Maastricht University

Multifactorial decision support systems in radiation oncology : clinical predictors and radiomics

Citation for published version (APA):

Rios Velazquez, E. (2014). *Multifactorial decision support systems in radiation oncology : clinical predictors and radiomics*. [Doctoral Thesis, Maastricht University]. Maastricht University. https://doi.org/10.26481/dis.20141024er

Document status and date:
Published: 01/01/2014

DOI:
10.26481/dis.20141024er

Document Version:
Publisher's PDF, also known as Version of record

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

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Download date: 20 Apr. 2024

Summary

SUMMARY

The development of decision support systems to predict patients outcome in radiation oncology is needed to facilitate clinical shared decision making. Therefore, this thesis investigates the development of prognostic models for lung and head and neck cancer patients to identify patients at different risk levels before treatment.

The work of this thesis is divided in two sections; in the first section, this thesis investigated the integration of patient clinical and treatment characteristics in lung and head and neck cancer to derive prognostic models of outcome. In the second part, we investigated the use of advanced quantitative imaging features, extracted from conventional medical imaging, many of which are not currently used, to improve patient's prognostic information in lung and head and neck cancer.

The concept of decision support systems in radiation oncology is introduced in **Chapter 1**, along with a general introduction of the work presented in this thesis.

In **Chapter 2**, a comprehensive review of current factors that have been associated with outcomes in radiation oncology is presented, as well as a thorough discussion of the methodology needed for the development of prediction models.

Part 1: Clinical predictors

This section presents the development of predictive models using patient clinical and treatment characteristics. Here, we investigated what factors have a relevant association with patient's outcome. Also, we evaluated whether these models can be validated in external datasets and how their prediction accuracy compares with currently used factors to assess patient's prognosis.

In lung cancer, early identification of patients with residual metabolic activity is essential as this enables selection of patients who could potentially benefit from additional therapy. **Chapter 3** presents a study in which we evaluated the most important patient, tumor and treatment factors associated with residual metabolic activity after treatment. Metabolic response assessment has been associated with survival and treatment failure. This study was performed in a MAASTRO dataset of 101 NSCLC patients.

Chapters 4 and 5 are focused on the development of predictive nomograms in head and neck cancer. **Chapter 4** describes the development of a prognostic nomogram for the prediction of overall survival and local control in laryngeal carcinoma patients treated with radiotherapy. It also shows the validation of the same prognostic tool in four external datasets. This model has been made publicly available on www.predictcancer.org. In **Chapter 5,** a similar nomogram was developed for oropharyngeal carcinoma patients for prediction of overall survival and progression-free survival. This model combines important patient and tumor characteristics with the human papilloma virus status, an established important

prognostic factor in this patient population. It also shows a comparison of the developed nomogram with TNM and HPV status alone, and its validation in an independent patient cohort.

Part 2: Radiomics: Extracting more information from medical images using advanced feature analysis

This second part of the thesis deals with the potential of extracting advanced quantitative features from medical images for outcome prediction. We investigated whether there is more information in medical imaging than what is currently used, and if quantitative imaging traits are prognostic in lung and head and neck cancer.
In **Part 2** of this thesis we proposed a methodology for high-throughput extraction of quantitative imaging parameters, evaluated methods for robust target definition and assessed the prognostic value of these imaging parameters in lung and head and neck cancer cohorts.

Chapter 6, puts forward the concept of Radiomics: the high-throughput extraction of large amounts of image features from radiographic images. This review addresses the hypothesis, methodological aspects, and challenges underlying the Radiomics approach.
Towards the extraction of reproducible quantitative imaging features, **Chapter 7**, evaluates the relevance of a semiautomatic CT-based segmentation method, by comparing it to manual delineations made by radiation oncologists and to pathological tumor measurements considered as "gold standard" in NSCLC patients.

Chapter 8, evaluates an open source, freely available method for lung tumors segmentation, and evaluates its usefulness by comparing it again, against the gold standard pathological measurements and radiation oncologists delineations, and a step further, examining whether its use reduces variability during tumor segmentation.
Following these results, **Chapter 9** evaluates whether quantitative imaging features extracted from semi-automatically segmented tumors have lower variability and are more robust compared to features extracted from manual tumor delineations. This study analyzes the robustness of imaging features derived from semi-automatically and manually segmented primary NSCLC tumors in twenty patients.

Chapter 10, presents an analysis of 440 quantitative imaging features quantifying phenotypic differences based on tumor appearance, i.e., shape, intensity and texture, in CT images of more than 1000 patients with lung or head and neck cancer. In this study we found that a large number of radiomic features have prognostic power in independent data sets, many of which were not identified as significant before. Radiogenomics analysis revealed that a prognostic radiomic signature, capturing intratumour heterogeneity, is associated with underlying gene-expression patterns. These results can have a clinical impact as imaging is routinely used in clinical practice, providing an unprecedented opportunity to improve decision-support in cancer treatment at low cost.

Finally, in Chapter 11, the results presented in this thesis are discussed along with its outlook and future perspectives. These studies show how the analysis of existent routine clinical and imaging data, will facilitate personalized medicine in radiation oncology. However, the key factor in the future development of decision support systems is standardization. Standardization of data through the application of protocols and semantic-interoperability through different centres; and the creation of a framework for reproducible data sharing, research and predictions.