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EDITORIAL

Tumour oxygenation measurements using computed tomography and magnetic resonance imaging

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Multiple factors determine the resistance of tumours against radiation treatment (RT) and chemotherapy. Tumours may show an intrinsic, genetically determined inherent resistance. However, extrinsic physiological (environmental) factors are also important. Most critical is the presence of less or inadequate and heterogeneous vascular networks leading to chronic 'diffusion-limited' tumour hypoxia. Tumour hypoxia is also an acute cyclic phenomenon as part of a dynamic process in which the vessels periodically open and close. The latter type is translated as 'perfusion-limited' hypoxia.

There is strong evidence that for some human tumours treatment may fail due to the presence of hypoxia[1]. Therefore, the presence of tumour hypoxia needs to be identified and quantified, not only as predictor of outcome, but also to select patients for concomitant radiosensitising therapy to overcome the hypoxia effect. Treatments such as hyperbaric oxygen or carbogen (95–98% O_2 with 2–5% CO_2) breathing during RT have been extensively investigated and initiated in clinics[2]. The adequate appreciation of tumour hypoxia may also lead to the efficient use of hypoxia-directed treatments such as bioreductive drugs or gene therapy. Also the modulation of hypoxia from targeting tumour vasculature is another area of clinical interest that can profit from such measurements.

Direct quantification of tumour oxygenation can thus be expected to be of important prognostic and therapeutic value. However, until now appreciation of tumour oxygenation needs the application of invasive methods, such as biopsy-based immunohistochemistry using pimonidazole, or the use of Eppendorf oxygen-sensitive electrodes to screen tumours for hypoxia.

Tumour oxygenation as evaluated with oxygen-sensitive needle electrodes was shown to be of prognostic interest in certain human tumours, such as in metastatic neck adenopathies, cervix carcinoma, sarcomas and recurrent pelvic tumours[3]. However, oxygen-sensitive needle electrodes can only to a certain extent be used, as some primary tumours are deeply seated, difficult to reach and close to critical anatomic structures.

There is a clear need for *non-invasive* methods to measure tumour oxygenation. Increasingly more studies are demonstrating that imaging methods, such as computed tomography (CT) and magnetic resonance imaging (MRI), classically used to demonstrate the anatomic position and extent of tumours, are able to provide additional, biological information. For example, lymph node density on contrast-enhanced CT images reflects both tissue perfusion and degree of contrast agent diffusion in the tissue interstitium. Within neck adenopathies, appearing hypodense ('necrotic') on routine contrast-enhanced CT-images, hypoxic conditions are present, as measured with oxygen-sensitive electrodes[4]; such nodal hypodensity on CT images was the only independent predictor of locoregional failure in patients with stage III/IV head and neck cancer receiving RT alone or simultaneous radiation and chemotherapy[5]. A significant lower complete response rate to chemotherapy in patients with advanced head and neck cancer was reported in patients showing nodal hypodensity on CT, attributed to a reduced functional vascularisation of such lymph nodes for efficient drug delivery[6]. Other studies failed to confirm nodal necrosis, as visible on CT studies, as a prognostic factor for locoregional outcome in patients treated with RT or neoadjuvant chemotherapy. One of the explanations for these conflicting results may be that pure morphological parameters do not correlate sufficiently with impaired vascularisation and hypoxia.

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Intuitively, one expects an inverse relationship between maximum tumour diameter and tumour oxygenation: larger cancers show a progressive rarefaction of the vascular bed, structural and functional abnormalities of the tumour microcirculation and development of necrosis. Tumour volume can be quantified using routine cross-sectional imaging studies; such radiologically determined tumour volume is significantly related to local outcome, as has been demonstrated for several head and neck cancer sites and uterine cervical cancer. Compared to biological predictive assays as doubling time (T_{pot}) and surviving fraction (SF_2), tumour volume allows a much more precise prediction of response to RT[7]. Presumably, the prognostic value of tumour volume is not only determined by its possible correlation to tumour oxygenation, but also by the more or less linear relationship between tumour volume and number of clonogenic cells: success in controlling a tumour depends on killing all clonogenic cells.

Another approach to estimate tumour hypoxia seems to be feasible with 'dynamic' contrast-enhanced imaging techniques; such methodology allows a combined estimation of tissue perfusion, blood volume and permeability of vessels. A relationship between dynamic contrast-enhanced MRI parameters and tumour oxygenation has for example been shown in cervical carcinoma, using polarographic needle electrodes as reference[8].

Several other approaches to measuring tumour oxygenation are available with MRI. Tumour oxygenation can be measured indirectly with Phosphorus-31 MR spectroscopy. Experiments have been done using Fluor-19-MR spectroscopy, by using perfluorocarbon compounds as oxygen sensor[9], but these perfluorocarbon compounds are currently not available for clinical use.

Another possibility is to use hydrogen-MRI, to test the reoxygenation of a particular tumour while the patient is breathing carbogen, using the principle of fMRI. The blood oxygenation level-dependent (BOLD) contrast depends on the endogenous switch from paramagnetic deoxyhemoglobine to diamagnetic oxyhemoglobin, a conversion that is translated in changes of MR signals. This principle is extensively used in functional MRI to assess brain activity triggered with exercise or other external stimuli. Typically, tumour oxygenation data are collected using a single-slice gradient-recalled echo (GRE) technique at very high field strength[10]. Recently, the feasibility of using BOLD-fMRI with echo planar imaging (EPI) in a 1.5 T clinical MR scanner, allowing evaluation of the entire tumour volume, was demonstrated in a rat rhabdomyosarcoma tumour model[11]. In this study, a large intertumour variability as well as an important intratumour difference in response, both when the rats breathed air or carbogen, was observed. Whereas in the majority of tumours the signal intensity increases were positive (indicating improved oxygenation), a negative change in signal intensity (indicating reduced oxygenation) was seen both in separate as well as in the same tumours. Such a heterogeneous response to carbogen breathing was also observed in a recent clinical study, where the principle of BOLD-fMRI was applied to patients with head and neck cancer[12]. In this perspective of heterogeneity, the possibility to analyse the whole tumour in a short time is an attractive (and even necessary) feature to quantitate the variable effects of oxygenation modifying compounds.

With the continuous improvement of MRI hardware and software, the development of new contrast agents and more refined methods of image data analysis, further progress in this field of acquiring non-invasively biologic information on tumours can only be anticipated.

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