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Biopsies as surrogate marker for clinical trials using immunotherapy

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Background: The therapeutic efficacy of immunotherapy is still poor, with a remission rate in the range of 10-20 per cent. There is thus a great need for predictive tests identifying potential responders. A successful immune reactivity to cancer is the final outcome of the co-operation of multiple factors. Consequently, surrogate end-points closely related to immune mediated tumour control should be chosen. Results: CD4+ lymphocytes, determined in final needle aspirates (FNA) pretreatment, were closely correlated ($p<0.001$) to response to interferon-α (IFN-α) in systemic disease. Similar results were also obtained in patients with regional metastatic disease. CD4+ TILs also predicted the outcome of biochemotherapy (IFN-α, cisplatinum, DTIC). Patients with this subset of TILs had a significantly prolonged time to progression and over-all survival. In untreated patients and during the first week, TILs were localised in the intra-tumoural stroma, whereas during the second week, CD4+ lymphocytes migrated into the tumour nodules. Also during the second week, histopathological analysis showed regressive tumour changes. After biochemotherapy, these areas where found in about 70% of the biopsies from patients with regional as well as systemic disease. In patients with regional disease more than 75% of the tumours were eradicated in half of the patients. This group also showed a longer survival compared to those with lower degrees of regressive changes. To better understand why regressive changes (< 75%) do not translate into prolonged remissions, two lymphocyte function markers, the ζ-chain of the T-cell receptor (TCR) and CD28, were analysed.

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MR Imaging of Angiogenesis in Cancer

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The development of novel therapeutic agents that target tumoural angiogenesis requires the development of biological surrogate markers of the angiogenic process. Magnetic Resonance Imaging (MRI) offers several minimally invasive methods for quantified imaging of the angiogenic process, which may be of value both in therapeutic trials of novel agents and in clinical monitoring. MRI imaging techniques using rapid acquisition of multiple images allows the collection of 4 dimensional time course data that can be used to quantify the effects of the passage of a contrast agent following systemic injection. This data can be analyzed using either simplistic curve shape descriptions or by the application of pharmacokinetic models of contrast distribution to provide information about the microvasculature. This data can be used to generate maps of regional blood volume, recirculational abnormality and endothelial permeability surface area product. These maps relate to the typical histological changes of increased microvascular density, vascular tortuosity and increased endothelial permeability that are seen in angiogenic tissues. These imaging markers can be highly reproducible and have been shown to correlate with tumour type, grade and prognosis.