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CLINICAL INVESTIGATION **Head and Neck Cancer**

IMAGING TUMOR PERFUSION AND OXIDATIVE METABOLISM IN PATIENTS WITH HEAD-AND-NECK CANCER USING 1- [^{11}C]-ACETATE PET DURING RADIOTHERAPY: PRELIMINARY RESULTS

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Background: A growing body of *in vitro* evidence links alterations of the intermediary metabolism in cancer to treatment outcome. This study aimed to characterize tumor oxidative metabolism and perfusion *in vivo* using dynamic positron emission tomography (PET) with 1- [^{11}C]-acetate (ACE) during radiotherapy.

Methods and Materials: Nine patients with head-and-neck cancer were studied. Oxidative metabolic rate (k_{mono}) and perfusion (rF) of the primary tumors were assessed by dynamic ACE-PET at baseline and after 15, 30, and 55 Gy was delivered. Tumor glucose uptake (Tglu) was evaluated with [^{18}F]-fluorodeoxyglucose PET at baseline. Patients were grouped into complete (CR, $n = 6$) and partial responders (PR, $n = 3$) to radiotherapy.

Results: The 3 PR patients died within a median follow-up period of 33 months. Baseline k_{mono} was almost twice as high in CR as in PR ($p = 0.02$) and Tglu was lower in CR than in PR ($p = 0.04$). k_{mono} increased during radiotherapy in PR ($p = 0.004$) but remained unchanged in CR. There were no differences in rF between CR and PR at any dosage. k_{mono} and rF were coupled in CR ($p = 0.001$), but not in PR.

Conclusions: This study shows that radiosensitive tumors might rely predominantly on oxidative metabolism for their bioenergetic needs. The impairment of oxidative metabolism in radioresistant tumors is potentially reversible, suggesting that therapies targeting the intermediary metabolism might improve treatment outcome. © 2012 Elsevier Inc.

1- [^{11}C]-acetate PET, Perfusion, Oxidative metabolism, Head-and-neck cancer, Radiotherapy.

INTRODUCTION

In locally advanced head-and-neck cancer, the 5-year progression-free survival is about 50% with combined radiotherapy, chemotherapy, and surgery (1). Further improvement of current outcome rates could be achieved by carefully studying and targeting the factors that are related to treatment failure. Among these, tumor hypoxia is an important factor determining treatment response (2), because poor tumor oxygenation correlates to radioresistance and local failure (3). Intracellular oxygen is involved in increasing the DNA damage induced by radiation (4), but is also necessary for the tumor to maintain oxidative phosphorylation (5). Lack of oxygen resulting from insufficient perfusion would force the tumor cells to switch from cellular respiration toward anaerobic glycolysis for survival. However, it has been well known since the days of Warburg that many cancers share a common glycolytic phenotype, even in the presence of oxygen (6). Warburg attributed this phenomenon to a deranged mitochondrial function, causing impaired oxidative phosphorylation and disease progression. *In vitro* studies along this line seem to confirm Warburg's observation. Tumor cells with deficient oxidative metabolic capacity represent a more malignant phenotype (7), and oxidative metabolism may be a key factor in controlling cancer growth (8). Increased tumor glycolysis is detectable *in vivo* by [^{18}F]-fluorodeoxyglucose (FDG)-positron emission tomography (PET) (9) and quantification of tumor FDG uptake using PET appears to carry prognostic information (10). However, glucose uptake appears unrelated to the distribution of hypoxia (11). These findings imply that imaging tumor oxidative metabolism and perfusion *in vivo* might provide insights into the bioenergetic mechanisms and ultimately predict tumor response.

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Conflicts of interest: none

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Acetate has a pivotal role in the intermediary metabolism of all organisms. 1- [^{11}C]-acetate (ACE) was developed and validated as a PET tracer of myocardial oxidative metabolism many years ago (12, 13). Exogenous ACE is extracted into most tissues at rates close to blood flow (14, 15). Inside the cell, ACE is converted into [^{11}C]-acetyl-CoA and effectively trapped. In mitochondria, terminal oxidation of [^{11}C]-acetyl-CoA through the tricarboxylic acid cycle results in the formation of [^{11}C]-CO_2 and clearance of radioactivity from tissue by diffusion back into the circulation. More recently, ACE PET has been used clinically for localizing various cancers that are not FDG-avid (16–18). This aspect of imaging uses the fact that acetyl units not consumed in oxidation are used anabolically for proliferative support (19). This study used serial dynamic ACE PET aiming to evaluate the role of tumor perfusion and oxidative metabolism during radiotherapy.

METHODS AND MATERIALS

Patients

Ten consecutive patients with histologically confirmed squamous cell carcinoma of the head and neck were prospectively included into the study. All patients were untreated before this study and were candidates for radiotherapy. One patient was omitted from analysis from lack of PET data at the baseline investigation. The clinical characteristics for the remaining 9 patients, including the stage and the location of the primary tumors, are shown in Table 1. Staging of the tumors was performed by computed tomography (CT) or magnetic resonance imaging, histopathology, panendoscopy, and clinical examination. The study was approved by the local ethical committees. All participating patients provided written informed consent.

PET imaging

Twenty-nine dynamic ACE PET scans were performed in the 9 patients. Five patients were scanned with a dedicated PET device (Siemens ECAT HR$^+$, Knoxville, TN). Four patients were scanned with a hybrid PET-CT device (GE Discovery ST, Milwaukee, WI). ACE PET was studied in all patients within 7 days before the start of radiotherapy (baseline). However, because of logistic problems, not all patients could be scanned at all subsequent time points. Five patients were scanned after a mean dose of 15 Gy (dose range, 9.6–20 Gy), 7 patients after a mean dose of 30 Gy (range, 24–37 Gy), and 8 patients after a mean dose of 55 Gy (range, 42–68 Gy).

In a subset of ACE scan sessions (n = 23) an image-derived arterial input function for absolute quantification of tumor perfusion was acquired by dynamic imaging of the heart immediately after injection of a 0.5 MBq/kg body weight ACE bolus.

Ten minutes after the heart scan, the head-and-neck region was imaged immediately after an intravenous bolus injection of 10 MBq/kg body weight ACE. The scan time was 32 minutes with time frames 12 × 5 s, 6 × 10 s, 4 × 30s, 4 × 60 s, 2 × 120 s, and 4 × 300 s.

FDG-PET was performed at baseline using a standard clinical whole-body protocol, in which the head-and-neck area was scanned 1 h after intravenous injection of 5 MBq/kg body weight FDG. Baseline ACE and FDG scans were performed on the same or adjacent days.

PET data analysis

All PET images were rigorously co-registered to dose-planning CT images for anatomical localization, using Hermes MultiModality software (Hermes, Stockholm, Sweden). PET images were further analyzed with commercially available software (PMOD 2.7, PMOD Technologies Ltd, Switzerland). The location of the primary tumor was identified and outlined by two of the authors in consensus. Primary tumors were clearly visualized in all scans. After realignment of serial images, a region-of-interest (ROI) analysis was performed by locating the tumor hotspot and tracing a threshold of 50% corrected for background activity in one slice. ROIs were then manually corrected to account for high uptake in adjacent tissues and to assure that approximately same part of the tumor was covered serially, when needed. A time-activity curve (TAC) of the primary tumor was obtained from the ROI in all ACE scans. Data were exported to a personal computer running Microsoft Excel 2003 (Redmond, WA) for further analysis.

Tumor clearance rate

TACs were analyzed by fitting an exponential curve to the data collected between 4 and 32 min (Fig. 1). Tumor oxidative metabolism was derived from the equation below.

$$Y = Ae^{-k_{mono} * t}$$

where Y is the tumor radioactivity (Bq/ml), A is a constant, t is time (min), and k_{mono} is the clearance rate of [^{11}C] in min^{-1}. Fitting was performed using the trend-line feature incorporated into the diagrams view in the Excel software. The average R^2 of the fit was 0.93.

Table 1. Clinical characteristics of patients with squamous cell carcinoma of the head and neck

Patient No	Sex	Age (y)	Stage	Location	Tglu	Histology diff	Follow up (m)
1	M	77	T4N2c	Larynx	13.8	Low	31
2	F	57	T2N0	Nasal cavity	3.9	Moderate	46
3	M	53	T3N0	Nasal cavity	4.6	Low	35
4	M	59	T3N1	Tonsilla	8.5	Low	36
5	M	47	T4N3	Epipharynx	6.8	Low	45
6	M	64	T2N2a	Tonsilla	4.9	Low	33
7	M	59	T2N0	Nasal cavity	26.1	High	31
8	F	67	T4N3	Tonsilla	13.4	Low	26
9	M	18	T3N3	Epipharynx	16.3	Low	31

Abbreviations: M = male; F = female; T = tumor stage; N = lymph node stage; diff = cell differentiation; Tglu = the baseline tumor glucose uptake expressed by standard uptake value; m = month.