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We evaluated the effectiveness of combined intra-arterial chemotherapy and radiotherapy on head and neck squamous cell carcinomas using fluorodeoxyglucose (FDG) PET. **Methods:** Fifteen patients with squamous cell carcinoma of the head and neck were included in the study. Fourteen patients completed the treatment regimen and underwent FDG PET before and 4 wk after chemoradiotherapy. One patient underwent pretreatment FDG PET only. The pretreatment and post-treatment PET images were compared with clinical and histopathologic evaluations of the effects of chemoradiotherapy. For the quantitative evaluation of regional radioactivity, standardized uptake values (SUVs) with an uptake period of 50 min were used. **Results:** Before treatment, FDG PET detected neoplasms in all 15 patients. The overall clinical response rate to chemoradiotherapy in the 14 patients who were imaged before and after treatment was 100%. Before treatment, the neoplastic lesions showed high SUVs (mean 7.77 mg/mL), which significantly decreased after therapy (3.62 mg/mL, $P < 0.01$). Lesions with higher pretreatment SUVs (>7 mg/mL) showed residual viable tumor cells after the treatment in 3 of 8 patients, whereas those with lower SUVs (<7 mg/mL, 6 patients) were successfully treated. Three of seven tumors with post-treatment SUVs > 4 mg/mL had viable tumor cells, whereas all tumors (7/7) with post-treatment SUVs < 4 mg/mL showed no viable cells. With concomitant chemoradiotherapy monitored by FDG PET, 5 patients avoided surgery entirely, and the remaining 9 patients underwent a reduced form of surgery. **Conclusion:** FDG PET is useful in evaluating the effects of combined chemotherapy and radiotherapy in patients with head and neck carcinoma. Pretreatment FDG PET is useful in predicting the response to treatment, and post-treatment FDG PET can evaluate residual viable cells. Hence, FDG PET is a valuable tool in the treatment of head and neck tumors.

Key Words: PET; fluorodeoxyglucose; head and neck; chemotherapy; radiotherapy

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The effectiveness of anticancer treatment has previously been evaluated primarily on the basis of morphologic changes measured by CT, MRI or sonography. Because the size of neoplasms is not directly related to their viabilities, these imaging techniques have limitations in estimating therapeutic effects. Many neoplasms are characterized by increased glucose metabolism (*1,2*), which can be monitored with PET using ^{18}F-fluorodeoxyglucose (FDG). FDG PET has the advantage of detecting changes in glucose metabolism, which are closely related to the viability of the cancer cells. In this study, we investigated the glucose uptake of head and neck squamous cell carcinomas before and after combined chemotherapy and radiotherapy with FDG PET, which has been effective in previous studies of primary tumors of the head and neck (*3,4*). Particular emphasis was placed on the evaluation of the residual neoplastic tissue after the treatment.

MATERIALS AND METHODS

Patients

Fifteen patients (10 men, 5 women; age range 47–85 y; mean age 64.7 y) with squamous cell carcinoma of the head and neck were included in the study. The protocol was approved by the Ethics Committee of Fukui Medical University, and all patients gave written informed consent. Patient information is summarized in Table 1. The clinical staging was based on the International Union Against Cancer (UICC, 1987 [5]) and American Joint Committee on Cancer (AJCC, 1988 [*6*]) tumor, node, metastasis classification. Of 15 patients, 9 were in stage 3 or 4. Biopsies followed the first PET examination in all patients to eliminate the influence of surgical intervention on PET results. Twelve patients had a well-differentiated squamous cell carcinoma, and the remaining 3 patients had a moderately differentiated one.

Treatment Regimen

All patients received neoadjuvant chemoradiotherapy (Fig. 1) (*7*). Of 15 patients, 14 completed the full regimen. Another subject (patient 4; Table 1) entered the regimen but dropped out because of idiopathic thrombocytopenic purpura that was not related to the chemotherapy. Hence, patient 4 was excluded for data analysis of treatment effect.

For intra-arterial infusion of anticancer drugs, a plastic catheter was retrogradely placed from the superficial temporal artery and inserted into the main feeding artery of the tumor. The catheter was

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TABLE 1
Clinical and Histological Data of the 15 Study Patients

Patient no.	Age	Sex	Location	Differentiation	TNM classification		Stage	Clinical response	Histologic evaluation*	Further treatment
1	63	F	Tongue	Well	T4N2b	M0	IV	PR	2b	S + R
2	85	F	Tongue	Well	T2N0	M0	II	CR	4	R
3	71	M	Tongue	Well	T2N0	M0	II	CR	4	R
4†	72	F	Tongue	Well	T3N0	M0	III			S
5	50	M	Tongue	Well	T4N1	M0	IV	CR	2b	S + R
6	63	M	Floor of the mouth	Moderate	T2N0	M1	IV	CR	4	R
7	66	M	Buccal mucosa	Well	T3N2b	M0	IV	CR	4	R
8	70	M	Maxillary gingiva	Well	T2N0	M0	II	CR	4	
9	73	F	Maxillary gingiva	Moderate	T1N0	M0	I	CR	4	S
10	71	F	Tongue	Well	T2N0	M0	II	CR	4	S
11	47	M	Lower lip	Well	T2N1	M0	III	CR	4	S
12	51	M	Mandible	Moderate	T4N1	M0	IV	PR	2b	S + R
13	66	M	Tongue	Well	T2N0	M0	II	CR	4	S
14	48	M	Mandibular gingiva	Well	T2N1	M0	III	CR	4	S + R
15	74	M	Floor of the mouth	Well	T3N1	M0	III	CR	4	S + R

Well = well-differentiated squamous cell carcinoma; Moderate = moderately-differentiated squamous cell carcinoma; CR = complete response; PR = partial response; S = surgery; R = radiation.
*Histologic evaluation according to Table 2.
†Patient 4 did not receive the regimen of chemoradiotherapy because of idiopathic thronbocytopenic purpura.

placed unilaterally in 12 patients and bilaterally in 3 patients with advanced tumors crossing the midline. The regimen of intra-arterial chemoradiotherapy consisted of tetrahydropyranyl adriamycin (20 mg/m^2, bolus intra-arterial infusion, day 1), 5-fluorouracil (5-FU) (250 mg/d, continuous intra-arterial infusion for 120 h, day 2–day 6) and carboplatin (intra-arterial infusion with a mean dose of 368 mg/course for 2 h, day 7). During two courses of chemotherapy, patients received concomitant radiotherapy. External-beam irradiation was performed 5 d/wk, with one fraction per day (1.8–2.0 Gy per treatment) for a total tumor dose of 30–40 Gy to the primary tumor and metastatic lymph nodes, using 4-MV photons from a linear accelerator. Individual treatment plans consisted of parallel-opposed fields and a single lateral field.

Four weeks after the chemoradiotherapy, the clinical responses were evaluated using the World Health Organization (WHO) criteria (*8*). Histologic evaluation of the effects of the neoadjuvant chemoradiotherapy using the surgical or biopsy specimens was also performed according to Shimosato et al. (*9*) (Table 2).

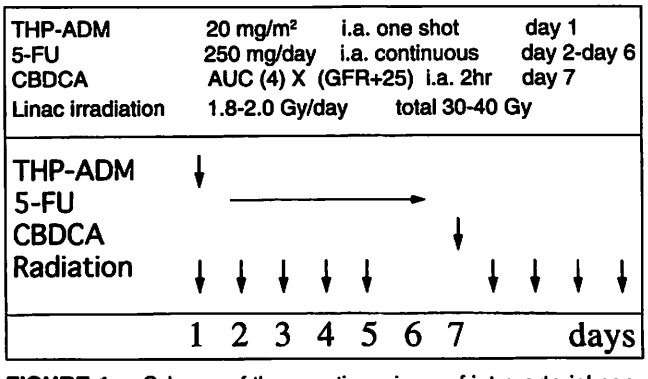

FIGURE 1. Schema of therapeutic regimen of intra-arterial concomitant chemoradiotherapy. THP-ADM = tetrahydropyranyl adriamycin; i.a. = intra-arterial; 5-FU = 5-fluorouracil; CBDCA = carboplatin; AUC = area under curve; GFR = glomerular filtration rate.

FDG PET and Other Imaging Modalities

All patients underwent serial FDG PET, MRI and CT before and after the treatment. In addition, ^{67}Ga scintigraphy was performed for pretreatment evaluation.

FDG was produced by the method of Hamacher et al. (*10*) with an automated FDG synthesis system (NKK, Tokyo, Japan) with a small cyclotron (OSCAR3; Oxford Instruments, Oxford, UK). PET scanning was performed with a GE Advance system (General Electric, Milwaukee, WI). The physical characteristics of this scanner have been described in detail by DeGrado et al. (*11*). This system permits the simultaneous acquisition of 35 transverse slices with interslice spacing of 4.25 mm with septa (two-dimensional

TABLE 2
Criteria for Histologic Evaluation of Effects of Radiotherapy and Chemotherapy according to Shimosato et al. (*9*)

Grade	Description
0	No recognized changes in tumors
1	Minimal cellular changes present, but a majority of tumor cells appear viable.
2a	Despite the presence of cellular changes and partial destruction of the tumor, the tumor is still readily recognizable, and a good number of tumor cells appear viable.
2b	The tumor destruction is extensive, but viable cell nests are present in small areas of the tumor (<one-quarter of the tumor mass, excluding areas of coagulation necrosis).
3	Only a few scattered, markedly altered, presumably nonviable tumor cells are present singly or in small clusters; viable cells are hardly encountered.
4	No tumor cells remain in any section.

mode). Images were reconstructed to a full width at half maximum of 4.2 mm in both the transaxial and axial directions. The field of view and pixel size of the reconstructed images were 256 and 2 mm, respectively. Transmission scans were obtained for 10 min with a standard pin source of $^{68}Ge/^{68}Ga$ for attenuation correction of the emission images.

Fourteen patients underwent FDG PET before and over 4 wk after the chemoradiotherapy (mean 38 d after the treatment). One patient (patient 4) underwent pretreatment FDG PET only. The patients were administered 244–488 MBq (6.6–13.2 mCi) FDG in a fasting state in the cubital vein over 10 s. In 6 patients, static images were obtained for 20 min, starting at 40 min postinjection without arterial samplings. Of 15 patients, 9 also underwent dynamic scanning. Dynamic scans were obtained up to 60 min after the injection with arterial sampling. The mode of dynamic data acquisition consisted of four 30-s frames, eight 60-s frames and five 600-s frames. Plasma glucose levels were measured for all patients. Static images were obtained by averaging the last two frames of the dynamic data, from 40–60 min postinjection. From the time of the injection, 2 mL of arterial blood was sampled every 15 s in the first 2 min and then at 2, 3, 5, 7, 10, 15, 20, 30, 45 and 60 min after injection. Plasma radioactivity was measured with a scintillation counter against which the PET camera was cross-calibrated, using a cylindrical phantom filled with the ^{18}F solution.

Data Analysis

For the quantitative evaluation of regional radioactivity using the static FDG PET images, regions of interest (round, 5 mm in diameter) were examined in the area of highest accumulated radioactivity. These tissue radioactivities were corrected with injected dose and patients' body weight to calculate the standardized uptake values (SUVs) using the following formula:

$$SUV = \frac{\text{tissue radioactivity concentration (Bq/mL)}}{\text{injected dose (Bq)/body weight (g)}}.$$

For the 9 patients who underwent dynamic PET scanning, graphic analysis of Patlak and Blasberg (*12*) and Patlak et al. (*13*) was performed to calculate the net influx constant of FDG (Ki) and the glucose metabolic rate of the neoplasms on a pixel-by-pixel basis, using the following formula:

$$\frac{C(t)}{Ca(t)} = K_i \frac{\int_0^t Ca(\tau)d\tau}{Ca(t)} + Vn,$$

where Ca(t) is the radioactivity in the plasma at time t, C(t) is the radioactivity at time t in each pixel and Vn is the initial distribution volume of FDG in each pixel (*12,13*). To obtain the slope K_i, C(t)/Ca(t) was plotted against the integration of Ca(t) divided by Ca(t). Data from 10–30 min were used to calculate K_i. To confirm the feasibility of SUV as a measure of FDG accumulation, correlations of SUV and K_i were evaluated. Finally, we compared the pretreatment SUV and post-treatment SUV with the histologic evaluation of residual tumor cells. To evaluate the treatment effect, the size of the tumor was determined by measuring the maximum area in the single transaxial section of the contrast-enhanced MR image.

Statistical Analysis

A paired Student *t* test (two-tailed) was used for comparisons of before and after therapy values in each subject; an unpaired *t* test was used for all other comparisons. A correlation between two variables was analyzed with Pearson's coefficient of correlation.

RESULTS

Pretreatment Evaluation

All pretherapy FDG PET studies demonstrated a focal accumulation of radioactivity corresponding to the known tumor confirmed by other imaging modalities or visual inspection (Fig. 2).

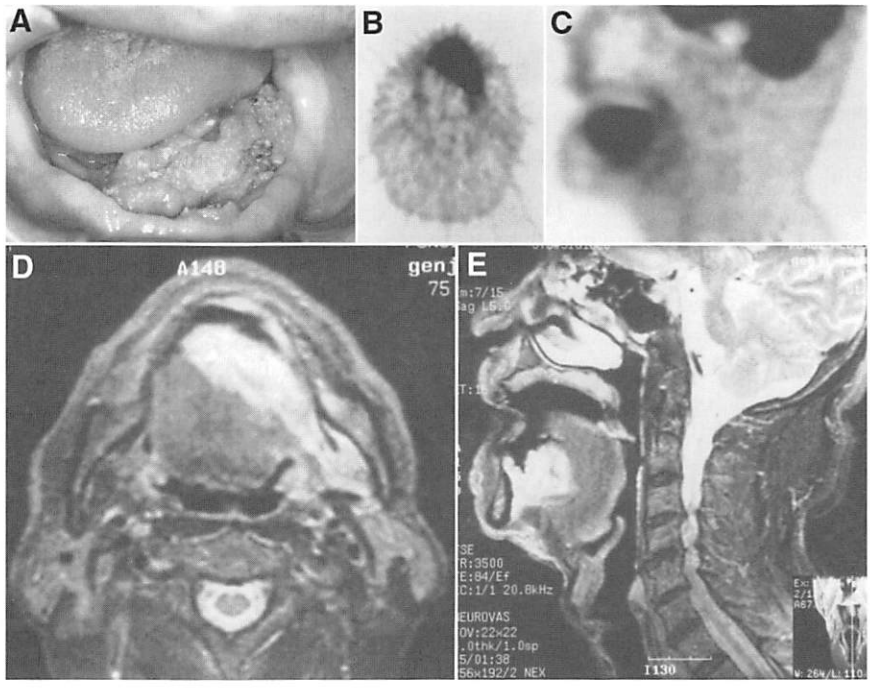

FIGURE 2. Male patient (74-y-old) with large squamous cell carcinoma on floor of left side of mouth (A). FDG PET of axial (B) and sagittal (C) views shows high accumulation of radioactivity (SUV = 14.54 mg/mL) on floor of mouth, consistent with MRI findings (D and E).

Response to Therapy

Evaluation with Conventional Criteria. With the WHO criteria, 12 of 14 patients showed clinical complete response. The clinical complete response rate was 85.7%, and the remaining 2 patients were assigned a partial response; hence, the overall response rate was 100%. All primary lesions showed obvious decrease in size on MRI or visual inspection after therapy (Fig. 3). As to the histologic evaluation of the treatment effects, 11 of 14 patients (78.6%) demonstrated grade 4: No viable cell was observed in any section. The remaining 3 patients were graded 2b: Tumor destruction was extensive but viable cell nests were present in small areas of the tumor (Table 1).

Evaluation with FDG. Net influx constant and SUV were highly correlated ($K_i = 0.0050 \times SUV + 0.0059$, $r^2 = 0.95$). Because the uptake period was set constant (midscan time was 50 min postinjection), SUV was used as a parameter of FDG uptake rate for monitoring the effect of the therapy in the same patient. All primary tumors, except one, showed decrease in SUV (Fig. 4). Mean SUV before therapy was 7.77 ± 3.39 mg/mL (range 4.07–14.54 mg/mL). After chemoradiotherapy, mean SUV was 3.62 ± 1.23 mg/mL (range 1.12–5.02 mg/mL). There was no correlation between pretherapy SUV and differentiation of the tumor.

We compared the post-therapy SUVs with the histologic evaluation of residual tumor cells. For the tumors graded 2b, indicating positive residual viable cells (n = 3), PET demonstrated an SUV of 4.61 ± 0.36 mg/mL (range 4.39–5.02 mg/mL). On the other hand, the tumors assigned a grade 4 rating, indicating no residual viable cells (n = 11), had a lower SUV: mean SUV of 3.35 ± 1.25 mg/mL (range 1.12–4.90 mg/mL). Of seven treated tumors with SUVs > 4, three had viable tumor cells, whereas seven of seven tumors with SUVs < 4 did not have viable cells.

The relationship between pretreatment SUV and post-treatment SUV is shown in Figure 5. Post-treatment SUVs were <6 mg/mL. No correlation between pretreatment SUV and post-treatment SUV was found. Lesions with higher pretreatment SUVs (>7 mg/mL) showed residual viable tumor cells after treatment in 3 of 8 patients, whereas those with lower post-treatment SUVs (<7 mg/mL, 6 patients) were successfully treated. Of seven tumors with post-treatment SUVs > 4 mg/mL, three had viable tumor cells, and these three tumors showed pretreatment SUVs > 7 mg/mL. On the other hand, all tumors with post-treatment SUVs < 4 mg/mL (7/7) were free of viable cells regardless of their pretreatment SUVs. With concomitant chemoradiotherapy monitored with FDG PET, 5 patients avoided surgery entirely, and the remaining 9 patients underwent a reduced form of surgery.

DISCUSSION

Combination chemoradiotherapy has been shown to be effective in controlling advanced squamous cell carcinoma of the head and neck. Either concomitantly (*14–16*) or alternately (*17,18*) combined, chemoradiotherapy is superior to radiotherapy alone, at the cost of increased acute toxicity (*14–16*). Therefore, we started a new regimen of combined chemotherapy and radiotherapy using intra-arterial infusion. Our results showed that this new regimen is effective in the local control of tumors, with an overall clinical complete response rate of 85.7%.

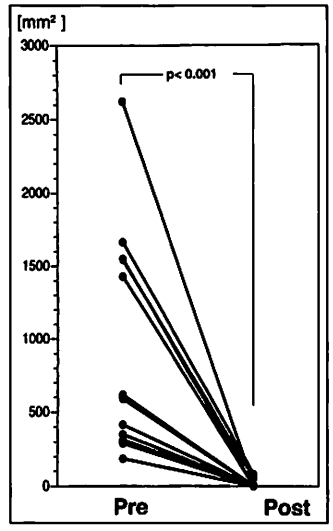

FIGURE 3. Post-treatment change in tumor size. Significant decrease in size (maximum cross-sectional area [mm²] of MR image) was noted.

To monitor the effects of the chemoradiotherapy, we selected FDG PET on the basis of past studies by other investigators (*19–25*). In animal tumor models, reduction of deoxyglucose uptake after chemotherapy or radiotherapy was associated with less viable residual tumor tissue (*19*). Decrease of FDG uptake after irradiation of a mouse mammary carcinoma has also been reported (*20*). Possible mechanisms of decrease in FDG uptake include radiation effects on cellular glucose transport or radiation-induced vascular damage that may result in a lower perfusion of tumors and, hence, less accumulation of the tracer. Clini-

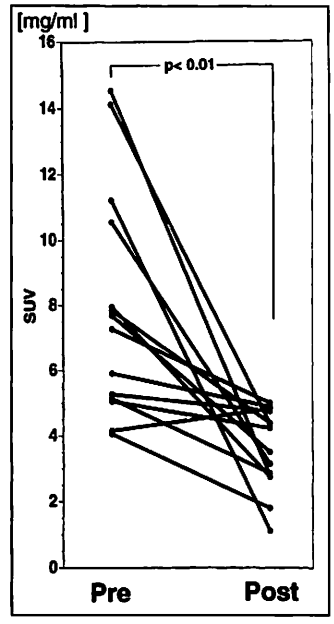

FIGURE 4. Change in FDG uptake (SUV) after therapy. All primary lesions, except one, showed obvious decrease in FDG uptake. Mean SUV significantly decreased from 7.77 ± 3.39 to 3.62 ± 1.23 mg/mL.

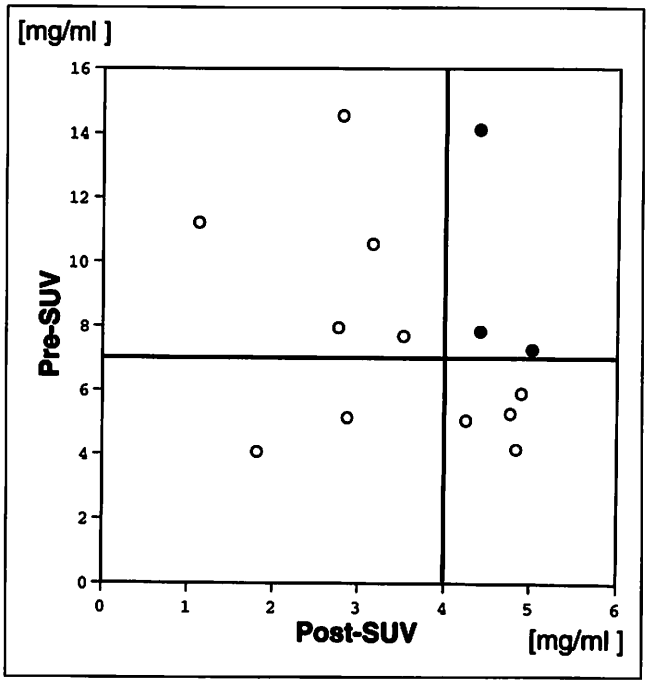

FIGURE 5. Pretherapy SUV plotted against post-therapy SUV. No significant correlation was observed between them. Open circles indicate no residual viable cells, and closed circles indicate area positive for residual viable cells confirmed histopathologically. Lesions with higher pretreatment SUVs (>7 mg/mL) showed residual viable tumor cells after treatment in 3 of 8 patients, whereas those with lower SUVs (<7 mg/mL, 6 patients) were successfully treated. Of seven tumors with post-treatment SUVs > 4 mg/mL, three had viable tumor cells, and these three tumors showed pretreatment SUVs > 7 mg/mL On the other hand, all tumors with post-treatment SUVs < 4 mg/mL (7/7) were free of viable cells regardless of their pretreatment SUV.

cally, FDG PET has been shown to be useful in the evaluation of the therapeutic response. There is a significant change in FDG uptake during radiotherapy between radiosensitive and radioresistant tumors (*21*). In the study by Ichiya et al. (*22*), decrement of FDG uptake after radiotherapy was more prominent in the partial response group than in the no change group, and FDG uptake before therapy was higher in the nonrelapse group than in the relapse group. High-dose irradiation has been reported to cause acute reduction of FDG uptake (*23*). As to chemotherapy, lesions with higher FDG uptake before therapy show more prominent decrease in volume after treatment with CDDP and 5-FU (*24*). With respect to combined chemotherapy and radiotherapy, there have been a few studies on head and neck tumors. Berlangieri et al. (*25*) demonstrated that decrease in tumor hypermetabolism, as seen on serial FDG PET, paralleled the clinical response to treatment with hyperfractionated irradiation and concurrent 5-FU and cisplatin.

Although SUV has been criticized for its variability as an index of tumor detection, recent studies, including this study, suggest that SUV can be controlled by keeping the uptake period after administration of FDG constant (*26*). Because 6 of 15 patients in this study did not undergo arterial sampling, we used SUV with an uptake period of 50 min as an index of tumor detection as well as of treatment effect.

This study shows that concomitant intra-arterial chemotherapy and radiotherapy are effective by conventional criteria and that change in FDG uptake parallels the treatment effect. These findings confirm the feasibility of FDG PET for monitoring overall treatment effects. Furthermore, this study shows additional advantages of FDG PET over conventional criteria.

First, prediction of response to the concomitant chemotherapy is partially possible with pretreatment SUV. Tumors with higher pretreatment SUV (>7 mg/mL, corresponding to K_i of 0.037 min^{-1}) appear to be more resistant to the treatment than those with lower pretreatment SUV. This may be explained by the fact that higher FDG uptake indicates greater cell viability (*19,27*) or a higher propensity for cells to divide (*21,28*) or both. No malignant tumor with low pretreatment SUV (<4 mg/mL) was observed in this study, and its treatment effect should be addressed in a future study.

Second, post-treatment SUV predicts the presence or absence of residual viable tumor cells. In this study, the quantitative threshold value for differentiating the presence or absence of residual tumor cells was determined as 4.0 mg/mL of post-treatment SUV, corresponding to K_i of 0.021 min^{-1}. With this cutoff value, all 3 post-therapy lesions with viable cells were diagnosed as true-positive (sensitivity 100%), whereas 4 of 11 lesions without viable cells were diagnosed as false-positive (specificity 64%). The high FDG uptake (SUV > 4 mg/mL) in 4 benign, eradicated tissues after therapy is probably due to mucositis induced by the treatment, because FDG accumulates in acute inflammatory lesions with macrophages and newly formed granulation tissue (*29*). These 4 patients showed severe mucositis at the time of post-treatment evaluation that was performed earlier than for the other patients (mean 28.5 d after treatment). Therefore, we are now tentatively performing post-treatment evaluation with FDG PET 40 d after the completion of the regimen to reduce false-positives, due to the inflammatory effect. Further study is necessary to determine the optimal imaging timing after the therapy.

We attempted to determine the selection of further treatment with FDG PET data. In 5 of the patients assigned complete response, with post-treatment SUVs < 4.0, we were able to avoid surgery (Table 1). Although the presence of remnant tumor cells was not ruled out for these 5 patients, biopsy samples taken after post-treatment PET examination confirmed absence of viable cells, and no local recurrence was observed at a maximum follow-up of 32 mo (range 20–32 mo, mean 26.2 mo). The remaining 9 patients underwent reduced surgery, with resultant clinical advantages such as lower risks from anesthesia and greater preservation of oral function. These results, although preliminary because of the limited number of subjects, suggest that FDG PET is a useful measure of therapeutic effect and can contribute to the improvement of the quality of life of patients with head and neck neoplasms.

CONCLUSION

Concomitant chemoradiotherapy is an effective treatment for head and neck carcinoma. FDG PET is useful in evaluating its therapeutic effects by predicting the response to treatment and by evaluating residual viable cells. FDG PET is a valuable tool in the treatment of head and neck tumors, allowing patients selection for reduced surgery.

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