7? | proportion relevant | >= 10% relevant | Decision |
| q 87 | Have you used a feeding tube? * | FE | n.a. | n.a. | 1 | 1.6 | 1 | 0.20 | 0 | 0.78 | 1 | 1–4 | 1 | 0.00 | 1 | 0.02 | 1 | 0.98 | 1 | 6 | 1 | 0.04 | 0 | remove |
| q 88 | Have you lost weight? * | WL | 0.82 | 0.87 | 0 | 1.8 | 1 | 0.22 | 0 | 0.77 | 1 | 1–4 | 1 | 0.00 | 1 | 0.01 | 1 | 0.98 | 1 | 6 | 1 | 0.05 | 0 | remove |
| q 89 | Have you worried about your weight being too low? | WL | 0.82 | 0.66 | 1 | 1.5 | 0 | 0.12 | 0 | 0.86 | 1 | 1–4 | 1 | 0.00 | 1 | 0.00 | 1 | 0.98 | 1 | 5 | 1 | 0.03 | 0 | keep |
| q 90 | Has weight loss been a problem for you? | WL | 0.82 | 0.74 | 1 | 1.4 | 0 | 0.09 | 0 | 0.88 | 0 | 1–4 | 1 | 0.01 | 1 | 0.01 | 1 | 0.97 | 1 | 4 | 0 | 0.01 | 0 | remove |

Abbreviations: LY, lymphedema; WOU, problems with wound healing; SKIN, skin problems; NEU, neurological problems; HEAR, problems with hearing; SP, speech problems; SHO, shoulder problems; TE, problems with teeth; PC, physical contact; SC, social contact; BI, body image; ANX, anxiety; PA, pain; SW, problems with swallowing; OM, opening mouth; DR, dry mouth and sticky saliva; SE, problems with senses; CO, coughing; FI, feeling ill; SO, social eating; PK, pain killers; NU, nutritional supplements; FE, feeding tube; WL, weight loss.
Note: When a criterion was fulfilled, the item is label with "1" in contrast to "0" if it was not fulfilled.
* Item was part of the previous module version QLQ-H&N35.

with less formal education did not report more difficulty in completing the questionnaire than others.

The QLQ-H&N43 is now ready for wider use. After completing phase III, EORTC QLQ modules can be used free of charge for academic research upon request at the EORTC Quality of Life Department and by sending an e-mail to the principal investigator.

We would like to confirm that the QLQ-H&N35 can still be used in ongoing or future trials if the investigators prefer to keep this head and neck module version. In studies investigating multimodal treatment or targeted therapies, however, the QLQ-H&N43 might be more suitable to detect differences between patient groups; it is therefore possible to use this version for future protocols. Both versions, the QLQ-H&N35 and the QLQ-H&N43, have overlapping items and scales; hence if clinicians wish to use the updated module in the future, existing data from the previous head and neck module can be used.

Investigators should be aware that, after completion of the final phase IV validation study, the QLQ-H&N43 may be further shortened based on psychometric characteristics.

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# Prognostic Value of FDG PET Imaging in Patients with Laryngeal Cancer

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## Abstract

*Background and Purpose:* To investigate the prognostic value of $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG-PET) in patients with laryngeal cancer.

*Materials and Methods:* The study included 51 patients of whom 30 underwent definitive radiotherapy with or without chemotherapy and 21 underwent radical surgery with or without adjuvant chemoradiation therapy. FDG uptake by both the primary lesion and the neck node was measured using the maximum standardized uptake value (SUVmax). The effects of clinicopathological factors including primary tumor SUVmax and nodal SUVmax on progression-free survival, local control, nodal progression-free survival, and distant metastasis-free survival were evaluated using the log-rank test and Cox method.

*Results:* The median duration of follow-up was 48.6 months (range 8 to 82.1 months). Univariate analysis showed that nodal SUVmax, N status, and tumor TNM stage were significantly associated with recurrence, whereas primary tumor SUVmax, age, treatment strategy and T status were not. Multivariate analysis demonstrated that only the nodal SUVmax was a significantly unfavorable factor for progression-free survival ($p=0.029$, hazard ratio 0.54, 95% CI 0.38-0.87) and nodal progression-free survival ($p=0.023$, hazard ratio 0.51, 95% CI 0.34-0.81). ROC curve analysis and log-rank test showed that patients with a high nodal SUVmax ($\geq 4$) had a significantly lower progression-free survival rate than those with a low SUVmax ($<4$; $p<0.0001$).

*Conclusions:* The pretreatment SUVmax of nodal disease in patients with laryngeal cancer is prognostic for recurrence.

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## Introduction

Various treatment strategies are used to improve outcome in patients with squamous cell carcinoma of the head and neck. Selection of appropriate treatment strategies and prognostication remain difficult for clinicians, despite careful evaluation of clinical factors, TNM staging, and anatomic subsite. Identification of novel pretreatment imaging biomarkers that would potentially predict long-term outcome would be clinically significant.

With the use of $^{18}$F-fluorodeoxyglucose (FDG), a glucose analog, positron emission tomography (PET) allows non-invasive assessment of glucose metabolism in a wide variety of tumor types including head and neck cancer. Tumor FDG uptake has been associated with various cellular characteristics such as cell viability and proliferation activity [1,2]. Thus, analyses of metabolic parameters, which are independent of morphologic changes, are expected to offer an important opportunity to predict individual tumor behavior.

Although several studies have found that metabolic activity evident FDG-PET in patients with a variety of head and neck cancer subtypes (i.e. nasopharynx, oropharynx, hypopharynx, larynx, oral tongue, gum, buccal mucosa, mouth floor) has prognostic significance [3,4], the prognostic value of FDG-PET for squamous cell carcinoma of head and neck cancer remains controversial. Moreover, there is no information on the prognostic value of FDG-PET in only laryngeal cancer, and it remains uncertain whether FDG-PET in patients with laryngeal cancer actually yields prognostic information. We performed a retrospective review of 51 patients with laryngeal cancer who underwent FDG-PET at initial presentation to determine whether FDG uptake by the primary tumor and neck lymph nodes is correlated with recurrence.

## Materials and Methods

### Patient

Written prior informed consent to undergo FDG-PET imaging and receive treatments was obtained from all patients. The institutional review board (Kobe University Hospital, Japan) approved this retrospective study (No 1401); patient informed consent for inclusion in this study was waived. To protect patient privacy, we removed all identifiers from our records at the completion of our analyses. Our primary selection criteria for patients included those who underwent FDG-PET scan as a pretreatment staging examination at our institution within 2 weeks before treatment for biopsy proven squamous cell laryngeal carcinoma, between October 2006 and September 2011. On the basis of these primary criteria, 60 consecutive patients were selected. Of these, 9 were excluded because of (a) a follow-up duration of less than 6 months (n = 6), and (b) presence of distant metastasis (n = 3). A total of 51 patients (46 males, 5 females; average age at diagnosis 69.1 years, range 56–86 years) meeting the eligibility criteria for this study were included in the analysis.

Pretreatment systematic evaluations were performed along with a routine physical examination, laryngoscopy and tissue biopsy, serum chemistry, chest radiography, contrast-enhanced CT or MRI of the head and neck, and FDG-PET scan. Clinical staging and treatment choices were decided using the information derived from these examinations at the Head and Neck Cancer Board conference of Kobe University Hospital which consisted of head and neck surgeons, radiation oncologists, medical oncologists and radiologists.

Clinical assessment of prognostic factors was performed retrospectively in all 51 patients with laryngeal cancer, in a subgroup of 30 patients who underwent definitive radiotherapy (RT) with or without chemotherapy (RT group), and in a subgroup of 21 patients who underwent radical surgery and neck dissection with or without adjuvant chemoradiation therapy (surgery group). Subsequent follow-up included physical examination, laryngoscopy, contrast-enhanced CT, and FDG-PET.

### FDG-PET study

All whole-body FDG-PET scans were acquired with a PET scanner (Philips Allegro, Philips Medical System, Best, the Netherlands) that provided 45 trans-axial images at 4-mm intervals over a distance of 18.0 cm. After at least 6 h of fasting, patients received an intravenous injection of 222 to 333 MBq (6 to 9 mCi) of FDG. After positioning the patient, a static emission scan was performed with 2.5 to 3 min of acquisition in each bed position, covering the upper thigh to the ear with a total of 9–10 bed positions. Then, a transmission scan using a $^{137}$Cs ring was performed over the same area for 23 s per bed position. Three-dimensional acquisition was performed and PET images were reconstructed using an ordered-subset expectation maximization iterative reconstruction algorithm (RAMLA). The field of view and pixel size of the reconstructed images were 57.6 cm and 4.0 mm, respectively, with a matrix size of 128×128.

After the FDG-PET scan had been completed, patients were moved to the CT room. The CT device was a multi-detector row CT system with an acceleration voltage of 120 kVp and a current of 80 mA. Both reconstructed PET and CT data were transferred to a workstation running viewing-dedicated software (Syntegra; SUN Microsystems, Milpitas, CA, USA) to create fused PET and CT images.

### Image analysis

PET images were retrospectively interpreted by two experienced nuclear medicine physicians. For semiquantitative analysis of FDG uptake, regions of interest (ROIs) were defined on the target lesions (primary lesion and neck lymph node) on the transaxial PET images. The maximum standardized uptake value (SUV) was calculated for quantitative analysis of tumor FDG uptake, as follows:

$$\mathrm{SUV} = \mathrm{C(kBq/ml)/ID(kBq)/body\ weight(kg)},$$

where C is the tissue activity concentration measured by PET and ID is the injected dose.

For nodal disease, the highest SUVmax was used for subsequent correlation with clinical outcomes.

### Statistical analysis

The actuarial progression-free survival (PFS), local control (LC), nodal progression-free survival (NPFS), and distant metastasis-free survival (DMFS) rates were calculated using the Kaplan-Meier method. The duration was calculated from the initial date of treatment to the date of an event or the last follow-up visit. PFS was defined as absence of death due to any cause or recurrence. LC was defined as only primary site control. NPFS was defined as any regional nodal failure after treatment as an event. DMFS was defined as the absence of any distant metastasis.

Survival data were analyzed using Kaplan–Meier plots and the log-rank test. The prognostic value of individual variables was evaluated using Cox proportional hazards logistic regression. We determined the statistically significant SUV cutoff value for survival analysis using the log-rank test and receiver operating characteristic (ROC) curve analysis.

Univariate Cox proportional hazards modeling was used to quantify the risk for recurrence of the following variables: age, treatment strategy, T status, N status, tumor TNM stage, primary tumor SUVmax, and nodal SUVmax. Subsequently, the significant or borderline univariate variables ($p<0.1$) were entered into multivariate analysis. The results from the Cox models were expressed as hazard ratios with 95% confidence intervals, and p values of $<0.05$ were considered to indicate statistical significance. All analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC).

## Results

### Patient characteristics

Patient demographics and clinicopathologic variables are demonstrated in Table 1. With regard to the distribution of TNM stages in the 51 patients, eight were at stage I, 17 were at stage II, 12 were at stage III, and 14 were at stage IV.

In the RT group (n = 30), 20 patients received only RT at doses of 66.0 to 74.4 Gy and 10 received RT (66.0-73.2 Gy) concomitant with chemotherapy, generally two or three cycles of cisplatin with or without continuous infusion of 5-flurouracil and/or docetaxel. In the surgery group (n = 21), all patients underwent radical surgery with neck dissection. Moreover, 4 received adjuvant chemoradiation therapy and 1 received radiotherapy.

### Prognostic factors in the patients overall

After a median follow-up of 48.6 months for the patients overall, 11 (21.6%) of the 51 patients had recurrence. Among these 11 patients, four developed local recurrence, two neck nodal recurrence, and five lung metastasis. The median overall follow-

**Table 1.** Patient characteristics.

| | RT group | Surgery group | Total |
|---|---|---|---|
| **Characteristics** | **n=30** | **n=21** | **n=51** |
| Median age, years (range) | 67 (58–83) | 69 (56–86) | 69 (56–86) |
| Sex: male/female | 29/1 | 17/4 | 46/5 |
| T status | | | |
| T1 | 7 | 2 | 9 |
| T2 | 18 | 4 | 22 |
| T3 | 5 | 7 | 12 |
| T4 | 0 | 8 | 8 |
| N status | | | |
| N0 | 27 | 11 | 38 |
| N1 | 1 | 2 | 3 |
| N2 | 1 | 8 | 9 |
| N3 | 1 | 0 | 1 |
| TNM stage (AJCC) | | | |
| I | 7 | 1 | 8 |
| II | 15 | 2 | 17 |
| III | 6 | 6 | 12 |
| IV | 2 | 12 | 14 |
| Primary tumor SUVmax | | | |
| Median (range) | 2.85 (1.2–8.52) | 8.6 (3.6–16.65) | 4.25 (1.2–16.65) |
| Nodal SUVmax | | | |
| Median (range) | 1.45 (0.8–9.29) | 2.0 (1.0–14.76) | 1.75 (0.8–14.76) |

RT: radiotherapy.
n: number of patients.
AJCC: American Joint Committee on Cancer.
SUV: standardized uptake value.
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up duration was 53.5 months (range 17.6 to 82.1 months) for the 40 patients without recurrence, and 21.3 months (range 8.0 to 43.4 months) for the 11 patients with recurrence at follow-up.

The median primary tumor SUVmax was 4.25 (range 1.2–16.65). Using best discriminative cut-off for the primary tumor SUVmax (4.6) to establish two groups based on ROC curve analysis, the high SUVmax ($\geq$4.6) subgroup showed a shorter median PFS time than the low SUVmax (<4.6) subgroup, but the difference did not reach statistical significance (42.7 vs. 57.3 months; p = 0.66) (Fig 1). The 4-year PFS rates were 44.0% versus 53.8%, respectively. The median nodal SUVmax was 1.75 (range 0.8–14.76). Using the best cut-off for nodal SUVmax (4.0) based on the ROC curve analysis, the high SUVmax ($\geq$4.0) subgroup showed a significantly shorter median PFS time than the low SUVmax (<4.0) subgroup (30.4 vs. 52.2 months; p<0.0001) (Fig 2). The 4-year PFS rates were 22.2% versus 54.8%, respectively. Univariate analysis showed that nodal SUVmax (p<0.0001), N status (p = 0.0099, Fig 3), and tumor TNM stage (p = 0.015, Fig 4) were significantly related to PFS, whereas primary tumor SUVmax (p = 0.66), age (p = 0.11), treatment strategy (p = 0.71), and T status (p = 0.53) were not (Table 2). Multivariate analysis showed that only nodal SUVmax (risk ratio 0.54, 95% confidence interval [CI] 0.38–0.87, p = 0.029) was an independent predictor of PFS.

As shown in Table 2, no factors were found to affect LC. Nodal SUVmax, N status, and tumor TNM stage were significantly related to NPFS and DMFS, whereas primary tumor SUVmax, age, treatment strategy, and T status were not. Multivariate analysis showed that only nodal SUVmax (risk ratio 0.51, 95% CI 0.34–0.81, p = 0.023) was an independent predictor of NPFS.

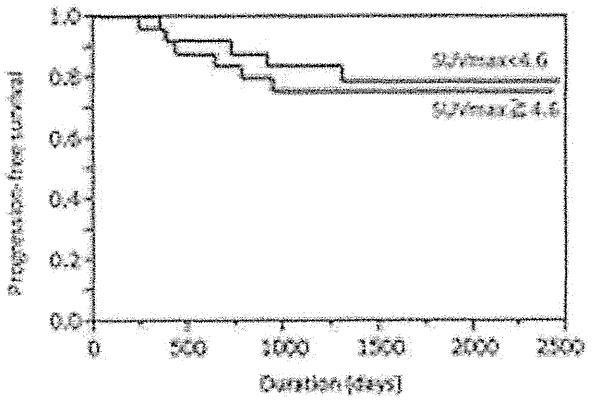


**Figure 1. The high SUVmax ($\geq$4.6) subgroup showed a slightly shorter median progression-free survival time than the low SUVmax (<4.6) subgroup (42.7 vs. 57.3 months; p = 0.66).**
doi:10.1371/journal.pone.0096999.g001

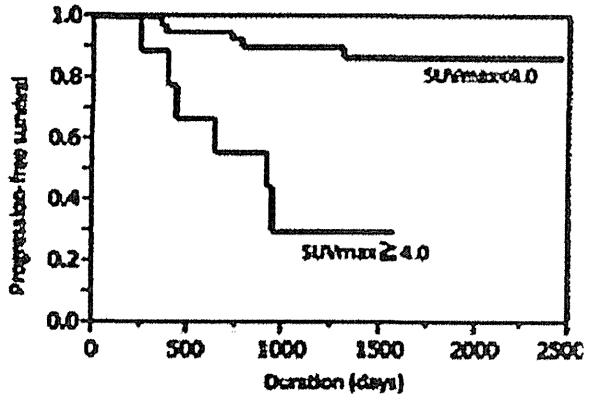


**Figure 2. The high SUVmax (≥4.0) subgroup showed a significantly shorter median progression-free survival time than the low SUVmax (<4.0) subgroup (30.4 vs. 52.2 months; p<0.0001).**
doi:10.1371/journal.pone.0096999.g002

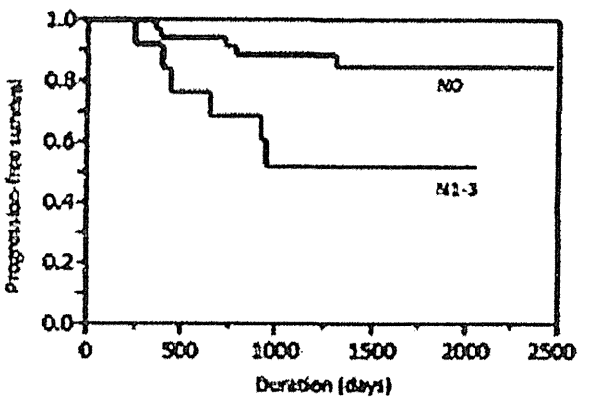


**Figure 3. The positive lymph node status (N1-3) subgroup showed a significantly shorter median progression-free survival time than the N0 subgroup (31.3 vs. 50.9 months; p=0.0099).**
doi:10.1371/journal.pone.0096999.g003

## Prognostic factors in the RT group

Six (20.0%) of the 30 RT patients suffered recurrence: local recurrence in three, neck nodal recurrence in one, and lung metastasis in two. The median overall follow-up duration was 53.5 months (range 17.6 to 82.1 months) in the 24 patients without recurrence, and 25.0 months (range 8.0 to 43.4 months) in the six patients with recurrence at follow-up.

The median SUVmax values for the primary tumor and neck nodes were 2.85 (range 1.2–8.52) and 1.45 (range 0.8–9.29), respectively. Using a best discriminative SUVmax cut-off of 4.0 for the primary tumor, the high SUV (≥4.0) subgroup showed a shorter median PFS time than the low SUV (<4.0) subgroup, but the difference did not reach statistical significance (38.6 vs. 57.3 months; p = 0.63). The 4-year PFS rates were 37.5% versus 54.5%, respectively. Using a best cut-off nodal SUVmax value of 4.0, the high SUVmax (≥4.0) subgroup showed a significantly shorter median PFS time than the low SUVmax (<4.0) subgroup (19.2 vs. 50.9 months; p<0.0001). The 4-year PFS rates were 0% versus 53.6%, respectively. Univariate analysis showed that nodal SUVmax (p<0.0001), N status (p = 0.018), and tumor TNM stage (<0.0001) were significantly related to PFS, whereas primary tumor SUVmax (p = 0.63), age (p = 0.31), and T status (p = 0.12) were not (Table 3). Multivariate analysis revealed no factors that were related to PFS.

As shown in Table 3, none of the examined factors affected LC. Nodal SUVmax, N status, and tumor TNM stage were significantly related to NPFS and DMFS, whereas primary tumor SUVmax, age, treatment strategy, and T status were not. Multivariate analysis showed that only nodal SUVmax (risk ratio 0.48, 95% confidence interval [CI] 0.32–0.78, p = 0.018) was an independent predictor of NPFS.

## Prognostic factors in the surgery group

Five (23.8%) of the 21 surgery patients suffered recurrence: local recurrence in one, neck nodal recurrence in one, and lung metastasis in three. The median overall follow-up duration was 55.4 months (range 29.6 to 80.8 months) in the 16 patients without recurrence, and 14.2 months (range 11.5 to 31.3 months) in the five patients with recurrence at follow-up.

The median SUVmax values for the primary tumor and neck nodes were 8.6 (range 3.6–16.65) and 2.0 (range 1.0–14.76), respectively. Using a best discriminative SUVmax cut-off of 9.8 for the primary tumor, the high SUVmax (≥9.8) subgroup showed a shorter PFS time than the low SUVmax (<9.8) subgroup, but the difference did not reach statistical significance (42.7 vs. 47.3 months; p = 0.50). The 4-year PFS rates were 50.0% versus 46.7%, respectively. Using a best nodal SUVmax cut-off of 4.0, the high SUVmax (≥4.0) subgroup showed a significant shorter median PFS time than the low SUVmax (<4.0) subgroup (30.7 vs. 60.5 months; p = 0.013). The 4-year PFS rates were 28.6% versus 57.1%, respectively. Univariate analysis showed that only nodal UVmax (p = 0.013) had a significant relationship with PFS, whereas primary tumor SUVmax (p = 0.50), age (p = 0.17), T status (p = 0.56) N status (p = 0.12), and tumor TNM stage (p = 0.29) did not (Table 4). Multivariate analysis showed that none of the examined factors affected PFS.

As shown in Table 4, none of the factors examined were related to LC. Nodal SUVmax and N status were significantly related to DMFS, whereas primary tumor SUVmax, age, T status and tumor TNM stage were not. Multivariate analysis showed that

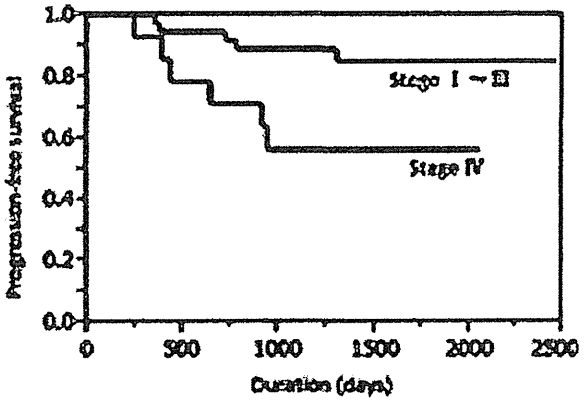


**Figure 4. The high stage (stage IV) subgroup showed a significantly shorter median progression-free survival time than the lower stage (stage I-III) subgroup (35.1 vs. 54.3 months; p = 0.015).**
doi:10.1371/journal.pone.0096999.g004

**Table 2.** Univariate analysis of clinicopathological factors associated with clinical outcome in the patients overall (n = 51).

| Characteristics | n | p-value (log-rank) | | | |
|---|---|---|---|---|---|
| | | PFS | LC | NPFS | DMFS |
| Age at diagnosis (years) | | | | | |
| <65 | 18 | 0.11 | 0.42 | 0.26 | 0.88 |
| ≥66 | 33 | | | | |
| Primary tumor SUVmax | | | | | |
| <4.6 | 26 | 0.66 | 0.38 | 0.96 | 0.16 |
| ≥4.6 | 25 | | | | |
| Nodal SUVmax | | | | | |
| <4.0 | 42 | <0.0001 | 0.44 | 0.0006 | <0.0001 |
| ≥4.0 | 9 | | | | |
| Treatment | | | | | |
| RT group | 30 | 0.71 | 0.55 | 0.78 | 0.37 |
| Surgery group | 21 | | | | |
| T status | | | | | |
| T1–2 | 31 | 0.53 | 0.65 | 0.69 | 0.28 |
| T3–4 | 20 | | | | |
| N status | | | | | |
| N0 | 38 | 0.0099 | 0.29 | 0.011 | 0.0018 |
| N1–3 | 13 | | | | |
| NM stage (AJCC) | | | | | |
| Stage I–III | 37 | 0.015 | 0.29 | 0.016 | 0.0037 |
| Stage IV | 14 | | | | |

n: number of patients.
PFS: progression-free survival.
LC: local control.
NPFS: nodal progression-free survival.
DMFS: distant metastasis-free survival.
SUVmaximum: maximum standardized uptake value.
RT: radiotherapy.
AJCC: American Joint Committee on Cancer.
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none of these factors was related to DMFS.

## Discussion

To our knowledge, this is the first study to have evaluated the clinical usefulness of FDG-PET for providing prognostic information on patients with only squamous cell laryngeal carcinoma. Although several studies have demonstrated that metabolic activity evident on FDG-PET has prognostic significance in patients with a variety of head and neck cancer subtypes (i.e. nasopharynx, oropharynx, hypopharynx, larynx, oral cavity) [3,4], the various primary tumor burdens may differ, thus affecting FDG uptake, treatment response and survival, all of which could cause potential biases.

In our series, nodal SUVmax rather than the primary tumor, was significantly associated with PFS and NPFS. A similar tendency has also been reported in three previous studies [5–7]. Demirci et al. [5] demonstrated that a nodal SUV exceeding 4.45 posed a greater risk of recurrence in 64 patients with various head and neck cancers including those of the nasopharynx (n = 29), larynx (n = 16), oropharynx (n = 13), or hypopharynx (n = 6) treated by radiotherapy or surgery. Inokuchi et al. [6] reported that a nodal SUV exceeding 6.0 posed a greater risk of poor outcome (in terms of DFS, NPFS, and DMFS) in 178 patients with various head and neck cancers including those of the oral cavity (n = 61), nasopharynx (n = 38), oropharynx (n = 34), hypopharynx (n = 27), larynx (n = 13), or nasal sinus (n = 5) treated using chemoradiation. They also showed that among the patients with a greater nodal SUVmax (>6.0), those who underwent planned neck dissection had longer NPFS than those in the observation only group. Kubicek et al. [7] showed that a nodal SUV exceeding 10.0 posed a greater increased risk of distant failure in 212 patients with various head and neck cancers including those of the oropharynx (n = 89), larynx (n = 54), oral cavity (n = 29), salivary gland (n = 13), nasal sinus (n = 9), hypopharynx (n = 3), or unknown primary (n = 5) managed using various types of therapy. We suggest that high FDG uptake in neck nodes is correlated with poor outcome, and that such patients should receive more aggressive treatment combinations.

The prognostic value of primary tumor SUVmax in patients with head and neck cancer remains controversial, and many reports have indicated that it has positive [8] or negative [9] associations with outcome. Allal et al. [8] demonstrated that a primary tumor SUV exceeding 4.76 posed a greater risk of poor outcome in 120 patients with various head and neck cancers including those of the oropharynx (n = 46), oral cavity (n = 32), larynx (n = 26), hypopharynx (n = 13), or unknown primary (n = 3) managed by radiotherapy or surgery. Tang et al. [9] showed that

**Table 3.** Univariate analysis of clinicopathological factors associated with clinical outcome in the RT group (n = 30).

| Characteristics | n | p-value (log-rank) | | | |
|---|---|---|---|---|---|
| | | PFS | LC | NPFS | DMFS |
| Age at diagnosis (years) | | | | | |
| <65 | 13 | 0.31 | 0.73 | 0.34 | 0.20 |
| ≥66 | 17 | | | | |
| Primary tumor SUVmax | | | | | |
| <4.0 | 22 | 0.63 | 0.33 | 0.075 | 0.46 |
| ≥4.0 | 8 | | | | |
| Nodal SUVmax | | | | | |
| <4.0 | 28 | <0.0001 | 0.78 | <0.0001 | 0.0045 |
| ≥4.0 | 2 | | | | |
| T status | | | | | |
| T1–2 | 25 | 0.12 | 0.28 | 0.77 | 0.14 |
| T3–4 | 5 | | | | |
| N status | | | | | |
| N0 | 27 | 0.018 | 0.64 | 0.0007 | 0.0040 |
| N1–3 | 3 | | | | |
| NM stage (AJCC) | | | | | |
| Stage I–III | 28 | <0.0001 | 0.79 | <0.0001 | 0.0045 |
| Stage IV | 2 | | | | |

RT: radiotherapy.
*n: number of patients.*
PFS: progression-free survival.
LC: local control.
NPFS: nodal progression-free survival.
DMFS: distant metastasis-free survival.
SUVmaximum: maximum standardized uptake value.
AJCC: American Joint Committee on Cancer.
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primary tumor SUV was not significantly associated with survival in 83 patients with various head and neck cancers including those of the oropharynx (n = 45), nasopharynx (n = 22), hypopharynx (n = 8), oral cavity (n = 4), larynx (n = 4), or unknown primary (n = 2) managed by radiotherapy.

As is the case for all novel biomarkers, there are also potential limitations and concerns regarding the widespread applicability of SUV. For example, it has been demonstrated that SUV varies with respect to time after injection of FDG [10]. The exact plasma glucose value may also affect SUV, even in the absence of frank hyperglycemia/diabetes [11]. The body habitus of the patient (independent of his/her actual weight) may also affect SUV, because fatty tissue shows relatively low FDG uptake. Finally, there are a number of technical factors that can affect SUV, as has been reviewed in a comprehensive editorial by Keyes [12]. These factors include the recovery coefficient (the ratio of the measured activity of a ROI relative to its true activity) and partial volume averaging, which are affected by individual nuances of the hardware and software of the PET scanner, the size and geometry of the lesion, and respiratory motion [13].

Moreover, although convenient to measure and widely used, SUVmax has a disadvantage. It is a single-pixel value representing the most intense FDG uptake in the tumor and may not represent total uptake for the whole tumor mass, as well as being vulnerable to statistical noise, which might explain the current results. Recently, volume-based metabolic parameters measured by FDG-PET have emerged as new prognostic factors. Metabolic tumor volume (MTV) is defined as the volume of FDG activity in the tumor, and total lesion glycolysis (TLG) as the summed SUV within the tumor. Unfortunately, in our series, we were unable to measure MTV and TLG due to technical limitations of the PET machine. This is one of several limitations to our present study.

There were other limitations. First, it was a retrospective study performed at a single institution with a relatively small number of patients, especially in surgery group. Second, FDG-PET was not performed initially for every patient with laryngeal cancer, as only selected patients were referred for PET scanning. The use of FDG-PET in only selected patients might have introduced bias and influenced the results, which may therefore not be generalizable to all subjects. Third, the volumetric analyses such as MTV and TLG were not undertaken because of PET technological problem. Finally, we were unable to analyze overall survival because there were only three disease-related deaths among the study population.

## Conclusions

Laryngeal cancer patients showing high FDG uptake in neck nodes should be considered at increased risk of poor outcome and may benefit from more aggressive multimodality treatment combinations. These results remain to be confirmed in a larger prospective and more homogeneous study.