Carbon-11-Methionine and PET Is an Effective Method To Image Head and Neck Cancer

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Methionine metabolism is altered in cancer, and methionine labeled with ^{11}C has been successfully used for imaging of brain, lung, and breast cancer and lymphoma. Uptake of L-[methyl-^{11}C]methionine (^{11}C-methionine) in head and neck cancer of 23 patients was studied with PET. Accumulation of ^{11}C-methionine in the tumors was assessed by two different methods: the influx constant, K_i, and the standardized uptake value (SUV). All 23 cancers accumulated ^{11}C-methionine. The mean K_i was 0.147 ± 0.070 min^{-1} and the mean SUV 8.5 ± 3.5. There was a strong correlation between the two measures of tumor uptake ($r = 0.92$, $p < 0.0001$). There was no correlation between the uptake of ^{11}C-methionine and the histological grade of cancer. Head and neck cancer can thus be effectively imaged with ^{11}C-methionine. Carbon-11-methionine PET imaging may be useful in delineating tumors for therapy planning.

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Cancer of the head and neck has usually not given rise to distant metastases when first detected, and it is, therefore, often potentially curable by locoregional therapy only. If treatment of head and neck cancer is to be successful, the extent of the primary tumor and nodal metastases needs to be known with accuracy for planning of appropriate treatment strategies. This may be difficult with the available imaging techniques, such as ultrasonography, computed tomography and magnetic resonance imaging. Thus far, there has been no general nuclear medicine procedure available for imaging various types of head and neck cancer.

Methionine is needed for protein synthesis and as a precursor of S-adenosylmethionine. S-Adenosylmethionine is the most important methyl group donor, and it is a precursor of polyamine synthesis. These reactions are accelerated in malignant cells (*1*). Hence, radiolabeled methionine is a potential agent to image cancer, and L-[methyl-^{11}C]methionine (^{11}C-methionine) has been successfully used to image human brain tumors, lung cancer, breast cancer, and lymphoma (*2–5*). Furthermore, there is some evidence that its uptake may be associated with the histological grade of cancer (*2,3*).

The aim of this study was to investigate whether human head and neck cancer can be imaged with ^{11}C-methionine and PET and to study the association between the uptake of ^{11}C-methionine and the histological grade of cancer.

PATIENTS AND METHODS

Patients

Twenty-three consecutive patients who were admitted to this institution for evaluation of head and neck cancer were studied. None of the patients received therapy for cancer before the PET study. The patient and tumor characteristics are given in Table 1. Eighteen patients had squamous-cell carcinoma, one had anaplastic small-cell carcinoma, one adenocarcinoma, one transitional cell carcinoma, one malignant schwannoma, and one acinar cell carcinoma of the salivary gland. The maximum diameter of the tumors ranged from 20 to 120 mm. Seven patients had regional lymph node metastases from 15 to 30 mm in diameter. The nature of the lymph node metastases was confirmed by histological examination or by fine-needle aspiration. Staging of the tumors followed the UICC TNM-classification (1987). Histological grading of the tumors was done according to the WHO classification (*6*). All patients had a light low-protein breakfast 3–4 hr before the PET study.

All patients gave informed consent, and the study was approved by the Ethical Committee of Turku University Central Hospital.

PET Imaging

An ECAT PET scanner type 931/08-12 was used for imaging. The device acquires 15 contiguous slices simultaneously with a slice thickness of 6.7 mm; the full width at half maximum is 6.1 mm transaxially in the center of the field of view (*7*).

Carbon-11-methionine was produced at the Turku Medical Cyclotron Laboratory as described in detail (*8,9*). The radiochemical purity of ^{11}C-methionine was over 91%.

Transmission scanning was performed for attenuation correction immediately before the emission scan. After the transmission scanning, ^{11}C-methionine (280 ± 50 MBq, mean ± s.d.) was injected into a peripheral vein of the upper extremity. Following the injection, dynamic scanning was performed for 40 min.

The PET images were compared with the computed tomography images by visual alignment for 15 patients.

Blood Sampling

Frequent venous blood samples were taken from an antecubital vein contralateral to the injection site. The hand and arm

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TABLE 1
Patient and Tumor Characteristics

Patient no.	Age/Sex	Location	Histology	Histologic grade	K_i	SUV	TNM	Metastasis K_i	Metastasis SUV
1	36/M	Hard palate	SCC	II	0.072	2.9	T2N0M0		
2	67/M	Nasal cavity	AC	II	ND	3.7	T4N0M0		
3+	70/M	Neck metastasis	ASC	II	0.058	3.8	TXN2M0		
4	62/F	Neck	MS	III	0.049	4.8	T4N0M0		
5	66/M	Neck metastasis	SCC	II	0.079	5.6	TXN3M0		
6	49/M	Parotid region	SCC	II	0.080	6.6	T4N1M0	NFV	
7	41/M	Floor of mouth	SCC	II	0.102	6.9	T2N0M0		
8	64/M	Larynx	SCC	I	0.120	7.4	T3N2M0	0.132	8.8
9	49/F	Hypopharynx	SCC	I	0.150	7.4	T4N0M0		
10	80/M	Facial skin	ACC	—	0.108	7.8	T2N0M0		
11	85/F	Maxillary sinus	TCC	—	ND	8.2	T4N0M0		
12	58/M	Tonsil	SCC	II	0.140	8.5	T4N1M0	NFV	
13	79/M	Nasopharynx	SCC	III	0.115	9.0	T4N0M0		
14	65/M	Lip	SCC	II	0.131	9.0	T1N0M0		
15	83/M	Facial skin	SCC	I	0.169	9.2	T2N0M0		
16	62/M	Larynx	SCC	II	0.182	9.2	T3N1M0	0.086	4.5
17	38/M	Tongue	SCC	II	0.222	9.3	T4N1M0	0.081	6.8
18	62/M	Gingiva	SCC	II	0.184	9.6	T4N2M0	0.197	9.2
19	56/M	Gingiva	SCC	II	0.193	9.8	T3N1M0	NFV	
20	73/M	Larynx	SCC	II	ND	12.3	T3N0M0		
21	71/M	Maxillary sinus	SCC	I	0.222	12.5	T4N0M0		
22	66/M	Maxillary sinus	SCC	I	0.253	14.6	T4N0M0		
23	73/M	Maxillary sinus	SCC	III	0.310	18.3	T4N0M0		

SCC = squamous-cell carcinoma, AC = adenocarcinoma, MS = malignant schwannoma, TCC = transitional cell carcinoma, ACC = schwannoma cell carcinoma, ASC = anaplastic small-cell carcinoma, + = metastatic relapse, ND = not defined, and NFV = not in the field of view.

were warmed with a pad. The blood samples were immediately centrifuged, and the radioactivity of the plasma was determined. The low molecular weight fraction of the plasma taken at 20, 40 and 60 min after injection was separated by fast-gel filtration using Sephadex PD-10 columns (Pharmacia Fine Chemicals, Uppsala, Sweden) for radioactivity measurements (*10*).

Analysis of PET Data

Several regions of interest (ROIs) were selected from the total tumor tissue, because ^{11}C-methionine accumulation was heterogenous in several cases. The ROI with the highest average radioactivity concentration at 35–40 min after injection was copied to all frames, and a time-activity curve was used for analysis. The size of the ROIs was always smaller than the total tumor area per plane, ranging from 20 to 55 pixels. The relative standard deviation of the measured average radioactivity in the area of the ROI was less than 10% in the last frames of each study.

Standardized uptake values (SUV) were calculated for each patient as follows:

$$\text{SUV} = \frac{\text{Average radioactivity in ROI (Bq/cm}^3\text{)}}{\text{Dose (Bq)/weight of the patient (g)}}$$

where average radioactivity is the radioactivity measured by PET, corrected for calibration and decay. The dose is the injected tracer dose. The ROIs with maximum average counts in the last frame from 35 to 40 min after injection were selected to represent ^{11}C-methionine uptake in the tumors.

A graphical approach according to Patlak et al. (*11*) was used to analyse the kinetics of ^{11}C-methionine uptake. With this method, normalized plasma time values are plotted on the horizontal and tissue activity values divided by plasma activity values on the vertical axis:

$$x(T) = \int_0^T C_p(t)\,dt/C_p(T)$$

$$y(T) = C_n(T)/C_p(T),$$

where $C_p(t)$ is the radioactivity concentration of the low molecular weight fraction of plasma at time t, T is frame mean time after injection and $C_n(T)$ is tracer concentration of tumor tissue at time T. If the assumptions of the Patlak model are met, a straight line with a slope of K_i (influx constant) is obtained, when y(T) is plotted against x(T). K_i represents the accumulation rate of the tracer from plasma to the irreversible tissue compartment.

The influx constant was calculated from the last seven data points in the Patlak curve representing the evaluation time from 11 min after injection to the end of the study.

Statistical Analysis

The correlation between the K_i values and the SUV was calculated by linear regression. All p values are two-tailed. A p value of <0.05 was considered statistically significant.

RESULTS

In all 23 patients, head and neck cancer accumulated ^{11}C-methionine, but the intensity of the uptake varied

considerably among patients (Table 1). The K_i values ranged from 0.049 min^{-1} to 0.310 min^{-1} (mean 0.147 ± 0.070 min^{-1}) and the SUVs from 2.9 to 18.3 (mean 8.5 ± 3.5). There was a close correlation between the uptake rate of ^{11}C-methionine (K_i) and the SUVs calculated at 35–40 min after injection ($r = 0.92$, $p < 0.0001$, (y) = 46.3 (x) + 1.8, standard error of the (y) estimate 1.3, standard error of the (x) coefficient 4.1, Fig. 1). The Patlak plots were found to be linear (r^2 ranged from 0.9713 to 0.9925, $p < 0.001$).

There was clinical evidence of regional metastatic spread of the disease in seven patients, but in three the metastatic nodes were outside the field of view. In two patients, the uptake in a cervical nodal metastasis was of similar magnitude as in the primary tumor (Patients 8 and 18), and in the remaining two it was lower than that in the primary tumor (Patients 16 and 17). The lower uptake measured in these nodal metastases may be affected by their small size (diameter 15 mm).

The uptake of ^{11}C-methionine was generally higher in head and neck cancer than in the bone marrow (mean K_i of the bone marrow 0.091 ± 0.029 min^{-1}, n = 17; mean SUV 5.5 ± 1.4; n = 17), the parotid gland (mean K_i 0.072 ± 0.022 min^{-1}, n = 21; SUV 4.4 ± 1.0, n = 26), the submandibular gland (mean K_i 0.078 ± 0.022 min^{-1}, n = 28; SUV 4.5 ± 1.0, n = 30), the lacrimal gland (mean K_i 0.044 ± 0.006 min^{-1}, n = 4; SUV 2.7 ± 0.3; n = 4) and the cerebellum (mean K_i 0.027 ± 0.010, n = 3; SUV 2.2 ± 0.7, n = 5) (Fig. 2). There was a strong correlation between the K_i and SUV values of ^{11}C-methionine accumulation in normal tissues ($r = 0.79$, $p < 0.001$, n = 73, (y) = 39.5(x) + 1.5, standard error of the (y) estimate 0.8, standard error of the (x) coefficient 3.6, Fig. 3).

There was no correlation between the accumulation of ^{11}C-methionine and the histopathological grade of head and neck cancer (Figs. 4 and 5). Similarly, there was no correlation between the quantitative uptake data of ^{11}C-methionine and the size of the tumor. Computed tomography scans were compared visually with the PET images in 15 cases, and tumor localization and its extent in the PET image corresponded well with those in computed tomography scans in all cases, although delineation of the tumors was better visualized on the PET image (Fig. 6).

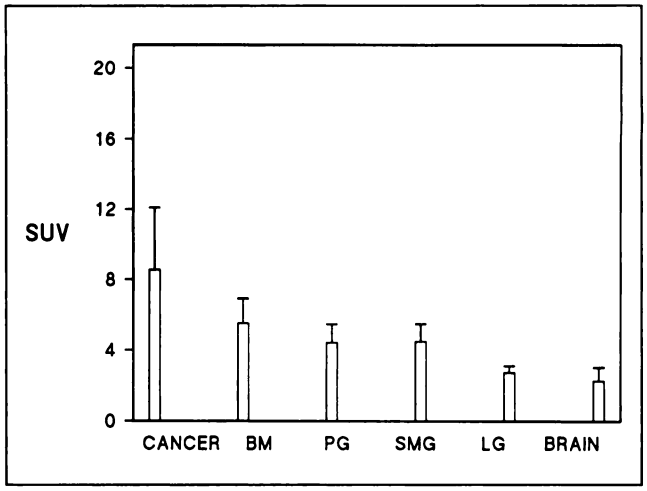


FIGURE 2. Mean uptake of ^{11}C-methionine in head and neck cancer (n = 23), bone marrow (BM, n = 17), parotid gland (PG, n = 26), submandibular salivary gland (SMG, n = 30), lacrimal gland (LG, n = 4) and cerebellum (brain, n = 5). The standard deviation is indicated by bars.

DISCUSSION

Carbon-11-methionine accumulated in all 23 head and neck cancers with varying histology and histological

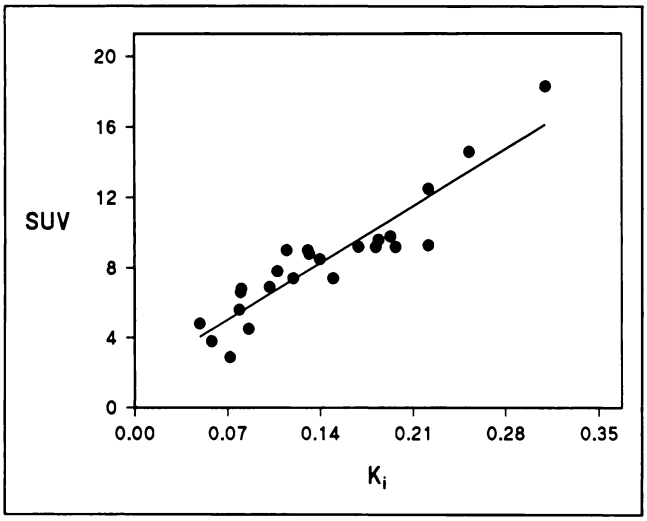


FIGURE 1. Correlation between influx constant (K_i) and standardized uptake value (SUV) in head and neck cancer (n = 20) and their metastases (n = 4) ($r = 0.92$, $p < 0.0001$, n = 24, (y) = 46.3 (x) + 1.8, standard error of the (y) estimate 1.3, standard error of the (x) coefficient 4.1).

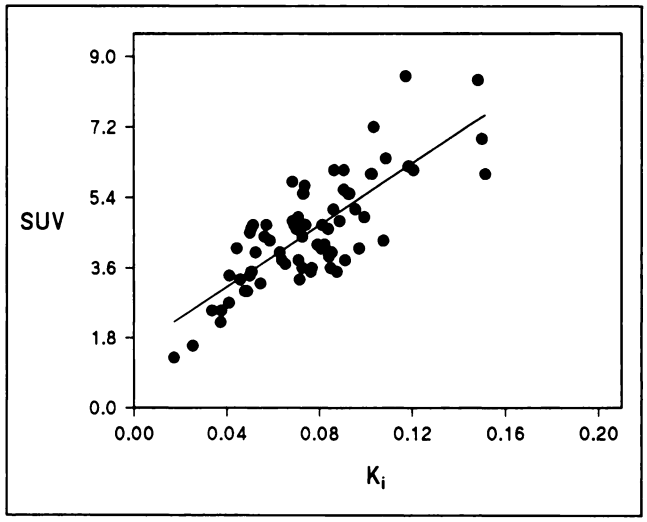


FIGURE 3. Correlation between the influx constant K_i and the SUVs of bone marrow, salivary glands, lacrimal glands and cerebellum ($r = 0.79$, $p < 0.0001$, n = 73, (y) = 39.5 (x) + 1.5, standard error of (y) estimate 0.8, standard error of (x) coefficient 3.6).

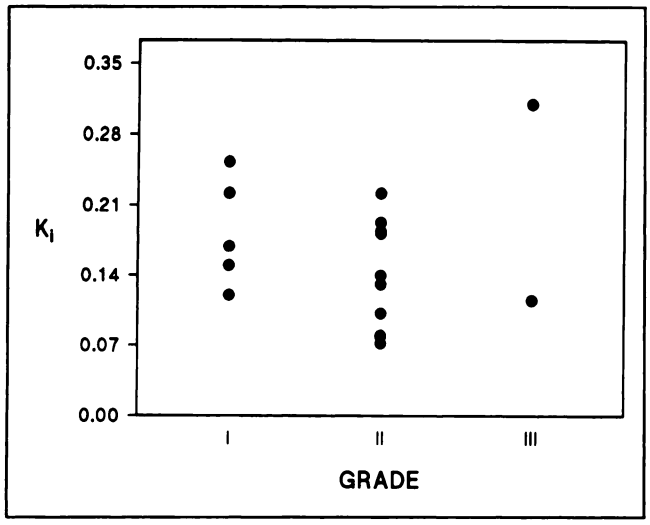


FIGURE 4. Uptake of ^{11}C-methionine, assessed by the influx constant K_i as compared to the histological grade in squamous-cell carcinoma of the head and neck region.

grades. Carbon-11-methionine imaging with PET is an effective method for evaluating head and neck cancer and, apparently, other types of human cancer (*2–5*). Furthermore, PET images of the tumors appeared to correlate well with the extent of cancers determined by other methods. We are therefore evaluating the role of PET imaging in radiotherapy treatment planning. Mosskin et al. have postulated that brain tumors can be more accurately delineated with ^{11}C-methionine PET than by computed tomography (*12*). Normal tissues such as the bone marrow and the salivary glands, however, accumulate ^{11}C-methionine, which may impair the detection of small tumors with a low uptake.

There was no association between ^{11}C-methionine uptake and histological grade (Figs. 4 and 5). In light of this finding, tumor studies with [^{18}F]fluorodeoxyglucose and PET have found no correlation between tracer uptake and

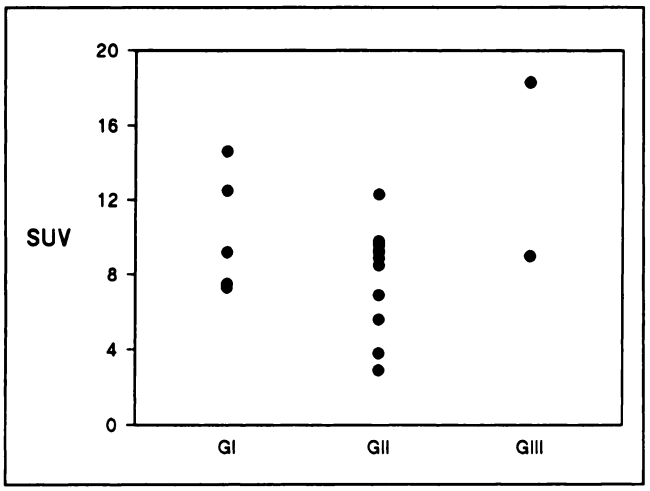
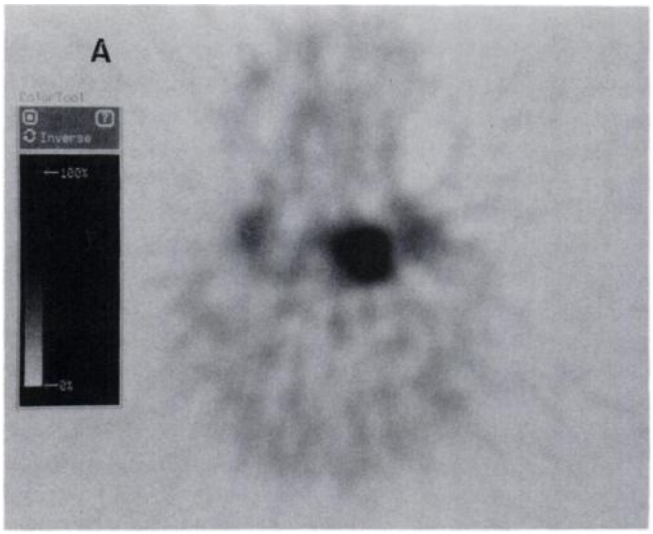


FIGURE 5. The uptake of ^{11}C-methionine, measured as SUV, as compared to the histological grade in squamous-cell carcinoma of the head and neck region.



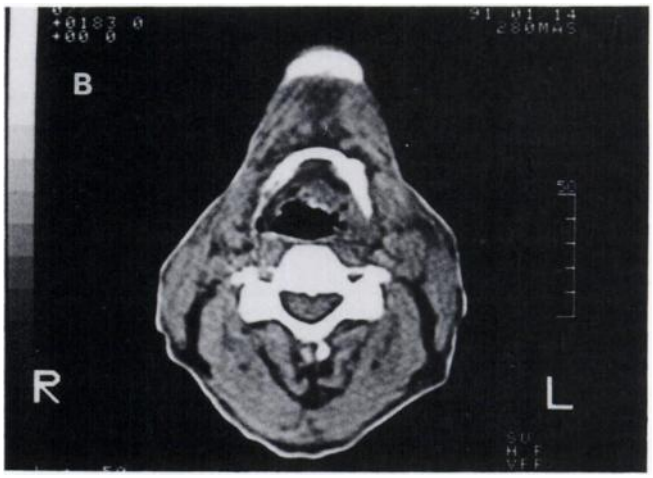


FIGURE 6. A ^{11}C-methionine PET image (A) and a computed tomography scan (B) taken from the same level in Patient 16.

histological grade of head and neck cancer, but an association between the size of the S-phase fraction of the cell cycle measured with flow cytometry and the uptake of [^{18}F]fluorodeoxyglucose has been found in head and neck cancer (*13,14*). Carbon-11-methionine uptake has been reported to be associated with histological grade in both lung cancer and glioma (*2,3*). The assessment of histological grade is, however, notoriously subjective, and the S-phase fraction assessed by flow cytometry may be a more appropriate measure of cancer aggressiveness (*15*). Further studies are needed to evaluate whether the uptake of ^{11}C-methionine is associated with the size of the S-phase fraction or other measures of cell proliferation in head and neck cancer.

The uptake of ^{11}C-methionine was surprisingly high in all three squamous-cell carcinomas of the maxillary sinus with varying histological grades (two patients had Grade I and one patient had Grade III tumors). These patients had a large tumor with a rapidly fatal clinical course. An accompanying inflammatory process may not explain the high uptake of ^{11}C-methionine because the uptake of ^{11}C-

methionine has been reported to be low in benign lesions (*16*). There was no significant accumulation of ^{11}C-methionine in an inflammatory process induced by carragenan and croton oil in the rat (*17*), but we have detected some uptake of ^{11}C-methionine in an abscess (*4*). Further studies are needed to examine whether cancers of the maxillary sinus have a tendency to accumulate particularly high amounts of ^{11}C-methionine.

There was a strong correlation between K_i values and SUVs. The correlation was somewhat weaker when normal tissues were analyzed, possibly because of the poorer statistics caused by lower activity in the normal tissue ROIs. The graphical analysis method of Patlak et al. (*11*) is an established method to estimate the rate of [^{18}F] fluorodeoxyglucose uptake, and the method also appears to be of value in ^{11}C-methionine studies (*5,18*). This method allows easy calculation of tracer uptake rate from plasma to tumor.

Bustany et al. have presented a three-compartment model for measuring the protein synthetic rate in the normal brain with ^{11}C-methionine and PET (*19,20*), but the use of the model seems to be inadequate in tumors where the transmethylation and polyamine synthesis rates are accelerated (*1,21,22*). The graphical approach of Patlak et al. measures the influx rate in the irreversible compartment, and its calculation is based on the measured tissue and blood data, while the three-compartment model includes assumptions, such as a negligble k_4, which cannot be assessed in a 40-min scanning time. The three-compartment model has been applied to ^{11}C-methionine brain PET study by Ericson et al., who concluded that the accumulation rate of ^{11}C-methionine in the normal brain tissue is similar if calculated with the three-compartment model or with the Patlak method (*23*).

Because of the rapid metabolism of ^{11}C-methionine in the blood, ^{11}C-methionine needs to be separated from the plasma for uptake rate measurements. This is conveniently achieved by measuring the radioactivity concentration of the low molecular weight fraction of the plasma (*5,10*). In this study, however, the uptake rate measurements (K_i values) did not give additional information as compared to the simpler SUV analysis.

In summary, head and neck cancers of varying histology can be imaged with ^{11}C-methionine. Although accumulation of the tracer in the bone marrow and the salivary and lacrimal glands may occasionally interfere with image interpretation, ^{11}C-methionine PET is an effective method for imaging head and neck cancer. It may also be useful in the assessment of tumor extent when radiotherapy or surgery is planned.

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