

Optimization of radiotherapy in locally advanced lung cancer

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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.

List of publications

This thesis is based on the following papers, referred to in the text by their Roman numerals:

- 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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Abbreviations

BID	Bis in die (twice a day)
CK	Cytokeratin
CR	Complete response
CTC	Common toxicity criteria
EBUS	Endobronchial ultrasound
ED	Extensive disease
EGFR	Epidermal growth factor receptor
EORTC QLQ C-30	European organisation for research and treatment of cancer, quality of life questionnaire C-30
EUS	Endoscopic ultrasound
FEV1	Forced expiratory volume in one second
FISH	Fluorescence in situ hybridization
FNA	Fine needle aspiration
G-CSF	Granulocyte colony stimulating factor
Gy	Gray
HART	Hyperfractionated accelerated radiotherapy
HRQL	Health related quality of life
KRAS	Kirsten rat sarcoma viral oncogene
LC 14	Lung cancer module 14
LD	Limited disease
NSCLC	Non small cell lung cancer
PCI	Prophylactic cranial irradiation
PD	Progressive disease
PET-CT	Positron emission tomography - computed tomography
PR	Partial response
PS	Performance status
RECIST	Response evaluation criteria in solid tumours
RTOG	Radiation therapy oncology group
SCC	Squamous cell carcinoma
SCLS	Small cell lung cancer
SD	Stable disease
TKI	Thyrosin kinase inhibitor
TTF1	Thyroid transcription factor 1
TTP	Time to progression

1 Background

1.1 Introduction

Lung cancer is the leading cause of cancer death worldwide as well as in Sweden. Each year more than 1.6 million people around the globe acquire lung cancer and about 3500 in our country [1, 2]. The incidence is unfortunately increasing in most countries in the developing world but in some western countries e.g. Sweden, there has been a decreasing incidence among men which now seem to have reached a plateau. On the contrary the incidence in women has risen and last year the majority of new lung cancer cases were diagnosed in females. Globally the prevalence is still higher in men but the equalization between sexes is a common feature. Lung cancer occurs predominantly in the elderly patients where about 50% are >70 years at time of diagnosis and only 1% are <40 years in Sweden [2].

The main cause is smoking, where the total tobacco exposure over time correlates to an increasing risk. Other known risk factors are of minor importance compared to smoking but includes radon, arsenic and asbestos which increase the risk, especially in combination with smoking. However, as a substantial part of the lung cancer population is represented by never smokers more research in this field is warranted.

1.2 Diagnostic procedure

The investigational procedure aims to decide the tumour type as well as properly stage the patients to make it possible to determine the best treatment. As new and better technologies are developed, the staging procedure becomes more accurate. The diagnostic tools in use have to be adapted to the actual findings, and according to today's standard a complete diagnostic and staging procedure, before a treatment with curative potential is given, could include CT scan of the thorax, bronchoscopy, CT or MRI of the brain, PET-CT, mediastinoscopy and preferably endobronchial ultrasound (EBUS) plus esophageal ultrasound (EUS). The optimal staging procedure is as expected changing over time so the patients studied in this thesis are not staged optimally according to today's standard.

Tumour tissue for analysis of histological type is usually obtained through bronchoscopy, preferably biopsies from bronchial mucosa or with cytology on bronchoalveolar fluid. Another option is biopsies via mediastinoscopy, transthoracic biopsies or fine needle aspiration (FNA) from tumour sites during EBUS or EUS. As the knowledge about genetic differences in lung cancer tumours, and the importance of genetic alterations regarding choice of therapy, is rapidly growing, one should strive to attain proper tumour tissues samples instead of cytology specimen.

1.3 Histological classification

Lung cancer has historically been subdivided into two main groups based on their histological appearance and different clinical features, namely small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for the majority of cases, around 80-85%, whereas SCLC constitutes around 15-20% and the incidence is decreasing. The latter almost always correlates to smoking in contrast to NSCLC where around 10-15% are never-smokers. NSCLC is further divided into various subtypes. Recently a proposal of a new histopathological classification was published, taking the possibility of cytology and immunohistochemical staining into account [3]. It can be seen in table 1 but despite all the subgroups one of the main messages is that either the tumour is an adenocarcinoma or a squamous cell carcinoma. Therefore a more elaborate classification is nowadays rarely used in the clinic other than: adenocarcinoma, squamous cell carcinoma or NSCLC NOS (not otherwise specified).

As for the immunohistochemical staining, adenocarcinomas usually are CK 7 and TTF-1 positive and CK 5 and CK 20 negative but a minor proportion could be TTF-1 negative or CK 20 positive. Squamous cell carcinomas are in general CK 7, CK 20 and TTF-1 negative and CK 5/6 and p63 positive, a small percentage of cases will be positive for CK 7 or TTF-1. SCLC are most often TTF-1 positive but CK 7, CK 20, CK 5 and p63 negative [4].

1.4 Staging

In addition to pathological classification the tumours are also classified according to the extent of their growth using the TNM system (table 2). This staging system relates to the size and growth of the primary tumour (T), the presence of nodal metastases (N) and distant metastases (M). The TNM classification regarding lung cancer has recently been up-dated (7th edition) [5], but the tumours in the papers included in this thesis are classified according to the 6th edition, both versions are shown in table 3. Depending on the TNM classification the tumours are further categorized into a certain stage, also seen in table 3. In short, stage I comprises small tumours without any metastases or growth into other organs than the lung. Stage II can either mean larger tumours and/or nodal metastases in the ipsilateral hilus. Stage III signify that there are nodal metastases in the mediastinum or supraclavicular nodes and/or advanced growth of the primary tumour into neighbouring organs such as big vessels, vertebrae or mediastinum. Finally stage IV means that there are distant metastases.

2004 WHO classification	Biopsy/cytology: 2011 IASLC/ATS/ERS
Adenocarcinoma Mixed subtype Acinar Papillary Solid BAC (non mucinous) BAC (mucinous) Fetal/ mucinous (colloid)/ signet ring/ clear cell No 2004 WHO counterpart	Adenocarcinoma (morphologic patterns clearly present) Adenocarcinoma, describe identifiable patterns present Adenocarcinoma, describe identifiable patterns present Adenocarcinoma, describe identifiable patterns present Adenocarcinoma, describe identifiable patterns present Adenocarcinoma with lepidic pattern Mucinous adenocarcinoma Adenocarcinoma with fetal/ mucinous (colloid) patterns or adenocarcinoma with signet ring/ clear cell features. Morphologic adenocarcinoma pattern not present (special stain): Nonsmall cell carcinoma, favour adenocarcinoma
Squamous cell carcinoma Papillary Clear cell Small cell Basaloid No 2004 WHO counterpart	Squamous cell carcinoma (morphologic patterns clearly present) Squamous cell carcinoma Squamous cell carcinoma Squamous cell carcinoma Squamous cell carcinoma Morphologic squamous cell carcinoma pattern not present (special stains): Nonsmall cell carcinoma, favour squamous cell carcinoma
Large cell carcinoma Large cell NE carcinoma Large cell carcinoma with NE morphology	Nonsmall cell carcinoma NOS Nonsmall cell carcinoma with NE morphology (positive markers) Nonsmall cell carcinoma with NE morphology (negative markers)
Adenosquamos carcinoma No 2004 WHO counterpart	Nonsmall cell carcinoma with squamous cell and adenocarcinoma patterns Morphologic squamous cell carcinoma or adenocarcinoma patterns not present: Nonsmall cell carcinoma NOS (results of immunohistochemical stains and their interpretation should be specified)
Sarcomatoid carcinoma	Nonsmall cell carcinoma (poorly differentiated, with spindle and/or giant cell carcinoma, mention if adenocarcinoma or SCC are present)
Small cell carcinoma	Small cell carcinoma

Table 1. Histological classification of lung cancer.

This system should now be applied regardless of subtype (SCLC or NSCLC) [6], however until recently SCLC was classified into two categories: Limited disease (LD) which indicate that no growth outside of the thorax would be present and the tumour should also be possible to encompass within one irradiation field, and extensive disease (ED) with distant metastases outside of the thorax. LD and ED correspond to stage I-III and stage IV respectively.

In Sweden around 50% of the patients with NSCLC have distant metastases by the time of diagnosis (stage IV), around 20% have tumours confined to the lung or with limited nodal spread (stage I-II), and the remaining 30% have advanced regional lymph node metastases (stage III). Regarding SCLC around 35% have stage I-III and 65% stage IV by the time of diagnosis [2].

T1	Tumour < 3 cm, surrounded by lung tissue, no invasion more proximal than the lobar bronchus. T1a ≤ 2 cm, T1b ≤ 3 cm.
T2	Tumour 3-7 cm, or involves main bronchus 2 cm distal to the carina, involves visceral pleura, associated with atelectasis or obstructive pneumonitis that extends to the hilar region but not the entire lung. T2a 3-5 cm, T2b 5-7 cm.
T3	Tumour > 7 cm or invading chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium or growth in the main bronchus less than 2 cm distal to the carina, or atelectasis or obstructive pneumonitis of the entire lung, or separate tumour nodule in the same lobe as the primary.
T4	Tumour of any size invading mediastinum, heart, great vessels, trachea, recurrent nerve, oesophagus, vertebral body, carina, separate tumour nodule in ipsilateral lobe.
N1	Metastases in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension.
N2	Metastases in ipsilateral mediastinum and/or subcarinal lymph nodes.
N3	Metastases in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph nodes
M1	Distant metastases. M1a separate tumour nodules in contralateral lung, tumour with pleural nodules or malignant pleural or pericardial effusion. M1b distant metastases.

Table 2. TNM descriptors in lung cancer.

T and M		N0	N1	N2	N3
6th edition	7th edition	Stg	Stg	Stg	Stg
T1 (≤ 3cm)	T1a (≤ 2cm)	IA	IIA	IIIA	IIIB
	T1b (> 2-3cm)	IA	IIA	IIIA	IIIB
T2 (> 3cm)	T2a (> 3-5cm)	IB	IIA (IIB)	IIIA	IIIB
	T2b (> 5-7cm)	IIA (IB)	IIB	IIIA	IIIB
	T3 (> 7cm)	IIB (IB)	IIIA (IIB)	IIIA	IIIB
T3 (invasion)	T3	IIB	IIIA	IIIA	IIIB
T4 (nodule in same lobe)	T3	IIB (IIIB)	IIIA (IIIB)	IIIA (IIIB)	IIIB
T4 (extension)	T4	IIIA (IIIB)	IIIA (IIIB)	IIIB	IIIB
M1 (ipsilateral lung)	T4	IIIA (IV)	IIIA (IV)	IIIB (IV)	IIIB (IV)
T4 (pleural effusion)	M1a	IV (IIIB)	IV (IIIB)	IV (IIIB)	IV (IIIB)
M1 (contralateral lung)	M1a	IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Table 3. Stage depending on TNM status, grey areas represent changes from the 6th to the 7th edition.

1.5 Brief summary of treatment strategies

1.5.1 NSCLC

The treatment has to be adjusted to the patients' general condition but provided the patients are deemed fit for therapy the standard strategies are as follows: Stages I-III are considered to have a curative potential and surgery is the current standard procedure for operable patients in the early stages I and II, where a lobectomy or pulmectomy is performed. Smaller surgery like sleeve resection is still investigational. A lobectomy is to be preferred as it will result in lower morbidity and mortality [7, 8]. Survival data can be seen in table 4 where the 5-year survival is around 80% [9]. Following surgery it is now also seen as standard procedure to administer adjuvant chemotherapy to patients in stage Ib-II [10]. A possible alternative to surgery for stage I tumours or stage II without hilar spread is stereotactic radiotherapy. This is a precise delivery of radiation to very high doses in a short period of time. It is routinely delivered to inoperable patients in many centres. The 5-year survival is somewhere around 40-50% [11] but one has to keep in mind that this population is deemed

unfit for surgery and has a worse prognosis regardless of type of therapy. Recently survival data on stereotactic radiotherapy in operable patients has been presented and is comparable to survival after surgery [12, 13]. This finding warrants randomized prospective trials between surgery and stereotactic radiotherapy which are ongoing.

Standard procedure for stage III patients is chemotherapy and radiotherapy, see below. Surgery can be an option in selected patients with stage IIIA disease but so far surgery has no proven role in stage III disease where two studies have failed to show an improvement with radiochemotherapy plus surgery vs. radiochemotherapy alone [14, 15], hence different combined bi- or trimodality approaches with surgery are still investigational. If surgery is performed in stage III disease adjuvant or neoadjuvant chemotherapy should be given. Survival (table 4) depends on subgroup in question where stage IIIA patients have a 5-year survival of 15-25 % and stage IIIB patients 5-15 % [16, 17].

Stage IV patients with distant metastases can generally not be cured and the treatment is palliative aiming to prolong life, reduce symptoms and increase their quality of life. The main treatment is chemotherapy or targeted therapy such as Thyrosine Kinase Inhibitors (TKI), together with palliative radiotherapy towards problematic lesions e.g. symptomatic primary tumours or bone and brain metastases.

Stage	5-year survival	
	NSCLC	SCLC
I	40-80 %	40-60 %
II	30-50 %	10-30 %
IIIA	15-25 %	
IIIB	5-15 %	
IV	<5 %	<3 %

Table 4. Survival by stage.

1.5.2 SCLC

SCLC behaves differently from NSCLC as it usually is particularly sensitive to chemotherapy and radiation, rendering surgery a minor role in this disease. However, an improved survival has been seen in stage I patients, and surgery in early stages has attained an increasing interest in recent years and could be considered in T1-T2N0 patients, especially in mixed tumours (NSCLC + SCLC), then followed by chemotherapy [18-21].

Despite this susceptibility to treatment with radiation and cytotoxic drugs SCLC has a very high relapse rate resulting in rather poor survival data (table 4). Stage I-III (former LD) has a better prognosis and a curative potential with today's standard composed of combined radiochemotherapy and prophylactic cranial irradiation, resulting in a 5-year survival of 10-

30%. Stage IV (ED) is routinely treated with palliative chemotherapy as well as palliative irradiation if needed. Recently it has been shown that patients with SCLC-ED also benefit from prophylactic cranial irradiation with increased survival [22]. Nevertheless the 5-year survival is < 3 % [23].

1.6 Accurate treatment of stage III disease in NSCLC

1.6.1 Radiotherapy

During the last decades there has been a development in radiation strategies. Radiotherapy emerged as an effective treatment option in the 1970's and in the 1980's radiotherapy with 2 Gy daily to 60 Gy became a practical standard due to a three armed study comparing 40, 50 and 60 Gy [24]. The highest dose level was superior regarding short term survival. A Chinese study comparing involved field 68-74 Gy vs. elective nodal irradiation 60-64 Gy showed improved local control and OS at 2 years with the higher dose, implying a dose-response relationship above 60 Gy [25]. There is also an escalation study on hyperfractionated therapy where the high dose group (69.6 Gy) had a better survival compared to lower dose groups [26]. Apart from these studies there are surprisingly little data on dose comparisons. As the radiation technique has been improved, feasibility of higher doses has been shown which has lead to most centres now delivering somewhere between 60-70 Gy in clinical practice, even though higher dose levels have not been substantially proven in a randomized manner. There are several studies trying to further escalate the dose beyond 70 Gy to 80-90 Gy [27-30], where the maximum tolerable dose (MTD) often is limited by doses to the lung. Data have so far showed feasibility, but notably most of the escalation studies also include stage I and II which will make it easier to escalate the dose as the toxicity from mediastinal irradiation in that setting will be of minor importance. It has also been shown that it is safe to escalate the dose with concurrent chemotherapy to 74 Gy [31-33].

Another option to increase radiation efficacy could be altered fractionation. To give doses of <1.8-2 Gy is called hyperfractionation, and the opposite >2 Gy hypofractionation. If the total treatment time is shorter than for the corresponding time with conventional fractionation (2 Gy daily, once a day, five days a week), it is called accelerated treatment. In comparisons between conventional radiotherapy and hyperfractionated schedules tendencies to higher efficacy with the more fractionated regimen has been shown [34] but generally studies on hyperfractionated regimens have not proven superior unless they also are accelerated. The latter on the other hand has shown superiority compared to conventional fractionation in several studies [35, 36] where the British CHART trial is the most striking one, improving 2 year survival from 20 to 33 % by giving the radiotherapy in a much accelerated schedule

within 12 days. There are also indirect data supporting a short overall treatment time as it has been shown that interruption of the radiotherapy course results in decreased survival [37].

Recently there has been a growing interest in hypofractionated strategies, which have been shown to be effective and feasible both per se and with sequential or concurrent chemotherapy [38-40]. Furthermore a randomized trial of hypofractionated radiotherapy comparing sequential and concurrent chemotherapy was just reported where the concurrent arm had a superior survival [41]. There are no published trials comparing hypofractionated regimens to conventionally fractionated or hyperfractionated accelerated treatment.

1.6.2 Combined radiochemotherapy

When radiotherapy alone was considered standard treatment in stage III disease, addition of chemotherapy was explored. Several studies showed improved survival [34, 42, 43] and this finding was later confirmed in three meta-analyses [44-46]. Chemotherapy gave a reduction of risk of death of 13% corresponding to an absolute benefit of 4% at 2 years. This effect was due to reduction of distant metastases. The chemotherapy was initially given in a sequential manner with induction chemotherapy followed by radiation. The next step was to evaluate the addition of chemotherapy concurrently with radiotherapy, as it was known that cytotoxic agents had the possibility to enhance radiation because of their radiosensitizing effect, see below section 1.8.

A few studies compared concurrent chemoradiotherapy with radiotherapy alone [47-49] and the superiority of chemotherapy in this setting has in a meta-analysis also been calculated to an absolute survival gain of 4% at two years [50]. Later on trials comparing the sequential versus the concurrent approach were made, where the concurrent schedules showed higher efficacy and survival due to improved local control [51-55]. The superiority of concurrent schedules with significantly improved survival over sequential has been confirmed in three meta-analyses [56-58]. Now there are also data that indicate that survival is not further improved by adding induction chemotherapy when treating with concurrent chemoradiation [59, 60]. However there are not much data published on that issue and in the most cited study the survival data were poor in both arms and the arm with induction chemotherapy had a higher median survival albeit not significant [59].

The concurrent chemotherapy can be administered as full dose courses or as low dose on a weekly or daily basis. In theory the latter is enhancing the radiation effect thereby improving local control whereas the former should have a higher possibility to eradicate micrometastatic disease. There are no direct comparisons between these two treatment strategies but as distant metastases is a considerable problem and it has been shown that the metastatic frequency can be lowered with induction chemotherapy, some would argue that just delivering radiopotentiating low-dose treatment without induction will not be enough

and that data imply that schedules with full dose chemotherapy tend to have somewhat higher survival figures [17].

Concurrent chemotherapy has also been shown to be feasible in hyperfractionated accelerated schedules [61], in dose escalation studies [31-33] and recently concurrent chemotherapy has been reported to be feasible and superior to sequential therapy in hypofractionated treatment [41].

1.6.3 Choice of chemotherapy

Regarding choice of chemotherapy to be integrated into the irradiation schedule most of the data are extrapolations from trials in stage IV disease. There is a broad consensus that the chemotherapy treatment should be platinum-based, since platinum-containing combinations in the 1980's showed superiority to non-platinum regimens [62]. Initially platinum was usually combined with etoposide, mitomycin, vindesine or ifosfamide where the combination of cisplatin/etoposide showed the best survival data seen by that time, rendering it a status as standard regimen [63]. Later studies on the "third generation" cytotoxics with combinations of platinum plus either of gemcitabine, paclitaxel or docetaxel showed improved efficacy compared to platinum/etoposide and cisplatin/mitomycin/ifosfamide [64-68]. In stage IV disease it has also been proven that a doublet is more effective than a single agent [69], hence standard therapy usually is a platinum doublet, cis- or carboplatin with one of the "third generation" cytotoxic agent, where paclitaxel, docetaxel and gemcitabine has shown similar efficacy in stage IV disease [70]. Vinorelbine is considered as effective and is the only drug which in combination with cisplatin has robust long term data in the adjuvant setting [71]. On the other hand cisplatin plus docetaxel have shown higher efficacy than cisplatin/vinorelbine in a study in stage IV disease [72]. There is no consensus regarding the second drug, probably paclitaxel, docetaxel, gemcitabine and vinorelbine have comparable efficacy. One important issue however is that the compound needs to be able to integrate with radiotherapy without excessive toxicity, which for example is seen with gemcitabine. Therefore the most common combinations are cis- or carboplatin together with paclitaxel, docetaxel or vinorelbine. When it comes to the choice between cisplatin and carboplatin there are no direct comparison in NSCLC stage III disease. However a meta-analysis in stage IV disease showed cisplatin to be more effective when combined with third generation cytotoxics [73]. Furthermore cisplatin is superior in the adjuvant setting regarding long term survival, and in stage III disease regimens with cisplatin consistently reports higher survival rates [74]. Moreover in protocols using single carboplatin concurrent with radiation vs. radiation alone, it has been hard to show a benefit in favour of the combined arm [75, 76]. In fact a study aiming at comparing different concurrent schedules without induction therapy included five trials with single agent

carboplatin and none of these could show any benefit of carboplatin concurrent with radiation over radiation alone [77]. The choice differs around the globe strongly influenced by practical considerations; carboplatin is easier to administrate and has a milder toxicity profile. Nevertheless when considering available data, cisplatin is recommended in regimens with curative intent in fit patients both in the adjuvant postoperative setting and in combination with radiotherapy.

1.6.4 Newer drugs in combination with radiotherapy

As the therapeutic arsenal has expanded considerably when it comes to stage IV, the issue arises whether these compounds should be integrated in stage III protocols. So far feasibility has been shown regarding the TKI's erlotinib and gefitinib, both as single agents concurrent with radiation and concurrent with chemoradiation [78-81]. There are up to now no randomized trial evaluating the efficacy compared to standard chemoradiotherapy. Pemetrexed which is indicated in stage IV non-squamous cell carcinoma has been investigated in a number of phase I and II trials showing feasibility both with carboplatin and cisplatin together with radiation [82-84], but as for the TKI's there are no trials comparing pemetrexed with standard treatment regarding efficacy. As for the EGFR-directed antibody cetuximab, there are data on feasibility both as single agent combined with radiation and with chemoradiation [85-87]. A trial comparing radiochemotherapy with or without cetuximab is on-going and cetuximab in combination with chemotherapy has shown improved efficacy over chemotherapy alone in stage IV disease [88]. Combinations of the VEGFR-directed antibody bevacizumab and radiotherapy have been assessed in at least two phase two trials that both closed prematurely due to deaths caused by tracheoesophageal fistulas [89].

1.6.5 Consolidation therapy

Consolidation therapy is an option in stage IV disease, where both pemetrexed and erlotinib have shown increased survival [90, 91]. So far there are no trials showing a benefit of consolidation therapy after full dose radiochemotherapy in stage III disease, but there are reports on feasibility regarding docetaxel [92] and docetaxel/carboplatin [93]. Moreover gefitinib has been evaluated in a randomized manner but it had a detrimental effect with the placebo arm showing a significant superior survival [94]. This was probably due to tumour progression in the gefitinib arm and not because of toxicity.

1.6.6 Prophylactic cranial irradiation

As a high proportion of the patients develop brain metastases several attempts have been made to find out whether prophylactic cranial irradiation (PCI) would be beneficial. Almost all of the randomized trials show a delay in occurrence and/or reduction of brain metastases but no survival advantage. To resolve this question RTOG-0214 was launched being powered to detect a survival difference. Unfortunately it closed prematurely due to slow accrual, and did not meet its primary endpoint but as the other trials it showed a reduction of brain metastases but no significant impact on survival [95]. As for now, it is still not clear if stage III NSCLC patients would benefit from prophylactic cranial irradiation or not.

1.6.7 Conclusions on stage III NSCLC

Taking the above mentioned data into account there is a widespread opinion that today's standard treatment of stage III disease is concurrent chemoradiotherapy to 60-70 Gy. The chemotherapy should be a platinum based doublet but there is no more precise consensus about choice of drugs. Furthermore there is no consensus regarding high dose or low dose chemotherapy. Accelerated regimens are generally considered more effective than conventional fractionation but have at most centres not been routinely introduced, probably due to uncertainty about concurrent chemotherapy and for practical reasons. Adding targeted therapies to radiation, using consolidation therapies, further increase the radiation dose and hypofractionated schedules are all topics for future investigation.

1.7 Accurate treatment of stage III disease in SCLC

1.7.1 Radiotherapy

Historically radiotherapy proved to be superior to surgery [96], but how should it be delivered? Regarding dose there seem to be a dose-response relationship. Improved local control with a higher dose has been shown in studies comparing 25 vs. 37.5 Gy and 60 Gy vs. 30 Gy [97, 98], and in a single institution study, increasing dose over time resulted in enhanced local control and suggested a dose-response relationship between 30 and 50 Gy [99]. Feasibility has also been shown with conventional fractionation and concurrent chemotherapy to 70 Gy [100], and with >60 Gy with hyperfractionated protocols with concurrent chemotherapy [101] but no other randomized comparisons have been made between higher doses (≥ 60 Gy) and lower doses.

Altered fractionation with a hyperfractionated and accelerated regimen has proven to be beneficial over conventionally fractionated treatment, and 1.5 BID to 45 Gy are by many considered standard as the often cited study by Turrisi et al [102] has shown good survival (26% at five years). Data on accelerated therapy have not been conclusive and a similar study did not see a survival gain [103], but the radiotherapy was however delivered in a split-course manner and also delayed until the fourth chemotherapy cycle was given, see below, probably influencing the results. A meta-analysis later on confirmed the superiority of accelerated therapy [104].

The timing of radiotherapy onset relative to the chemotherapy courses seem to be of importance. The individual studies reported conflicting results [105-107] but there are at least five meta-analyses on the subject which all find early (i.e. concurrent with cycle nr 1 or 2) onset superior to late [104, 108-111]. This effect is even more pronounced if the radiotherapy is accelerated, hyperfractionated and if the chemotherapy is cisplatin-based [104]. Concerning timing it has also been shown that the total radiation treatment time is of importance, as for instance the best results have been observed in patients that started the irradiation early and finished their radiotherapy course within 30 days [108].

As the standard radiotherapy strategy still is debatable it is satisfactory that a study is ongoing comparing concurrent radiation with cisplatin/etoposide with three different radiotherapy approaches: 1.5 Gy BID to 45 Gy, conventionally irradiation to 70 Gy or 1.8 Gy, once daily in 16 days followed by 1.8 Gy BID in nine days to a total dose of 61.2 Gy [112].

1.7.2 Combined Radiochemotherapy

As has been said SCLC historically was treated by surgery, being replaced by radiotherapy when this was shown to be superior [96]. Later SCLC was found to be exceptionally sensitive to chemotherapy which became the standard treatment. Further progress was not achieved until the two modalities were combined, which was facilitated when it was shown that cisplatin/etoposide (EP) was as efficient as previously used regimens with anthracyclines in stage IV disease [113]. The latter is hard to integrate with radiotherapy due to its strong radiosensitizing effect, but EP was shown to be feasible in combination with concurrent radiotherapy [114]. Initial studies between chemotherapy and chemoradiotherapy were inconclusive with a majority being under-powered to detect survival differences, but hereafter two meta-analyses confirmed increased survival by adding radiotherapy, resulting in an absolute survival difference of 5% at three years [115, 116]. Several studies made favoured the concurrent approach [117-119].

1.7.3 Choice of chemotherapy

Many cytotoxic drugs have effect with good responses in SCLC but the most wide-spread and efficient regimen was initially CAV, cyclofosfamide, adriamycin and vincristine. This combination was later replaced by cisplatin/etoposide (EP) when combined radiochemotherapy became the treatment of choice as EP could be administered together with radiotherapy and had also shown equal efficacy to CAV in stage IV disease [113]. Furthermore in 2002 EP together with radiation was reported to significantly increase survival compared to CEV (cyclofosfamide, epirubicin, vincristine) in SCLC LD [120].

Several newer drugs as paclitaxel, topotecan, ifosfamide, and irinotecan have been tested in combination with radiation in phase II studies showing feasibility [100, 121-123]. None has been deemed efficient enough to justify further investigation in a phase III study, apart from irinotecan as this compound combined with platinum has been shown to be superior to EP in the metastatic setting [124]. There are no comparisons to EP published to this day in stage III disease but there are supporting data indicating that irinotecan/platinum are superior to EP, both a Scandinavian study on carboplatin/irinotecan in stage IV disease [125] and in a meta-analysis [126].

Regarding prolonged chemotherapy, there are no proofs that extending beyond six courses would be beneficial [127, 128]. Neither are there any data from randomized trial supporting consolidation therapy even if it has been shown to be feasible in phase I/II studies [129, 130]. Considering the sensitivity to chemotherapeutics seen in SCLC there has been a lot of research regarding dose-intensified regimens supported by G-CSF or stem-cell transplant, with some trials reporting higher efficacy with intensified strategies with G-CSF. Data are however not convincing and such approaches are not recommended outside clinical trials [131].

As for the choice between cisplatin and carboplatin a meta-analysis in stage IV disease was recently reported with no survival difference [132], but in stage III disease data are scarce. Solitary comparisons in stage III disease [133] imply similar efficacy, and feasibility of carboplatin has been shown in phase II studies [134, 135]. However, almost all published trials in the curative setting with thoracic radiotherapy, and thereby all the data in the meta-analyses, are done with cisplatin, and due to its possibly higher efficacy when combined with radiotherapy it is generally recommended in the treatment of SCLC Stage III (LD) [112, 136, 137].

1.7.4 Prophylactic cranial irradiation

Due to the high frequency of brain metastases, the question of prophylactic cranial irradiation (PCI) has been addressed in a number of studies. There are at least seven

randomized trials, which all show a decreased incidence of brain metastases but no significant effect on survival. However, PCI has been confirmed to improve survival in two meta-analyses, increasing the 3-year survival from around 15 to 20% [138, 139]. A survival improvement by adding PCI has now also been shown in stage IV disease (ED) [22].

1.7.5 Conclusions on stage III SCLC

When considering the data presented, and the conclusions that can be made the treatment discrepancies between various centres are less than for NSCLC. In SCLC there is a consensus that the treatment should consist of a platinum doublet with etoposide. The radiotherapy is preferably delivered early in a concurrent manner but whether it will be hyperfractionated differs to some extent between sites because of pragmatic reasons as hyperfractionated fractionation can be considered arduous. Differences are also seen regarding chemotherapy as carboplatin is easier to administrate than cisplatin with less toxicity. PCI should be given to all responding patients.

1.8 Radiosensitizing mechanisms

The rationale for combining a pharmaceutical agent with radiation is the possibility of achieving a synergistic effect. The research field of radiosensitizing drugs and their mechanisms is huge and complicated and will not be fully accounted for here, but in short different compounds can enhance radiotherapy e.g. by increased inhibition of repair of radiation induced damage, reduced repopulation, increased apoptosis and increased re-oxygenation thereby making the tumour cells more sensitive to irradiation. The cytotoxic agents combined with radiation used in the studies in this thesis are cisplatin, carboplatin, paclitaxel, docetaxel, etoposide and cetuximab. Cisplatin and carboplatin are alkylating agents that crosslink the DNA strands leading to DNA breakage during replication and cisplatin also directly can cause DNA strand breaks. They are not cell cycle specific but will induce DNA strand breaks and crosslinks in any phase of the cell cycle but exhibit their main effect in the S phase. They both are known to have synergistic effect with radiation even if most of the data are on cisplatin. They are believed to inhibit repair of radiation induced damage and cisplatin has also been shown to increase the number of radiation induced strand breaks. The taxanes paclitaxel and docetaxel stabilizes the mitotic spindle apparatus leading to death in the mitotic cell or accumulation of the cells in the G2/M phase where the cells are very sensitive to radiation. Most data are on paclitaxel where it also has been shown that additional interaction effect can be from tumour reoxygenation. Etoposide is a topoisomerase inhibitor, arresting the cells in S → early G2 phase in the cell cycle, and the interaction effect with radiation is probably due to impaired repair and apoptosis. Finally the

antibody cetuximab binds to the epidermal growth factor receptor and prevents ligand induced phosphorylation, stimulating increased receptor endocytosis and degradation thereby further inhibiting activation. A strong synergistic growth inhibition has been seen in cell lines together with radiotherapy. This synergistic effect seems at least partly to be caused by inhibition of repair of DNA damage [140-144].

1.9 The Epidermal Growth Factor Receptor (EGFR) pathway

1.9.1 The signalling process

There are numerous systems in the human cells transducing information from the extracellular side into the intracellular compartment, resulting in a variety of effects via complicated signalling systems. One of the most important is the epidermal growth factor receptor (EGFR)-directed pathway, as it is required for normal cell proliferation, survival, migration and differentiation. It is also known to be of vast importance in oncogenesis, as abnormalities might lead to dysregulation of the signalling cascade and thereby e.g. uncontrolled cellular growth and proliferation (figure 1). Furthermore it is clinically relevant as there are already chemical antitumoral compounds specifically targeting this system and the knowledge expands rapidly.

EGFR is a transmembranous receptor belonging to the erbB or Human Epidermal Growth Factor (HER) family. It is activated by dimerization with another EGFR or HER family receptor as a response to extracellular ligand binding. There are several known ligands to EGFR including epidermal growth factor (EGF), transforming growth factor alpha (TGF- α), amphiregulin, epiregulin and neuregulin among others. Dimerization leads to activation by phosphorylation of the tyrosine residue on the intracellular domain. This in turn results in further downstream phosphorylation and activation where the signal ultimately reaches the nucleus interacting with DNA (figure 1). Throughout the process there are several modulation steps which all can be a part of dysregulatory signalling. This complex and finely tuned balance might be disrupted which constitutes one of the explanations in oncogenesis.

Theoretically there are different mechanisms resulting in over-activation of the EGFR directed pathway: There could be an abundance of ligands, or the receptor itself could be overexpressed, both leading to an increased signalling. There could be mutations in the receptor or the downstream molecules resulting in constant activation and signalling. There might also be mutative changes in regulatory molecules along the main signalling pathway enhancing or weakening the signal [145, 146].

The most common alterations, driving lung cancer oncogenesis, in the EGFR signalling system known today, are activating mutations in the intracellular domain of EGFR, overexpression of EGFR and activating mutations in the downstream molecule KRAS. EGFR activating mutations occurs in exon 18-21, where the most common are an in-frame deletion in exon 19 and a point mutation in exon 21 that can be detected by PCR-based technologies. EGFR over expression can be estimated by immunohistochemistry but also on genomic level by fluorescence in situ hybridization (FISH). Finally mutated KRAS is almost exclusively a point mutation in exon 2 and is also detected by PCR-based technology [147, 148].

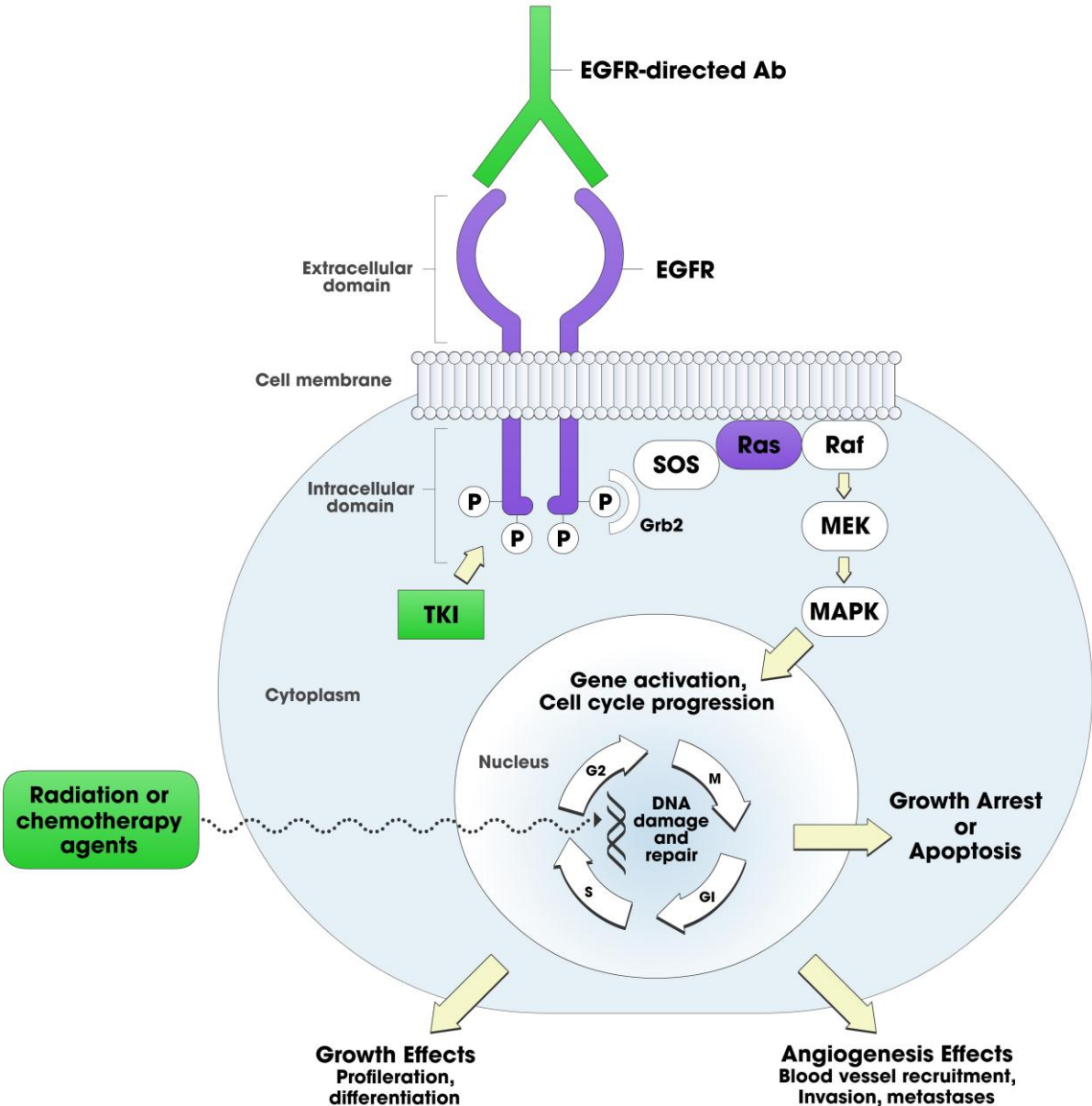


Figure 1. The EGFR-directed pathway with possible interventions marked in green. EGFR-directed Ab = antibody, TKI = tyrosine kinase inhibitor, p = phosphorylation.

1.9.2 EGFR-directed therapies

Hitherto several pharmaceuticals directed towards EGFR have been developed that are in clinical use. They are divided into two major classes; antibodies that bind the receptor on the extracellular domain and “small molecules” that will act inside the cell. Representing the antibody-class of molecules, cetuximab is an EGFR-directed IgG₁ monoclonal chimeric (mouse/human) antibody that when binding will block for ligand induced activation and cause internalization of the receptor complex resulting in reduced signalling. It can also destroy the cell by antibody dependent cell cytotoxicity (ADCC) [149]. In the second class there are so far two compounds in use: gefitinib and erlotinib which bind to the intracellular domain of the receptor, hereby preventing phosphorylation and further signalling. These molecules are usually referred to as Tyrosine Kinase Inhibitors (TKI's) [150, 151].

The treatment with TKI's have evolved during the last decade and the first real progress was reported in the BR21 trial where erlotinib showed improved survival compared to placebo in previously treated patients [152]. The analogous ISEL study with gefitinib did not however show a significant improved survival in the gefitinib arm [153], notably the best effect in both studies were observed in similar subgroups i.e. predominantly in non-smoking females with adenocarcinomas and of Asian ethnicity. When TKI's were combined with chemotherapy in first line treatment the results were disappointing; at least four large randomized phase III trials failed to show improved efficacy with the addition of gefitinib or erlotinib over chemotherapy alone [154-157]. Hence single agent TKI's were further studied and a step forward came with the IPASS trial where it was shown that patients with EGFR mutations had a significantly better PFS than wild type patients, and that EGFR mutations were also more common in patients with the clinical features that previously had been shown to respond to TKI therapy [158]. Recently a trial regarding patients with EGFR mutations randomized to either erlotinib or chemotherapy in the first line setting was reported showing improved PFS in the erlotinib arm [159]. EGFR mutations have now been established as predictive markers of response to TKI's. Regarding markers of resistance most data indicate that mutated KRAS renders insusceptibility to TKI's [160] but is so far rarely used in daily practice probably due to some inconsistencies in the studies made [161].

As previously been said regarding TKI's in the stage III setting, feasibility has been shown [78-81] but no efficacy data compared to concurrent chemoradiation are available. The second class of anti EGFR therapy with antibodies, here represented by cetuximab, showed quite disappointing results as a single agent in the initial trials. Hereafter cetuximab has however been shown to improve overall survival together with chemotherapy in stage IV disease (FLEX trial) [88]. The BMS099 trial with a similar approach did not show an advantage with the addition of cetuximab, the latter study had however about half the number of patients compared to the FLEX trial and neither did the BMS099 trial require positive immunohistochemical staining for EGFR [162]. Somewhat surprisingly neither of the

trials could detect any association with treatment effect and EGFR mutations, EGFR FISH positivity or KRAS mutations [163]. Recently however it was reported that there was an association between response to cetuximab and EGFR protein expression by immunohistochemistry in the FLEX trial [164].

Regarding locally advanced lung cancer and cetuximab combined with radiotherapy, feasibility has been shown [85-87] and randomized comparisons in the stage III setting are ongoing.

1.10 Health Related Quality of Life (HRQL)

1.10.1. Introduction

The intense combined radiochemotherapy given to this patient population with locally advanced lung cancer, and the lung cancer disease per se, is accompanied by several physical side effects and symptoms as well as psychological reactions. In the context of treatment optimization when different approaches are investigated it is important to study the patients' experience of the treatment strategies in addition to objective data. So, how to capture and describe the patients' Quality of Life? One of the most cited definitions on the topic of Health and Quality of life is the WHO-definition from 1948: "Health is a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity". It is a very ambitious and broad definition and to be able to distinguish between general wellbeing and a more distinct influence on Quality of Life by disease and/or treatment the term Health Related Quality of Life (HRQL) is used. It can be defined as the individual's experience of physical, mental and role functioning (family, spare-time), symptoms and general wellbeing but as a consequence of illness, injury or treatment. Attention to HRQL has increased considerably the last decade as it is now considered an important factor when analyzing clinical trials together with objective toxicity and survival data. It is now mandatory in sincere cancer studies as it is essential to understand the patients' experience of the natural course in a disease or the related treatment. It may also be of major significance when comparing two treatments with the same efficacy in terms of objective response or survival. Studying HRQL can be done by interviews or most commonly in trials with different questionnaires. The latter method assures a standardized manner, and makes it possible to compare between studies and/or different groups.

To ensure accuracy, questionnaires have to be tested psychometrically and they should be able to show validity, reliability, responsiveness and sensitivity. Validity means that the questionnaire should measure what it is intended to measure. Reliability suggests that the same result should be obtained if the test is performed repeatedly, provided the actual situation has not changed. If on the other hand the individual's experience has changed the

test has to show responsiveness i.e. to detect changes over time. Finally sensitivity means that the test should be able to distinguish between different groups [165]. All those criteria have been fulfilled regarding EORTC QLQ 30 which is one of the most widely used questionnaires in cancer research and HRQL [166-168].

1.10.2 EORTC QLQ 30

In the 1990's The European Organization for Research and Treatment of Cancer (EORTC) developed a questionnaire to be used in clinical cancer trials trying to capture HRQL of patients with malignant diseases and, if applicable, their treatment. It consists of a core questionnaire of 30 questions (referred to as items), about general health and overall disability. It is supplemented by disease specific modules, aiming to depict disease- and treatment related symptoms or side effects. The 30 items of the core questionnaire (QLQ 30) are aggregated into five functioning scales: physical (PF), role (RF), emotional (EF), cognitive (CF) and social functioning (SF), a global Quality of Life scale (QL), three symptom scales (fatigue, nausea/vomiting and pain), five single item measures (dyspnoea, appetite loss, sleep disturbance, constipation and diarrhoea), and a question about financial impact [166].

The lung cancer specific module LC14 contains 14 symptom measures that are associated with lung cancer or its standard treatment: dyspnoea, cough, haemoptysis, mucositis, dysphagia, peripheral neuropathy, alopecia, and pain [168]. The patients are usually asked to complete a questionnaire at base-line before any therapy is started, and then with different intervals during a time period with or without treatment.

When data from the EORTC questionnaires are analysed and presented, different approaches are used. Usually the mean values are calculated on group level, either as changes from base-line, or the actual values at different time points. When comparing longitudinally over time between different time points or different groups, there is no consensus about the statistical methods that should be used. Some will advocate the use of non-parametric statistics as the data are not normally distributed [169]. Others consider parametric approaches to be acceptable [170, 171].

Irrespective of which method you use, it is of outmost importance to distinguish between statistical significance and clinical significance. Regarding the EORTC questionnaire efforts have been made to clarify the size of a change in score points that is clinically meaningful. It has been stated that a change of 10 points (scale 0-100) is clinically significant [172], but a later study on minimal important difference (MID) indicate that it could vary depending on the variable in question and also if it is about improvement or deterioration, but nevertheless they found the MID to be in the same range (5-19 points) [173].

1.9.3 HRQL in lung cancer

Patients with lung cancer generally reports poorer HRQL than patients with other tumour types like breast cancer, gynaecological cancers or malignant melanomas [167, 174]. Most of the studies on HRQL in lung cancer are performed in the palliative setting, and generally it can be said that age, extent of disease and objective ratings like low performance status are associated with worse HRQL; in broad measures like physical-, role-, social- and cognitive functioning and global QL, as well as in symptom measures like pain, dyspnoea, cough and fatigue. When the patients receive treatment symptoms as pain and cough are often relieved during palliative chemotherapy but other treatment related problems like nausea and fatigue may transiently increase. Despite deterioration in several measures, most patients report stable or sometimes improved emotional functioning. When assessing HRQL during palliative treatment improved figures have also been associated to tumour response especially in SCLC whereas the correlation in NSCLC is less clear [174-177]. Palliative radiotherapy has been shown to ease symptoms as hemoptysis, pain, cough and sometimes dyspnoea [178, 179]. Regarding high dose radiotherapy with curative intent not that much is written and on the topic of concurrent radiochemotherapy even less. However, for lung cancer patients treated with high dose radiotherapy it can thus far generally be said that they in addition to possible side effect caused by chemotherapy in sequential protocols, experience a transient increase in dysphagia which can persevere a long time (months) before receding. Dyspnoea measures are usually persistently declining as are sometimes pain scores [180-182]. Finally low HRQL base line measures, in particular physical functioning and global QL, have in several studies been significantly correlated with inferior survival and often supersede classical clinical prognostic factors in multivariate analysis [183-185].

2 Aims of the thesis

The overall aim is evaluation of different strategies to optimize radiotherapy in patients with locally advanced lung cancer with a curative potential.

Specific aims:

Paper I: To evaluate the feasibility of giving 60 Gy with accelerated and hyperfractionated fractionation concurrent with chemotherapy to patients with SCLC LD and to look at possible differences regarding two different dose levels.

Paper II: To evaluate efficacy and toxicity in a 3-armed randomized trial in stage III NSCLC comparing three different strategies of optimizing local control; hyperfractionated therapy or concurrent chemotherapy given on a daily or weekly basis.

Paper III: To evaluate toxicity and efficacy of a new treatment strategy for NSCLC patients in a phase II trial delivering radiation concurrent with the EGFR-directed antibody cetuximab.

Paper IV: To investigate the prevalence of EGFR alterations and KRAS mutations in an unselected Caucasian population of stage III NSCLC patients, and study their possible prognostic impact on outcome.

Paper V: To study HRQL during high dose chemotherapy with concurrent chemotherapy or cetuximab and look at possible group differences.

3 Summary of papers

3.1 Paper I

Accelerated hyperfractionated radiotherapy and concomitant chemotherapy in small cell lung cancer limited-disease. Dose response, feasibility and outcome for patients treated in western Sweden, 1998-2004

The first paper is a retrospective analysis of survival and toxicity of a new regional treatment protocol for SCLC stage I-III (LD), which was introduced in the 1990's. Several trials during the 1980's and 1990's had shown that it was possible to increase survival for patients with SCLC LD when combining chemotherapy with thoracic irradiation. It was also shown that the largest improvement was obtained if the radiotherapy was administered concurrently with chemotherapy and favourably together with the early courses. Furthermore studies implied higher efficacy if the radiation was delivered accelerated and hyperfractionated, especially if the chemotherapy was cisplatin-based. Due to the high risk of brain metastases prophylactic cranial irradiation (PCI) had been studied and shown to reduce the incidence of brain metastases and increase survival. These findings were all addressed when the new treatment protocol was launched in 1997. It consisted of 6 courses of platinum/etoposide chemotherapy, thoracic irradiation with 1.5 Gy BID starting concurrent with the second or third course to 45 or 60 Gy, depending on lung function, patient's performance status and tumour burden. For complete responders or good partial responders PCI was administered with 30 Gy in 15 fractions.

The main aims were to evaluate feasibility of the high dose (60 Gy) group, as some would consider it too toxic concurrent with chemotherapy to this population, and look at possible dose-response relations.

All consecutive patients between 1998 and 2004 were identified and data were compiled from patient journals. The study population consists of 80 patients: mean age 62 years (38-83), 56% were females, mean Karnofsky performance status was around 80 (70-100). Number of chemotherapy courses was 5.6 (3-7), FEV1 around 70% and slightly more than 50% were given PCI. 46 patients received 60 Gy and 34 patients received 45 Gy. The two dose groups differed in some aspects as the 45 Gy group had somewhat lower lung function and performance status. There were a few more females in the low dose group, and the 45 Gy group also had somewhat larger volumes irradiated.

Median follow-up is 36 months. Regarding toxicity the major acute side effects was esophagitis where 15-17% experienced grade III toxicity (RTOG: severe dysphagia, dehydration or >15% weight loss, nasogastric tube or iv fluids), no difference depending on dose-level. There were low levels of pneumonitis (11%, only grade I-II). As for late toxicity we observed one esophageal stenosis in the 60 Gy group. Local control, defined as freedom from progression at last follow-up, in the 45 and 60 Gy group was 65% and 70% respectively. Overall survival according to the Kaplan-Meier method showed a 3- and 5-year survival of

25% and 16%. A cox-regression analysis taking gender, lung function, performance status, age and planning target volume into account did not show any difference in survival by dose level. We observed trends for improved survival in females, patients with N0 disease, higher FEV1, patients given radiotherapy early and in patients who attained local control. Complete responders and patients with good partial response received PCI and that group had a significantly better survival with a 3- and 5-year survival of 39% and 20% respectively.

In short the study showed that giving 60 Gy 1.5 Gy BID with concurrent chemotherapy to this patient population is clearly feasible. There was no survival difference between the two dose level groups even though there was a negative selection in the low dose group, which we found intriguing but might be explained by the relatively small material.

3.2 Paper II

How to improve loco-regional control in stage IIIa-b NSCLC?

Results of a three-armed randomized trial from the Swedish Lung Cancer Study Group

In the second paper we analyse a national randomized phase II study on locally advanced (stage III) NSCLC. Both local and distant relapse are of major concern in NSCLC, and this trial focuses on different ways to optimize the local control. In Sweden there were substantial discrepancies in the management of this disease and several approaches had been studied in the phase I and II setting including hyperfractionated accelerated radiotherapy (HART) and radiotherapy concurrent with chemotherapy on a weekly or daily basis, but no comparative studies had been made. In addition to the main aim of local control the study was also a way of unifying the treatment strategy. Hence the trial was designed as a randomized three-armed phase II study with identical induction chemotherapy consisting of two courses of carboplatin/paclitaxel to reduce the risk of distant metastases, followed by either A: HART with 1.7 Gy BID to 64.6 Gy delivered in a split-course manner concurrent with a third cycle of chemotherapy, B: conventional radiotherapy (2 Gy daily, five days a week) to 60 Gy concurrent with daily paclitaxel, or C: conventional radiotherapy to 60 Gy concurrent with weekly paclitaxel. The aims of the study were to look at efficacy in terms of time to progression (TTP), survival, toxicity and whether the results implied any differences between the three arms, with the possibility of converting the design to a two-armed trial if any of the arms showed to be inferior.

Between 2002 and 2005 152 patients were randomized and 151 deemed evaluable as one patient was excluded due to wrong inclusion (stage IV). Median age 62 (43-78), 55% performance status 0, pre-treatment weight loss of > 10% in 20 patients (13%), 66% stage IIIB, and 34% IIIA. The majority had adenocarcinomas 48%, and 32% had squamous cell carcinoma, and the different arms were well balanced regarding basic characteristics.

Median follow up is 52 months. The most important toxicity was esophagitis, where the grade 3-4 toxicity according to RTOG was seen in 20% in arm A, 8% in arm B and 19% in arm C. As for pneumonitis only 1% contracted grade 3-4 reactions. Median TTP was 9.8 months (A: 8.8, B: 10.3, C: 9.3). Median survival was 17.8 months (A: 17.7, B: 17.7, C: 20.6) and the 1-, 2-, 3- and 5 year survival were 63%, 40%, 31% and 24% respectively. Since the paper was published the survival figures have been updated with a 1-, 2-, 3- and 5-year survival in the different arms of: A: 61%, 41%, 33%, 14% B: 62%, 39%, 36%, 23% C: 62%, 38%, 21%, 10%. There were no significant differences between the arms regarding toxicity or survival. As for relapse pattern, distant metastases were most common as first relapse site, with a high proportion of brain metastases (34%). The factors affecting survival which were found to be significant in univariate analysis were stage and performance status, which both maintained their significance in the multivariate analysis.

In summary a median survival of 17.8 months and a 3- and 5-year survival of 31% and 24% in this population with predominantly stage IIIB disease, and 13% with excessive pre-diagnostic weight loss is a decent result. Toxicity was acceptable and we could not see a clear trend whether any of the treatment arms was superior. Stage and performance status were independent prognostic factors for survival.

3.3 Paper III

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

In the third paper we analyse a national one-armed prospective study on NSCLC stage III with the same inclusion criteria as in the RAKET-study (paper II). As long term survival is still poor for this patient group despite improvements in recent years with e.g. combined radiochemotherapy other treatment options are desirable. When it was shown that efficacy of radiation in head and neck cancer was increased by adding the epidermal growth factor receptor (EGFR)-directed antibody cetuximab, it seemed as an attractive approach in lung cancer as this tumour type also over expresses EGFR. As no data on potential lung toxicity existed by the time of study planning, the trial was designed as a one-armed phase II study without concurrent chemotherapy, as this might have added further toxicity, but we used induction chemotherapy to reduce the risk of distant metastases. In 2006 the Satellite trial was initiated consisting of two courses of induction chemotherapy with docetaxel and cisplatin followed by conventionally fractionated radiotherapy (2 Gy, once daily, 5 days a week) to 68 Gy concurrent with weekly infusions of cetuximab. The main aims were to evaluate feasibility, toxicity and efficacy.

Between 2006 and 2007 75 patients were included and 71 were evaluable as 4 had been incorrectly enrolled. Median age was 62.2 years (42-81), 51% females, 63% had stage IIIB disease and 37% stage IIIA. Fifty percent had adenocarcinoma and 39% squamous cell carcinoma. Sixty-two percent had performance status 0 and a high proportion (37%) had a pre-diagnostic weight loss of >5%.

Median follow up is 39 months and compliance to the protocol was good with 96% receiving the chemotherapy and 82% and 89% receiving full dose of cetuximab and radiotherapy respectively. Main toxicities were a few hypersensitivity reactions to cetuximab, esophagitis grade 3-4 (1.4%), pneumonitis grade 3-4 (4.2%) and one lethal pneumonitis grade 5 reaction that might be correlated to cetuximab and radiotherapy. The primary endpoint clinical benefit at 12 months (CR + PR + SD) was 30%. Median survival was 17 months with a 1-, 2- and 3 year survival of 66%, 37% and 29% respectively. The majority had distant failure as their first relapse site. Regarding prognostic factors pre diagnostic weight loss, stage and performance status were shown to be significant in multivariate analysis. A calculated estimation of patients with these three negative markers compared to those without, highlighted the immense importance and influence of patient selection on outcome as the former group had an estimated median survival of 7.2 months, whereas the median survival in the "good prognostic" group has not been reached during a follow-up of 39 months.

In conclusion induction chemotherapy followed by radiotherapy with concurrent cetuximab is clearly feasible with lower toxicity than most protocols with concurrent chemoradiation, and this with promising and comparable survival data. Notably there was an even higher proportion of patients with excessive weight loss in the Satellite trial compared to the RAKET trial.

3.4 Paper IV

Prevalence of EGFR and KRAS mutations in NSCLC in a northern European population, and KRAS as a negative prognostic factor in stage III disease

In the fourth paper we analyse the prevalence of three important genetic alterations, mutated EGFR, EGFR FISH positivity and mutated KRAS, in an unselected Scandinavian, predominantly Caucasian, population of stage III NSCLC, and investigate their potential prognostic impact. It is known that activating EGFR mutations is a prognostic positive marker per se as well as predictive of response to TKI's. EGFR FISH positivity has also been shown to correlate with response to TKI's. Mutated KRAS renders insusceptibility to tumours regarding TKI's and is also associated with a pessimistic prognosis. Not as much is known about cetuximab in this context but there are data on EGFR FISH as a predictive marker but no correlation has been seen with EGFR mutations or KRAS mutations in lung cancer.

The aims of this study were to get an idea of the prevalence in a northern European population and look at possible prognostic impact of EGFR alterations and KRAS mutations. Another aim was to make indirect exploratory comparisons between patients that had received cetuximab and patients that had not.

The study population consisted of all the patients in the Satellite trial (paper III) that were diagnosed on biopsy (n=34) and a group of the same size from the RAKET trial (paper II) adding up to a total number of 69 patients. Tissue specimen were analysed regarding EGFR and KRAS mutations by PCR-based technology and EGFR polysomy/amplification by FISH. The prevalence of EGFR mutations was 7.5%, (exon 19 deletions, exon 18 and 21 point mutations), hence the number was too small to draw any prognostic conclusions. EGFR FISH positivity was observed in 19.7% with a rather huge difference in the two subgroups, 32% vs. 7% in the Satellite and RAKET trials respectively. The FISH positive patients in the Satellite trial had a trend towards decreased survival. KRAS mutations were observed in 28.8% and were correlated to a significantly inferior survival in multivariate analysis.

In short the prevalence figures are roughly what are expected in an unselected Caucasian population and in accordance with earlier published data. Mutated KRAS is an independent negative prognostic factor for survival which has not previously been described in stage III disease.

3.5 Paper V

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

In the fifth paper we analyse Health Related Quality of Life (HRQL) in terms of EORTC QLO C-30 + LC 14 questionnaires in patients participating in the RAKET- or Satellite studies (paper II and III) with high dose radiotherapy and concurrent chemotherapy or cetuximab. HRQL data in NSCLC are mostly studied in stage IV disease in the palliative setting and in stage III disease data are scarce and even more so regarding concurrent therapy. In short earlier data indicate that most patients experience a slow deterioration in most functional scales (physical-, cognitive-, role- and social functioning) as well as in Global Quality of life (QL). Strict treatment related symptoms as nausea or dysphagia usually returns towards base-line but other symptoms like pain and dyspnoea most often are persistently increasing. The aims were to expand the knowledge about HRQL in patients treated with combined therapy with curative intent, as well as look at possible group differences regarding five pre-specified variables (physical functioning, global QL, pain, fatigue and dyspnoea) with an emphasis on potential differences between patients treated with concurrent chemotherapy and those treated with concurrent cetuximab.

Questionnaires were delivered at four time points: At baseline, before radiotherapy (i.e. after induction chemotherapy), 4-6 weeks after radiotherapy and at 3 months follow-up. Aggregated scale scores were calculated and analysed longitudinally for changes over time and between groups with repeated measures ANOVA.

Compliance was > 90% at every time point when corrected for drop-outs due to death during treatment or follow-up. Patients that did not complete all questionnaires reported inferior functioning and more symptoms and as this might obscure the interpretation only patients that completed the whole course are included in the longitudinal study (154/220 = 65%).

We found a significant decline over time regarding all functioning scales except emotional functioning, there was also significant decline without improvement regarding dyspnoea and fatigue, whereas cough improved after induction chemotherapy and then worsened after radiotherapy. Chemotherapy related symptoms as nausea, diarrhoea and constipation showed a transient decline, as did esophagitis, but the latter had not fully returned back to base-line at 3 months follow-up. As for group differences we did not observe any regarding gender, age or pre-diagnostic weight loss. Patients with stage IIIA disease had a tendency to recover regarding global QL, fatigue and dyspnoea compared to the stage IIIB patients. Performance status strongly influenced the score levels with PS 1 patients reporting higher symptom scores and lower functioning scores. Moreover PS 0 patients in contrast to PS 1

patients showed an improved global QL and fatigue over time. Patients with esophagitis evaluated according to CTC consequently reported higher scores on dysphagia, but this correlation was not seen with pneumonitis and patient-reported dyspnoea. Regarding the two different treatment approaches patients in the Satellite study, that had received concurrent cetuximab, in contrast to patients in the RAKET trial, treated with chemoradiotherapy, had an improvement in fatigue scores, experienced less influence on global QL and reported less dysphagia.

Base-line quality of life in terms of physical functioning was also analysed regarding impact on survival and found to be significantly correlated to survival in a multivariate analysis.

In short NSCLC stage III patients treated with high dose radiotherapy with concurrent chemotherapy or cetuximab experience a gradual decline in most 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 IIIA and/or PS 0 seem to tolerate combined treatment better and concurrent radiotherapy with cetuximab influences HRQL less than concurrent chemoradiation.

4 Discussion

4.1 Comments on study results

The results in paper I on outcome in SCLC LD with a median survival of 20.8 months and a 5-year survival of 16% is a good result considering that it is consecutive patients treated and not a prospective study with selection bias. The 3- and 5-year survival in responding patients given PCI of 39% and 20% is also an encouraging figure bearing in mind the poor reputation accompanying this disease. Regarding PCI patients it can be added that the prevalence of brain metastases in the PCI group was 18% (8/44) compared to 47% (17/36) in the non PCI group. It is, at least partly, a selection effect but nonetheless an interesting observation.

Survival data in the RAKET and Satellite trial are very similar with a median survival of 17.8 and 17 months and 3-year survival of 31% and 29% respectively. It is a decent result but there are several studies with higher survival figures. However, as patients with excessive weight loss, who have a worse prognosis, were not excluded from our trials indirect comparisons are hard to do. Notably the patients in the Satellite trial without weight loss had a median survival of 24 months which is a good result.

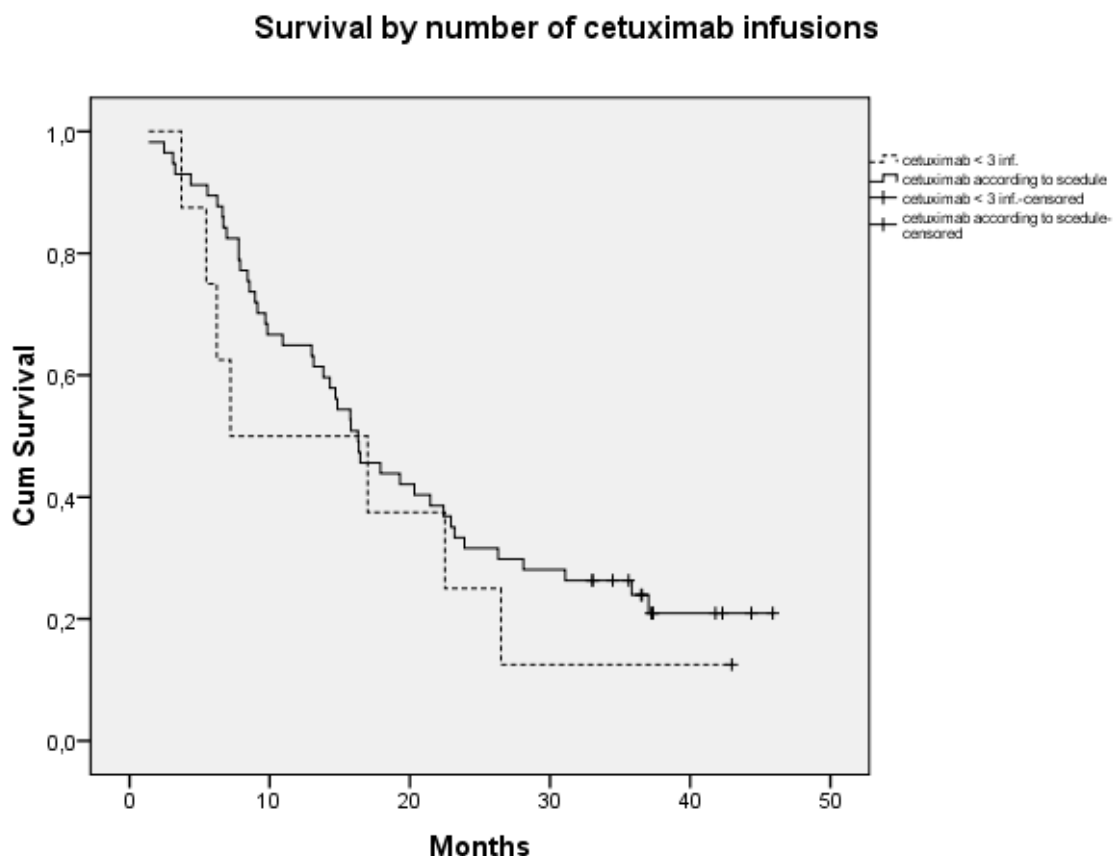


Figure 2. Survival in the Satellite trial by number of cetuximab infusions (< 3 vs. 8).

The relatively larger proportion of patients with excessive pre treatment weight loss in the Satellite trial compared to the RAKET trial also makes comparisons between our trials harder.

Compliance to therapy is overall good in both the RAKET and Satellite trials. In some cases the treatment course cannot be completed due to progression and deterioration but there is a proportion of the patients in the Satellite trial that did not receive cetuximab as planned because of hypersensitivity reactions. A per protocol comparison between the patients completing the course as planned and the patients where cetuximab was omitted showed a tendency towards decreased survival in the latter group which could imply superiority with radiotherapy plus cetuximab over radiotherapy alone (figure 2).

When comparing the three different cohorts in paper I-III there are some observations to be made. The grade III esophagitis is 15-17% among patients treated for SCLC in paper I and 8-20% in paper II compared to 1.4% in the Satellite trial. The former two were treated with concurrent chemoradiation and this further emphasizes what previously has been said: concurrent chemotherapy is correlated with increased acute toxicity compared to concurrent cetuximab. Whether a certain amount of toxicity is acceptable or not, varies between different investigators. We consider the esophageal toxicity of \geq grade 3 seen in these studies up to 20% as clearly acceptable when appropriate care is given to the patients. One has to keep in mind that the treatment strategy is aiming to cure which increases the threshold for side effect acceptance. One other important factor is whether the toxicity in question is transient or if it will result in any late side effects. Regarding esophagitis it improves substantially during the weeks after radiotherapy and late effects are extremely rare in this material as only one patient (out of 300) has experienced an esophageal stenosis. You could argue that the follow-up time is not long enough to capture all of the late side effect (median 36-52 months) but as the major problem still is progressive disease and death, late esophageal toxicity has not so far been a clinically important issue. When comparing survival the patients with SCLC have a higher median survival (20.8 months) compared to the NSCLC trials (17.8 and 17 months). The long-term data are however in the other direction with a 3- and 5-year survival of 25% and 16% among the SCLC patients whereas the NSCLC trials showed 3- and 5-year survival of 29-31% and 24%. The inferior long term survival in the SCLC study could reflect a selection bias with "healthier" patients in the prospective trials, but the pattern with superior median survival and worse long term survival could also reflect the different behaviour of NSCLC vs. SCLC. SCLC is highly sensitive to treatment rendering a higher survival probability in a shorter period of time, but as the relapse rate however is very high, with even more pronounced incidence of distant metastases than in NSCLC, and about the same degree of local control, the probability of long term survival and cure is less than in NSCLC.

Another reflection regarding local control is that in the RAKET trial, with a median follow up of 52 months, we observed distant metastases in 54% and loco-regional relapses in 28.5%* (a small proportion have combined relapses). In the Satellite trial on the other hand we observed distant metastases in 41% of cases and loco-regional relapses in 38% (including combined relapses) during a median follow up of 28 months (i.e. when followed for a shorter period of time where we had not detected distant metastases in more than 41% the Satellite patients still had loco-regional relapses in 38% of cases). This could imply that cetuximab in combination with radiotherapy is not as effective as concurrent chemotherapy.

Another observation is that the inclusion criteria in the RAKET and Satellite trial were the same and the basic characteristics of the study populations are very similar, but when comparing baseline HRQL data, the RAKET population consistently reports somewhat lower function scores and higher symptom scores hence they are probably slightly more affected by their disease or comorbidities than the Satellite cohort, despite the similar objective data. This could to some extent influence outcome and comparisons between the trials as it is known that a worse HRQL and PS is associated with an inferior survival. It also implies that base-line HRQL should be presented together with all the other known basic, possibly prognostic, characteristics when comparing different study arms.

4.2 Methodological strengths and weaknesses

What strengths and flaws might there be in these studies? Paper I is a retrospective study where data has been compiled from patients journals. This will bring an amount of uncertainty especially regarding issues where there is some kind of subjective judgement involved e.g. toxicity. However as toxicity increases the estimation gets more reliable as an esophagitis grade III reaction, which is in need of tube feeding, or pneumonitis grade III in need of oxygen, is more evident compared to the lower grades which are more subtle. This uncertainty is surely present also considering response evaluation and relapse pattern as some information will be almost impossible to achieve retrospectively. All those data, toxicity, response and relapse pattern are probably more accurate in the two prospective trials in paper II and III, but there are problems with inter-investigator discrepancies, also when evaluating lower toxicity scores in these studies. Nevertheless the most important data regarding survival will be correct in both types of studies. Another important difference between paper I-III is the study population. In paper I all consecutive patients treated between 1998 and 2004 in the western region are included and this gives a fairly accurate picture of outcome in the whole population. A rough estimation and comparison with the expected number of cases in the region during that time period, shows that somewhere

* In the discussion in paper II the figures are wrong; they are in the text expressed as percentages but are actual number of patients.

around 40-50% of the patients with SCLC LD are included. Some of the remaining 50-60% are most probable not deemed fit enough for combined therapy because of age, performance status, lung function etc, and some are likely to not have been referred due to lack of knowledge at that time. Nevertheless it is a huge difference compared to the two prospective trials where about 5-10% of the plausible population is included in the trials. There are of course natural reasons like patients' general condition and several centres not participating, but even if the largest centres were involved, there is a vast variation in enrolment rate between contributing sites, and with <10% of the possible stage III patients enrolled there is the inevitable problem with selection bias; including individuals with good performance status and excluding patients with special needs thereby making the generalizability of the results to the whole population doubtful. This also highlights the fact that it is important to analyse the actual outcome in all treated patients and not just refer to survival data in prospective trials when addressing the whole population. Usually outcome data regarding survival from trials are somewhat better than registry data and "real life" data.

Another weakness with the studies in paper I-III is the insufficient staging; they are staged with CT of the thorax and upper abdomen, no CT or MRI of the brain, and PET-CT was rarely used. Surely this will influence the results as there probably are some patients with stage IV disease in the study population.

Regarding the primary endpoints in the prospective trials (paper II and III) some comments can be made. The primary endpoint in the RAKET trial was time to progression (TTP). In the protocol it was stipulated that if any of the arms, when the first step in the Simon two step design was analysed, should be less than 12 months, that arm should be closed. In fact neither of the arms reached a median TTP of 12 months hence the steering committee decided to go on with the study as all arms showed comparable efficacy. TTP is a somewhat difficult endpoint in radiotherapy trials in lung cancer as there will be a lot of radiation induced changes, e.g. fibrosis, and it can sometimes be hard to distinguish between relapse and radiotherapy related changes. Even more so for the primary endpoint in the Satellite trial, clinical benefit at 12 months, defined as CR, PR or SD, assessed by RECIST criteria [186]. As for the TTP endpoint it can be rather difficult to discriminate between these response variables and pneumonitis/fibrosis in a high dose irradiated lung. The endpoint, clinical benefit at 12 months, was a compromise between several centres involved and we would not recommend it in future radiotherapy trials. It harbours too much uncertainty and is rarely used thereby making it almost impossible to compare with other trials in the field.

Turning to paper IV where the main problem is the small material. In the Satellite trial (paper III) all available biopsies were gathered, but as only around 50% were diagnosed on biopsies the number is still small (n=34). For simplicity we chose a group with comparable size (n=35) from the RAKET trial (paper II) with the samples that could be obtained locally. This was also a pragmatic solution as it is very hard and time consuming to collect tissues samples from different sites. Notably in the Satellite trial where the analyses were pre-specified in the

protocol it took nonetheless two years just to get the 34 samples to be sent to the laboratory in Gothenburg where the analyses were to take place. Perhaps it would have been faster to perform the analyses locally at the site in question, but it is also an advantage that all samples are analysed at the same site diminishing the risk of investigator dependent biases. The small material leads to uncertainty in regard to the genetic alterations with low prevalence (i.e. EGFR mutations) where the pattern seen in the present study, with several exon 18 mutations in squamous cell carcinoma differs from the most frequently reported pattern with the most common mutations being exon 19 deletions and exon 21 mutations, predominantly in adenocarcinomas. There is also a disturbing and unexplained difference regarding EGFR FISH positivity between the two cohorts (RAKET and Satellite), that possibly can be explained by low sample size.

In the HRQL study there is not a lot that could be done differently, the compliance is high (>90%) with few missing data in the questionnaires. There is an uncertainty at time point 3 (after radiotherapy) where it differs somewhat between the studies (4-6 weeks). Unfortunately it has not been possible from registered data to obtain the actual assessment time. This could obscure the interpretation when comparing the two studies. However the trend is clear regarding the variables in question (Global QL, fatigue and dysphagia) also at the last time point and congruent with toxicity data, why the conclusion of lesser influence on HRQL with cetuximab compared to chemotherapy seems reasonable.

Moreover it would have been interesting to have a long term follow up for survivors at e.g. 12 months, unfortunately this was not planned for in the design of the study.

4.3 Our present standard treatment outside of clinical trials.

As there are still ambiguous areas regarding the optimal radiotherapy delivery, chemotherapeutics and their combination, as has been accounted for in chapter one, every treatment centre makes its own interpretation taking local factors into account. Regarding NSCLC our present standard, when the patients are not included into clinical trials, is combined radiochemotherapy with a slightly accelerated regimen to 70 Gy in 6 weeks (2 Gy/fraction, 6 fractions/week in five days). The chemotherapy is given in three full dose courses, one as induction and two concurrently. We believe that cisplatin is somewhat better than carboplatin in the stage III setting and most often use cisplatin and docetaxel. Prophylactic cranial irradiation or consolidation therapies are not used as there are not enough supporting data.

When it comes to SCLC our interpretation is that stage III should be treated with 4-6 cycles of chemotherapy where concurrent irradiation should start together with cycle 2 or 3. It should be given hyperfractionated and accelerated with 1.5 Gy BID to at least 45 Gy, but as their might be a continuous dose-relationship we will deliver 60 Gy with the same fractionation if

it is possible taking organs at risk (i.e. lungs) into account. All patients with complete or good partial response will get PCI 30 Gy in 15 fractions. Regarding choice of chemotherapy there is to this day no new regimen that has shown better results than cisplatin/etoposide, but we use carboplatin/etoposide for practical reasons. Personally I would advocate for the use of cisplatin in the curative setting.

4.4 Have our findings contributed to the general knowledge?

The title of the thesis is optimization of radiotherapy in locally advanced lung cancer, which has been investigated regarding accelerated radiotherapy and different strategies with concurrent treatment, chemotherapy as well as antibody. Optimization of a treatment strategy also encompasses the patients' experience of the disease and/or treatment course. So how have these results contributed to the knowledge in the field?

In paper I we have shown that it is clearly feasible to give accelerated hyperfractionated treatment with concurrent chemotherapy to this unselected SCLC population. There are still many within the SCLC field that consider 45 Gy with concurrent chemotherapy to be the MTD (maximal tolerable dose), despite dose escalation studies performed mainly in NSCLC. In paper II all strategies were feasible but as no arm showed to be superior or inferior we could not pursue with a phase III study. Even if the RAKET study is not designed to make direct comparisons between the three arms, it nonetheless does not seem likely that there should be a clinical significant difference between the diverse approaches of optimizing local control used in the study. Giving weekly or daily chemotherapy or hyperfractionated accelerated radiotherapy in that manner will not be enough to substantially improve the results and further attempts to enhance outcome probably have to include other strategies.

The Satellite trial (paper III) was the first phase II study to be published on thoracic irradiation with concurrent cetuximab showing feasibility and that it is less toxic than concurrent chemotherapy.

Paper IV is the first publication that has showed mutated KRAS to be a negative independent prognostic factor in stage III disease. Finally in paper V, HRQL data on radiation with concurrent cetuximab, where the patients experienced less toxicity than with concurrent chemoradiotherapy, is new knowledge supporting the observation with inferior toxicity. The study also shows that stage IIIA patients with good PS find it easier to endure combined therapy.

4.5 Future optimization

What strategies might be used in the future to further optimize the treatment for patients with locally advanced lung cancer? One of the most important issues that precedes the actual treatment is staging and patient selection. A more accurate staging with PET-CT, EBUS, EUS and surgical lymph node sampling will result in the right group of patients receiving intense combined treatment, where a substantial probability of long term survival justifies the therapy related toxicity. However, even if the staging procedure is satisfying we have to further explore who will benefit considering the vast impact of prognostic factor seen in the Satellite trial (figure 3). The population seems to be rather homogenous with stage III patients in performance status 0-1, but the survival probability varies enormously by clinical (e.g. performance status, stage, weight loss) and/or genetic (e.g. KRAS) factors. Hence you have to be very careful when selecting patients and when interpreting data, especially when comparing outcome from different trials.

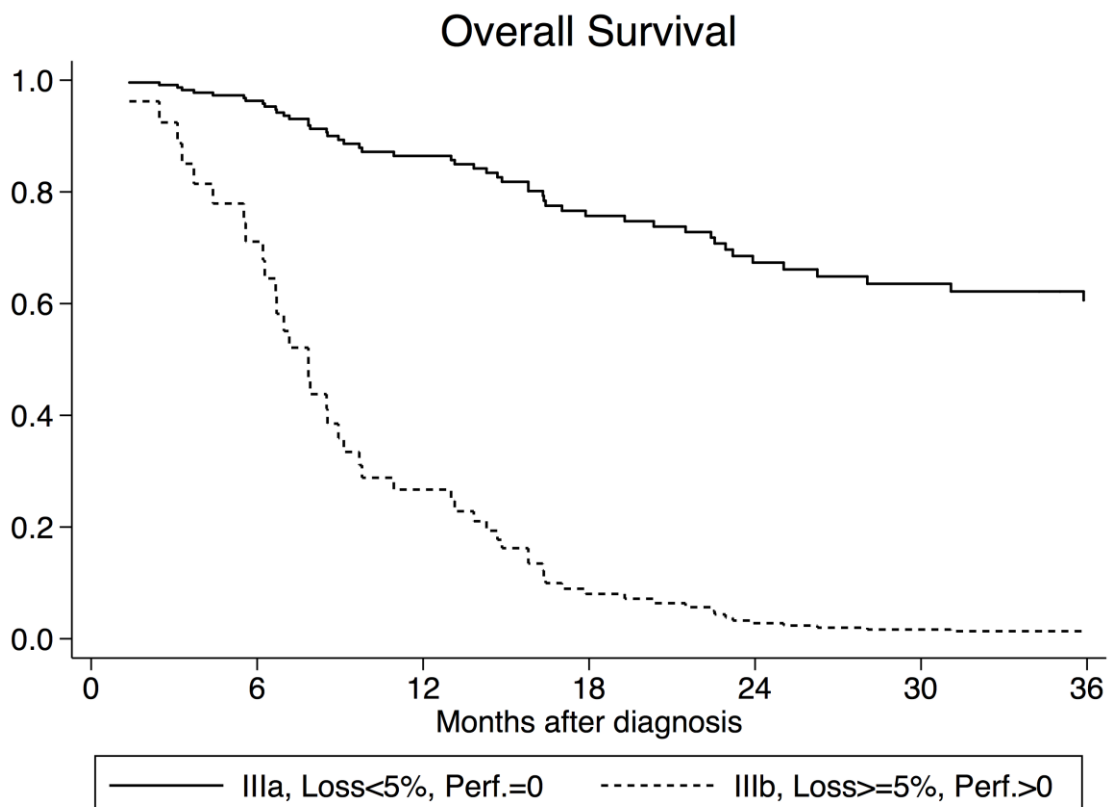


Figure 3. The calculated estimation of survival according to a cox regression model. Good prognostic factors (PS 0, stage IIIA, weight loss < 5 %) vs. poor factors (PS 1, stage IIIB, weight loss > 5 %)

When considering the treatment strategies the main problems are still local relapse and a high proportion of distant metastases, and successful new approaches have to address both areas. This will inevitable result in toxicity issues as it can be hard to strengthen and intensify systemic therapy and at the same time increase the local treatment. In addition to unwanted side effects it may also be difficult to evaluate outcome in regard to several different modalities introduced simultaneously in the treatment protocol.

As for intensified local therapy it seems likely that higher radiation doses will increase efficacy, but toxicity is a substantial problem. New irradiation techniques facilitate the delivery of higher doses without severe damage to normal tissue, and this approach is under intensive investigation. Several dose escalation studies have been published delivering doses of 80-90 Gy showing feasibility but further research is needed regarding maximum tolerable dose, toxicity and dose constraints to normal tissue, how to add concurrent chemotherapy, how to select patients for this strategy and if it is superior to standard treatment. However, even with a more precise radiation technique there is still the problem with targeting the exact spot harbouring tumour cells. The likelihood of correct marking the areas affected by cancer growth has increased with PET-CT but there is nevertheless room for considerate improvements on the topic of target delineation. If increased local radiation dose is one way to go, it is already well known that accelerated regimens are superior to conventional regimens regarding both local control and survival. A shortened radiation overall treatment time may however be problematic if you aim to give concurrent chemotherapy or targeted drugs. The treatment course might simply be too short, actualizing questions of induction chemotherapy or consolidation therapy in spite of what earlier has been said on those issues. On the topic of systemic therapy it does not seem likely that giving higher doses or prolonged therapy with known cytotoxics would substantially improve outcome. It is not known what the optimal total amount of chemotherapeutic compounds in stage III disease is, but in stage IV disease it has not been proven beneficial to give more than 4-6 courses of chemotherapy. To alternate the chemotherapeutics and give maintenance treatment could be other options but have so far no proven role in stage III disease. Nor does it seem likely that there will emerge a new chemotherapeutic agent that remarkably would increase survival in all lung cancer patients. Probably the most likely scenario is a more personalized approach which is becoming the reality in stage IV disease, either by using predictive markers of response or predictive markers of resistance. For example in metastatic disease it is already in clinical praxis to adjust chemotherapy depending on histology regarding pemetrexed, and mutated EGFR is predictive for response to TKI's. Many more markers are in pipe-line and the challenge in the stage III setting is how to integrate all the new compounds with radiotherapy. This will be difficult as all the new agents and different radiotherapy strategies result in endless combination possibilities. As not all theoretically potential studies can be performed, intelligent study designs will be even more important in future research.

5 General conclusions and future perspective

From this thesis the following conclusions are made:

- To give 60 Gy, 1.5 BID concurrent with chemoradiation to patients with SCLC LD is clearly feasible but there was no survival difference between patients receiving 60 Gy or 45 Gy even though there was a negative selection in the low dose group.
- To optimize local treatment either by hyperfractionated accelerated radiotherapy or concurrent chemotherapy on a weekly or daily basis seem to result in similar efficacy and toxicity.
- Induction chemotherapy followed by radiotherapy with concurrent cetuximab is clearly feasible with lower toxicity than most protocols with concurrent chemoradiation.
- Basic clinical characteristics have a huge impact on survival even in a patient group initially considered homogenous and has to be carefully considered when selecting patients and designing trials.
- The prevalence of EGFR mutations, EGFR FISH positivity and KRAS mutations in an unselected Scandinavian population are roughly in accordance with previous data on Caucasians from other parts of the world.
- KRAS mutation is an independent prognostic factor for survival in patients with locally advanced NSCLC treated with high dose radiotherapy
- HRQL measures in stage III NSCLC patients, treated with high dose radiotherapy with concurrent chemotherapy or cetuximab, experience a gradual decline in most functional scales. Treatment related side effects return towards base-line but there is for the majority a persistent worsening of dyspnoea and fatigue.
- NSCLC patients with IIIA and/or PS 0 seem to tolerate combined treatment better with regard to HRQL and concurrent radiotherapy with cetuximab influences HRQL less than concurrent chemoradiation.

Future research

So, how do we go from here and how is further optimization to be achieved? As previously been said there is still a major challenge to tackle the poor prognosis resulting from both insufficient local control and distant metastases. Personally I believe in individualizing treatment in the future, with the systemic treatment being dependent on histology, and/or genetic markers, and radiation being dependent on individual patient factors regarding normal tissue complication probability, as well as tumour factors like e.g. hypoxia. As Sweden is quite a small country I think it will be difficult for us to perform trials that are large enough to select patients with diverse molecular features and integrating different drugs with radiotherapy for each distinctive patient group. Hopefully these important studies will be made in cooperative projects worldwide. I think our main contribution might be in performing smaller trials with interesting and hopefully innovative hypotheses. Sweden may also continue to contribute in the radiotherapy field where the cooperation regarding national trials in locally advanced lung cancer is making satisfactory progress. The next study, the PLANET trial, will start enrolling patients during autumn 2011 (Phase II randomized study on **Locally Advanced Non small cell lung cancer, Escalated dose on individual basis, Treatment with radiochemotherapy**). It is a randomized two-armed dose escalation trial where we compare concurrent chemoradiation with an increased total dose depending on individual normal tissue constraints to a standard arm of concurrent chemoradiation. Several one-armed escalation studies have been performed internationally but so far data on individually escalated treatment are scarce and high dose approaches have not been compared to standard chemoradiation.

6 Populärvetenskaplig sammanfattning på svenska

Lungcancer är den sjukdom leder till flest dödsfall i cancer, både globalt och i Sverige. Här insjuknar ungefär 3500 patienter varje år i lungcancer. En hög andel, ca 50% har spridd sjukdom med fjärrmetastaser vid diagnos och behandlas med palliativ intention. En mindre andel, ca 20% har så begränsad tumörutbredning att det kan vara aktuellt med operation i botande syfte. De återstående 30% har för avancerad metastasering regionalt till lymfkörtlar i bröstkorgen och kan inte opereras. Däremot har de inga fjärrmetastaser och kan vara aktuella för onkologiskt terapi med strålbehandling och cytostatika med en kurativ potential. Denna grupp kallas ofta för lokalt avancerad lungcancer eller lungcancer stadium III. Forskning har visat att man får bäst effekt om man kombinerar strålbehandling med cytostatika men de flesta progredierar ändå i sin sjukdom och långtidsöverlevnaden är omkring 5-25% varför ytterligare förbättrad behandling är av stor vikt.

Huvudfrågeställningen i avhandlingen är behandlingsoptimering av patienter med lokalt avancerad lungcancer - stadium III, och analyserar två prospektiva studier, en retrospektiv genomgång, samt biologiska markörer och livskvalitet under kurativt syftande fulldosbehandling.

Arbete 1 är en retrospektiv analys av alla patienter med småcellig lungcancer "limited disease" (SCLC LD), dvs. utan fjärrmetastasering, som fick strålterapi och cytostatika 1998-2004 enligt ett nytt behandlingsprotokoll som då infördes. Det bestod av 4-6 cykler kemoterapi, konkomitant hyperfraktionerad strålterapi till 45 eller 60 Gy samt profylaktisk hjärnbestrålning för patienter med bra respons. Frågeställningarna var huruvida det var genomförbart att behandla till den högre dosnivån med tanke på toxicitet, och om det fanns några skillnader i behandlingsutfall mellan dosnivåerna. Studien visar att behandlingen helt klart är möjlig att genomföra med acceptabel toxicitet och överlevnad i paritet med andra publicerade data, och vi såg ingen skillnad i resultat beroende på stråldos.

Arbete 2 analyserar en randomiserad trearmad fas II studie av lokalt avancerad icke-småcellig lungcancer (NSCLC) där man jämför tre olika sätt att öka effekten av strålbehandling (accelererad strålterapi, tillägg av veckovis eller daglig konkomitant kemoterapi). Frågeställningarna var överlevnad, toxicitet, och huruvida man kunde se tendenser till att något behandlingssätt skilde sig vad gäller effekt eller biverkningar. Resultaten visar att de tre strategierna gav likvärdig överlevnad och toxicitet som var på en acceptabel nivå, ingen arm var bättre än de andra.

Arbete 3 analyserar även det en prospektiv fas II studie av lokalt avancerad NSCLC där vi försöker att potentiella effekten av strålterapi med hjälp av konkomitant veckovisa infusioner av antikroppen cetuximab. Detta var aldrig tidigare beskrivit i kombination med lungbestrålning så frågeställningen var genomförbarhet, toxicitet och effekt. Studien visar att behandlingen är väl tolerabel, med lägre toxicitet än vid kombinerad terapi med cytostatika men bibehållen överlevnad. Vi såg också att tumörstadium, "performance status" samt viktförlust var oberoende prognostiska faktorer för överlevnad.

Arbete 4 studerar biologiska markörer för prognos genom att undersöka tumörvävnad hos patienter med NSCLC stadium III. Avsikten var att få ett grepp om förekomsten av tre kända genetiska förändringar (muterat KRAS, muterat EGFR samt EGFR FISH positivitet) i en skandinavisk population, samt förändringarnas betydelse för behandlingsutfall. Studien visar att frekvensen av EGFR- och KRAS mutationer är likvärdig med beskrivningar från andra delar av världen medan andelen EGFR FISH-positiva tumörer är ngt lägre. Muterat KRAS var en oberoende prognostisk faktor för överlevnad, vilket tidigare inte är visat vid stadium III.

Arbete 5 studerar patienternas livskvalitet under behandling med fulldos strålterapi och konkomitant cytostatika eller antikropp. Livskvaliteten mättes longitudinellt under behandlingen och uppföljning med EORTC QLQ 30 + LC 14. Resultaten visade att patienterna upplever en successiv försämring i flera allmänna mått under terapin såsom fysisk funktion och global livskvalitet medan andra behandlingsrelaterade symptom såsom dysfagi går över. Patienter i bättre allmäntillstånd med ngt mindre tumörbörda tenderar att återhämta sig snabbare, och antikropp i kombination med strålterapi ger mindre påverkan på livskvaliteten än cytostatika.

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9 Papers