

within the submental and submandibular region in patients with hypopharyngeal cancer.

The 5-year OS was 76.7 % (95 % CI 58.8–87.6) for the ND group and 73.9 % (95 % CI 58.6–84.3) for the non-ND

Table 1 Patients' characteristics ($N = 84$)

Characteristics	<i>n</i>	%
Age		
Median (range)	59 (36–80)	
Sex		
Male	75	89
Female	9	11
Primary tumor site		
Oropharynx	59	70
Hypopharynx	25	30
T classification		
1	10	12
2	39	46
3	22	26
4	13	16
N classification		
2a	15	18
2b	35	42
2c	22	26
3	12	14
UICC stage		
4a	72	86
4b	12	14
Neck treatment		
Observe	48	57
Neck dissection	36	43

UICC Union for International Cancer Control

group ($P = 0.883$) (Fig. 1), while the 5-year RC was 91.6 % (95 % CI 76.1–97.2) for the ND group and 81.1 % (95 % CI 65.4–90.2) for the non-ND group ($P = 0.252$) (Fig. 1). Stratified by primary tumor site, the 5-year RC was 96.3 % (95 % CI 76.5–99.5) for the ND group and 78.6 % (95 % CI 58.0–89.9) for the non-ND group ($P = 0.072$) among oropharyngeal squamous cell carcinoma patients, and 77.8 % (95 % CI 36.5–93.9) for the ND group and 85.9 % (95 % CI 54.0–96.3) for the non-ND group ($P = 0.541$) among hypopharyngeal squamous cell carcinoma patients (Fig. 2).

Impact of neck dissection on OS and RC

Table 2 shows the results of uni- and multivariate analyses of clinical factors for OS. Although other factors, including ND, were not significantly associated with OS in OHSCC patients, a T classification suggested a trend toward an increased hazard ratio for death based on a multivariate analysis ($P_{\text{trend}} = 0.186$).

Table 3 shows the results of uni- and multivariate analyses of clinical factors for RC. Since there were in fact no neck relapses in the N2a group, we defined the N2b group as a reference group in these analyses. ND showed a trend, though not a significant one, toward decreasing the hazard ratio for neck recurrence (HR 0.48, 95 % CI 0.11–2.15, $P = 0.335$).

Interaction between neck treatment and primary tumor site on clinical outcome

We also examined the interaction between neck treatment and primary tumor site on clinical outcome (Table 4). A significant interaction was observed for OS (P for

Fig. 1 Kaplan–Meier survival curves for neck treatment. **a** The 5-year overall survival was 76.7 % [95 % confidence interval (CI) 58.8–87.6] for the neck dissection (ND) group, and 73.9 % (58.6–84.3) for the non-ND group, respectively ($P = 0.883$). **b** The 5-year regional control rate was 91.6 % (76.1–97.2) for the ND group, and 81.1 % (65.4–90.2) for the non-ND group ($P = 0.252$)

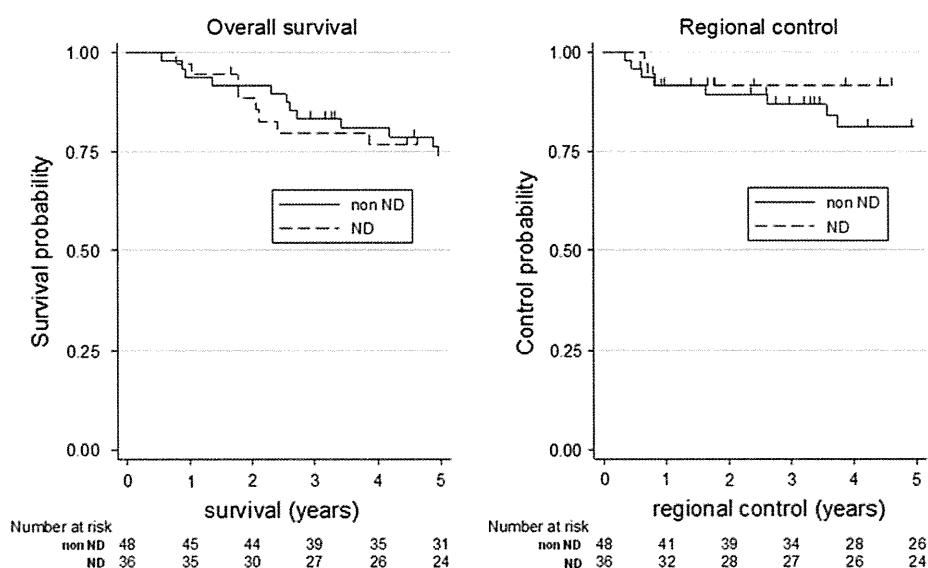


Fig. 2 Regional control rate for neck treatment according to primary tumor site. The 5-year regional control was 96.3 % [95 % confidence interval (CI)] for the neck dissection (ND) group and 78.6 % (58.0–89.9) for the non-ND group among oropharyngeal squamous cell carcinoma patients ($P = 0.072$), and 77.8 % (36.5–93.9) for the ND group and 85.9 % (54.0–96.3) for the non-ND group among hypopharyngeal squamous cell carcinoma patients ($P = 0.541$)

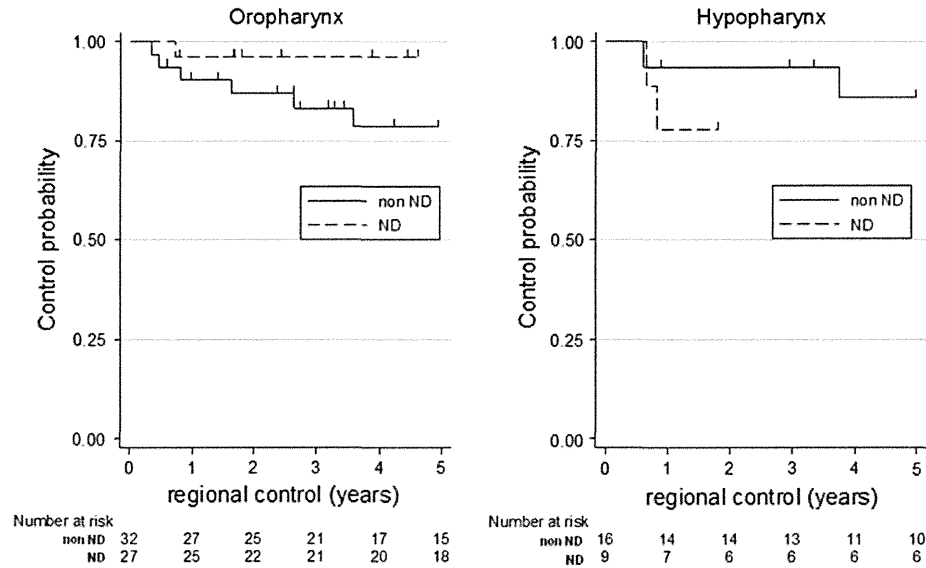


Table 2 Univariate and multivariate analyses of overall survival in OHSCC patients

Characteristics	n	Univariate analysis		Multivariate analysis	
		HR (95 % CI)	P value	HR (95 % CI)	P value
Primary tumor site					
Oropharynx	59	Reference	–	Reference	–
Hypopharynx	25	1.15 (0.51–2.59)	0.729	0.98 (0.40–2.39)	0.960
T classification					
1	10	Reference	–	Reference	–
2	39	1.17 (0.25–5.43)	0.840	0.99 (0.20–4.88)	0.994
3	22	2.08 (0.45–9.63)	0.350	1.75 (0.34–8.99)	0.501
4	13	3.02 (0.61–15.02)	0.176	2.05 (0.35–12.06)	0.429
		<i>P</i> _{trend} = 0.049		<i>P</i> _{trend} = 0.186	
N classification					
2a	15	Reference	–	Reference	–
2b	35	1.42 (0.46–4.40)	0.547	1.06 (0.32–3.52)	0.922
2c	22	1.32 (0.38–4.52)	0.661	1.32 (0.34–5.08)	0.687
3	12	1.20 (0.27–5.39)	0.812	1.32 (0.27–6.43)	0.733
Adjusted by age and sex					
<i>HR</i> hazard ratio, <i>CI</i> confidence interval, <i>OHSCC</i> oro- and hypopharyngeal squamous cell carcinoma					
Neck treatment					
Observe	48	Reference	–	Reference	–
Neck dissection	36	1.06 (0.49–2.31)	0.883	1.55 (0.63–3.82)	0.345

heterogeneity = 0.005), while a suggestive interaction was also observed for RC (P for heterogeneity = 0.094).

Relapse and complications

During follow-up, 14 of 36 patients with ND (38.9 %) suffered a relapse: 7 in local recurrence (19.4 %), 1 in regional metastasis (2.8 %), 4 in distant metastasis (11.1 %), and 2 in both regional and distant metastases (5.6 %). The neck failure rate was 8.3 % (3/36). As for pathological diagnosis of ND, all neck failure cases had

extracapsular spread (ECS) within lymph nodes. Twenty of 48 patients with non-ND (41.7 %) experienced a relapse: 6 in local metastasis (12.5 %), 6 in regional metastasis (12.5 %), 7 in distant metastasis (14.6 %), and 1 in both local and regional metastases (2.1 %). The neck failure rate was 14.6 % (7/48).

Among patients with ND, salvage surgery was performed on 8 patients who relapsed in local or regional sites (8/8 patients, 100 %). Among patients with non-ND, salvage surgery was performed on 8 patients who relapsed in local and/or regional sites (10/13 patients, 76.9 %).

Table 3 Univariate and multivariate analyses of regional control in OHSCC patients

Characteristics	<i>n</i>	Univariate analysis		Multivariate analysis	
		HR (95 % CI)	<i>P</i> value	HR (95 % CI)	<i>P</i> value
Primary tumor site					
Oropharynx	59	Reference	–	Reference	–
Hypopharynx	25	1.31 (0.38–4.48)	0.667	1.08 (0.28–4.21)	0.916
T classification					
1	10	Reference	–	Reference	–
2	39	1.32 (0.15–11.29)	0.801	0.86 (0.08–9.00)	0.897
3	22	0.97 (0.09–10.71)	0.981	0.50 (0.04–6.68)	0.598
4	13	2.82 (0.29–27.21)	0.371	0.96 (0.07–13.89)	0.976
N classification					
2a	15	Not estimated	–	Not estimated	–
2b	35	Reference	–	Reference	–
2c	22	0.43 (0.09–2.09)	0.298	0.35 (0.07–1.85)	0.219
3	12	0.92 (0.19–4.43)	0.918	0.57 (0.09–3.47)	0.545
Neck treatment					
Observe	48	Reference	–	Reference	–
Neck dissection	36	0.47 (0.12–1.77)	0.264	0.48 (0.11–2.15)	0.335

Adjusted by age and sex

HR hazard ratio, *CI* confidence interval, *OHSCC* oro- and hypopharyngeal squamous cell carcinoma**Table 4** Interaction between neck treatment and primary tumor site in clinical outcomes of OHSCC patients

Primary tumor site	<i>n</i>	Overall survival			Regional control		
		HR (95 % CI)	<i>P</i> value	<i>P</i> for heterogeneity	HR (95 % CI)	<i>P</i> value	<i>P</i> for heterogeneity
Oropharynx							
Observe	32	Reference	–		Reference	–	
Neck dissection	27	0.73 (0.23–2.31)	0.587	0.005	0.17 (0.02–1.86)	0.146	0.094
Hypopharynx							
Observe	16	Reference	–		Reference	–	
Neck dissection	9	7.76 (0.58–103.83)	0.121		0.32 (0.02–5.93)	0.445	

Adjusted by age, sex, tumor and nodal classification

OHSCC oropharyngeal and hypopharyngeal squamous cell carcinoma, *HR* hazard ratio, *CI* confidence interval

Nine patients (25.0 %) experienced postoperative complications from ND; 3 for laryngeal edema, 3 for lymph fluid leaks, 2 for dysphagia, and 1 for lingual nerve paralysis. Two patients with laryngeal edema underwent tracheostomy. No patients died as a result of ND.

Discussion

In the present study, we demonstrated that ND was feasible, safe and correlated with clinical outcomes in OHSCC patients with residual nodal disease after definitive CRT. Such an association might differ by primary tumor sites.

Among HNSCC patients with N2–3 disease, the effectiveness of PND after definitive RT has been demonstrated.

Mendenhall et al. [12] reported that PND after definitive RT is associated with improved regional control. Recently, CRT has become as widely accepted as organ preservation treatment for locoregionally advanced HNSCC. That treatment has resulted in improved local control and survival [13–15], though PND following definitive CRT has remained controversial. McHam et al. [16] suggested that PND should be considered for all HNSCC patients with N2–3 disease, because the clinical parameters did not identify those patients with residual neck node disease or those at risk for regional failure after definitive CRT. Other investigators have favored PND only for patients with less than a CR in the neck after definitive CRT [12, 17]. Recently, two large-scale reviews corroborated the latter [18, 19]. In this study, we found that in the ND group, those

who were non-responders after definitive CRT were not significantly different from those in the non-ND group who were responders after CRT on their clinical outcomes. We also might agree that ND should be performed in OHSCC patients who did not achieve CR after definitive CRT. To establish this strategy, an appropriate imaging assessment regarding residual nodal disease is important.

In the near future, patients with N2–3 disease who require ND after definitive CRT may be selected based on a series of imaging studies. Although positron emission tomography (PET) is expected eventually to become a routine assessment tool following definitive CRT, it still does not always accurately assess the degree of response of nodal disease after definitive CRT. The timing of PET scans might prove important. Gourin et al. [20] reported that PET was not sufficiently specific or sensitive to reliably predict the need for ND after definitive CRT. Recently, a systematic review suggested that the timing of imaging examinations, including PET, for optimum sensitivity would need at least 8–12 weeks after the end of CRT [18, 21]. Therefore, we might be able to recommend the observation if clinical and imaging examination, including PET, are all negative.

In this study, we found that ND might be more effective for oropharyngeal cancer patients than for hypopharyngeal cancer patients. Although this association may be due to human papilloma virus (HPV) infection, its underlying mechanism remains unclear.

As for neck failure cases after ND, all cases had ECS within lymph nodes. Adjuvant treatments might be needed for these cases. Additionally, we obtained high salvage rates among both ND and non-ND groups in local and/or regional sites following definitive CRT. In general, the salvage treatments for a relapse after definitive RT pose serious problems. Mabanta et al. [22] reported that only 18 of 51 patients (35 %) with nodal recurrence after definitive RT were fit enough to undergo salvage treatment. For this reason, PND continues to be needed as a supplementary treatment after definitive CRT. However, we here demonstrated the feasibility of salvage surgery in local and/or regional sites following definitive CRT.

Postoperative complication rates from ND after CRT have been reported to range from 26 to 35 %, and have most often reflected impaired wound healing [23–25]. Our complication rate from ND was consistent with recent reports. Although a tracheostomy for postoperative laryngeal edema had to be performed on two patients, there were no fatal complications.

Several methodological limitations to this study warrant mention. First, although we tried to estimate bias by potential confounders in multivariate analysis, residual confounders, including HPV infection, cannot be completely ruled out. Second, the current moderate sample size

may be a study limitation that necessitates duplicating this work in another independent cohort.

In conclusion, we demonstrated that ND was feasible, safe and correlated with clinical outcomes in OHSCC patients with residual nodal disease following definitive CRT. In addition, this association might differ by the primary tumor site. The correlation between appropriate assessments of residual nodal disease after definitive CRT and the performance of ND may be attributable to non-responders after definitive CRT in OHSCC patients with N2–3 disease. To confirm these findings, a further prospective investigation is warranted.

Acknowledgments The authors gratefully acknowledge the energy and contribution of the doctors, nurses, and hospital administration staff at the Aichi Cancer Center Hospital. This study was supported by a Grant-in-Aid for Cancer Research and a Health and Labour Sciences Research Grant from the Ministry of Health, Labor and Welfare of Japan.

Conflict of interest The authors have declared no conflicts of interest.

References

1. Ferlay J, Shin HR, Bray F et al (2010) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 127(12):2893–2917
2. Tanaka S, Sobue T (2005) Comparison of oral and pharyngeal cancer mortality in five countries: France, Italy, Japan, UK and USA from the WHO Mortality Database (1960–2000). *Jpn J Clin Oncol* 35(8):488–491
3. Seiwert TY, Cohen EE (2005) State-of-the-art management of locally advanced head and neck cancer. *Br J Cancer* 92(8):1341–1348
4. Mehanna H, West CM, Nutting C et al (2010) Head and neck cancer—part 2: treatment and prognostic factors. *BMJ* 341:c4690
5. Barkley HT Jr, Fletcher GH, Jesse RH et al (1972) Management of cervical lymph node metastases in squamous cell carcinoma of the tonsillar fossa, base of tongue, supraglottic larynx, and hypopharynx. *Am J Surg* 124(4):462–467
6. Narayan K, Crane CH, Kleid S et al (1999) Planned neck dissection as an adjunct to the management of patients with advanced neck disease treated with definitive radiotherapy: for some or for all? *Head Neck* 21(7):606–613
7. Peters LJ, Weber RS, Morrison WH et al (1996) Neck surgery in patients with primary oropharyngeal cancer treated by radiotherapy. *Head Neck* 18(6):552–559
8. Pletcher SD, Kaplan MJ, Eisele DW et al (2003) Management of cervical metastases in advanced squamous cell carcinoma of the base of tongue. *Arch Otolaryngol Head Neck Surg* 129(9):983–986
9. Pignon JP, Bourhis J, Domenge C et al (2000) Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-analysis of chemotherapy on head and neck cancer. *Lancet* 355(9208):949–955
10. Kutler DI, Patel SG, Shah JP (2004) The role of neck dissection following definitive chemoradiation. *Oncology (Williston Park)* 18(8):993–998 (discussion 999, 1003–1004, 1007)

11. Cancer AJ (2002) Manual for staging of cancer. Springer, Heidelberg
12. Mendenhall WM, Villaret DB, Amdur RJ et al (2002) Planned neck dissection after definitive radiotherapy for squamous cell carcinoma of the head and neck. *Head Neck* 24(11):1012–1018
13. Adelstein DJ, Saxton JP, Lavertu P et al (1997) A phase III randomized trial comparing concurrent chemotherapy and radiotherapy with radiotherapy alone in resectable stage III and IV squamous cell head and neck cancer: preliminary results. *Head Neck* 19(7):567–575
14. Brizel DM, Albers ME, Fisher SR et al (1998) Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 338(25):1798–1804
15. Wendt TG, Grabenbauer GG, Rodel CM et al (1998) Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: a randomized multicenter study. *J Clin Oncol* 16(4):1318–1324
16. McHam SA, Adelstein DJ, Rybicki LA et al (2003) Who merits a neck dissection after definitive chemoradiotherapy for N2–N3 squamous cell head and neck cancer? *Head Neck* 25(10):791–798
17. Wolf GT, Fisher SG (1992) Effectiveness of salvage neck dissection for advanced regional metastases when induction chemotherapy and radiation are used for organ preservation. *Laryngoscope* 102(8):934–939
18. Wee JT, Anderson BO, Corry J et al (2009) Management of the neck after chemoradiotherapy for head and neck cancers in Asia: consensus statement from the Asian Oncology Summit 2009. *Lancet Oncol* 10(11):1086–1092
19. Ferlito A, Corry J, Silver CE et al (2010) Planned neck dissection for patients with complete response to chemoradiotherapy: a concept approaching obsolescence. *Head Neck* 32(2):253–261
20. Gourin CG, Williams HT, Seabolt WN et al (2006) Utility of positron emission tomography-computed tomography in identification of residual nodal disease after chemoradiation for advanced head and neck cancer. *Laryngoscope* 116(5):705–710
21. Isles MG, McConkey C, Mehanna HM (2008) A systematic review and meta-analysis of the role of positron emission tomography in the follow up of head and neck squamous cell carcinoma following radiotherapy or chemoradiotherapy. *Clin Otolaryngol* 33(3):210–222
22. Mabanta SR, Mendenhall WM, Stringer SP et al (1999) Salvage treatment for neck recurrence after irradiation alone for head and neck squamous cell carcinoma with clinically positive neck nodes. *Head Neck* 21(7):591–594
23. Stenson KM, Haraf DJ, Pelzer H et al (2000) The role of cervical lymphadenectomy after aggressive concomitant chemoradiotherapy: the feasibility of selective neck dissection. *Arch Otolaryngol Head Neck Surg* 126(8):950–956
24. Newman JP, Terris DJ, Pinto HA et al (1997) Surgical morbidity of neck dissection after chemoradiotherapy in advanced head and neck cancer. *Ann Otol Rhinol Laryngol* 106(2):117–122
25. Lavertu P, Bonafede JP, Adelstein DJ et al (1998) Comparison of surgical complications after organ-preservation therapy in patients with stage III or IV squamous cell head and neck cancer. *Arch Otolaryngol Head Neck Surg* 124(4):401–406

Significant improvement in superselective intra-arterial chemotherapy for advanced paranasal sinus cancer by using indocyanine green fluorescence

Junkichi Yokoyama · Shinichi Ohba ·
Mitsuhisa Fujimaki · Masataka Kojima ·
Michimasa Suzuki · Katsuhisa Ikeda

Received: 3 October 2013 / Accepted: 26 November 2013
© The Author(s) 2013. This article is published with open access at Springerlink.com

Abstract Recent advances in indocyanine green (ICG) fluorescence imaging have enabled the visualization of the blood supply to tissues. For advanced head and neck cancer, intra-arterial chemotherapy has been applied for improving the prognosis and organ preservation. To identify the tumor-feeding artery, CT angiography has been shown to be useful. However, the presence of dental metals sometimes disturbs the precise evaluation of paranasal sinus cancer patients by CT angiography. The objectives of the study were to assess the feasibility of the ICG fluorescence technique during intra-arterial chemotherapy for advanced maxillary cancer. Thirty-six patients with paranasal sinus cancer who were treated by intra-arterial chemotherapy were included. Conventional CT angiography followed by 5 mg of ICG injection was performed to confirm the areas in which the drug had dispersed. Intra-arterial chemotherapy was administered at 150 mg/m² of CDDP four times weekly. Additional information about the arteries feeding the tumors provided by ICG was evaluated. Out of 36 cases, in 17 (47%) the blood supply to the cancer was clearly detected by CT angiography. By adding the infrared ICG evaluation, the blood supply to the tumor was confirmed easily in all cases without radiation exposure. The information obtained from fluorescence imaging was helpful for making decisions concerning the administration

of chemo-agents for paranasal sinus cancers in cases involving dental metal, or skin invasion. ICG fluorescence imaging combined with intra-arterial chemotherapy compensated for the deficiencies of CT angiography for paranasal sinus cancer. ICG fluorescence provided us clearer and more useful information about the feeders to cancers.

Keywords Paranasal sinus cancer · Indocyanine green (ICG) · Superselective intra-arterial chemotherapy · CT angiography

Abbreviations

ICG Indocyanine green
NIR Near-infrared
I-A Intra-arterial
CT Computed tomography
DSA Digital subtraction angiography

Introduction

For advanced paranasal sinus cancer, which is resistant to conventional systemic chemotherapy, superselective intra-arterial chemotherapy is believed to increase the concentration of anti-cancer drugs in the tumor [1–6]. To obtain precise information about the blood supply of the tumors, we conducted CT angiography for head and neck cancer in 1998 for the first time in the world [7]. This procedure can provide accurate and detailed information about the vascular supply to head and neck cancers [1, 8–11]. However, it is difficult to confirm the drug distribution areas when the tumor is superficially invasive or the patient has undergone dental treatment with metal. When conducting intra-arterial

J. Yokoyama (✉) · S. Ohba · M. Fujimaki · M. Kojima ·
K. Ikeda
Department of Otorhinolaryngology-Head and Neck Surgery,
Juntendo University School of Medicine, Hongo 3-1-3,
Bunkyo-ku, 113-8431 Tokyo, Japan
e-mail: jyokoya@juntendo.ac.jp

M. Suzuki
Department of Radiology, Juntendo University School of
Medicine, Tokyo, Japan

Table 1 Patients' characteristics (TNM classification)

T/ N	0	1	2b	2c	
3	3				3
4a	11	2	4	1	18
4b	12	1	1	1	16
	26	3	5	2	36

Fresh:recurrent 32:4

chemotherapy for maxillary cancer, indigo carmine dye is thought to provide useful information concerning the tumor-feeding arteries [1, 2]. For deeply invasive tumors; however, conventional blue dye is not useful [1]. Furthermore, the duration for which the enhancement of the selected artery feeding can be observed is so short that it's difficult to evaluate precisely. Recent advances in indocyanine green (ICG) fluorescence imaging have enabled visualization of the blood flow in tissues [3, 12–15]. However, the only one report using ICG technique with intra-arterial chemotherapy has been applied to oral cancer [16]. We have applied this ICG fluorescence technique in combination with CT angiography for advanced paranasal sinus cancer.

The purpose of this study was to assess the feasibility of the ICG fluorescence technique during intra-arterial chemotherapy for advanced paranasal sinus cancer, especially maxillary cancer.

Materials and methods

Thirty-six patients with paranasal sinus cancer who were treated by intra-arterial (I-A) chemotherapy concurrent to radiotherapy from April 2010 to January 2012 were included in this study. The patients' characteristics are shown in Table 1. CT angiography was performed after the branch of a possible tumor-feeding artery was selected using conventional DSA. At the same time, 5 mg of indocyanin green (ICG) was injected and we observed whether the tumor territories were stained by using an infrared camera system (Hypereye Medical System Handy, Mizuho Ikakogyo Co. Ltd).

I-A chemotherapy was performed weekly over a 4-week period. 150 mg/m² of CDDP was administered superselectively through feeding arteries at 5 mg/min. Sodium thiosulfate at a dose of 200-fold that of the CDDP was injected concurrently intravenously to neutralize the adverse effects of CDDP.

We used both a retrograde approach via a temporal artery and a femoral artery. I-A chemotherapy was performed via the femoral artery when the tumor invaded the

contralateral side or when contralateral side lymph node metastasis occurred. When the targeted artery had many branches that were not blood supplies to the cancer, we used a microcatheter through a 5 Fr guide catheter positioned inside the targeted artery.

We evaluated the diagnostic sensitivity of CT angiography and ICG fluorescence technique. Furthermore, when the tumor extended beyond the midline, the drug distribution could be made to extend to the contralateral tumor by manual compression of the contra-carotid artery, confirmed using the ICG fluorescence technique. Informed consent was obtained from each patient before treatment and the study was approved by the Human Ethics Review Committee of Juntendo University.

Results

Thirty-six patients with advanced paranasal sinus cancer received definitive chemoradiation with I-A chemotherapy. These advanced cases were not suitable for surgical treatment for organ preservation. Superselective I-A chemotherapy via a superficial temporal artery was performed in 18 patients. We initially carried out superselective I-A chemotherapy via the femoral artery twice in 3 cases of N2c and 15 cases of T4, in which the contralateral nasal or paranasal sinus was invaded by cancer. After this procedure, the patients were treated by superselective I-A chemotherapy via a superficial temporal artery carried out twice. There were no significant complications. Table 2 shows a list of the infused arteries. The total number of I-A chemotherapies was 164. The mean I-A chemotherapy was 4.56 (range 3–6). The total number of superselectively infused arteries was 413. Of the 413 infused arteries, the numbers of infused maxillary arteries, facial arteries, transverse facial arteries, and internal carotid arteries were 164, 79, 64, and 72, respectively.

CT angiography revealed the vascular territories of selected arteries in only 17 cases (47 %). The reasons for the failure in detecting the tumor-feeding arteries included dental metals (10 cases) and mucosal or skin invasions (superficially invasive tumor) (8 cases). Additionally, CT angiography could not detect communicating branches between the feeders (7 cases). With the infrared ICG evaluation, the arteries supplying the tumors were confirmed accurately in all cases (Figs. 1, 2). In the cases with a tumor invading the cheek or facial skin, the use of communicating branches of the maxillary artery for drug delivery to the whole tumor was confirmed by manual compression of the ipsilateral facial artery (Fig. 3). The alteration of blood flow by manual facial artery compression could be directly observed using the ICG fluorescence technique (Fig. 3). In the case of a tumor crossing the midline, drug delivery to the

Table 2 The summary of infused arteries

Infused artery	Maxillary A	Facial A	Transverse facial A	Superficial temporary A	Occipital A
Total	164	79	64	12	10
Average	4.56	2.19	1.8	0.33	0.28
Range	2–6	0–5	0–5	0–5	0–2

Infused artery	Internal carotid A	Posterior auricular A	Contralateral maxillary A	Contralateral internal carotid A	Ascending pharyngeal A	Total
Total	72	2	6	2	2	413
Average	2	0.06	0.17	0.06	0.06	
Range	0–6	0–2	0–4	0–2	0–2	

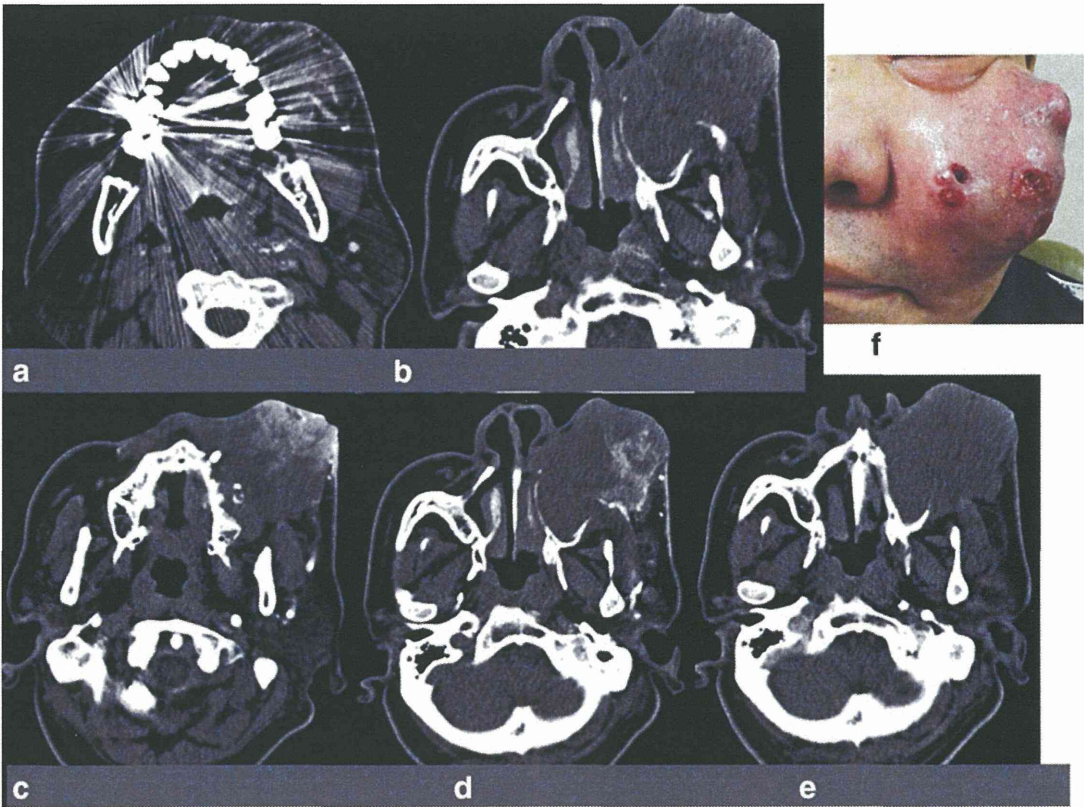


Fig. 1 Case 1: a 66-year-old man with maxillary cancer (T4AN2bM0). **a** CT angiography obtained in the selected left side maxillary artery. It was difficult to confirm the vascular territory due to dental metals. **b** CT angiography obtained in the selected left side maxillary artery. It was difficult to confirm the vascular territory due to obstacle enhancement. **c** CT angiography obtained in the selected left side facial artery. It was sufficiently clear to confirm the vascular

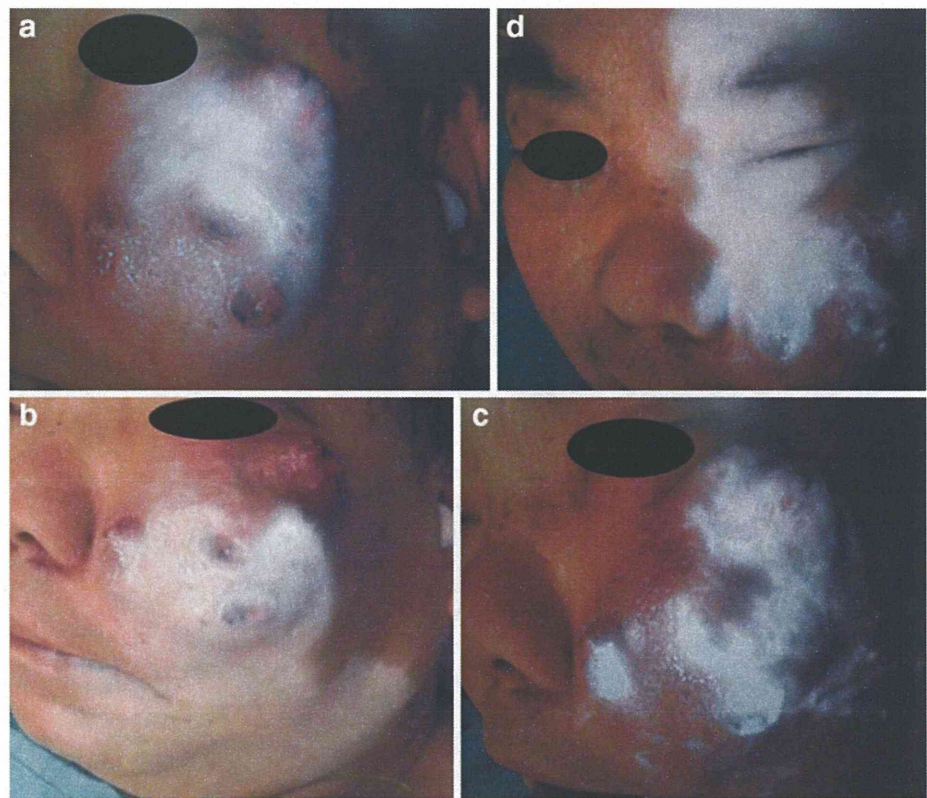
territory. **d** CT angiography obtained in the selected left side transverse facial artery. It was sufficiently clear to confirm the vascular territory. **e** CT angiography obtained in the selected left side internal carotid artery. It was difficult to confirm the vascular territory due to obstacle enhancement. **f** Maxillary cancer invading the face before treatment

whole tumor was confirmed by manual compression of the contralateral carotid artery, or maxillary artery. The alteration of blood flow by manual contralateral artery compression was directly viewed using the ICG fluorescence technique (Fig. 3).

Confirmation of the tumor-feeding arteries was established using CT angiography and ICG fluorescence imaging, as shown in Fig. 4.

The effect of I-A chemotherapy was that CR and PR were 86 and 14 %, respectively.

Fig. 2 ICG fluorescence imaging. **a** ICG fluorescence imaging of the left maxillary artery. **b** ICG fluorescence imaging of the left facial artery. **c** ICG fluorescence imaging of the left transverse facial artery. **d** ICG fluorescence imaging of the left internal carotid artery. The cancer involving the facial skin was clearly visualized under fluorescent imaging of each vascular area



Of the definitive chemoradiation group, the overall survival rates of the cases, stage III and IVA group, and stage IVB group were 78, 82, and 77 %, respectively (Fig. 5). The difference between the overall survival rate of the stage III and IVA group and the overall survival rate of the stage IVB group was not significant (Fig. 5).

Discussion

Chemoradiotherapy for head and neck cancer plays an important role in organ preservation, but there are many cases such as paranasal sinus cancer for which conventional systemic chemotherapies do not work at all. CDDP is the most promising drug for head and neck cancer. When high doses of CDDP are used, various adverse effects can be observed, such as gastrointestinal toxicity, renal toxicity, and hematotoxicity. For such chemo-resistant cancers including paranasal sinus cancer, superselective intra-arterial chemotherapy is considered to increase the concentration of the anti-cancer drug in the cancer tissue, exerting powerful effects on the primary cancer [1–6]. This procedure is reportedly capable of achieving a positive prognosis as well as good organ preservation.

To achieve an effective therapeutic result for paranasal sinus cancer with intra-arterial chemotherapy, precise

evaluation of the tumor-feeding artery and drug distribution territories is required. Digital subtraction angiography (DSA) is applied for all cases of I-A chemotherapy; however, DSA cannot clearly detect the border between the oral mucosa and surface invasion tumor. CT angiography clearly detects the border between the normal paranasal sinus and deeply invasive cancer by using three-dimensional sections. Therefore, CT angiography in addition to DSA has provided more precise identification of the blood supply to the tumor [1, 7, 8]. However, we are sometimes not able to confirm the tumor-feeding artery in paranasal sinus cancer patients with dental metal fillings or when the tumor has spread to oral cavities or superficially to the facial skin. Furthermore, repeated CT angiography increases the X-ray exposure, which is a significant problem not only for patients but also for the medical staff, especially when a manual carotid compression technique is applied. Previously, indigo carmine dye was often used to confirm the blood supply to the tumor. However, the stain disappears soon after the injection and cannot be observed in cases of deeply invasive tumors [1, 2].

Recently, the ICG fluorescence technique was developed and has been used in various fields [3, 12–15]. The excitation and emission profiles for ICG lie in the near-infrared wavelengths, which allow penetration and imaging of vessels below a few millimeters of tissue [12]. It

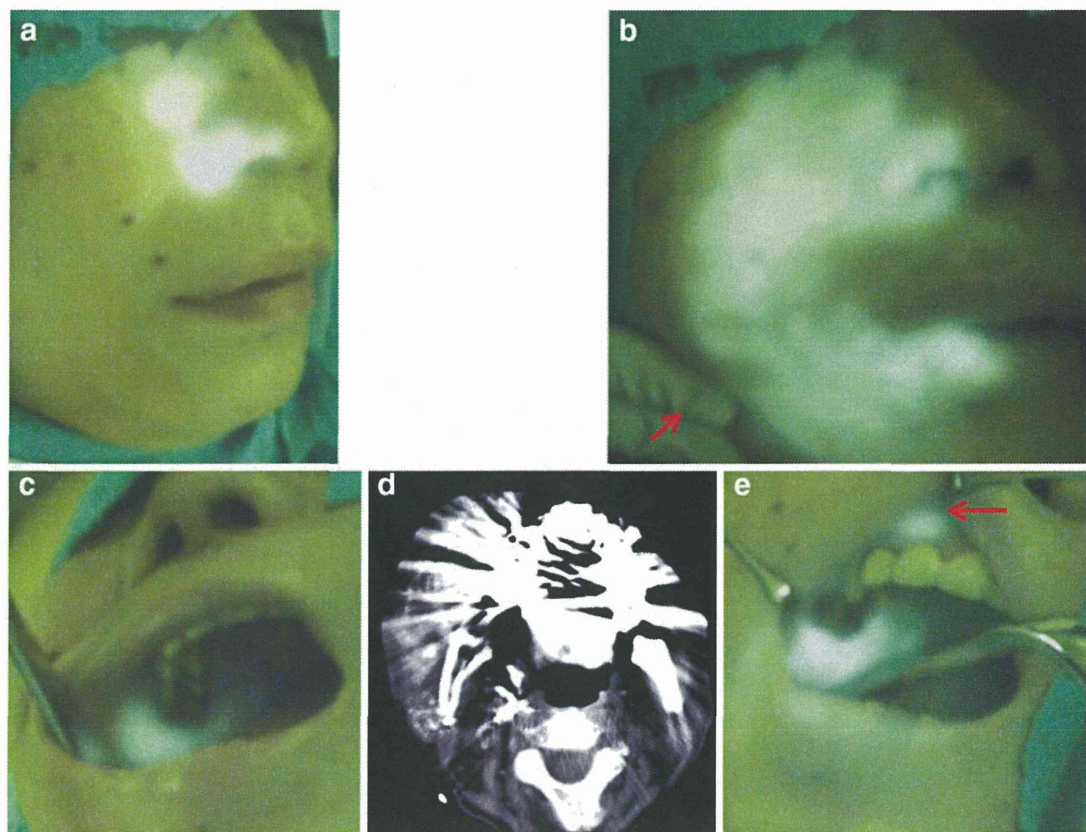


Fig. 3 Case 2: a 60-year-old woman with maxillary cancer (T4aN0M0), which extended to the oral cavity and cheek with communicating branches between the maxillary artery and facial artery. **a** The right cheek by ICG fluorescence imaging at the right maxillary artery. **b** The right cheek by ICG fluorescence imaging with right manual facial artery compression. The ICG fluoresced areas extended throughout the maxillary artery and the facial artery was infused at the right maxillary artery with right manual facial artery

compression (*arrow*). **c** The oral cavity by ICG fluorescence imaging at the right maxillary artery. **d** CT angiography obtained in the right maxillary artery. It was difficult to confirm the vascular territory due to dental metal. **e** The oral cavity by ICG fluorescence imaging with right manual facial artery compression. The ICG fluoresced oral cavity extended throughout the maxillary artery and the facial artery with right manual facial artery compression

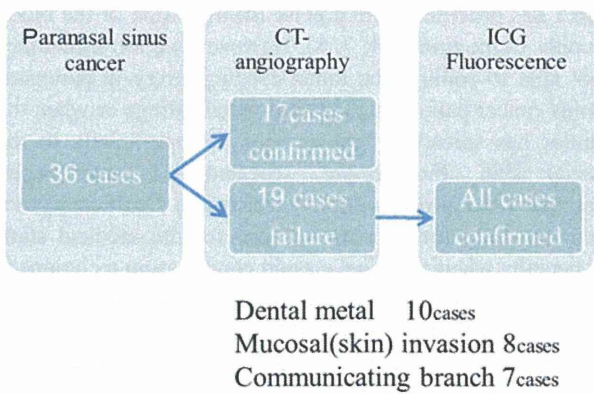


Fig. 4 The confirmation rate of the tumor-feeding arteries with CT angiography and ICG fluorescence imaging

provides visualization of the blood supply to reconstructed organs, and sentinel lymph nodes in cancer surgery including head and neck cancer surgery [3, 13, 15, 17].

ICG fluorescence has been used for navigation surgery and intraoperative detection of cancers [12, 18, 19].

We have reported that the ICG fluorescence technique can be a very useful method for treating oral cancers with I-A chemotherapy in patients with dental metal [16].

In this study, we also report our success in identifying the tumor-feeding arteries in paranasal sinus cancer by ICG fluorescence imaging. We found that the ICG fluorescence technique was a very useful method even in patients with dental metal. For tumors with multiple feeding arteries, ICG fluorescence in selectively infused arteries could be evaluated clearly and lucidly. Accordingly, we were able to confirm that the whole tumor was covered and infused with the anti-cancer drug.

We sometimes performed the I-A infusion chemotherapy with manual compression of the contralateral facial artery or lingual artery in cases of oral cancer with tumors spreading to the contralateral oral cavity. This enabled