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### Prediction of toxicity in concurrent chemoradiation for non-small cell lung cancer

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# Chapter 7

Discussion and  
future perspectives

Concomitant chemo radiotherapy (CCRT) is the current treatment of choice for locally advanced non-small cell lung cancer (NSCLC), although prognosis remains poor (1;2). Radiation therapy (RT) alone or a sequential combined modality approach is only indicated in case of extensive treatment volumes or a poor performance status (PS). Although CCRT has a slightly improved survival over sequential chemo-RT and RT, the toxicity profile is more profound. Therefore, a balanced decision making is indicated with respect to the individual patient.

This thesis focusses on the prediction of toxicity induced by Intensity Modulated Radiotherapy (IMRT) and concurrent daily low dose cisplatin. In the Netherlands Cancer Institute - Antoni van Leeuwenhoek (NKI-AVL) cisplatin 6 mg/m<sup>2</sup> is administered as a bolus injection once daily prior to each of the 24 fractions of radiation . Although worldwide most concurrent regimens consist of (3)-weekly platinum doublets, low dose cisplatin as a sensitizing agent has proven to be locally effective with less toxicity (3;4). Despite the mild toxicity profile compared to full dose chemotherapy, the clinical implications of concurrent low dose cisplatin and IMRT justifies detailed analysis on the incidence of toxicity, prognostic parameters and supportive care management. In **Chapter 2** we correlated clinical and dosimetric parameters with toxicity. A more personalized approach is necessary to select those patients at risk for severe toxicity. In this study we learned that age >70 was not a predictor for toxicity although in clinical practice this parameter is used to exclude patients from treatment. To further enhance personalized toxicity risk assessment, blood biomarkers and single nucleotide polymorphisms (SNP's) could possibly contribute to this process in the near future (5). Acute oesophagus toxicity (AET) is one of the main side effects associated with thoracic RT. When severe, pain, obstruction and weight loss are the main symptoms. In case of CTC grade 1-2 toxicity, mild analgesics and proton pump inhibitors are sufficient to manage this toxicity. In case of grade >2 toxicity, however, naso-gastric tube feeding and/or hospitalization for intravenous analgesics should be considered. In **Chapter 3** we present the results of 3 studies focusing on predictive parameters for severe acute and late AET. Grade >2 AET was seen in 20% of the patients and 50% of this population developed late toxicity, like stenosis and/or a fistula between the trachea and oesophagus. This information helps us again to balance treatment benefits and risks, to educate patients and to initiate

proactive supportive care management. A step forward in the prediction of AET regards the volume of the oesophagus receiving 50 Gy (V50oes) which seemed a significant better prognosticator than the V35oes which has been used in 3-dimensional conformal radiotherapy (6;7). Esophagus toxicity compared equally in patients with or without cetuximab in addition to CCRT. In **Chapter 4** we report on efficacy and safety of additional cetuximab to concurrent chemo radiotherapy in a multi-center phase II randomized clinical trial in 102 patients. Cetuximab is a monoclonal antibody that binds to the epidermal growth factor receptor (EGFR) and blocks signaling involved in tumor growth, differentiation and treatment resistance. Cetuximab has shown promising results in locally advanced head and neck cancer in combination with RT (8). In our study, patients were randomized 1:1 and followed up by CT/PETCT, pulmonary function and patient reported outcome (PRO). This study was preceded by a feasibility study in 12 patients showing a partial metabolic response in 8 patients with no increased toxicity except for mild acneiform rash (9). These outcomes, however, were not reproduced by the consecutive phase II trial in which cetuximab did not show improved survival. Also, a significant difference in toxicity was seen regarding dysphagia in the latter study. A possible explanation for the differences between both studies is the statistical power with only 12 patients in the feasibility study. The most important conclusion of the phase II trial with cetuximab added to the CCRT was that no survival benefit was observed. These findings were confirmed in a RTOG study by Bradley et al. (10; 11). Health related quality of life (HRQL) was the secondary endpoint of the trial and analysis is still ongoing. In **Chapter 5** we tested the hypothesis that daily intravenous prehydration reduced renal toxicity and enhanced treatment adherence. This hypothesis was based on preceding research regarding toxicity discussed in **Chapter 1**. Cisplatin is one of the most potent antitumor agents known, displaying clinical activity against a wide variety of solid tumors and frequently combined with other compounds (12). Cisplatin is an alkylating agent and its cytotoxic mode of action is mediated by its interaction with DNA to form DNA adducts, primarily intrastrand crosslink adducts, which activate several signal transduction pathways and leads to cell death. Although effective, cisplatin is known for its toxicity like nausea and vomiting, bone marrow suppression and nephrotoxicity (13;14). In combination with improper hydration, diabetes mellitus (DM) and the use of non-steroid anti-inflammatory steroids, cisplatin can lead to irreversible renal damage and even death (15).



Despite the low dose of cisplatin applied in our CCRT schedule, we observed an increased serum creatinine of 30% from baseline in 39% of the patients. The chemotherapy treatment had to be discontinued in 31% of the patients. When an intravenously prehydration regimen with 1 liter of sodium chloride 0.9% was applied, only 9% of the population had a 30% increase of the serum creatinine and discontinuation of chemotherapy occurred in 11% ( $p=0.001$ ). The 1 year overall survival compared equally between both groups. Ongoing survival analysis is necessary to confirm these outcomes. Interestingly, a reduction of severe AET was also observed in the prehydrated cohort; 34% versus 62% in non prehydrated patients ( $p=0.001$ ). When these observations were tested against the prognostic V50oes model (Chapter 3), the proportion of AET grade  $> 2$  was not significantly different from the predicted value of 0.60 ( $p=0.46$ ). However, for the prehydrated group, the proportion of AET grade  $> 2$  was significantly lower than the model predicted value of 0.56 ( $p=0.001$ ). Although the kinetics of low dose cisplatin has not been studied thoroughly, one can agree on the comparable mechanisms for higher doses of cisplatin (16;17). When the glomerular filtration (GFR) rate is less than 60 ml/min; the area under the curve (AUC) of cisplatin will increase, resulting in a higher exposure of cisplatin and thus more toxicity. One other late toxicity with clinical implications is the fracture of thoracic vertebrae. **Chapter 6** reports on vertebral fractures (VF) in a large cohort of NSCLC patients treated with IMRT. A retrospective study and a case control study were subsequently initiated to analyze the association of VF with clinical and dosimetric parameters. Eight percent of the population suffered from  $\geq 1$  fractured vertebra with a median time to discovery around 7 months after treatment. This knowledge is of vital importance for the education of physicians and patients. In this study, the optimal volume parameter is 30 Gy and for the equivalent uniform dose the optimal  $n$  parameter is 1 and both were significantly associated with vertebral fractures ( $p=0.01$ ). These findings are theoretically and clinically important and additional research should provide us with information on the possibilities of dose reduction on the vertebrae. Besides, prospective health related quality of life assessment will help us to understand the impact of VF in daily practice.

In conclusion, locally advanced non-small cell lung cancer is an aggressive disease with a poor prognosis despite the curative intention of the treatment. Therefore, risks and benefits of concurrent chemo radiotherapy, sequential

chemo radiotherapy or radiotherapy alone, should be balanced, ideally in each individual patient. Although effective in a subset of patients, concurrent chemo radiotherapy for locally advanced non-small cell lung cancer is associated with significant toxicity. The aim of this thesis is to better understand, predict and manage toxicity. Because of the limited life expectancy, quality of life is of vital importance. Therefore, to predict efficacy and to exclude patients who will not benefit from this treatment, and thus will not be exposed to unnecessary toxicity, individualized patient characteristics and blood biomarkers are needed for future research (18). In this thesis, esophageal toxicity has a prominent place because of its clinical implications. Pain, obstruction and weight loss decrease the patients physical condition and as a result it impairs quality of life. In the near future with the possibility of new treatment options, we must be aware of the toxicity profile and continue to weigh efficacy and toxicity. A prolonged life expectancy without disabling toxicity will be the main challenge.



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