Characterizing response in head and neck cancer with cluster analysis of multi-parametric MRI data

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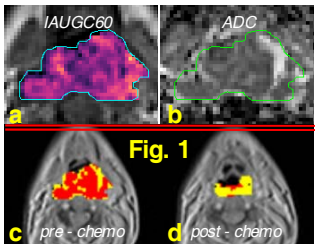
Introduction

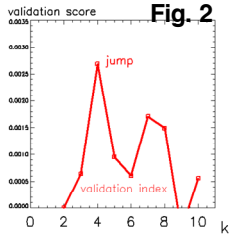
One of the main challenges in the management of head and neck squamous cell carcinomas (HNSCC) is the inability to predict outcome because of tumour heterogeneity [1]. Concurrent chemoradiation therapy, currently the standard treatment for locally advanced disease, delivers high doses of radiation which may result in toxicity to critical and adjacent normal tissues, and the adopted "one size fits all" approach can result in poor outcomes. There is therefore a pressing need to describe functional heterogeneity: radiotherapy delivery has become increasingly conformal and it would be possible to intensify treatment and escalate the radiation dose to a biological target volume, in an attempt to increase locoregional control. Multi-parametric functional imaging, by imaging different biological processes, may identify sub-volumes of the tumours likely to be resistant to treatment. We propose to divide lesions into sub-regions with similar functional characteristics in a cohort of patients with histologically proven HNSCC undergoing radical chemoradiotherapy, applying cluster analysis to MRI data acquired with a multi-parametric approach. The evolution of different sub-regions during treatment will be investigated and areas with similar functionality which are not reducing will be identified and characterized by a set of functional parameters.

Materials and Methods

Clinical Examinations: Nine subjects were scanned after written consent - as approved by the Local Ethics Committee - at the following time-points: baseline, following two cycles of induction chemotherapy (Cisplatin and 5-fluorouracil), after 40 Gy of chemoradiation, three and six months post-treatment. The MRI protocol at 1.5T included: Dynamic Contrast Enhanced (DCE), following Gadolinium injection (0.2 mg/kg), with a transaxial 3D FFE (TE = 1 ms, TR = 4 ms, 2x2x5 mm voxel, 1.5 s temporal resolution, 100 time-points) and Diffusion Weighted Imaging (DWI) (b = 0, 100, 500, 1000 s/mm^2, TE = 91 ms, TR = 2000 ms, 2x2x5 mm voxel, with SPAIR used for fat suppression), aligned over the same volume.

Data Analysis: Data were analysed using in-house software developed in IDL (Exelis Visual Information Solutions). Regions Of Interest (ROI) were drawn by a radiation oncologist on DCE data, for each slice, around all primary tumour (PT) and malignant lymph nodes (LN), and the central slice (largest cross-section, > 1.5 cm in short axis diameter) was identified. The in-plane misalignment between DWI and DCE images was estimated registering the b = 0 with the most enhanced image with a mutual information algorithm [2], and applied before transferring the ROIs to DWI data. The following parameters were computed voxel-wise: the Initial (60 s) Area Under the Gadolinium Curve (IAUGC60), and the Apparent Diffusion Coefficient (ADC) using a monoexponential model. The K-means clustering method [3] was used in the two-dimensional feature space formed by these two parameters, and data were partitioned in k = 2, 3, 4 clusters. The clustering algorithm was run on cumulative distributions of voxels including all the central slices from the lesions of all patients, and combining data from the first two time-points (pre and post-chemotherapy). Preliminary evaluation was performed to assess consistency of the results when including all the ROIs, when considering single lesions, and when separating PT and LN. Principal Component Analysis (PCA) was used to evaluate the contribution of single parameters to the partitioning. For cluster validation, the "jump method" was employed [4]: this approach is derived from the rate distortion theory and determines the number of clusters which maximizes efficiency while minimizing error by information theory standards. After classification, pre and post-chemotherapy data were separated and the evolution of clusters with treatment was evaluated, counting the number of voxels before and after treatment for each cluster and comparing for k = 2, 3, 4.





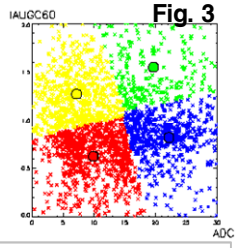


Table 1

	cluster 1		cluster 2		cluster 3		cluster 4	
k = 2								
	IAUGC60	*ADC*	*IAUGC60*	*ADC*				
centres	17.8	0.73	8.8	1.21				
reduction	66%		24%					
k = 3								
	IAUGC60	*ADC*	*IAUGC60*	*ADC*	*IAUGC60*	*ADC*		
centres	22.5	0.93	9.6	0.67	9.1	1.40		
reduction	83%		25%		24%			
k = 4								
	IAUGC60	*ADC*	*IAUGC60*	*ADC*	*IAUGC60*	*ADC*	*IAUGC60*	*ADC*
centres	22.2	0.82	19.7	1.55	9.9	0.63	7.2	1.27
reduction	83%		81%		23%		9%	

Figures. **Figure 1:** Parameter maps for a representative PT; (a) IAUGC60 (b) ADC (c,d) segmentation pre and post-chemo, in the simplest case of k = 2. **Figure 2:** Curve for the validation index [4], showing a "jump" for k = 4. **Figure 3:** Cumulative distribution of voxels, partitioned with k = 4. **Table 1:** Results from cluster analysis and percentage reduction after chemotherapy; IAUGC60 is expressed in units of mmol.s, ADC in units of 10^{-3} mm^2/s.

Results

Fourteen lesions were considered in the analysis, 5 PTs and 9 LNs. The area of contrast enhancement was found to extend further than the area of restricted diffusion, justifying the use of ROIs contoured on DCE images. The registration algorithm found and corrected a shift between the DCE and DWI images occurring only in the phase-encode direction, caused by an offset of the water frequency [5]. The preliminary analysis showed consistent results between the classification including all the slices and the central slice only, indicating that the central slice represents the functional heterogeneity of the whole lesion. Cluster centres of single lesions have reproducible values across lesion type (PT or LN). PCA on cumulative data indicates that the ADC component contributes 96.8% towards the difference in the data. Cluster validation reports that k = 4 is the optimal number of clusters, corresponding to the largest "jump" in the validation curve (Figure 2) and associated with a sharp increase in performance [4]. The total number of voxels partitioned was 2179 (Figure 3), with a global reduction of 48% after chemotherapy. Table 1 details the values of the cluster centre and the percentage reduction per cluster for k = 2, 3, 4, showing that regions with poor perfusion (low IAUGC60) are more likely to be resistant to treatment.

Discussion and Conclusions

We propose a method to robustly partition head and neck lesions in sub-regions using complementary functional information from DCE and DWI and cumulative data. This approach allows identification of sub-regions which are affected differently by treatment (Figure 1c,d) and their characterization with functional parameters. Compared with IAUGC60, ADC has a more discrete distribution of values, where the area of restricted diffusion (low ADC) can be clearly identified (Figure 1b); this is reflected in the results from PCA analysis. However, cluster analysis was able to separate high from low values in both parameters for all the number of cluster specified; but it is particularly interesting that the choice of k which best describes the differences in the data (k = 4) results in the best separation of reducing from non-reducing regions (Table 1). This indicates that the differences that we are describing are likely to be related to real functional heterogeneity and highlights the importance of cluster validation. A complete description of tissue functionality cannot be derived without comparison with histology; nevertheless, the cluster centre values, which summarize the functional parameters of the clusters, indicate the presence of regions of high perfusion and regions that are more likely to be necrotic. This approach is therefore able to spatially describe functional heterogeneity (Figure 1c,d), and could help in stratifying patients who are at high risk for locoregional failure and might benefit from intensifying local treatment. The proposed method could potentially identify a resistant biological target volume.

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