Zusammenfassung (Englisch)

Lung cancer is the leading cause of cancer-related death worldwide. Approximately 85 % of all lung cancers are histologically grouped as non-small-cell lung cancer (NSCLC). Besides surgery and chemotherapy, radiotherapy is firmly established as an important modality in curative treatment of localized as well as locally advanced NSCLC and in palliative care. Nevertheless, systemic and localized relapse is frequently observed. Recent developments have led to a more refined typing of advanced NSCLC by incorporating biomarkers of oncogenic pathway activation. This has allowed the successful introduction of "targeted pharmacotherapies" that are better tailored towards biological differences between histologically uniform NSCLC entities. In contrast, radiotherapy still does not take advantage of biological disease heterogeneity, and radiosensitization protocols are empirically derived, rather than based on validated biomarkers.

Against this background, it was hypothesized that an improved understanding of the modulation of the radiotherapy response of NSCLC by signal transduction pathways may open new avenues for the development of more specific protocols to combine radiotherapy with pharmacotherapies. To this end, a systematic assessment of the functional impact of selected regulators of apoptosis, oncogenes, and signal transduction mediators on irradiation-induced cell death was initiated in a small-scale screen of lung cancer models.

Anti-apoptotic members of the BCL-2 family have been selected as the first group of potential biomarkers for the radiotherapy response in NSCLC. BCL-xL as well as MCL-1 conferred resistance against irradiation in A431 cells. Expression of both modulators led to decreased radiation-induced cell death and additionally gave a competitive edge in clonogenic survival *in vitro*. Studies obtained by radiation therapy of tumor-bearing mice *in vivo* supported the relevance of BCL-xL for radioresistance in an organismal context. Surprisingly, these findings were not convincingly explained by BCL-xL and MCL-1 mediating radioresistance by inhibition of apoptosis, as radiotherapy induced only negligible amounts of apoptosis. Also no impact of BCL-xL on cell cycle kinetics following irradiation was observed. Studying the influence of BCL-xL on deoxyribonucleic acid (DNA) double-strand break (DSB) repair pathways as a potential effector mechanism revealed that BCL-xL-mediated radioresistance relied on functional homologous recombination repair (HRR) and involved enhanced repair through error-prone alternative end-joining (alt-EJ). This led to the propagation

of cells with gross chromosomal aberrations, possibly promoting survival of more resistant and aggressive lung cancer subclones. To circumvent this, combining irradiation with targeted therapies against anti-apoptotic BCL-2 family members was suggested as a useful strategy. Thus, BCL-xL and/or MCL-1 were antagonized on a genetic or functional level. These strategies, including shRNA-mediated knockdown, conditional overexpression of pro-apoptotic BAK, as well as pharmacological treatment with BH3-mimetics, sensitized lung cancer cells to radiotherapy. Based on this, it is proposed to select patients with high expression of the respective drug targets in recent tumor biopsies for clinical proof-of-principle studies combining radiotherapy with pharmacologic antagonists of the BCL-2 family such as Navitoclax.

The signal transduction mediator RAF-1 was identified as the second potential biomarker for the radiotherapy response in NSCLC. Conditional activation of RAF-1 reduced the number of irradiation-induced cell death significantly. Clonogenic survival could not be evaluated as RAF-1 activation itself inhibited colony formation in general, possibly due to induction of a cell cycle arrest or senescence. It was further shown that activation of RAF-1 even after irradiation had still radioprotective effects. The underlying mechanisms remain to be elucidated in technically more appropriate models, in particular *in vivo*.

In conclusion, two modulators of the radiotherapy response in NSCLC were identified and functionally validated. In addition, targeting non-apoptotic functions of BCL-2 family proteins was nominated as a novel strategy for biologically rational radiosensitization protocols.