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EDITORIAL COMMENTARY

Invited editorial for the paper by Silvoniemi et al. "Repeatability of tumor hypoxia imaging using [^{18}F]EF5 PET/CT in head and neck cancer." in this issue of EJNMMI

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Dear Sir,

The paper "Repeatability of Tumor Hypoxia Imaging using [^{18}F]EF5 PET/CT in Head and Neck Cancer" by Silvoniemi et al. and reported in this month's issue of EJNMMI [1], makes a great leap forward in the subject area of PET-based hypoxia imaging. Compared with earlier reports, the results demonstrate enhanced signal and repeatability, furthermore using the smallest voxel size yet reported. One would never expect improvements in all three critical imaging parameters, since typically any improvement in one would be expected to negatively impact the others. The repeatability of the images, with detailed summaries in the tables and figures, indicates that prior suggestions of cycling hypoxia (see below) are not supportable at the resolution of voxels of size about $(3.5\ mm)^3$. Interestingly, an area of $(3\ mm)^2$ is about the minimum possible size for modulation of radiation therapy, so this work sets the stage for realistic dose modulation (image-guided radiation therapy - IGRT, or dose painting) in tumors. Of critical importance, even tumors with very low numbers of hypoxic voxels had reproducible locations of these voxels. Thus, it may be relatively easy to make image-guided boosts to such voxels in tumors that are mostly aerobic. Former studies, using EF5 at higher concentrations for immunohistochemical estimates of tumor pO_2 levels, found many examples of essentially non-hypoxic human tumors [2, 3], in agreement with the current data. But for situations involving sparse occurrence of hypoxia, the IHC method did not have the key advantage of non-invasive imaging, namely access to the entire volume of tumor tissue.

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The authors defined a hypoxic voxel using a threshold tumor:muscle ratio (TMR) for EF5 uptake of 1.5, based on therapeutic outcome in a former study [4]. This represents a more than 2-fold enhancement in signal compared with studies using other compounds [5–7], facilitating ease of regional-target identification. The lack of the need to monitor the blood concentration of EF5 also represents a much easier study for the patient. Prior studies have used hypoxic-threshold criteria as low as tumor:blood ratios (TBR) of 1.2. The known rapid equilibration of EF5 between blood and normal tissues such as muscle involves EF5's lipophilicity, which is more than ten times higher than the least hydrophilic alternative (FMISO) [8, 9]. EF5's high lipophilicity may also be responsible for the enhanced signal seen for this compound [10].

A remarkable finding in the Silvoniemi study is the similarity in size, location, and indeed absolute value of signal intensities between the 1st and 2nd images. This has never been previously observed, with former results using low TBRs allowing many regions of normal tissue to satisfy the criterion of 'hypoxia'. Yet another novel aspect of the present work is the 7-day interval between images (up to sevenfold longer than prior comparisons) - this suggests long-term stability of hypoxic regions in tumors.

Dependable and reproducible measurements of the location and degree of hypoxia are critical for the diagnosis and planning of therapy. An early study suggested large-scale variations in these parameters [5] and this in turn supported the popular concept of cycling hypoxia [11–14]. If true, such variations would completely invalidate the principle of dose painting based on hypoxia, and indeed the inherent value of hypoxia measurements. Since the initial imaging study that supported such problems [5], two additional ones have lent more credence to the relative stability of PET-based hypoxia measurements, one using FMISO and the second using HX4 [6, 7]; nevertheless, the relatively short time between test/retest remained worrisome. The present study

dramatically tips the balance towards hypoxic regional stability, albeit for a relatively small number of H&N cancer patients. Hopefully, this will provide the impetus for more comprehensive studies in this and other cancers.

The Turku group has previously demonstrated yet another important capability of PET-EF5, namely its ability to accurately quantify blood flow, compared with the 'gold-standard' of labeled water [15]. In fact, their images demonstrated higher contrast using dynamic scans of PET-EF5, likely due to its relatively long half-life compared with O-15. We believe that monitoring blood-flow deficiencies in tumors is very important due to a 'new type' of hypoxia described as arising from extended longitudinal blood-flow gradients and producing macroscopic regions of hypoxia [16, 17]. Interestingly, this capability marries the popular view in the MRI field that tumor hypoxia arises from perfusional limitations, rather than the more classical radiobiological view of hypoxia arising from diffusional limitations.

EF5 was originally designed to be an extremely stable chemical (it survives boiling TFA in the synthesis of the F-18-labeled compound), to have reliable oxygen-dependent reduction characteristics (only metabolized by one-electron reductases) and most importantly, its high lipophilicity was built in to provide very rapid tissue distribution. Rapid biodistribution of lipophilic compounds is well known in the pharmacology literature and detailed biodistribution studies showed that the tissue biodistribution of EF5 was indeed about tenfold faster than that of FMISO [9, 18]. Unfortunately, the current emphasis on hydrophilic compounds (much slower and incomplete biodistribution) that have easier synthetic routes may be defeating the most essential properties of hypoxia-marking drugs. That is why detailed studies such as are presented in the Silvoniemi paper are so essential to the use of hypoxia as a diagnostic and prognostic indicator.

Compliance with ethical standards

Conflict of interest The author developed the EF5 drug but its patents are now expired and he has never held financial interests in its clinical use. In vitro and animal use of EF5 and detecting antibodies are provided by the National Cancer Institute and a non-profit service center that is being transferred to EMD-Millipore.

References

1. Silvoniemi A, Suilamo S, Laitinem T, Forsback S, Loyttyniemi E, Vaittinen S, Solin O, Gronroos TJ, Minn H. Repeatability of tumour hypoxia imaging using [^{18}F]EF5 PET/CT in head and neck cancer. Eur J Nuc Med Molecular Imaging 2018.
2. Ziemer LS, Koch CJ, Maity A, Pook-Magarelli D, Horan A-M, Evans SM. Hypoxia and VEGF mRNA expression in human tumors. Neoplasia. 2001;3:500–8.
3. Evans SM, Du KL, Chalian AA, Mick R, Zhang PJ, Hahn SM, et al. Patterns and levels of hypoxia in head and neck squamous cell carcinomas and their relationship to patient outcome. Int J Radiat Oncol Biol Phys. 2007;69:1024–31.
4. Komar G, Lehtio K, Seppänen M, Eskola O, Levola H, Lindholm P, et al. Prognostic value of tumour blood flow,[^{18}F]-EF5 and [^{18}F]-FDG PET/CT imaging in patients with head and neck cancer treated with radiochemotherapy. Eur J Nuc Med Mol Imaging. 2014;41:2042–50.
5. Nehmeh SA, Lee NY, Schroder H, Squire O, Zanzonico PB, Erdi YE, et al. Reproducibiliy of intratumor distribution of ^{18}F-fluoromisonidazole in head and neck cancer. Int J Radiat Oncol Biol Phys. 2008;70:235–42.
6. Okamoto S, Shiga T, Yasuda K, Ito YM, Magota K, Kasai K, et al. High reproducibility of tumor hypoxia evaluated by ^{18}F-Fluoromisonidazole PET for head and neck cancer. J Nuc Med. 2013;54:201–7.
7. Zegers CML, van Elmpt W, Szardenings K, Kolb H, Waxman A, Subramanian RM, et al. Repeatability of hypoxia PET imaging using [^{18}F]HX4 in lung and head and neck cancer patients: a prospective multicenter trial. Eur J Nuc Med Mol Imaging. 2015;42:1840–9.
8. Koch CJ, Scheuermann JS, Divgi C, Judy KD, Kachur AV, Freifelder R, et al. Biodistribution and dosimetry of ^{18}F-EF5 in cancer patients with preliminary comparison of ^{18}F-EF5 uptake *versus* EF5 binding in human glioblastoma. Eur J Nuc Med Mol Img. 2010;37:2048–59.
9. Lin LL, Silvoniemi A, Stubbs JB, Rengan R, Suilamo S, Solin O, et al. Radiation dosimetry and biodistribution of the hypoxia tracer ^{18}F-EF5 in oncologic patients. Cancer Bioth Radiopharmaceut. 2012;27:412–9.
10. Raleigh JA, Koch CJ. The importance of thiols in the reductive binding of 2-nitroimidazoles to macromolecules. Biochem Pharmacol. 1990;40:2457–64.
11. Brown JM. Evidence for acutely hypoxic cells in mouse tumours, and a possible mechanism of reoxygenation. Brit J Radiol. 1979;52:650–6.
12. Trotter MJ, Chaplin DJ, Durand RE, Olive PL. The use of fluorescent probes to identify regions of transient perfusion in murine tumors. Int J Radiat Oncol Biol Phys. 1989;16:931–4.
13. Cardenas-Navia LI, Mace D, Richardson RA, Wilson DF, Shan S, Dewhirst MW. The pervasive presence of fluctuating oxygenation in tumors. Cancer Res. 2008;68:5812–9.
14. Rofstad EK, Gaustad JV, Egeland TAM, Mathiesen B, Galappanthi K. Tumors exposed to acute cycling hypoxic stress show enhanced angiogenesis, perfusion and metastatic dissemination. Int J Cancer. 2010;127:1535–46.
15. Komar G, Seppänen M, Eskola O, Lindholm P, Grönroos JT, Forsback S, et al. ^{18}F-EF5: a new PET tracer for imaging hypoxia in head and neck cancer. J Nuc Med. 2008;49:1–8.
16. Koch CJ, Evans SM. In: Molecular Imaging Probes for Cancer Research, X Chen ed, World Scientific, Singapore, 2012; Chapter 10: "Non-Invasive Imaging of Hypoxia - Challenges and Opportunities" pp 286–315.
17. Koch CJ, Jenkins WT, Jenkins KW, Yang XY, Shuman AL, Pickup S, et al. Mechanisms of blood flow and hypoxia production in rat 9L-epigastric tumors. Tumor Microenv & Ther. 2012b;1:1–13.
18. Cascieri JJ, Graham MM, Rasey JS. A modelling approach for quantifying tumor hypoxia with [F-18]fluoromisonidazole PET time-activity data. Med Phys. 1995;22:1127–39.