Measuring Response to Novel Therapies: Thinking Differently

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Key points:

1. Established tumor response criteria based on tumor size measurement before and after treatment may fail to identify responders or non-responders to novel therapies.

2. Functional MRI techniques provide quantitative measurements that reflect tumor biology. Quantitative values obtained from summary statistics and histogram analysis are being qualified as response biomarkers.

3. Multiparametric approach to response assessment may provide further insights into heterogeneity of tumor response, clonal evolution of tumors and the development of drug resistance.

Target audience:
Radiologists, technologists and allied scientists with an interest in oncologic imaging, particularly in clinical drug trials.

Outcomes/Objectives:

1. Understand functional MR imaging techniques and the biological correlates of the quantitative parameters derived.

2. Learn the changes in summary statistics and parameters derived from histogram analysis observed in responders to treatment.

3. Appreciate how multi-parametric imaging may improve understanding of tumor and response heterogeneity.

Introduction

Novel therapies include small molecules targeted at specific cancer pathways, immunotherapy and tumor vaccines. These treatments can be effective in arresting tumor growth without significant tumor size regression. Consequently, conventional tumor response criteria based on tumor size measurement on CT or MRI, are unreliable in identifying responders or non-responders to treatment.

Response evaluation not based on tumor size measurement

Radiologists are adept in using visually perceptible qualitative features for assessing diseases on imaging. However, in recent years, it has been shown that quantitative evaluation of CT images of both visually perceptible (e.g. CT density) and imperceptible (e.g. CT texture) features, may be useful in identifying responders and non-responders to a number of targeted treatments.

MR imaging is a versatile imaging technique, which can be performed in a variety of ways to obtain quantitative information that reflects tumor vascularity (transfer constant, rate constant, extravascular extracellular volume), tumor cellularity (apparent diffusion coefficient), tumor hypoxia (R2* relaxivity) and tumor metabolism (spectra concentration on MR spectroscopy). These quantitative techniques are increasingly used in early phase clinical trials, to evaluate drug effects and treatment response.

Many studies have utilized summary statistic values (e.g mean or median) derived from these tests, which have been observed to change in responders to effective treatment. In well-controlled studies, a number of these parameters have also demonstrated good measurement reproducibility. The measurement reproducibility is used to define the level of quantitative change that is likely to indicate a real drug effect. However, it must be remembered that an observable drug effect may not be biologically meaningful, and this has to be determined by corroborating the magnitude of parameter change with patient outcomes.

As data acquisition and analysis become more sophisticated, there is considerable interest in performing data analysis on a voxel-by-voxel basis. However, the success of such an approach is highly reliant on the data quality and is easily confounded by noise and data misregistration. Nonetheless, histogram analyses of the distribution of voxel values are being widely investigated. Changes in histogram skewness, kurtosis and the percentage of voxels above/ below a set threshold have been used to describe treatment response.

Multiparameter imaging

Recognizing that each quantitative imaging technique provides insight into a particular aspect of tumor pathophysiology, combining the imaging information from different MR imaging, CT imaging and/or PET imaging studies can help to cross-validate observations and also improve understanding of tumor heterogeneity associated with treatment. Furthermore, by combining quantitative information from two or more imaging techniques, it may be possible to gain insights into the clonal evolution of tumors and improve understanding of the development of tumor resistance to treatment. Last but not least, multiparameter imaging also provides the opportunity to investigate non-visually perceptible imaging features, which could be developed into response or predictive biomarkers for disease assessment in the future.