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EDITORIAL COMMENTARY

Imaging of tumour hypoxia using PET and ^{18}F-labelled tracers: biology meets technology

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One current major goal in non-invasive nuclear imaging of cancer is prediction of the fractional hypoxic volume, i.e. the proportion of hypoxic cells within a solid tumour. Hypoxic cells in both rodent and human tumours are about threefold more resistant to radiation therapy than their well-oxygenated counterparts [1], and there is also strong evidence to link hypoxia with malignant progression leading to increased invasive potential and metastasis [2]. Ever since the discovery that 2-nitroimidazole-based compounds bind to cellular macromolecules under a low oxygen concentration [3], attempts have been made to utilise this chemical property to design a probe capable of external imaging of hypoxic tumour cells. Such a probe is desired by the radiotherapy community to help overcome the limited success in clinical trials in which tumour oxygenation has been targeted. One might assume that detection of hypoxic tumours with functional imaging will lead to a therapeutic gain through the use of methods permitting selective cell kill in poorly oxygenated regions within a larger tumour volume [4, 5].

The development of nitromidazole derivatives and thiosemicarbazone ligands labelled with short-lived radionuclides, such as ^{123}I ($T_{1/2}$=13.3 h), ^{64}Cu ($T_{1/2}$=12.7 h) and ^{18}F ($T_{1/2}$=109.8 min), as tools for hypoxia imaging utilising SPECT and PET has been a major task during recent decades [6]. With the advent of integrated PET and CT scanners featuring full radiation therapy planning capability, it is obvious that PET tracers in particular will receive much attention in the near future. The key issue is the ability to translate the volumetric information from a functional imaging study to the treatment planning system. In this context, both scanner resolution and target-to-background uptake ratio are important, since quantitation of hypoxia-specific radionuclide uptake is relevant for optimisation of intensity-modulated radiotherapy (IMRT). Inverse planning IMRT utilises a so-called dose painting by numbers technique, which assumes that small irregular volumes inside a tumour should receive a higher than standard photon dose to control hypoxic and radioresistant cells [7]. Combining IMRT with planning PET/CT using a hypoxia-avid tracer is an attractive but as yet unproven method for delivery of higher doses to a hypoxic tumour subvolume.

The first clinical studies to image tumour hypoxia using PET were based on seminal works by Rasey et al. [8], who introduced ^{18}F-labelled fluoromisonidazole ([^{18}F]FMISO) to quantify the hypoxic fraction in patients with lung, head and neck, and prostate cancers. Since then, both experimental and clinical studies with [^{18}F]FMISO have shown the potential of this tracer as a hypoxia imaging agent [9, 4]. However, [^{18}F]FMISO has failed to gain wider acceptance for routine clinical application because of a number of limitations, such as slow accumulation in hypoxic tumours, a low target-to-background contrast and, finally, a significant amount of radioactive metabolite products. Therefore, several other ^{18}F-labelled nitroimidazole-based hypoxia tracers have been synthesised and preclinically evaluated, including fluoroerythronitroimidazole ([^{18}F]FETNIM) [10, 11], fluoroetanidazole ([^{18}F]FETA) [12], fluoroazomycinar-

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abinoside ([^{18}F]FAZA) [13, 14], [^{18}F]EF3 [15] and [^{18}F]EF5 [16, 17]. Clinical experience with nitroimidazole agents other than [^{18}F]FMISO is limited, but evaluation of [^{18}F]FETNIM in patients with head and neck cancer showed a higher and heterogeneously distributed tracer uptake in tumours than in adjacent neck muscle [18]. High uptake of [^{18}F]FETNIM prior to radiation therapy was also associated with a trend towards poor overall survival [19]. Although [^{18}F]FETNIM showed a low and favourable background signal as compared with [^{18}F]FMISO [20], the high hydrophilicity of [^{18}F]FETNIM caused early tumour uptake, up to 90 min post injection, to be largely perfusion dependent [18]. The early flow dependency, also seen with [^{18}F]FMISO and [^{18}F]FAZA, is not a desirable feature for radiation therapy planning but may not be an issue if static images after the wash-out period are used in the phase during which 2-nitromidazole binding in the macromolecular fraction dominates the tumour uptake.

In this issue of *European Journal of Nuclear Medicine and Molecular Imaging*, Souvatzoglou et al [21] have evaluated the uptake of [^{18}F]FAZA in 11 patients with untreated head and neck cancer. They all had large (T4 stage) primary tumours and nine patients had advanced neck disease (N2c stage) as well, making the presence of clinically significant radiobiological tumour hypoxia likely in most, if not all, patients. [^{18}F]FAZA is a sugar-coupled 2-nitroimidazole derivative, which was developed based on encouraging results achieved by the use of the iodinated form ([^{123}I]IAZA) and SPECT imaging [22]. This is the first time that [^{18}F]FAZA has been clinically evaluated, and the reported mean tumour-to-muscle (T/M) ratio of 2.3±0.3 (range 1.6–2.3) at 2 h after tracer injection is quite similar to the values reported previously for other ^{18}F-labelled hypoxia tracer candidates. Imaging at a later time point, in this case at 4 h after tracer injection, did not increase the hypoxia-specific signal of [^{18}F]FAZA. Visually and quantitatively, several soft tissues, and in particular the hepatobiliary system, showed tracer uptake close to, or higher than, that of tumour, indicating the presence of as yet unidentified metabolites of [^{18}F]FAZA and suggesting that some tumours, e.g. musculoskeletal sarcomas, may not be amenable to [^{18}F]FAZA imaging owing to suboptimal tumour-to-background uptake. The authors found that seven out of 11 primary tumours and three out of 11 lymph node metastases showed focal uptake graded as moderately or markedly higher than background uptake, which suggests that the head and neck area is indeed suitable for [^{18}F]FAZA PET. The uptake of [^{18}F]FAZA has previously been evaluated and compared with that of [^{18}F]FMISO using both in vitro and in vivo methods in rat sarcoma cells [13]. In that study, a similar oxygen-dependent uptake was seen with both tracers. However, in another study, in which the ex vivo biodistribution of [^{18}F]FAZA was compared with that of [^{18}F]FMISO in both healthy and tumour tissues [14], [^{18}F]FAZA showed significantly lower uptake than [^{18}F]FMISO in most organs while uptake of the two tracers in AR42J tumours was similar; hence higher and favourable tumour-to-blood (T/B) and T/M ratios were obtained for [^{18}F]FAZA compared with [^{18}F]FMISO (9.1±4.1 and 5.5±2.3 vs 3.39±0.52 and 2.92±0.66, respectively) at 3 h after tracer injection.

Although this new hypoxia tracer is now available for clinical application, it faces the same challenges as [^{18}F]FMISO and [^{18}F]FETNIM, which have both passed the first test of positive imaging of presumably hypoxic tumour regions. Additional knowledge about the behaviour of all hypoxia tracers is warranted in different therapeutic settings in order to fully understand the information that is provided by non-invasive imaging. We need to validate the extent of hypoxia required so as to receive a good hypoxia-specific signal. To make things more complicated, this extent is not necessarily identical for chemically related but pharmacokinetically different nitroimidazole compounds and may furthermore vary among different tumour histologies and therapeutic interventions. In order to use the information obtained by non-invasive imaging of hypoxia for radiation therapy planning, we further need at least to distinguish moderately hypoxic but radiocurable tumours from severely hypoxic and radioresistant ones. In addition, we need more knowledge about molecular and biological pathways which affect the uptake of hypoxia tracers. These questions can only be answered by pooling data achieved from both preclinical and clinical studies. For the moment we need more clinical studies evaluating the existing hypoxia tracers in well-defined and similarly treated patient groups. These prospective imaging protocols should preferably be coupled with detailed information on how PET-measured hypoxia is associated with tumour control. This is the only way to learn whether molecular imaging of tumour oxygenation has a clinical role.

The initial clinical data from Souvatzoglou et al. [21] encourage further evaluation of [^{18}F]FAZA in head and neck cancer while some questions about the behaviour of this tracer in vivo remain unanswered. In the current study, the uptake of [^{18}F]FAZA was not evaluated at 3 h after tracer injection, which in preclinical studies performed by the same research group was shown to give the highest T/M ratio [14]. Furthermore, the amount of ^{18}F-labelled metabolites formed in blood and tissues after injection of [^{18}F]FAZA has not been investigated so far. Blood metabolites affect kinetic tracer modelling and should be considered when combined analysis of blood flow and metabolism in heterogeneous and hypoxic tumour tissue is performed to predict outcome. [^{18}F]FAZA has previously been shown to clear faster from blood than [^{18}F]FMISO [13, 14], which is theoretically a clear advantage. We conclude that [^{18}F]FAZA

is a promising tracer to image hypoxia in head and neck cancer and expect that the true potential of this and other novel nitroimidazole tracers will become evident in the near future. Recent technical improvements in the delivery of radiation therapy remain hollow and may be unexploited without proof of the biological impact shown by functional imaging. PET is there at the cutting edge.

References

1. Horsman MR, Overgaard J. The oxygen effect and tumour microenvironment. In: Steel GG, editor. Basic clinical radiobiology. London: Arnold; 2002; p. 158–68.
2. Graeber TG, Osmanian C, Jacks T, Housman DE, Koch CJ, Lowe SW, et al. Hypoxia-mediated selection of cells with diminished apoptotic potential in solid tumours. Nature 1996;379:88–91.
3. McCalla DR, Reuvers A, Kaiser C. Mode of action of nitrofurazone. J Bacteriol 1970;104:1126–34.
4. Rischin D, Hicks RJ, Fisher R, Binns D, Corry J, Porceddu S, et al. Prognostic significance of ^{18}F-misonidazole PET-detected tumor hypoxia in patients with advanced head and neck cancer randomly assigned to chemoradiation with or without tirapazamine: a substudy of Trans-Tasman Radiation Oncology Group study 98.02. J Clin Oncol 2006;24:2098–104.
5. Thorwarth D, Eschmann SM, Paulsen F, Alber M. Hypoxia dose painting by numbers: a planning study. Int J Radiat Oncol Biol Phys 2007;68:291–300.
6. Chapman JD. Hypoxic sensitizers—implications for radiation therapy. N Engl J Med 1979;301:1429–32.
7. Bentzen SM. Theragnostic imaging for radiation oncology: dose-painting by numbers. Lancet Oncol 2005;6:112–7.
8. Rasey JS, Koh WJ, Evans ML, Peterson LM, Lewellen TK, Graham MM, et al. Quantifying regional hypoxia in human tumors with positron emission tomography of [^{18}F]fluoromisonidazole: a pretherapy study of 37 patients. Int J Radiat Oncol Biol Phys 1996;36:417–28.
9. Kubota K, Tada M, Yamada S, Hori K, Saito S, Iwata R, et al. Comparison of the distribution of fluorine-18 fluoromisonidazole, deoxyglucose and methionine in tumour tissue. Eur J Nucl Med 1999;26:750–7.
10. Yang DJ, Wallace S, Cherif A, Li C, Gretzer MB, Kim EE, et al. Development of F-18-labeled fluoroerythronitroimidazole as a PET agent for imaging tumor hypoxia. Radiology 1995;194:795–800.
11. Grönroos T, Eskola O, Lehtiö K, Minn H, Marjamäki P, Bergman J, et al. Pharmacokinetics of [^{18}F]fluoroerythronitroimidazole: a potential hypoxia marker for PET. J Nucl Med 2001;42:1397–404.
12. Rasey JS, Hofstrand PD, Chin LK, Tewson TJ. Characterization of [^{18}F]fluoroetanidazole, a new radiopharmaceutical for detecting tumor hypoxia. J Nucl Med 1999;40:1072–9.
13. Sorger D, Patt M, Kumar P, Wiebe LI, Barthel H, Seese A, et al. [^{18}F]fluoroazomycinarabinofuranoside (^{18}FAZA) and [^{18}F]fluoromisonidazole (^{18}FMISO): a comparative study of their selective uptake in hypoxic cells and PET imaging in experimental rat tumors. Nucl Med Biol 2003;30:317–26.
14. Piert M, Machulla HJ, Picchio M, Reischl G, Ziegler S, Kumar P, et al. Hypoxia-specific tumor imaging with ^{18}F-fluoroazomycin arabinoside. J Nucl Med 2005;46:106–13.
15. Mahy P, De Bast M, Gillart J, Labar D, Gregoire V. Detection of tumour hypoxia: comparison between EF5 adducts and [^{18}F]EF3 uptake on an individual mouse tumour basis. Eur J Nucl Med Mol Imaging 2006;33:553–6.
16. Dolbier WR, Li AR, Koch CJ, Shiue CY, Kachur AV. [^{18}F]-EF5, a marker for PET detection of hypoxia: synthesis of precursor and a new fluorination procedure. Appl Radiat Isot 2001;54:73–80.
17. Ziemer LS, Evans SM, Kachur AV, Shuman AL, Cardi CA, Jenkins WT, et al. Noninvasive imaging of tumor hypoxia in rats using the 2-nitroimidazole ^{18}F-EF5. Eur J Nucl Med Mol Imaging 2003;30:259–66.
18. Lehtiö K, Oikonen V, Grönroos T, Eskola O, Kalliokoski K, Bergman J, et al. Imaging of blood flow and hypoxia in head and neck cancer: initial evaluation with [^{15}O]H_2O and [^{18}F]fluoroerythronitroimidazole PET. J Nucl Med 2001;42:1643–52.
19. Lehtiö K, Eskola O, Viljanen T, Oikonen V, Grönroos T, Sillanmäki L, et al. Imaging perfusion and hypoxia with PET to predict radiotherapy response in head-and-neck cancer. Int J Radiat Oncol Biol Phys 2004;59:971–82.
20. Grönroos T, Bentzen L, Marjamäki P, Murata R, Horsman MR, Keiding S, et al. Comparison of the biodistribution of two hypoxia markers [^{18}F]FETNIM and [^{18}F]FMISO in an experimental mammary carcinoma. Eur J Nucl Med Mol Imaging 2004;31:513–20.
21. Souvatzoglou M, Grosu AL, Krause BJ, Beck R, Reischl G, Picchio M, et al. Tumour hypoxia imaging with [^{18}F]FAZA PET in head and neck cancer patients: a pilot study. Eur J Nucl Med Mol Imaging 2007; DOI 10.1007/s00259-007-0424-3.
22. Stypinski D, McQuarrie SA, Wiebe LI, Tam YK, Mercer JR, McEwan AJ. Dosimetry estimations for ^{123}I-IAZA in healthy volunteers. J Nucl Med 2001;42:1418–23.