Prediction of Survival and Therapy Outcome with ^{11}C-Tyrosine PET in Patients with Laryngeal Carcinoma

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Choosing the optimal treatment for an individual with squamous cell carcinoma of the head and neck is a difficult challenge because of the unpredictable clinical behavior of this malignancy. A reliable method for assessing the clinical behavior and predicting the radiocurability of tumors would assist in the therapy strategy and prognosis. This study evaluated whether quantitative PET using L-[1-^{11}C]-tyrosine (TYR) has predictive value for survival and therapy outcome in patients with primary squamous cell carcinoma of the larynx. **Methods:** Thirty-four patients with histologically confirmed laryngeal carcinomas underwent dynamic ^{11}C-TYR PET before receiving definitive therapy. Various methods for quantification of tumor activity were used: assessment of protein synthesis rate (PSR), calculation of standardized uptake value, and estimation of tumor-to-nontumor ratio. Treatment consisted of radiotherapy (n = 20) or surgery (n = 14). The median follow-up was 40 mo. **Results:** All malignancies were identified correctly, with no false-negative results. Cumulative survival was compared between patients with tumor PSR equal to or higher than the median (2.0 nmol/mL/min) and those with tumor PSR lower than the median and was found not to be significantly different (P = 0.07). When the radiotherapy group was evaluated separately, the difference in survival was significant (P = 0.03; 5-y survival, 30% vs. 73%) and high ^{11}C-TYR uptake correlated with poor prognosis. In multivariate analysis, PSR was an independent predictor for survival. Because differences (P = 0.08) between patients with and patients without recurrence were not significant, no predictive value of PSR for disease recurrence could be demonstrated. **Conclusion:** Prediction of survival of patients undergoing radiotherapy for laryngeal squamous cell carcinoma is feasible primarily by using ^{11}C-TYR PET to quantify activity before treatment.

Key Words: L-[1-^{11}C]-tyrosine; PET; head and neck tumors; prediction; survival; therapy outcome

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Primary treatment of squamous cell carcinoma of the larynx consists of radiotherapy, surgery, or a combination of these (*1*). The optimal choice of therapy depends mainly on the stage, type, and location of the tumor as assessed by clinical and morphologic examinations. Although tumor stage is the only independent factor predicting the treatment outcome of laryngeal cancer (*2*), the TNM classification has limitations in the management of a particular patient with head and neck cancer. Individual tumors with a similar clinical stage differ greatly in response to radiotherapy. The factors influencing this unpredictable clinical behavior and decreased radiocurability are generally unknown. Despite the large number of histopathologic and biologic studies that have been performed, no morphologic or cytologic markers are currently available to predict outcome in head and neck cancer. A reliable method for assessing the clinical behavior and predicting the radiosensitivity of a tumor would assist in selection of the optimal treatment and evaluation of prognosis.

Metabolic activity is suggested to be related to the behavior of disease. Tumor metabolism can be determined in vivo by PET, in which radiopharmaceuticals labeled with positron-emitting nuclides assess metabolic and pathophysiologic processes. The most widely used radiopharmaceutical in PET is the glucose analog ^{18}F-FDG, an indicator of tumor metabolism based on increased glycolysis in tumor cells. In head and neck tumors, ^{18}F-FDG PET has demonstrated a correlation between tracer uptake and prognosis (*3*). However, ^{18}F-FDG proved not to be a tumor-specific radiotracer because it accumulates also in benign lesions and inflammatory tissues and may cause false-positive results (*4*). Consequently, a search for alternative and more specific tumor tracers is ongoing. The carboxyl-labeled amino acid L-[1-^{11}C]-tyrosine (TYR) is less avidly metabolized by inflammatory cells and has proved to be a reliable tracer for detection and quantification of head and neck tumors (*5*). ^{11}C-TYR is an appropriate compound for quantification of protein synthesis rate (PSR) in tumor tissue (*6*)

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and has been successfully used for quantification of a variety of primary and recurrent tumors (*7–9*).

The aim of the study was to evaluate whether quantitative ^{11}C-TYR PET has predictive value for survival and therapy outcome in patients with primary squamous cell carcinoma of the larynx.

MATERIALS AND METHODS

Patients

Thirty-four patients (3 women and 31 men; age range, 44–81 y; median age, 58 y) with newly diagnosed and histologically confirmed laryngeal squamous cell carcinoma were included in this prospective study. Tumors were clinically staged according to the International Union Against Cancer TNM classification system (*10*), which includes physical examination of the head and neck, endoscopic examination under general anesthesia, biopsies of all suspected areas of the upper aerodigestive tract, and CT. The study was approved by the medical ethics committee of Groningen University Hospital, and written informed consent was obtained from all patients. In addition to the current diagnostic modalities, dynamic ^{11}C-TYR PET was performed before definitive therapy.

Curative therapy was planned according to the type, location, and stage of the disease. Twenty patients received definitive megavoltage radiotherapy with a conventional fractionation schedule to a total absorbed tumor dose of 66–70 Gy, 2 Gy per fraction, 5 fractions weekly. The other 14 patients underwent total laryngectomy, including neck dissection in 7 subjects. All operated patients received additional radiotherapy to the tumor. The dosage was 60–70 Gy and was given in 30–35 fractions.

After radiotherapy and surgery, patients were followed up at 3-mo intervals for the first 2 y and at 6-mo intervals for the following 3 y. Follow-up was calculated from the time of the ^{11}C-TYR PET study, and the median follow-up time was 40 mo (range, 5–60 mo). If residual or recurrent disease was clinically suspected during follow-up in patients treated with radiotherapy, additional CT and biopsy were performed to verify disease status. Persistent or increased edema, impaired vocal cord mobility, local ulceration, or persistent complaints of pain, otalgia, or swallowing problems were reasons for suspecting progression of disease. If residual or recurrent disease was confirmed by biopsy, patients were scheduled for total laryngectomy.

PET

Dynamic ^{11}C-TYR PET studies were performed on all patients at least 2 wk after biopsy (median, 16 d; range, 15–29 d). ^{11}C-TYR was produced via a modified microwave-induced Bücherer-Strecker synthesis (*11*). The synthesis time was 40 min, including high-performance liquid chromatography purification, with a radiochemical purity of more than 99%.

The PET images were acquired using an ECAT 951/31 PET camera (Siemens/CTI). This device has a 56-cm-diameter patient aperture and acquires 31 planes simultaneously. The axial field of view is 10.8 cm, and the resolution is 6 mm in full width at half maximum. The head of the patient was fixed in position with the Frankfurter horizontal plane (line between the external acoustic meatus and the lower orbital rim) making an angle of 110° with the horizontal bed position. Patients fasted for at least 8 h (except for water and their usual medication) before the study.

A venous cannula was placed in the antecubital vein of the forearm for injection of ^{11}C-TYR. In the radial artery of the contralateral arm, an arterial cannula was placed under local anesthesia to allow for rapid blood sampling. Before injection of ^{11}C-TYR, a 20-min transmission scan was obtained to correct for photon attenuation by body tissues in the imaged area. ^{11}C-TYR was administered intravenously over a 1-min period. The injected dose varied from 144 to 400 MBq (median, 369 MBq). Dynamic scanning with 16 time frames was performed from the time of injection to 50 min after injection at the level of the tumor. The protocol included ten 30-s images, three 5-min images, and three 10-min images. Arterial blood samples were taken simultaneously at set time points (0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2.25, 2.75, 3.75, 4.75, 7.5, 12.5, 17.5, 25, 35, and 45 min after injection) to assess the ^{11}C-TYR plasma time–activity curve, $^{11}CO_2$ concentration, and other ^{11}C-labeled metabolites by radiolabeled high-performance liquid chromatography (*6*). The plasma tyrosine levels ranged from 0.031 to 0.090 mmol/L, which is within the reference range for our laboratory and in accordance with values reported in the literature.

Data Analysis

PET acquisition data were reconstructed using filtered backprojection and a 0.5 cycle/pixel Hann filter to obtain transaxial images, which were displayed by applying standard ECAT software.

To determine primary tumor PSR, a region of interest was placed in the plane with the most intense uptake at the site of the tumor as observed at visual analysis, using a 70% threshold of maximum intensity. The tissue time–activity curve obtained from this region of interest, together with the plasma-input data (MBq of ^{11}C-TYR per milliliter, corrected for $^{11}CO_2$ and ^{11}C-labeled proteins), were used to calculate PSR in nanomoles per milliliter of tumor tissue per minute (nmol/mL/min) using a modified Patlak analysis as published earlier (*6*). By visually masking nontumor regions with physiologically high uptake of ^{11}C-TYR (e.g., salivary glands), these regions were prevented from contributing to the average tumor time–activity curve. Also, less elaborate semiquantitative analyses were performed by calculating standardized uptake values (SUV) and estimating tumor-to-nontumor ratio (T/N) to compare absolute quantification (PSR) with semiquantitative methods. The SUV based on body weight (SUV_{BW}) was defined as the tumor tissue activity (MBq/mL) in a region of interest, as measured by PET, divided by the injected dose (MBq) per kilogram of body weight. In addition, nontumor uptake was assessed from the right trapezius muscle and T/N could be calculated. SUV_{BW} and T/N were calculated from the summed data obtained from the last 3 frames (20–50 min after injection) to create a single static scan.

Statistical Analysis

Cumulative survival was assessed using the product-limit method of Kaplan–Meier, and the log-rank test was used to compare survival between the groups. The relative importance of prognostic factors was analyzed using the Cox proportional hazards model. The Mann–Whitney *U* test was used to compare differences in PSR between the groups. All *P* values were 2-tailed, and $P < 0.05$ was considered to be statistically significant.

RESULTS

In 34 patients with primary squamous cell carcinoma of the larynx, dynamic ^{11}C-TYR PET was performed before definitive treatment. The patient characteristics and clinical data are listed in Table 1. To summarize, 47% glottic, 50% supraglottic, and 3% transglottic laryngeal carcinomas, all

TABLE 1
Patient Characteristics

Characteristic	No. of patients
Sex	
Male	31
Female	3
Primary site	
Glottic	16
Supraglottic	17
Transglottic	1
Primary tumor stage	
T1	3
T2	18
T3	5
T4	8
Lymph node stage	
N0	24
N1	3
N2	7
N3	0
UICC stage	
I	3
II	15
III	5
IV	11

UICC = International Union Against Cancer (*10*).

with tumor diameters larger than 1.5 cm, were included in the study. The tumor stage contained 3 T1, 18 T2, 5 T3, and 8 T4 primary tumors.

In the qualitative evaluation of ^{11}C-TYR PET studies, all 34 primary malignancies were identified correctly (Fig. 1). No results were false negative. Of the 10 patients with lymph node metastases (N1 in 3, N2 in 7) clinically staged by physical examination and CT (*10*), the N2 patients and 1 N1 patient were clearly identified by ^{11}C-TYR PET. In the 2 other clinically staged N1 patients, metastases were not adequately shown by PET, but neither cytologic nor histologic confirmation was performed for either of these subjects. The parotid, submandibular, and sublingual glands showed high uptake in all cases.

PET results, treatment modalities, and follow-up are listed in Table 2. The tumor PSR ranged from 0.72 to 6.96 nmol/mL/min, with a median of 2.01 nmol/mL/min. The median SUV_{BW} and T/N of tumor tissue were 4.22 (range, 1.42–7.34) and 4.64 (range, 1.69–9.09), respectively. In 6 patients only SUV and T/N could be calculated, because of the absence of arterial cannulation for technical reasons.

Cumulative survival was assessed between patients with tumor PSR equal to or higher than the median (2.0 nmol/mL/min) and those with tumor PSR lower than the median. The median was the most optimal cutoff value and demonstrated an insignificant difference ($P = 0.07$) in outcome between the groups (Fig. 2).

When patients treated with primary radiotherapy ($n = 20$) were evaluated separately, a significant difference ($P = 0.03$) was found in survival rate between patients with tumor PSR equal to or higher than the median (5-y survival rate, 30%) and those with tumor PSR lower than the median (5-y survival rate, 73%). Figure 3 shows the cumulative survival curves (Kaplan–Meier) of the 2 groups. The median PSR values of the high-PSR group and the low-PSR group were 2.38 nmol/mL/min (range, 2.06–3.30 nmol/mL/min) and 1.39 nmol/mL/min (range, 0.72–1.95 nmol/mL/min), respectively. A tumor PSR higher than the median tended to be related to poor survival. No marked differences in clinical factors were present between the 2 groups (Table 3), except for a small difference in histologic grade. The low-PSR group contained more highly differentiated tumors, but in multivariate analysis tumor grade had no independent influence on survival.

Similarly, the survival of patients with an SUV_{BW} higher than the median (4.22) and a T/N higher than the median (4.22) differed significantly ($P < 0.05$) from patients with SUVs lower than the median. When the quantitative parameters were corrected for age in a multivariate analysis (Cox proportional hazards model), only PSR ($P = 0.049$; relative risk, 4.2; 95% confidence interval, 1.0–17.2) had an independent influence on survival.

In the group of patients treated with primary surgery, no differences were found in survival times between the group with values higher than and the group with values lower than the median quantitative values.

When pretreatment PSR was used for the evaluation of therapy outcome after radiotherapy, no significant differences ($P = 0.08$) in PSR values were observed between patients with recurrent disease (median, 2.17 nmol/mL/min; range, 1.58–3.30 nmol/mL/min) and patients without recurrence (median, 1.47 nmol/mL/min; range, 0.72–3.14 nmol/mL/min) during follow-up. In the search for a cutoff value, differences in recurrence rates were observed between patients with a PSR higher than the median (recurrence rate, 50%) and patients with a PSR lower than the median (recurrence rate, 17%), but PSR was not a predictive factor of recurrent disease in univariate analysis.

DISCUSSION

Choosing the optimal treatment for an individual with squamous cell carcinoma of the head and neck is a chal-

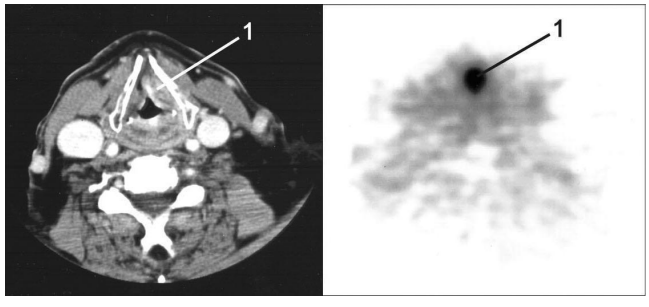

FIGURE 1. Transaxial CT and ^{11}C-TYR PET scans of patient 28, with T3 N0 supraglottic squamous cell carcinoma (1), show increased ^{11}C-TYR uptake in tumor.

TABLE 2
PET Results, Treatment, and Follow-up Data

Patient no.	Sex	Age (y)	Tumor and node stage	PSR*	SUV	T/N	Therapy	Follow-up	
								Finding	Months
1	M	60	T4 N0	4.16	7.34	9.09	OP + RT	NED	32
2	M	43	T3 N0	2.40	4.60	5.81	OP + RT	NED	73
3	M	67	T2 N0	2.16	4.46	4.73	RT	DOD	9
4	M	81	T3 N2	2.32	5.43	4.88	OP + RT	DOD	32
5	M	69	T1 M0	1.14	2.43	2.42	RT	NED	35
6	M	76	T2 N0	1.14	4.22	4.79	RT	DOD	24
7	M	55	T1 N0	0.89	1.60	1.81	RT	NED	40
8	M	70	T4 N2	NA	3.95	3.73	OP + RT	DOD	8
9	M	54	T2 N0	1.58	3.55	4.69	RT	REC	8
								DOD	32
10	M	50	T4 N2	NA	6.25	7.32	OP + RT	NED	46
11	M	56	T1 N0	0.72	1.42	1.69	RT	NED	56
12	M	66	T2 N0	0.82	2.29	4.23	RT	NED	69
13	F	58	T2 N0	1.35	4.23	5.40	RT	DOD	44
14	M	55	T4 N0	1.38	3.45	3.70	OP + RT	DOD	20
15	M	54	T2 N0	1.43	2.59	2.33	RT	NED	56
16	M	75	T4 N2	NA	6.95	7.20	OP + RT	DOD	15
17	M	64	T2 N0	1.44	1.85	3.01	RT	NED	70
18	M	43	T2 N1	1.51	2.91	2.20	RT	NED	67
19	M	44	T2 N0	1.66	4.07	3.21	RT	REC	8
								NED	66
20	F	52	T4 N0	NA	3.87	4.71	OP + RT	NED	45
21	M	59	T2 N0	1.95	4.26	4.96	RT	NED	64
22	M	63	T2 N0	2.06	3.79	3.90	RT	REC	14
								DOD	25
23	M	68	T2 N0	2.19	3.23	3.33	RT	DOD	40
24	M	46	T2 N0	2.28	4.20	4.67	RT	REC	7
								NED	56
25	M	56	T2 N2	2.48	5.49	4.89	OP + RT	NED	65
26	M	57	T3 N2	NA	4.68	6.26	OP + RT	NED	47
27	M	79	T2 N0	2.50	5.21	4.22	RT	DOD	19
28	M	63	T3 N0	2.62	6.61	6.46	OP + RT	DOD	10
29	M	59	T2 N1	2.68	5.88	5.08	RT	REC	17
								DOD	42
30	M	63	T4 N0	2.81	5.52	5.48	OP + RT	NED	42
31	M	52	T2 N0	3.14	5.47	4.48	RT	NED	59
32	M	65	T2 N0	3.30	5.21	4.66	RT	REC	12
								DOD	35
33	M	53	T3 N0	3.75	4.82	4.54	OP	NED	33
34	M	61	T4 N2	NA	3.92	3.68	OP + RT	NED	49

*Data are nmol/mL/min.

OP + RT = surgery with postoperative radiotherapy; NED = no evidence of disease; RT = radiotherapy; DOD = dead of disease; NA = not available; REC = recurrent disease; OP = surgery of the primary site or neck dissection.

lenge because of the unpredictable clinical behavior of this malignancy. TNM classification is the only independent prognostic value but has limitations in the management of a particular patient with laryngeal cancer (*12*). In patients with T2, T3, and small T4 laryngeal carcinomas, a more accurate way of determining which will and which will not have a total response to radiotherapy is needed to help with selection of the therapy and evaluation of prognosis. Because we were interested in gaining insight into the prognosis of laryngeal carcinoma based on ^{11}C-TYR uptake, we also included patients with T1 carcinomas.

When using ^{18}F-FDG PET to study untreated head and neck tumors, Minn et al. (*3*) found that high ^{18}F-FDG uptake was associated with poor prognosis. This finding suggests that ^{18}F-FDG PET may predict survival in head and neck cancer. Previous studies on other tumors suggested that a relatively low ^{18}F-FDG uptake before therapy indicates a good response to the subsequent treatment and that high ^{18}F-FDG uptake indicates a poor response (*13,14*). However, the drawbacks of ^{18}F-FDG for monitoring therapy, such as accumulation of the tracer in benign tumors and inflammatory tissue, have led to the application of other radiotracers (*4*).

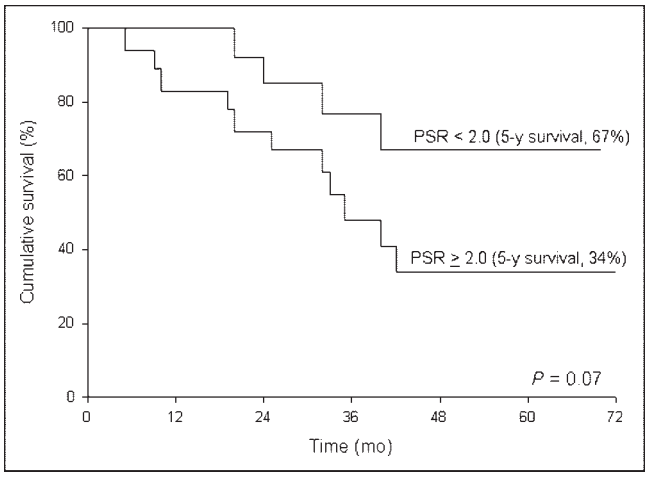

FIGURE 2. Cumulative survival of patients with T1–T4 laryngeal carcinomas (n = 34). Differences between patients with tumor PSR equal to or higher than the median (2.0 nmol/mL/min) and patients with tumor PSR lower than the median are demonstrated (P = 0.07).

L-[methyl-^{11}C]-methionine (MET) is the most frequently used radiolabeled amino acid, and head and neck cancer has been extensively investigated with ^{11}C-MET PET (*15,16*). In a recent study on the prediction of clinical outcome by ^{11}C-MET PET, no relationship was found between the calculated SUV and the length of survival (*17*). ^{11}C-MET is involved in several metabolic pathways, such as transmethylation and polyamine synthesis, and is converted in *S*-adenosylmethionine, potentially leading to the accumulation of nonprotein metabolites in tumor tissue (*18*). The complicated metabolism of methionine has made it impossible to construct a precise metabolic model, and quantification with this radiotracer is therefore difficult if not impossible. Lindholm et al. (*17*) suggested that more specific PET tracers, such as ^{11}C-TYR, are needed for basic studies on cancer biology. They stated also that because ^{11}C-TYR uptake is related to PSR, investigation of the association between tumor ^{11}C-TYR uptake and prognosis in head and neck cancer would be of interest. Recently, the feasibility of ^{11}C-TYR PET for detection and PSR quantification of squamous cell carcinoma of the larynx and hypopharynx has been demonstrated (*5*).

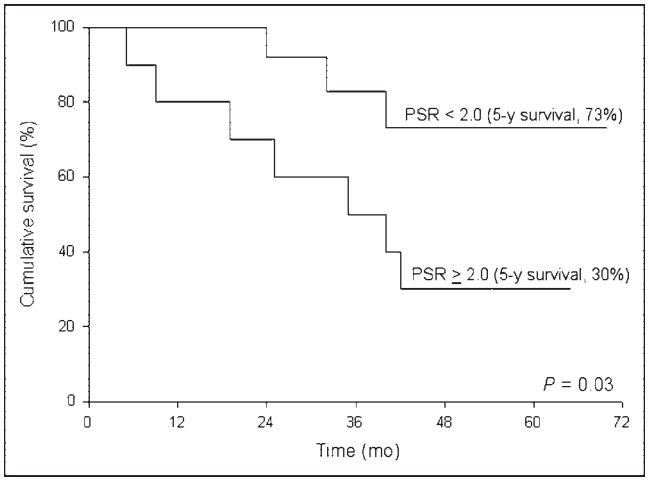

FIGURE 3. Survival curves (Kaplan–Meier) for patients with laryngeal carcinomas treated with primary radiotherapy (n = 20). Significant differences (P = 0.03) are demonstrated between patients (n = 9) with tumor PSR equal to or higher than the median (2.0 nmol/mL/min) and patients (n = 11) with tumor PSR lower than the median.

TABLE 3
Patient Characteristics According to Median PSR (2.0 nmol/mL/min)

Characteristic	No. of patients: PSR < median (n = 11)	No. of patients: PSR ≥ median (n = 9)
Sex		
Male	10	8
Female	1	1
Age (y)		
≤64	6	4
>64	5	5
Type		
Glottic	7	6
Supraglottic	4	3
Primary tumor stage		
T1	3	0
T2	8	9
Lymph node stage		
N0	10	7
N1	1	1
N2	0	0
UICC stage		
I	3	0
II	8	7
III	0	1
IV	0	1
Histologic grade		
G1	5	2
G2	4	5
G3	1	1
Gx	1	1

UICC = International Union Against Cancer (*10*).

Nearly all amino acids have been radiolabeled to study potential imaging characteristics, but mainly ^{11}C-MET and ^{11}C-TYR have been studied with regard to the ease of synthesis, biodistribution, and formation of radiolabeled metabolites in vivo. More recently, artificial amino acids such as L-3-^{18}F-fluoro-α-methyltyrosine and *O*-2-^{18}F-fluoroethyl-L-tyrosine (FET), L-3-^{123}I-iodo-α-methyl-tyrosine, 1-aminocyclopentane carboxyl acid, α-aminoisobutyric acid, ^{18}F-fluoro-L-phenylalanine, and [^{11}C-methyl]-α-aminoisobutyric have been studied (*18*). Special interest should be taken in artificial tyrosine analogues, such as FET, which demonstrate results comparable to those of ^{11}C-MET. FET is not metabolized or incorporated into proteins and therefore is thought to reflect the rate of amino acid transport rather than protein synthesis (*19*).

In the present study, a significant relationship was observed between ^{11}C-TYR uptake and survival in patients with laryngeal carcinoma treated by radiotherapy. A PSR, SUV_{BW}, and T/N higher than the median values correlated with poor prognosis, and quantitative values of individual tumors may therefore predict radiocurability. ^{11}C-TYR PET may have a future role in the strategy for treating laryngeal cancer, in particular for planning radiotherapy. However, for clinical practice, recurrence of disease after radiotherapy is also of interest. Because we demonstrated no statistically significant difference ($P = 0.08$) between PSR values of patients with and patients without recurrent disease, the predictive value of PSR for disease recurrence remains unclear. The small number of recurrences ($n = 6$) in this study could be a possible explanation for this observation, and future investigations are necessary to assess whether PSR has value for predicting disease recurrence.

Our study included patients with different tumor stages, but all tumors were larger than 1.5 cm in diameter. Because this diameter is more than twice the resolution of the PET camera, the influence of partial-volume effects and of underestimation of ^{11}C-TYR uptake in smaller lesions seems negligible in our series.

The dispersion of the quantitative values of the 2 groups is, however, a matter of concern, and larger series of patients are needed to assess the optimal cutoff value of ^{11}C-TYR PET for therapy planning. Furthermore, we did not observe a difference in survival for patients with larger tumors treated by surgery, suggesting the influence of other factors on metabolic tumor activity.

Although tracer uptake in head and neck tumors and other malignancies may be assessed in a simple, qualitative way, our study supports quantitative tumor-activity evaluation that adds information not available with other modalities. Although PSR was the only independent prognostic factor in multivariate analysis, we observed comparable results in predicting survival between PSR and SUV_{BW} in univariate analysis. SUV calculations are preferable to absolute quantification (PSR) because of the absence of arterial sampling and the reduction in scanning time. These qualities would also improve the applications of ^{11}C-TYR PET and other amino acid tracers for clinical routine use. Whether pretreatment SUV is an independent predicting factor has to be investigated in larger series.

In this study, we observed a small difference in histologic grade between the 2 groups of patients who underwent radiotherapy. ^{11}C-TYR PET of in vivo tumor metabolism is currently under investigation—as is the in vitro biologic activity of laryngeal carcinomas as reflected by tumor grade, number of mitoses, and amount of proliferating cells—to evaluate the association between histopathologic parameters and PSR.

CONCLUSION

Predicting the survival of patients undergoing radiotherapy for laryngeal squamous cell carcinoma is feasible through the use of ^{11}C-TYR PET to quantify tumor uptake of tracer before treatment. Survival differed significantly between patients with ^{11}C-TYR uptake equal to or higher than the median and those with ^{11}C-TYR uptake lower than the median. Multivariate analysis proved that PSR was an independent predictor of survival, but PSR was not a distinct predictor for disease recurrence. However, pretreatment quantitative ^{11}C-TYR PET may have an additional role in the planning of therapy for squamous cell carcinoma of the head and neck.

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