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Chapter 8

Summary

The main focus of this thesis is the prediction of toxicity in concurrent chemo radiotherapy (CCRT) for locally advanced non-small cell lung cancer (NSCLC). **Chapter 1** is a general introduction on the efficacy and safety of CCRT. Because of the poor prognosis of locally advanced NSCLC with a 3 year overall survival (OS) of 33%, it is important to balance efficacy and toxicity and maintain health related quality of life (HRQL). Daily low dose cisplatin as a radiosensitizing agent is being discussed as well as other treatment options. In a subset of patients, CCRT is not feasible due to increased toxicity risks and in these cases sequential chemo radiotherapy or radiotherapy is chosen. In order to select those patients at risk for severe toxicity we studied several clinical and dosimetric parameters. We also report on efficacy and safety on the addition of cetuximab to CCRT. In **Chapter 2** we correlated clinical (age, performance status (PS), co-morbidities) and dosimetric parameters (gross tumor volume (GTV) and the percentage of the oesophagus irradiated with 50 Gy (V_{50oes})) with prospectively scored acute toxicity in patients treated with concurrent cisplatin-based chemoradiation. In 35% of the 188 patients acute toxicity grade ≥ 3 was reported. V_{50oes} and PS ≥ 2 were significantly correlated with acute toxicity \geq grade 3. No differences in toxicity were observed between age groups < 70 vs. ≥ 70 years and those with a Charlson Comorbidity Index (CCI) score < 5 vs. ≥ 5 . In addition to these findings, the 1 and 2 year OS in patients with stage III disease undergoing concurrent chemo radiotherapy was 78% and 52% respectively. Patients with a poor PS or a high CCI score had similar survival outcomes. **Chapter 3** reports on acute and late esophagus toxicity. Firstly, the dose-effect-relation between acute esophageal toxicity (AET) and dose-volume-parameters of the esophagus after IMRT and concurrent chemotherapy in 139 NSCLC patients was analyzed. Dose-volume-parameters V_5 to V_{70} , D_{mean} and D_{max} of the esophagus were calculated. In this patient group 9% did not develop AET, 31% developed grade 1, 38% grade 2 and 22% grade 3 AET. The incidence of grade 2 and 3 AET was not different between patients treated with CCRT using 3-Dimensional Conformal Radiotherapy (3DCRT) versus Intensity Modulated Radiotherapy (IMRT). The V_{50oes} turned out to be the most significant dosimetric predictor for grade ≥ 3 AET. The derived V_{50} -model was shown to predict grade ≥ 2 significantly better compared to the clinical V_{35} -model. In addition to these findings we then analyzed patient and treatment characteristics in relation to AET, including the V_{50} model. We performed univariate and multivariate analyses to correlate clinical, tumor, dosimetric and chemotherapy dose variables to AET grade ≥ 2

and grade 3. AET grade 2 occurred in 37% and grade 3 in 20% of the patients. The median onset of AET was around day 15 for all grades and the median onset of the maximum grade was day 30 for both grade 2 and 3. The median duration was 43 days for grade 1, 50 days for grade 2 and >80 days for grade 3. Of the grade 3 AET patients, 48% recovered within 3 months. V50(oes), ethnic background, and the number of cisplatin administrations were significantly correlated with grade 3 AET. Finally, late esophagus toxicity (LET) was analyzed in 171 locally advanced NSCLC patients treated from 2008 until 2011 with hypofractionated IMRT (66 Gy/2.75 Gy/24 fractions) and concurrent daily low dose cisplatin. The association between AET and severe LET was tested through Cox proportional hazards regression. Additionally, the dose to the esophagus was transformed into an equivalent uniform dose (EUD) as well as the percentage of volume receiving a certain threshold dose of x Gy (Vx). Severe LET was observed in 11 patients (6%) at a median follow-up of 33 months with a median OS of 24 months. Both the maximum grade of AET and the AET recovery rate were significantly associated with severe LET. The strongest predictive dosimetric variables were: esophagus dose and the volume of the esophagus receiving 76.7 Gy, respectively. **Chapter 4** reports on efficacy and safety outcomes of a phase 2 randomized clinical trial in 102 patients with locally advanced NSCLC treated with concurrent chemoradiotherapy with or without the addition of the EGFR-mono-clonal antibody cetuximab. In this study we found no improved disease control in patients receiving cetuximab. The objective local control rate was 84% for concurrent chemoradiotherapy only and 92% in patients receiving additional cetuximab ($p=0.36$). The one-year local progression free interval and overall survival were 69 and 82% for concurrent chemoradiotherapy only and 73 and 71% for the cetuximab group, respectively (both statistically non-significant). Toxicity compared equally between both groups except acneiform rash which occurred in the cetuximab arm only. In **Chapter 5** we tested the hypothesis that daily intravenous pre-hydration decreases renal toxicity and improves chemotherapy adherence in 232 patients receiving daily cisplatin to concurrent radiotherapy for locally advanced NSCLC. Patients were divided in a pre-hydrated (PH) and non-pre-hydrated (NPH) cohort. Serum-creatinine and glomerular filtration rate (GFR) were assessed twice weekly during treatment and, retrospectively, baseline data, toxicity, treatment adherence and efficacy data were compared. The median of the maximum decrease in GFR was 24% and 8% for NPH and PH respectively ($p=0.01$). Sixty-nine percent of the patients



in the NPH group completed the 24 administrations of cisplatin, as compared to 83% of the PH group ($p=0.01$). Nineteen percent versus 2% of the patients in the NPH and PH group discontinued cisplatin treatment because of renal toxicity. Surprisingly, the incidence of acute esophageal toxicity grade ≥ 2 decreased following prehydration: 62% versus 34% for the NPH and PH group, respectively ($p=0.001$). The one-year OS was comparable between groups (75% for NPH and 71% for PH) ($p=0.441$). **Chapter 6** reports on the incidence of vertebral fractures (VF) and the association with clinical parameters in 336 patients treated with IMRT to a total dose of ≥ 51 Gy with or without sequential/concurrent chemotherapy. Subsequently, a case control study in 50 patients was performed to study the association between the radiotherapy dose and the incidence of VF. Twenty-eight patients (8%) in the unmatched group developed a VF with a median time to discovery of 7 months after treatment. Age was associated with VF in the univariate analysis ($p=0.01$) and gender borderline significant ($p=0.09$), but both parameters were no longer significant in the case control study when dosimetric parameters were added; only the V30 (Volume of the vertebra receiving 30 Gy) and the EUD (Equivalent uniform dose) $n=1$ were significantly associated with VF ($p=0.01$). **Chapter 7** contains the discussion of this thesis. Although effective, concurrent chemo radiotherapy for locally advanced non-small cell lung cancer is associated with significant acute and late toxicity. Several clinical and dosimetric parameters were associated with severe toxicity. Selection of patients who will benefit from treatment and those at risk for severe toxicity is therefore of utmost importance. Because of the limited life expectancy, HRQL should be taken into account when balancing efficacy and toxicity.