Innovations in the treatment of non-small cell lung cancer

CHAPTER 9

Valorisation

VALORISATION

Relevance

Approximately half of the patients with non-small cell lung cancer have incurable stage IV disease at diagnosis. For stage I- III NSCLC the outcome is slightly better, but with a 5-year overall survival of 70% (stage I), 50% (stage II) or 20-40% (stage III), prognosis is still poor [1,2]. Efforts to improve the (effect of) currently available treatments have not lead to a substantial increase in the chance of curation. In the current thesis several studies were undertaken, aiming to improve the prospects of NSCLC patients.

In early stage NSCLC, we searched for significant risk factors for isolated regional recurrence and distant recurrence following SABR. We could not identify significant risk factors, despite a large cohort of patients. This is a relevant result, as it highlights the need for further research for possible predictive factors. These variables can be incorporated in prediction models and decision support systems, to help clinical decision making in this often heterogeneous population.

In the study on metformin use, we did not research a new, expensive and rare systemic agent. On the contrary, metformin is widely available as first choice oral treatment for type II diabetes. From a cost-effective standpoint, it is an attractive medication to repurpose for the treatment of cancer because it is very cheap. The pill costs only around 2 euros a month, versus approximately 5300 euros a month for two nivolumab infusions or 5700 euro for one pembrolizumab infusion, for example (www.farmacotherapeutischkompas.nl). In a retrospective study, we showed an improved progression free survival and distant metastasis free survival for locally advanced NSCLC patients using metformin during concurrent chemoradiotherapy [3]. These results merit confirmation in a randomised controlled trial including non-diabetic patients. If confirmed, metformin could be added to the treatment of NSCLC without greatly increasing treatment costs, provided treatment related toxicity is not significantly increased.

Proton therapy is a sophisticated, innovative technique with the potential to reduce dose to organs at risk [4]. The optimal clinical context for proton therapy for the treatment of NSCLC remains to be defined. As (comparative) clinical experience is limited, intermediate outcome measures are needed. Planning studies like the two we have performed are needed to specify the most relevant indications for this new technique.

Target groups

Non-small cell lung cancer patients (mainly stage I-III) are the most important target group of the current study. They may benefit directly or indirectly (in follow-up stud-

ies) from the results obtained in the current thesis. We showed that the addition of metformin to concurrent chemoradiotherapy has the potential to significantly improve prognosis for locally advanced NSCLC patients, although the results from prospective trials (NCT02186847 and NCT02115464) need to be awaited. Furthermore, clinicians in the field of pulmonary oncology and radiotherapy are likely to be interested in the results of our studies. The study on metformin received great attention at the IASLC World Lung Cancer Conference in Vienna in 2016, where the abstract was awarded with the Daniel C. Ihde Lectureship Award. Our results can also inspire other researchers in clinical practice or researchers working in the field of radiobiology or radiation technology. Examples include combining metformin with immunotherapy (pre-clinical and/or in clinical studies) or continuing and expanding the search for prognostic variables for recurrence following SABR.

Knowledge utilisation

Further research is needed before most of our results can be of use in clinical practice, as described in the 'future perspectives' section of the general discussion. The results we have obtained in the two retrospective observational studies (chapter 3 and chapter 4) can serve as a starting point for prospective trials. Both *in silico* trials are relevant for the specification of the best indications for proton therapy in NSCLC, as mentioned earlier. However, to evaluate the clinical efficacy and cost-effectiveness of this new technique, not only dosimetric data, but also clinical trials and modelling studies are essential [5].

Innovation

Each of the studies in the current thesis has an innovative aspect. Using the pre-SABR planning CTs as surrogate for visceral pleural invasion was a unique feature of our study on regional recurrence following SABR. Repurposing the well-known and often prescribed anti-diabetic drug metformin for another indication, the treatment of NSCLC, is another form of innovation. In both the planning studies we performed within the ROCOCO consortium, the potential dosimetric advantages of innovative radiotherapy techniques as proton therapy and carbon-ion therapy were evaluated. Furthermore, the set-up and digital framework of these studies, with multiple international partners creating treatment plans with different modalities on the same patient datasets can also be considered innovative.

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