PET/CT findings and dose distribution during radiotherapy in T1N0M0-T2N0M0 glottic cancer

Yukinori Okada[1] MD, Tatsuhiko Zama[1] MD, Tomohiro Itonaga[1] MD, Ryuji Mikami[1] MD, Mitsuru Okubo[1] MD, Shinji Sugahara[1] MD, Masahiko Kurooka[2] MD, Motoki Nakai[1] MD, Koichiro Abe[1] MD, Mana Yoshimura[1] MD, Kazuhiro Saito[1] MD

1. Tokyo Medical University Department of Radiology, Tokyo, Japan
2. Tokyo Medical University Hospital Department of Radiation Therapy, Tokyo, Japan

Keywords: PET/CT - Glottic cancer - Radiotherapy - ^{18}F-FDG

Corresponding author:
Yukinori Okada MD
Tokyo Medical University
Department of Radiology, Tokyo, Japan
igaueno512@yahoo.co.jp

Received:
13 November 2023
Accepted revised:
19 April 2024

Abstract

Objective: To investigate the positron emission tomography/computed tomography (PET/CT) findings of T1/T2N0M0 glottic cancer (hereafter referred to as T1/T2) and dose distribution in radiotherapy. **Subjects and Methods:** We retrospectively collected data from patients diagnosed with T1/T2N0M0 glottic cancer who received radiotherapy. The extent of fluorine-18-fluorodeoxyglucose (^{18}F-FDG) accumulation in primary tumors, maximum standardized uptake value (SUVmax), total lesion glycolysis (TLG), tumor volume of primary tumors on PET/CT were compared. Furthermore, the tumor identified on PET/CT was incorporated into the radiotherapy plans. A dummy plan (radiation field 6×6cm, prescription point facing the vertebral body, maximum dose ≤107%, T1/T2 66Gy/33 fractions) was developed for three-dimensional conformal radiotherapy, and the dose distribution of primary tumors was calculated. **Results:** Twenty-nine patients (27 men and two women) were included; their mean age was 67.2±15.0 years. Increased ^{18}F-FDG accumulation in primary tumors was observed on PET/CT in 22/29 (78.5%; T1: 14/21 [67%], T2: 8/8 [100%]) patients. The median SUVmax, TLG, and primary tumor volume were significantly different between T1 and T2 (SUVmax, T1: 4.56 vs. T2: 8.43, P=0.035; TLG, T1: 1.01 vs. T2: 3.71 SUV×mL, P<0.01; primary tumor volume, T1: 0.38mL vs. T2: 0.80mL, P=0.01). At a TLG cut-off value of 3.470, the area under the curve was 0.875, sensitivity was 0.875, and specificity was 0.929 for T1-T2 differentiation. In 20 patients with ^{18}F-FDG accumulation, the minimum radiation dose was significantly different between T1 and T2 (66Gy vs. 64Gy, P<0.01) at the same 66Gy prescription. The minimum radiation dose and primary tumor volume show the correlation value (r=−0.516, P=0.02). **Conclusion:** In glottic cancer, T1 and T2 can be differentiated by the extent of ^{18}F-FDG accumulation in primary tumors on PET/CT. The minimum radiation dose rate decreases as volume increases.

Hell J Nucl Med 2024; 27(1): 27-34 *Published online: 30 April 2024*

Introduction

Glottic cancer is a malignant tumor that develops in the glottis. In early-stage T1N0M0-T2N0M0 glottic cancer, endoscopic laser surgery or radiotherapy is preferred for preserving vocal function and morphology [1]. A review of 13,808 cases in the UK, comparing 1988-1993, 1994-1999, and 2000-2006, reported an increase in the use of radiotherapy [2]. Forty-one patients with T2N0M0 glottic cancer reportedly had a good quality of life, reduced symptoms, and improved vocal function after radiotherapy [3]. The 2020 Radiotherapy Planning Guidelines in Japan specify that for T1N0M0-T2N0M0 glottic cancer treatments, the field size should range from 5×5cm to 6×6cm across all T1N0M0-T2N0M0 cases. The prescribed radiation dose is set at 60-66Gy across 30-33 fractions for T1N0M0 and 70Gy over 35 fractions for T2N0M0 [4]. A Japanese report stated that a 60-66 Gy radiotherapy dose applied to 96 T1N0M0 and 32 T2N0M0 cases (≥70Gy for some T2N0M0 cases) resulted in a 5-year local control rate of 85% for T1N0M0 cases and 71% for T2N0M0 cases [5]. An overseas report stated that radiotherapy with a median dose of 63Gy for 315 T1N0M0 cases and 83 T2N0M0 cases resulted in a 5-year local control rate of 85% in T1N0M0 cases and 70% in T2N0M0 cases [6]. In glottic cancer, the T1 classification is confined to the vocal cords, including either the post-anterior or posterior commissure, with normal glottal movements. The T2 classification, however, refers to supraglottic or subglottic extension and/or a limitation of vocal fold movement [7]. However, these definitions alone cannot sufficiently explain the difference in the local control rate of radiotherapy between the T1N0M0 and T1N0M0 cases. Meanwhile, positron emission tomography/computed tomography (PET/CT) using fluorine-18-fluorodeoxyglucose (^{18}F-FDG) is performed to diagnose malignant tumors. Positron emission tomography/CT can semi-quantitatively evaluate the extent of ^{18}F-FDG accumulation. This study aimed to investigate whether there is a difference in the extent of ^{18}F-FDG accumulation in T1N0M0-T2N0M0 glottic cancer

cases and if there is a factor that explains the difference in the local control rate in radiotherapy from that in the extent of accumulation.

Subjects and Methods

Patient selection

Patients diagnosed with T1N0M0-T2N0M0 glottic cancer at Tokyo Medical University Hospital between 1 July 2019 and 31 March 2023, and for whom radiotherapy planning was developed in the radiotherapy department, were included in this retrospective, case-control study. The inclusion criteria were the diagnosis of histopathological squamous cell carcinoma, PET/CT performed at this hospital before radiotherapy planning, and age 20-100 years at the time of diagnosis and treatment. The exclusion criteria were untreated double cancers detected by histopathological examination, endoscopy, CT, PET/CT, and magnetic resonance imaging at the time of glottic cancer diagnosis and a high possibility of untreated double cancers; metastasis or recurrence of other malignant tumors at the time of glottic cancer diagnosis and undergoing drug, radiation, or surgical treatment; one glottic cancer lesion on each side at the same time, removal of part of glottic cancer by laryngeal microsurgery before PET/CT; PET/CT not performed; refusal to consent to data use; and participation in other research or clinical trials. However, even in patients with a history of malignant tumors, those who had not undergone radiotherapy for glottic cancer or who were being followed up were included in the study.

In this study, a total of 29 patients (27 men and two women) were included; their mean age was 67.2±15.0 years. All patients were diagnosed with squamous cell carcinoma. There were 21 patients with T1N0M0 and eight with T2N0M0. The glottic cancer sites were the right vocal cord (21 cases), left vocal cord (seven cases), and anterior commissure (one case). The data of 22 patients with ^{18}F-FDG accumulation in the primary tumor on PET/CT were examined. The mean blood glucose level was 111.7±13.1mg/dL, while the mean ^{18}F-FDG dose was 242.1±42.5MBq. Characteristics of patients are shown in Table 1.

Table 1. *Patients characteristics.*

Factors	Details
Number of patients	29
Age, years	67.2±15.0
Sex	27 males, 2 females
TNM classification	T1N0M0: 21 patients T2N0M0: 8 patients
Glottic cancer site	Right vocal chord: 21 patients Left vocal chord: 7 patients Anterior commissure: 1 patient

TNM: Tumor, Node, Metastasis.

T1N0M0 and T2N0M0 diagnosis

In addition to PET/CT findings and examination by an otolaryngologist with a laryngoscope, T1N0M0-T2N0M0 glottic cancer was diagnosed based on the comprehensive determination from in-hospital cancer boards, weekly radiotherapy department and otolaryngology conferences for patients undergoing radiotherapy, and conferences within the radiotherapy department.

PET/CT and analysis of PET/CT images

Fluorine-18-FDG (Nihon Medi-Physics Co., Ltd., Tokyo, Japan) was administered intravenously according to the patient's body weight, and PET/CT (Discovery MI, use SiPM, Q clear: GE Healthcare, Hino, Japan) was performed after approximately 60min of rest. The ^{18}F-FDG dose is 3.7MBq/kg.

Positron emission tomography/CT images were analyzed by a radiation oncologist (Y.O), nuclear medicine specialist, and certified PET nuclear medicine specialist. Visual evaluation was performed to evaluate the depiction of cancer lesions on PET/CT. 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, and PET/CT accumulation was observed through visual evaluation. Maximum standardized uptake value (SUVmax), primary tumor volume (mL), and total lesion glycolysis (TLG) were measured by setting a region of interest in the primary tumor for cases at MIM Maestro by visual evaluation. We used the following formula: TLG= SUVmean (mean standard uptake value)×primary tumor volume.

Radiation treatment plan by dummy plan

A dummy plan was created for patients who had previously undergone radiotherapy. In all patients, radiotherapy was administered with the patient immobilized on a treatment table by a fixture (thermoplastic shell). Images were acquired with a 16-slice radiotherapy planning CT scanner (Aquilion: Canon Medical Systems Co., Ltd., Otawara, Japan), featuring a slice thickness of 2mm. Positron emission tomography/CT images were then co-registered using MIM Maestro. Lesions identified through visual assessment on PET/CT images in the radiotherapy planning CT scans were delineated as the gross tumor volume (GTV). Subsequently, data were imported into Eclipse (Varian Medical Systems Co., Ltd., Palo Alto, CA, USA) for the development of a radiotherapy plan. AAA 1612 was used as the calculation algorithm. A radiation oncologist (Y.O) (a radiation oncologist specialist, nuclear medicine specialist, and certified PET nuclear medicine specialist) drafted a radiotherapy plan using a dummy plan. The linear accelerator was True Beam STx (Varian Medical Systems Co., Ltd.). Three-dimensional conformal radiotherapy was performed as the radiation method and was set into four fixed fields on the left and right using the in-field technique. Based on the 2020 Radiotherapy Planning Guidelines, the radiation field measured 6×6cm in

width, the superior margin was marked above the thyroid notch to the inferior margin of the hyoid, the inferior margin was the inferior border of the cricoid cartilage, the anterior aspect was present at 5–10mm from the occipital skin surface, and the posterior aspect was detected along the anterior border of the vertebral body [4]. The X-ray energy was set to 6MV because the treatment outcome was poor at 10MV, and the local control rate was satisfactory at 6MV in T1N0M0-T2N0M0 cases [4, 8, 9]. The anterior border of the vertebral body was designated as the prescription point, with a prescribed dose of 66 Gy over 33 fractions for T1N0M0 and T2N0M0, facilitating straightforward comparison. The maximum dose within the radiation range was set at 105%-107%, and the high dose region above 108% was shielded using the in-field technique. The minimum, maximum, and average doses were measured for GTV using a dose-volume histogram. Furthermore, we used round-off for radiation dose.

Statistical analysis

Eazy ZR (EZR) developed by the Jichi Medical University Saitama Medical Center, was used as the statistical software [10]. The Mann-Whitney U test and Fisher's test were performed to compare the two groups. Cut-off values were calculated using receiver operating characteristic (ROC) analysis. The correlation between the two groups was evaluated by Spearman's rank correlation coefficient. Statistical significance was set at $P < 0.05$. Given the small sample size, we used non-parametric tests.

Ethical considerations

The study was conducted with the approval of Tokyo Medical University Hospital (Ethics Committee Approval No. 2022-0203). Informed consent was obtained for the questionnaire survey from all patients in the radiotherapy department. This research employed an opt-out method on the hospital website.

Results

^{18}F-FDG accumulation in primary tumors

Overall, 22 (78.5%) patients exhibited ^{18}F-FDG accumulation in the primary tumor of glottic cancer: 14 (67%) patients in the T1N0M0 group and eight in the T2N0M0 group (100%). The data of 22 patients with ^{18}F-FDG accumulation in the primary tumor on PET/CT were examined, and SUVmax, TLG, and primary tumor volume were calculated.

Primary SUVmax

The mean SUVmax of the primary tumor was 6.22±3.01. There was a significant difference in median SUVmax between T1N0M0 and T2N0M0 (4.56 vs. 8.43, P=0.035).

In the ROC analysis, with an SUVmax cut-off value of 7.82, the area under the curve reached 0.777, exhibiting a 95% confidence interval of 0.566-0.988. The sensitivity and specificity for distinguishing between T1N0M0 and T2N0M0 were 0.750 and 0.786, respectively.

TLG

The mean TLG of primary tumors was 2.70±2.85 SUV×mL. There was a significant difference in median TLG between T1N0M0 and T2N0M0 (1.01 vs. 3.71 SUV×mL, P<0.01; Figure 1). In ROC analysis, at a TLG cut-off value of 3.470 SUV×mL, the area under the curve was 0.875, 95% confidence interval was 0.703-1, sensitivity was 0.875, and specificity was 0.929 for differentiating between T1N0M0 and T2N0M0 (Figure 2).

Primary tumor volume

The mean primary tumor volume was 0.61±0.42mL. There was a significant difference in median primary tumor volume between T1N0M0 and T2N0M0 (0.38mL vs. 0.80mL, P<0.01) (Figu-

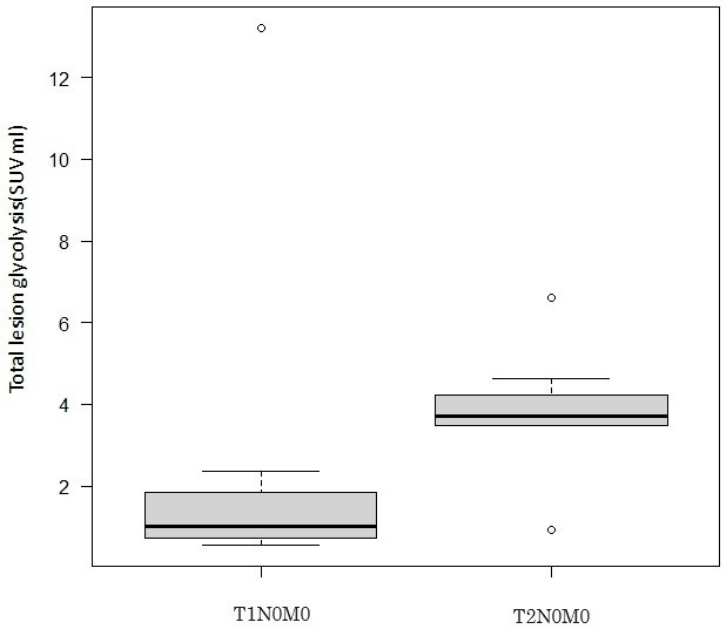

Figure 1. Differences in total lesion glycolysis of primary tumors between T1N0M0 and T2N0M0 glottic cancer.

re 3). In ROC analysis, at a primary tumor volume cut-off value of 0.59mL, the area under the curve was 0.84, the 95% confidence interval was 0.635-1, sensitivity was 0.875, and specificity was 0.857 for differentiating between T1N0M0 and T2N0M0 (Figure 4).

Notably the results for the comparison between T1N0M0 and T2N0M0 based on age, sex and PET/CT data are shown in Table 2.

Radiation treatment plan by dummy plan

A dummy plan was developed for 20 of the 22 patients with PET/CT findings showing ^{18}F-FDG accumulation in the primary tumor. One T2N0M0 patient was excluded due to challenges encountered during the fusion of radiotherapy planning

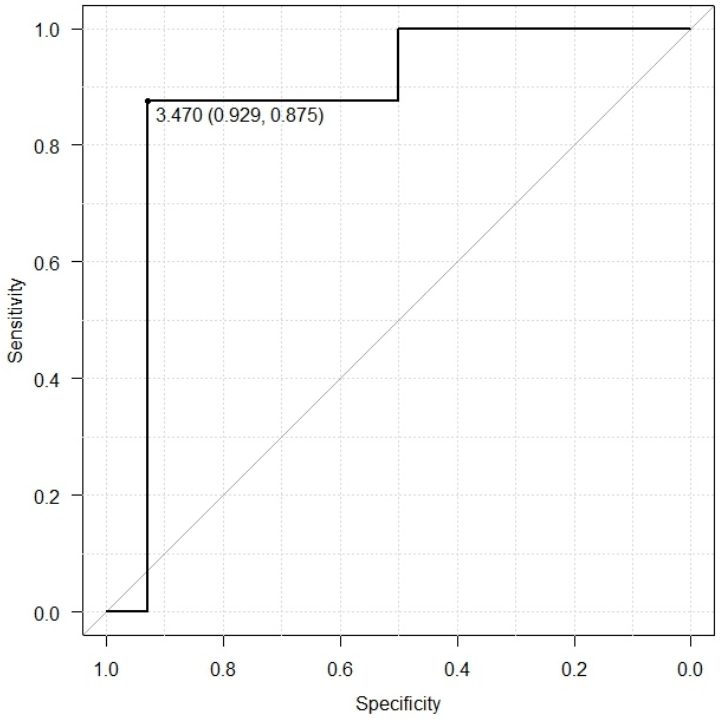

Figure 2. Receiver operating characteristic analysis for total lesion glycolysis of primary tumors to differentiate between T1N0M0 and T2N0M0 glottic cancer.

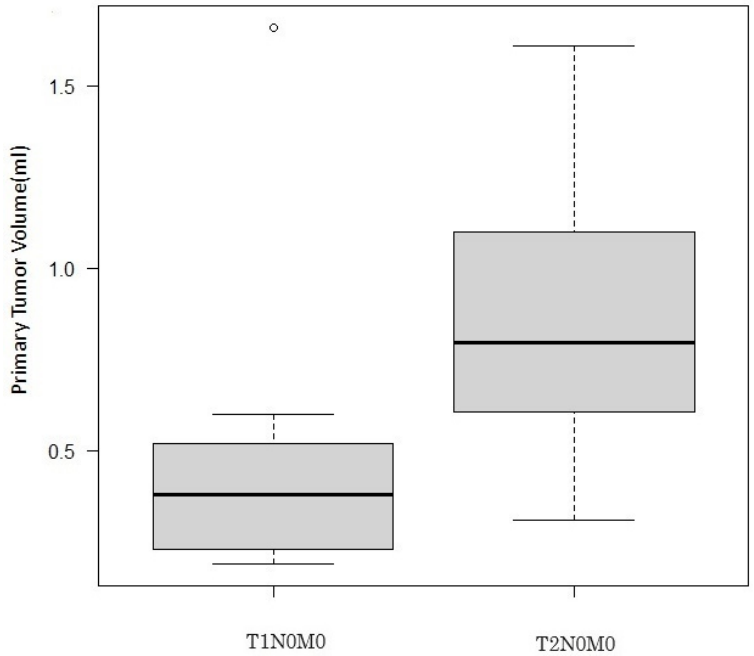

Figure 3. Difference in primary tumor volume between T1N0M0 and T2N0M0 glottic cancer.

CT and PET/CT. One patient with a T1N0M0 anterior commissure tumor was excluded as an outlier due to their minimum radiation dose rate being significantly lower than that observed in other cases (minimum radiation dose 27Gy, markedly distinct from other minimum radiation dose) The global maximum dose within the radiation range for both T1N0M0 and T2N0M0 cases was 106%, with no statistically significant difference observed between the two groups at the same 66Gy prescription (P=0.86).

The minimum radiation dose was 66Gy for T1N0M0 and 64Gy

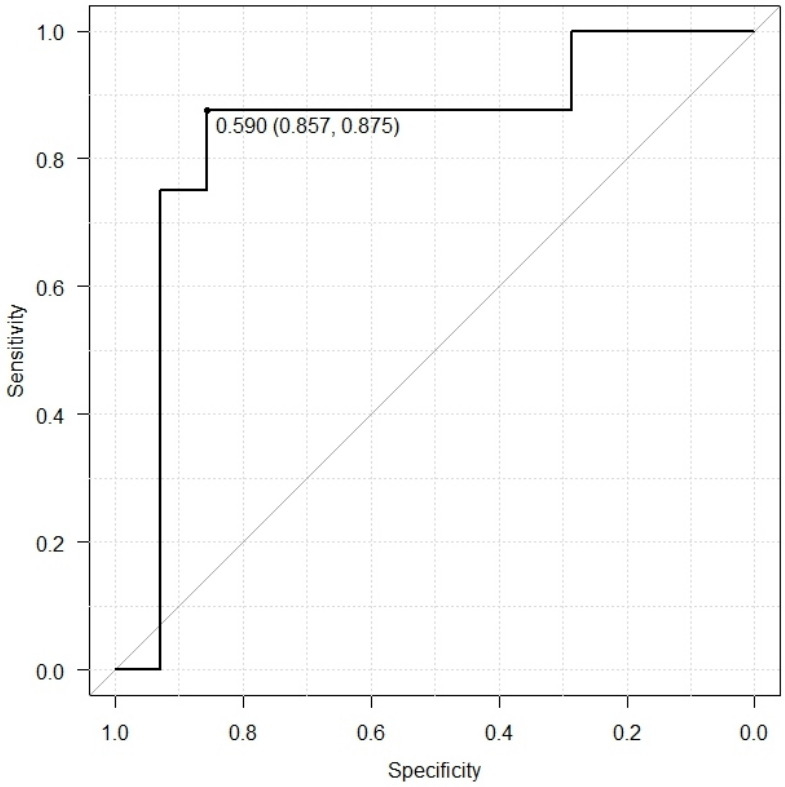

Figure 4. Receiver operating characteristic analysis for primary tumor volume to differentiate between T1N0M0 and T2N0M0 glottic cancer.

Table 2. *Comparison T1N0M0 and T2N0M0 patients' data.*

Factors	T1N0M0	T2N0M0	P-value
Age	66.0	69.5	0.76
Sex	19 males 2 females	8 males 0 females	1.00
Blood glucose level	109mg/dL	112mg/dL	0.88
^{18}F-FDG dose	238.5MBq	243.1MBq	0.90
Accumulation by PET/CT	14/21 (67%)	8/8 (100%)	0.14
SUVmax of the primary tumor	4.56	8.43	0.035
TLG	1.01 SUVmL	3.71 SUVmL	<0.01
Primary tumor Volume	0.38 mL	0.80 mL	<0.01

^{18}F-FDG dose: Fluorine-18 Fluorodeoxyglucose dose; PET/CT: Positron Emission Tomography/Computed Tomography; SUVmax: Maximum Standardized Uptake Value; SUVmL: Standardized Uptake Value per milliliter; TLG: Total Lesion Glycolysis.

for T2N0M0, indicating a statistically significant difference between the two groups at the same 66 Gy prescription (P< 0.01; Figure 5).

The maximum radiation dose was 68Gy for T1N0M0 and 69Gy for T2N0M0, with no statistically significant difference between the two groups at the same 66Gy prescription (P= 0.073).

The average dose was 68Gy for both T1N0M0 and T2N0M0, with no statistically significant difference between the two groups at the same 66Gy prescription (P=1.00).

These results are shown in Table 3.

The minimum radiation dose and primary tumor TLG, along with primary tumor volume, demonstrate a correlation value (primary tumor TLG: r=-0.43, P=0.056; primary tumor volume: r=-0.516, P=0.02; see Figure 6).

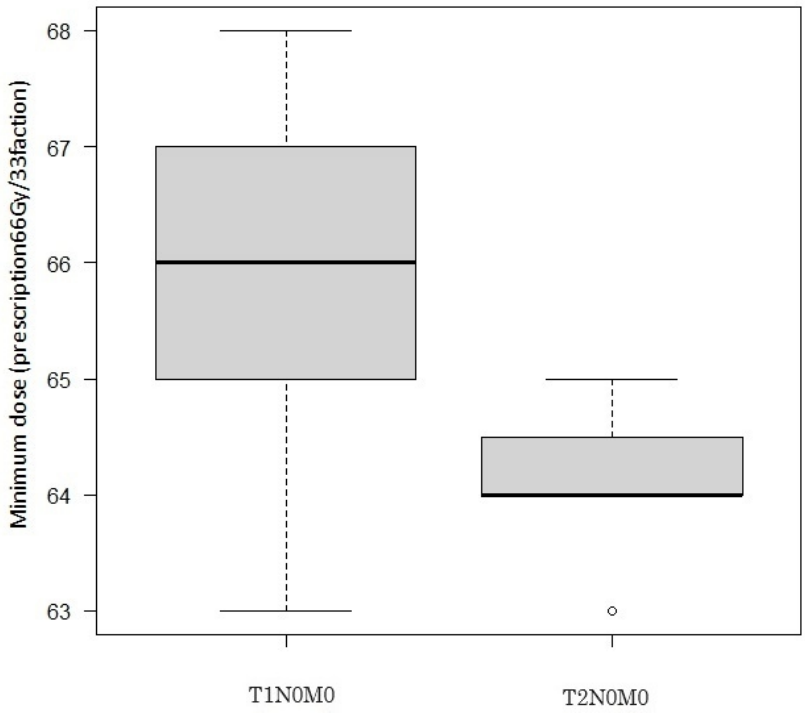

Figure 5. Difference in minimum radiation dose (prescription 66Gy) between T1N0M0 and T2N0M0 in 20 cases.

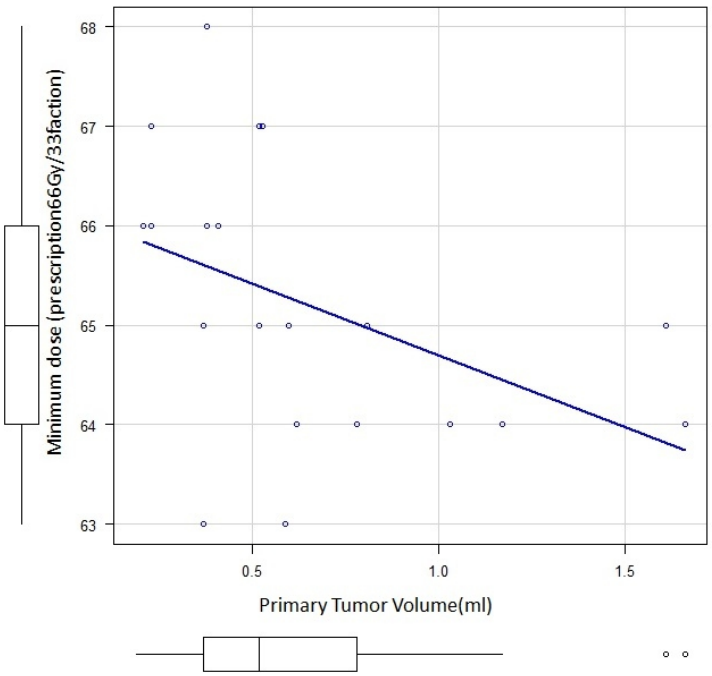

Figure 6. Correlation between primary tumor volume and Minimum radiation dose (prescription: 66Gy) in 20 cases.

Discussion

The usefulness of PET/CT in glottic cancer has been reported. In a study of 54 patients, the primary tumor detection rate by PET/CT was 96.3% (52/54) [11]. However, a large number of T3-T4 and N1-N2 advanced cases were selected [11]. Here, 14 (67%) patients with T1N0M0 and eight (100%) patients with T2N0M0 exhibited ^{18}F-FDG accumulation in primary tumors. Moreover, there are statistically significant differences in the primary tumor SUVmax, TLG, and primary tumor volume between T1N0M0 and T2N0M0 in glottic cancer. We believe that these PET/CT data are useful for initial staging. The staging of glottic cancer is based on gross evaluation and can be influenced by the subjective judgment of the attending physician. In other words, there is a risk of over-or under-radiation dose prescription due to staging errors. However, it is conceivable that PET/CT can be used for objective diagnosis of T1N0M0 and T2N0M0. In this study, the absence of ^{18}F-FDG accumulation in primary tumors on PET/CT was considered T1N0M0. However, T1N0M0 was diagnosed based on ^{18}F-FDG accumulation and can be differentiated from T2N0M0 based on SUVmax, TLG, and primary tumor volume. Moreover, total lesion glycolysis was considered the most useful indicator for differentiating between T1N0M0 and T2N0M0 by sensitivity, specificity, and AUC value. For this reason, we believe that PET/CT is beneficial for the initial staging, as it helps not only in detecting lymph node metastasis (N factor) or distant metastasis (M factor) but also in identifying the primary tumor (T factor). This study allows us to explore the reasons behind the variation in local control rates among T1N0M0-T2N0M0 cases. Tumors are hypoxic and metabolized mainly by glycolysis, which can produce energy even under hypoxic conditions [12]. Glycolysis is inefficient in energy metabolism and requires multiple energy sources, resulting in ^{18}F-FDG accumulation in tumors. In a review of 55 cases of glottic or hypopharyngeal cancer, the expression of glucose transporter 1, a glucose carrier, and the transcription factor hypoxia-inducible factor-1 increased under hypoxic conditions; moreover, hypoxia-inducible factor-1, a glucose transporter 1, and SUVmax are reportedly correlated [13]. Regarding the radiotherapy outcomes for 59 patients with early-stage glottic cancer (44 with T1N0M0 and 15 with T2N0M0), the 5-year progression-free survival was 53.4% in the group with a primary tumor SUVmax of ≥3.4, compared to 95.4% in the group with an SUVmax <3.4 [14]. This study suggests that SUVmax serves as a prognostic factor for glottic cancer. In our analysis, when comparing patients with T1N0M0 to those with T2N0M0, both the median SUVmax and the median primary tumor volume demonstrated a two-fold increase, while the median TLG exhibited a four-fold difference. These findings indicate significant disparities in tumor malignancy (SUVmax), primary tumor volume, and metabolic activity (TLG) between T1N0M0 and T2N0M0 glottic cancers. Furthermore, the radiation dose difference between T1N0M0 and T2N0M0 ranged from 4 to 10 Gy, implying that T2N0M0 cases might have been underdosed based on tumor grade and primary tumor volume.

Moreover, an increase in primary tumor volume could have led to a decrease in the Minimum radiation dose received. There was a statistically significant difference between T1N0M0 and T2N0M0 in terms of minimum radiation dose, and the minimum radiation dose and primary tumor volume showed an inverse correlation, i.e., the former decreased as the primary tumor volume increased, indicating that the radiation dose was insufficient. The possibility of recurrence at sites where the minimum radiation dose was declining can also be considered. A feature of glottic cancer is that the tumor is in direct contact with air. Due to build-up and rebuild-up, relative electron equilibrium is not established in the area in contact with air, and the dose consequently decreases. From this study, as TLG and primary tumor volume increased, the area of the surface in contact with air increased, and it is hypothesized that this area caused a relative dose deficiency due to build-up and rebuild-up. A study of 163 T1N0M0 cases reported that even T1b glottic cancer requires a dose of 67-70Gy to achieve local control [15]. The reason for the decreased local control rate in T2N0M0 cases based on the extent of accumulation on PET/CT in glottic cancer was hypothesized to be a) a difference in tumor malignancy and tumor burden (biological aspect) and b) a difference in the dose radiated to the tumor (physical aspect) as the primary tumor vo-

Table 3. *Difference in dose distribution between dummy plans.*

Factors	Average (All patients)	T1N0M0	T2N0M0	P-value
Global maximum	106±0.6%	106%	106%	0.86
Minimum radiation dose	65.2±1.40 Gy	66Gy	64Gy	<0.01
Maximum radiation dose	68.6±1.05Gy	68Gy	69Gy	0.073
Average radiation dose	67.1±0.85Gy	67Gy	67Gy	1.00

lume increases. We think that the 1) hypofractionated radiation therapy (increase minimum radiation dose), 2) combination chemotherapy (improve radiation sensitivity), 3) intensity-modulated radiotherapy (reduce normal organ radiation dose and increase glottis cancer dose), 4) image guides radiotherapy (minimize misalignment) may improve the outcome of T2N0M0 glottis cancer. But more prospective study is necessary. There are several limitations to this study. First, it included a small number of cases and lacked comparison based on clinical prognosis. Second, radiation oncologists, although having PET research experience [35, 36], provided target-related input, and subjective factors could not be excluded. In the future, it will be necessary to conduct prospective clinical trials designed to increase the number of cases, compare them with clinical prognosis, and objectively evaluate images using artificial intelligence-based software.

In conclusion, PET/CT is useful for accurate staging and precise radiotherapy planning for patients with early T1N0M0-T2N0M0 glottic cancer.

Acknowledgments

We would like to thank Dr. Yasuo Kosugi of the Department of Radiation Oncology, Juntendo University, for his valuable advice regarding radiotherapy for glottic cancer.

The authors declare that they have no conflicts of interest

Bibliography

1. Boyle K, Jones S. Functional outcomes of early laryngeal cancer - endoscopic laser surgery versus external beam radiotherapy: a systematic review. *J Laryngol Otol* 2022; 136: 898-908.
2. Zhang H, Travis LB, Chen R et al. Impact of radiotherapy on laryngeal cancer survival: a population-based study of 13,808 US patients. *Cancer* 2012; 118: 1276-87.
3. Hendriksma M, Heijnen BJ, Verbist BM et al. Long-term functional outcomes in tumour stage T2 glottic carcinoma after radiotherapy. *J Laryngol Otol* 2023; 137: 685-90.
4. JASTRO Guidelines 2020 for radiotherapy Treatment planning. 2020: 123-27.
5. Nishimura Y, Nagata Y, Okajima K et al. Radiation therapy for T1, 2 glottic carcinoma: impact of overall treatment time on local control. *Radiother Oncol* 1996; 40: 225-32.
6. Le QT, Fu KK, Kroll S et al. Influence of fraction size, total dose, and overall time on local control of T1-T2 glottic carcinoma. *Int J Radiat Oncol Biol Phys* 1997; 39: 115-26.
7. Brierly JD, Gospodarowicz MK, Wittekind C et al. TNM Classification of Malignant Tumours. 8th ed. John Wiley & Sons, LTD: New York; 2017.
8. Akine Y, Tokita N, Ogino T et al. Radiotherapy of T1 glottic cancer with 6 MeV X rays. *Int J Radiat Oncol Biol Phys* 1991; 20: 1215-8.
9. Franchin G, Minatel E, Gobitti C et al. Radiotherapy for patients with early-stage glottic carcinoma: univariate and multivariate analyses in a group of consecutive, unselected patients. *Cancer* 2003; 98: 765-72.
10. Kanda Y. Investigation of the freely available easy-to-use soft software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013; 48: 452-8.
11. Albano D, Dondi F, Paderno A et al. ^{18}F-FDG PET/CT in laryngeal cancer: comparison with conventional imaging and prognostic role. *Rev Esp Med Nucl Imagen Mol (Engl Ed)* 2021; 40: 229-38.
12. Warburg O. On the origin of cancer cells. *Science* 1956; 123: 309-14.
13. Shen LF, Zhou SH, Yu Q. Relationships between expression of glucose transporter protein-1 and hypoxia inducible factor-1α, prognosis and ^{18}F-FDG uptake in laryngeal and hypopharyngeal carcinomas. *Transl Cancer Res* 2020; 9: 2824-37.
14. Park JW, Lee SW, Kim JS, Song SY. Prediction of local control in early glottic carcinoma using the maximum standardised uptake value. *Cancer Radiother* 2017; 21: 205-9.
15. Nomiya T, Nemoto K, Wada H et al. Long-term results of radiotherapy for T1a and T1bN0M0 glottic carcinoma. *Laryngoscope* 2008; 118: 1417-21.