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Original article

Parotid gland fat related Magnetic Resonance image biomarkers improve prediction of late radiation-induced xerostomia

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ABSTRACT

Purpose: This study investigated whether Magnetic Resonance image biomarkers (MR-IBMs) were associated with xerostomia 12 months after radiotherapy (Xer_{12m}) and to test the hypothesis that the ratio of fat-to-functional parotid tissue is related to Xer_{12m}. Additionally, improvement of the reference Xer_{12m} model based on parotid gland dose and baseline xerostomia, with MR-IBMs was explored.

Methods: Parotid gland MR-IBMs of 68 head and neck cancer patients were extracted from pre-treatment T1-weighted MR images, which were normalized to fat tissue, quantifying 21 intensity and 43 texture image characteristics. The performance of the resulting multivariable logistic regression models after bootstrapped forward selection was compared with that of the logistic regression reference model. Validity was tested in a small external cohort of 25 head and neck cancer patients.

Results: High intensity MR-IBM P90 (the 90th intensity percentile) values were significantly associated with a higher risk of Xer_{12m}. High P90 values were related to high fat concentration in the parotid glands. The MR-IBM P90 significantly improved model performance in predicting Xer_{12m} (likelihood-ratio-test; $p = 0.002$), with an increase in internally validated AUC from 0.78 (reference model) to 0.83 (P90). The MR-IBM P90 model also outperformed the reference model (AUC = 0.65) on the external validation cohort (AUC = 0.83).

Conclusion: Pre-treatment MR-IBMs were associated to radiation-induced xerostomia, which supported the hypothesis that the amount of predisposed fat within the parotid glands is associated with Xer_{12m}. In addition, xerostomia prediction was improved with MR-IBMs compared to the reference model.

Xerostomia is one of the most frequently reported side-effects following radiotherapy for head and neck cancer, and has a major impact on quality of life [1,2]. Normal Tissue Complication Probability (NTCP) models have been developed to predict radiation-induced xerostomia and have demonstrated a clear relationship with parotid gland dose and baseline patient-rated xerostomia [3,4]. Nevertheless, substantial unexplained variance in predicting xerostomia remains. Better understanding of the aetiology of radiation-induced xerostomia is necessary to advance towards more individualised treatments and better sparing of normal tissues by further dose optimization, by means of new radiation techniques, such as proton therapy [5,6] and Magnetic Resonance Imaging (MRI) guided radiation [7].

Tumour-based image biomarkers (IBMs), which are shape, intensity and texture characteristics extracted from images, can contribute to the prediction of overall, disease-free and progression-free survival [8–13]. However, the role of these IBMs in normal tissues to predict radiation-induced toxicities is less explored, while these are imperative in supporting treatment decisions [5].

Our previous study based on IBMs from pre-treatment CT images, demonstrated that high heterogeneous parotid gland tissue, was associated with a higher probability of developing late xerostomia [14]. Qualitative evaluation of the parotid glands suggested that the predictive CT-IBM indicated the ratio between fatty and functional parotid parenchyma tissue. In a subsequent study, we showed that patients with low metabolic parotid glands,

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quantified in pre-treatment ^{18}FDG-PET IBMs, were more likely to develop late xerostomia. These associations also suggested that the non-functional (which can be fatty tissue) to functional tissue ratio is an important pre-treatment characteristic to improve prediction of xerostomia [15].

MRI is superior in imaging soft tissue contrast and therefore more accurate in differentiating fat from the parenchymal gland tissue compared to CT and ^{18}FDG-PET [16]. Hence, investigating the pre-treatment MR-IBMs of the parotid glands could, therefore, potentially provide better information for predicting late xerostomia.

The purpose of this study was to test whether MR-IBMs extracted from T1-weighted MRI scans were associated with the development of xerostomia 12 months after radiotherapy (Xer_{12m}) and to investigate whether MR-IBMs can improve the xerostomia prediction model based on parotid gland dose and baseline xerostomia only. The predictive MR-IBMs were evaluated to test the hypothesis that the fat-to-functional parenchymal parotid tissue ratio is related to Xer_{12m}. The findings were externally validated in an independent cohort.

Materials and methods

Patient demographics and treatment

The training and test cohort included head and neck cancer patients that were treated with definitive radiotherapy with or without concurrent chemotherapy or cetuximab between September 2012 and December 2014 at the University Medical Center Groningen (UMCG), and between October 2010 and March 2016 at Memorial Sloan Kettering Cancer Center (MSKCC), respectively. All patients were treated with Intensity-Modulated Radiation Therapy (IMRT) or Volumetric Arc Therapy (VMAT) using a simultaneous integrated boost (SIB) technique. The parotid glands were spared as much as possible. Patients received a total therapeutic dose of 70 Gy over 6–7 weeks. Most patients received bilateral neck radiation with a prophylactic dose of 54.25 Gy. Details about the radiotherapy regimens used are described in detail in previous studies [14,17].

Patients were excluded if they had salivary gland tumours or underwent surgery or radiotherapy in the head and neck area prior to or within one year after treatment. Moreover, patients without late follow-up data were excluded. Furthermore, MRI scan quality was visually evaluated, and if scans had considerable noise, limiting both visualisation of the parotid glands and reliable estimation of the local image intensity, patients were excluded. The final number of patients was 68 and 25 in the UMCG and MSKCC cohorts, respectively.

Endpoints

The primary endpoint was patient-rated moderate-to-severe late xerostomia (Xer_{12m}). In the UMCG cohort, this corresponds to the 2 highest scores of the 4-point Likert scale of the EORTC QLQ-H&N35 questionnaire and was consistently scored 12 months after treatment, which is part of a Standard Follow-up Program (SFP) for Head and Neck Cancer Patients (NCT02435576), as described in previous studies [4,18].

In the MSKCC cohort, xerostomia was scored with multiple questions with a 0–10 scale [19,20] (see Supplemental Materials 1). Xerostomia scores were collected between 6 and 17 months after treatment (mean ± SD: 11.0 ± 2.5 months). Moderate-to-severe xerostomia was considered if any of the questions was scored 6 or higher.

MRI acquisition and standardisation

In the UMCG, MR images were acquired in treatment position on a single scanner (MAGNETOM Aera 1.5 T scanner, Siemens Medical Systems, Knoxville, TN, USA) approximately 2 weeks before the start of radiotherapy (Spine 32, flexible 4 and 18 channel coils) for delineation purposes. T1-weighted Turbo Spin Echo (TSE) images (TE: 22 ms; TR: 457–606 ms) were acquired for all patients with a resolution of 0.36 × 0.36 × 4.00 mm without the use of intravenous contrast agents or fat-suppression.

In MSKCC, pre-treatment MR-images were acquired on MRI scanners of different manufacturers (GE, Phillips, Siemens) and scanners with field strength of 1.5 T (13 patients) and 3 T (12 patients). The resolution of the non-contrast enhanced T1-weighted TSE images (TE: 8–20 ms; TR: 400–697 ms) ranged from 0.35x0.35 to 1.01 x1.01 mm in-plane and the slice thickness from 3.0 to 5.0 mm.

The MRI intensity values of similar tissue types vary between scans. Therefore, only relative intensities within one scan can be compared. To make a comparison of the relative intensities between patients possible, scans had to be standardised. In this study, fat T1 characteristics were assumed consistent between patients, and should, consequently, have similar MR-intensity values. Subcutaneous fat was delineated in both the right and left cheek area in a minimum of 4 slices at the level of the parotid glands of all patients (Fig. 1I). The fat area was delineated laterally of the parotid gland, the masseter muscle and lip muscles, where the area is delineated as large as possible while excluding non-fat related structures. Subsequently, the MR images were multiplied by a fixed value, which was arbitrarily chosen to 350, and divided by the average subcutaneous fat intensity value. This

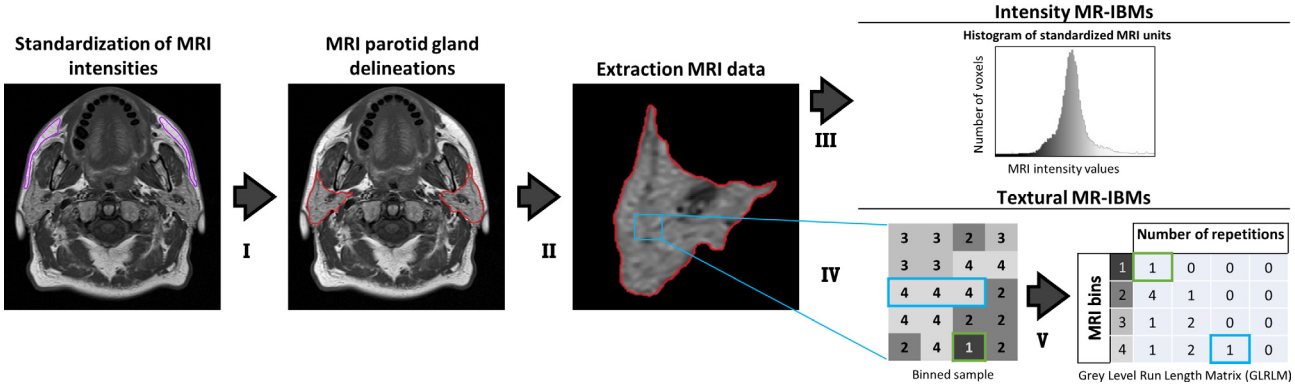

Fig. 1. MR-IBM extraction process. (I) MR scans were standardised with the average MR intensity, obtained from two delineated fat regions (purple). (II) MRI delineated parotid glands were extracted. (III) Intensity MR-IBMs were directly extracted. (IV) The MR intensities were binned. (V) Textural MR-IBMs were extracted from matrices reflection grey level transitions or repetitions. (For interpretation of the references to colour in this figure caption, the reader is referred to the web version of this article.)

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