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

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Chapter 1

Introduction

Lung cancer

Lung cancer is the leading cause of cancer-related death worldwide with an incidence in the Netherlands of 300 new patients per 100,000 inhabitants in 2011 (1). The prognosis remains poor with a 5-year overall survival (OS) of only 16%. Non-small cell lung cancer (NSCLC) accounts for 85% of the cases and 70% percent of these are locally advanced or metastasized at the time of diagnoses (2).

Locally advanced non-small cell lung cancer

In stage III NSCLC, resection of the primary tumor is seldom possible because of invasion of critical normal structures and/or tumor positive mediastinal or supraclavicular lymph nodes. Some patients are inoperable due to severe comorbidity like restricted pulmonary function or high age. For this group of patients, concurrent chemoradiation (CCRT) is the treatment of choice with a 3-year overall survival (OS) of 33%. In patients who present with large tumor volumes or poor performance status (PS), the concurrent treatment approach is considered not feasible and sequential chemoradiation (SCRT) or radiotherapy (RT) alone are chosen. This is however, less effective. At 3 years, the OS in SCRT and RT is 26% and 22% respectively, related to a decreased local control (3).

Most chemotherapy regimens used in CCRT are doublets containing cisplatin with either etoposide or vinorelbine given weekly or 3-weekly (3). In the Netherlands Cancer Institute - Antoni van Leeuwenhoek the use of daily low dose cisplatin has been found feasible with promising tumor control and overall survival (4; 5). Cisplatin is a radiosensitizer. It induces DNA adducts that, when present in the vicinity of radiation-induced double strand breaks, create complex DNA damage that is beyond the cell's repair capacity, inducing effective cell death. Cisplatin (6 mg/m^2) is administered daily as a iv injection 1-2 hour prior to each fraction of radiation.

New developments in RT have led to the introduction of Intensity Modulated Radiotherapy (IMRT). IMRT is an advanced type of high-precision radiotherapy that allows the dose to conform more precisely to the three-dimensional shape of the tumor by using multiple small radiation beams of varying intensity. This technique allows higher doses to the tumor, while minimizing the dose

to surrounding normal critical structures (6). For optimal visualization of the tumor as well as to account for its movements, a 4-dimensional CT scan is used to define the margins of the target volume to be treated.

Although CCRT is more effective than radiation only, the acute and late toxicity profile is more severe (7). Acute toxicity is defined as side effects occurring within 3 months after treatment and late toxicity from that time point onwards (8;9).

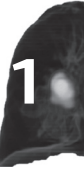
In this thesis we address both acute and late esophageal toxicity as well as late toxicity of the thoracic spine.

This thesis

Research described in this thesis is focused on toxicity induced by (concurrent) chemo-radiotherapy for locally advanced non-small cell lung cancer. The aim is to study predictive parameters for toxicity and to quantify acute and late toxicity as well as to investigate supportive care management options for the improvement of treatment adherence. Together, this information could help in (shared) decision making of the right treatment option, taking into account quality of life as well.

Outline of this thesis

Chapter 2 presents the results of a retrospective study on predictive parameters for acute toxicity in NSCLC patients treated with CCRT. Selection criteria for this treatment are not defined and as a result, patients can be under- or over-treated. We therefore correlate our findings with survival and patient characteristics, including toxicity. In **Chapter 3**, we investigate the dose-effect relation between acute esophagus toxicity (AET) and the dose-volume parameters of the esophagus after CCRT and IMRT. In 3D conformal RT the V35, the volume of the oesophagus receiving ≥ 35 Gy, was used as a parameter for possible severe oesophagus toxicity. With new RT techniques however, recalculation is necessary for the reduction of severe AET. Additionally, patient and treatment characteristics are correlated with severe AET. Grade ≥ 2 AET according to the Common Toxicity Criteria for adverse events (CTCAE) is associated with weight



loss and an impaired health related quality of life (HRQL) in patients. Palliation of symptoms is often difficult and tube feeding is frequently indicated. Proactive interventions in those patients at risk for severe AET are warranted to ensure treatment adherence. Finally, we report on the incidence of severe late esophagus toxicity (LET) in locally advanced NSCLC patients treated with CCRT and IMRT. AET and the dose to the esophagus are analysed for their associations with severe LET like stenosis and broncho-esophageal fistula. In **Chapter 4**, efficacy and toxicity results of adding cetuximab to concurrent low dose cisplatin and RT are reported. This approach has proven to be effective in squamous cell carcinoma of the head and neck and colorectal cancers (10,11). In our study, patients were randomised to receive CCRT with or without cetuximab in a multi-centre clinical setting. This study was preceded by a feasibility study in our institute (12). The management of low-dose cisplatin induced renal toxicity is discussed in **Chapter 5**. Due to a significant increase in serum creatinine, patients are at risk for not completing all 24 administrations of cisplatin and may therefore not benefit optimally from this treatment. Since January 2011, we apply prehydration all patients before every cisplatin administration with 1 litre of NaCl 0.9% intravenously. We compared the serum creatinine of these patients with those who had not been prehydrated and correlated it with overall survival.

Because patients treated with a radical radiotherapy schedule (≥ 51 Gy) (with or without concurrent/sequential chemotherapy) may develop fractures of the vertebral column, we investigated possible causes and looked for predictive parameters. Results of a retrospective and case control study on vertebral fractures of the thoracic spine are reported in **Chapter 6**. First, we describe the incidence of the vertebral fractures and its relation with the radiation dose. Additionally, a control group was matched to further analyse the effect of the radiation dose on the fractured vertebrae taking the clinical parameters into account. Future perspectives are presented in **Chapter 7** followed by a summary.

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