Longitudinal radiomics for prognosis in non-small cell lung cancer

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Valorization addendum
Personalized medicine
Cancer is estimated to cause 9.6 million deaths worldwide in 2018. This number is increasing yearly, caused by a growing population and aging. Cancers accounting for a large proportion of cancer deaths include breast cancer, colorectal cancer, stomach and liver cancer, but of all cancer types, lung cancer causes most cancer deaths worldwide. Lung patients currently have a poor 5-year survival rate of about 20%. A more effective use of healthcare data could help to choose the optimal treatment for each patient: personalized treatment, replacing the one-size-fits-all principle.

In today’s society, more and more data are collected, saved and analyzed. These large amounts of data (i.e. ‘big data’) are no longer restricted to large companies. The trend of big data is also apparent in healthcare. For each individual patient, information such as demographics, medical history, medical images and laboratory results are collected and saved in Electronic Health Records (EHR). These data can be mined to find trends on population basis, which could help to improve general disease management. Moreover, disease prevention is also facilitated by big data in healthcare. Data in the EHRs, as well as patient preferences, help to guide individual treatment decisions using so-called clinical decision support systems (CDSS). To this extend, prediction models are being built in order to translate different sources of information to a predictive value (i.e. effectiveness of one treatment compared to another) or prognostic value (i.e. treatment outcome irrespective of the type of treatment). The hypothesis is that prediction models are able to improve the survival chances of patients because of better informed decisions about the treatment initialization or adaptations, which could also reduce the risk of toxicities. This also implies that the collection of data in healthcare is able to reduce healthcare costs by disease detection, prevention and more effective treatments.

Prognostic value
Suitable data for prediction models include patient related factors, information about treatment, stage of the disease and imaging data. This thesis focused on prognosis for non-small cell lung cancer (NSCLC), the major subtype of lung cancer. Several prognostic factors have already been identified for NSCLC patients, including TNM-stage, histological subtype (e.g. adenocarcinoma, squamous cell carcinoma) and mutation status. Besides that, parameters derived from medical images (e.g. radiomics) are being investigated for their relationship with disease development and patient outcome, which was the main topic of this thesis. In case of a positive correlation, these image-derived features could be incorporated in a CDSS to improve patient outcome by enhanced personalized medicine. Whereas the prognostic value of radiomics was described for lung cancer in this thesis, the methods, approaches and conclusions are easily transferable to other disease sites as well, e.g. head-and-neck cancer, esophageal or rectal cancer. Moreover, the patients that were evaluated in this thesis have all received radiation treatment, but the methodologies could also be applied for patients receiving chemotherapy or surgery. So, although the research question of this thesis was relatively specific, the principle of acquiring quantitative features from medical images acquired in clinical practice could contribute to the general management of cancer, as this principle is applicable to many disease sites.
and treatment choices.

Data sharing
The distribution of prognostic models over the scientific community is important to further develop and validate them, to be able to proceed to a clinical implementation. One of initiatives to distribute prediction models is the website www.predictcancer.org, which is a database of prognostic and predictive models for several disease sites and the corresponding publication. The prognostic model that was validated in chapter 2 of this thesis was also published on this website. There exist also a mobile application of predictcancer, which is intended to serve as a decision support aid. The entire community can publish their models on this website, which contributes to the general use and evaluation of prognostic and predictive models. Currently, the website contains 25 cancer prediction models for a total of seven different cancers, including four for lung cancer. A platform that collects validated prediction models facilitates the integration of a prediction model in commercially available CDSSs, for instance implemented in mobile apps.

Besides sharing prognostic models, publicly available data will help the development and validation of these models. The data of chapter 2 was made publicly available on www.cancerdata.org (http://dx.doi.org/10.17195/candat.2017.02.1), which is an initiative of Maastro Clinic to share datasets, protocols and guidelines. Furthermore, The Cancer Imaging Archive (TCIA) on www.cancerimagingarchive.net collects medical images and corresponding patient information. This allows for finding external validation datasets more easily, but also to find suitable datasets for test-retest purposes, like the RIDER dataset which was used in chapter 6 and 9. Also one of the datasets that was used for model development in chapter 9 was acquired from an open-source publication.

Radiomics
The software that was used in this thesis is a research version of a commercially available software RadiomiX, which is distributed by the company Oncoradiomics (www.oncoradiomics.com). Besides the feature extraction procedure, it is also possible in this software to extract a radiomic signature or apply a certain machine learning approach in one-go. Another software that is used worldwide is PyRadiomics, which is an open source radiomics software developed in Python. Distribution of radiomics software, that are in agreement with standardization guidelines, is essential to spread the worldwide applicability of prognostic models that are being developed that contain radiomic features, as well as the development and validation of new prognostic models. The community is able to contribute to these open source implementations, which allows for knowledge exchange. Companies will benefit from this knowledge in the development of their commercial solutions available for use in clinical practice.

Information about radiomics is also published on www.radiomics.world. This website also contains the radiomics quality score (RQS), which was developed by our group in 2018 and is intended to improve the quality of future radiomic studies in terms of methodology, external validation and protocol descriptions. In chapter 4 of
this thesis, the RQS was used to improve the quality of the study. The website also provides the links to the digital phantom, which is intended to compare different radiomics implementations and to harmonize them. Standardization initiatives and guidelines for publications are essential to ensure robustness and generalizability of radiomics studies. This type of research will also improve the quality of commercial products, as manufacturers aim to develop state-of-the-arts solutions that satisfy existing quality standards.

Innovation

The main innovation of this thesis is the use of cone-beam CT images for radiomics and the corresponding longitudinal approach. These studies will help to guide future research for further development of this methodology, which could be of interesting for integration of tumor monitoring during treatment using conventional linacs (e.g. Varian, Elekta). The feature selection methodology described in chapter 3 of this thesis is relevant for other longitudinal studies, not necessarily including CBCT images. A potential future application includes radiomics analyses of longitudinal MRI images acquired from novel MR-linac systems (e.g. Elekta Unity, MRIdian linac, ViewRay), which could help future patients by allowing for early response assessment.

The last part of the thesis and specifically chapter 9, describes the potential of the recent development of deep learning for prognosis in NSCLC. Since the successes of Google contests using deep learning networks for image classification, for instance the ImageNet challenge, there is renewed interest for deep learning in medical image segmentation, analysis and classification. The application of deep learning for segmentation is beneficial for many fields: not only for radiomics which required a defined region of interest, but also for radiotherapy planning, including definition of the target and surrounding organs at risk, which could be integrated in existing treatment planning software (e.g. Eclipse, Raystation). Although the automatic segmentations might still require verification by a radiation oncologist, the use of deep learning would greatly reduce the amount of time required for treatment planning, which is beneficial for both the medical specialists and the patients awaiting treatment. The use of deep learning for classification includes differentiation between benign and malignant lesions, which reduces the amount of unnecessary biopsies. Moreover, as shown in chapter 9, it helps to improve predictions, potentially in combination with radiomics. The potential of deep learning in medicine is huge and it is to be expected that it will play a major role in modern healthcare.