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Biological imaging

Effects of hyperoxygenation on FDG-uptake in head-and-neck cancer

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Abstract

***Purpose*: Tumor hyperoxygenation results in high response rates to ARCON (accelerated radiotherapy with carbogen and nicotinamide). The effect of hyperoxygenation on tumor metabolism using [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET) was investigated.**

***Methods*: Within one week, FDG-PET was performed without and with hyperoxygenation by carbogen breathing and/or nicotinamide administration in 22 patients, eligible for ARCON for head-and-neck cancer. Maximum standardized uptake values (SUV_{max}) in both scans and the relative change were calculated in the primary tumor and in normal muscle.**

***Results*: Alteration of the tumor oxygenation state induced profound, but variable, metabolic changes (median ΔSUV_{max} −4%; range −61% to +30%). Metabolism in normal muscle was not affected. In three patients who did not achieve local tumor control, the SUV_{max} after hyperoxygenation differed less than 5% change as compared to baseline, whereas 13 of the 16 patients with local tumor control showed a larger difference ($p < 0.05$).**

***Conclusion*: Given the heterogeneous response pattern of nicotinamide and carbogen on FDG-uptake in head-and-neck carcinoma, the prognostic significance of semiquantitative FDG-PET before and after hyperoxygenation remains uncertain and requires confirmation in larger clinical studies before introducing the procedure as a predictive tool for oxygenation modifying treatments.**

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Keywords: Head-and-neck cancer; Positron emission tomography; [^{18}F]Fluorodeoxyglucose; Carbogen; Nicotinamide

Resistance of some malignant tumors is a major problem in radiation oncology. Tumor-cell repopulation and hypoxia are two important mechanisms responsible for radiotherapy resistance [8,16,21,23]. Application of accelerated radiotherapy with carbogen and nicotinamide (ARCON) tries to overcome these problems [15]. To counteract repopulation of clonogenic tumor cells during therapy, the overall treatment time is reduced by delivering the total radiation dose in multiple fractions per day. Tumor-cell hypoxia is counteracted with carbogen, a hyperoxic gas, consisting of 95–98% oxygen and 2–5% carbon dioxide in combination with the vasoactive agent nicotinamide. Oxygen mediates the biological effects of ionizing radiation, as the cellular damage of radiation depends strongly on the availability of oxygen [10]. Hypoxia has a negative effect on treatment outcome not only through enhanced radioresistance but also by promoting more aggressive tumor behavior [9,29]. Hypoxia is a powerful trigger for changes in gene expression and associated changes in the microenvironment [6,37,44]. Inhalation of carbogen is proposed to decrease diffusion-limited hypoxia and administration of nicotinamide to decrease perfusion-limited hypoxia. Chronic or diffusion-limited hypoxia occurs in cells that are located relatively far away from blood vessels [43]. Acute or perfusion-limited hypoxia results from local, temporary fluctuations in tumor blood perfusion [43].

Phase II trials indicate promising results with ARCON, especially in head-and-neck cancer [15]. However, questions about the precise mechanisms of action of hyperoxygenation of tumors remain to be answered. In humans, limited information on the pathophysiological and metabolic effects of carbogen and nicotinamide is currently available. Animal studies using nuclear medicine imaging techniques suggest that the metabolic activity is lower in hypoxic tumors compared to controls [24].

Many malignancies, including head-and-neck cancer, have increased glucose metabolism and accumulate the glucose analog [^{18}F]fluorodeoxyglucose (FDG) and can thus be visualized using positron emission tomography (PET) [14]. After internalization, FDG is trapped in the malignant cells, as it cannot be metabolized further [30]. FDG-PET has been used extensively in head-and-neck cancer for staging [36,38], surveillance and detection of recurrence [25,26], and assessment of treatment response [22,28] with

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promising results. The advantage of FDG-PET is that it is a non-invasive, in vivo method to detect, image and quantify FDG-uptake which is obviously not only dependent on the metabolic activity of the tumor but also on the perfusion and oxygenation status of the tumor. In the current study, we investigate the effect of carbogen and nicotinamide on tumor metabolism using FDG-PET in patients with head-and-neck cancer.

Methods and materials

Patients

Twenty-two patients (18 males, 4 females) with primary stage III—IV laryngeal, oropharyngeal or stage II—IV hypopharyngeal squamous cell carcinomas entered this prospective study. The mean age was 62 years (range 47—91 years). Patient characteristics are summarized in Table 1. All patients were considered eligible for a phase II ARCON study [18]. Exclusion criteria for the FDG-PET study were diabetes mellitus and pregnancy. The study was approved by the Institutional Review Board of the Radboud University Nijmegen Medical Centre. All patients gave written informed consent to participate in this study.

Patient groups

All patients were scanned twice; after baseline FDG-PET, a second FDG-PET was performed after hyperoxygenation (median interval between the two sessions 2 days, range 1—7 days). Of the 22 patients, 5 patients were given nicotinamide (60 mg/kg orally) one hour prior to the FDG injection and 11 patients were breathing a carbogen gas mixture of 95% O_2 and 5% CO_2 for 10 min, which is the optimal breathing time to overcome hypoxia [27]. During the second minute FDG was injected. The remaining 6 patients were given the combination of nicotinamide and carbogen.

FDG-PET

A dedicated, rotating half-ring PET-scanner (ECAT-ART, Siemens/CTI, Knoxville, TN, USA) was used for data acquisition. Prior to FDG-injection, patients were fasting for at least 6 h. Intake of sugar-free liquids was permitted. Immediately prior to the procedure, the patients were hydrated with 500 ml of water and the patients were given 5 mg diazepam orally for muscle relaxation. One hour after intravenous injection of 200—220 MBq FDG (Mallinckrodt Medical, Petten, The Netherlands), emission and transmission images of the head and neck area were acquired (2—3 bed positions, 10 min per bed position). The images were corrected for attenuation and reconstructed using the ordered-subsets expectation maximization (OSEM) algorithm.

Table 1
Tumor characteristics

	Characteristic	No. of patients
Primary tumor site	Larynx	4
	Oropharynx	7
	Hypopharynx	11
T stage	T1	2
	T2	6
	T3	10
	T4	4
N stage	N0	6
	N1	6
	N2a	1
	N2b	4
	N3	5

FDG-PET analysis

For quantification of FDG uptake, volumes of interest (VOI) were drawn around the primary tumor, using the 50% isocontour (enclosing pixels with 50% or more of the maximum radioactivity in the VOI). Maximum standardized uptake values (SUV_{max}) were calculated using the concentration of FDG in the tumor as measured by PET, divided by the injected dose and multiplied by body weight as a normalization factor. Both scans of each patient were matched in all planes using the 3D Extract Image software (courtesy of Dr. A.T. Willemsen, PET-centre, University Medical Centre Groningen, The Netherlands). The VOI of the baseline scan was copied into the second scan. FDG-uptake in the primary tumor after administration of nicotinamide, carbogen or the combination of both was quantitated and compared to baseline FDG-uptake.

To investigate whether the change in FDG-uptake after hyperoxygenation truly reflects differences in tumor biology and is not based on reproducibility problems or differences induced by variations in body physiology, FDG-uptake in the trapezius muscle was measured in triplicate in every PET-scan. Nicotinamide and carbogen do not induce changes in glucose metabolism in resting skeletal muscle. Resting muscle tissue has a low metabolic rate and does not exhibit increases in NAD+ and blood flow following nicotinamide administration [20]. The relative change (mean difference and standard deviation) in SUV in resting skeletal muscle was measured between the baseline PET and the PET after hyperoxygenation for each patient. The intrapatient interscan variability expressed in the repeatability coefficient was calculated [4].

Treatment

The primary tumor and bilateral neck nodes were irradiated through lateral-opposed photon beams (4 or 6 MV). After 30—40 Gy, an off-cord reduction of the lateral-opposed photon beams was made, and the posterior cervical chains were treated with lateral appositional electron beams. The mid and lower neck nodes were treated with an anterior photon field. In some cases, a posterior field was added to supplement the dose in the posterior midcervical chains. The boost dose was delivered through reduced lateral or oblique opposed portals, combined, when necessary, with an electron beam to boost nodal areas overlying the spinal cord or larynx. The total dose was 68 Gy for gross disease and 44 Gy for the electively treated areas. The dose per fraction was 2 Gy, and the overall treatment time was limited to 36—38 days by delivering 2 fractions daily during the last 1.5 weeks of treatment. The interval between fractions was at least 6 h. Dose specification was according to