Protocol Letter

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Guideline Letter

Protocol Letter: A multi-institutional retrospective case-control cohort investigating PREDiction models for mandibular OsteoRadioNecrosis in head and neck cancer (PREDMORN)

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Background

Osteoradionecrosis (ORN) of the mandible is a rare but severe radiation-induced toxicity observed in 4–8% [1–3] of head and neck cancer (HNC) cases treated with radiotherapy (RT) alone or combined with surgery and/or chemotherapy (CRT). Ionising radiation damages the vascularisation of the mandible. Consequently, necrosis of the bone can develop either spontaneously or triggered by trauma to the mandible bone (e.g. dental extractions, surgery, implants). Bone necrosis occurs because it is not able to heal due to reduced blood supply, hypoxia or hypo-cellularity caused by exposure to radiation [4]. The severity of ORN has been graded by Notani [5] into three categories, with the most severe cases experiencing significant pain levels and even pathological fracture of the mandible. Quality of life can be greatly affected in patients who develop mandibular ORN. Moreover, the management of ORN is often complex [6] and requires costly clinical interventions [7].

Normal tissue complication probability (NTCP) prediction models are a valuable treatment decision support tool that can be used to estimate the risk of individual patients developing a particular normal tissue toxicity outcome. Patient-specific prediction of potential ORN in the treatment of HNC may lead to more individualised treatment with risk-reduction measures such as reduced mandibular radiation dose near extraction sites when possible and more dedicated follow-up regimes for early detection and intervention of ORN. A number of case-control studies have investigated the correlation between dosimetric, clinical and demographic factors and ORN [1–3,8–15]. Efforts on patient-specific prediction of ORN, however, are more limited. An NTCP model for ORN was recently developed [16] based on mandible dose-volume parameters and clinical variables using multivariable stepwise forward selection regression analysis, resulting in a final model that was based on the D30% of the mandible bone and pre-RT dental extraction. Previous work [17] has shown that it is possible to use deep-learning (DL) methods to predict ORN incidence from 3D radiation dose distribution maps of the mandible.

Due to the low prevalence rate of mandibular ORN, low patient numbers represent a statistical limitation. External validation of models using data from multiple centres is an essential feature of effective model evaluation with a view to clinical translation but is often lacking in research studies [18]. Combining datasets from different institutions may not only improve the generalizability of the models but also highlight correlations between clinical practice and toxicity outcome. The present study is a multi-institutional effort involving six teaching hospitals (details provided in Appendix B in the protocol) and including the largest datasets worldwide to develop, train and validate robust and generalisable NTCP models for mandibular ORN.

Protocol summary

This is a retrospective case-control study where we hypothesise that mandibular ORN can be accurately predicted on an individual level. To test our hypothesis, we will develop and validate multiple NTCP models based on dosimetric parameters extracted from the mandible dose-volume histogram (DVH) and clinical and demographic variables using different mathematical approaches. Both

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the mandible DVH data and the resulting principal components (PCs) from a preliminary principal component analysis (PCA) will be considered as dosimetric variables in separate models. Data will be retrospectively collected by each centre based on well-described parameters (Appendix A in the protocol) and inclusion/exclusion criteria (Table 1 in the protocol). A case-control approach will be followed with a 2:1 control to ORN case ratio (the selection process of the control cohort is described in Fig. 1 of the protocol) .

Multiple NTCP models will be trained, validated and tested applying different modelling approaches (LASSO logistic regression, regularised greedy forest and Bayesian neural network) to clinical and dosimetric variables. The different models will be compared and ranked according to their predictive performance, interpretability, parsimony and clinical applicability. Identification of the best performing NTCP model and the most highly predictive variables will provide valuable information for clinical decision-making and treatment optimisation. Clinically applicable mandible radiation dose constraints for radiation treatment plan optimisation will contribute to reduced complication probability.

Planned future work

NTCP models have traditionally used DVH parameters and this study will use such DVH metrics, along with clinical factors, as variables. However, in a DVH the spatial localisation, dose gradient and direction information is lost. Spatial dosimetric information is, however, of great clinical interest in the investigation of radiation damage to the organs at risk in the HN region. Some studies [17,27,28] have already successfully implemented DL methods such as convolutional neural networks (CNNs) in NTCP models. The CNNs are trained to automatically predict the toxicity probability by adaptively learning the most predictive deep features directly from the 3D radiation distribution maps. Future work will aim to validate and update the existing DL-based ORN NTCP model [17] through the inclusion of the multi-institutional image dataset containing 3D radiation dose distribution maps.

Study limitations

The primary limitation of this study results from challenges in the standardisation of retrospective data across different centres and potential biases in the data.

The case control design may result in a dataset where the underrepresented groups, i.e. the primary tumour site groups with low event rates, may be oversampled compared to clinical practice. This might introduce complications in the modelling and interpretation of the models. However, sampling the entire HNC population is not feasible for all institutions. In order to compensate for this sampling bias, the actual total number of events and non-events will be recorded per primary tumour site group in order to accurately predict the proportions.

Follow-up time period differences between institutions make it difficult to perform a time-to-event analysis. However, we will perform time-independence prediction models using fixed rates of ORN at a given interval and will look at continuous right censoring approaches as well as a post hoc analysis.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.09.014.

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