Early Response to Chemotherapy in Hypopharyngeal Cancer: Assessment with ^{11}C-Methionine PET, Correlation with Morphologic Response, and Clinical Outcome

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Neoadjuvant chemotherapy in hypopharyngeal cancer globally improves survival, but some patients do not respond to chemotherapy and adjuvant therapy is delayed. Prediction of response to chemotherapy may allow physicians to optimize planned treatment. The aim of this study was to compare treatment response assessed early with ^{11}C-methionine PET and morphologic response assessed after treatment completion with MRI. **Methods:** Thirteen patients with previously untreated squamous cell carcinoma of the hypopharynx, T3 or T4, were included. All patients received 3 courses of chemotherapy comprising cisplatin and 5-fluorouracil. ^{11}C-Methionine PET was performed before and after the first course of chemotherapy. PET estimation of response was expressed in relative variation of mean standardized uptake value (SUVmean), maximal standardized uptake value (SUVmax), volume of ^{11}C-methionine tumor uptake, and total tumor uptake. Posttreatment response was assessed with MRI, which was performed before the first course and after treatment completion, and expressed in relative variation of tumor volume. Patients were considered responders if their tumor volume was reduced by more than 50%. **Results:** The relative decrease in all PET parameters correlated significantly with the relative decrease in MRI volume. The larger area under the receiver operating characteristic curve was obtained for SUVmean (0.883), but that area was close to the area of SUVmax (0.857). For methodologic considerations, SUVmax was more reproducible. The optimal threshold of response for SUVmax was −25%, leading to a mean of 83% (range, 36%–93%) sensitivity and 86% (range, 42%–100%) specificity. Using this threshold, survival at 2 y was improved for responders (83%), compared with nonresponders (57%), but the difference was not statistically significant. **Conclusion:** ^{11}C-Methionine PET provides early useful information about changes in tumor metabolism induced by chemotherapy in hypopharynx cancer. ^{11}C-Methionine PET measurements correlate with end-of-treatment response evaluated with MRI and may thus be helpful to physicians in treatment planning by avoiding unnecessary chemotherapy courses for nonresponding patients.

Key Words: PET; ^{11}C-methionine; chemotherapy monitoring; hypopharyngeal cancer

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Chemotherapy and radiotherapy have made avoiding or delaying surgery in hypopharyngeal cancer possible. However, if improvement in the quality of life has been demonstrated, survival benefit due to neoadjuvant chemotherapy is still slight: 4% both at 2 y and at 5 y (1). Tumor shrinkage after chemotherapy varies widely among patients and as yet cannot be predicted by conventional imaging or histologic analysis (2). Early distinction between responders and nonresponders could lead to a potential change in planned treatment allowing cost-effectiveness, decreased morbidity, and early surgical treatment for nonresponders by stopping the chemotherapy course before completion, while preserving survival benefit for responders. CT and MRI are primarily anatomic modalities that have criteria for malignancy that depend exclusively on morphology. Morphologic changes after treatment cannot be estimated before treatment completion.

Metabolic imaging with ^{18}F-FDG has been used for assessment of treatment response, and promising results were reported in 2 types of study settings: either for early evaluation of treatment response after 1 cycle of chemotherapy or for evaluation after completion of neoadjuvant chemotherapy or radiotherapy. In the first setting, differential uptake between the 2 PET examinations correlated well with end-of-treatment response in breast cancer (3,4), lymphoma (5), germ cell cancer (6), and esophagogastric junction carcinoma (7) and led to a potential impact on treatment planning. In the second setting, metabolic response using

^{18}F-FDG also correlated well with the outcome in primary bone tumor ([8]), lung cancer ([9]), non-Hodgkin's lymphoma ([10,11]), head and neck cancer ([12,13]), esophagogastric cancer ([14]), and pancreatic cancer ([15]), but the impact on treatment planning was often unclear.

Radiolabeled methionine, by giving relevant information on amino-acid transport, is an interesting radiopharmaceutical for early assessment of treatment response. Methionine is needed for protein synthesis as a precursor of S-adenosylmethionine, that being the most important methyl-group donor and precursor to polyamine synthesis. It has been suggested that increased uptake of methionine reflects increased transport, transmethylation rate, and protein synthesis of malignant tissue ([16]). L-methyl-^{11}C-Methionine (^{11}C-methionine) PET has already proved efficient in delineation of tumor ([16,17]), but results are discordant in treatment evaluation, with a prognostic value after radiotherapy in low-grade astrocytoma ([18]) but no correlation with response after radiotherapy in head and neck cancer ([19]). Antineoplastic chemotherapy in cases of advanced malignancies can be debilitating for patients. For individual treatment planning, it is important to evaluate the clinical effect of therapy as soon as possible, so that the therapy modalities for nonresponders can be changed at an early stage of treatment.

The aim of this prospective study was, first, to evaluate the correlation between metabolic response after the first course of chemotherapy using ^{11}C-methionine PET and posttreatment response using MRI. The second aim was to determine the optimal threshold of PET parameters to distinguish responders from nonresponders and, finally, to compare the clinical outcome of these 2 populations of patients.

MATERIALS AND METHODS

Patients

Thirteen patients with a histologically proven diagnosis of squamous cell carcinoma of the hypopharynx, T3 or T4, were included in the study from June 1999 to March 2001. The regional ethical committee for clinical research approved the protocol of the study, and signed informed consent was obtained from the patients. The patient group comprised 11 men and 2 women, with an age range of 45–76 y and a mean age of 59 y. Staging of the tumors was based on the TNM classification ([20]).

Treatment and Imaging Protocol

No patient had received previous antineoplastic treatment. Patients received 3 courses of chemotherapy, consisting of the following regimen: day 1, cisplatin, 100 mg/m²; days 1–4, 5-fluorouracil, 1,000 mg/m². Courses were repeated every 3 wk. ^{11}C-Methionine PET was performed twice for each patient. The first PET study (PET 1) took place within a week before the first course of chemotherapy, and the second (PET 2), 15 d after this first course. MRI was also performed twice for each patient: the first examination (MRI 1) before the first course of chemotherapy and the second (MRI 2) after treatment completion, 15 d after the third course (Fig. 1).
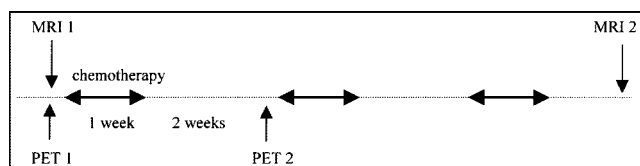

FIGURE 1. Treatment and imaging protocol.

PET Imaging

All ^{11}C-methionine PET imaging was performed on a dedicated PET scanner (ECAT EXACT HR+; Siemens/CTI, Knoxville, TN), from 20 to 40 min after injection of 3.7 MBq of ^{11}C-methionine per kilogram of body weight (Fig. 2). Slice thickness was 5.1 mm, and full width at half maximum was 4.6 mm, axially in the center of the field of view. Radiochemical purity, sterility, and pyrogenicity were tested for each sample. Images were corrected for attenuation and reconstructed with filtered backprojection. Two steps were realized, with a longitudinal field of view of 15.5 cm each.

PET Analysis

Evaluation of the standardized uptake value (SUV) is a crucial point of methodology. There is no widely accepted method in the literature: Regions of interest (ROIs) are circular ([21]) or rectangular ([11,22]), of variable size, and repeated on either 1, 3 ([23]), or more slices ([15]) of the study. The only common point is that the medium plane of the ROIs contains the maximum pixel count of the tumor. Some recommendations to evaluate SUV have been reported by the European Organization for Research and Treatment of Cancer ([24]). Most of these recommendations have been assumed in our study.

Acquisition Parameters and Image Treatment

All emission scans were acquired from 20 to 40 min after injection, in 3-dimensional acquisition mode. Transmission scans were realized before injection, using a [68]Ge source. Attenuation was corrected for each scan. Reconstruction was realized with filtered backprojection using a Hanning filter, at a cutoff frequency of 0.5. Correction of radioactive decay between injection and emission scans was assumed. Calibration of the camera was tested once a week.

Treatment Protocol

Pretreatment PET was performed within 2 wk of the start of treatment. Posttreatment PET was performed 2 wk after the end of the first cycle of chemotherapy.

Whole-Tumor Uptake

Because coregistration was not achievable in this study, tumor uptake was delineated with an SUV isocontour. The value of this isocontour was chosen to obtain a similar value for MRI 1 volume and PET 1 tumor uptake volume (Table 1). Given the MRI 1 volume, this method allowed a reproducible delineation of tumor uptake. The same isocontour value was kept to delineate PET 2 tumor uptake.

Because only T3 or T4 tumors were studied, all tumors had a diameter greater than 2 cm, more than twice the full width at half maximum of 0.46 cm, and therefore partial-volume effects could be ignored ([25]).

Once tumor uptake is delineated, the following can be evaluated: mean SUV (SUVmean) and maximum SUV (SUVmax),
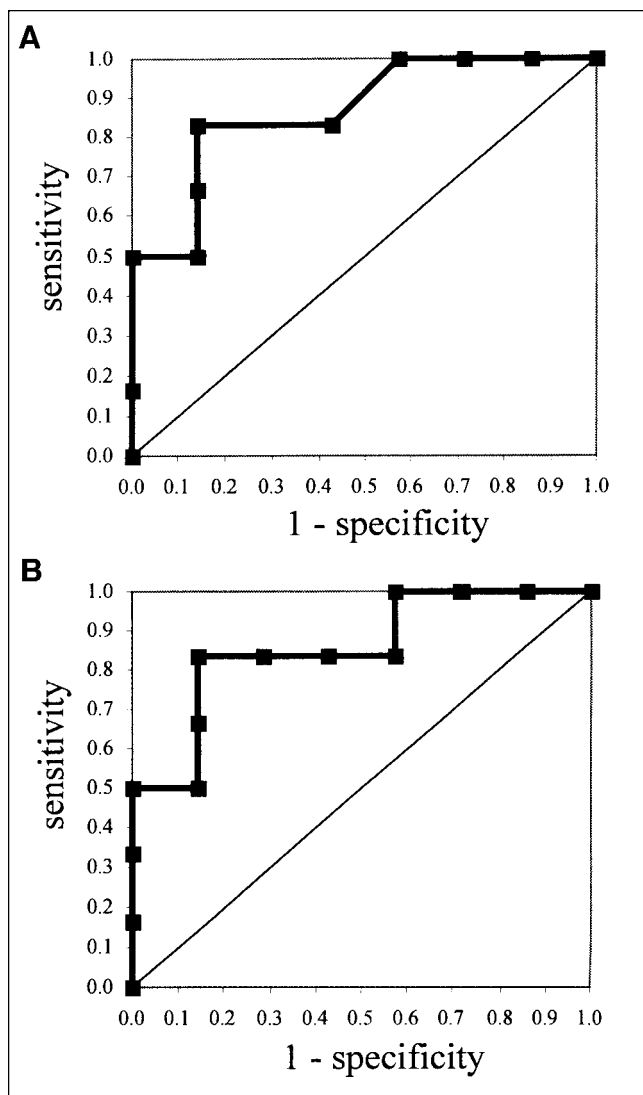
FIGURE 2. ROC curves for SUVmean (A) and SUVmax (B). Areas under curves are 0.883 (A) and 0.857 (B).

volume of tumor methionine uptake (VOLmu), and total tumor uptake (TTU) of methionine, also equal to SUVmean × VOLmu. The parameters were studied to assess which proved most significant. The endpoint of the study was to determine a response threshold for significantly correlated PET parameters and to evaluate its accuracy in distinguishing, after 1 course of chemotherapy, responders from nonresponders.

Normalization of SUV to body surface area or to lean body mass has proved not to be statistically different from normalization to body weight in ^{18}F-FDG PET (*21*). Normalization of SUV to body weight was therefore measured and is defined as the following: SUV = (pixel count/pixel volume)/(injected dose/body weight).

MRI Protocol

All MRI examinations were performed with the same 1.5-T system (Signa; General Electric Medical Systems, Milwaukee, WI). Sequences included sagittal T1-weighted, axial T2-weighted, 3-dimensional axial T1-weighted, axial T1-weighted with gadolinium injection, axial fat-saturated with gadolinium injection, and coronal fat-saturated with gadolinium injection. Regions of abnormal contrast were manually delineated on each slice of the axial T1-weighted sequence to estimate the tumor volume.

Statistical Analysis

All correlations, relative MRI response with PET 1 parameters and with relative PET response, were analyzed using the Spearman rank correlation. Correlations were considered significant for $P <$ 0.05. For significantly correlated PET parameters, a response threshold was calculated corresponding to the MRI threshold of 50% of relative volume decrease, to distinguish nonresponders from complete or partial responders (*26*). Best thresholds of PET response were determined by analyzing receiver operating characteristic (ROC) curves. PET response using these thresholds was compared with the clinical outcome of the patient. The survival rate at 2 y was estimated by Kaplan–Meier analysis, and the log-rank test was used to determine the significance of comparison between responders and nonresponders.

RESULTS

All known primary tumors were detected and delineated at the first ^{11}C-methionine PET examination. As shown in Table 1, a wide range of treatment responses was observed, from −100% to +28% of relative variation for MRI volume. Among these patients, the rate of methionine uptake also varied widely on PET 1: from 2.5 to 6.8 for SUVmean, from 3.8 to 14.6 for SUVmax, from 4.1 to 35 cm^3 for the volume of uptake, and from 11.4 to 239 for TTU.

Correlations

No significant correlations were found between PET 1 parameters and relative decrease in MRI volume: $\rho =$ −0.539, −0.522, −0.176, and −0.522 for VOLmu, SUVmax, SUVmean, and TTU, respectively; $P > 0.05$ for all parameters.

Relative decrease in all PET parameters correlated significantly with relative decrease in MRI volume: $\rho = 0.808$ ($P = 0.01$), 0.791 (0.01), 0.651 (0.016), and 0.670 (0.012) for SUVmean, SUVmax, VOLmu, and TTU, respectively (Table 1). SUVmean and SUVmax correlated more strongly with MRI response than did VOLmu and TTU.

ROC Curve Analysis

ROC curves were analyzed to determine the best threshold of response and to estimate its sensitivity and specificity. For all PET parameters, 0.5 was outside the confidence interval of the area under curve, thus indicating that these parameters were significantly better than randomization for this patient population. Mean areas under the ROC curves were 0.883 (range, 0.658–1), 0.857 (0.643–1), 0.833 (0.582–1), and 0.857 (0.625–1) for SUVmean, SUVmax, VOLmu, and TTU, respectively (Fig. 2).

For SUVmax, a response threshold of −25% led to a mean sensitivity of 83% (range, 36%–93%) and a mean specificity of 86% (42%–100%). For SUVmean, with a response threshold of −6%, the same sensitivity and specificity were obtained, with values of 83% (36%–100%) and 86% (42%–100%), respectively.

TABLE 1
PET Parameters and MRI Measurements

Patient no.	MRI volume (cm³) I	MRI volume (cm³) RD	SUVmean I	SUVmean RD	SUVmax I	SUVmax RD	PET volume (cm³) I	PET volume (cm³) RD	TTU I	TTU RD
1	6.0	+7	4.9	−2	5.9	+17	6.3	−62	30.9	−62
2	31.7	−90	6.8	−39	14.6	−66	35.0	−97	239.0	−98
3	11.0	+28	3.6	+3	5.7	+19	12.5	+13	44.7	+15
4	6.8	−39	4.2	−26	6.3	−40	4.7	−48	20.2	−61
5	8.3	−55	5.5	−7	10.6	−4	11.4	−38	63.3	−42
6	20.0	−100	4.7	−31	9.9	−53	27.8	−81	130.0	−87
7	10.9	−63	2.5	−16	3.8	−30	9.4	−75	23.2	−78
8	4.7	−26	2.8	−5	3.9	−24	4.1	−41	11.4	−47
9	9.4	+21	6.9	−6	9.4	−13	11.4	−80	79.0	−81
10	32.9	−56	4.3	−5	7.4	−38	26.9	−97	116.0	−97
11	11.1	−44	4.7	−6	6.4	−8	9.0	−75	42.1	−77
12	10.2	−31	3.6	−3	5.6	+9	10.9	−38	39.2	−22
13	23.7	−99	6.2	−31	11.1	−46	15.1	−93	93.6	−95

I = initial measurements on first examination, MRI or PET; RD = relative decrease on second examination, MRI or PET, in % = ([2 − 1]/1) × 100.

Clinical Outcome

Among responders, at an SUVmax threshold of −25%, 5 of 6 patients were alive with a mean follow-up of 23.4 mo (Table 2). Patient 4 died after experiencing acute thoracic pain, probably from a pulmonary embolism. Among nonresponders at the same threshold, only 3 of 7 patients were alive with a mean follow-up of 26.4 mo. Survival estimate at 2 y was 83% (range, 44%–97%) for responders and 57% (range, 25%–84%) for nonresponders, but the difference is not statistically significant. All received adjuvant therapy: surgery (2/13 patients) or radiotherapy (13/13 patients).

DISCUSSION

The study was designed to assess the usefulness of ^{11}C-methionine PET for determining early response to chemotherapy in hypopharyngeal cancer. About 400,000 cases of head and neck squamous cell carcinoma are diagnosed worldwide annually (27), most of which are locally advanced at presentation. Assessment of the efficiency of antineoplastic chemotherapy is of critical value to the clinical oncologist and is the main objective of trials in which treatment modalities with severe side effects are used in patients with rapidly progressive disease. A slight improvement in survival among patients receiving chemotherapy for malignant tumors of the hypopharynx has been proved (1). Neither the overall disease stage nor the degree of differentiation of these tumors can be used to predict tumor response to chemotherapy (2).

Because antineoplastic chemotherapy is debilitating, early determination of the response to treatment is crucial in avoiding the severe side effects of unnecessary therapy in nonresponders. PET has made tumor imaging, based on tumor metabolism, possible. ^{18}F-FDG PET provides additional and clinically relevant information for the detection

TABLE 2
Clinical Outcome and PET Response According to SUVmean and SUVmax Optimal Thresholds

Patient no.	Stage	Adjuvant surgery	Follow-up (mo)	Death	Response, SUVmean threshold −6%	Response, SUVmax threshold −25%
1	T4 N3 M0	−	9	+	−	−
2	T3 N0 M0	−	40	−	+	+
3	T3 N1 M0	−	7	+	−	−
4	T4 N3 M0	−	3	+	+	+
5	T3 N2 M0	−	27	+	+	−
6	T4 N2 M0	−	26	−	+	+
7	T4 N2 M0	−	20	−	+	+
8	T3 N2 M0	−	20	−	−	−
9	T3 N3 M0	+	17	−	−	−
10	T4 N3 M0	+	17	−	−	+
11	T4 N2 M0	−	16	−	−	−
12	T3 N0 M0	−	8	+	−	−
13	T4 N0 M0	−	14	−	+	+

of primary and metastatic carcinomas as well as for the early detection of recurrent or persistent head and neck cancer after radiotherapy (28–30). One study has shown that ^{18}F-FDG PET evaluation of the metabolic activity of head and neck malignancy before and after the first chemotherapy cycle of cisplatin and fluorouracil provides early information about the responsiveness of the tumor to this chemotherapy. However, uptake of this radiopharmaceutical may depend on other factors than glycolysis alone and, thus, is not specific to malignant tissue (31).

Malignant tumors of the head and neck have an increased uptake of ^{11}C-methionine similar to that of ^{18}F-FDG (4). Previous studies demonstrated that ^{11}C-methionine is effective in imaging hypopharyngeal cancer (16,32). Nuutinen et al. (33) evaluated early response to radiotherapy in head and neck cancer measured with ^{11}C-methionine PET. The study demonstrated a significant decrease in uptake during the first 2–3 wk after radiotherapy of head and neck cancer. But it appeared that the rate of decrease in tracer uptake was comparable in relapsing disease and in disease remaining locally controlled. In vivo studies evaluating ^{11}C-methionine PET after chemotherapy indicated that this tracer could be of clinical value in predicting the treatment response of breast cancer (34,35) and meningioma (36).

Until now, no in vivo study has compared the therapeutic response to ^{18}F-FDG with that to methionine, even though in vitro studies have suggested that methionine uptake is more rapidly reduced than ^{18}F-FDG uptake after radiotherapy (37). Furthermore, methionine uptake correlates better than ^{18}F-FDG uptake with tumor proliferative activity in squamous head and neck cancer cell lines (38). ^{11}C-methionine was thus selected instead of the more widely available ^{18}F-FDG for the following reasons: rapid synthesis of ^{11}C-methionine with a high radiochemical purity (39), low uptake of methionine in nonviable cells and macrophages (40), better correlation with tumor proliferative activity than ^{18}F-FDG provides, and faster reduction of methionine uptake after treatment than ^{18}F-FDG provides. Concerning morphologic response assessed with MRI, the wide range of responses, from complete response to progressive disease, indicates that early discrimination inside this range could improve the clinical benefit of neoadjuvant chemotherapy in hypopharyngeal cancer (Fig. 3).

In our study, all malignant lesions were detected on the initial pretreatment PET scans. The exact mechanism of ^{11}C-methionine uptake in tumors is still uncertain but is likely to be influenced by amino-acid transport and protein synthesis (40). A thorough knowledge of normal distribution and anatomic, physiologic, and pathologic variants is required to avoid misinterpretation. In the neck, bone marrow may appear quite focal at the medial tips of the clavicles and cause false-positive interpretations in investigations of lymph node involvement (31). Intense physiologic uptake in salivary glands and often in the mucosa of the oral cavity may also contribute to misinterpretation when the tumor is close to one of these.
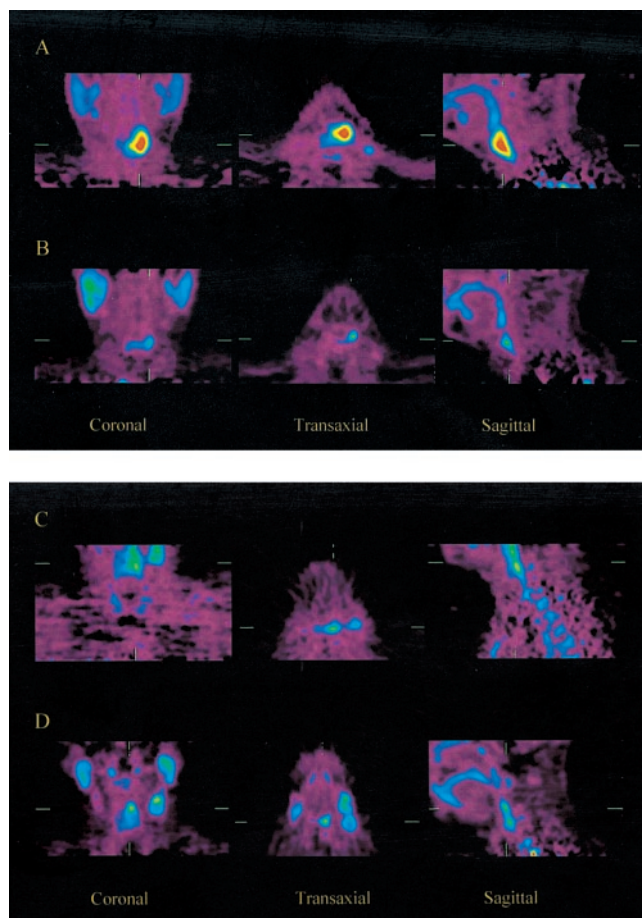

FIGURE 3. (A and B) Patient 13, with left hypopharynx cancer. ^{11}C-Methionine PET scans before (A) and after (B) first course of chemotherapy show complete response after treatment completion, with 99% decrease in MRI volume. (C and D) Patient 3, with left hypopharynx cancer and left cervical metastatic lymph node. ^{11}C-Methionine PET scans before (C) and after (D) first course of chemotherapy show progressive disease after treatment completion, with 23% increase in MRI volume. Note intense physiologic uptake in salivary glands.

Even though quantification with SUV in the assessment of therapeutic response seems to be promising, the methodology for SUV measurement is not yet well established. It was for that reason that the following objectives were considered: a homogeneous population of patients, measurement of whole-tumor uptake, and reproducibility for pre- and posttreatment examinations of the same patient.

No correlation was found between PET 1 parameters and treatment response, confirming that 2 PET examinations are mandatory to predict end-of-treatment response (25). In our patient population, the decrease in SUVmean correlated best with MRI response. SUVmean has already proved to be more significant than SUVmax in the diagnosis of pulmonary abnormalities (21), but there has been little comparison of these parameters in the evaluation of treatment response. SUVmean is closer to SUVmax when estimated on a circular or rectangular ROI of small size than when the whole tumor is considered. If whole-tumor uptake is measured,

SUV depends not only on tumor metabolism but also on tumor morphology, giving more information on tumor response to treatment. However, the results indicate only a small difference between SUVmean and SUVmax for all statistical analyses: correlation, area under the ROC curve, and sensitivity and specificity for optimal response thresholds. The SUVmax threshold appears to be more suitable than the SUVmean threshold for clinical application because the interval of the optimal threshold is larger for SUVmax, with values of -24% to -29%, compared with -6% to -7% for SUVmean. Furthermore, SUVmax measurements are more reproducible. For that reason, Keyes recommended the use of SUVmax rather than SUVmean (25).

If a threshold of -25% had been applied to SUVmax obtained from ROC curve analysis, unnecessary chemotherapy could have been avoided in 6 of 13 patients. The 4 patients who died from tumor progression had the highest relative increase in SUVmax: patients 1, 3, 5, and 12 (Table 2). Nevertheless, the difference in survival estimate at 2 y between responders (83%) and nonresponders (57%) is not statistically significant, because of the small number of patients and the short follow-up: a median of 24.1 mo.

Although this study showed promising results about the use of PET in chemotherapy monitoring, many concerns remain, including the choice of the best radiopharmaceutical ([18]FDG or ^{11}C-methionine); the influence of lymph node involvement, independent of the primary tumor, on survival; and the impact of delaying radiotherapy on disease progression.

CONCLUSION

[11]C-Methionine PET provides early useful information about metabolic changes in hypopharynx tumors induced by chemotherapy. ^{11}C-Methionine PET measurements correlate with end-of-treatment response evaluated with MRI and can thus be helpful to physicians in treatment planning by avoiding unnecessary chemotherapy cycles for nonresponding patients. Maximum SUV seems to be the optimal PET parameter for this purpose, with a threshold response of -25% after 1 course of chemotherapy.

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