

Optimization of radiotherapy in locally advanced lung cancer

Akademisk avhandling

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The thesis is based on the following papers:

- I. A. Hallqvist, H. Rylander, T. Björk-Eriksson and J. Nyman. Accelerated hyperfractionated radiotherapy and concomitant chemotherapy in small cell lung cancer limited-disease. Dose response, feasibility and outcome patients treated in western Sweden, 1998-2004. *Acta Oncologica*, 2007; 46: 969-974
- II. J. Nyman, S. Friesland, A. Hallqvist, M. Seke, S. Bergström, L. Thaning, B. Löden, C. Sederholm and G. Wagenius. How to improve loco-regional control in stages IIIa-b NSCLC? Results of a three-armed randomized trial from the Swedish Lung Cancer Study Group. *Lung Cancer*, 65 (2009) 62-67
- III. A. Hallqvist, G. Wagenius, H. Rylander, O. Brodin, E. Holmberg, B. Löden, S-B. Ewers, S. Bergström, G. Wichardt-Johansson, K. Nilsson, L. Ekberg, C. Sederholm and J. Nyman. Concurrent cetuximab and radiotherapy after docetaxel-cisplatin induction chemotherapy in stage III NSCLC: Satellite - A phase II study from the Swedish Lung Cancer Study Group. *Lung Cancer*, 71 (2011) 166-172
- IV. A. Hallqvist, F. Enlund, C. Andersson, H. Sjögren, A. Hussein, E. Holmberg, J. Nyman. Prevalence of EGFR and KRAS mutations in NSCLC in a northern European population, and KRAS as a negative prognostic factor in stage III disease. Submitted
- V. A. Hallqvist, B. Bergman, J. Nyman. Health Related Quality of Life in locally advanced NSCLC treated with high dose radiotherapy and concurrent chemotherapy or cetuximab - pooled results from two prospective clinical trials. Submitted



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Abstract

Lung cancer is the leading cause of cancer death worldwide as well as in Sweden, where the incidence is around 3500 new cases per year. About 50% have distant metastases by the time of diagnosis and are treated with palliative intent. Early stages where the tumour is confined to the lung without regional spread constitute around 20% and may be candidates for surgery aiming to cure. The remaining 30% represent an intermediate group where the patients have metastasized to regional lymph nodes in the thorax making them inappropriate for surgery. They do not however have distant metastases and this group, often referred to as locally advanced lung cancer or stage III lung cancer, may be suitable for oncologic treatment with radiotherapy and chemotherapy with curative intent. It is established that a combination of these two modalities should be used, but since long term survival is still poor with a 5-year survival of 5-25%, there are many questions on how to further improve the treatment strategies.

This thesis aims to evaluate different approaches to optimize radiotherapy for this patient group with locally advanced lung cancer analysing one retrospective study, two prospective trials and also looking into clinical and genetic prognostic factors as well as studying Health Related Quality of Life (HRQL) during intense combined therapy.

In the first study we analyse a new treatment protocol for limited Small Cell Lung Cancer (SCLC), that was initiated in 1997, consisting of concurrent chemoradiotherapy, where the radiotherapy was delivered with 1.5 Gy, twice a day, five days a week to a total dose of 60 or 45 Gy depending on lung function, performance status and tumour burden. Complete responders and good partial responders were given prophylactic cranial irradiation to 30 Gy in 15 fractions. The results show that it is clearly feasible to give 60 Gy with concurrent chemotherapy to this patient population. Median survival was 20.8 months with a 3- and 5-year survival of 25% and 16%. There was no survival difference between the two dose groups even if there was a negative selection in the low dose group. The second study evaluates the RAKET trial, a three-armed randomized phase II trial which compares three different ways of intensifying the local treatment in locally advanced Non Small Cell Lung Cancer (NSCLC); either by hyperfractionated accelerated radiotherapy or with concurrent chemotherapy on a weekly or daily basis. The median survival was 17.8 months and 3- and 5-year survival were 31% and 24% respectively. The three strategies were equal in regard to efficacy and toxicity. In the third study we analyse outcome in the Satellite trial, a one-armed phase II study addressing the same patient population as in the RAKET trial i.e. NSCLC stage III, receiving induction chemotherapy followed by radiotherapy concurrent with the antibody cetuximab. This treatment had previously showed good results in head and neck cancer but had not been studied in NSCLC together with thoracic irradiation. The results show that it is feasible with comparable survival data to the previous trial with concurrent chemotherapy. The median survival was 17 months and 3-year survival 29%. Furthermore we found less toxicity with this regimen compared to what usually is described in concurrent chemoradiation. We also observed an immense impact on survival regarding basic clinical factor as stage (IIIA or IIIB), performance status (0, 1) and pre diagnostic weight loss. In the fourth paper we analyse the prevalence of important genetic alterations in NSCLC, namely EGFR mutations, EGFR FISH positivity and KRAS mutations and investigate their possible prognostic impact in stage III disease. The results show that the prevalence figures are as expected in an unselected population of Caucasians with EGFR mutations, EGFR FISH positivity and KRAS mutations being present in 7.5%, 19.7% and 28.8% respectively. EGFR FISH positive patients in the Satellite trial (paper III) had a trend towards inferior survival but most importantly mutated KRAS was found to be an independent prognostic marker for survival in multivariate analysis. Finally in the fifth study we evaluate HRQL in patients treated with high dose radiotherapy and concurrent chemotherapy or cetuximab. This was done by using the EORTC QLQ C30 and LC14 questionnaires during therapy and at three months follow-up. The results show that most patients experience a gradual decline in nearly all functional scales. Treatment related side effects return towards base-line but there is for the majority a persistent worsening of dyspnoea and fatigue. Patients with stage IIIA and/or performance status 0 seem to tolerate combined treatment better with regard to HRQL, and concurrent radiotherapy with cetuximab influences HRQL less than concurrent chemoradiation.