Clinical applications of imaging biomarkers. Part 3. The neuro-oncologist's perspective

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ABSTRACT. Radiation therapy is an important treatment modality in the management of brain tumours. Imaging biomarkers continue to be a focus of active investigation and there is increasing evidence of the utility of biomarkers in refining the overall management plan. This article briefly reviews the literature and outlines the possible clinical applications of imaging biomarkers in neuro-oncology.

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Advanced imaging in radiotherapy planning

Radiation therapy continues to play an important role in the treatment of brain tumours. As an initial step in radiotherapy planning, patients undergo a contrast-enhanced CT scan in the treatment position. This serves two purposes: (1) delineation of target volumes and organs at risk and (2) electron density information is used for dosimetry. MRI has been used to improve the accuracy of outlining tumours owing to the superiority of magnetic resonance (MR) in identifying intracranial anatomical structures.

Thornton et al [1] presented their clinical experience gained since the introduction of MR fusion to CT planning. They noted fusion of MR images to CT planning images allowed for display of MR-defined organs onto CT images, treatment planning could be carried out on composite images and doses could be displayed onto either set of images. They found that target outlining had to be changed because of the delineation of structures on MR images that were not visible on CT images. They reported that MR increased the clinical target volume (CTV) compared with that seen on CT and felt that the integration of MR data with CT information was of significant practical value in treatment planning.

Datta et al [2] prospectively outlined the CTV and gross tumour volume (GTV) separately on CT and MR images in 21 patients. The volumes were estimated and their congruence studied. They noted that, compared with MR, CT underestimated the volumes with significant differences in the mean CTV and GTV. They concluded that target delineation for brain tumours should be based on MRI to reduce geographic misses.

Aoyama et al [3] developed an MRI system for radiotherapy planning, and GTVs were independently outlined on MR–CT and CT in 41 patients by 4 clinicians. The differences between observers and imaging modalities were analysed. They reported that MR fusion reduced target volumes and significantly reduced inter-observer variability. Welten et al [4] assessed the inter-observer variation on CT planning and the additional impact of MR information. 9 clinicians outlined GTV in 5

patients on CT images and on MR images 2 weeks later. It was noted that there was a high interobserver variability in GTV delineation on CT, which was not reduced by the addition of MR data. However, they recommended a combination of the two modalities for treatment planning.

In a study of 30 patients comparing ^{123}I -alpha-methyl-tyrosine single photon emission computed tomography (IMT-SPECT) with MRI, Grosu et al [5] showed that additional information from IMT-SPECT led to an increase in the target volumes by an average of 20% and suggested that the findings of IMT-SPECT may significantly modify the target volume for radiotherapy planning. Krengli et al [6] studied the effect of $^{99\text{m}}\text{Tc}$ -methoxyisobutylisonitrile (MIBI)-SPECT fused with MR in target delineation. In 21 patients, they outlined GTV on SPECT and MR images and analysed three volumes: combined volumes on SPECT and MR, volume overlap between SPECT and MR and volume extension beyond MR. The average SPECT GTV was larger than the MR GTV and they concluded that $^{99\text{m}}\text{Tc}$ -MIBI-SPECT fusion to MR in radiotherapy planning increased the fused GTV by 33% on average.

Narayana et al [7] studied the use of MR spectroscopy and functional MRI (fMRI) in treatment planning. They studied 12 patients who underwent MR spectroscopy and functional imaging prior to radiotherapy. After obtaining the various parameters, the choline/creatinine (Cho/Cr) ratio was converted into a greyscale grading system, fused with the MR images and then transferred to planning CT images for target volume outlining. They noted that MR spectroscopic imaging (MRSI)-defined volumes (MRSI-defined Cho/Cr ≥ 3) were 40% larger than T_1 with gadolinium-defined volumes and fMRI assisted in optimising beam orientation. Pirzkall et al [8] also evaluated the use of MRSI in target delineation. 34 patients had MR and MRSI pre-operatively. Target volumes were outlined on T_1 +gadolinium, necrosis and T_2 regions on the data sets acquired. MRSI parameters for Cho and *N*-acetylaspartic acid (NAA) were acquired and converted into a quantitative index, which was displayed as three-dimensional contours. They showed that MR spectroscopy defined metabolically active tumour extended beyond the T_2 volume by nearly 3 cm. They concluded that MRSI would optimise the target volume with the potential to improve local control while reducing complications. Liu et al [9] showed,

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in small study of 3 patients undergoing stereotactic radiosurgery, that using fMRI information in treatment planning could reduce the dose delivered to eloquent cortex by an average of 32% and suggested that fMRI provided additional information in planning.

Price et al [10] studied the correlation of diffusion tensor imaging (DTI) with image-guided biopsies and demonstrated that, using diffusion tissue signatures, it was possible to differentiate gross tumour from tumour infiltration with high sensitivity and specificity and concluded that DTI can improve target volume delineation. Jena et al [11] studied the value of DTI for deriving individualised treatment plans for patients with high-grade gliomas. DTI-based volumes were compared with standard CT-based planning volumes. They showed that the use of DTI caused non-uniform margins to be added to GTV but demonstrated that the planning target volumes were reduced by one-third on average.

Predicting treatment response

MRI has also been used to predict the outcome of patients treated with radiation. Tarnawski et al [12] in their study of 51 patients also analysed the prognostic significance of MR spectroscopy in post-operative radiotherapy for malignant gliomas. They revealed a statistically significant decrease in the NAA/Cr ratio and increases in the Cho/Cr, Cho/NAA and myoinositol/Cr ratios following surgery. The lactate/NAA ratio correlated strongly with survival and they concluded that MR spectroscopy demonstrated the ability to distinguish between patients with favourable prognosis and poor outcomes. Li et al [13] also identified pre-treatment MR and MRSI parameters that may predict survival in patients with malignant gliomas. Recursive partitioning methods were applied to various parameters, which included MR and MRSI variables. Older age, large contrast enhancement and high Cho/Cr, high Cho/NAA, high lipid lactate (L/L) and low Cr/NAA ratios predicted poorer outcomes. Tsien et al [14] measured the quantitative changes in signal intensity in the enhancing tumour rim and non-enhancing core on serially obtained MRI performed on 20 patients 1 week before, during and every 1–3 months after radiotherapy in high-grade gliomas. They observed signal intensity changes in all patients during weeks 1 and 3 of radiotherapy. Signal intensity changes in the non-enhancing core was found to be predictive of overall survival. They concluded that these changes may provide information regarding early response to treatment. Alexander et al [15] studied the prognostic significance of serial MR spectroscopy over the course of radiation therapy for gliomas. In a prospective study of 14 patients, MRSI was performed prior to radiotherapy, at week 4 and 2 months after radiotherapy. Normalised levels of Cho, NAA, Cr, lipid and lactate were calculated. They observed a reduction in the mean tumour Cho/NAA ratio with a highly significant difference in the mean normalised Cho ratio. Patients who demonstrated a >40% decrease in the normalised Cho ratio between week 4 and after the radiotherapy study showed significantly poorer survival. These authors concluded that the changing pattern of spectral studies over the course of radiotherapy appeared to be prognostic of tumour response and outcome.

Balmaceda et al [16] evaluated the role of MR spectroscopy in assessing the chemotherapy response in low-grade gliomas. They studied 14 patients and compared changes associated with chemotherapy by longitudinal comparisons of regional levels of Cho, NAA and lactate with changes on MR images and clinical status. They found a significant association between increased L/Cr and Cho/Cr ratios during treatment and a decreased progression-free survival. They suggested that Cho/Cr and L/Cr appeared to be the most reliable markers of tumour progression.

Diffusion MR has also been found to be sensitive to therapy-induced changes in cell structure. Chenevert et al [17] studied water diffusion and relaxation times using the intracranial 9L model. They noted diffusion MR could detect water diffusion changes after BCNU chemotherapy that resulted in 0.2 log cell kill. Mean apparent diffusion coefficients (ADCs) were highly sensitive to changes in tumour cellularity. Schepkin et al [18] compared sodium and proton diffusion MRI to detect cellular changes in tumours treated with BCNU chemotherapy. They noted that, in subcutaneous 9L cells treated with a single dose of drug, both modalities were able to detect early changes in cellularity as early as 2 days and these changes continued to evolve. These were predictive of subsequent tumour shrinkage, which occurred 10 days later. Babsky et al [19] also examined the effects of BCNU chemotherapy on ²³Na-MRI and water ADC in subcutaneously implanted 9L glioma cells in rats. Measurements were performed before chemotherapy and then 1, 3 and 5 days after chemotherapy administration. They noted higher values of signal intensity and water ADC in responders than in non-responders; values increased with tumour growth and these values were altered by chemotherapy. Their conclusions were that ²³Na-MRI and water ADC measurements may be useful in predicting and monitoring chemotherapeutic response.

Moffat et al [20] examined 20 patients with tumours with standard and diffusion MRI before treatment. Additional images were acquired 3 weeks later. They reported that the functional diffusion map (fDM) were found to predict patient response and concluded that fDM analysis provided an early biomarker for predicting treatment response in brain tumour patients. Hamstra et al [21] postulated that diffusion MRI using a functional diffusion map should predict patient survival. They studied 60 patients with high-grade glioma who underwent MRI at 1, 3 and 10 weeks of therapy. They observed a greater treatment-related increase in ADC in patients alive at 1 year than in those who died of disease. They concluded that, compared with conventional imaging, fDM provided an earlier assessment of equal predictive value and a combination of fDM and response rate provided more accurate prediction of survival.

Identification of radiation necrosis

Distinguishing between tumour recurrence and secondary radiation necrosis is a significant clinical problem. Zeng et al [22] performed MR spectroscopy examinations in 28 patients and analysed spectral data for NAA, Cho and Cr values. They reported that Cho/NAA and Cho/Cr ratios were significantly elevated in

recurrent tumours, whereas NAA/Cr ratios were correspondingly lower. The Cho/Cr and Cho/NAA ratios were significantly lower in radiation injury than in normal white matter. They concluded that MR spectroscopy could reliably differentiate recurrent tumour from injury. A study by Weybright et al [23] reached similar conclusions and suggested that the Cho/NAA and Cho/Cr ratios might be the best discriminators between recurrent tumour and radiation injury.

Hein et al [24] studied diffusion-weighted MRI as a means to differentiate between morphological features, including oedema, necrosis and recurrent tumour, by measuring differences in ADC. Ratios of ADC of enhancing lesion to ADC of contralateral white matter were calculated. They found that recurrence and non-recurrence could be differentiated by using mean ADC values and ADC ratios. These parameters were significantly lower in recurrent tumours.

Sundgren et al [25] also evaluated the use DTI in the differentiation of recurrent tumour from treatment-related injury. Mean ADC values, fractional anisotropy, eigenvalue indices and their ratios to the contralateral side were compared in patients with recurrent disease against radiation injury. ADC values were higher for recurrent disease; ADC ratios in the perilesional white matter oedema were higher for injury, as were the fractional anisotropy (FA) ratios in normal-appearing white matter. Eigenvalues were significantly higher in the recurrent group. They concluded that assessment of diffusion properties could assist in differentiation of recurrent tumour from radiation injury.

Other workers have also suggested that dynamic contrast-enhanced techniques may be useful in differentiating between tumour recurrence, characterised by high CBV and contrast transfer coefficient (K^{trans}) and radiation necrosis characterised by low values [26–29]. However, radiation necrosis represents a heterogeneous process with features resembling inflammation. Immature vessels may grow into previously necrotic areas [30], and viable tumour cells may still be found in the areas with decreased blood volume. Therefore, when this technique is used to monitor irradiated areas, the risk of overlooking the active tumour sites cannot be excluded [31].

Conclusions

The role of radiotherapy in the management of brain tumours continues to evolve. MRI is increasingly being used in radiotherapy planning to accurately outline target volumes. There is increasing evidence of the clinical utility of advanced MRI techniques to further improve tumour volume delineation and to differentiate between recurrent disease and treatment-related changes. Whether these refinements will translate into superior outcomes remains to be seen.

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