ORIGINAL PAPER

Nagoya J. Med. Sci. **80**. 541–550, 2018
doi:10.18999/nagjms.80.4.541

# Clinical T staging is superior to fluorodeoxyglucose positron emission tomography for predicting local outcomes after intra-arterial infusion chemoradiotherapy for maxillary sinus squamous cell carcinoma

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## ABSTRACT

Concomitant intra-arterial infusion chemoradiotherapy (IA-CRT) has been used to treat locally advanced maxillary sinus squamous cell carcinoma (MSSCC) with positive outcomes. However, an optimal predictive prognostic factor for MSSCC treated with IA-CRT remains elusive. The aim of the present study was to assess the feasibility of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), including volumetric parameters, to predict the prognosis of MSSCC treated with IA-CRT. Twenty-four patients with newly diagnosed MSSCC receiving FDG-PET imaging before IA-CRT treatment were analyzed in this retrospective study. All patients underwent radiotherapy with a total tumor dose of 60–66 Gy in a conventional fractionation schedule, using three-dimensional conformal radiation therapy or intensity-modulated radiation therapy. Radiotherapy was performed concurrently with concurrent intra-arterial infusion chemotherapy (cisplatin). The IA-CRT response rate was 83.33%. The 1- and 3-year survival rates were 81.30% and 64.34%, respectively. The 1- and 3-year local failure-free rates were 57.21% and 40.96%, respectively. Local failure was significantly associated with poor survival (P = 0.0152). Further, clinical T staging clearly stratified local control outcomes among patients with clinical T3 or less, T4a, and T4b (P = 0.0312). Moreover, patients with stage T4b showed a significantly poorer local control compared with T3 or less (P = 0.0103). However, FDG-PET parameters provided no significant predictive information regarding treatment outcome. To conclude, pretreatment T stage predicts local control by IA-CRT, which is associated with survival.

Keywords: concurrency, intensity-modulated radiation therapy, paranasal sinus, intra-arterial infusion chemotherapy, maxillary sinus, radiotherapy



Received: February 1, 2018; accepted: May 9, 2018
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## INTRODUCTION

Malignant paranasal sinus tumors are rare, accounting for approximately 3.0% of head and neck carcinomas and about 0.5% of all malignancies.[1] Maxillary sinus squamous cell carcinoma (MSSCC) has the highest incidence among paranasal sinus malignancies.

Radical surgery (with or without ophthalmectomy) is a standard treatment for MSSCC.[2] However, radical surgery for MSSCC is sometimes challenging due to several factors, including anatomical barriers, the possibility of disfigurement, and anatomical dysfunction of tissues in proximity to the surgical margins. Radiotherapy, therefore, is a promising alternative treatment option for MSSCC.

Chemoradiotherapy is one of the most successful treatment options for squamous cell carcinoma in the larynx and pharynx. However, conventional chemoradiotherapy can lead to unsatisfactory outcomes for MSSCC.[3] Concomitant intra-arterial infusion chemoradiotherapy (IA-CRT) has been demonstrated to have positive treatment outcomes for MSSCC.[4-6] However, the optimal predictive factors for the prognosis of MSSCC treated with IA-CRT remains unknown.

Fluorodeoxyglucose positron emission tomography (FDG-PET) can measure glucose uptake by malignant cells and has been advocated for assessing the biological aggressiveness of tumors, as well as a factor to predict patient outcomes. Many studies have presented the metabolic activity of FDG-PET as a prognostic factor in a variety of cancer patients, including those with head and neck cancers.[7-9] Volume-based quantitative FDG-PET/computed tomography (CT) parameters, including metabolic tumor volume (MTV) and total lesion glycolysis (TLG), have recently been reported as independent predictors for the outcomes of various malignancies.[10,11] However, only a few studies have examined the correlation between FDG uptake by the primary tumor and the prognosis of MSSCC.[9] In addition, the true clinical utility of volume-based quantitative FDG-PET/CT parameters is presently unclear.

Therefore, we conducted a retrospective study to assess prognostic predictive factors, including FDG uptake using volumetric parameters, at the initial diagnosis of MSSCC before the definitive treatment for locally advanced MSSCC using IA-CRT.

## MATERIALS AND METHODS

*Patients*

This retrospective study was approved by the institutional review board (Approval No. 2567). Informed consent was obtained from all individual participants in the study prior to treatment.

We analyzed the medical records of patients with newly diagnosed MSSCC who underwent FDG-PET imaging before definitive IA-CRT at Hyogo College of Medicine College Hospital between January 2007 and June 2016. These patients were required to have follow-ups longer than six months without local failure. Twenty-eight consecutive patients met these criteria, and four of them who received radiotherapy <60 Gy or had planned surgery were excluded. After applying the inclusion criteria, 24 patients remained for analysis. All patients underwent clinical staging, performed using CT and/or magnetic resonance imaging (MRI), and FDG-PET/CT according to the systematic TNM classification of the American Joint Committee on Cancer.[12] A summary of the patients' characteristics in this study is shown in Table 1. The median follow-up time was 378 days (range, 49–2865 days).

**Table 1** Summary of patient clinicopathological characteristics.

| Clinicopathological characteristic | | Patients ($n$ = 24) |
|---|---|---|
| Age, years [median (range)] | | 63.5 (31–82) |
| Sex, $n$ (%) | | |
| | Male | 20 (83.33%) |
| | Female | 4 (16.67%) |
| ECOG-PS, $n$ (%) | | |
| | 0 | 23 (95.83%) |
| | 1 | 1 (4.17%) |
| TNM classification, $n$ (%) | | |
| T stage | | |
| | ~3 | 6 (25.00%) |
| | 4a | 9 (37.50%) |
| | 4b | 9 (37.50%) |
| N stage | | |
| | 0 | 15 (62.50%) |
| | 1 | 3 (12.50%) |
| | 2b | 2 (8.33%) |
| | 2c | 4 (16.67%) |
| M stage | | |
| | 0 | 22 (91.67%) |
| | 1 | 2 (8.33%) |
| Radiotherapeutic technique, $n$ (%) | | |
| | 3D-CRT | 15 (62.50%) |
| | VMAT | 9 (37.50%) |
| Total radiotherapeutic dose | | |
| | 60 Gy | 13 (54.17%) |
| | 66 Gy | 11 (45.83%) |
| Number of fractions, $n$ (median [range]) | | 30 (30–33) |
| Fraction size, Gy | | 2 (all patients) |
| Treatment duration, days (median [range]) | | 43.5 (36–60) |

Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group - Performance Status; 3D-CRT, three-dimensional conformal radiation therapy; VMAT, volumetric modulated arc therapy.

*FDG-PET/CT*

We have described the imaging techniques in detail in a previous report.[9] Briefly, FDG-PET/CT was performed before radiotherapy with a PET/CT scanner (Gemini GXL16 or a Gemini TF64; Philips Medical Systems, Eindhoven, The Netherlands). Patients were injected with 4.0 MBq/kg body weight FDG for the GXL16 scanner or 3.0 MBq/kg for the TF64 scanner. No patients had glucose levels greater than 150 mg/dL. CT images were obtained using the parameters as follows: tube voltage 120 kV, effective tube current auto-mA (up to 120 mA s for the GXL16 or 100 mA s for the TF64), gantry rotation speed 0.5 s, detector configuration 16×1.5 mm (GXL16) or 64×0.625 mm (TF64), 2-mm slice thickness, and a transverse field of view of 600 mm. PET images from the head to the mid-thigh were acquired for 90 s per bed position, and the region from the mid-thigh to the toes for 30 s per bed position immediately after the completion of CT. Then, images at 12–14 bed positions, each for 90 s, and 6–7 bed

positions, each for 30 s, were taken in the three-dimensional (3D) mode. Attenuation-corrected PET images were reconstructed with a line-of-response row-action maximum likelihood algorithm for the GXL16; an ordered-subset expectation maximization iterative reconstruction algorithm (33 subsets, 3 iterations) was used for the TF64.

All FDG-PET/CT images were reviewed using commercially available software, GI-PET (AZE Co., Ltd., Tokyo, Japan), which can harmonize the SUVs across different PET/CT systems using phantom data, as well as assist clinicians in monitoring treatment response. SUVmax was defined as the maximum activity concentration in the primary tumor divided by the injected dose/body weight. SUVmax was normalized to SULmax (SUVmax×[lean body mass]/[total body mass]). SUVpeak was calculated from a 1.2 cm diameter volume region of interest (ROI) placed on the hottest site of the tumor. The SUVpeak was normalized to SULpeak (SUVpeak×[lean body mass]/[total body mass]). It was also determined if the tumor SULpeak was higher than 1.5 times the liver SUL mean + 2 SDs (using a 3 cm-diameter spherical ROI in the normal right lobe of liver). The MTV (metabolic tumor volume) was defined as the FDG-avid tumor volume and TLG (tumor lesion glycolysis) as MTV × SULmean, where SULmean represents the mean SUL.

*Radiotherapy*

The chemoradiotherapy techniques have been previously described.[6,13] Briefly, an Aquilion LB CT scanner (Toshiba, Ohtawara, Japan) was used to obtain the planning CT images. A XiO® treatment planning system (TPS) (Elekta, Stockholm, Sweden) was used to segment the volumes of interest in the CT dataset. A 3D conformal radiotherapy technique was performed using a Primus MD2 linear accelerator (Siemens, Munich, Germany) and a Synergy® linear accelerator (Elekta, Crawley, UK).[6] Volumetric modulated arc therapy (VMAT) was used for intensity-modulated radiation therapy (IMRT). VMAT treatment plans were generated with a Monaco TPS (Elekta, Maryland Heights, MO, USA) and delivered with a Synergy® linear accelerator (Elekta, Crawley, UK).[6,13] Radiotherapy was performed with daily 2-Gy fractions (Table 1). Concurrent IA-CRT using cisplatin was performed as previously described.[6] Lesions of the neck were irradiated in patients with nodal metastasis.

*Follow-up*

Overall survival (OS) was defined as the time from the initiation of the radiotherapy course to death, or to the last follow-up. Local control (LC) was defined as the time from the initiation of the course of radiotherapy to the date of local failure based on CT, MRI, and pathological diagnosis, or the last follow-up. Local failure was defined as the pathological confirmation of a viable tumor or regrowth in images after IA-CRT. Toxicities were graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.[14]

*Statistical analysis*

Data were indicated as the median values, with the associated range in parentheses, unless otherwise indicated. Each specific time was defined from the initiation of the course of radiotherapy to the day of a confirmed event. The Kaplan-Meier method was used to estimate cumulative local control (LC) and survival estimates, and statistical differences were evaluated with the log-rank test. The Cox proportional hazards model was used to examine potential predictors that may affect treatment outcomes. Results were reported as hazard ratios (HR), with corresponding 95% confidence intervals (CI). Multivariate analyses were not performed due to the small number of patients. JMP software version 12.2.0 (SAS Institute, Cary, NC, USA) was used for all statistical analyses. A P-value $<0.05$ was used to assess statistical significance.

## RESULTS

The response rate of IA-CRT was 83.33%, including complete and partial response in 11 and 9 patients, respectively. Of the 24 study patients, 7 (29.17%) died in the follow-up term of 24 (3–94) months. The 1-, 2-, and 3-year survival rates were 81.30%, 70.78%, and 64.34%, respectively (Fig. 1). Fourteen patients (58.33%) experienced local failure, including four residual tumors and progression after IA-CRT. The LC time was 9 (1–42) months. The 1-, 2-, and 3-year LC rates were 57.21%, 46.81%, and 40.96%, respectively (Fig. 2). Among the 14 patients experiencing local failure, eight patients received additional local salvage treatment (six salvage surgery, one re-irradiation, and one intra-arterial infused chemotherapy).

A summary of acute toxicities attributed to IA-CRT is shown in Table 2. Regarding non-hematological late toxicities, one patient had decreased visual acuity, one developed corneal ulceration, one developed blepharoptosis, one developed a cataract, one developed xerostomia, one developed osteomyelitis, four developed osteonecrosis, and one patient developed blindness due to an obstruction of the central retinal vein. In addition, no apparent symptoms were observed in 17 patients.

Univariate analysis showed that locoregional failure was associated with poor survival (Table 3 and Fig. 3). In addition, T4b disease was related with the incidence of loco-regional failure (Table 3). Clinical T stage clearly stratified local control among patients with clinical stage T3 or less, T4a, and T4b (Fig. 4). Moreover, patients with stage T4b showed significantly poorer local control when compared to those with stage T3 or less.

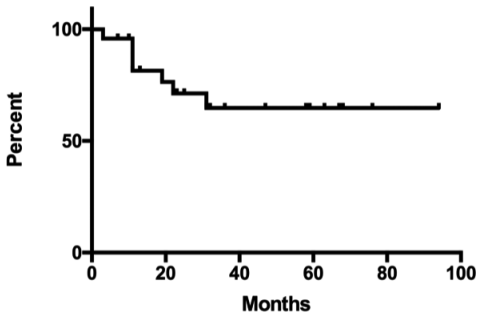


**Fig. 1** Overall survival of 24 patients.
For the 24 patients, the median survival time was not available in this study

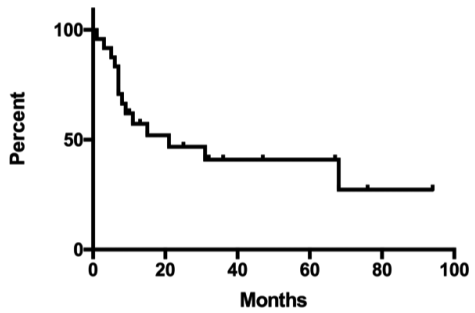


**Fig. 2** Local control in 24 patients.
For the 24 patients, the median local control time was 666 days

**Table 2** Summary of toxicities.

| Toxicity | Grade | Number of patients ($n$ = 24) |
|---|---|---|
| Leukocytopenia | Any | 4 (16.67%) |
| | 1 | 1 (4.17%) |
| | 3 | 3 (12.50%) |
| Neutropenia | Any | 3 (12.50%) |
| | 2 | 2 (8.33%) |
| | 3 | 1 (4.17%) |
| Anemia (hemoglobin) | 1 | 1 (4.17%) |
| Hemorrhage | 1 | 1 (4.17%) |
| Keratitis | 1 | 14 (58.33%) |
| Dermatitis | Any | 21 (87.50%) |
| | 1 | 19 (79.17%) |
| | 2 | 1 (4.17%) |
| | 4 | 1 (4.17%) |
| Mucositis | Any | 24 (100.00%) |
| | 1 | 1 (4.17%) |
| | 2 | 18 (75.00%) |
| | 3 | 5 (20.83%) |

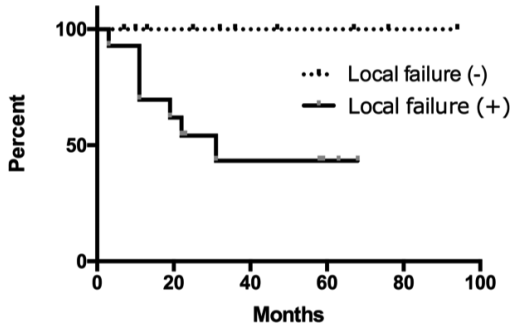


**Fig. 3** Local failure is associated with poor survival.
Patients who developed local failure after treatment showed significantly worse survival (P = 0.0152) than those who did not.

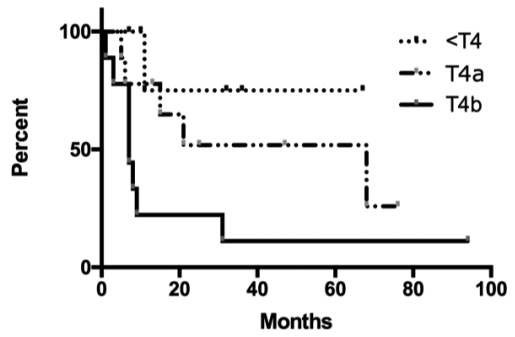


**Fig. 4** Pretreatment clinical T stage is associated with local control.
A significant difference was found among the three groups (P = 0.0312). In addition, the pairwise comparisons of <T4 vs. T4a, <T4 vs. T4b, and T4a vs. T4b showed P values of 0.4057, 0.0103, and 0.1060, respectively.

**Table 3** Univariate analysis of overall survival and local control

| Clinicopathological parameter | Patients ($n$ = 24) | 2-year survival rate (%) | Overall survival HR (95% CI) | Overall survival P value | Local control HR (95% CI) | Local control P value |
|---|---|---|---|---|---|---|
| Age, years | | | | | | |
| <65 | 13 | 62.86 | 1 | 0.7278 | 1 | 0.6290 |
| ≥65 | 11 | 78.75 | 0.7674 (0.1510–3.4846) | | 0.7695 (0.4477–3.9786) | |
| Sex | | | | | | |
| Male | 20 | 63.50 | 1 | 0.0548 | 1 | 0.1095 |
| Female | 4 | 100.00 | 1.3273e-9 (1.0475–1.0475) | | 0.2503 (0.0137–1.2925) | |
| Body mass index, kg/m$^2$ | | | | | | |
| <20 | 9 | 66.67 | 1 | 0.3551 | 1 | 0.5128 |
| ≥20 | 15 | 73.33 | 0.4951 (0.0973–2.2515) | | 0.6918 (0.2288–2.1585) | |
| TNM stage | | | | | | |
| ≤T3 | 6 | 75.00 | 1 | 0.6530 | 1 | 0.0462 |
| T4 | 18 | 69.11 | 1.5876 (0.2682–30.1059) | | 5.2089 (1.0234–94.9364) | |
| ≤T4a | 17 | 78.97 | 1 | 0.2044 | 1 | 0.0036 |
| T4b | 7 | 50.00 | 2.7694 (0.5402–12.7146) | | 5.5681 (1.7907–17.8825) | |
| N0 | 15 | 76.15 | 1 | 0.5858 | 1 | 0.7566 |
| ≥N1 | 9 | 60.00 | 1.5258 (0.3001–6.9359) | | 1.1870 (0.3828–3.4771) | |
| M0 | 22 | 72.93 | 1 | 0.4896 | 1 | 0.8439 |
| M1 | 2 | 50.00 | 2.3038 (0.1197–14.4654) | | 0.8185 (0.0447–4.2243) | |
| Stage | | | | | | |
| ≤IVa | 16 | 77.38 | 1 | 0.3427 | 1 | 0.0204 |
| IVb and c | 8 | 57.14 | 2.1180 (0.4136–9.7130) | | 3.7867 (1.2377–11.9607) | |
| Radiotherapeutic dose, Gy | | | | | | |
| 60 | 13 | 74.07 | 1 | 0.8291 | 1 | 0.2296 |
| 66 | 11 | 68.18 | 1.1811 (0.2312–5.3956) | | 0.4975 (0.1345–1.5323) | |
| PDG-PET parameters | | | | | | |
| SUVmax | | | | | | |
| <14.5 | 12 | 68.18 | 1 | 0.3991 | 1 | 0.8776 |
| ≥14.5 | 12 | 72.19 | 0.5264 (0.1033–2.3980) | | 0.9205 (0.3133–2.7077) | |
| SULmax | | | | | | |
| <10 | 12 | 79.55 | 1 | 0.9276 | 1 | 0.9063 |
| ≥10 | 12 | 63.49 | 1.0723 (0.2340–5.4927) | | 1.0653 (0.3632–3.1269) | |
| SULpeak | | | | | | |
| <9.5 | 12 | 79.55 | 1 | 0.9276 | 1 | 0.9063 |
| ≥9.5 | 12 | 63.49 | 1.0723 (0.2340–5.4927) | | 1.0653 (0.3632–3.1269) | |
| Metabolic tumor volume (MTV) | | | | | | |
| (primary site) | | | | | | |
| <58 | 12 | 68.57 | 1 | 0.6474 | 1 | 0.9049 |
| ≥58 | 12 | 72.73 | 1.4161 (0.3115–7.2015) | | 1.0663 (0.3633–3.1311) | |
| (primary site plus all metastatic sites) | | | | | | |
| <58 | 11 | 76.19 | 1 | 0.2448 | 1 | 0.7132 |
| ≥58 | 13 | 66.67 | 2.5264 (0.5424–17.6793) | | 1.2206 (0.4211–3.7384) | |
| Total lesion glycolysis (TLG) | | | | | | |
| (primary site) | | | | | | |
| <345 | 12 | 68.57 | 1 | 0.6819 | 1 | 0.8634 |
| ≥345 | 12 | 71.59 | 1.3656 (0.3007–6.9383) | | 1.097 (0.3736–3.2224) | |
| (primary site plus all metastatic sites) | | | | | | |
| <345 | 12 | 68.57 | 1 | 0.6819 | 1 | 0.8634 |
| ≥345 | 12 | 71.59 | 1.3656 (0.3007–6.9383) | | 1.097 (0.3736–3.2224) | |
| Local failure | | | | | | |
| Yes | 14 | 52.75 | 1 | 0.0035 | not applicable | not applicable |
| No | 10 | 100.00 | 7.165e-10 (0.3738–0.3738) | | not applicable | |

Abbreviations: HR, hazard ratio; CI, confidence interval; FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; SUV, maximum standardized uptake value; SULmax, maximum standard uptake value corrected for lean body mass; SULpeak, peak standard uptake value corrected for lean body mass.

## DISCUSSION

Surgery is a well-established therapeutic strategy for tumors in the paranasal sinus. However, MSSCC may require intensive surgery, including a total maxillectomy or craniofacial resection with the complete obliteration of the components of the orbit, followed by reconstruction.[2] These surgical procedures can cause marked disfigurement, and functional impairment is often intensive. In addition, postoperative radiotherapy of a locally advanced parasinus tumor might be needed since residual disease can exist macroscopically or microscopically despite intensive surgery. Further, treatment outcomes are unsatisfactory after surgical intervention.[15-17] As far as we know, there is little reported evidence on the tumor staging system predicting the outcomes of maxillary sinus tumors after definitive radiotherapy.

Chemoradiotherapy is a treatment option for unresectable diseases, as well as for patients who refuse surgery. In addition, IA-CRT seems to be feasible and could lead to favorable tumor control in the treatment of paranasal sinus carcinomas.[4-6]

Homma, *et al.* have reported the 5-year local progression-free rates are 75.8%, 62.5%, and 59.7%, for T2-3, 4a, and 4b disease, respectively.[5] In addition, our previous report has indicated consistent outcomes in the patient sub-group who received radiotherapy of ≥60 Gy.[6] The present study indicated slightly inferior LC rates than in previous reports, since retrospective studies focusing on rare diseases may include relatively large biases. In addition, the present study used relatively small doses of radiotherapy (up to 66 Gy), although high doses of intra-arterial cisplatin and the definition of local evaluation were similar to those used in previous studies.[5] In this retrospective study, we examined the clinical findings and images in locally advanced MSSCC patients who underwent IA-CRT. We found that local failure had a strong association with poor survival, and pretreatment T stage was correlated with the risk of local failure.

MSSCC survival rates depend on disease stage, with a rapid decrease in survival as the tumor stage increases from T1 to T4, and with lymph node and distant metastases being infrequent.[18,19] We have previously reported the utility of FDG-PET using SUVmax for predictions of maxillary sinus cancer.[9] In the previous report, we showed that SUVmax of the primary tumor, determined by FDG-PET/CT before treatment, was a surrogate marker for the prognosis of maxillary sinus cancer. However, that report included a varied patient population, a heterogeneity of treatments, and differences in the PET/CT systems. To minimize these biases, we selected patients who received IA-CRT and PET/CT before IA-CRT. In addition, FDG-PET/CT images were normalized using GI-PET in this study. However, no superiority of FDG-PET plus morphologically-based staging was demonstrated. Large tumors can have central necrosis, with primary tumors in close proximity to the brain, possibly causing chronic inflammation.[18] These features of MSSCC can complicate a precise diagnosis using PET imaging, and may affect FDG-PET uptake and morphological tumor volume.

The metabolic activity of FDG-PET has been assessed as a prognostic factor in a variety of cancer patients.[7-9] Volume-based quantitative FDG-PET/ CT parameters have recently been suggested to be better predictors of the outcomes of various malignancies, including cancers in the head and neck.[10,11] We have recently reported that high TLG values are independent negative predictors for malignant pleural mesothelioma, regardless of the treatment modality, namely surgery, chemotherapy alone, and trimodal treatment. Thus, we hypothesized that volume-based quantitative FDG-PET/ CT parameters can also be predictors for treatment outcomes in MSSCC, as investigated in this study. As noted above, tumors in the maxillary sinus might confound the volume-based quantitative FDG-PET/ CT parameters.[11] Therefore, further analyses are needed to develop ideal detection methods using PDG-PET for parasinus tumors including MSSCC.

Bird, *et al.* have assessed the tumor response between the PET/CT scan prior to and 12

weeks after definitive CRT, to determine the need for salvage treatment following radical CRT for locally advanced oropharyngeal squamous cell carcinoma.[20] Their results showed the potential for early detection of high risk groups that should be considered to receive salvage therapy. The present study showed volumetric PET/CT parameters prior to definitive IA-CRT; thus, following early scans might lead to the early prediction of treatment outcomes like recurrence and survival. The utility of PET/CT for predicting treatment outcomes has been poorly understood and, to the best of our knowledge, only there has only been one report on PET scans as a predictor of prognosis in patients with maxillary sinus tumors. Herein, this is the first report of FDG-PET to determine the volumetric parameters of maxillary sinus tumors.

There are several limitations in this retrospective study, including its relatively small number of eligible patients. Even though tumors in the paranasal sinus are rare, the treatment protocol and FDG-PET imaging data were highly controlled in this study. In addition, to minimize the inter-scanner variability of SUV measurements between the two PET scanners, an SUV equalization method was utilized. Therefore, we believe that our data is sufficiently reliable. We found no significant information regarding outcomes provided by using FDG/PET prior to IA-CRT. However, pretreatment morphologic T staging predicted local control, which was significantly associated with survival outcomes.

A multimodal treatment strategy including surgery can improve loco-regional tumor control and lead to good survival outcomes, compared to those of concurrent chemoradiotherapy, with disappointing outcomes for inoperable advanced parasinus tumors.[3,16] Previous reports have recently suggested that modern chemoradiotherapy, such as IMRT and IA-CRT, can improve outcomes, to the point of matching surgery-associated outcomes.[4,5,15,17] A limited number of reports have compared modern chemoradiotherapy techniques, such as IMRT and high-dose chemotherapy, with surgery. The present study did not indicate an apparent benefit between 60 and 66 Gy of radiotherapy in the IA-CRT setting using cisplatin. However, 66 Gy may be a relatively small dose for definitive radiotherapy against squamous cell carcinoma in the head and neck, even in the IA-CRT setting.[4,5] The present study presented poor local control in T4b tumors when compared to that of a previous report using a similar protocol, although similar results were found for <T4b stage tumors.[5] Dose-responses can exist at dose ranges higher than 66 Gy (e.g. ≥70 Gy) and in locally advanced disease. We suggest that elevated doses of radiotherapy are needed to achieve better local control of T4b disease, even if radiotherapy is performed with concomitant intra-arterial (cisplatin-based) infusion. Moreover, we determined that clinical T stage can be a predictive factor of local control; however, no significant difference in survival was found in this patient population. Future clinical trials including larger patient populations with homogeneous characteristics may predict stronger prognostic factors.

To conclude, pretreatment T stage predicts local control by IA-CRT, with FDG-PET showing no significant predictive information for these patients. Dose escalation may be needed to successfully treat T4b disease.

## ACKNOWLEDGEMENTS

This work was supported by a Grant-in-Aid for Young Scientists (B) Grant Number 17K16493. We would like to acknowledge Editage (www.editage.jp) for language editing.

## COMPETING INTERESTS

There are no conflicts of interest to declare.

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