Chapter 14
CADrx for GBM Brain Tumors: Predicting Treatment Response from Changes in Diffusion-Weighted MRI

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ABSTRACT

The goal of this chapter is to describe a Computer-Aided Therapeutic Response Assessment (CADrx) system for early prediction of drug treatment response for Glioblastoma Multiforme (GBM) brain tumors with Diffusion Weighted (DW) MR images. In conventional Macdonald assessment, tumor response is assessed nine weeks or more post-treatment. However, this chapter will investigate the ability of DW-MRI to assess response earlier, at five weeks post treatment. The Apparent Diffusion Coefficient (ADC) map, calculated from DW images, has been shown to reveal changes in the tumor's microenvironment preceding morphologic tumor changes. ADC values in treated brain tumors could theoretically both increase due to the cell kill (and thus reduce cell density) and decrease due to inhibition of edema. In this chapter, the authors investigate the effectiveness of features that quantify changes from pre- and post-treatment tumor ADC histograms to detect treatment response. There are three parts in this technique: First, tumor regions were segmented on T1w contrast enhanced images by Otsu's thresholding method and mapped from T1w images onto ADC images by a 3D Region of Interest (ROI) mapping tool. Second, ADC histograms of the tumor region were extracted from both pre- and five weeks post-treatment scans and fitted by a two-component Gaussian Mixture Models (GMM). The GMM features as well as standard histogram-based features were extracted. Finally, supervised machine learning techniques were applied for classification of responders or non-responders. The approach was evaluated with a dataset of 85 patients with GBM under chemotherapy, in which 39 responded and 46 did not, based on tumor volume reduction. The authors compared adaBoost, random forest, and support vector machine classification algorithms, using ten-fold cross validation, resulting in the best accuracy of 69.41% and the corresponding area under the curve (Az) of 0.70.

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INTRODUCTION

The general aim of this chapter is to discuss the application of machine learning techniques in treatment response monitoring using advanced MR imaging protocol in clinical trials. Computer-Aided Diagnosis (CADx) in GBM brain tumor is an active research area, and many promising MR methods have been developed for detecting and characterizing cancer, its treatments and adverse effects (e.g. T1-weighted MR, T2-weighted MR, MR spectroscopy, perfusion-weighted MR, and diffusion-weighted MR). In our study, we focused on T1-weighted and DW-MRI. We name our proposed system Computer-Aided Therapeutic Response Assessment (CADrx).

We developed a computer-aided system to explore an early imaging biomarker using diffusion MR in a phase II clinical trial. Conventionally, tumor size change on T1w images is the only imaging biomarker that is accepted by the FDA as a surrogate endpoint of clinical outcome after chemotherapy and radiotherapy for phase III trials (2007). Diffusion MRI has been explored for early detection of GBM brain tumor treatment response prior to the tumor size changes.

Machine learning and statistical pattern recognition have potential for significant contributions to the biomedical community because they can improve the sensitivity and/or specificity of detection and diagnosis of disease, while at the same time increasing objectivity of the decision-making process (Sajda, 2006). The need for machine learning is perhaps greater than ever given the dramatic increase in medical data being collected, new detection, and diagnostic modalities being developed, as well as the complexity of the data types and importance of multimodal analysis. In all of these cases, machine learning can provide new tools for interpreting the high-dimensional and complex datasets with which the clinician is confronted (Sajda, 2006). In this chapter we explore three different classification methods: AdaBoost, random forest, and support vector machine in our CADrx system.

BACKGROUND

Glioblastoma Multiforme (GBM) is the most common and most aggressive type of the primary brain tumors. GBM is an anaplastic, highly cellular tumor with poorly differentiated, round, or pleomorphic cells, occasional multinucleated cells, nuclear atypia, and anaplasia. The median survival time from the time of diagnosis without any treatment is 3 months, but with treatment, survival of 1-2 years is common. Although the prognosis of GBM is uniformly poor, treating patients in an attempt to improve the quality of life is worthwhile. GBM treatment consists of a combination of surgical resection, radiation therapy, and chemotherapy. Surgical resection is the mainstay of GBM treatment, and radiation therapy usually follows surgery. The U.S. Food and Drug Administration approved Avastin (bevacizumab) to treat patients with glioblastoma at progression after standard therapy. Bevacizumab (trade name Avastin, Genentech/Roche) is a humanized monoclonal antibody that recognizes and blocks vascular endothelial growth factor A (VEGF-A). VEGF-A is a chemical signal that stimulates the growth of new blood vessels (angiogenesis). Blood vessels grow uncontrollably in cancer, retinal proliferation of diabetes in the eye, and other diseases. Bevacizumab can block VEGF-A from creating new blood vessels. Bevacizumab was the first clinically available angiogenesis inhibitor in the United States.

The conventional way to assess treatment response in a phase II in vivo clinical trial is based on Macdonald criteria and evaluated on T1-weighted contrast enhanced (T1wCE) MR images. The Macdonald criteria define tumor response by use of tumor size change, steroids, and neurological function. There are four 'response' categories: Complete response (CR) is defined as disappearance of enhancing tumors, off steroids, and neurologically stable or improved. Partial response (PR) is >50% reduction in size of enhancing tumor, steroids stable or reduced, neurologically stable or improved. Progressive disease (PD) is