Delta Radiomics in Head and Neck Oncology

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The clinical management of head and neck carcinomas (HNC) involves a number of challenges, both regarding tumour control and normal tissue toxicity owing to the particularities of head and neck anatomy and radiobiology. Resistance to radio- and/or chemotherapy are common factors leading to treatment failure or loco-regional recurrence. There are some key tumour characteristics, including hypoxia, proliferative ability, the fraction of cancer stem cells, intrinsic radio-resistance, as well as the human papillomavirus (HPV) status, which should be considered when treating HNC patients. Biomarkers for the identification of the above tumour properties are available and can assist with patient stratification to increase tumour control. Medical images are fundamental tools for the establishment of diagnosis, response to therapy and patient monitoring during and post therapy. A powerful tool in the evaluation and interpretation of image features is the assessment of changes exhibited by these features over the course of therapy. The change in quantitative features extracted from longitudinal images acquired at different time points along the course of treatment and follow-up is known as delta-radiomics. Current applications of delta-radiomics in head and neck oncology show various trends that evolved along (1) treatment response monitoring, (2) prediction of normal tissue toxicity and also (3) treatment adaptation based on changing image features over time.

radiomics sequential imaging radiotherapy chemotherapy

1. Delta Radiomics in Diagnostic Accuracy

Most studies on delta radiomics fit into one of the aforementioned categories. Nevertheless, the evaluation of sequential image features can be applied for other purposes, such as differentiating between benign and malignant entities in HNC [1]. In their PET/CT-based study retrospectively undertaken on 56 patients with suspected or confirmed head and neck malignancy, Pietrzak et al. employed sequential FDG-PET examinations to compare the fluctuations in metabolic activity over time (60 and 90 min post injection) for staging purposes [1]. Using the standardized uptake value and the retention index as parameters, they showed that sequential FDG-PET/CT scanning increases specificity and provides more accurate information to assist in differentiating between benign and malignant lymph nodes in HNC.

2. Delta Radiomics in Tumour Response Evaluation

Various imaging techniques were employed for tumour-response evaluation via sequential image analysis or delta radiomics (**Table 1**). Quantitative evaluation of ultrasound (US) images was undertaken by Tran et al. during the course of radiotherapy in 36 HNC patients as part of a clinical trial (NCT03908684) having as its main objective the

identification of US-based parameters that can serve as early predictors of complete or partial response to radiotherapy. Lymph-nodes images were acquired 24 h, 1 week and 4 weeks after the start of radiotherapy [2]. Quantitative US spectral analysis was applied to compute US parameters for texture features. The naïve-Bayes algorithm used for classification was found to be the best predictor of tumour response to treatment for all time points, showing the potential of US delta radiomics for the early assessment of response to radiotherapy, with a prediction rate of 85% at 4 weeks after the start of treatment.

Table 1. Compilation of delta radiomics studies for evaluation/prediction of tumour response to therapy.

Study [Ref]	Aim of Study	Imaging Technique for Delta Radiomics	Outcome
Tran et al., 2020 [2] 36 HNC patients	Treatment-response monitoring	Quantitative ultrasound (spectral and texture parameters)	The best prediction accuracy was offered by single-feature naïve-Bayes classification (80% at 24 h; 86% at 1 week and 85% at 4 weeks after commencement of RT).
Fatima et al., 2021 [3] 51 HNC patients	Prediction of recurrence	Quantitative ultrasound (spectral and texture parameters)	The support vector machine classifier showed the best performance using delta radiomics in terms of accuracy (80% at week 1 and 82% at week 4) and AUC (0.75 at week 1 and 0.81 at week 4).
Morgan et al., 2021 [4] 90 HNC patients	Prediction of local failure	CT and intra-treatment CBCT	The highest (AUC = 0.871) at predicting local failure was achieved by the fused ensemble model. The same model scored the highest (AUC = 0.910) at predicting local failure for HN nodes.
Sellami et al., 2022 [5] 93 HNC patients	Prediction of response to radiotherapy	CBCT	Coarseness was the most significant radiomic feature, while haemoglobin level was most significant for the clinically relevant features. The combined clinical + radiomic model achieved AUD = 0.99 for treatment-response prediction.
Xi et al., 2022 [6] 272 HNC patients (nasopharynx)	Prediction of response to induction chemo + chemoradiotherapy	Multi-parametric MRI	LASSO-based feature selection was conducted: seven feature subsets were identified for the pre-treatment MRI radiomic model and 12 subsets for the delta-radiomics model. Both models were able to predict tumour response to therapy.
Corino et al., 2022 [7] 50 HNC patients (sinonasal)	Prediction of response to induction chemotherapy	Multi-parametric MRI	Three mono-modality delta-radiomics signatures determined for T1-weighted (AUC = 0.79), T2-weighted (AUC = 0.76) and apparent diffusion coefficient maps

Study [Ref]	Aim of Study	Imaging Technique for Delta Radiomics	Outcome
			(AUC = 0.93). Fused signature for all features was 0.89.

radiation, n-induced s, another umber of patients in the above studies would strengthen their prediction power and shed more light on the role of US delta radiomics for the early prediction of treatment-response monitoring and/or recurrence, allowing clinicians to intervene with treatment adjustments for a further optimized outcome.

Abbreviations: MRI = magnetic resonance imaging; CT = computed tomography; FDG-PET = fluorodeoxyglucose-positron emission tomography; CBCT = cone beam computed tomography; RT = radiotherapy; AUC = area under the curve; SUV = standardized uptake value.

The use of CBCT in image-guided HNC therapy was exploited by others, through the analysis of radiomic signature changes between baseline CBCT and subsequent CBCT images acquired during treatment [5]. The study aimed to gather longitudinal information of radiomic features and to evaluate treatment-induced changes in these features for the prediction of outcome in combination with clinical factors. Patients having at least four CBCT image acquisitions (including the baseline) were considered eligible for the study. Single time-point feature selection was conducted based on the receiver operating characteristic (ROC) curves, conditioned by an AUC > 0.65. For the longitudinal features selection, the 95% confidence interval was determined for the smallest detectable change, with relevant features being considered those that underwent a detectable change during therapy for at least 5% of patients [5]. Of the three developed models (clinical-based, radiomics-based and combined), the combined model showed the highest accuracy in identifying poor responders. The coarseness (measure of the difference between the central voxel and its neighbourhood) was identified as the most significant radiomic parameter undergoing longitudinal change, while among clinical parameters the change in haemoglobin levels correlated the best with outcome. Radiomic features extracted from the 4th-week CBCT already showed prognostic power for treatment response.

Next to ultrasound and CBCT-based delta radiomics, the role of MRI features was also investigated in radiomics settings. Xi et al. performed pre-treatment MRI radiomics on a large patient lot, with the aim to extract the most optimal features for treatment-response prediction and to compare the radiomics model with the delta radiomics based on MRI images (sequential MRI of axial-fat-suppressed T2-weighted image (FS T2WI) followed by axial-fat-suppressed contrast-enhanced T1-weighted image (FS CE-T1WI)) acquired within 2 weeks before and after chemo-radiotherapy [6]. Both the single time point (radiomics) (AUC = 0.865) and delta-radiomics model (AUC = 0.941) showed good predictive power for tumour response to chemo-radiotherapy in nasopharyngeal cancer patients using MR imaging, potentially allowing for early treatment adaptation and optimisation.

Another multi-parametric MRI study undertaken on 50 patients with sinonasal cancers investigated the value for treatment outcome prediction after induction chemotherapy. The investigation included both mono-modality delta-radiomics signatures as well as fused signature for T1-weighted, T2-weighted, and apparent diffusion coefficient (ADC) maps [7]. The addition of ADC map information to either T1- or T2-weighted features improved the AUC values, confirming the importance of ADC maps for the predictive model. The study showed that early prediction of response to induction chemotherapy in this patient group using radiomics signature is superior to RECIST (Response Evaluation Criteria in Solid Tumours)-based radiological predictions. The clinical use of the radiomic model leads to the possibility of early treatment adjustments for non-responsive patients after induction

chemotherapy, avoiding unnecessary toxicities. The conclusions of this study are in line with similar reports showing that delta-radiomics models are preferred to single time-point models in predicting tumour response to therapy [7].

3. Delta Radiomics in Normal Tissue Toxicity Evaluation

Patients undergoing radiotherapy for HNC often develop severe and debilitating side effects. One of the most common normal tissue toxicities affects the functionality of the parotid glands, leading to xerostomia. Therefore, it is not surprising that most studies involving delta radiomics developed such models to analyse their predictive power for acute or late xerostomia, allowing for interventions during treatment to reduce the magnitude of side effects .

Daily CT images were employed for delta-radiomics analysis of 59 HNC patients in order to identify possible correlations between the severity of acute xerostomia and changes in CT-histogram texture features [8]. Among all parameters investigated, the changes in mean CT number and in the parotid volume were correlated with xerostomia grades when combined in the same predictive model ($r = 0.71$, $p < 0.00001$). The highest precision of acute xerostomia severity was predicted by the 5th-week delta radiomics. In a study conducted on 35 nasopharyngeal cancer patients, the changes in the amount of saliva were found to be an important predictor of acute xerostomia, next to changes in normalized feature values assessed on CT images between fraction 0 and fraction 10 of radiotherapy [9].

The risk of chronic xerostomia after HNC radiotherapy was evaluated using CBCT-based delta radiomics in a retrospective study of 119 patients [10]. Delta radiomics consisted of average weekly changes in the assessment of mean Hounsfield unit intensity and parotid volume, using week-1 CBCT images as baseline. A significant correlation was found between mid-treatment volume change and mean parotid dose. The predictive value of the radiomics model was compared with clinical and dose-volume histogram models by means of AUC. The delta-radiomics model showed slightly higher prediction value for grade-1 xerostomia as compared to the clinical model (AUC = 0.719 vs. 0.709), while the addition of delta-radiomic features (changes in contralateral parotid volume) to the clinical model improved the predictive performance for higher grade toxicities from AUC = 0.692 to 0.776 [10].

An interesting study looking at the temporal evolution of radiomic features rather than at changes between different time points (delta radiomics) was recently reported by Barua et al. [11]. The focus of the study was the risk evaluation of osteoradionecrosis in the mandibular bone of oropharyngeal cancer patients, using temporal trajectories of radiomic features that were derived from serial contrast-enhanced CT images acquired at three different time points: pre-treatment, 2 months, and 6 months post-radiotherapy. Their aim was to develop a predictive model using multivariate functional principal component analysis to assess temporal (kinetic) CT changes in mandibular subvolumes of patient at high risk for osteoradionecrosis. AUC-based model evaluation showed superiority over the radiomic kinetics model when compared to clinical or even delta radiomics, opening new avenues for image analysis through novel statistical approaches [11].

4. Delta Radiomics as a Potential Tool for Treatment Adaptation

Imaging plays an essential role in monitoring the treatment response of oncological patients. While the evaluation of post-treatment and follow-up images offer important information regarding treatment success, image analysis during the course of therapy can potentially assist with treatment adaptation, thus contributing to a more customized therapy. A number of recent studies using sequential PET/CT images acquired during treatment confirmed that changes in tumour dynamics based on hybrid image-feature variations call for treatment adjustments to improve patient outcome [12][13].

Given that tumour hypoxia is associated with resistance to therapy and cancer recurrence, Lazzeroni et al. investigated the association between the dynamic nature of hypoxia during chemo-radiotherapy in head and neck cancer patients and outcome prediction by analysing sequential PET/CT image features. The study employed ^{18}FMISO (^{18}F-fluoromisonidazole) as an imaging agent, which is a PET radiotracer with selective uptake in hypoxic cells. Oxygen partial-pressure maps were then evaluated and compared through the progression and severity of hypoxic sub-volumes within the tumour, which revealed good correlations between the hypoxic areas and treatment outcome. PET/CT image features derived from the first two weeks of chemo-radiotherapy demonstrated the predictive power of delta radiomics in radio-resistant head and neck cancer patients [13]. Another study undertaken in head and neck cancer patients with hypoxic tumours, in line with the above-presented findings, reported that radiomic features of hypoxia-specific PET/CT images, but also variations in these features during chemo-radiotherapy, predict survival in this patient group. The study revealed that a higher homogeneity of tumour hypoxia during therapy is associated with a better treatment outcome [12].

Tumour proliferation during therapy is another common feature of HNC which can hinder treatment success. In view of this, ^{18}F-FLT PET (3′-deoxy-3′-(18)F-fluorothymidine), a proliferation-specific tracer, was employed to monitor early tumour response to treatment and to identify possible correlations between PET parameters and outcome [14]. The study involved 48 HNC patients who underwent sequential ^{18}F-FLT PET scans before and during the 2nd and 4th weeks of radio/chemotherapy. A decline in SUVmax higher than 45%, and of the PET-segmented gross tumour volumes using visual delineation (GTVVIS) greater than the median, during the first 2 weeks of therapy correlated with superior 3-year disease-free survival. A further decrease in the GTVVIS in the 4th week of treatment also correlated with better 3-year loco-regional control (100% vs. 68%, p = 0.021), showing that a change in ^{18}F-FLT uptake early during treatment is a strong predictor of clinical outcome and could serve as a biomarker for treatment personalisation and adaptation [14][15].

An important aspect that often needs intervention and adaptation of the treatment plan in HNC radiotherapy is tumour volume alteration due to weight loss, tumour shrinkage or variations in tumour position and shape [16]. Changes in tumour volume over the course of therapy impact not only the tumour dosage but also on the surrounding healthy organs that could receive an overdose, leading to side effects. To predict early volumetric changes, Illiadou et al. developed a delta-radiomic model based on weekly CBCT images in a cohort of 40 HNC patients, focusing on parameters related to the clinical target volume and the parotid glands [17]. A recursive-feature

elimination with correlation bias (RFE-CBR) feature-selection procedure combined with support vector machine (SVM) classifiers was employed to predict anatomical changes in the initial tumour volume. A 0.90 prediction accuracy was achieved (AUD = 0.91) with the selected radiomic features (13 features for the tumour volume and 6 for the parotids). Delta radiomics of weekly CBCT images during HNC radiotherapy using week 1 CBCT as a baseline was shown to provide important information on volume changes from the first week of therapy, which could identify the need for and guide treatment adaptation.

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