Monitoring Tumor Response to Therapy with MRI

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Monitoring tumour response to radiotherapy and chemotherapeutic agents is most commonly performed using simple metrics of tumour burden derived from clinical CT or MRI images. This reflects the cytoreductive mode of action of these therapies, which are designed to kill tumour cells directly resulting in significant decreases in tumour volume. The use of tumour regression as the endpoint for clinical trials screening of new agents for evidence of anti-tumour effect is supported by years of evidence, suggesting that, for many solid tumours, agents which produce tumour shrinkage in a proportion of patients, have a reasonable chance of subsequently demonstrating an improvement in overall survival. In 1981 the World Health Organisation published tumour response criteria [1] . They introduced the concept of assessing tumour burden by summing the products of by dimensional lesion measurements and evaluating response to therapy by valuation of change from baseline. However, the WHO criteria were often modified leading to confusion in the interpretation of clinical trial results. Indeed the use of different response criteria was shown to lead to very different conclusions about the effectiveness of the therapeutic regime [2]. New criteria known as RECIST (Response Evaluation and Criteria in Solid Tumours) were published in 2000 defining the minimum size of measurable lesions, clearly describing how many lesions to follow and using unit dimensional rather than by dimensional measurements for over all evaluation of tumour burden [3,4]. The RECIST criteria are now a de-facto standard and were revised in 2009, reducing the maximum number of lesions assessed and including an assessment of pathological lymph nodes. In some tumour types, notably the brain, modified versions of the volumetric criteria have been produced, such as the RANO (Revised Assessment in Neuro-Oncology), designed to better reflect the behaviour and appearance of specific disease entities. Despite the design of volumetric response criteria targeted at specific tumours there continues to be very significant debate arising from the interpretation of this data particularly with novel targeted therapies. For example, the introduction of antiangiogenic therapies led to a recognition that definition of tumour volume based entirely on enhancing images failed to identify significant tumour recurrence in patients with glioma. Whilst it is clear that standardized markers of tumour burden are essential there is also significant evidence that these must be adapted in an ongoing way to address changes in therapeutic response behavior with novel drug therapies.

The monitoring of tumour responses also significantly affected by the mechanism of the therapeutic strategy. In some cases therapy may be expected to produce a cytostatic effect so that reduction in growth rate becomes a more appropriate indicator of therapeutic response. The measurement of growth rate is problematic particularly in small tumours. There is clear evidence from studies of Vestibular Schwannoma that the use of formal 3-D volumetric measurements produces significant improvement in the documentation and quantification of tumour response. Increasingly volumetric data is being included in clinical trials as one of a pattern of response criteria used to assess the activity of the therapy.

More importantly, the availability of advanced MR techniques such as diffusion weighted imaging (DWI) and dynamic contrast enhanced-MR (DCE-MRI) have led to extensive inclusion of these methodologies into early phase clinical trials. This is justified for the study of targeted therapeutic agents designed to produce changes in interstitial oedema (DWI) or in the vascular micro-environment (DCE-MRI). In addition to the recognition that non-volumetric criteria can be used as an index of tumour response it has become clear that there is an increasing need to assess tumour response at a far earlier stage. The introduction of targeted and combination therapies are increasingly leading to the availability of a range of therapeutic options for individual tumours at a given stage. Early identification of patients who will respond to a specific therapy is potentially highly beneficial since ineffective expensive therapies can be avoided and effective therapies instigated at the earliest possible stage. This patient targeted approach to therapy has led to the development of a number of approaches designed to predict tumour response either prior to therapy or very early during therapy.

Finally, it is increasingly evident that early effective therapeutic responses may be reflected heterogeneously within an individual tumour. The use of summary metrics such as the average value of an MR derived parameter can fail to detect therapeutic response by failing to extract the relevant information from the data. This has led to an increasing interest in metrics of tumour heterogeneity with a specific focus on identifying early responses to therapy that are predictive of tumour behaviour.

References

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