Biomarkers in non-small cell lung cancer

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.