

Biomarkers in non-small cell lung cancer

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SUMMARY

Main goal of this thesis is to investigate the use of non-invasive sources of information, specifically imaging and blood biomarkers, for disease management and overall survival assessment of non-small cell lung cancer (NSCLC) patients. This follows the premise of an individualized and personalized medicine, further explained in **Chapter 2**, in which data mining approaches and outcomes modelling, to tailor treatment and enhance outcomes in oncology, by means of a rapid learning health care approach in radiotherapy are discussed.

To describe tumours' heterogeneity in a non-invasive manner from medical imaging, derive from it prognostic information, and potentially capture its underlying genomic and proteomic profile resumes the main hypothesis behind Radiomics, presented in **Chapter 3**. This thesis, is focused particularly on the metabolic distribution of ^{18}F -fluorodeoxyglucose (FDG) uptake patterns, as measured by positron emission tomography (PET) in NSCLC patients, treated radically with radiotherapy. **Chapter 4** presents a study conducted for intensity volume histograms (IVH - similar in concept to the dose-volume histograms (DVH), describing tumour's FDG uptake distribution as a function of its volume, and vice-versa) derived from baseline scans (prior to radiotherapy). These features showed great potential for survival assessment on a large dataset of NSCLC patients (n=220). In **Chapter 5**, an integrated stability analysis of Radiomics features is discussed. In a test-retest setting, PET scans of 11 liver cancer patients were acquired one day apart, with no treatment administered in between. In an inter-observer cohort, manual segmentations of the primary tumour were made by five independent and experienced radiation oncologist, blinded to each other's delineations (23 patients). Solely features achieving a high stability in both tests, measured by an intraclass correlation (ICC) were retained for analysis presented in sequent chapters. In **Chapter 6** the percentage variation of Radiomics features early during radiotherapy was analysed - "Delta Radiomics". A multivariable model was developed (n=52), and validated in two independent datasets (n=32 and 26). Final model included, at least, one variable from each category, and reached an performance of a concordance-index of 0.66 (external = 0.64 and 0.57). Finally, in **Chapter 7** the hypothesis that metastatic lymph nodes provide extra prognostic value in addition to the primary tumour was investigated through Radiomics features derived from each structure. A prognostic model was fitted on data from 262 patients and validated on an external cohort (n=50). Model selection amongst features exclusively extracted from the metastatic lymph nodes achieved a statistically higher performance (0.62) than solely from primary tumour (0.53).

Chapter 8 summarizes the improvement of a validated clinical model (from 0.66 to 0.70) by adding blood markers of hypoxia (Osteopontin) and tumour load (cytokeratin fragment 21-1) for 182 patients, and validated in 181 independent ones.