Characteristics of PET/CT uptake in the salivary glands in T1N0M0-T2N0M0 glottic cancer

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Abstract

Objective: This study aimed to identify factors influencing salivary gland uptake in fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT). **Subjects and Methods:** We retrospectively reviewed patients aged 20-95 years diagnosed with T1N0M0 or T2N0M0 glottic carcinoma between July 2019 and March 2025, who underwent PET/CT for initial staging and radiotherapy planning. Maximum standardized uptake value (SUVmax) and total lesion glycolysis (TLG) were measured and compared based on gender, smoking history, hypertension, diabetes mellitus, dyslipidemia, stage, and primary tumor site. **Results:** A total of 61 patients were included (mean age, 68.3±12.4 years; 57 male, 4 female). The cohort included 41 patients with T1N0M0 and 20 with T2N0M0 disease. Hypertension status was negative in 32, positive in 28, and unknown in 1; diabetes status was negative in 54, positive in 6, and unknown in 1; dyslipidemia status was negative in 51, positive in 9, and unknown in 1. Smoking history was negative in 7, positive in 53, and unknown in 1. Primary tumor accumulation was observed in 44 patients, while 17 showed no uptake at the primary site. The mean SUVmax of the right submandibular gland was 3.16±0.70 on the left, it was 3.05±0.76. In the right gland, median SUVmax was significantly higher in patients without hypertension 3.350 than in those with hypertension 2.725; P<0.01. In the left gland, median SUVmax was significantly higher in patients without hypertension 3.18 than in those with hypertension 2.56; P<0.01). **Conclusions:** In T1N0M0-T2N0M0 glottic carcinoma, ^{18}F-FDG uptake in the submandibular glands is reduced in patients with hypertension.

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Introduction

The salivary glands are secretion organs in the body, present as paired structures on the left and right sides. They are classified into major and minor salivary glands. The parotid, submandibular, and sublingual glands comprise the major salivary glands. Minor salivary glands are located in the oral and pharyngeal mucosa. Technetium-99m-pertechnetate ($^{99m}TcO_4^-$) salivary gland scintigraphy is used to evaluate salivary gland function. Both scintigraphy and single photon emission computed tomography (SPECT) detect gamma rays. Positron emission tomography (PET) detects annihilation radiation emitted in two opposing directions. In PET practice, glucose analog radiopharmaceuticals, such as fluorine-18-fluorodeoxyglucose (^{18}F-FDG), are used to diagnose tumors, cardiac disease, and large vessel vasculitis. Fluorine-18-FDG accumulation occurs in normal organs as well as tumors and inflammation. In 78 head and neck cancer-free patients, visual and quantitative evaluations at 11 sites showed accumulation in the sublingual gland in 72%, the submandibular gland in 53%, and the parotid gland in 51% of cases [1]. The mean standardized uptake value (SUV) was reported as 2.93 for the sublingual gland, 2.11 for the submandibular gland, and 1.90 for the parotid gland [1]. In a review of 98 cases, the mean SUV of the sublingual gland was reported as 3.3±1.5 [2].

The accumulation dose of ^{18}F-FDG in the salivary glands is associated with salivary gland function and has been reported as useful in evaluating adverse events following radiotherapy [3]. In 47 patients with head and neck cancer, the parotid gland volume decreased by 3.9%±1.9% for every 10Gy increase in mean dose post-radiotherapy and by 16.9%±1.9% within 3 months after treatment. Additionally, in these 47 individuals, the parotid gland volume decreased by 3.9%±1.9% with each 10Gy dose increment and by 16.5%±7.3% within 3 months following radiotherapy. The mean SUV of ^{18}F-FDG in the pa-

rotid gland SUVmean was 1.63±0.48 before treatment initiation. The mean salivary gland dose decreases by 5.2%± 2.5% with more than a 10Gy increase, and salivary gland function declines when the mean dose exceeds 32Gy [4].

Conversely, other studies suggest that salivary gland function may also be reduced due to systemic conditions. In basic medical research, salivary gland function was shown to be impaired in the presence of hypertension [5, 6]. Furthermore, individuals with diabetes exhibit reduced salivary gland function under both stimulated and unstimulated conditions [7]. In a cohort of 4544 patients with head and neck cancer, comorbidities were reported in over 90% of cases, with hypertension and diabetes present in approximately 60% and 17%-18% of patients, respectively [8]. In 131 individuals over 70 years old with T1N0M0 Stage I glottic carcinoma, hypertension, ischemic heart disease, emphysema, diabetes mellitus, and Chen's disease were observed in about 60% of cases [8]. Poor survival outcomes were reported in individuals with three or more of the following five conditions: hypertension, ischemic heart disease, emphysema, diabetes mellitus, and a history of myocardial infarction [9]. These findings suggest a potential for salivary gland dysfunction in patients with head and neck cancer even before initiating radiotherapy due to comorbidities such as hypertension and diabetes; however, detailed investigations are lacking. This study aimed to evaluate factors influencing ^{18}F-FDG accumulation in the salivary glands on PET/CT among patients with early-stage glottic carcinoma, a group in which radiotherapy is the primary treatment and which commonly presents with lifestyle factors such as alcohol consumption and smoking, as well as hypertension and diabetes.

Subjects and Methods

Study design

This was a single-center, retrospective, and case-control study.

Patient selection

We selected patients with T1N0M0 and T2N0M0 glottic carcinoma (squamous cell carcinoma) who underwent PET/CT for initial staging and radiotherapy planning at Tokyo Medical University Hospital from July 2019 to March 2025. The age range at selection was 20 to 95 years. We excluded the following patients: those with untreated overlapping cancers identified through clinical judgment, histopathology, endoscopy, CT, PET/CT, or magnetic resonance imaging (MRI) at the time of glottic carcinoma diagnosis; those with a history of other cancers (excluding glottic carcinoma) who had undergone drug therapy, radiotherapy, or surgery for metastatic or recurrent disease during radiotherapy for glottic carcinoma; those whose PET/CT was not performed at our hospital; those who declined data use; those whose families declined data use due to difficulty in decision-making caused by significant cognitive decline; and those enrolled in other clinical trials or studies. However, we included the following: patients with a history of cancer who were untreated or under observation at the time of radiotherapy for glottic carcinoma, patients not initially enrolled in clinical trials at the time of radiotherapy but later included for other purposes in other departments. Patients with synchronous bilateral glottic carcinomas (double cancer) and those with partial tumor removal by microlaryngeal surgery were also included.

PET/CT analysis

We used PET/CT performed prior to radiotherapy planning for initial staging. Fluorine-18-FDG (Nihon Medi-Physics Co., Ltd., Tokyo, Japan) was administered intravenously at a dose of 3.7MBq/kg based on body weight. The patient then rested for 1h. Positron emission tomography/CT imaging was performed using a Discovery MI (SiPM, Q clear, GE Healthcare, Hino, Japan). Positron emission tomography/CT analysis was conducted by Y.O, a board-certified radiation oncologist, nuclear medicine specialist, and certified PET nuclear medicine specialist. Positron emission tomography/CT images were imported into MIM Maestro (Euro Meditech Co., Ltd., Tokyo, Japan/MIM Software Co., Ltd., Cleveland, OH, USA) for analysis. Maximum SUV and, when applicable, total lesion glycolysis (TLG) were measured in the bilateral submandibular and parotid glands. The SUVmax and TLG values were automatically calculated from regions of interest configured by Y.O.

Contrast with clinical background

Fluorine-18-FDG accumulation was compared across age, gender, medical history, and the presence or treatment of hypertension, diabetes, dyslipidemia, other comorbidities, smoking history, blood glucose level at PET/CT and ^{18}F-FDG dose. The presence of hypertension, diabetes mellitus, dyslipidemia, other comorbidities, and smoking history was defined based on corresponding entries in the medical records; the absence of these conditions was defined as the lack of corresponding documentation.

Statistical analysis

Easy R (EZR), developed by the Jichi Medical University Saitama Medical Center, was used as the statistical software [10]. The Mann-Whitney U test was employed to compare the two groups. A logistic model was applied for univariate and multivariate analysis. Receiver operating characteristic (ROC) analysis was used to calculate the cut-off vale, area under the curve, sensitivity and specificity. Statistical significance was defined as $P<0.05$.

Ethical considerations

This study was approved by the Tokyo Medical University Hospital Ethics Committee (Approval No. T2025-0015). This study was conducted in accordance with the principles of the 1964 Declaration of Helsinki. An opt-out form was published on the hospital website. Only patients who provided consent for data use through the patient questionnaire at the Radiation Therapy Department consultation were included.

Previous study

This study includes patients from a previous study by Okada

et al. (2022) [11]. That study focused on primary tumor accumulation and radiotherapy dose distribution. In contrast, the design of the current study targeted salivary gland accumulation, differentiating it from the prior work. Accordingly, this was conducted as a new and independent study.

Results

Patient selection

From 62 patients who met the inclusion criteria, one 82-year-old male patient (T2N0M0, squamous cell carcinoma) was excluded due to intense ^{18}F-FDG accumulation in the cervical muscles, which interfered with salivary gland evaluation. A total of 61 patients were included in this study.

The mean age was 68.3±12.4 years (range 40 year to 94 year); 57 were male, and 4 were female. In total, 41 had T1N0M0 Stage I, and 20 had T2N0M0 Stage II disease.

Unilateral primary glottic cancer was present in 57 patients. Bilateral primary glottic cancer was observed in one T1N0M0 case and three T2N0M0 cases. All patients had squamous cell carcinoma.

Hypertension status was positive in 32 patients, negative in 28, and unknown in 1. Antihypertensive medication names were recorded in 26 cases.

Furthermore, diabetes status was positive in 6, negative in 54, and unknown in 1.

Dyslipidemia status was positive in 9, negative in 51, and unknown in 1. Seven patients had no smoking history, 53 had a history of smoking, and 1 patient's smoking status was unknown. Data are summarized in Table 1.

Other comorbidities were noted in 11 patients: hyperthyroidism (n=1), hypothyroidism (n=1), collagen disease (n=3), dialysis (n=1), sarcoidosis (n=1), heart failure (n=2), myocardial infarction (n=1), and cardiac surgery (n=1)). These results are shown in Table 1.

Table 1. *Patient background.*

Factor	Result
Patients	61
Age	68.3±12.4
Sex	Male: 57 Female: 4
Stage	T1N0M0: 41 T2N0M0: 20
Tumor site	Unilateral: 57 Bilateral: 4
Hypertension	No: 32 Yes: 28 Unknown: 1
Diabetes	No: 54 Yes: 6 Unknown: 1
Dyslipidemia	No: 51 Yes: 9 Unknown: 1
Smoking history	No: 7 Yes: 53 Unknown: 1
Other comorbidities	Hyperthyroidism: 1 Hypothyroidism: 1 Collagen disease: 3 Dialysis: 1 Sarcoidosis: 1 Heart failure: 2 Myocardial infarction: 1 Cardiac surgery: 1
^{18}F-FDG dose	243.3±45.0MBq
Blood glucose level at PET/CT	106.7±13.5mg/dL
Primary site at PET/CT uptake	Yes: 44 No: 17

Mbq, mega becquerel; mg/dL, milligrams per deciliter; PET/CT, posit-ron emission tomography-computed tomography; ^{18}F-FDG, fluorine-18 fluorodeoxyglucose

PET/CT

The dose of ^{18}F-FDG was 243.3±45.0MBq. The blood glucose level at the time of PET/CT examination was 106.7±13.5 mg/dL. Positron emission tomography/CT showed accumulation at the primary lesion in 44 patients and no accumulation in 17 patients. The results are shown in Table 1.

Evaluation of PET/CT in submandibular gland

The mean value of SUVmax in the right submandibular gland was 3.16±0.70, and the mean value of TLG was 14.6±8.57mL ×SUV. The mean value of SUVmax in the left submandibular gland was 3.05±0.76, and the mean value of TLG was 13.7±6.81mL ×SUV. The mean value of sum SUVmax in the right plus left submandibular gland (both side) was 6.21±1.43 and The mean value of sum TLG in right and left submandibular gland (both side) 28.3±12.8mL×SUV.

In the right submandibular gland, the median SUVmax was 3.350 in the group without hypertension and 2.725 in the group with hypertension; this difference was statistically significant (P<0.01) (Figure 1). In the left submandibular gland the median SUVmax was 3.18 in the group without hypertension and 2.56 in the group with hypertension; this difference was statistically significant (P<0.01) (Figure 2). In the right plus left (both) submandibular gland, the median sum of SUVmax (in the right plus left submandibular gland) was 6.61 in the group without hypertension and 5.38 in the group with hypertension; this difference was statistically signi-

ficant (P<0.01) (Figure 3). By univariate and multivariate analysis for for the sum (right plus left submandibular gland) of the SUVmax (median value <5.97 and ≥5.97) using age, sex (male/female), smoking history (yes/no), diabetes (yes/no), dyslipidemia (yes/no), other comorbidities (yes/no), ^{18}F-FDG dose, blood glucose level at PET/CT, a statistically significant value was found for hypertension in univariate analysis [odds ratio (OR), 0.18; 95% confidence interval (CI), 0.06-0.55; P< 0.01) and blood glucose level at PET/CT [odds ratio (OR), 0.95; 95% confidence interval (CI), 0.91-0.993; P =0.022) A a statistically significant values were found for hypertension (OR, 0.17; 95% CI, 0.04-0.62; P<0.01). and blood glucose level at PET/CT [odds ratio (OR), 0.94; 95% confidence interval (CI) 0.88-1.00; P=0.04] in multivariate analysis.There results are shown in Table 2.

In the right submandibular gland, the median TLG was 14.0mL ×SUV in the group without hypertension and 12.6mL ×SUV in the group with hypertension; this difference was no statistically significant (P =0.84). In the left submandibular gland, the median TLG was 14.8mL ×SUV in the group without hypertension and 12.5mL ×SUV in the group with hypertension; this difference was no statistically significant (P =0.39) In the right plus left (both) submandibular gland, the median sum TLG (in the right plus left submandibular gland) was 28.8mL ×SUV in the group without hypertension and 24.0mL ×SUV in the group with hypertension; this difference was no statistically significant (P=0.65).

About the median sum of SUVmax (in the right plus left submandibular gland), ROC analysis show the area under the curve 0.758, 95% confifence interval 0,633- 0.883, sensitivity 0,714, specificity 0,750 with cut-off vale 5.730 (Figure 4). By univariate analysis for the sum (right plus left submandibular gland) of the SUVmax (cut-off vale value <5.73 and ≥5.73, a statistically significant value was found for hypertension in univariate analysis [odds ratio (OR), 0.19; 95% confidence interval (CI), 0.06–0.56; P <0.01.

About the blood glucose level at PET/CT, ROC analysis show the area under the curve 0.585, 95% confifence interval 0,436-0.735, sensitivity 0,429, specificity 0,781 with cut-off vale 114mg/dL. By univariate analysis for the blood glucose level at PET/CT, a statistically significant value was found for hypertension in univariate analysis [odds ratio (OR), 3.25; 95% confidence interval (CI), 1.02-10.40; P =0.047).

Evaluation of PET/CT in the parotid gland

The SUVmax of the right parotid gland was 2.44±0.40 and the mean value of TLG was 33.6±13.1mL ×SUV. The SUVmax of the left parotid gland was 2.49±0.63 and the mean value of TLG was 35.0±17.5mL ×SUV.

The mean value of sum SUVmax in the right plus left parotidar gland (both side) was 4.4±0.93 and the mean value of sum TLG in right and left parotid gland (both side) 69.6± 29.1mL ×SUV.

By univariate and multivariate analysis for for the sum

Table 2. *Correlation between the sum of f SUVmax (in the right plus left submandibular gland) and other factors.*

Factors for sum of SUVmax at right plus left (both) submandibular gland (median value <5.97 and ≥5.97)	**Single variate analysis**			**Multivariate analysis**		
	Odds ratio	95%CI	P value	Odds ratio	95%CI	P value
Age	0.98	0.94-1.01	0.27	1.02	0.95-1.09	0.57
Sex (male/female)	1.04	0.14-7.87	0.97	18.8	0.181900	0.21
Smoking history (yes/no)	0.36	0.06-2.01	0.24	0.04	0.00-2.13	0.11
Hypertension (yes/no)	0.18	0.06-0.55	<0.01	0.17	0.04-0.62	<0.01
Diabetes (yes/no)	0.17	0.02-1.58	0.12	0.12	0.00-1.70	0.12
Dyslipidemia (yes/no)	1.30	0.31-5.40	0.72	1.81	0.30-11.1	0.52
Other comorbidities (yes/no)	0.49	0.13-1.87	0.30	0.35	0.05-2.21	0.26
Blood glucose level	0.95	0.91-0.99	0.02	0.94	0.88-1.00	0.04
^{18}F-FDG dose	1.00	0.99-1.01	0.61	1.00	0.98-1.01	0.65

SUVmax, maximum standardized uptake value; CI, confidence interval; P, P-value; OR, odds ratio.

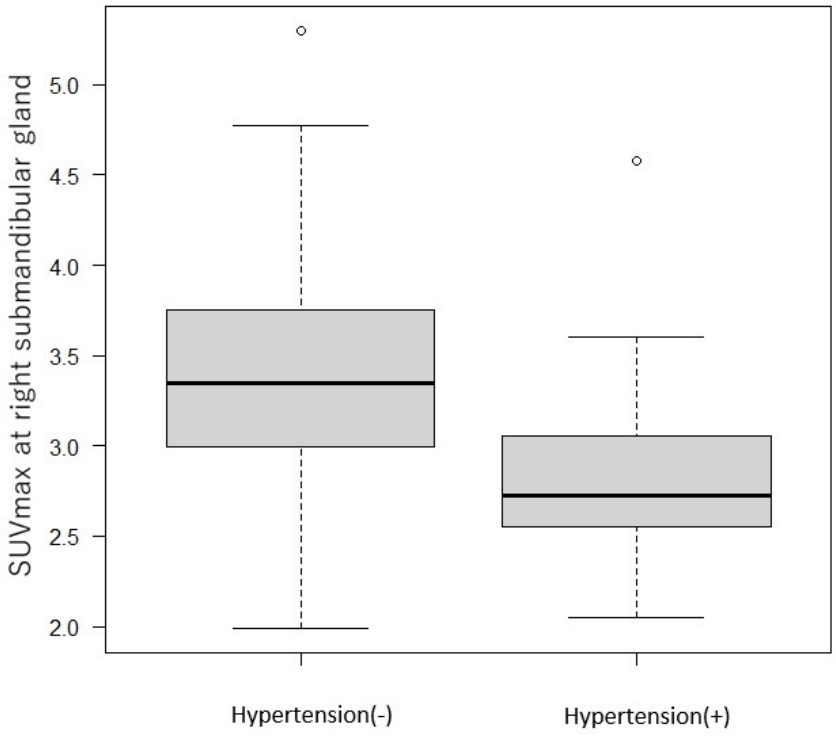

Figure 1. Relationship between SUVmax in the right submandibular gland and hypertension.

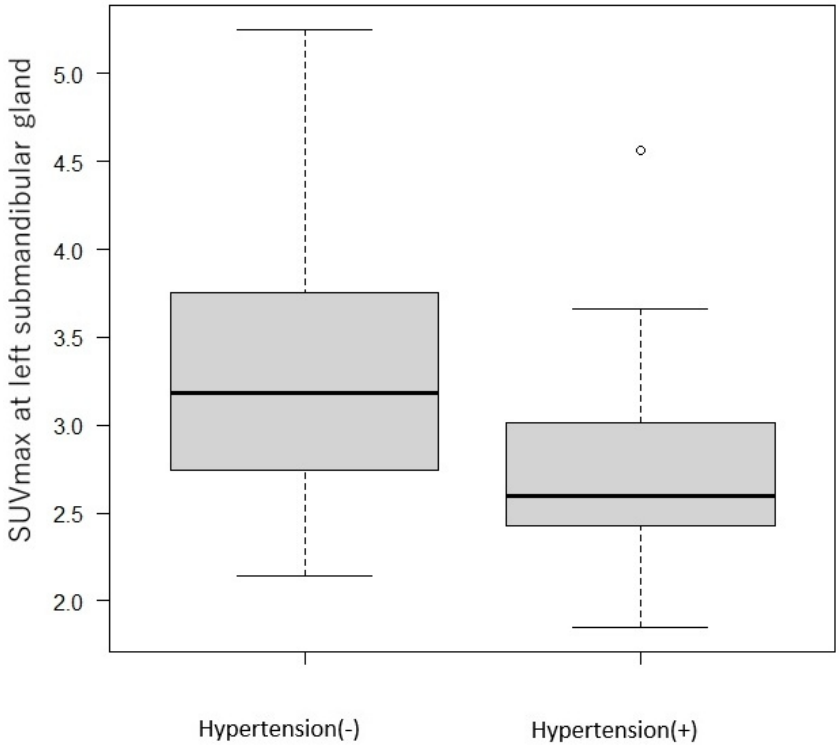

Figure 2. Relationship between SUVmax in the left submandibular gland and hypertension.

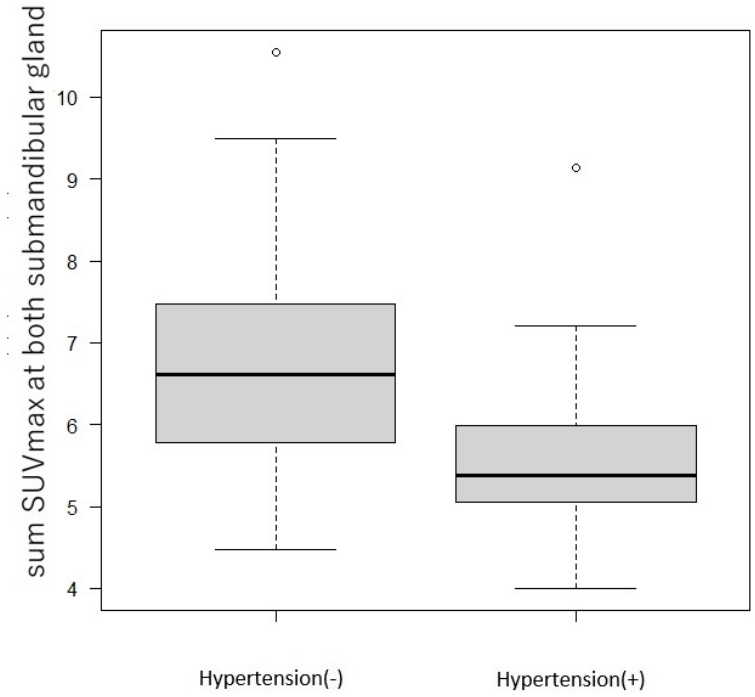

Figure 3. Relationship between the sum of SUVmax in the right plus left (both) submandibular gland and hypertension.

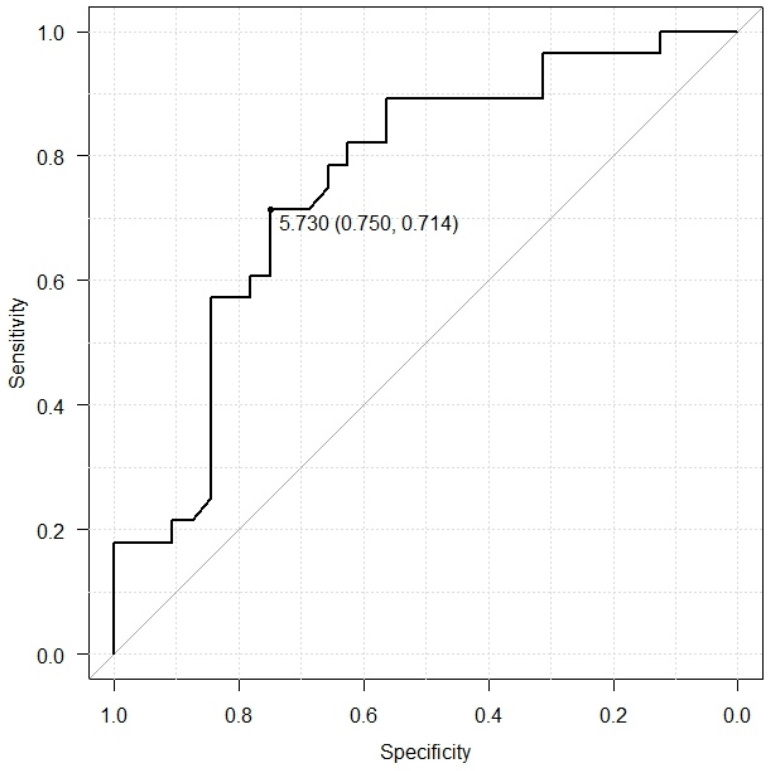

Figure 4. ROC analysis about the sum of SUVmax in the right plus left (both) submandibular gland and hypertension.

(right plus left parotidr gland) of the SUVmax (median value <4.85 and ≥4.85) using age, sex (male/female), smoking history (yes/no), diabetes (yes/no), dyslipidemia (yes/no), other comorbidities (yes/no), ^{18}F-FDG dose, blood glucose level at PET/CT, a there are no statistically significant factor. There results are shown in Table 3.

Discussion

In this study the blood glucose level at the time of PET/CT is associated the sum of SUVmax at right and left (both) submandibular gland. But, no statistically significant association was found between diabetes and the sum of SUVmat at right and left (both) submandibular gland in this study. Although the small number of diabetic patients may have influenced this result, it cannot be concluded that diabetes is associated with submandibular ^{18}F-FDG accumulation based on our findings. In head and neck cancer, salivary gland hypofunction is a significant side effect following radiotherapy. In 137 patients treated for head and neck cancer, 40% developed moderate-to-severe xerostomia 12 months after treatment. A predictive model using the 90th percentile ^{18}F-FDG uptake in the parotid gland and the average uptake level was reported to outperform models based on baseline xerostomia or salivary gland dose. In 161 head and neck cancer patients, 90th percentile uptake and texture analysis of ^{18}F-FDG in the parotid gland were also reported to be associated with oral dryness 12 months after radiotherapy [14]. In 56 patients with head and neck cancer, 29 (51.8%) developed Grade 2 or higher xerostomia, and the overall and relative changes in median SUV in the parotid gland (SUVmedian) 3 weeks after the start of radiotherapy correlated with moderate-to-severe xerostomia at 6 months [15]. Median SUV increased in both the ipsilateral and contralateral parotid glands at 3 weeks compared to baseline, and increases in ipsilateral SUVmedian and contralateral mean parotid dose were correlated with xerostomia [16]. Fluorine-18-FDG may be useful in predicting salivary gland hypofunction and xerostomia during radiotherapy, and in 2024, a model was developed to predict these outcomes based on ^{18}F-FDG accumulation in 540 patients with head and neck cancer [17]. In contrast, Itonaga et al. (2022) reported the utility of salivary gland scintigraphy using $^{99m}TcO_4^-$ [18]. In that study of 31 patients with head and neck cancer treated with radiotherapy, 46Gy was identified as the threshold for salivary gland recovery [18]. The 90th percentile signal intensity on T1-weighted MRI performed before radiotherapy in 68 patients was reported as a predictor of intraoral dryness 12 months post-treatment [19]. A 2024 meta-analysis indicated that decreased ^{18}F-FDG PET/CT uptake and increased ADC on MRI during radiotherapy for head and neck cancer were associated with reduced patient numbers [20]. Magnetic resonance imaging during

Table 3. *Factors affecting the accumulation of ^{18}F-FDG in the parotid gland.*

Factors for sum of SUVmax at right plus left (both) parotid gland (median value <4.85 and ≥4.85)	**Single variate analysis**			**Multivariate analysis**		
	Odds ratio	95%CI	P value	Odds ratio	95%CI	P value
Age	0.98	0.18-55.5	0.44	0.95	0.90-1.02	0.20
Sex (male/female)	3.33	0.33-34.0	0.31	1.10	0.06-18.0	0.95
Smoking history (yes/no)	1.49	0.30-7.33	0.82	3.51	0.43-26.8	0.24
Hypertension (yes/no)	0.39	0.14-1.10	0.08	0.45	0.14-1.41	0.17
Diabetes (yes/no)	0.43	0.07-2.56	0.35	0.30	0.04-2.39	0.26
Dyslipidemia (yes/no)	1.20	0.29-5.00	0.80	2.06	0.41-10.4	0.38
Other comorbidities (yes/no)	0.30	0.07-1.24	1.00	0.34	0.06-1.78	0.20
Blood glucose level	0.99	0.95-1.02	0.45	1.01	0.96-1.05	0.80
^{18}F-FDG dose	1.00	0.99-1.01	0.78	0.99	0.9-1.00	0. 15

SUVmax, maximum stand; SUVmax, maximum standardized uptake value; ^{18}F-FDG, fluorine-18-fluorodeoxyglucose; P, P-value.

treatment was also reported as predictive of post-radiotherapy oral dryness and decreased salivary gland function [20]. Although this study did not assess periodontal disease, a large prospective cohort of 2,588 individuals in Suita, Osaka, reported an association between hypertension and periodontal disease [21]. Taken together, hypertension may contribute to oral deterioration, including submandibular gland hypofunction, oral dryness, and periodontal disease. We believe that reducing the radiation dose to the submandibular gland is just as important as dose reduction to the parotid gland during radiotherapy planning, particularly in patients with hypertension. Attention should also be given to oral environment deterioration linked to submandibular gland dysfunction.

Recently, Intensity-Modulated Radiation Therap (IMRT) is performed for cancer radiotherapy. IMRT can reduce the radiation dose at normal organ. By using IMRT for head and neck cancer patietns and reduce the mean parotid radiation dose under 30.0Gy, the oral health-related quality of life (HRQOL) after radiotherapy was well preserved [22]. From the results of this research, we think that reduce the radiation dose at submandibular gland using IMRT is useful in protecting salivary duct function in head and neck cancer patients with hypertension.

There are some limitations in this study. It was restricted to early-stage glottic cancer; the number of cases was limited; it was a retrospective analysis; and there was no comparison with salivary secretory function or periodontal disease. Further research through prospective clinical trials with larger sample sizes is needed.

In conclusion, in T1N0M0–T2N0M0 glottic carcinoma, PET/CT findings indicate that ^{18}F-FDG accumulation in the submandibular gland is reduced in patients with hypertension.

The authors declare that they have no conflicts of interest.

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