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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PLOS ONE

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 (≥ 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.
doi:10.1371/journal.pone.0096999.t001

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.

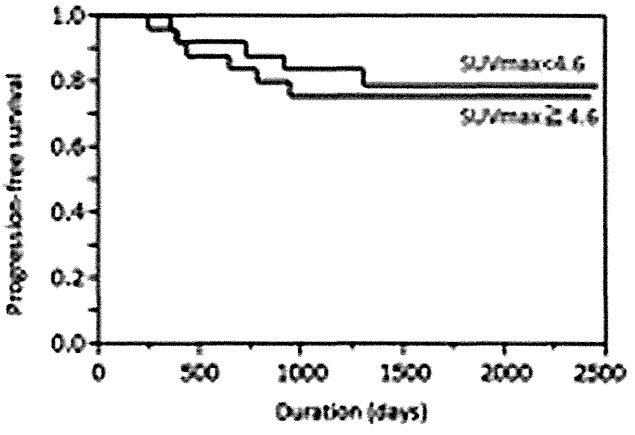

Figure 1. The high SUVmax ($\geq$4.6) subgroup showed a slightly shorter median progression-free survival time than the low SUVmax (<4.6) subgroup (42.7 vs. 57.3 months; $p = 0.66$).
doi:10.1371/journal.pone.0096999.g001

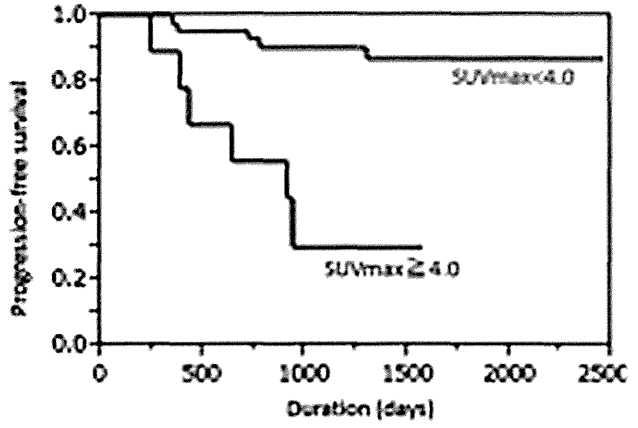

Figure 2. The high SUVmax (≥4.0) subgroup showed a significantly shorter median progression-free survival time than the low SUVmax (<4.0) subgroup (30.4 vs. 52.2 months; p<0.0001).
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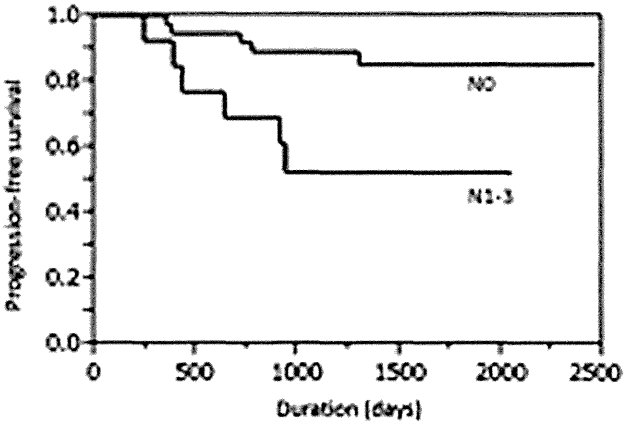

Figure 3. The positive lymph node status (N1-3) subgroup showed a significantly shorter median progression-free survival time than the N0 subgroup (31.3 vs. 50.9 months; p = 0.0099).
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Prognostic factors in the RT group

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

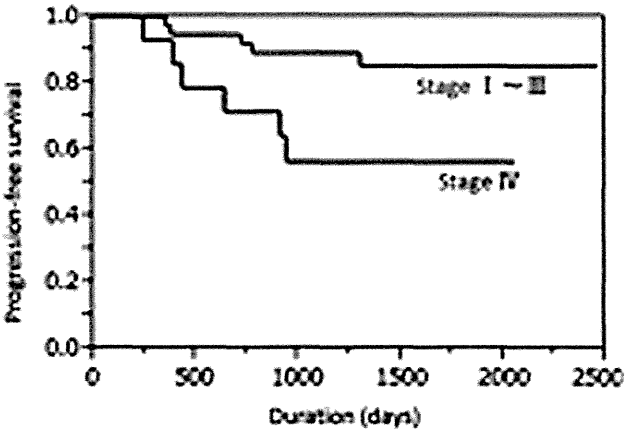

Figure 4. The high stage (stage IV) subgroup showed a significantly shorter median progression-free survival time than the lower stage (stage I-III) subgroup (35.1 vs. 54.3 months; p = 0.015).
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Table 2. Univariate analysis of clinicopathological factors 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.

Table 4. Univariate analysis of clinicopathological factors associated with clinical outcome in the surgery group (n = 21).

Characteristics	n	p-value (log-rank)			
		PFS	LC	NPFS	DMFS
Age at diagnosis (years)					
<65	5	0.17	0.58	0.56	0.27
≥66	16				
Primary tumor SUVmax					
<9.8	15	0.50	0.53	0.13	0.74
≥9.8	6				
Nodal SUVmax					
<4.0	14	0.013	0.48	0.17	0.0037
≥4.0	7				
T status					
T1–2	6	0.56	0.11	0.56	0.87
T3–4	15				
N status					
N0	11	0.12	0.34	0.32	0.049
N1–3	10				
NM stage (AJCC)					
Stage I–III	9	0.29	0.25	0.41	0.12
Stage IV	12				

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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Author Contributions

Conceived and designed the experiments: DM KY YE RS MS NO KN NK KS. Performed the experiments: YS TK HK TM. Analyzed the data: KK. Contributed reagents/materials/analysis tools: YS TK. Wrote the paper: KK. Manuscript editing & review: KK YS TK DM KY YE RS HK MS NO KN NK TM KS.

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Salvage operations for patients with persistent or recurrent cancer of the maxillary sinus after superselective intra-arterial infusion of cisplatin with concurrent radiotherapy

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Abstract

Our aim was to evaluate the feasibility of salvage operations for patients with persistent or recurrent cancer of the maxillary sinus after superselective intra-arterial infusion of cisplatin with concurrent radiotherapy. We retrospectively analysed the records of 61 patients with cancer of the maxillary sinus who were treated in this way. Chemotherapy comprised 100–120 mg/m^2 superselective intra-arterial infusions of cisplatin given a median of 4 times weekly (range 2–5). Concurrent radiotherapy was given in a median dose of 65 Gy (range 24–70 Gy). Persistent or recurrent cancer of the maxillary sinus was found in 17 patients, of whom 11 had salvage surgery. The disease was controlled in 8 of the 11, and 7 of the 11 survived with no evidence of disease. Their 5-year overall survival was 61%. Two of the 11 developed serious operative complications. Salvage surgery for patients with persistent or recurrent cancer of the maxillary sinus treated by superselective chemoradiotherapy is both safe and successful. Salvage surgery is a good option when this sort of persistent or recurrent cancer is followed up after the regimen of chemoradiotherapy described.

Keywords: Maxillary sinus cancer; Salvage surgery; Squamous cell carcinoma; Chemotherapy; Radiotherapy; Intra-arterial

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Introduction

Cancer of the maxillary sinus is rare. It comprises only about 3% of cancers of the head and neck and about 0.5% of all malignant disease.[1] The annual incidence is 0.5–1.0/100,000 population, and squamous cell carcinoma is the most common histological type, being found in over half of all patients with the disease.[1–3]

Many authors have recommended combined treatments consisting of en bloc radical resection together with irradiation.[4–6] However, the cosmetic problems for patients who have en bloc resection are considerable, so multiple treatments have been introduced to avoid cosmetic problems and to preserve ocular function and improve outcomes. In Japan, superselective intra-arterial cisplatin infusion with concurrent radiotherapy has been introduced to preserve the orbital contents and ocular function in patients with advanced cancers of the maxillary sinus.[7,8] This non-surgical treatment is both safe and highly effective.

Salvage surgery is generally attempted when localised persistent or recurrent primary tumours are found after initial chemoradiotherapy.[9–12] However, we know of no reports of salvage surgery for patients with persistent or recurrent cancer of the maxillary sinus after intensive chemoradiotherapy to date. The purpose of this study was to evaluate the feasibility of salvage surgery and to assess its efficacy for patients with persistent or recurrent cancer of the maxillary sinus after chemoradiotherapy.

Method

Patients

We retrospectively analysed the records of 61 patients with squamous cell carcinoma of the maxillary sinus who had superselective intra-arterial infusion of cisplatin with concurrent radiotherapy at Hokkaido University Hospital, Japan between September 1999 and July 2012. T and N stages were classified according to the American Joint Committee on Cancer (AJCC) staging system 2010. Details of patients are shown in Table 1.

Radiotherapy

The irradiation plan during the period 2006–2012 was 40 Gy in 20 fractions of 2 Gy over four weeks for the primary site and involved nodal areas, immediately followed by a boost of 30 Gy in 15 fractions to the primary cancer over an additional three weeks (total dose 70 Gy). Between 1999 and 2005, involved nodal areas and the primary site were irradiated with 40 Gy in 16 fractions of 2.5 Gy over four weeks, with a boost irradiation of 25 Gy in 10 fractions to the primary tumour over an additional 2.5 weeks (total dose 65 Gy).

Table 1
Details of the 61 patients. Data are expressed as number (%) unless otherwise stated.

Variable	
Sex	
Male	50 (82)
Female	11 (18)
Age (years)	
Median (range)	61 (34–74)
Duration of follow up (months)	
Median (range)	64 (9–143)
T classification	
T2	1 (1)
T3	17 (28)
T4a	30 (49)
T4b	13 (21)
N classification	
N0	49 (80)
N1	7 (11)
N2b	5 (9)

Chemotherapy

Chemotherapy comprised 100–120 mg/m^2 superselective intra-arterial cisplatin given a median of 4 times weekly (range 2–5). At the same time, sodium thiosulphate was given intravenously (24 g/body weight) to effectively neutralise the cisplatin.

Salvage surgery

Patients who were not given a full course of irradiation (<65 Gy) were referred for salvage surgery at the end of the course of radiotherapy. Patients given a full course of irradiation (>65 Gy), had a computed tomographic (CT) or magnetic resonance (MR) scan, or both, taken within 3 months of the completion of treatment. If there was persistent primary disease we attempted to biopsy it, and salvage surgery was recommended if viable tumour cells were found.

Patients were usually monitored monthly for recurrence during the first year, every 2 months during the second year, and every 6 or 12 months thereafter until death or the data were censored. CT or MR scans were taken routinely every 3 months during the first year, and every 6 or 12 months thereafter. Surgical complications were graded using the Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0.(from National Cancer Institute web site http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06- 14_QuickReference 5x7.pdf, National Cancer Institute, US)

Statistics

The Kaplan–Meier test was used to compare survival and local control from the start of treatment to death or failure. Probabilities of less than 0.05 were accepted as significant. The software JMP Pro 10.0.2 statistical software (SAS Institute, Cary, NC) was used to aid the statistical analysis.

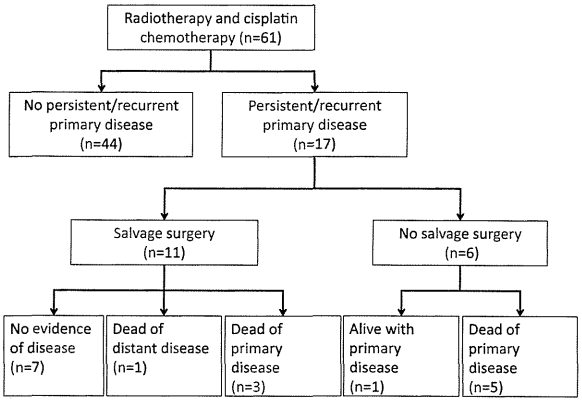

Fig. 1. Clinical outcomes in 61 patients with cancer of the maxillary sinus after intra-arterial infusion of cisplatin with concurrent radiotherapy.

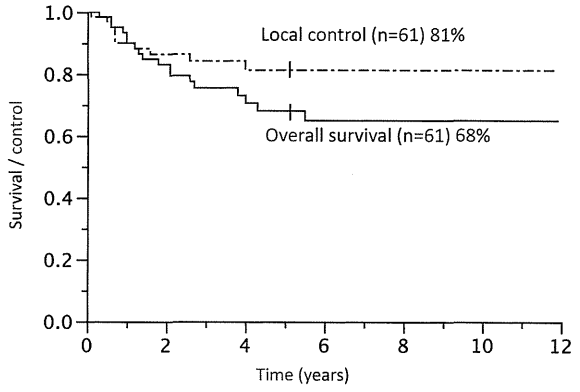

Fig. 2. Overall survival curve and local control curve of all 61 patients with cancer of the maxillary sinus after intra-arterial infusion of cisplatin with concurrent radiotherapy.

Results

Chemoradiotherapy

A median of 4 doses of intra-arterial chemotherapy was given (range 2–5). The median irradiation dose was 65 Gy (range 24-70 Gy) Fifty-eight patients (95%) had a full course of irradiation (>65 Gy). In one patient, chemoradiotherapy was cancelled because of severe neutropenia and sepsis after the second intra-arterial infusion of cisplatin, and palliative treatment was given. In another patient, ischaemic colitis developed after the first intra-arterial infusion of chemotherapy, which was therefore suspended, and he was treated with 50 Gy of radiotherapy followed by salvage surgery. In the final patient, intra-arterial chemotherapy was given 4 times. However, the patient chose to suspend the subsequent radiotherapy after being given 48 Gy of irradiation because he had concerned about possible late complications.

Clinical outcomes

We found persistent or recurrent cancer of the maxillary sinus in 17 patients (28%), and salvage surgery was used in 11 of the 17. Three patients developed local recurrence at a median (range) of 5(2–22) months after the operation. All 3 patients died of their primary disease. Another patient developed distant metastasis 15 months after salvage surgery and he died of distant disease 20 months later. The remaining 7 patients survived with no evidence of disease (Fig. 1). Persistent or recurrent primary disease was controlled in 8/11 patients who had salvage surgery, and 7 of the 17 with persistent or recurrent disease survived with no evidence of disease after salvage surgery.

Of the 17 patients with persistent or recurrent primary disease, we did not operate on 6 patients (Table 2). Various types of chemotherapy were used for 3 of them depending on their general condition. Only one of the 3, who was given adjunctive chemotherapy, remains alive with primary disease.

The 5-year overall survival of all 61 patients was 68%. The 5-year local control by our regimen of chemoradiotherapy and salvage surgery was 81% (Fig. 2). Fig. 3 shows the overall survival curves for the 17 with persistent or recurrent primary disease, the 11 patients who had salvage surgery, and the 6 patients who did not. The 5-year overall survival of the 11 patients who had salvage surgery was 61%.

Salvage surgery

Salvage surgery was done for 11 patients at a median of 4 months (range 1–46) after the completion of chemoradiotherapy (Table 3). Two patients developed postoperative complications in the form of deep vein thrombosis in one and local infection and sepsis in the other.

Discussion

For most squamous cell carcinomas of the maxillary sinus the standard treatment is a combination of radical surgery

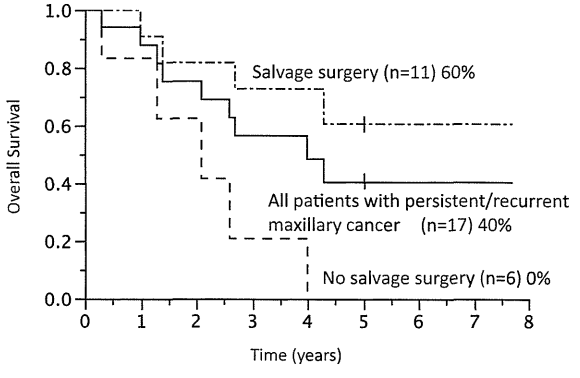

Fig. 3. Overall survival curves of the 17 patients with persistent or recurrent maxillary cancer, 11 patients who had salvage surgery and 6 patients who did not.

Table 2
Details of the 7 patients who did not have salvage surgery.

Case no	Age (years)	Sex	Classification		Radiation dose (Gy)	No of cycles of chemotherapy	Reason for not having salvage surgery	Additional treatment	Outcome (observation period after recurrence (months))
			T	N					
1	72	M	4b	0	65	3	Poor general condition	Chemotherapy	Died of disease (11)
2	68	M	3	0	65	3	Poor general condition	Palliation	Died of disease (12)
3	57	M	4b	2b	65	4	Tumour unresectable	Chemotherapy	Died of disease (7)
4	70	M	4b	0	70	4	Poor general condition	Palliation	Died of disease (1)
5	72	M	3	0	70	2	Refused	Chemotherapy	Alive with disease (3)
6	73	M	4a	0	24	2	Poor general condition	Palliation	Died of disease (3)

and preoperative or postoperative irradiation. Total maxillectomy, with or without orbital exenteration, is the most common operation for these cancers. However, functional and cosmetic outcomes after surgical treatment for patients with advanced tumours are far from satisfactory. In our hospital superselective chemoradiotherapy was attempted to preserve ocular function and avoid cosmetic problems for patients who hoped to have non-surgical treatment. In particular, we think that the unresectable tumours or tumours with orbital invasion may be good indications for chemoradiotherapy. In Japan it has been reported to be both safe and effective for patients with cancer of the maxillary sinus.[7,8] However, additional treatment is often problematic when the tumour is persistent or recurrent. We therefore focused on salvage surgery for patients with persistent or recurrent disease after chemoradiotherapy, and evaluated the results of salvage surgery in terms of morbidity and salvage.

The complication rate of salvage surgery after intensive chemoradiotherapy for patients with head and neck cancer has been reported to be 11%–63%.[9–12] In 1998, Curran et al. reported salvage surgery after radiotherapy for patients with paranasal malignancies,[13] and reported their complication rate to be 24% of 34 patients undergoing salvage surgery. Our postoperative complication rate was 2/11, which is comparable to those published in recent reports. Salvage surgery after intensive chemoradiotherapy is therefore both safe and feasible.

Intensive chemoradiation such as ours is used to avoid surgical stress. However, salvage surgery may be almost the only alternative for the treatment of persistent or recurrent primary disease after intensive chemoradiation. It has been reported that salvage surgery for persistent or recurrent cancers of head and neck can be difficult in terms of surgical technique, and have not only high morbidity but also low rates of salvage.[14,15] In addition, salvage surgery for patients with recurrent cancers of the upper aerodigestive tract may often cause fistulas to form, or lead to severe infective complications that may cause bleeding from the carotid artery or prolong the stay in hospital. In cases of persistent or recurrent cancer of the maxillary sinus we think that salvage surgery is safer, as there is no potential for fistulas to form associated with maxillectomy.

Persistent or recurrent primary disease was controlled in 8/11 patients who were treated by salvage surgery. Seven of the 17 patients with persistent or recurrent cancer of the maxillary sinus survived with no evidence of disease after salvage surgery. The reason for this favourable salvage rate may be that persistent or recurrent primary disease is often localised and oncologically resectable after chemoradiotherapy in patients with cancer of the maxillary sinus.

In conclusion, salvage surgery for patients with persistent or recurrent maxillary cancer after superselctive chemoradiotherapy is safe and successful. We also considered that the overall survival of patients undergoing salvage surgery is favourable and that it is therefore a good option in such cases. It is also important to recognise persistent or recurrent primary disease as soon as possible so that we do not miss the opportunity for salvage surgery.

Conflict of interest

All authors declared no conflict of interest.

Ethics statement/confirmation of patient permission

Approval for this study was obtained from the institutional review board at Hokkaido University. Informed consent for this research and publication was obtained from all participants. Completion of the survey was considered as implied consent for participation.

Table 3
Details of the 11 patients who had salvage surgery.

Case no	Age (years)	Sex	Classification		Radiation dose (Gy)	No of cycles of chemotherapy	Type of operation	Reconstruction for palatal defects	Orbital exenteration	Complications	Outcome (postoperative observation period)[a]
			T	N							
1	60	M	4a	0	65	1	Total maxillectomy	STSG + prothesis	+	–	Dead of primary disease (13 months)
2	69	F	3	0	65	3	Frontal craniotomy + ESS	None	+	–	No evidence of disease (4)
3	67	M	4a	0	50	2	Total maxillectomy	STSG + prothesis	–	–	No evidence of disease (6)
4	48	M	4b	0	48	4	Partial maxillectomy	None	–	–	No evidence of disease (5)
5	37	M	4a	0	70	4	Partial maxillectomy	STSG + prothesis	+	–	No evidence of disease (4)
6	73	M	4a	1	64	4	Total maxillectomy	VRAM flap	+	Sepsis (Gr3)	No evidence of disease (4)
7	64	M	3	1	70	4	Total maxillectomy	STSG + prothesis	–	DVT (Gr2)	Dead of distant disease (20 months)
8	62	M	4a	1	70	5	Total maxillectomy	STSG + prothesis	+	–	Dead of primary disease (3 1/2)
9	63	M	4a	0	70	5	Partial maxillectomy	None	–	–	No evidence of disease (2)
10	60	M	4a	0	50	1	Total maxillectomy	STSG + prothesis	–	–	No evidence of disease (2)
11	60	M	4a	2b	70	4	Total maxillectomy	Prothesis	+	–	Dead of primary disease (7 months)

ESS = endoscopic sinus surgery, STSG = split thickness skin graft, VRAM = vertical rectus abdominis myocutaneous flap, DVT = deep vein thrombosis.
[a] Years, unless otherwise stated.

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抗がん剤の副作用と支持療法

—より適切な抗がん剤の安全使用をめざして—

VII　臓器別がん腫レジメンの副作用と対策

局所進行頭頸部扁平上皮癌

CDDP＋RT療法

清田尚臣

局所進行頭頸部扁平上皮癌

CDDP＋RT療法

Concurrent chemoradiotherapy with cisplatin for locally advanced squamous cell carcinoma of head and neck

清田尚臣

Key words：シスプラチン，放射線性粘膜炎，放射線性皮膚炎，腎障害，聴力障害

はじめに

一般的にStage I/IIの頭頸部扁平上皮癌の治療成績は良好であり，外科的治療もしくは放射線治療のいずれか1つのmodalityを用いることで根治を目指すことが可能である．一方で，Stage III/IVの局所進行頭頸部がんの予後は不良であり複数のmodalityを用いた，いわゆる集学的治療戦略が必要である．特に化学放射線療法が適応となるのは，以下の3つの場合である．いずれも，標準治療はシスプラチン併用化学放射線療法（CDDP＋RT療法）である．

（1）切除不能局所進行頭頸部扁平上皮癌に対する化学放射線療法[1]

（2）咽喉頭機能温存目的の切除可能局所進行頭頸部扁平上皮癌に対する化学放射線療法[2]

（3）術後再発高リスク患者に対する補助化学放射線療法[3,4]

本稿では，頭頸部扁平上皮癌で最も使用頻度の高いCDDP＋RT療法の副作用と支持療法について解説する．

1 CDDP＋RT療法

シスプラチン　100 mg/m^2，day 1，22，43
放射線治療　2 Gy/回 ×33–35回，総線量66–70 Gy

※シスプラチンの用量については，100 mg/m^{2}を3週間ごとに放射線治療期間中に投与するのが最も一般的であり，日本人における耐用性も確認されている[5,6]．ただし，個々の患者の状態を評価したうえで80 mg/m^{2}に減量して使用されることもある．

※放射線治療の総線量は局所進行例では70 Gy，術後照射では66 Gyのことが多い．

2 CDDP＋RT療法の副作用とその管理

1）嘔気・嘔吐

高用量のシスプラチンを用いるため，高度催吐性の抗がん薬使用時の予防投与（5HT$_3$拮抗薬＋NK1受容体拮抗薬＋ステロイド薬）を行う．**表1**に投与例を示す．過去の臨床試験でも，Grade 3/4の頻度は16–30％程度認めている[1–7]．

2）放射線性粘膜炎

局所進行頭頸部癌に対して化学放射線療法を施行すると，照射野内に粘膜炎が89–100％（Grade 3以上が34–57％）に生じ[8]，さらに嚥下困難・味覚障害・口腔乾燥なども生じる．粘膜炎に伴う疼痛はアセトアミノフェンやオピオイドにて積極的にコントロールを行う．

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表1 高用量シスプラチン投与時の制吐薬の投与例

制吐薬	day 1	day 2	day 3
$5HT_3$拮抗薬	グラニセトロン塩酸塩 1mg or パロノセトロン塩酸塩 0.75mg	—	—
NK1受容体拮抗薬	アプレピタント 125mg	アプレピタント 80mg	アプレピタント 80mg
ステロイド薬	デキサメタゾン 6.6mg	デキサメタゾン 3.3mg	デキサメタゾン 3.3mg

しかし，放射線性粘膜炎だけでなく嚥下困難・味覚障害・口腔乾燥なども重なるため，しばしば経口摂取が困難となり栄養状態の悪化を招く．これにより，化学放射線療法の予定外の休止や治療期間の延長が生じる．放射線治療の予定外の休止や治療期間の延長は治療効果に悪影響を与えることが知られている[9-11]．このため，局所進行頭頸部癌における化学放射線療法時の栄養管理も非常に重要となる．

栄養管理の手段としては，経皮的内視鏡的胃瘻造設術(percutaneous endoscopic gastrostomy: PEG)，経鼻胃管(naso-gastric tube: NG tube)を用いての経腸栄養法や，高カロリー輸液を用いた完全静脈栄養法(total parenteral nutrition: TPN)が挙げられる．ASPEN(American Society for Parenteral and Enteral Nutrition)のガイドラインにおいても，悪性腫瘍の治療中に栄養摂取が不十分になることが予想される場合には比較的早い段階(治療開始後1-2週間)で何らかの栄養サポートを行うことを勧めており[12]，また経口摂取困難な状態が長期化(4週間以上が目安)することが予想される場合には，経静脈栄養よりも長期的に使用できるPEGなどの方法での経腸栄養を行うことを勧めている[13,14]．

3）放射線性皮膚炎

過去の報告ではGrade 3/4以上の放射線性皮膚炎は3-24％に認めているが，湿性落屑やびらんを伴うようなGrade 2以上のものも含めれば頻度は高い[1-7]．基本的には局所の清潔を保ち，刺激の少ない弱酸性の石けんを使用する，照射野内の皮膚を擦過するような衣服を着ない，照射野内の皮膚にテープ処置などを行わないなどの対応を行う．Grade 2以上の皮膚炎を生じた場合には，イソプロピルアズレンの塗布やガーゼ処置が必要になる．

4）腎障害，電解質異常

過去の報告ではGrade 3/4以上の腎障害は2-8％程度であるが，治療に影響を与えるGrade 2の腎障害を含めれば頻度は高くなる[1-7]．また，電解質異常も低ナトリウム血症や低マグネシウム血症の頻度は過去の臨床試験のデータでは反映されていないが，臨床的には遭遇することが多い．症状としては低ナトリウム血症では，頭痛・嘔気・食欲低下・倦怠感・意識障害などを生じ，低マグネシウム血症では低カルシウム血症を伴うことも多く倦怠感・テタニー・不整脈などを呈する．

以下に腎障害や電解質異常への対応法を記載する．

(1) シスプラチンは，Clが多く含まれる生理食塩液に溶解して2時間程度かけて投与することが望ましい．

(2) シスプラチン投与中および投与当日は100mL/hを目安に尿量確保に努めることが，腎障害の予防に重要とされており，シスプラチン投与に伴う低ナトリウム血症の予防のためにも生理食塩液もしくは細胞外液を主体に補液を行うことが望ましい．

(3) 総補液量が多くなるため，in-out balanceおよび体重の増減に注意しつつ，適宜利尿剤(フロセミド・マンニトールなど)を使用して尿量を確保する．

(4) 低マグネシウム血症は腎障害を助長することや，低カルシウム血症を遷延させることが知られているため適宜チェックし，必要に応じて$MgSO_4$(硫酸マグネシウム)を点滴で補充する．

(5) シスプラチン投与当日は，非ステロイド系抗炎症薬のような腎障害を惹起する薬剤は投与しない．

5) 聴力障害

過去の臨床試験ではあまり報告されていないが，シスプラチン投与後の聴力障害は高音域優位の感音性難聴であり日常会話の範囲ではあまり気づかれていない可能性が高い．しばしば耳鳴りを伴い，症状は用量依存性に進行する．体温計のアラームなどが聞こえるかなどが日常診療では目安となる．症状は不可逆性のことも多く，明らかな症状を伴うようなGrade 2ではシスプラチンを20％減量，補聴器を必要とするようなGrade 3では投与中止も検討する必要がある．

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CASE REPORT

Lymph node metastasis in the suprasternal space from thyroid papillary cancer

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Abstract The suprasternal space is a narrow space between the superficial and deep layers of the investing layers of the deep cervical fascia above the manubrium of the sternum. The suprasternal space has been paid little attention as a space with the potential for lymph node metastasis from both thyroid cancer and head and neck cancer. We experienced 2 patients who were found to have a lymph node in the suprasternal space preoperatively. Both of them had well-differentiated thyroid papillary carcinomas and level III and IV lymph node metastases as well as metastasis in the suprasternal space. We have not previously dissected the suprasternal space prophylactically in other patients with thyroid papillary cancer, but no patient has developed metastasis in this space to date. The suprasternal space is not usually dissected in patients with thyroid cancer. However, suprasternal space metastasis has been reported to occur occasionally in patients with lymph node metastases in levels III and IV. We consider that dissection of the suprasternal space, which is not routinely performed, should be done when preoperative examination suggests lymph node metastasis in the suprasternal space as dissection of this space is less invasive, easy to achieve, and is not time consuming. Greater attention should be paid to the suprasternal space as an area with the potential for lymph node metastasis from thyroid cancer.

Keywords Thyroid cancer · Papillary cancer · Lymph node metastasis · Suprasternal space

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Introduction

The suprasternal space, which is also known as the 'Burns space', is a narrow space between the superficial and deep layers of the investing layers of the deep cervical fascia above the manubrium of the sternum (Fig. 1). According to Gray's anatomy, it contains a small amount of areolar tissue, the lower parts of the anterior jugular veins and the jugular venous arch, as well as the sternal heads of the sternocleidomastoid muscles and sometimes a lymph node [1].

Little attention has been paid to date to the suprasternal space as an area with the potential for lymph node metastasis from either thyroid cancer or head and neck cancer. Sun et al. [2] first reported lymph node metastasis between sternocleidomastoid and sternohyoid muscles (LNSS) in clinically node-positive papillary thyroid carcinoma (Fig. 2). They mentioned that the space is part of the suprasternal space. We read with great interest the paper by Sun et al. and herein report two cases of lymph node metastasis in the suprasternal space from thyroid papillary cancer, and discuss the importance of the suprasternal space in thyroid papillary cancer.

Case 1

A 54-year-old female patient visited Hokkaido University Hospital complaining of lumps in the left lower neck of 1.5 years duration. CT scans and ultrasound examination showed a small nodule in the left lobe of her thyroid, several lymph nodes, of which the largest is 2.1 cm in diameter, at levels III and IV in her left neck, and a lymph node of 1 cm in diameter in the left suprasternal space [T1N1bM0 (UICC 7th) stage IVA, Fig. 3]. Fine needle