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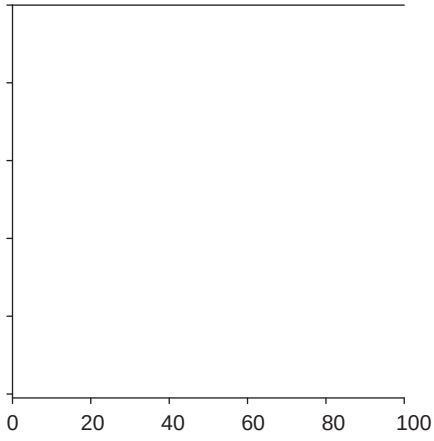
Histograph. Such principle was the first to demonstrate the prognostic significance of hypoxia in solid tumors [4] followed by other [5–8], but has never been established as a routine clinical assay due to assay related limitations. The method is restricted to accessible tumors only, and cannot differentiate between pO_2 values obtained from necrotic or viable hypoxic cells. The second principle is using markers reduced under hypoxic conditions. These are mainly nitroimidazole compounds that can be detected by e.g. immunohistochemistry or fluorinated radioactive nitroimidazoles detected by Positron Emission Tomography (PET). Nitroimidazoles enters the cell by passive diffusion and undergo reduction forming reactive species. If oxygen is present the compound is reoxygenated and leaves the cell, but under hypoxic conditions further reduction occurs binding the compound covalently to macromolecules and thereby `trapping` it inside the cell [9]. This process is dependent on enzymatic activity and thus occurs in viable hypoxic cells only [9–11]. Immunohistochemical analysis requires a tumor biopsy, whereas PET is a non-invasive method that allows repeated measurements of the same tumor and can determine spatial and temporal changes in hypoxia. A range of hypoxia specific PET tracers have been investigated. ^{18}F-fluoromisonidazole (^{18}F-FMISO) was the first generation of hypoxia specific PET tracers and so far the most widely used

[12,13]. Results obtained by ^{18}F-FMISO PET have shown that the degree of hypoxia varies within individual tumors and between tumors of identical histology [14]. Re7rcy(t thusree oot tr specifis-)]T 71854701 0 TD0 Tc4.058 Tw[c ( )]TJ71854705 -1.2 TD373046 Twhasnd (

being hypoxic. Thus, for each tumor the percentage of pO_2 values □ 5 mmHg was determined for each "Eppendorf virtual voxel" (e.g. if 3/7 pO_2 values were □ 5 mmHg □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