Hypoxia Tracers

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Clinical impact of tumor hypoxia:
Tumor hypoxia can regularly be found in advanced solid tumors. Factors leading to an inadequate oxygen supply are an impaired function of tumor blood vessels, increased diffusion distances from blood vessels to tumor cells, as well as a reduced oxygen transport capacity of the blood in anemic patients. Hypoxic tumors are associated with a more aggressive local tumor growth, they show an increased risk of developing metastasis and exhibit a higher resistance to chemotherapy or radiotherapy (RT) than normoxic tumors (1).

Methods to assess tumor hypoxia:
The gold standard for the measurement of tissue oxygenation is the invasive direct measurement with a polarographic electrode. Ex-vivo methods include staining for exogenous or endogenous markers of hypoxia, such as e.g. HIF-1 (1). Noninvasive in-vivo methods are MR imaging, mostly assessing surrogates of hypoxia (e.g. blood oxygenation, flow and volume) and PET imaging using hypoxia specific tracers.

PET tracers for hypoxia imaging:
One group of hypoxia specific PET tracers is based on the 2-nitroimidazole structure, including FMISO, FAZA, FETNIM, FETA, EF1, EF3 and EF5. Of these, FMISO remains the most extensively evaluated hypoxia PET tracer in clinical trials up to now. FMISO is enzymatically reduced and retained in vital hypoxic cells, but not in areas of necrosis (2). Cu-ATSM is a hypoxia specific tracer that is not based on the 2-nitroimidazole structure. It has been postulated that under hypoxic conditions, Cu-ATSM is intracellularly reduced, dissociates, and the copper ion is taken up into the intracellular copper pool, thus trapping the activity in vital hypoxic cells (3). Radiotracers targeting hypoxia have to reach hypoxic areas in sufficient amounts, however hypoxia typically occurs in areas with diminished perfusion. Thus these compounds should be capable to penetrate tissues easily, which can be achieved best with substances showing balanced hydrophilic / lipophilic properties (4).

Potential clinical applications:
As tumor hypoxia is associated with an increased malignant potential, higher therapy resistance and decreased overall patient outcome, knowledge of the oxygenation status of individual tumors could be valuable information regarding risk stratification, therapy planning and therapy monitoring. As PET imaging of hypoxia allows the generation of a three-dimensional map of tumor oxygenation, state-of-the-art irradiation techniques such as IMRT (intensity-modulated radiotherapy), allowing the precise delivery of tightly conformal intratumoral dose distributions, could potentially be used for selective dose escalation to the hypoxic tumor subvolumes based on the biological information delivered by PET imaging (‘dose painting’) (5).

Limitations:
The spatial resolution of PET imaging methods is in the millimeter-range, however hypoxia is a process that occurs on the microscopic level. Small, but potentially biologically relevant areas might be missed by PET imaging. Moreover, the signal-to-noise ratio (contrast) of images delivered by many hypoxia PET tracers, especially FMISO, is poor compared to other PET tracers used in the clinical routine, such as e.g. FDG. This might be improved by new hypoxia tracers with enhanced pharmacokinetic properties like e.g. FAZA (6) or Cu-ATSM, which typically shows a higher signal-to-noise ratio than FMISO (7). Also the acquisition of dynamic PET data might improve the delineation of hypoxic tumor subvolumes, though this approach is more complex and time consuming compared to static PET imaging protocols. Lastly, recent studies showed variances in the reproducibility of FMISO PET in patients. (8) These findings have to be further investigated to validate hypoxia PET data as a base for radiation therapy planning.

Conclusion:
Numerous clinical studies have shown the feasibility of hypoxia imaging with PET techniques and its predictive value regarding patient outcome. However, hypoxia PET has not yet arrived in the clinical routine setting. To gain acceptance in the clinical workflow, its prognostic value and its validity as a base for RT planning is currently being further evaluated in clinical trials.

References

