

## Correlation Between $^{18}\text{F}$ -FDG-uptake and *In Vitro* Chemosensitivity of Cisplatin in Head and Neck Cancer

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**Abstract.** Aim: High [ $^{18}\text{F}$ ]-2-fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) -uptake of primary tumor, assessed by pretreatment positron emission tomography combined computed tomography (PET/CT), has indicated poor overall survival (OS) in head and neck cancer (HNC). We investigated the correlation between  $^{18}\text{F}$ -FDG-uptake and *in vitro* chemosensitivity of cisplatin using histoculture drug response assay in HNC. Patients and Methods: Twenty-eight patients were evaluated. The maximum standardized uptake value ( $\text{SUV}_{\text{max}}$ ) and inhibition index (I.I.) cisplatin were calculated as  $^{18}\text{F}$ -FDG-uptake and *in vitro* chemosensitivity of cisplatin. Results: Each  $\text{SUV}_{\text{max}} \geq 10.5$  or I.I. cisplatin  $< 50$  could significantly differentiate shorter survival group by OS analyses. I.I. cisplatin of patients with  $\text{SUV}_{\text{max}} \geq 10.5$  was significantly greater. In 19 patients with  $\text{SUV}_{\text{max}} \geq 10.5$ , those who received treatment with cisplatin-based chemotherapy exhibited a significant correlation with longer OS. Conclusion: Cisplatin has the potential to improve OS for HNC patients that were predicted as shorter OS by  $^{18}\text{F}$ -FDG-PET/CT.

Positron emission tomography with computed tomography (PET/CT) employing a glucose analogue, [ $^{18}\text{F}$ ]-2-fluorodeoxyglucose ( $^{18}\text{F}$ -FDG), are widely used imaging procedures for accurately staging various cancers (1, 2). The semi-quantitative measurement of the maximum  $^{18}\text{F}$ -FDG-uptake in the primary tumor, which is assessed using  $^{18}\text{F}$ -FDG-PET/CT, is usually obtained according to the maximum standardized uptake value ( $\text{SUV}_{\text{max}}$ ) (3-13). Many reports of

patients with head and neck squamous cell carcinoma (SCC), non-small cell lung cancer and other cancers have demonstrated that a high  $\text{SUV}_{\text{max}}$  of the primary tumor is reported to predict shorter overall survival (OS) (3-12). Several investigators have suggested that patients who are predicted as poor-prognosis by high  $\text{SUV}_{\text{max}}$  of primary tumor need more aggressive treatment, such as chemotherapy. The correlation, however, between  $\text{SUV}_{\text{max}}$  and chemosensitivity, which is reported as a useful predictor of response to chemotherapy, has not been fully investigated (3, 4).

The histoculture drug response assay (HDRA), which is an *in vitro* chemosensitivity assay, has been reported as a useful predictor for response to chemotherapy in various cancers (14-18). We have investigated the appropriate concentration in the HDRA for cisplatin, which is the most commonly used agent for head and neck cancer (HNC) (14). Moreover, the results from the HDRA in several cancers, such as HNC, non-small lung cancer and esophageal cancer, have been significantly correlated with survival (15-17). To our best knowledge, correlation between  $\text{SUV}_{\text{max}}$  and HDRA of cisplatin in patients with HNC has not been investigated so far.

In the present study, we studied the correlation between  $\text{SUV}_{\text{max}}$  and HDRA of cisplatin in patients with HNC.

### Patients and Methods

**Patients.** Tumor specimens from patients undergoing both pretreatment with  $^{18}\text{F}$ -FDG-PET/CT at the Nagoya PET Imaging Center and radical treatment for HNC at the Department of Head and Neck Surgery, Aichi Cancer Center were included in the present study. Twenty-eight tumor specimens from primary tumor sites, which were collected from radical surgery without preoperative chemotherapy or biopsy before treatment, were successfully subjected to HDRA analysis of cisplatin between August 2004 and February 2006. This study was approved by the institutional review board and all patients provided informed consent for all treatments and examinations. Sites of primary tumors were as follows: oropharynx, 9; oral cavity, 7; major salivary gland, 6; maxillary

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sinus, 2; hypopharynx, 2; larynx, 2. Histologic types of head and neck cancer were 21 patients with SCC and 7 patients with non-SCC (mucoepidermoid carcinoma, 2; adenoid cystic carcinoma, 1; carcinoma ex pleomorphic adenoma, 1; salivary duct carcinoma, 1; epithelial-myoepithelial carcinoma, 1; adenocarcinoma, not otherwise specified, 1). At the first visit, a routine physical examination, nasopharyngoscopy and a blood chemistry test, including blood glucose level were performed; the mean blood glucose level at the first visit was  $102.8 \pm 18.0$  mg/dl (mean  $\pm$  standard deviation (S.D.)). The clinical TNM classification of the international Union against Cancer (sixth edition) was diagnosed by the aforementioned examinations, enhanced cervical computed tomography or magnetic resonance imaging and  $^{18}\text{F}$ -FDG-PET/CT.

**Treatments.** Ten of the patients underwent radical treatment with chemotherapy, while the remainder underwent radical treatment without chemotherapy. The treatment included radiotherapy with chemotherapy or induction chemotherapy and the regime of chemotherapy was cisplatin-based chemotherapy, which comprises combination of cisplatin and 5-fluorouracil (5-FU) (19). In accordance with a previous report, 28 patients were grouped by primary treatment modality: curative surgery with or without radiotherapy (surgery group,  $n=21$ ) and radical radiotherapy with cisplatin-based chemotherapy (radiation group,  $n=7$ ) (5). The selection of primary treatment modality depended on the histologic type and on whether patients hoped for their organ preservation. Following the completion of treatment, the patients were followed-up at our outpatient clinic. Those identified with early locoregional recurrence underwent radical salvage therapy.

**HDRA and inhibition index (I.I.) cisplatin.** For the tumor specimens, the *in vitro* chemosensitivity of cisplatin (Nippon Kayaku, Tokyo, Japan) was examined using the HDRA according to methods described previously (14, 18). The tumor specimens obtained from surgery or biopsy were immediately placed in 35 ml of RPMI 1640 (Sigma, St. Louis, MO, USA) and stored at  $4^\circ\text{C}$ . The specimens were washed three times with HBSS (Sigma) and aseptically cut in 10 mg fragments. Collagen sponge gel (Gel Foam; Pharmacia & Upjohn, Kalamazoo, MI, USA) was cut into 1 cm squares and placed into a 24-well microplate (Becton Dickinson Labware, Franklin Lakes, NJ, USA), which contained RPMI 1640 with 20% fetal calf serum (FCS) (Gibco, Grand Island, NY, USA) at a concentration of 20  $\mu\text{g}/\text{ml}$  for cisplatin; an amount just sufficient to contact the collagen gel. Two fragments of the cut specimens, which were placed on the collagen gel, were cultured for 7 days at  $37^\circ\text{C}$  in 5%  $\text{CO}_2$  atmosphere. For the control group, the same approach was followed and specimens were cultured for 7 days in culture medium containing only 1640 RPMI with 20% FCS. The specimens were cultured in two or three wells each for the control and cisplatin groups. After histoculture, 100  $\mu\text{l}$  HBSS containing 0.06% collagenase type I (Sigma) and 3-(4, 5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H tetrazolium bromide (MTT) (Sigma) buffer saline solution containing 0.1 M sodium succinate were added to each well and incubated for 16 h, time after which the media were removed. For the extraction of the MTT formazan product, the cells were incubated in 0.5 ml of dimethyl sulfoxide (Sigma) for 2 h. Samples of 100  $\mu\text{l}$  from each well were measured by a microplate reader (ImmunoMini NJ-2300; Nalge Nunc International, Rochester, NY, USA). The absorbance was measured at the wavelength of 540 nm by using a reference wavelength of 630 nm. The efficacy of cisplatin

was calculated by the following formula:  $\text{I.I. (\%)} = (1 - \text{mean absorbance per gram of treated tumor} / \text{mean absorbance per gram of control tumor}) \times 100$ . The interval between the start of the HDRA assay and the start of therapy was  $2.21 \pm 4.52$  days (mean  $\pm$  S.D.).

**$^{18}\text{F}$ -FDG-PET/CT.** All patients were scanned using a FDG-PET/CT (DiscoveryLS-GE; Fairfield, CT, USA). The intervals between the  $^{18}\text{F}$ -FDG-PET/CT examination and the start of HDRA assay was  $16.1 \pm 12.0$  days and the interval between the  $^{18}\text{F}$ -FDG-PET/CT examination and the start of therapy was  $17.0 \pm 11.5$  days. Patients underwent intravenous injection of  $^{18}\text{F}$ -FDG (186-315 MBq) after fasting for at least 6 h according to procedures published previously (13). Two experienced radiologists viewed all images on a Xeleris (GE) and the SUV was calculated by the following formula:  $\text{SUV} = \text{Tissue concentration (Bq/g)} / \{\text{Injection dose (Bq)} / \text{body weight (g)}\}$

The  $\text{SUV}_{\text{max}}$  of the primary tumor was obtained from a region of interest, which was designed as a site of abnormal accumulation on the coronal image.

**Statistical analysis.** The statistical analysis was carried out using the JMP software package (version 9; SAS; Cary, NC, USA). The relationship between  $\text{SUV}_{\text{max}}$  and I.I. cisplatin was analyzed by a simple regression analysis. Relationships between two parameters ( $\text{SUV}_{\text{max}}$  and I.I. cisplatin) and clinical parameters (clinical T and N classifications, clinical stage, age, sex, tumor site, treatment group, with/without cisplatin-based chemotherapy and histologic type) were analyzed using the Spearman's rank correlation and Mann-Whitney *U*-test. The definition of OS time was the period from pretreatment  $^{18}\text{F}$ -FDG-PET/CT to death or date of last contact. Applying the method described in our and others studies, the Kaplan-Meier technique was used to estimate OS rate. Various cutoff values of both  $\text{SUV}_{\text{max}}$  and I.I. cisplatin were tested using the log-rank test in a univariate OS analysis (3-5). The patients were divided into two groups based on the  $\text{SUV}_{\text{max}}$  ( $\text{SUV}_{\text{max}} \geq 10.5$ ;  $\text{SUV}_{\text{max}} < 10.5$ ) and the I.I. cisplatin (I.I. cisplatin  $\geq 50$ ; I.I. cisplatin  $< 50$ ) in the univariate OS analysis as a  $\text{SUV}_{\text{max}}$  of 10.5 and an I.I. cisplatin 50 were found to significantly differentiate the shorter survival group from the longer survival group. The correlation between the two groups ( $\text{SUV}_{\text{max}} \geq 10.5$ ;  $\text{SUV}_{\text{max}} < 10.5$  or I.I. cisplatin  $\geq 50$ ; I.I. cisplatin  $< 50$ ) on clinical parameters was compared by the chi-square test. The Mann-Whitney's test was used to estimate relationships between the two groups from  $\text{SUV}_{\text{max}}$  10.5 ( $\text{SUV}_{\text{max}} \geq 10.5$ ;  $\text{SUV}_{\text{max}} < 10.5$ ) on I.I. cisplatin and between the two groups from I.I. cisplatin 50 (I.I. cisplatin  $\geq 50$ ; I.I. cisplatin  $< 50$ ) on  $\text{SUV}_{\text{max}}$ . In the multivariate survival analysis, we used a Cox proportional hazards model. Further study of the multivariate analysis led to adjustments for the two groups from  $\text{SUV}_{\text{max}}$  10.5 ( $\text{SUV}_{\text{max}} \geq 10.5$ ;  $\text{SUV}_{\text{max}} < 10.5$ ) and the two groups from I.I. cisplatin 50 (I.I. cisplatin  $\geq 50$ ; I.I. cisplatin  $< 50$ ). In 19 patients with  $\text{SUV}_{\text{max}} \geq 10.5$ , two groups (radical treatment with cisplatin-based chemotherapy; without cisplatin-based chemotherapy) were compared by the log-rank test. A *p*-value of less than 0.05 was considered to be statistically significant.

## Results

The  $\text{SUV}_{\text{max}}$  and I.I. cisplatin of the primary tumor (mean  $\pm$  SD) were  $14.04 \pm 7.52$  and  $50.98 \pm 26.6$ , respectively. The  $\text{SUV}_{\text{max}}$  was significantly correlated with the I.I. cisplatin ( $p < 0.04$ ,  $R^2 = 0.17$ ) as shown in Figure 1.

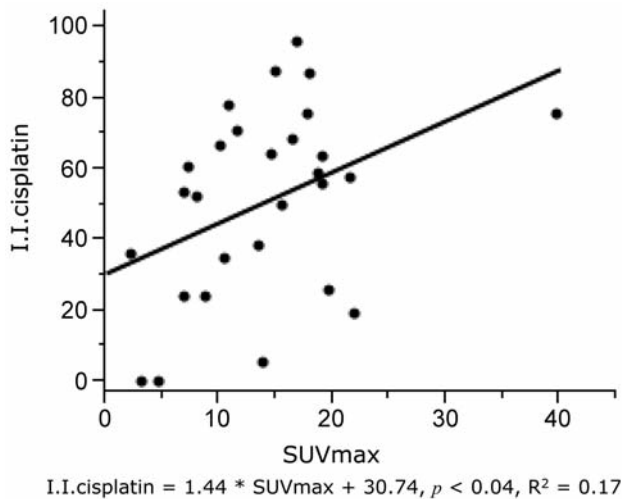


Figure 1. Relationship between SUVmax and I.I.cisplatin in 28 patients with head and neck cancer. SUVmax, maximum standardized uptake value; I.I., inhibition index.

**SUVmax and clinical parameters.** The relationships between  $\text{SUV}_{\text{max}}$  and clinical parameters (clinical T and N classifications, clinical stage, age, sex, tumor site, treatment group, with/without cisplatin-based chemotherapy and histologic type) is shown in Table I. The  $\text{SUV}_{\text{max}}$  of patients with SCC was significantly higher than in non-SCC ( $p < 0.02$ ) and that of the radiation group was closely greater than in the surgery group ( $p < 0.01$ ). The  $\text{SUV}_{\text{max}}$  of patients who received radical treatment with cisplatin-based chemotherapy was significantly higher than in patients without cisplatin-based chemotherapy ( $p < 0.02$ ).

**I.I.cisplatin and clinical parameters.** The relationships between I.I.cisplatin and clinical parameters is shown in Table II. The I.I.cisplatin of the radiation group was significantly greater than in the surgery group ( $p < 0.01$ ) and that of patients who received radical treatment with cisplatin-based chemotherapy was significantly higher than the one without cisplatin-based chemotherapy ( $p < 0.03$ ).

**Survival analysis.** At the end of this study, the mean  $\pm$  SD follow-up period among all patients, 17 patients who died (60.7% vs. all) and 11 patients found to be alive (39.3 %) was  $48.2 \pm 32.4$  months,  $70.7 \pm 32.3$  months and  $33.6 \pm 23.3$  months, respectively. Among the total patient population, the 3-year, 4-year and 5-year OS rates were 54.2%, 50.3% and 46.1%, respectively. Applying the method described previously in our and other studies (3-5), various  $\text{SUV}_{\text{max}}$  and I.I.cisplatin cut-off values were tested using the log-rank test in the OS analysis. The cut-off values with the lowest  $p$ -values were used in these analyses:  $\text{SUV}_{\text{max}} = 10.5$  and I.I.cisplatin = 50 (Figure

Table I. Relationship between SUVmax and clinical parameters ( $n = 28$ ).

Parameter	Number	SUVmax (Mean $\pm$ S.D.)	$p$ -Value
Clinical T classification			
T2	5	10.56 $\pm$ 7.14	0.434*
T3	12	14.23 $\pm$ 4.99	
T4	11	15.42 $\pm$ 9.84	
Clinical N classification			
N0	18	13.37 $\pm$ 8.81	0.25*
N1	3	13.47 $\pm$ 4.61	
N2	7	16.01 $\pm$ 4.64	
Clinical stage			
II	4	11.45 $\pm$ 7.91	0.48*
III	8	13.08 $\pm$ 5.76	
IV	16	15.18 $\pm$ 8.38	
Age			
<66	13	12.08 $\pm$ 6.18	0.30†
$\geq 66$	15	15.74 $\pm$ 8.35	
Gender			
Male	22	13.99 $\pm$ 7.71	0.58†
Female	6	14.23 $\pm$ 7.48	
Tumor site			
Oropharynx	9	15.79 $\pm$ 5.01	0.18†
Others	19	13.22 $\pm$ 8.46	
Treatment group			
Surgery	21	11.60 $\pm$ 8.24	<0.01†
Radiation	7	21.38 $\pm$ 8.24	
Cisplatin-based chemotherapy			
With	10	18.92 $\pm$ 8.32	<0.02†
Without	18	11.33 $\pm$ 5.62	
Histologic type			
SCC	21	15.95 $\pm$ 7.24	<0.02†
Non-SCC	7	8.33 $\pm$ 5.41	

SUV<sub>max</sub>, maximum standardized uptake value; Mean  $\pm$  S.D., mean  $\pm$  standard deviation; SCC, squamous cell carcinoma. \*Spearman's rank correlation, †Mann-Whitney  $U$ -test.

2). It was shown that each of the  $\text{SUV}_{\text{max}}$  of  $\geq 10.5$  ( $p < 0.02$ ) or I.I.cisplatin  $< 50$  ( $p < 0.04$ ) could be used to significantly differentiate the shorter survival group by the log-rank test (Figure 3). No significant correlation between the two groups ( $\text{SUV}_{\text{max}} \geq 10.5$ ;  $\text{SUV}_{\text{max}} < 10.5$ ) on clinical parameters is shown in Table III. The correlation between the two groups (I.I.cisplatin  $\geq 50$ ; I.I.cisplatin  $< 50$ ) on clinical parameters is shown in Table IV. Patients with I.I.cisplatin  $\geq 50$  were more frequently found in the radiation group ( $p < 0.03$ ) and radical treatment with cisplatin-based chemotherapy ( $p < 0.05$ ) than patients with I.I.cisplatin  $< 50$ . A significant correlation between the two groups from  $\text{SUV}_{\text{max}} 10.5$  ( $\text{SUV}_{\text{max}} \geq 10.5$ ;  $\text{SUV}_{\text{max}} < 10.5$ ) on I.I.cisplatin and no correlation between the two groups from I.I.cisplatin 50 (I.I.cisplatin  $\geq 10.5$ ; I.I.cisplatin  $< 10.5$ ) on  $\text{SUV}_{\text{max}}$  is shown in Figure 4. The I.I.cisplatin of patients with  $\text{SUV}_{\text{max}} \geq 10.5$  was significantly greater than that of patients with  $\text{SUV}_{\text{max}} < 10.5$  ( $p < 0.03$ ).

Table II. Relationship between I.I.cisplatin and clinical parameters (n=28).

Parameter	Number	I.I. cisplatin (Mean±S.D.)	p-Value
Clinical T classification			
T2	5	50.87±20.16	0.51*
T3	12	46.58±28.74	
T4	11	55.83±28.12	
Clinical N classification			
N0	18	48.74±25.89	0.25*
N1	3	49.82±32.80	
N2	7	57.26±29.43	
Clinical stage			
II	4	57.58±15.56	0.47*
III	8	37.16±29.52	
IV	16	56.25±26.00	
Age			
<66	13	44.45±25.42	0.19†
≥66	15	56.65±27.15	
Gender			
Male	22	50.83±29.88	0.58†
Female	6	51.55±8.44	
Tumor site			
Oropharynx	9	51.55±24.01	0.98†
Others	19	50.72±24.01	
Treatment group			
Surgery	21	43.06±25.27	<0.01†
Radiation	7	74.75±13.32	
Cisplatin-based chemotherapy			
With	10	67.05±17.08	<0.03†
Without	18	42.06±27.09	
Histologic type			
SCC	21	54.26±24.97	0.35†
Non-SCC	7	41.15±30.93	

I.I., Inhibition index; Mean±S.D., mean±standard deviation; SCC, squamous cell carcinoma. \*Spearman's rank correlation, †Mann-Whitney *U*-test.

**Multivariate survival analysis.** We performed multivariate analysis with adjustments for the two groups from SUV<sub>max</sub> 10.5 (SUV<sub>max</sub> ≥10.5; SUV<sub>max</sub> <10.5) and the two groups from I.I.cisplatin 50 (I.I.cisplatin ≥50; I.I.cisplatin <50) for OS. SUV<sub>max</sub> ≥10.5 (*p*<0.01) and I.I.cisplatin <50 (*p*<0.01) proved to be significantly shorter survival factors. Multivariate analysis for OS is shown in Table V.

**Results with/without cisplatin-based chemotherapy.** In 19 patients with SUV<sub>max</sub> ≥10.5, those who received radical treatment with cisplatin-based chemotherapy exhibited a significant correlation with longer OS than those who received radical treatment without cisplatin-based chemotherapy (*p*<0.05) (Figure 5).

Table III. Relationships between SUV<sub>max</sub> (<10.5/≥10.5) and clinical parameters (n=28).

Clinical parameter	SUV <sub>max</sub> <10.5 (n=9)	SUV <sub>max</sub> ≥10.5 (n=19)	p-Value
Clinical T classification			
T1-2	3	2	0.29*
T3-4	6	17	
Clinical N classification			
N0	7	11	0.42*
N1-2	2	8	
Clinical stage			
I-III	5	7	0.43†
IV	4	12	
Age			
<66	6	7	0.23*
≥66	3	12	
Gender			
Male	7	15	1.00 *
Female	2	4	
Tumor site			
Oropharynx	2	7	0.67*
Others	7	12	
Treatment group			
Surgery	9	12	0.06*
Radiation	0	7	
Cisplatin-based chemotherapy			
With	1	9	0.10*
Without	8	10	
Histologic type			
SCC	5	16	0.17*
Non-SCC	4	3	

SUV<sub>max</sub>, maximum standardized uptake value; SCC, squamous cell carcinoma. \*Fisher's exact test, †Chi-square test.

## Discussion

In the present study, we showed for the first time that the I.I.cisplatin of patients with SUV<sub>max</sub> ≥10.5 in HNC was significantly greater than that of patients with SUV<sub>max</sub> <10.5 and that both SUV<sub>max</sub> ≥10.5 (*p*<0.01) and I.I.cisplatin < 50 (*p*<0.01) proved to be significantly shorter survival factors in multivariate analysis.

Although <sup>18</sup>F-FDG-PET and <sup>18</sup>F-FDG-PET/CT are important imaging procedures for the diagnosis and staging of many cancers, their full potential has yet to be established (3-5). Many investigators have demonstrated in head and neck SCC, as well as lung cancer, including various types of carcinoma, such SCC and adenocarcinoma, that higher SUV<sub>max</sub> is correlated with shorter OS (3-9). Recently, a review and two meta-analyses of patients with head and neck SCC demonstrated that an increased SUV<sub>max</sub> indicates a poor OS (10-12). Moreover, in our previous reports, a high SUV<sub>max</sub> of the primary tumor was found to be associated

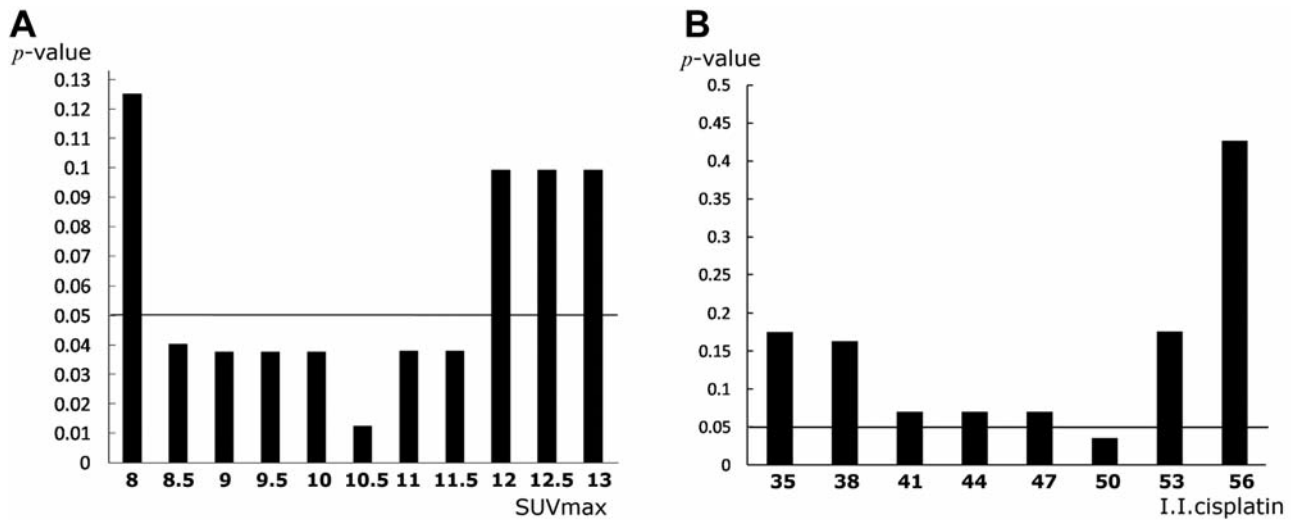


Figure 2.  $p$ -Values of log-rank test for overall survival using different cutoff levels for  $\text{SUV}_{\text{max}}$  (A) and I.I.cisplatin (B) for 28 patients with head and neck cancer.  $\text{SUV}_{\text{max}}$ , maximum standardized uptake value; I.I., inhibition index.

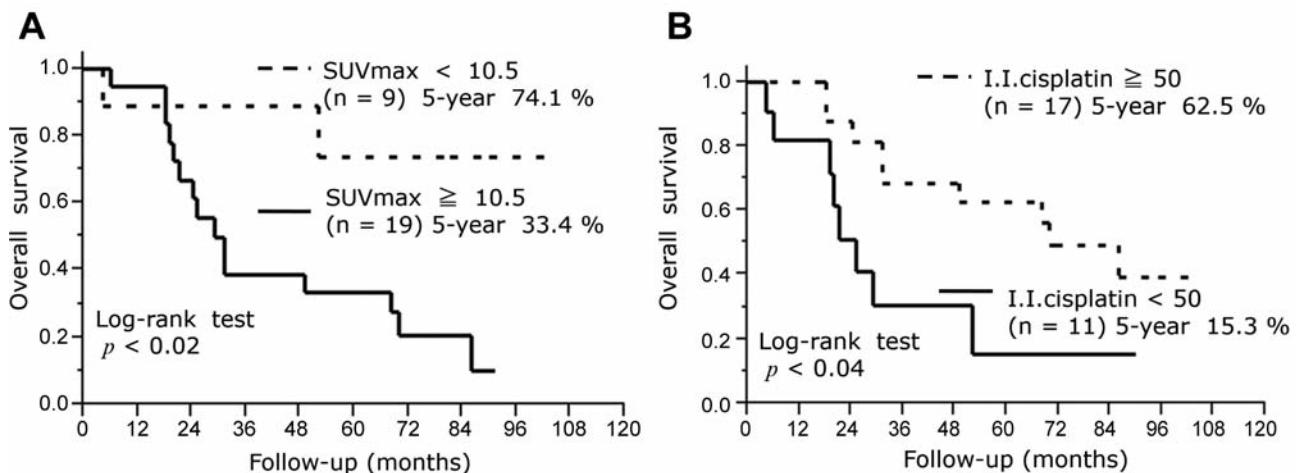


Figure 3. (A)  $\text{SUV}_{\text{max}} \geq 10.5$  and (B) I.I.cisplatin  $< 50$  were significantly correlated with shorter overall survival in 28 patients with head and neck cancer by log-rank test.  $\text{SUV}_{\text{max}}$ , maximum standardized uptake value; I.I., inhibition index.

with a shorter OS in patients with both oral SCC and pharyngeal SCC (5, 6). Our results, demonstrating a significant association between patients with  $\text{SUV}_{\text{max}}$  of  $\geq 10.5$  and poor OS, are in agreement with the findings of these previous studies (3-12).

The HDRA, an *in vitro* chemosensitivity assay used in several cancers, has been reported as a useful predictor for response to chemotherapy and survival (14-17). Singh *et al.* reported that in a group of 41 head and neck SCC, as assessed by HDRA of 5-fluorouracil and cisplatin, the patients who were chemosensitive had a significantly better 2-year cause-

specific survival than those of chemoresistant background (15). Jung *et al.* found that in a group of 104 epithelial ovarian cancer patients, including various types of histology, such as clear cell carcinoma, papillary serous adenocarcinoma and undifferentiated carcinoma, as assessed by HDRA of carboplatin, the patients who were chemosensitive to carboplatin exhibited a significantly longer progression-free survival than those who were resistant (16). Our results, demonstrating a significant association between patients with I.I.cisplatin  $< 50$  and poor OS are in line with the findings of these previous studies (15-17).

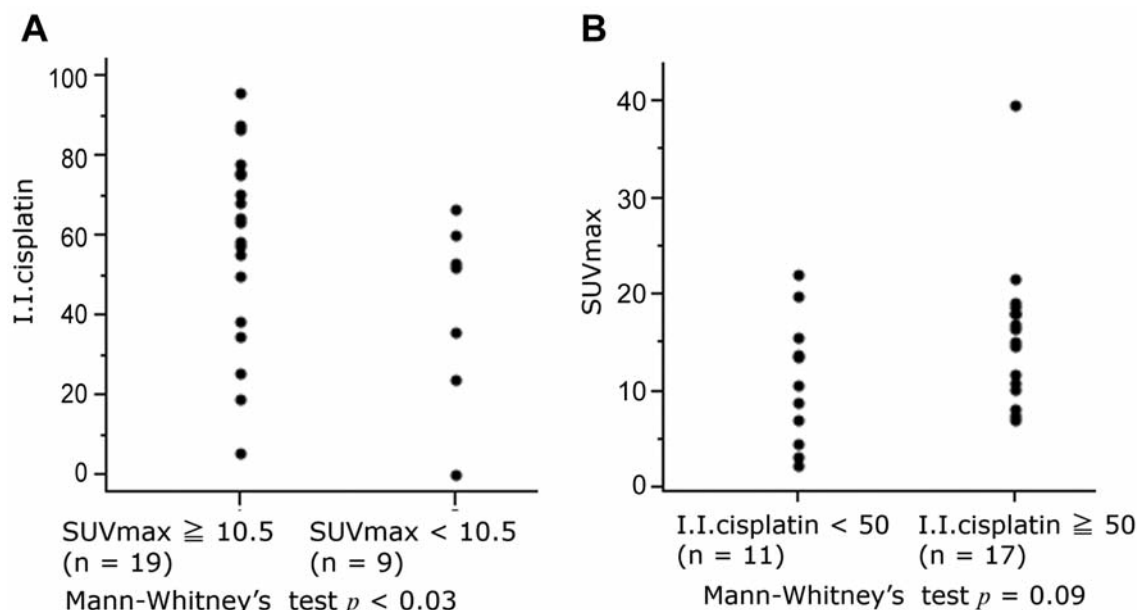


Figure 4. The Mann-Whitney's test was used to estimate relationships (A) between the two groups from SUVmax 10.5 ( $SUV_{max} \geq 10.5$ ;  $SUV_{max} < 10.5$ ) on I.I.cisplatin and (B) between the two groups from I.I.cisplatin 50 ( $I.I.cisplatin \geq 50$ ;  $I.I.cisplatin < 50$ ) on SUVmax. SUVmax, maximum standardized uptake value; I.I., inhibition index.

Many researchers have investigated various characteristics, such as chemosensitivity and useful prognostic parameters in many types of cancers and reported the appropriate concentration in the HDRA for cisplatin, which is the most commonly used agent for HNC (1-18). Moreover, the results from the HDRA in several cancers, such as HNC, non-small lung cancer and esophageal cancer, were significantly correlated with survival (15-17). However, to our best knowledge, the correlation between SUVmax and HDRA of cisplatin has not been investigated thus far. Our present work showed, for the first time, that  $SUV_{max} \geq 10.5$  ( $p < 0.01$ ) and I.I.cisplatin  $< 50$  ( $p < 0.01$ ) proved to be significantly shorter survival factors by multivariate analysis for OS. In the present study, the I.I.cisplatin of patients with  $SUV_{max} \geq 10.5$ , who were significantly correlated with poor OS, was significantly greater than that of patients with  $SUV_{max} < 10.5$ . This finding suggests that cisplatin has the potential to improve OS for HNC patients with  $SUV_{max} \geq 10.5$ , who were predicted as shorter OS by  $^{18}F$ -FDG-PET/CT.

Limitations of the present study include the relatively small number of subjects and various pathological type of carcinoma. Thus, in the future, analysis of larger cohorts and one pathological type of carcinoma should yield more statistically accurate results with, hopefully, applicable potential.

## Conclusion

We revealed that the I.I.cisplatin of HNC patients with  $SUV_{max} \geq 10.5$  was significantly greater than that of patients

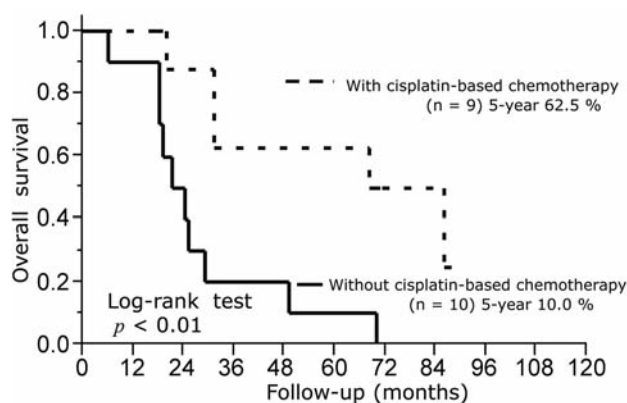


Figure 5. In 19 patients with  $SUV_{max} \geq 10.5$ , the patients who received radical treatment with chemotherapy were significantly correlated with longer overall survival.

with  $SUV_{max} < 10.5$  and that  $SUV_{max} \geq 10.5$  and I.I.CDDP  $< 50$  ( $p < 0.01$ ) proved to be significantly shorter survival factors by multivariate analysis for OS. Since patients who received radical treatment with cisplatin-based chemotherapy were significantly correlated with longer OS than those without in a group of 19 patients with  $SUV_{max} \geq 10.5$ , cisplatin exhibited a potential trait to improve OS for HNC patients who were predicted as shorter OS by pretreatment with  $^{18}F$ -FDG-PET/CT.

Table IV. Relationships between I.I. cisplatin ( $<50$  /  $\geq 50$ ) and clinical parameters ( $n=28$ ).

Clinical parameter	I.I. cisplatin $<50$ ( $n=11$ )	I.I. cisplatin $\geq 50$ ( $n=17$ )	$p$ -Value
Clinical T classification			
T1-2	2	3	
T3-4	9	14	1.00*
Clinical N classification			
N0	6	12	
N1-2	5	5	0.44 <sup>†</sup>
Clinical stage			
I-III	6	6	
IV	5	11	0.44 <sup>†</sup>
Age			
$<66$	6	7	
$\geq 66$	5	10	0.70 <sup>†</sup>
Gender			
Male	9	13	
Female	2	4	1.00*
Tumor site			
Oropharynx	4	5	
Others	7	12	1.00*
Treatment group			
Surgery	11	10	
Radiation	0	7	$<0.03$ *
Cisplatin-based chemotherapy			
With	1	8	
Without	10	9	$<0.05$ *
Histologic type			
SCC	7	14	
Non-SCC	4	3	0.39*

I.I., Inhibition index; SCC, squamous cell carcinoma. \*Fisher's exact test, <sup>†</sup>Chi-square test.

## Conflicts of Interest

The Authors have no conflicts of interests.

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Table V. Multivariate overall survival analysis\* of overall survival.

Parameter	Hazard ratio	95% Confidence interval	$p$ -Value
$\text{SUV}_{\max}$			
$<10.5$	1		
$\geq 10.5$	12.27	2.82-91.64	$<0.01$
I.I.cisplatin			
$\geq 50$	1		
$<50$	6.96	2.06-27.81	$<0.01$

$\text{SUV}_{\max}$ , maximum standardized uptake value; I.I., inhibition index.

\*The Cox proportional hazard model was used.

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