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Abstract:	Purpose: Image texture analysis (TA) is a heterogeneity quantifying approach that cannot be appreciated by the naked eye, and early evidence suggests that TA has great potential in the field of oncology. The aim of this study is to evaluate parotid gland texture analysis (TA) combined with formal dosimetry as a factor for predicting severe late xerostomia in patients undergoing radiation therapy for head and neck cancers. Methods We performed a retrospective analysis of patients treated at our Radiation Oncology Unit between January 2010 and December 2015, and selected the patients whose normal dose constraints for the parotid gland (Mean Dose < 26 Gy for the bilateral gland) could not be satisfied due to the presence of positive nodes close to the parotid glands. The parotid gland that showed the higher V30 was contoured on CT simulation and analysed with LifeX Software ©. TA parameters included features of grey-level co-occurrence matrix (GLCM), neighbourhood grey-level dependence matrix (NGLDM), grey-level run length matrix (GLRLM), grey-level zone length matrix (GLZLM), sphericity, and indices from the grey-level histogram.

	We performed a univariate and multivariate analysis between all the texture parameters, the volume of the gland, the normal dose parameters (V30 and Mean Dose), and the development of severe chronic xerostomia. Results Seventy-eight patients were included and twenty-five (31%) developed chronic xerostomia. The TA parameters correlated with severe chronic xerostomia included V30 (OR 5.63), Dmean (OR 5.71), Kurtosis (OR 0.78), GLCM Correlation (OR 1.34), and RLNU (OR 2.12). The multivariate logistic regression showed a significant correlation between V30 (0.001), GLCM correlation (p: 0.026), RLNU (p: 0.011), and chronic xerostomia ($p<0.001$, R2:0.664). Conclusions Xerostomia represents an important cause of morbidity for head and neck cancer survivors after radiation therapy, and in certain cases normal dose constraints cannot be satisfied. Our results seem promising as texture analysis could enhance the normal dose constraints for the prediction of xerostomia.
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- **Informed Consent:** Informed consent was obtained from all individual participants included in the study.

ABSTRACT

Purpose: Image texture analysis (TA) is a heterogeneity quantifying approach that cannot be appreciated by the naked eye, and early evidence suggests that TA has great potential in the field of oncology.
The aim of this study is to evaluate parotid gland texture analysis (TA) combined with formal dosimetry as a factor for predicting severe late xerostomia in patients undergoing radiation therapy for head and neck cancers.

Methods We performed a retrospective analysis of patients treated at our Radiation Oncology Unit between January 2010 and December 2015, and selected the patients whose normal dose constraints for the parotid gland (Mean Dose < 26 Gy for the bilateral gland) could not be satisfied due to the presence of positive nodes close to the parotid glands.
The parotid gland that showed the higher V30 was contoured on CT simulation and analysed with LifeX Software ©. TA parameters included features of grey-level co-occurrence matrix (GLCM), neighbourhood grey-level dependence matrix (NGLDM), grey-level run length matrix (GLRLM), grey-level zone length matrix (GLZLM), sphericity, and indices from the grey-level histogram.
We performed a univariate and multivariate analysis between all the texture parameters, the volume of the gland, the normal dose parameters (V30 and Mean Dose), and the development of severe chronic xerostomia.

Results Seventy-eight patients were included and twenty-five (31%) developed chronic xerostomia.
The TA parameters correlated with severe chronic xerostomia included V30 (OR 5.63), Dmean (OR 5.71), Kurtosis (OR 0.78), GLCM Correlation (OR 1.34), and RLNU (OR 2.12).
The multivariate logistic regression showed a significant correlation between V30 (0.001), GLCM correlation (p: 0.026), RLNU (p: 0.011), and chronic xerostomia ($p<0.001$, R2:0.664).

Conclusions Xerostomia represents an important cause of morbidity for head and neck cancer survivors after radiation therapy, and in certain cases normal dose constraints cannot be satisfied. Our results seem promising as texture analysis could enhance the normal dose constraints for the prediction of xerostomia.

Introduction

Radiation therapy (RT), with or without chemotherapy and/or surgery, represents the standard of care for the majority of head and neck cancer patients.

For many years, RT has evolved with better target definitions and healthy tissue avoidance criteria, resulting in an improvement of loco-regional control and overall survival [1-3].

In particular, the introduction of intensity modulated radiation therapy (IMRT), which allows for the simultaneous delivery of different fractional doses to the various planned target volumes (PTVs), has led to improved target irradiation, while limiting doses to normal tissues, thus reducing side effects and morbidity [4-7].

The most common side effect of head and neck RT is xerostomia, which results from permanent damage to the salivary glands, particularly the parotids, thus leading to a major impairment of the patient's quality of life [8,9]. Dosimetric studies have shown that, in this setting, IMRT may be useful for protecting the parotids against excessive radiation [4-7,10,11], and have shown that a mean radiation dose of 26 Gy is the threshold for preserving stimulated salivary flow [6,10]. A clear benefit was also obtained in terms of quality of life (QoL) after the parotid-sparing effect of IMRT was demonstrated [4,12].

However, this approach cannot be applied to a subset of patients in everyday clinical practice due to the presence of gross tumour or nodal disease close to the parotid glands [13,14]. Yet, despite this, only a certain percentage of head and neck patients, whose dose constraints could not be satisfied, develop radiation induced xerostomia due to the sensitivity and specificity of normal tissue complication probability (NTCP) models at the clinic [15].

These data suggest that, in addition to a formal dosimetric analysis, other parameters are required in order to obtain a more accurate prediction of xerostomia.

Image texture analysis (TA) is a heterogeneity quantifying approach that cannot be appreciated by the naked eye, and early evidence suggests that TA has a great potential in the field of oncology[16-18].

This analysis refers to numerous mathematical methods, which are used to evaluate the grey-level intensity and position of the pixels within an image in order to derive the so-called "texture features", which in turn provide for a measure of heterogeneity [19,20], and has already been applied to the parotid gland in terms of radiation induced structural modifications and diagnostic power [21-23].

The aim of this study is to evaluate parotid gland TA as a factor for predicting xerostomia.

Materials and Methods

Patient series. We performed a retrospective analysis of head and neck patients treated at our Radiation Oncology Unit between January 2010 and December 2015, and selected the patients whose normal dose constraints for the parotid gland (Mean Dose < 26 Gy for bilateral gland) could not be satisfied due to the presence of positive nodes close to the parotid glands.
All of the patients' clinical and pathological data were recorded before RT was begun. All the patients underwent CT simulation before RT treatment. The presence of xerostomia prior to RT was considered an exclusion criterion. A signature for informed consent was obtained for any treatments, as well as for the anonymous use of the clinical data. All the procedures were conducted in accordance with the ethical standards of the World Medical Association's Declaration of Helsinki (1964, most recently amended in 2008). This study has been authorized by the Institutional Review Board.

Radiotherapy and chemotherapy treatment. RT was delivered with a 6 MV photons Linear Accelerator, using the Intensity Modulated Radiation Therapy technique (IMRT). The target volume was identified by diagnostic CT with MRI image fusion. CT simulation was performed with a 2.5 mm slicing, 120 KV, 10 Noise Index, 100-440 mA Range, spiral 16 slice CT scanner. Chemotherapy (Cisplatinum 40mg/m^2, weekly) was accordingly prescribed following the National Cancer Network (NCCN) guidelines.

CT acquisition and segmentation. Planning CTs were acquired in our Department, according to the scanning protocol, using a GE "Lightspeed" © CT Scanner (GE Medical System, Milwaukee, WI, USA).
The parotid gland that showed a higher V30 was contoured by an expert radiation oncologist (GR, PT), taking into consideration both the diagnostic CT and MRI, and eventually using image fusion [24,13].
The impact of the variations on the contouring was analysed by having two delineations performed on each patient by different Radiation Oncologists (VN, PP), and the TA parameters were tested for reliability with the Intra-class Coefficient Correlation method (ICC).

Feature extraction and texture analysis. All the analysis for this work was carried out using LifeX Software ©. The selected parotid gland (i.e.: as above, the parotid that showed a higher V30) was used as the region of interest (ROI). The LifeX Software extracted the TA parameters of the ROI from the CT simulation scan. The TA parameters included features of grey-level co-occurrence matrix (GLCM), neighbourhood grey-level dependence matrix (NGLDM), grey-level run length matrix (GLRLM), grey-level zone length matrix (GLZLM), sphericity, and indices from the grey-level histogram (see **Table 1**).

Follow-up. After the RT was completed, the patients began a scheduled follow-up program, with repeated CT and MRI scans, in order to assess the recurrence of the pathology, at 4 weeks, 12-16 weeks, and every 3 months thereafter for the first two years, or, in the event that any clinical signs arose suggesting Progressive Disease (PD). General examinations were carried out every three months for the first two years, with toxicity

being recorded according the common toxicity criteria for adverse events (CTCAE v. 4.02) [25], blood counts and chemistry.

End-points and statistical analysis. The Common Toxicity Criteria of Adverse Events (CTCAEs) defines Xerostomia, or dry mouth, as a disorder characterized by reduced salivary flow in the oral cavity.

The presence of G3 grade xerostomia 12 months after the end of treatment was defined as the endpoint of severe chronic xerostomia [25].

We tested the reliability of the TA parameters, selecting the parameters with an ICC greater than 0.70, and analysed the correlation between the TA parameters.

If a correlation greater than 0.80 was observed, the variable with the lowest univariable correlation to the endpoint was omitted in order to avoid the risk of overfitting the model and the risk of multicollinearity [26].

These preselected texture analysis parameters and the known parameters of the parotid gland (volume, mean dose, V30) and clinical parameters (age, gender, use of chemotherapy) were correlated with the development of both acute and chronic xerostomia, using a univariate analysis and multivariate analysis (both with logistic regression analysis). ROC Curves were then generated for the known dosimetric parameters (volume, mean dose, V30), and for the integrated analysis of these known parameters with the TA parameters.

In order to validate the model's performance, the cohort was randomly separated into four partitions, with three partitions used as the training data sets, and the remaining one as the testing set (k-fold validation). The logistic regression analysis was optimized using the training data set, and the outcome of the testing data was then predicted by the optimized model. The training and testing were run four times, and the average performance was reported as the cross-validated performance. The prediction results were further interpreted using the receiver operating characteristic (ROC) curve.

The entire the statistical analysis was conducted using SPSS software 23.0.

Results

The main characteristics of our patient cohort are summarized in **Table 2.**

Seventy-eight patients were included, and twenty-five (31%) developed severe chronic xerostomia.

Out of 78 patients, 54 (69%) were male and 24 (31%) were female. The median age was 63 years (mean 61.8 years, s.d. 9.9 years, range 39-81 years).

Thirty-eight (48%) patients suffered from oropharyngeal cancer, twenty-eight (36%) from hypopharyngeal cancer, and twelve (16%) from nasopharyngeal cancer. Forty-one patients (53%) underwent concomitant chemo-radiation with Cisplatinum 40 mg/m^2, weekly.

During the observation period, 20 patients (25%) showed evidence of disease recurrence, and 14 patients (18%) died due to the progression of the disease. The median follow up time was 47.34 months (mean 49.24 months, s.d. 22.12 months, range 14-76 months).

Preselection of variables: -The reliability analysis performed with ICC showed that 27 out of 39 TA parameters resulted as significantly reproducible among the contouring of operators (ICC>0.70, single measure) (see **Table 3**).

We analysed the correlation between the significant TA parameters and, if a correlation greater than 0.80 was observed, the variable with the lowest univariable correlation to the ePD was omitted in order to avoid the risk of overfitting the model, and the risk of multicollinearity [26] in the univariate and multivariate analysis (binary logistic regression).

Factors predicting the development of xerostomia: We performed an analysis of the correlation between the preselected texture analysis parameters, the known parotid gland dose constraints, the clinical parameters, and the development of severe chronic xerostomia.

The TA parameters correlated with chronic xerostomia included V30 (OR 5.63), Dmean (OR 5.71), Kurtosis (OR 0.78), GLCM Correlation (OR 1.34) and RLNU (OR 2.12) (see **Table 4**).

The multivariate logistic regression showed a significant correlation between V30 (0.001), GLCM correlation (p: 0.026), RLNU (p: 0.011) and severe chronic xerostomia (p<0.001, R2:0.664) (see **Table 4**).

ROC curves were generated from the logistic regression with and without the TA parameters, and the AUC increased from 0.766 to 0.911 for chronic xerostomia (difference -0.140, p: 0.023) (see **Figure 1**) [27].

The k-fold validation was successful, as the AUC calculated on the four training sets were within the 95% confidence interval of the AUC calculated on the original population, both for the prediction of acute and chronic xerostomia (see **Table 6**).

Discussion

Radiation-induced xerostomia is the most common side effect suffered by head and neck cancer patients. RT-induced damage to the salivary glands includes changes in volume, consistency, and pH of the secreted saliva, with greater demineralization, and an increased incidence of dental caries [7,3].

Salivary dysfunction can be evaluated with different clinical endpoints, including analytical methods like stimulated salivary flow [28,29], operator rated outcomes graded according to toxicity classification systems (i.e. CTCAEs, LENT-Soma) [8,13,30], and patient-rated outcomes obtained using specific questionnaires [11,31,32].

The probability of xerostomia depends on the dose distributions to the salivary glands [33-35], whereas the contribution of the parotid gland's microarchitecture needs to be investigated. The use of IMRT has been shown to be useful for protecting the parotids against excessive radiation [4-7,10,11], even in prospective trials [36].

In this context, the texture analysis of the parotid gland has been recognized as a useful tool, even potentially correlated with the changes induced by radiation therapy [21,37], and diagnostic discrimination of parotid lesions on MRI [22].

A study of radiation induced parotid injury in head and neck patients has also been conducted, which analyses the ultrasound GLCM texture parameters [23].

These previous studies showed a decrease in *mean*, *entropy*, and *fractal dimension* between the start and the end of the radiation treatment, supposedly due to the loss of acinar cells and the increase in the adipose ratio, as also demonstrated by comparing CT images with histopathological slides [38].

Texture analysis allows for the identification of other textural features that characterize the structure of the parotid glands with respect to simple mean density, and provides for a greater exploitation of the CT images' information content. Van Dijk et al. [39,40] recently investigated the role of CT image biomarkers in the prediction of radiation-induced xerostomia and sticky saliva. According to his results, the prediction of late xerostomia could be significantly improved by adding the TA parameter ''Short Run Emphasis" (SRE), which quantifies the heterogeneity of parotid tissue, to a model with mean contra-lateral parotid gland dose and baseline values of xerostomia. For late sticky saliva, the TA parameter of maximum CT intensity for the submandibular gland was selected, in addition to baseline sticky saliva and the mean dose to the submandibular glands.

The Authors conclude that, although the clinical impact of the model's improvement remained limited in terms of classification and performance, the study was still important, as it represented an initial step towards improving the understanding of the patient-specific response of healthy tissue to RT, thus resulting in a better identification of the patients at risk of developing side effects.

In a reply Letter [41] to the preliminary results of our work [40], the same Authors asked for our results to be submitted as a full manuscript, as the information on this topic will contribute to a better understanding and prediction of the development of side effects in head and neck patients.

The univariate analysis in our work showed a correlation with the development of acute and chronic xerostomia with many of the textural features, and this is probably due to the high correlation between the textural parameters. The multivariate logistic regression showed a significant correlation between V30, GLCM Correlation, RLNU and chronic xerostomia ($p<0.001$, R2:0.695). If the motivation for the dosimetric parameter V30 is intuitive [33-35], RLNU refers to the length of the homogeneous run, and belongs to the Grey-Level Run Length Matrix (GLRLM), which provides the size of the homogeneous runs for each grey-level with the same matrix as the SRE parameter, which refers to the distribution of the short homogeneous runs in an image. According to Van Dijk et al. [39], like the SRE parameter, high values indicate heterogeneous parotid tissue or, in other words, indicate that the parotid gland parenchyma is irregular in these patients, and is significantly higher in patients developing chronic xerostomia.

The GLCM Correlation parameter refers to the dependency of grey-levels in the arrangements of pairs of voxels and belongs to the Co-occurrence Matrix (GLCM), which takes into account the arrangements of pairs of voxels to extract textural indices.

Both RLNU and GLCM correlation are higher in patients who are developing severe chronic xerostomia, and, in the absence of studies comparing these textural features with histopathological specimens, this could be associated with an increased radiosensitivity of the parotid gland, perhaps linked to a lower number of acinar cells, a reduction in vascularization, and/or a greater ratio of adipose tissue.

Limitations of the study. Our results may be worthy of critical consideration for possible methodological and technical refinements.

In particular, our study has the limitations of a mono-institutional retrospective study, and the correlations between the textural parameters and the clinical outcome require further investigation, even including other anatomical, clinical and dosimetric parameters, as proposed in previous works [42,43], in order to understand whether these structural parameters are related to the risk of xerostomia.

While our population of patients was inferior to that of Van Dijk et al. [39], we nevertheless believe that it is crucial to have more information and different methodologies, in order to further validate these models in clinical practice.

This study could also be extended by including other organs potentially correlated with the endpoint, such as other salivary glands and swallowing structures, in order to provide a more comprehensive framework of the structural and dosimetric parameters correlated with the development of xerostomia.

Furthermore, we need to investigate the actual reproducibility and reliability of this kind of analysis in other departments and hospitals, with different CT acquisition parameters.

Conclusions

Xerostomia is a major cause of morbidity for head and neck cancer survivors following radiation therapy, and normal dose constraints are unable to be satisfied in certain cases.

Our results appear to be promising, as TA seems to improve the knowledge of the predictive factors of this kind of radiation therapy's toxicity.

Further studies on a large population are needed to better estimate the actual preliminary data.

Conflict of Interest Statement

All the Authors declare not to have any conflicts of interest.

References

1. Dirix P, Nuyts S (2010) Evidence-based organ-sparing radiotherapy in head and neck cancer. The Lancet Oncology 11 (1):85-91. doi:10.1016/S1470-2045(09)70231-1
2. Retel VP, van der Molen L, Hilgers FJ, Rasch CR, L'Ortye AA, Steuten LM, van Harten WH (2011) A cost-effectiveness analysis of a preventive exercise program for patients with advanced head and neck cancer treated with concomitant chemo-radiotherapy. BMC cancer 11:475. doi:10.1186/1471-2407-11-475
3. Vissink A, Jansma J, Spijkervet FK, Burlage FR, Coppes RP (2003) Oral sequelae of head and neck radiotherapy. Critical reviews in oral biology and medicine : an official publication of the American Association of Oral Biologists 14 (3):199-212
4. Chao KS, Ozyigit G, Blanco AI, Thorstad WL, Deasy JO, Haughey BH, Spector GJ, Sessions DG (2004) Intensity-modulated radiation therapy for oropharyngeal carcinoma: impact of tumor volume. International journal of radiation oncology, biology, physics 59 (1):43-50. doi:10.1016/j.ijrobp.2003.08.004
5. Chao KS, Deasy JO, Markman J, Haynie J, Perez CA, Purdy JA, Low DA (2001) A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: initial results. International journal of radiation oncology, biology, physics 49 (4):907-916
6. Eisbruch A, Ship JA, Dawson LA, Kim HM, Bradford CR, Terrell JE, Chepeha DB, Teknos TN, Hogikyan ND, Anzai Y, Marsh LH, Ten Haken RK, Wolf GT (2003) Salivary gland sparing and improved target irradiation by conformal and intensity modulated irradiation of head and neck cancer. World journal of surgery 27 (7):832-837
7. Eisbruch A, Ten Haken RK, Kim HM, Marsh LH, Ship JA (1999) Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. International journal of radiation oncology, biology, physics 45 (3):577-587
8. Vissink A, Burlage FR, Spijkervet FK, Jansma J, Coppes RP (2003) Prevention and treatment of the consequences of head and neck radiotherapy. Critical reviews in oral biology and medicine : an official publication of the American Association of Oral Biologists 14 (3):213-225
9. Epstein JB, Emerton S, Kolbinson DA, Le ND, Phillips N, Stevenson-Moore P, Osoba D (1999) Quality of life and oral function following radiotherapy for head and neck cancer. Head & neck 21 (1):1-11
10. Blanco AI, Chao KS, El Naqa I, Franklin GE, Zakarian K, Vicic M, Deasy JO (2005) Dose-volume modeling of salivary function in patients with head-and-neck cancer receiving radiotherapy. International journal of radiation oncology, biology, physics 62 (4):1055-1069. doi:10.1016/j.ijrobp.2004.12.076
11. Pow EH, Kwong DL, McMillan AS, Wong MC, Sham JS, Leung LH, Leung WK (2006) Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage

nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. International journal of radiation oncology, biology, physics 66 (4):981-991. doi:10.1016/j.ijrobp.2006.06.013
12. McMillan AS, Pow EH, Kwong DL, Wong MC, Sham JS, Leung LH, Leung WK (2006) Preservation of quality of life after intensity-modulated radiotherapy for early-stage nasopharyngeal carcinoma: results of a prospective longitudinal study. Head & neck 28 (8):712-722. doi:10.1002/hed.20378
13. Bhide SA, Gulliford S, Schick U, Miah A, Zaidi S, Newbold K, Nutting CM, Harrington KJ (2012) Dose-response analysis of acute oral mucositis and pharyngeal dysphagia in patients receiving induction chemotherapy followed by concomitant chemo-IMRT for head and neck cancer. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 103 (1):88-91. doi:10.1016/j.radonc.2011.12.027
14. Logemann JA, Pauloski BR, Rademaker AW, Colangelo LA (1997) Speech and swallowing rehabilitation for head and neck cancer patients. Oncology 11 (5):651-656, 659; discussion 659, 663-654
15. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, Bentzen SM, Nam J, Deasy JO (2010) Use of normal tissue complication probability models in the clinic. International journal of radiation oncology, biology, physics 76 (3 Suppl):S10-19. doi:10.1016/j.ijrobp.2009.07.1754
16. Davnall F YCSP, Ljungqvist G, et al. (2012) Assessment of tumor heterogeneity: an emerging imaging tool for clinical practice? Insights Imaging 3:573 – 589
17. Nardone V, Tini P, Carbone SF, Grassi A, Biondi M, Sebaste L, Carfagno T, Vanzi E, De Otto G, Battaglia G, Rubino G, Pastina P, Belmonte G, Mazzoni LN, Banci Buonamici F, Mazzei MA, Pirtoli L (2017) Bone texture analysis using CT-simulation scans to individuate risk parameters for radiation-induced insufficiency fractures. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. doi:10.1007/s00198-017-3968-5
18. Nardone V, Tini P, Sebaste L, Biondi M, Banci Buonamici F, Pirtoli L (2016) Bone structure texture analysis as a potential tool to estimate radiation induced insufficiency fracture risk. Radiother Oncol. doi:10.1016/j.radonc.2016.06.001
19. Alobaidli S, McQuaid S, South C, Prakash V, Evans P, Nisbet A (2014) The role of texture analysis in imaging as an outcome predictor and potential tool in radiotherapy treatment planning. The British journal of radiology 87 (1042):20140369. doi:10.1259/bjr.20140369
20. Coroller TP, Agrawal V, Narayan V, Hou Y, Grossmann P, Lee SW, Mak RH, Aerts HJ (2016) Radiomic phenotype features predict pathological response in non-small cell lung cancer. Radiother Oncol. doi:10.1016/j.radonc.2016.04.004
21. Scalco E, Fiorino C, Cattaneo GM, Sanguineti G, Rizzo G (2013) Texture analysis for the assessment of structural changes in parotid glands induced by radiotherapy. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 109 (3):384-387. doi:10.1016/j.radonc.2013.09.019
22. Fruehwald-Pallamar J, Czerny C, Holzer-Fruehwald L, Nemec SF, Mueller-Mang C, Weber M, Mayerhoefer ME (2013) Texture-based and diffusion-weighted discrimination of parotid gland lesions on MR images at 3.0 Tesla. NMR in biomedicine 26 (11):1372-1379. doi:10.1002/nbm.2962
23. Yang X, Tridandapani S, Beitler JJ, Yu DS, Yoshida EJ, Curran WJ, Liu T (2012) Ultrasound GLCM texture analysis of radiation-induced parotid-gland injury in head-and-neck cancer radiotherapy: an in vivo study of late toxicity. Medical physics 39 (9):5732-5739. doi:10.1118/1.4747526
24. Eisbruch A, Kim HM, Terrell JE, Marsh LH, Dawson LA, Ship JA (2001) Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. International journal of radiation oncology, biology, physics 50 (3):695-704
25. Meirovitz A, Murdoch-Kinch CA, Schipper M, Pan C, Eisbruch A (2006) Grading xerostomia by physicians or by patients after intensity-modulated radiotherapy of head-and-neck cancer. International journal of radiation oncology, biology, physics 66 (2):445-453. doi:10.1016/j.ijrobp.2006.05.002
26. van der Schaaf A, Xu CJ, van Luijk P, Van't Veld AA, Langendijk JA, Schilstra C (2012) Multivariate modeling of complications with data driven variable selection: guarding against overfitting and effects of data set size. Radiother Oncol 105 (1):115-121. doi:10.1016/j.radonc.2011.12.006
27. Hanley JA, McNeil BJ (1982) The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 143 (1):29-36. doi:10.1148/radiology.143.1.7063747

28. van Acker F, Flamen P, Lambin P, Maes A, Kutcher GJ, Weltens C, Hermans R, Baetens J, Dupont P, Rijnders A, Maes A, van den Bogaert W, Mortelmans L (2001) The utility of SPECT in determining the relationship between radiation dose and salivary gland dysfunction after radiotherapy. Nuclear medicine communications 22 (2):225-231
29. Buus S, Grau C, Munk OL, Rodell A, Jensen K, Mouridsen K, Keiding S (2006) Individual radiation response of parotid glands investigated by dynamic 11C-methionine PET. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 78 (3):262-269. doi:10.1016/j.radonc.2006.02.013
30. Braam PM, Roesink JM, Moerland MA, Raaijmakers CP, Schipper M, Terhaard CH (2005) Long-term parotid gland function after radiotherapy. International journal of radiation oncology, biology, physics 62 (3):659-664. doi:10.1016/j.ijrobp.2004.12.015
31. Pellegrino F, Groff E, Bastiani L, Fattori B, Sotti G (2015) Assessment of radiation-induced xerostomia: validation of the Italian version of the xerostomia questionnaire in head and neck cancer patients. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 23 (4):925-932. doi:10.1007/s00520-014-2438-2
32. Lee TF, Fang FM (2013) Quantitative analysis of normal tissue effects in the clinic (QUANTEC) guideline validation using quality of life questionnaire datasets for parotid gland constraints to avoid causing xerostomia during head-and-neck radiotherapy. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 106 (3):352-358. doi:10.1016/j.radonc.2012.11.013
33. Beetz I, Steenbakkers RJ, Chouvalova O, Leemans CR, Doornaert P, van der Laan BF, Christianen ME, Vissink A, Bijl HP, van Luijk P, Langendijk JA (2014) The QUANTEC criteria for parotid gland dose and their efficacy to prevent moderate to severe patient-rated xerostomia. Acta Oncol 53 (5):597-604. doi:10.3109/0284186X.2013.831186
34. Miah AB, Gulliford SL, Clark CH, Bhide SA, Zaidi SH, Newbold KL, Harrington KJ, Nutting CM (2013) Dose-response analysis of parotid gland function: what is the best measure of xerostomia? Radiother Oncol 106 (3):341-345. doi:10.1016/j.radonc.2013.03.009
35. Tribius S, Sommer J, Prosch C, Bajrovic A, Muenscher A, Blessmann M, Kruell A, Petersen C, Todorovic M, Tennstedt P (2013) Xerostomia after radiotherapy. What matters--mean total dose or dose to each parotid gland? Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al] 189 (3):216-222. doi:10.1007/s00066-012-0257-2
36. Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, Miles EA, Miah AB, Newbold K, Tanay M, Adab F, Jefferies SJ, Scrase C, Yap BK, A'Hern RP, Sydenham MA, Emson M, Hall E, group Ptm (2011) Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol 12 (2):127-136. doi:10.1016/S1470-2045(10)70290-4
37. Scalco E, Moriconi S, Rizzo G (2015) Texture analysis to assess structural modifications induced by radiotherapy. Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Annual Conference 2015:5219-5222. doi:10.1109/EMBC.2015.7319568
38. Teshima K, Murakami R, Yoshida R, Nakayama H, Hiraki A, Hirai T, Nakaguchi Y, Tsujita N, Tomitaka E, Furusawa M, Yamashita Y, Shinohara M (2012) Histopathological changes in parotid and submandibular glands of patients treated with preoperative chemoradiation therapy for oral cancer. Journal of radiation research 53 (3):492-496
39. van Dijk LV, Brouwer CL, van der Schaaf A, Burgerhof JG, Beukinga RJ, Langendijk JA, Sijtsema NM, Steenbakkers RJ (2016) CT image biomarkers to improve patient-specific prediction of radiation-induced xerostomia and sticky saliva. Radiother Oncol. doi:10.1016/j.radonc.2016.07.007
40. Nardone V, Tini P, Nioche C, Biondi M, Sebaste L, Mazzei MA, Banci Buonamici F, Pirtoli L (2016) Texture analysis of parotid gland as a predictive factor of radiation induced xerostomia: A subset analysis. Radiother Oncol. doi:10.1016/j.radonc.2016.09.004
41. van Dijk LV, Langendijk JA, Sijtsema NM, Steenbakkers RJHM (2017) Reply letter to “Texture analysis of parotid gland as a predictive factor of radiation induced xerostomia: A subset analysis”. Radiotherapy and Oncology 122 (2):322. doi:http://dx.doi.org/10.1016/j.radonc.2016.11.002

42. Fiorino C, Rizzo G, Scalco E, Broggi S, Belli ML, Dell'Oca I, Dinapoli N, Ricchetti F, Rodriguez AM, Di Muzio N, Calandrino R, Sanguineti G, Valentini V, Cattaneo GM (2012) Density variation of parotid glands during IMRT for head-neck cancer: correlation with treatment and anatomical parameters. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 104 (2):224-229. doi:10.1016/j.radonc.2012.06.003
43. Beetz I, Schilstra C, Burlage FR, Koken PW, Doornaert P, Bijl HP, Chouvalova O, Leemans CR, de Bock GH, Christianen ME, van der Laan BF, Vissink A, Steenbakkers RJ, Langendijk JA (2012) Development of NTCP models for head and neck cancer patients treated with three-dimensional conformal radiotherapy for xerostomia and sticky saliva: the role of dosimetric and clinical factors. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 105 (1):86-93. doi:10.1016/j.radonc.2011.05.010

table

Tables and Figures

Table 1 Texture analysis parameters calculated with Lifex Software, and corresponding description.

Type of TA Feature	TA Feature Name	Description
Co-occurrence Matrix (GLCM): takes into account the arrangements of pairs of voxels to extract textural indices.	**Homogeneity**	Homogeneity of gray-level voxel pairs
	Energy	Uniformity of gray-level voxel pairs.
	Correlation	Linear dependency of gray-levels in GLCM.
	Contrast	Local variations in the GLCM.
	Entropy	Randomness of gray-level voxel pairs.
	Dissimilarity	Variation of gray-level voxel pairs.
Gray-Level Run Length Matrix (GLRLM): gives the size of homogenous runs for each gray-level.	**SRE (short-run emphasis)**	Distribution of the short homogeneous runs in an image.
	LRE (long-run emphasis)	Distribution of the long homogeneous runs in an image.
	LGRE (low gray-level run emphasis)	Distribution of the low gray-level runs.
	HGRE (high gray-level run emphasis)	Distribution of the high gray-level runs.
	SRLGE (short-run low gray-level emphasis)	Distribution of the short homogenous runs with low gray-levels.
	SRHGE (short-run high gray-level emphasis)	Distribution of the short homogenous runs with high gray-levels.
	LRLGE (long-run low gray-level Emphasis)	Distribution of the long homogeneous runs with low gray-levels
	LRHGE (long-run high gray-level emphasis)	Distribution of the long homogeneous runs with high gray-levels
	GLNUr (gray-level non-uniformity for run)	Non-uniformity of the gray-levels of the homogeneous runs.
	RLNU (run-length non-uniformity)	Length of the homogeneous runs
	RP (run percentage)	Homogeneity of the homogeneous runs
Neighbourhood Gray-Level Different Matrix (NGLDM): corresponds to the difference of gray-level between one voxel and its 26 neighbourhoods in 3 dimensions.	**Coarseness**	Level of spatial rate of change in intensity.
	Contrast	Intensity difference between neighbouring regions.
	Busyness	Spatial frequency of changes in intensity.
Gray-Level Zone Length Matrix (GLZLM): provides information on the size of homogenous zones for each gray-level in 3 dimensions.	**SZE (short-zone emphasis)**	Distribution of the short homogeneous zones in an image.
	LZE (long-zone emphasis)	Distribution of the long homogeneous zones in an image.
	LGZE (low gray-level zone emphasis)	Distribution of the low gray-level zones.
	HGZE (high gray-level zone emphasis)	Distribution of the high gray-level zones.
	SZLGE (short-zone low gray-level emphasis)	Distribution of the short homogenous zones with low gray-levels
	SZHGE (short-zone high gray-level emphasis)	Distribution of the short homogenous zones with high gray-levels
	LZLGE (long-zone low gray-level emphasis)	Distribution of the long homogeneous zones with low gray-levels
	LZHGE (long-zone high gray-level emphasis)	Distribution of the long homogeneous zones with high gray-levels
	GLNUz (gray-level non-uniformity for zone)	Non-uniformity of the gray-levels of the homogeneous zones
	RLNU (zone length non-uniformity)	Length of the homogeneous runs
	ZP (zone percentage)	Homogeneity of the homogeneous zones
Indices from Sphericity	**Sphericity**	Measures how spherical a Volume of Interest is.
	Compacity	Measures the degree to which the Volume of Interest is compact
Indices from Histogram: provides informations derived from global histogram analysis	**Skewness**	measures the asymmetry of the gray-level distribution in the histogram.
	Kurtosis	measures whether the gray-level distribution is peaked or flat relative to a normal distribution.
	Entropy	mesures the randomness of the distribution
	Energy	measures the uniformity of the distribution

Table 2

Characteristics of patients.

Characteristic	Number and Percentage
Sex	
Males	54 (69%)
Females	24 (31%)
Age	
<50 years	14 (18%)
>50 years	64 (72%)
Localization	
Rhynopharinx	12 (15%)
Oropharinx	28 (36%)
Hypopharinx	38 (49%)
Stage (T)	
T1	4 (5%)
T2	48 (61%)
T3	16 (20%)
T4	10 (14%)
Stage (N)	
N0	20 (25%)
N1	22 (29%)
N2	34 (43%)
N3	2 (3%)
Chronic Xerostomia	
No	53 (69%)
Yes	25 (31%)

Table 3: Reliability analysis of TA parameters

TA Parameter	ICC (single measure)	ICC (average measure)
Volume.ml	0.911	0.953
Volume.vx	0.946	0.972
Skewness	0.782	0.878
Kurtosis	0.628	0.772
Entropy	0.807	0.893
Energy	0.748	0.857
Sphericity	0.921	0.959
Compacity	0.964	0.981
GLCM.homogeneity	0.816	0.899
GLCM.energy	0.648	0.787
GLCM.contrast	0.627	0.771
GLCM.correlation	0.763	0.865
GLCM.entropy	0.797	0.887
GLCM.dissimilarity	0.781	0.877
SRE	0.822	0.902
LRE	0.680	0.810
LGRE	0.863	0.926
HGRE	0.692	0.818
SRLGE	0.862	0.926
SRHGE	0.691	0.818
LRLGE	0.738	0.849
LRHGE	0.757	0.862
GLNU	0.960	0.980
RLNU	0.807	0.893
RP	0.811	0.896
COARSENESS	0.986	0.993
CONTRAST	0.853	0.921
BUSYNESS	0.057	0.108
SZE	0.260	0.412
LZE	0.757	0.862
LGZE	0.742	0.852
HGZE	0.653	0.790
SZLGE	0.658	0.794
SZHGE	0.561	0.719
LZLGE	0.766	0.868
LZHGE	0.534	0.696
GLZLM.GLNU	0.808	0.894
ZLNU	0.379	0.550
ZP	0.820	0.901

Table 4

Univariate Analysis				
Endpoint	**Parameter**	**p-value**	**B**	**OR (95% CI)**
Chronic Xerostomia	V30	0.001	1.653	5.63 (2.12-16.13)
	Dmean	0.002	1.652	5.71 (1.65-15.55)
	Kurtosis	0.043	-0.652	0.78 (0.45-0.98)
	GLCM Correlation	0.024	0.567	1.34 (1.01-3.64)
	RLNU	0.008	1.424	2.12 (1.55-6.24)
Multivariate Analysis				
Chronic Xerostomia	V30	0.001	2.324	8.45 (2.56-26.56)
	GLCM-Correlation	0.026	1.624	3.64 (1.35-16.42)
	RLNU	0.011	1.623	5.35 (1.35-11.21)

Table 5: Characteristics of the ROC Curves. 2LL: 2 log-likelihood; R^2: Nagelkerke $R^{2,}$, AUC: Area Under the Curve of the ROC; SE: standard error; HL: Hosmer–Lemeshow; TA: Texture Analysis Parameters.

	Chronic Xerostomia	
	Without TA	With TA
-2LL	65.53	38.95
R^2	0.374	0.664
AUC	0.766 (0.649-0.882)	0.911 (0.745-0.983)
SE	0.059	0.035
HL X^2	10.43	5.63
HL p-value	0.236	0.651

Table 6: Internal validation (k-fold) for the logistic regression analysis.

Endpoint	**Dataset**	**AUC**	**95% CI**
Chronic Xerostomia	All patients	0.911	0.745-0.983
	Validation set 1	0.778	0.516-1.00
	Validation set 2	0.907	0.747-1.00
	Validation set 3	0.812	0.602-0.938
	Validation set 4	0.982	0.927-1.00

Figure 1: ROC Curves for the prediction of severe chronic xerostomia.

Dotted line: ROC curve without the TA Parameters, Continuous line: ROC Curve with the TA Parameters.

line figure

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