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Analysis of overall survival and potential prognostic factors among lung cancer patients treated with curative radiotherapy between 2002 and 2016 in Region Västra Götaland

Degree Project in Medicine

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Programme in Medicine

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Abstract

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Background: Radiotherapy is an important treatment modality for lung cancer patients of all stages: from high dose curative intended treatment in stage I-III to palliative treatment in stage IV disease. More than 100 patients are treated with potentially curative radiotherapy each year in Region Västra Götaland (VGR), but outcome measures on a population-basis remains to be evaluated.

Aim: To evaluate overall survival for lung cancer patients treated with radiotherapy with curative intent in VGR during 2002-2016 and to compare survival depending on time interval, radiation dose, as well as other potential prognostic factors.

Methods: Patient and tumor information were retrospectively collected from quality registers, medical records and radiotherapy databases. Patients were analyzed in three groups: stereotactic body radiation therapy (SBRT) for stage I non-small cell lung carcinoma (NSCLC), chemoradiotherapy for locally advanced NSCLC and chemoradiotherapy for small cell lung carcinoma (SCLC). Multivariate survival analyses were performed using the Cox proportional hazards model.

Results: 1421 patients were included in the study. Three-year overall survival was 47-55 %, 24-35 % and 20-28 % for the SBRT, locally advanced NSCLC and SCLC groups respectively. There was no significant difference in survival rates between time intervals in any group but trends for improved survival among locally advanced NSCLC patients and declining survival among SCLC patients were observed. Male sex, a poor performance status and NSCLC tumors located in the lower lobe were associated with an inferior survival.

Conclusion: The real-life data from this study indicates that overall survival for NSCLC patients in VGR are comparable to previously reported results in clinical trials. A trend for improved survival over time was seen among locally advanced NSCLC patients, albeit not statistically significant. Overall survival for SCLC patients was lower than expected and may also have declined over time.

Introduction/Background

Epidemiology

In the beginning of the 20th century lung cancer was an uncommon disease, viewed as "a medical curiosity too rare to be of much practical importance" (1, 2). This was to radically change by the midth-20th-century following the dawn of the global smoking epidemic (3). Today, lung cancer constitutes a huge burden on society around the globe. With an estimated 1.6 million deaths due to lung cancer in 2012 and approximately 1.8 million new cases the same year, lung cancer is the leading cause of cancer death in the world as well as one of the most frequently diagnosed cancers (4). In Sweden about 3650 people are diagnosed with lung cancer each year, and consistent with the rest of the world the prognosis for diagnosed patients is poor here as well, with a relative 5-year survival rate of approximately 13.6% for men and 19.4% for women (5).

Risk factors and prevention

Cigarette smoking is undisputedly the largest risk factor for developing lung cancer, accounting for the vast majority of all lung cancer cases. An excess relative risk of at least 20 has been observed in current smokers compared with lifetime nonsmokers in several studies (6). The number of cigarettes smoked and duration of smoking is determinant to the excess risk but no risk-free level of smoking has been observed (6). Passive smoking, or inhalation of so called environmental tobacco smoke, in nonsmokers is also considered a carcinogen, although not nearly as strong as active smoking is for developing lung cancer (7). Other well-established risk factors are exposure to asbestos, radon, arsenic and previous inflammatory lung diseases such as chronic bronchitis or chronic obstructive pulmonary disease (8). Indoor air pollution, in particular coal smoke, is an important risk factor in developing countries, where nonsmokers constitutes a much larger proportion of lung cancer patients (9). Growing

evidence suggests that lung cancer in never-smokers is in part a different disease than lung cancer attributable to cigarette smoking, and that further research is needed to determine the optimal treatment strategies for these separate groups of lung cancer (7). Dietary and nutritional factors are also thought to play a role in prevention of lung cancer since several retrospective investigations have shown protective effects of high intake of fruit and vegetables, although no single dietary nutrient has been successfully isolated (8).

Histology

Traditionally, lung cancer has been divided into two groups based on their histopathological and clinical presentation: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), where NSCLC constitutes the vast majority, 80-85%, of lung cancer cases (10). However, this traditional classification has developed, and in the recent publication of the 2015 World Health Organization Classification of Lung tumors, the major histologic types of carcinomas are: squamous cell carcinoma, adenocarcinoma, and (now belonging to the neuroendocrine tumors) SCLC and large-cell carcinoma (11, 12). One important reason for this revision of lung tumor classification is the development of specific therapies targeting oncoproteins found in various NSCLC tumors, mainly adenocarcinomas but also in squamous cell carcinomas (12). Subsequently, adenocarcinomas and squamous cell carcinomas are further classified into several subgroups, but the use of a more specific classification than simply adenocarcinoma, squamous cell carcinoma or NSCLC NOS (not otherwise specified) is not common in clinical practice today (13).

Presenting signs and symptoms

More than 9/10 of patients with lung cancer are symptomatic when first diagnosed, but most of the symptoms will not emerge before the tumor has reached an advanced stage (14).

Presenting signs and symptoms can therefore be predictive of the prognosis of the cancer: Patients who are asymptomatic at diagnosis have significantly improved survival rates compared to symptomatic patients (15).

The most common symptoms related to the primary lung tumor is cough with or without sputum, dyspnea, hemoptysis and diffuse chest discomfort. Intrathoracic extension of the primary lung tumor or lymphatic spread that affects nerves and large blood vessels within the thoracic region could cause mass effects like Horner syndrome; hoarseness or dysphagia caused by recurrent laryngeal nerve palsy; phrenic nerve paralysis; and vena cava superior syndrome. Intrathoracic metastases to the pericardium and myocardium of the heart also occurs, usually presenting with arrhythmias or cardiac tamponade (14, 16). Chest pain that is more severe and localized could be an indication of primary tumor invasion of the pleura or chest wall, or worse, a sign of rib metastasis. The metastatic pattern of lung cancer varies depending on histological type, sex and age of the patient, but the most common metastatic sites overall are the liver, bones, central nervous system, respiratory system, adrenal gland and lymph nodes (14, 17). Typical signs of metastasized lung cancer include bone pain; weakness and weight loss caused by hepatic metastases; seizures, confusion, personality changes, focal neurologic signs, etc. produced by brain metastases; and palpable lymphadenopathy in the supraclavicular fossa (14, 16).

Diagnosis and staging

In order to give the patient the best possible treatment, a comprehensive diagnostic investigation is needed to accurately determine the tumor type and the lung cancer stage. The best initial diagnostic tool for assessment of extra-thoracic disease remains a thorough anamnesis and physical examination of the patient (2). Based on clues from the clinical evaluation, the investigational procedure continues with the most appropriate diagnostic tests.

Commonly required investigations for lung cancer, apart from medical history and physical examination, include imaging techniques such as chest X-ray, CT of the thorax, PET/CT (see below) and brain MRI; blood test analyses, e.g. liver, renal and bone status; tissue samples essentially obtained with bronchoscopy, transthoracic techniques or biopsies from metastasis sites. Additionally, endobronchial ultrasound and/or esophageal ultrasound for fine needle aspiration and evaluation of regional lymph nodes is used in selected cases (18). The biopsies are in addition to histopathological assessment also utilized to perform a variety of molecular pathology analyses in order to identify tumors sensitive to biological therapies such as EGFR tyrosine kinase inhibitors or other kind of targeted therapies. (11, 16).

The current basis for staging of lung carcinomas is the tumor-nodes-metastases (TNM) system as revised and described in the 8th edition of the TNM Classification of Malignant Tumors, effective since January 2017 (18, 19). In this classification system, T refers to size and growth of the primary tumor; N to the presence of nodal metastases; and M refers to presence of distant metastases. The TNM classification correlates to a certain cancer stage between I and IV. For instance, stage I includes small tumors confined to the lung (T1-T2), whereas presence of distant metastases (M1a-M1b) always translates into stage IV regardless of Tumor or Nodal classification (19).

Simultaneously with the tumor-directed investigations, a complete analysis of patient factors such as lung function, physical function, estimated postoperative quality of life, comorbidities (e.g. chronic obstructive lung disease or cardiovascular diseases) and performance status is performed and is decisive for choosing the best treatment strategy for the patient in each individual case (20, 21).

PET/CT

PET/CT scans has seized an important role in the management of lung cancer patients. PET is a nuclear medicine technique used to detect tissues with increased metabolic activity, like cancer cells or inflammation, by tracing uptake of positron-emitting fluorodeoxyglucose. By combining PET with a CT scan, three-dimensional images with both anatomical and metabolic information is accomplished. PET-CT is primarily used as a standard imaging technique for staging of patients considered for radical treatment, and its negative predictive values are excellent at 85-95 % (16, 22, 23). However, there are some well-known limitations of this technique, for example inability to detect cancers with low metabolic activity or to distinguish cancer from inflammation. In addition to initial staging, PET/CT is used to improve planning of radical radiotherapy for lung cancer (24). In VGR, PET/CT was introduced as a standard diagnostic/staging technique for lung cancer in 2010, but its impact on treatment outcomes has not yet been evaluated.

Treatment

One important reason for the poor prognosis of lung cancer is the fact that the disease has often already spread to other organs when diagnosed. More than 50% of patients have a metastasized disease when diagnosed and cannot be treated curatively (13). Potentially curative treatment options is possible in most cases for the remaining patients but the therapeutic strategy depends on stage and histology of the cancer as well as the comorbidity and, not least, the wish of the patient (13).

Surgery

Surgical radical resection of the tumor is the foremost curative treatment for patients with lung cancer. It is the first-line therapy for NSCLC of stage I-II and in selected cases of stage

III, and a viable alternative to chemoradiotherapy in some cases of stage I SCLC (16, 25).

Lobectomy is the surgical procedure of choice for tumors confined to one lobe, whereas

pulmectomy is performed when the cancer involves all lobes in one lung or the main

bronchus (16). Limited resections as a method of parenchyma-saving surgery could be

preferable in some specific instances, but does generally not replace complete resection (18).

Moreover, resected patients should in most cases (except stage IA) be treated with

postoperative adjuvant chemotherapy, as it reduces the risk for recurrence and improves

survival. In case of non-radical dissection, chemoradiotherapy for locally advanced NCSLC

as described below should be considered postoperatively (16).

Surgery as a treatment strategy for lung cancer should always be curative in its intent and

not offered as a palliative measure. In total, only 20-25 % of patients with NSCLC are eligible

for surgery (26), and many of them will suffer a postoperative recurrence with deadly

outcome (27). In spite of being the primary curative treatment, the total five-year survival rate

after surgical resection of lung cancer is just over 50 % in Sweden (16).

Radiotherapy

While surgery is the main curative treatment for early stage NSCLC, radiotherapy is an

essential curative modality too, and in addition used broadly as palliative treatment. It is used

in the curative setting in many cases of NSCLC, e.g. for locally advanced cancer or smaller

tumors in patients that are medically inoperable, and chemoradiotherapy is virtually the only

effective option when it comes to treatment of SCLC (16). Radiotherapy is however not

without risk. Common side-effects related to normal tissue irradiation include pneumonitis,

lung fibrosis, and acute esophagitis (16). Different fractionation strategies and total doses are

used depending on tumor and patient factors in order to optimize treatment effect while

reducing the risk for normal tissue reactions. The standard radiotherapy fractionation

technique in clinical practice is so called conventional fractionation, where the dose is

delivered with one fraction of 1.8-2.0 Gy daily for five days a week during several weeks

until the total dose is reached. Hyperfractionation and hypofractionation are other commonly

used techniques. Hypofractionation means that the total dose is divided into fewer and larger

fractions, with the overall treatment period considerably shorter than in conventional

(standard) radiotherapy. Conversely, hyperfractionated radiotherapy means that the total dose

is split into a large number of smaller fractions than in conventional radiotherapy, and usually

delivered with more than one fraction per day. In this way, hyperfractionation allows for the

possibility to achieve a higher total dose during a conventional overall treatment period.

Finally, radiotherapy can be delivered with accelerated fractionation, where the overall

treatment period is considerably shortened but the numbers and doses of fractions are

typically conventional. Accelerated fractionation may also be combined with hypo- or

hyperfractionated regimens (28).

Radiotherapy in early-stage NSCLC

Despite an early-stage cancer, many patients are medically inoperable when diagnosed with

NSCLC due to poor lung function or other comorbidities. These inoperable patients were

earlier treated with conventionally fractioned radiotherapy doses of 1.8-2.0 Gy/day for a total

radiation dose of around 60 Gy. However, as concluded by Qiao et al. in their review from

2003, the outcome of conventionally fractionated radiotherapy as treatment of stage I NSCLC

was disappointing with a mean 3-year overall survival of 34 % and local tumor control rate of

50 % (29). These results were of course significantly lower than what could be achieved with

surgery on operable stage I NSCLC patients, and mainly attributed to too low total radiation

doses (16). During the last decade, a different radiation technique has been developed:

stereotactic body radiotherapy (SBRT). This is a high precision technique of hypofractionated

radiotherapy that allows for deliverance of very large radiation therapy doses against the tumor in just a few fractions, whilst sparing surrounding normal tissues to a great extent. Due to a substantial amount of literature describing excellent results in quality of life and survival, SBRT has become a new standard therapy for inoperable patients with stage I NSCLC. Furthermore, a recent comparison to conventionally fractionated radiotherapy showed less toxicity and improved quality of life with SBRT (16, 30, 31). Different doses and fractionation for SBRT has been used both internationally and in Sweden, but the most common setup in Sweden and in VGR is currently 45 Gy given in 3 fractions of 15 Gy during one week (16). This fractionation has been extensively studied in clinical trials in the last decade, and its usefulness in treating peripherally located early stage NSCLC is well-established (32, 33). However, some studies have reported an unacceptably high risk for major toxicities when such intensified fractionations are used to treat central tumors located too close to the bronchial tree or other critical mediastinal structures (34, 35). Haasbeek et al. found that both satisfactory treatment results and no excess risk in toxicity could be achieved by using a less intensified, risk-adapted SBRT delivered in 8 fractions of 7 Gy against centrally located lung tumors (36). In VGR today, similar risk-adapted and less intensified SBRT schedules that results in biologically lower doses (currently 56 Gy in 8 fractions) are commonly used to treat early stage NSCLC tumors in high-risk locations. However, clinical outcomes for the different types of SBRT in VGR remains to be evaluated, and there is currently a lack of studies comparing outcomes for different SBRT doses.

Radiotherapy in locally advanced NSCLC

Patients with stage III NSCLC, i.e. locally advanced disease, are a heterogeneous group comprising almost 3/10 of newly diagnosed lung cancer cases. Most of these patients are not eligible for surgery, but approximately 50% can be offered curative radiotherapy with

concurrent platinum-based chemotherapy (16). The degree of nodal invasion is determinant of the prognosis (37), which remains poor even with curative treatment: the 2-year survival rate has been reported to be only 20% (16). Since NSCLC stage III is such a diverse group of patients, it is all the more important to conduct a comprehensive diagnostic investigation, which should include contrast enhanced CT scans, brain MRI and PET/CT, and sometimes mediastinal invasive staging. Treatment strategy decisions should always be rooted in multidisciplinary team meetings (18).

There are strong indications of a dose-response relationship for irradiation of locally advanced NSCLC, although somewhat conflicting findings on the subject have been observed (38-40). Based on up-to-date research, the previous standard radiation dose of 60 Gy is now regarded as inadequate and total doses exceeding 70 Gy are deemed experimental and not recommended in clinical practice. While the optimal total dose remains uncertain, the effectiveness of concomitant chemotherapy and radiotherapy with total doses exceeding 60 Gy is well-supported. Hence, currently recommended total doses in Sweden are 66-70 Gy, dose levels that are considered well-documented despite a lack of randomized clinical trials (16). The typical fractionation schedule in clinical use is conventional fractionation (2 Gy per day up to 10 Gy per week), though several studies have shown promising results from accelerated radiotherapy regimens compared to conventional fractionation (41). However, additional randomized clinical trials are required before unconventional fractionation can be safely implemented into clinical guidelines (16). In VGR, patients with stage III NSCLC are treated according to current recommendations with a slight acceleration (70 Gy in 6 fractions per week plus 3 cycles of chemotherapy), but as with SBRT, clinical outcomes of this treatment, and its predecessors, are yet to be evaluated.

Radiotherapy in SCLC

In contrast to NSCLC, the standard treatment for most cases of SCLC is not surgery, but chemoradiotherapy. This is due to the fact that SCLC is a very fast-spreading cancer that has usually already advanced to an unresectable stage by the time of diagnosis. It is, however, very chemo- and radiosensitive. (42). Hence, platinum-based chemotherapy constitutes the foundation of the treatment strategy of SCLC, while combination with radiotherapy significantly improves the prognosis.

As the risk for brain metastasis is considerable in SCLC patients, with a cumulative incidence of 50 % at two years after diagnosis (43), patients with SCLC in complete or almost complete remission after first-line therapy should be offered prophylactic cranial irradiation, as it significantly reduces the risk for brain metastases and improves survival rates (16).

Thoracic irradiation in addition to chemotherapy has been shown to improve long term survival rates (44). Hyperfractionation is superior to conventional fractionation because of the rapid proliferation of SCLC tumors, a theory which was supported in a randomized study by Turrisi et al. in 1999 (45), and a dose-response relationship has also been determined for radiation therapy in SCLC (46). However, there is currently a lack of consensus regarding optimal total doses in SCLC, as very few randomized clinical trials comparing different doses of radiotherapy has been published so far. The best clinical outcomes has been observed for doses ranging from 45 to 60 Gy delivered in a hyperfractionated schedule, and the recommendation in Sweden is concurrent chemotherapy and hyperfractionated radiotherapy with 1.5 Gy two times daily to a total dose of 45-60 Gy (16). Clinical practice for treatment of SCLC patients in VGR is in line with this recommendation, but the clinical outcomes still need to be evaluated.

Specific objectives

The aim of this degree project is

❖ To evaluate overall survival for patients with stage I NSCLC treated with SBRT during 2002-2016 and to compare overall survival rates depending on time interval, radiation dose, staging with PET/CT as well as other potential prognostic factors.

❖ To evaluate overall survival rates for patients with stage III NSCLC treated with chemoradiotherapy during 2002-2016 and to compare overall survival rates depending on time interval, radiation dose, staging with PET/CT as well as other potential prognostic factors.

❖ To evaluate overall survival rates in patients with stage I-III SCLC treated with concurrent chemoradiotherapy with hyperfractionated accelerated radiotherapy during 2002-2016 and to compare overall survival rates depending on time interval, radiation dose, staging with PET/CT as well as other potential prognostic factors.

Methods and material

Study design

We conducted a quantitative retrospective population-based study of all the patients in Region Västra Götaland with NSCLC or SCLC that received radiotherapy with curative intent during 2002-2016. The aim was to study overall survival depending on time period, ECOG performance status, smoking habits, age at the start of treatment, gender, TNM classification and stage, radiation dose and technical aspects as use of PET/CT. Since much has happened between 2002 and 2016 in the field of curative radiotherapy for lung cancer, we wanted to divide the patient population into different time intervals of appropriate and equal lengths, in order to appreciate how the continuous development has affected survival. The time period between 2002-2016 was therefore divided into three time intervals: 2002-2006, 2007-2011 and 2012-2016. A cutoff in follow-up time after the radiotherapy was set to three years, in order to control for survival bias favoring more recent treatment regimens.

Study population and data collection

The inclusion criteria were patients with pathologically or, in event of missing pathological diagnosis, clinically and radiologically diagnosed lung cancer, who had received radiotherapy with curative intent between 2002 and 2016, either at Sahlgrenska University Hospital in Gothenburg (SU) or Södra Älvsborgs Hospital in Borås (SÄS). The patients were primarily identified through databases at the radiation therapy units at SU and SÄS, where all cancer patients treated in VGR were listed. Lung cancer patients were extracted from the databases by searching for patients with lung cancer as their primary diagnosis code. The total radiation dose and type of radiation treatment for each one of the patients were determined from the radiotherapy data and, when necessary, medical records. Patients from this primary material were in the next step excluded due to any of the following exclusion criteria: lung tumors

other than SCLC or NSCLC; postoperative radiotherapy; palliative treatment; concurrent radiotherapy for malignancies other than lung cancer; bilateral tumors i.e. stage IV disease; interrupted treatment/suboptimal total radiation dose; missing social security number. If a patient had suffered a relapse or a second primary lung cancer and therefore received more than one radiotherapy course during the time period, only the first course was included.

All included patients were then classified into three different main groups: SBRT for stage I NSCLC, curative chemoradiotherapy for locally advanced NSCLC and curative chemoradiotherapy for SCLC.

Thereafter, the patient data was matched against the national Swedish Lung Cancer Registry for extraction of patient and tumor variables i.e. ECOG performance status, smoking habits, use of PET/CT, date of death, TNM classification and stage, histology and anatomical location. Patients that were not found in the lung cancer registry were rescreened using medical records and could be excluded due to previously mentioned reasons. If they still fulfilled the inclusion criteria, missing data were extracted from the medical records and added to the database.

Statistical analysis

The statistical analyses were made in R version 3.4.3. The Kaplan-Meier method was used to calculate survival rates. The Log-Rank test was used to compare the survival rate for each variable. A multivariate survival analysis was performed using the Cox proportional hazards model. The final model was adjusted for treatment period, age, gender, performance status, smoking habits, stage of cancer, histology, location of tumor, use of PET/CT and total radiation dose. The Wald test was used to test the significance of individual regression coefficients. A result was considered significant when the P value was <0.05.

Age was analyzed as a continuous variable and not by age-group. Supplementary analyses were performed for five-year survival and PET/CT. Five-year OS was only estimated for the two earlier treatment intervals (2002-2006 and 2007-2011) and staging with PET/CT was only analyzed for the two latter (2007-2011 and 2012-2016), since it was implemented in clinical practice as late as 2010.

Ethics

After the collection of data, all patient data were anonymized by giving every patient an individual code. The coding key was stored separately from patient data. Moreover, the study is a retrospective analysis of patient records. Thus, it has not affected treatment or management of participating patients in any way. Permission from The Regional Ethical Review Board in Gothenburg to conduct this retrospective patient record study has been granted.

Results

The extracted files from the radiation therapy system of lung cancer patients treated in VGR between 2002 and 2016 included 2232 patients. 2044 of these patients were treated at Sahlgrenska University Hospital and 188 patients at Södra Älvsborgs Hospital. The primary files of radiation therapy, medical records and quality registers were used for sorting and exclusion, and in the end 1421 lung cancer patients that met the inclusion criteria remained. Data for 173 patients were missing in the quality register and these patients were rescreened using medical records. 159 of the rescreened patients were included in the study. Details on exclusions are showed in Figure 1.

Gender distribution in the entire population was even with 51 % female patients and 49 % male. The ECOG performance status (PS) score in the majority of patients were 1, but a relatively large proportion (16 %) were classified as PS=2. Only a very small proportion had PS=3-4 (see Table 1a-b, 2a-b, 3a-b).

346 of the lung cancer patients were treated with SBRT for stage I NSCLC disease, 806 patients received chemoradiotherapy for locally advanced NSCLC, 269 patients received hyperfractionated accelerated chemoradiotherapy for SCLC. Details on the study population for each group are shown in Table 1a-1b, 2a-2b and 3a-3b.
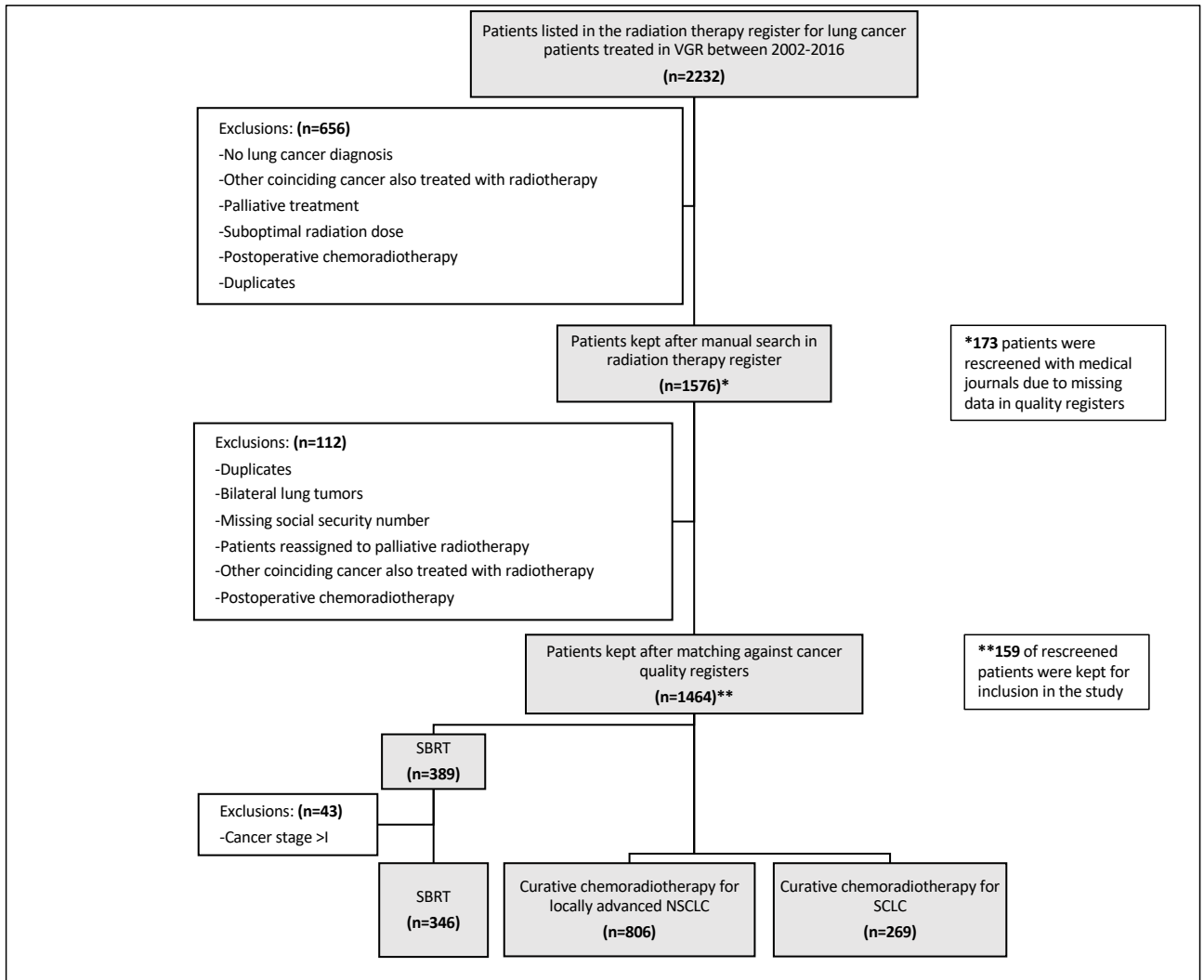
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┌─────────────────────────────────────────────────┐
│  Patients listed in the radiation therapy        │
│  register for lung cancer patients treated in     │
│  VGR between 2002-2016                             │
│  (n=2232)                                          │
└─────────────────────────────────────────────────┘

┌──────────────────────────────────────────┐
│  Exclusions: (n=656)                       │
│  -No lung cancer diagnosis                 │
│  -Other coinciding cancer also treated     │
│   with radiotherapy                        │
│  -Palliative treatment                     │
│  -Suboptimal radiation dose                │
│  -Postoperative chemoradiotherapy          │
│  -Duplicates                               │
└──────────────────────────────────────────┘

┌─────────────────────────────────┐       ┌──────────────────────────┐
│  Patients kept after manual      │       │  *173 patients were       │
│  search in radiation therapy     │       │  rescreened with medical  │
│  register                         │       │  journals due to missing  │
│  (n=1576)*                         │       │  data in quality registers│
└─────────────────────────────────┘       └──────────────────────────┘

┌──────────────────────────────────────────┐
│  Exclusions: (n=112)                       │
│  -Duplicates                               │
│  -Bilateral lung tumors                    │
│  -Missing social security number           │
│  -Patients reassigned to palliative        │
│   radiotherapy                             │
│  -Other coinciding cancer also treated     │
│   with radiotherapy                        │
│  -Postoperative chemoradiotherapy          │
└──────────────────────────────────────────┘

┌─────────────────────────────────┐       ┌──────────────────────────┐
│  Patients kept after matching    │       │  **159 of rescreened      │
│  against cancer quality registers │       │  patients were kept for   │
│  (n=1464)**                        │       │  inclusion in the study   │
└─────────────────────────────────┘       └──────────────────────────┘

        ┌──────────┐
        │  SBRT     │
        │  (n=389)  │
        └──────────┘

┌─────────────────────┐
│  Exclusions: (n=43)  │
│  -Cancer stage >I    │
└─────────────────────┘

┌──────────┐   ┌────────────────────┐   ┌────────────────────┐
│  SBRT     │   │  Curative           │   │  Curative           │
│  (n=346)  │   │  chemoradiotherapy  │   │  chemoradiotherapy  │
│           │   │  for locally        │   │  for SCLC           │
│           │   │  advanced NSCLC     │   │  (n=269)            │
│           │   │  (n=806)            │   │                     │
└──────────┘   └────────────────────┘   └────────────────────┘
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Figure 1, Flow chart detailing the exclusion and inclusion of patients in the study

SBRT for stage I NSCLC

The use of SBRT clearly increased between the time intervals: 53 patients received SBRT in the first interval (2002-2006), 115 in 2007-2011 and finally 178 patients between 2012 and 2016 (Table 1a). Three-year survival for the SBRT treatment groups was 55 % in the 2002-2006 period, 47 % between 2007-2011 and 54 % in the 2012-2016 period (Fig. 1.1). Five-year survival was analyzed for the first two treatment periods and was 30 % for both 2002-2006 and 2007-2011 (see Fig. 1.2 in Appendix A). Median survival was 33.2 months for the 2007-2011 time interval and 38.5 months for 2002-2006. No median value was available for 2012-2016. There was no significant difference in survival between treatment intervals (Table 1c). The results of the Cox proportional hazard model are showed in Table 1c. When analyzing potential factors for survival a gender difference could be observed in the multivariate analysis where males had an inferior survival compared to women with a hazard ratio (HR) of 1.6 for both three- and five-year OS (95 % confidence interval 1.2 – 2.2, p=0.002 and 1.1 – 2.5, p=0.016 respectively). There was also a lower survival among patients with higher ECOG PS scores: for example, patients with PS=2 had a doubled mortality rate in three year-survival compared to PS=0 (HR=2.1, 95 % CI 1.2 – 3.8, p<0.05).

Tumors located in the inferior lobe were associated to an adverse effect on three-year survival compared to the middle and superior lobe (HR=1.44, 95 % CI 1.04 – 1.98, p=0.03). Five-year survival was also inferior but not statistically significant (HR=1.49, 95 % CI 1.0 – 2.23, p=0.052).

Use of PET/CT significantly improved survival in univariate analysis but this significance was not maintained in the multivariate model. No significant differences could be observed in the multivariate analysis with regard to time interval, age at the start of treatment, smoking habits, T-stage, tumor laterality or total radiation doses, albeit trends were noted with regard to T1 vs T2 tumors (Fig. 1.2) and 45 vs 56 Gy (see Fig. 1.7 in Appendix A). Histological

diagnosis and tumor laterality were analyzed but did not have an impact on survival and was therefore not included in the model. The following factors were seen as important factors and included in the model: treatment period, gender, smoking habits, ECOG PS, lobar location of the tumor, T-stage, age and total radiation dose. The Kaplan-Meier graphs for these factors in univariate analyses are shown in Figure 1.1-1.8 (Fig. 1.6-1.8 are shown in Appendix A).

Table 1a: Demographics of patients treated with SBRT

	2002-2006	2007-2011	2012-2016	Total
Median age (range)	78 (58-91)	76 (52-94)	77 (56-91)	-
	No. of patients (%)			
Patients treated with SBRT	53 (100)	115 (100)	178 (100)	346 (100)
Gender				
Female	27 (50.9)	59 (51.3)	108 (60.7)	216 (56.1)
Male	26 (49.1)	56 (48.7)	70 (39.3)	173 (43.9)
Smoking status				
Smokers	19 (35.8)	43 (37.4)	72 (40.4)	134 (38.7)
Ex-smokers	30 (56.6)	59 (51.3)	91 (51.1)	180 (52.0)
Non-smokers	3 (5.7)	12 (10.4)	15 (8.4)	30 (8.7)
Missing	1 (1.9)	1 (0.9)	0 (0.0)	2 (0.6)
Diagnostic PET-CT				
No	49 (92.5)	27 (23.5)	9 (5.1)	85 (24.6)
Yes	4 (7.5)	88 (76.5)	169 (94.9)	261 (75.4)
ECOG PS*				
0	7 (13.2)	19 (16.5)	20 (11.2)	46 (13.3)
1	33 (62.3)	61 (53.0)	96 (53.9)	190 (54.9)
2	12 (22.6)	32 (27.8)	54 (30.3)	98 (28.3)
3-4	1 (1.9)	3 (2.6)	7 (3.9)	11 (3.2)
Missing	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
Total radiation dose				
40 Gy	1 (1.9)	14 (12.2)	11 (6.2)	26 (7.5)
45 Gy	52 (98.1)	100 (87.0)	154 (86.5)	306 (88.4)
56 Gy	0 (0.0)	0 (0.0)	12 (6.7)	12 (3.5)
Missing	0 (0.0)	1 (0.9)	1 (0.6)	2 (0.6)

*=Eastern Cooperative Oncology Group Performance status

Table 1b: Tumor information of patients treated with SBRT

	2002-2006	2007-2011	2012-2016	Total
	No. of patients (%)			
Histological diagnosis				
Squamos cell carcinoma	13 (24.5)	18 (15.7)	23 (12.9)	54 (15.6)
Adenocarcinoma	19 (35.8)	27 (23.5)	57 (32.0)	107 (29.8)
NSCLC NOS**	21 (39.6)	70 (60.9)	89 (55.1)	189 (56.6)
Tumor location, side				
Right	35 (66.0)	65 (56.5)	104 (58.4)	204 (59.0)
Left	18 (34.0)	50 (43.5)	74 (41.6)	142 (41.0)
Tumor location, lobe				
Upper lobe	30 (56.6)	66 (57.4)	105 (59.0)	201 (58.1)
Middle lobe	3 (5.7)	7 (6.1)	7 (3.9)	17 (4.9)
Lower lobe	20 (37.7)	41 (35.7)	66 (37.1)	127 (36.7)
Missing	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.3)
T (primary tumor)				
T1	31 (58.5)	76 (66.1)	125 (70.2)	232 (67.1)
T2	22 (41.5)	39 (33.9)	53 (29.8)	114 (32.9)

*=NSCLC Not otherwise specified

Table 1c: p-values and Hazard ratios for variables in the SBRT group

Variable	p-value in univariate analysis	HR (95% CI)	p-value in multivariate analysis
Treatment interval	0.436		
2002-2006		Reference	
2007-2011		1.22 (0.75 - 1.98)	0.426
2012-2016		0.97 (0.6 - 1.57)	0.912
Gender	0.001		
Female		Reference	
Male		1.60 (1.15 – 2.22)	0.005
Smoking habits	0.378		
Smoker		Reference	
Ex-smoker		0.75 (0.53 – 1.04)	0.087
Never-smoker		0.54 (0.28 – 1.04)	0.067
Tumor location, lobe	0.047		
Upper lobe		Reference	
Middle lobe		0.72 (0.29 – 1.79)	0.478
Lower lobe		1.44 (1.04 – 1.98)	0.029
ECOG Performance status	0.002		
0		Reference	
1		1.60 (0.90 – 2.83)	0.108
2		2.12 (1.17 – 3.84)	0.013
3-4		4.67 (1.98 – 11.00)	<0.001
T-stage	0.035		
T1		Reference	
T2		1.27 (0.91 – 1.78)	0.154
Age at start of treatment	0.115		
Continuous variable		1.02 1.00 – 1.05)	0.059
Total radiation dose	0.309		
40 Gy		Reference	
45 Gy		0.75 (0.43 – 1.28)	0.287
56 Gy		0.75 (0.36 – 2.56)	0.933
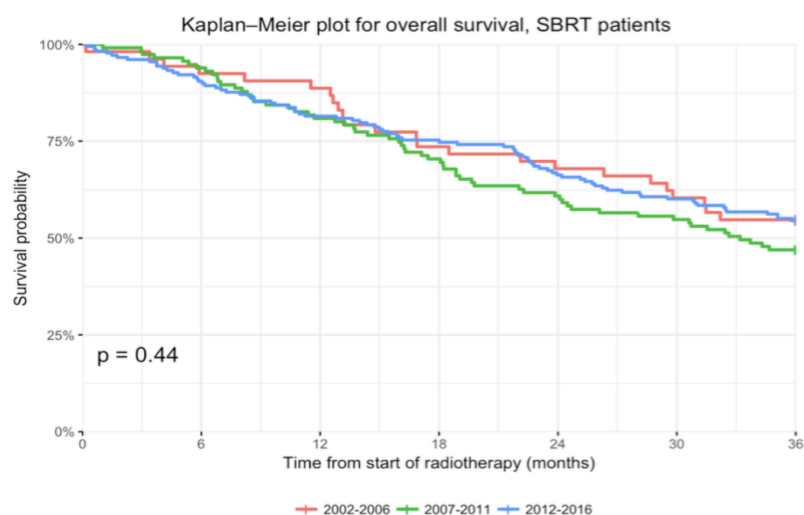
Figure 1.1, Overall survival among lung cancer patients treated with stereotactic body radiotherapy depending on during in which time interval patients received their treatment.

Figure 1.2, Overall survival among lung cancer patients treated with stereotactic body radiation therapy depending on the stage of the tumor
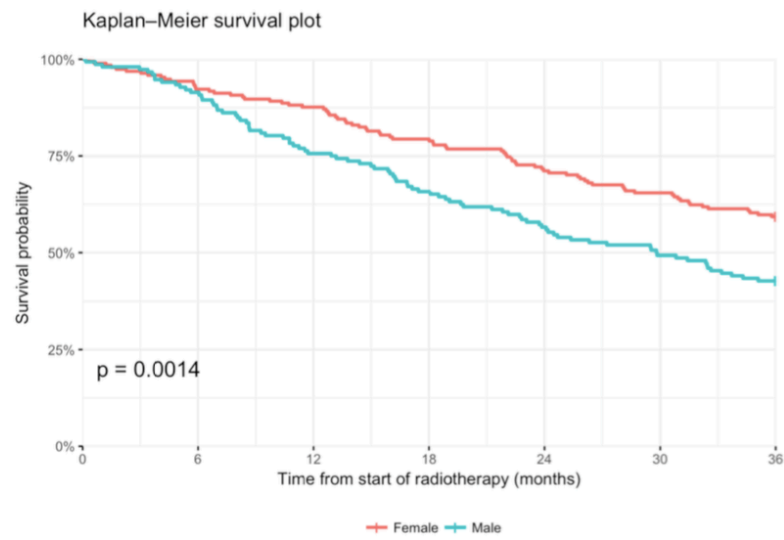

Figure 1.3, Overall survival among lung cancer patients treated with stereotactic body radiation therapy depending on the gender of the patients
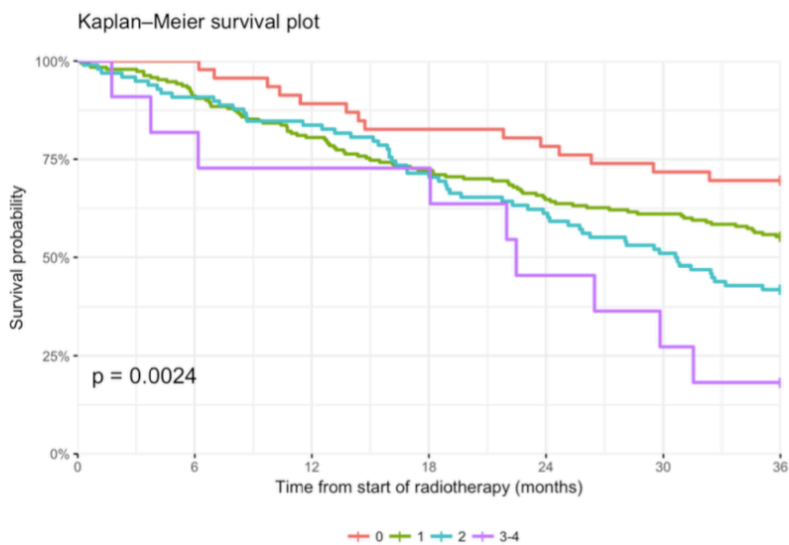

Figure 1.4, Overall survival among lung cancer patients treated with stereotactic body radiotherapy depending on the ECOG performance status score of patients
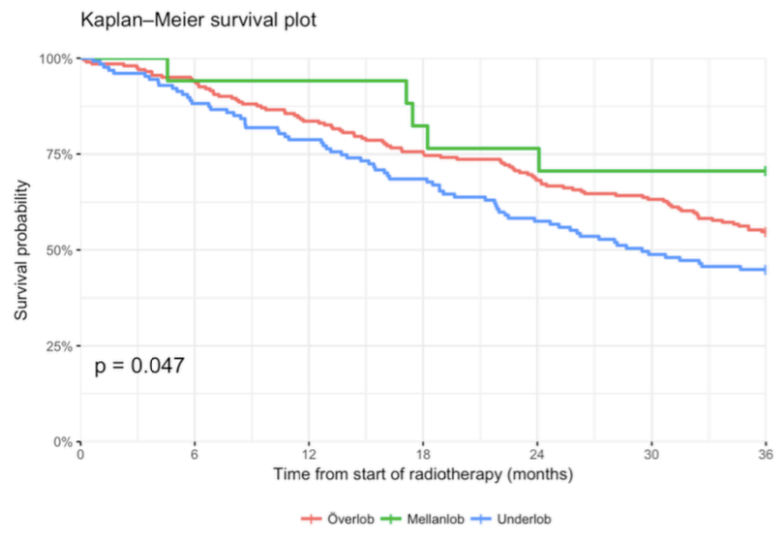
Kaplan–Meier survival plot

Figure 1.5, Overall survival depending on the lobar location of the tumor among lung cancer patients treated with stereotactic body radiation therapy

Curative chemoradiotherapy for locally advanced NSCLC

Details on the locally advanced NSCLC population are shown in Table 2a-2c. Three-year survival in the locally advanced NSCLC chemoradiotherapy group was 24 %, 27 % and 35 % for 2002-2006, 2007-2011 and 2012-2016, respectively (Fig. 2.1). Five-year survival was estimated to 15 % for 2002-2006 and 18 % for 2007-2011 (Fig. 2.5 in appendix). There was a significant difference in three-year survival between the time periods (p=0.037) in the univariate analysis, but this difference was not maintained in multivariate analyses. No significant difference was found when five-year survivals was compared. Median survival was 15.3, 18.2 and 18.4 months for each time interval.

The results of the Cox proportional hazard model are showed in Table 2c. Total radiation dose was divided into four groups: 54-63 Gy (n=141), 64-66 Gy (n=298), 68-70 Gy (n=354) and >70 Gy (n=5). 8 patients had a missing total dose. The patients with >70 Gy were included in a trial and already known to have an inferior survival.

Patient survival was negatively affected by more advanced stages of cancer. However, the results in three- and five-year survival analyses were significant only when stage IIIB or IV was compared to IA-IIB, not IIIA. 52 patients were categorized as stage IV lung cancer and they suffered the greatest risk (HR=2.0, 95 % CI 1.36 – 2.97, p<0.001). The 325 patients with stage IIIB showed a 50 % higher risk compared to stage IA-IIB (HR=1.5, 95 % CI 1.14 – 1.87, p=0.003).

25 % of patients (n=198) with locally advanced NSCLC had ECOG PS=0, and 64 % (n=516) had ECOG PS 1. 10.7 % (n=86) had PS=2 and only 0.6 % (n=5) had PS=3-4. Our analysis showed that higher ECOG PS score were associated with lower three-year survival: HR=1.4 for PS=1 (p=0.007), 2.0 for PS=2 (p<0.001) and a borderline significant HR=3.0 for PS=3-4 (p=0.06). The same trend was seen in the five-year survival analysis. There was no significant difference with regard to age at start of treatment, smoking habits, tumor laterality,

histological diagnosis and TNM-stage. Borderline significant results were observed with regard to in which lung lobe the tumors were located. Tumors located in the lower lobe had an adverse effect on survival in the three-year survival (HR=1.44, 95 % CI 1.00 – 2.08, p=0.050) and in the supplementary PET/CT analysis, tumors located in the middle lobe were associated with a better chance for survival (HR=0.43, 95 % CI 0.19 – 0.99, p=0.048).

Table 2a: Demographics of the locally advanced NSCLC group

	2002-2006	2007-2011	2012-2016	Total
Median age (range)	66 (41-84)	68 (15-86)	69 (38-87)	-
	No. of patients (%)			
Patients treated with radiotherapy for NSCLC	233 (100)	293 (100)	280 (100)	806 (100)
Gender				
Female	103 (44.2)	139 (47.4)	139 (49.6)	381 (47.3)
Male	130 (55.8)	154 (52.6)	141 (50.4)	425 (52.7)
Smoking status				
Smokers	139 (59.7)	131 (44.7)	136 (48.6)	406 (50.4)
Ex-smokers	74 (31.8)	133 (45.4)	121 (43.2)	328 (40.7)
Non-smokers	19 (8.2)	28 (9.6)	22 (7.9)	69 (8.6)
Missing	1 (0.4)	1 (0.3)	1 (0.4)	3 (0.4)
Diagnostic PET-CT				
No	232 (99.6)	193 (65.9)	16 (5.7)	441 (54.7)
Yes	1 (0.4)	100 (34.1)	264 (94.3)	365 (45.3)
ECOG PS*				
0	41 (17.6)	76 (25.9)	81 (28.9)	198 (24.6)
1	162 (69.5)	187 (63.8)	167 (59.6)	516 (64.0)
2	27 (11.6)	28 (9.6)	31 (11.1)	86 (10.7)
3-4	3 (1.3)	2 (0.7)	0 (0.0)	5 (0.6)
Missing	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Total radiation dose				
54-63 Gy	56 (24.0)	51 (17.4)	34 (12.1)	141 (17.5)
64-66 Gy	162 (69.5)	129 (44.0)	7 (2.5)	298 (37.0)
68-70 Gy	7 (3.0)	112 (38.2)	235 (83.9)	354 (43.9)
>70 Gy	0 (0.0)	1 (0.3)	4 (1.4)	5 (0.6)
Missing	8 (3.4)	0 (0.0)	0 (0.0)	8 (1.0)

=Eastern Cooperative Oncology Group Performance status

Table 2b: Tumor information of locally advanced NSCLC patients

	2002-2006	2007-2011	2012-2016	Total
	No. of patients (%)			
Histological diagnosis				
Squamos cell carcinoma	82 (35.2)	104 (35.5)	110 (39.3)	296 (36.7)
Adenocarcinoma	112 (48.1)	136 (46.4)	126 (45.0)	374 (46.4)

NSCLC NOS*	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Tumor location, side				
Right	140 (60.1)	163 (55.6)	162 (57.9)	465 (57.7)
Left	90 (38.6)	126 (43.0)	117 (41.8)	333 (41.3)
Missing	3 (1.3)	4 (1.4)	1 (0.4)	(1.0)
Tumor location, lobe				
Main bronchus	24 (10.3)	11 (3.8)	17 (6.1)	52 (6.5)
Upper lobe	129 (55.4)	155 (52.9)	148 (52.9)	432 (53.6)
Middle lobe	12 (5.2)	14 (4.8)	10 (3.6)	36 (4.5)
Lower lobe	59 (25.3)	102 (34.8)	95 (33.9)	256 (31.8)
Missing	9 (3.9)	11 (3.8)	10 (3.6)	30 (3.7)
Cancer stage				
IA-IIB	49 (21.0)	62 (21.2)	48 (17.1)	159 (19.7)
IIIA	53 (22.7)	89 (30.4)	123 (43.9)	265 (32.9)
IIIB	113 (48.5)	122 (41.6)	90 (32.1)	325 (40.3)
IV	18 (7.7)	19 (6.5)	15 (5.4)	52 (6.5)
Missing	0 (0.0)	1 (0.3)	4 (1.4)	5 (0.6)

=NSCLC Not otherwise specified

Table 2c: p-values and Hazard ratios for variables in the locally advanced NSCLC group

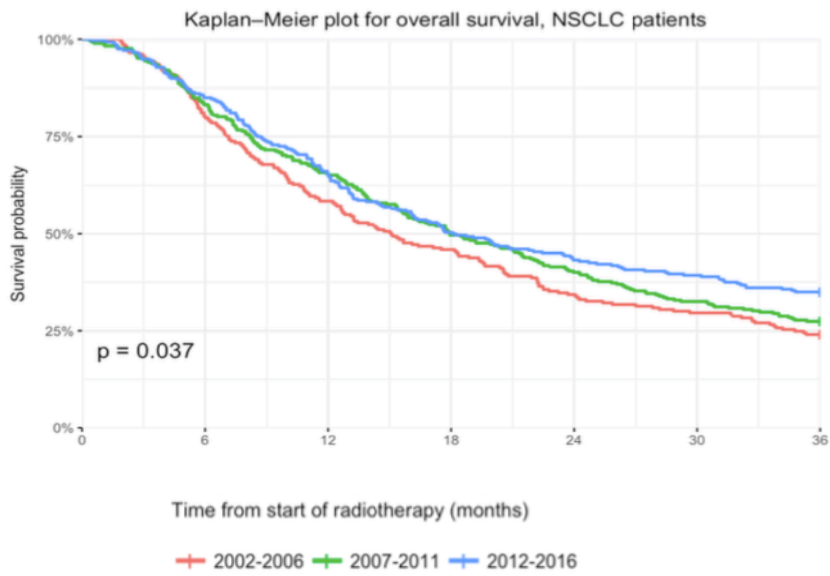| Variable		p-value in univariate analysis	HR (95% CI)	p-value in multivariate analysis
Treatment interval		0.037		
	2002-2006		Reference	
	2007-2011		1.01 (0.80 - 1.27)	0.926
	2012-2016		0.95 (0.70 - 1.30)	0.761
Gender		<0.001		
	Female		Reference	
	Male		1.35 (1.13 – 1.61)	<0.001
Smoking habits		0.045		
	Smoker		Reference	
	Ex-smoker		0.95 (0.79 – 1.15)	0.617
	Never-smoker		0.75 (0.53 – 1.05)	0.091
Tumor location, lobe		0.004		
	Main bronchus		Reference	
	Upper lobe		1.05 (0.73 – 1.49)	0.796
	Middle lobe		0.69 (0.39 – 1.22)	0.197
	Lower lobe		1.44 (1.00 – 2.08)	0.0501
Stage of cancer		<0.001		
	IA-IIB		Reference	
	IIIA		1.24 (0.96 – 1.60)	0.093
	IIIB		1.46 (1.14 – 1.87)	0.003
	IV		2.01 (1.36 – 2.97)	<0.001
ECOG Performance status		<0.001		
	0		Reference	
	1		1.36 (1.09 – 1.70)	0.007
	2		1.98 (1.45 – 2.70)	<0.001
	3-4		3.05 (0.93 – 9.94)	0.065
Age at start of treatment		0.91		
	Continuous variable		1.00 (0.99 – 1.01)	0.558
Total radiation dose		<0.001		
	54-63 Gy		Reference	
	64-66 Gy		1.01 (0.80 – 1.29)	0.911
	68-70 Gy		0.82 (0.62 – 1.07)	0.147
	>70 Gy		3.11 (1.21 – 8.02)	0.019

Figure 2.1, Overall survival among patients with locally advanced Non-Small Cell Lung Carcinoma depending on during which time interval patients received their treatment

Figure 2.2, Overall survival among patients with locally advanced Non-Small Cell Lung Carcinoma depending the gender of the patients
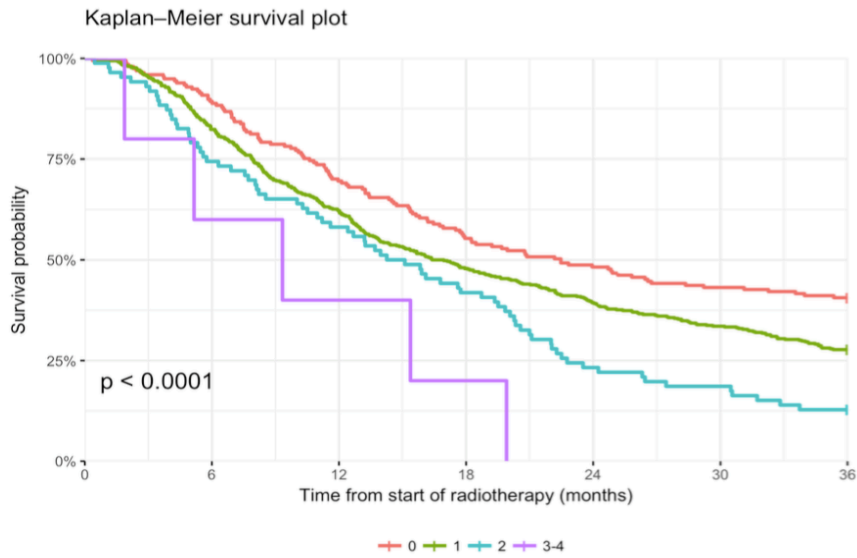
Figure 2.3, Overall survival among patients with locally advanced Non-Small Cell Lung Carcinoma depending on the ECOG performance status score of patients
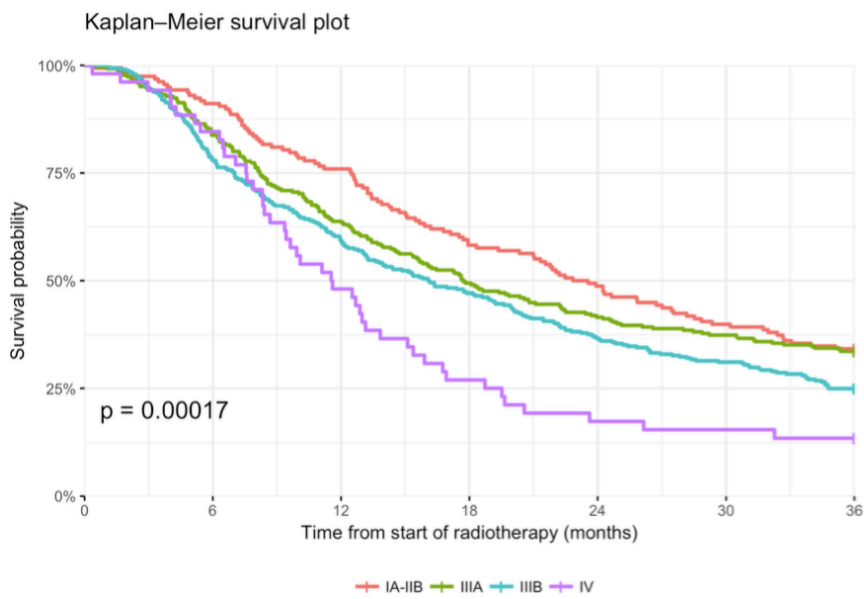

Figure 2.4, Overall survival among patients with locally advanced Non-Small Cell Lung Carcinoma depending on the stage of the cancer

Curative chemoradiotherapy for SCLC

Three-year survival in the SCLC chemoradiotherapy group was 28 %, 25 % and 20 % for 2002-2006, 2007-2011 and 2012-2016 respectively. Estimates of five-year survival was calculated to 18 % for 2002-2006 and 17 % for 2007-2011. There were no significant differences in survival between time intervals (Figure 3y SCLC-5y SCLC). Median survival was estimated to 18.5, 16.7 and 16.1 months for each treatment period. Details on the SCLC population is shown in Table 3a-b. The results of the Cox proportional hazard model are showed in Table 3c.

In the analysis of potential factors for survival, a borderline significant gender difference in favor of female sex was observed, with a HR of 1.37 for three-year survival (95 % CI 1.00 – 1.89, p=0.051). No significant gender difference was observed in five-year survival. A trend for inferior three- and five-year survival with regard to increased ECOG PS score was also observed, with significant differences between PS=0 vs. PS=1.

Age at the start of treatment was analyzed as a continuous variable. Age did not have an impact on five-year survival, but a significant result was noted in three-year survival (HR=1.02, 95 % CI 1.00 – 1.04, p=0.04).

There were no significant differences in survival with regard to time interval, laterality or lobar location of the tumor, stage of cancer or TNM-stage, smoking habits or radiation dose. However, a positive trend favoring 60 Gy over 45 was noted (see Fig. 3.5 in Appendix C).

Treatment interval, smoking habits, gender, ECOG PS, stage of cancer, lobar location of the tumor and radiation dose were considered important factors and were included in the model. TNM and side of the tumor were also analyzed but did not have an impact on survival and was not included in the model.

Table 3a: Demographics of the SCLC group

	2002-2006	2007-2011	2012-2016	Total
Median age (range)	65 (37-78)	67 (44-85)	67 (47-84)	-
	No. of patients (%)			
Patients treated with radiotherapy for SCLC	100	90	79	269
Gender				
Female	54 (54.0)	48 (53.3)	50 (63.3)	152 (56.5)
Male	46 (46.0)	42 (46.7)	29 36.7)	117 (43.5)
Smoking status				
Smokers	66 (66.0)	60 (66.7)	62 (78.5)	188 (69.9)
Ex-smokers	34 (34.0)	27 (30.0)	16 (20.3)	77 (28.6)
Non-smokers	0 (0.0)	3 (3.3)	0 (0.0)	3 (1.1)
Missing	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.4)
Diagnostic PET-CT				
No	100 (100.0)	82 (91.1)	49 (62.0)	231 (85.9)
Yes	0 (0.0%)	8 (8.9)	30 (38.0)	38 (14.1)
ECOG PS				
0	18 (18.0)	14 (15.6)	18 (22.8)	50 (18.6)
1	63 (63.0)	53 (58.9)	44 (55.7)	160 (59.5)
2	15 (15.0)	18 (20.0)	13 (16.5)	46 (17.1)
3-4	4 (4.0)	5 (5.6)	4 (5.1)	13 (4.8)
Total radiation dose				
45 Gy	42 (42.0)	46 (51.1)	50 (63.3)	138 (51.3)
60 Gy	57 (57.0)	44 (48.9)	28 (35.4)	129 (48.0)
Missing	1 (1.0)	0 (0.0)	1 (1.3)	2 (0.7)

Table 3b: Tumor information of SCLC patients

	2002-2006	2007-2011	2012-2016	Total
	No. of patients (%)			
Tumor location, side				
Right	60 (60.0)	51 (56.7)	55 (69.6)	166 (61.7)
Left	34 (34.0)	37 (41.1)	23 (29.1)	94 (34.9)
Missing	6 (6.0)	2 (2.2)	1 (1.3)	9 (3.3)
Tumor location, lobe				
Main bronchus	9 (9.0)	14 (15.6)	12 (15.2)	35 (13.0)
Upper lobe	52 (52.0)	43 (47.8)	37 (46.8)	132 (49.1)
Middle lobe	4 (4.0)	4 (4.4)	4 (5.1)	12 (4.5)
Lower lobe	20 (20.0)	16 (17.8)	16 (20.3)	52 (19.3)
Missing	15 (15.0)	13 (14.4)	10 (12.7)	38 (14.1)
Cancer stage				
IA-IIB	14 (14.0)	8 (8.9)	12 (15.2)	34 (12.6)
IIIA	22 (22.0)	17 (18.9)	17 (21.5)	56 (20.8)
IIIB	56 (56.0)	56 (62.2)	43 (54.4)	155 (57.6)
IV	8 (8.0)	9 (10.0)	6 (7.6)	23 (8.6)
Missing	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.4)

Table 3c: p-values and Hazard ratios for variables in the SCLC group

Variable	p-value in univariate analysis	HR (95% CI)	p-value in multivariate analysis
Treatment interval	0.495		
2002-2006		Reference	
2007-2011		0.97 (0.67 – 1.40)	0.852
2012-2016		1.25 (0.85 – 1.84)	0.255
Gender	<0.001		
Female		Reference	
Male		1.37 (1.00 – 1.89)	0.051
Smoking habits	0.353		
Smoker		Reference	
Ex-smoker		0.96 (0.68 – 1.37)	0.840
Never-smoker		0.00 (0.00 – Inf)	0.993
Tumor location, lobe	0.920		
Main bronchus		Reference	
Upper lobe		0.81 (0.51 – 1.28)	0.374
Middle lobe		0.81 (0.38 – 1.71)	0.573
Lower lobe		0.81 (0.47 – 1.38)	0.433
Stage of cancer	0.022		
IA-IIB		Reference	
IIIA		0.79 (0.46 – 1.36)	0.398
IIIB		0.86 (0.53 – 1.39)	0.541
IV		1.34 (0.69 – 2.61)	0.391
ECOG Performance status	0.058		
0		Reference	
1		1.91 (1.18 – 3.09)	0.008
2		1.76 (0.98 – 3.16)	0.060
3-4		1.98 (0.77 – 5.10)	0.156
Age at start of treatment	0.008		
Continuous variable		1.02 (1.00 – 1.04)	0.037
Total radiation dose	0.174		
45 Gy		Reference	
60 Gy		0.95 (0.67 – 1.34)	0.759

Figure 3.1, Overall survival among patients with Small Cell Lung Carcinoma depending on during which time interval patients received their therapy
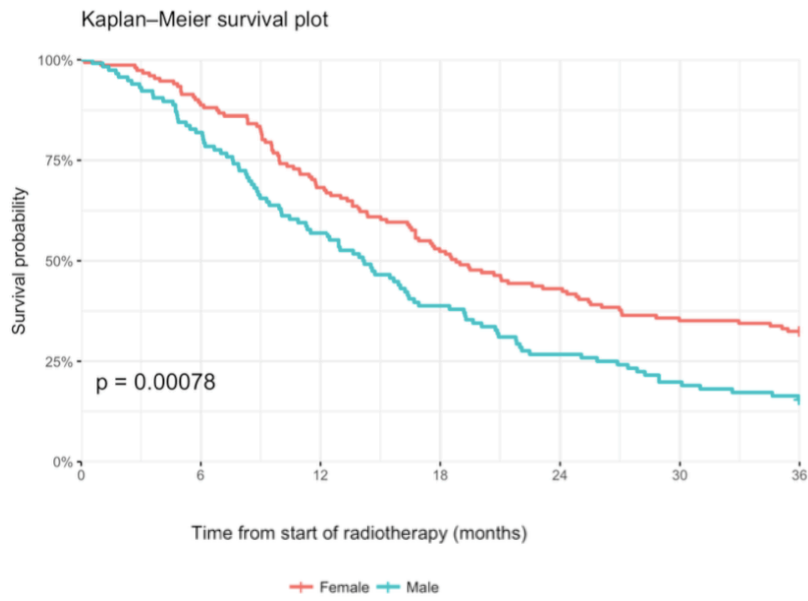
Figure 3.2, Overall survival among patients with Small Cell Lung Carcinoma depending on the gender of the patients
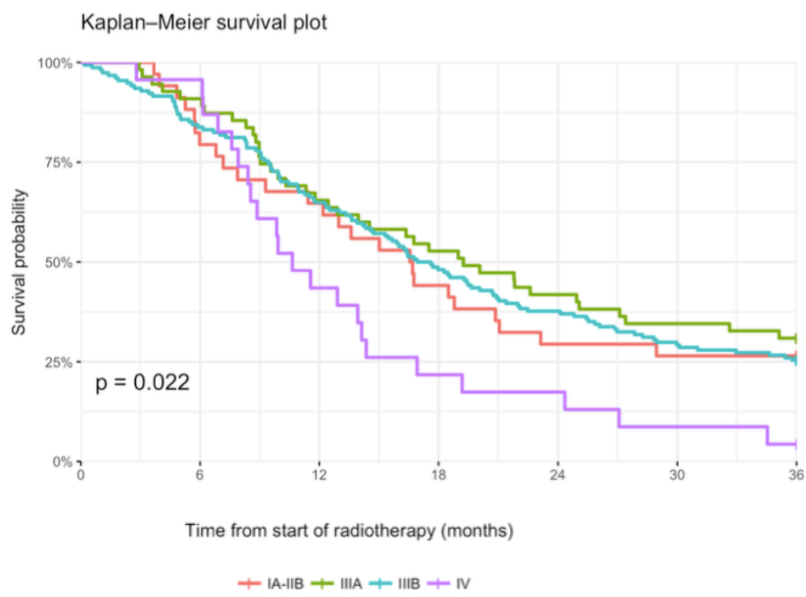
Figure 3.3 Overall survival among patients with Small Cell Lung Carcinoma depending the stage of the cancer

Discussion

This is one of the first studies that provides real life data on overall survival for lung cancer patients treated with modern radiotherapy with curative intent in Sweden. During the time period of the study (2002-2016) the patient number has increased with regards to SBRT, initially increased and then been rather stable for NSCLC treated with chemoradiotherapy, and slightly decreased with regard to SCLC. More than 3 times as many patients received SBRT in 2012-2016 compared to 2002-2006 (see Table 1a). There has been a gradual rise in popularity in SBRT lung cancer treatment after it was first described in 1995 by Blomgren et al. (47). One explanation for this is that more patients with comorbidities previously considered too severe to qualify for either surgery or conventional radiotherapy have in more recent years been referred to SBRT, and another explanation could be a more frequent use of CT of the thorax and implementation of PET/CT in diagnostic and staging procedures of lung cancer, that has led to the diagnosis of more T1 and T2 tumors than before – tumors that are potentially eligible for SBRT. The decreased number treated for SCLC probably reflects the overall declining incidence of SCLC (see Table 3a).

Regarding the overall survival rate for SBRT, the real-life data (47-55 % in three-year survival and 30 % for five-year survival) actually comes close to what is reported in prospective clinical trials. A few prospective trials including one randomized clinical trial on similar patient populations in Sweden treated with SBRT has been published previously. In the randomized SPACE-study from 2016 performed by Nyman et al., a 3-year overall survival of 54 % for SBRT patients was reported (30), while two prospective phase II trials estimated a three-year overall survival of 60 % and a five-year overall survival of 30 % respectively (33, 48). The same finding was observed for patients with locally advanced NSCLC. Hallqvist et al. and Nyman et al. have performed two clinical trials (published in 2011 and 2009 respectively) on locally advanced NSCLC patient populations in Sweden and

found three-year OS rates of 29 % and 31 % respectively (49, 50), compared to 24-35 % in this study. Generally, it is important not to be too hasty and presume that study results from clinical trials apply on everyday patients, since they often overestimate the effect in clinical reality due to the selection of the included patients. However, this study suggests that NSCLC patients in VGR actually have comparable survival rates to what is reported in these clinical trials, and the trend over time for patients treated with chemoradiotherapy is at least in the right direction.

With regard to the SCLC group, a more discouraging trend was observed in survival by treatment interval, albeit not statistically significant. Data suggests that the survival rate for SCLC patients may have declined in recent years (see Fig. 3.1), despite the presumed improvements in staging and radiation techniques. Furthermore, OS appears to be lower than data from contemporary prospective trials. A Norwegian trial published in 2016 reported a five-year survival of 25 % for SCLC patients treated with chemoradiotherapy, and patients treated with 45 Gy in 30 twice daily fractions had a median OS of 25.1 months (51, 52). Moreover, a 22 % five-year survival for limited disease SCLC was reported by Shild et al. in a randomized clinical phase II trial in 2004, while Chen et al. reported a median OS of 24 months in their clinical trial from 2005 (53, 54). Survival rates in VGR are markedly lower according to our study - five-year survival is only 16.7-18.2 % and the median OS 16.1-18.5 months. The inferior results could be due to selection bias in the prospective trials, but the downward trend need further scrutinizing. Does dose matter (see below)? Or could choice of concurrent chemotherapy impact on the results? All SCLC patients in the previously mentioned studies with superior outcomes were treated with cisplatin-based chemotherapy regimens (51-54). However, carboplatin is widely used instead of cisplatin as it is much easier to administrate, and it is nowadays used in the standard therapy in VGR (55). Some efforts have been made to evaluate if there is a difference in efficacy between carboplatin and

cisplatin but no significant difference has been found in SCLC. There are, however, only very few randomized clinical trials comparing the two and they are all conducted on small populations in which a majority of patients had stage IV disease (56-59). The results from these studies are therefore not necessarily applicable to SCLC patients with limited disease receiving radiotherapy, and one could speculate whether cisplatin is in fact more effective than carboplatin in treating stage I-III SCLC. Most international guidelines argue for the use of cisplatin in chemoradiotherapy of SCLC with curative intent, referring to the lack of comparative phase III data on carboplatin vs cisplatin and the extensive amount of data on the effectiveness of cisplatin as e.g. stated by Woolf et al. and Stinchcombe et al. (60, 61). Taking all this into account, it is possible that the gradual transition to more carboplatin-based chemoradiotherapy regimens in VGR could have contributed to the impaired outcome of stage I-III SCLC patients in recent years.

One of the objectives of this report was to evaluate the impact of total radiation dose on survival and to compare the outcome from currently recommended doses to previous recommendations. In the SBRT group, the 45 Gy is the current standard SBRT dose and the other regimens of 40 Gy (4 x 10 Gy) and 56 Gy (7 x 8 Gy) are two variants of risk-adapted SBRT for tumors in high-risk locations that results in a lower biological effective dose (BED) than 45 Gy in 3 fractions (16, 55). Therefore, one could hypothesize those regimens to have inferior treatment results compared to the more potent dose 15 x 3 Gy. In this data set, however, the 45 Gy group performed only numerically better – there were no significant difference in survival between regimens. It could be that the lower doses are enough – 7 Gy x 8 is still a potentially curative dose, but it could also be due to small group sizes: 26 patients received 40 Gy while only 12 received 56 Gy, compared to 306 patients with 45 Gy. No significant differences in OS with regard to radiation dose could be observed for locally advanced NSCLC patients treated with chemoradiotherapy either. The different dose levels in

this group (54-63 Gy, 64-66 Gy, 68-70 Gy) are biologically rather similar, so it would probably take a very large patient population to detect any possible difference in treatment outcome. However, a reassuring trend was observed favoring the currently recommended 68-70 Gy compared to the other doses (see Figure 2.6 in Appendix C), indicating that the current clinical practice for treatment of locally advanced NSCLC probably is a step in the right direction. In the SCLC group, hyperfractionated radiotherapy of either 45 Gy or 60 Gy were used (1.5 Gy twice daily for 30-40 days). 45 Gy in this setting is biologically a lower dose than 60 Gy, and the recommendation in VGR is to use 45 Gy in patients with poor lung function and/or other severe comorbidities (55). Despite this potentially negative selection, only a statistically not significant tendency for improved survival with 60 Gy was observed. Maybe small group sizes could explain why the more potent dose did not result in significantly superior survival, but when taking the radiosensitivity of SCLC tumors into account it is possible that 45 Gy is a high enough radiation dose. On the other hand, the use of the 60 Gy schedule has decreased compared to the 45 Gy schedule in recent years, coinciding in time with the period of decreased survival. A Norwegian trial comparing 45 Gy vs 60 Gy in SCLC (in which Sahlgrenska University Hospital participated) has just finished, and it will be interesting to see how our results compare to theirs when they are published.

PET/CT significantly improved survival in the univariate analysis with regard to patients treated with SBRT, but not in the multivariate analysis. Patients that are suited for SBRT generally have other severe comorbidities that make them unfit for surgery, and most deaths in the SBRT group are presumably from other causes than lung cancer, as this has been the case in similar studies on SBRT populations (33). Impact on lung cancer survival from technical advances like PET/CT could therefore be difficult to illustrate in this kind of population with relatively frail patients. It would therefore be interesting to investigate the impact of PET/CT on early stage NSCLC patients *eligible* for surgery, since it would

neutralize this particular problem with SBRT cohorts. Somewhat surprisingly, no significant effect was observed due to PET/CT in NSCLC patients treated with chemoradiotherapy either. However, since data on use of PET/CT was only available from 2007, a separate analysis taking only the two latter treatment periods into account were performed to more accurately estimate the impact PET/CT had on survival. A negative aspect of analyzing PET/CT in this way is that it resulted in a much smaller amount of data with too many different variables in the analysis, thus making the results unreliable.

There was a gender difference in survival in favor of women in the SBRT group as well as for the patients with locally advanced NSCLC. A borderline significant difference in 3-year survival for the SCLC chemoradiotherapy group (HR=1.4, 95 % CI 1.00 – 1.89, p=0.051) was also observed. These results are not surprising since there is consistent evidence from previous research that female sex predicts better survival in lung cancer, especially in NSCLC (62, 63). Concerning gender, it is also noteworthy that the growing proportion of women in the SCLC population over time should be associated to an increase in survival rather than the decrease seen in this study.

Age of the patient was not shown to have an impact on survival in either of the SBRT or locally advanced NSCLC groups. This finding is in line with several previously published studies that has concluded that advanced age alone does not cause a poorer survival (64, 65). The results emphasize that assessment before therapy should be focused on comorbidities and performance status of the patient rather than age as a growing risk due to increased ECOG PS score was observed throughout all treatment groups. Patients should therefore not be denied effective curative radiotherapy solely because of old age, and our results highlights the importance of consistent performance status assessments of lung cancer patients before a treatment strategy is decided upon. Regarding the SCLC group, age seemed to significantly affect survival. The increased risk regarding old age was estimated to a HR=1.02, which

translates to a substantial annual increase in risk for a patient. This result is somewhat surprising, as the impact of old age is usually diminished when considered together with performance status (30, 49). However, age was analyzed as a continuous variable and not by age-groups in this study, which may have affected the result. This divergent result needs to be evaluated further, and our intention is to re-analyze age divided into age-groups and then see if a significant difference regarding age still remains.

The prognostic value of the site of the tumor was also assessed. The results suggest that survival in NSCLC is affected by the lobar location – the lower lobe was associated with an inferior survival in both the locally advanced NSCLC group and the SBRT group. Lobar location of lung cancer and its impact on survival is a controversial subject. In the field of thoracic surgery, lung tumors located in the left lower lobe are traditionally considered to predict an increased mortality (66-68), a notion that is in line with our findings. As the amount of literature describing survival based upon lobar location is scarce in the context of radiotherapy, further investigation of this concept is of interest.

As expected, stage significantly impacts on survival, and in NSCLC patients treated with chemoradiotherapy, it was also evident in stage in stage IIIA to IIIB. A trend was observed between T1 and T2 tumors treated with SBRT but for patients with SCLC the outcome for patients without distant spread was similar.

Methodological considerations

This study is one of the first retrospective studies that provides real-life data on lung cancer patients in VGR, which is an advantage in itself. A major strength is that it is a comprehensive population-based study including all lung cancer patients in VGR that have received radiotherapy between 2002-2016, rather than a selected cohort, thus minimizing the risk for selection bias.

There are, however, several shortcomings in this study. One of them is that we did not include patient data on weight loss (since no such data was recorded in the quality registers we used), which is a very important independent prognostic factor (69-71). Major weight loss in lung cancer patients before the start of treatment results in substantially worse outcome. It is possible that there were imbalances in distribution of weight loss between the patient cohorts, consequently affecting the results unbeknownst to us.

One of the problems with performing a retrospective cohort study is that one has to rely on others for correct recordkeeping. This should not have been a major problem in this study, since we mainly used solid data recorded in quality registers (assuming data have been accurately documented in the quality registers). However, there were 159 patients in our material that were missing in the quality registers, and for whom we had to go through medical journals and interpret recorded information on variables such as performance status, smoking habits and TNM-stage. As this information was not always straightforwardly documented in the medical records, there is a possible risk that we have misinterpreted some of the data for these patients.

Chemoradiotherapy regimens in lung cancer usually starts with a cycle of chemotherapy before the radiotherapy is started. On rare occasions, cancer patients suffer fatal infections during chemotherapy before their radiotherapy is finished or even started. A limitation with this study is that no such cases are taken into account, since only patients that completed their entire chemoradiotherapy schedule were included.

Regarding the PET/CT analyses, we chose to exclude all patients treated in the earliest time interval (2002-2006), as PET/CT was implemented in clinical practice in 2010. PET/CT was then analyzed together with the other variables in separate multivariate models. However, this resulted in a much smaller amount of data and there are uncertainties in the multivariate models regarding the PET/CT analyses, especially since there are so many variables included

in the model. This is an important limitation of this study, since one of our main objectives

was to evaluate the impact that use of PET/CT for staging and diagnostics has had on the

outcome for lung cancer patients.

Conclusion

This study suggests that overall survival for NSCLC patients in VGR treated with SBRT or chemoradiotherapy is equal to what has been reported in clinical trials previously. No significant differences in survival over time was observed for either of the three groups but a trend for improved survival was seen in the locally advanced NSCLC group, albeit not statistically significant. In contrast, SCLC patients in VGR seem to have slightly inferior survival rates compared to corresponding studies, and there is also a trend for declining survival in more recent years, which warrants further investigation.

Female sex had a protective impact on survival for both NSCLC and SCLC patients. Our results also indicate that it is more important to consider a poor performance status rather than old age before deciding on potentially curative treatments for NSCLC patients.

Tumors located in the lower lobe were associated with an inferior survival in NSCLC patients. The reason for this association is unknown and needs to be further studied.

Acknowledgements

Populärvetenskaplig sammanfattning

Utvärdering av behandlingsresultat för lungcancerpatienter i Västra Götalandsregionen som fått strålbehandling i botande syfte

Lungcancer är en av världens vanligaste cancersjukdomar och samtidigt den cancer som dödar flest människor årligen. Huvudsakligen delas lungcancer in i två undergrupper med olika karakteristika och som kräver olika behandlingsstrategier: Småcellig lungcancer (SCLC) och icke-småcellig lungcancer (NSCLC). Kirurgi, strålbehandling och cellgifter är de främsta potentiellt botande behandlingsmetoderna mot lungcancer. Strålbehandling, även kallat radioterapi eller radiokemoterapi när det kombineras med cellgifter, ges årligen till över hundra lungcancerpatienter i Västra Götalandsregionen (VGR), men hur behandlingsresultaten ser ut i praktiken är ännu inte utvärderat. Det här projektets syfte var därför att utvärdera överlevnaden bland lungcancerpatienter som har strålbehandlats i VGR mellan år 2002 och 2016. I studien undersöktes ett antal olika faktorer som förmodas kunna ha en inverkan på överlevnaden, t ex kön, ålder, hälsotillstånd, rökning, total stråldos, tidsperiod för behandling eller användning av nya tekniker såsom PET/CT.

För att besvara vår frågeställning utförde vi en retrospektiv studie, dvs en studie där vi tittade tillbaka på hur det gått för lungcancerpatienter som behandlats med strålterapi i VGR mellan år 2002 och 2016. Totalt räknades 1421 lungcancerpatienter med i studien och information om dem, deras lungcancer och strålbehandlingen hämtades från patientjournaler och olika cancerregister. Patienter delades in i tre olika huvudgrupper: strålbehandling för lokalt begränsad NSCLC, radiokemoterapi för lokalt spridd NSCLC och radiokemoterapi för SCLC. Överlevnaden samt hur denna påverkades av de olika faktorerna analyserades sedan inom varje grupp.

I våra statistiska analyser kunde vi till att börja med se att överlevnaden i princip hållit sig oförändrad över tid för de olika patientgrupperna trots de tekniska framsteg som gjorts inom

strålbehandling och diagnostik på senare år. I gruppen med lokalt avancerad NSCLC kunde möjligen en tendens till förbättring ses för senare år, men detta fynd var osäkert. Vi kunde också se att överlevnaden för NSCLC-patienter i vår studie var jämförbar med överlevnaden som rapporterats i tidigare liknande studier. Patienter med SCLC uppvisade dock en klart sämre överlevnad än vad som tidigare rapporterats, dessutom med en tendens till en allt sämre överlevnad på senare år. Orsaken till varför det ser ut så här är okänd och behöver utredas vidare.

När det gäller de olika faktorerna med potentiell påverkan på överlevnaden så kunde vi se att manligt kön och ett dåligt hälsotillstånd vid behandlingsstarten medförde en sämre överlevnad vid strålbehandling för lungcancer. För patienter med NSCLC spelade det inte någon roll hur gammal patienten var vid behandlingsstarten – gamla patienter gynnades lika mycket av botande strålterapi som unga. För patienter med SCLC verkade det däremot som att en hög ålder medförde en sämre överlevnad, vilket talar för att botande strålterapi kan vara för farligt för de äldsta patienterna med SCLC oavsett hur bra deras hälsotillstånd är. Våra resultat visar också att NSCLC-tumörer som sitter i lungans underlob är farligare än tumörer belägna på andra ställen i lungan. Orsaken till detta samband är inte heller känt utan behöver utredas vidare.

Appendices

Appendix A: Graphs and tables of the supplementary multivariate PET/CT analysis for the SBRT group

Figure 1.6, Three-year survival for SBRT patients by smoking habits

Figure 1.7, Three-year survival for SBRT patients by total SBRT dose

Table 1d: p-values and Hazard ratio of the supplementary PET/CT analysis for the SBRT group

Variable	p-value in univariate analysis	HR (95% CI)	p-value in multivariate analysis
Treatment interval	0.23		
2007-2011		Ref.	
2012-2016		0.87 (0.60 – 1.26)	0.46
Gender	0.003		
Female		Ref.	
Male		1.59 (1.11 – 2.27)	0.01
Smoking habits	0.71		
Smoker		Ref.	
Ex-smoker		0.82 (0.57 – 1.18)	0.28
Never-smoker		0.62 (0.32 – 1.22)	0.17
Tumor location, lobe	0.02		
Upper lobe		Ref.	
Middle lobe		0.95 (0.38 – 2.40)	0.92
Lower lobe		1.52 (1.07 – 2.16)	0.02
Use of PET/CT	0.03		
No		Ref.	
Yes		0.78 (0.48 – 1.27)	0.32
ECOG Performance status	0.003		
0		Ref.	
1		1.51 (0.81 – 2.81)	0.20
2		1.87 (0.98 – 3.58)	0.06
3-4		5.22 (2.16 – 12.58)	<0.001
T-stage	0.005		
T1	(<0.01?)	Ref.	
T2		1.46 (1.01 – 2.10)	0.04
Age at start of treatment	0.20		
Continuous variable		1.02 (0.99 – 1.04)	0.20
Total radiation dose	0.23		
40 Gy		Ref.	
45 Gy		0.71 (0.41 – 1.22)	0.22
56 Gy		0.91 (0.34 – 2.45)	0.85

Appendix B: Graphs and tables of the supplementary multivariate PET/CT analysis for the locally advanced NSCLC group

Table 2d: p-values and Hazard ratios of the supplementary PET/CT analysis for the locally advanced NSCLC group

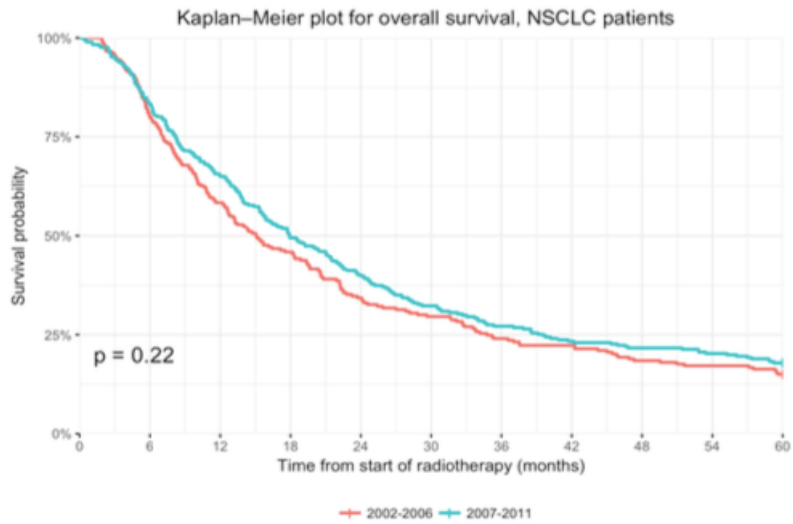| Variable	p-value in univariate analysis	HR (95% CI)	p-value in multivariate analysis
Treatment interval	0.15		
2007-2011		Ref.	
2012-2016		0.98 (0.73 – 1.32)	0.91
Gender	0.002		
Female		Ref.	
Male		1.44 (1.16 – 1.78)	<0.001
Smoking habits	0.09		
Smoker		Ref.	
Ex-smoker		0.96 (0.77 – 1.20)	0.74
Never-smoker		0.78 (0.51 – 1.18)	0.24
Tumor location, lobe	0.002		
Main bronchus		Ref.	
Upper lobe		1.13 (0.70 – 1.84)	0.61
Middle lobe		0.43 (0.19 – 0.99)	0.048
Lower lobe		1.49 (0.91 – 2.44)	0.11
Use of PET/CT	0.07		
No		Ref.	
Yes		0.91 (0.69 – 1.21)	0.53
Stage of cancer	0.005		
IA-IIB		Ref.	
IIIA		1.32 (0.97 – 1.79)	0.08
IIIB		1.52 (1.12 – 2.08)	0.01
IV		2.32 (1.43 – 3.76)	<0001
ECOG Performance status	<0.001		
0		Ref.	
1		1.50 (1.15 – 1.96)	0.003
2		1.86 (1.27 – 2.74)	0.001
3-4		1.29 (0.16 – 10.05)	0.81
Age at start of treatment	0.053		
Continuous variable		1.01 (1.00 – 1.02)	0.08
Total radiation dose	0.002		
54-63 Gy		Ref.	
64-66 Gy		0.99 (0.71 – 1.40)	0.97
68-70 Gy		0.82 (0.60 – 1.11)	0.20
>70 Gy		3.35 (1.28 – 8.77)	0.01

Figure 2.5, Five-year survival by time interval for locally advanced NSCLC patients
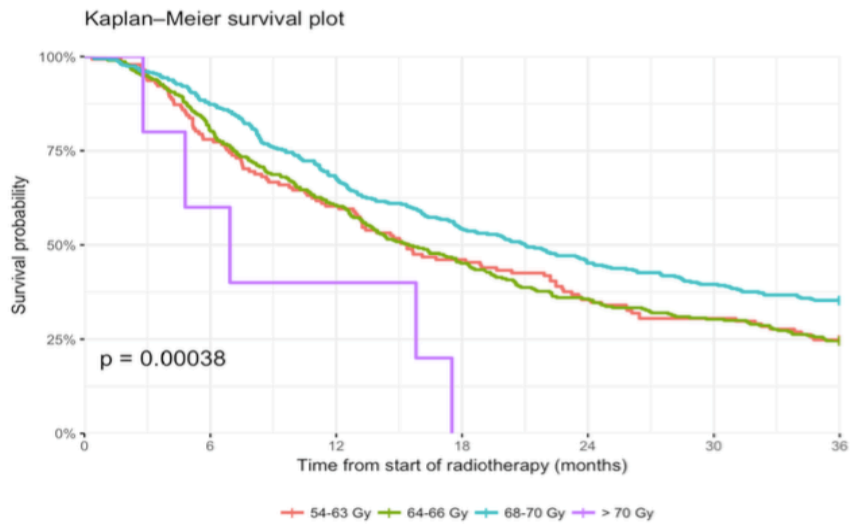

Figure 2.6, Three-year survival by total radiotherapy dose for locally advanced NSCLC patients

Figure 2.7, Three-year survival by smoking habits for locally advanced NSCLC patients

Appendix C: Graphs and tables of the supplementary multivariate PET/CT analysis for the SCLC group

Table 3d: p-values and Hazard ratios of the supplementary PET/CT analysis for the SCLC group

| Variable	p-value in univariate analysis	HR (95% CI)	p-value in multivariate analysis
Treatment interval	0.42		
2007-2011		Ref.	
2012-2016		1.28 (0.85 – 1.94)	0.24
Gender	0.08		
Female		Ref.	
Male		1.28 (0.85 – 1.91)	0.23
Smoking habits	0.35		
Smoker		Ref.	
Ex-smoker		0.77 (0.49 – 1.23)	0.28
Never-smoker		0.00 (0.00 – inf.)	0.99
Tumor location, lobe	0.95		
Main bronchus		Ref.	
Upper lobe		0.88 (0.50 – 1.55)	0.66
Middle lobe		0.78 (0.29 – 2.08)	0.62
Lower lobe		0.92 (0.47 – 1.79)	0.80
Use of PET/CT	0.71		
No		Ref.	
Yes		0.83 (0.49 – 1.40)	0.48
Stage of cancer	0.054		
IA-IIB		Ref.	
IIIA		0.49 (0.24 – 0.99)	0.046
IIIB		0.53 (0.28 – 1.00)	0.051
IV		0.92 (0.38 – 2.21)	0.85
ECOG Performance status	0.48		
0		Ref.	
1		1.68 (0.94 – 2.98)	0.08
2		1.53 (0.75 – 3.13)	0.24
3-4		1.43 (0.43 – 4.68)	0.56
Age at start of treatment	0.003		
Continuous variable		1.04 (1.01 – 1.06	0.003
Total radiation dose	0.20		
45 Gy		Ref.	
60 Gy		0.91 (0.58 – 1.43)	0.68
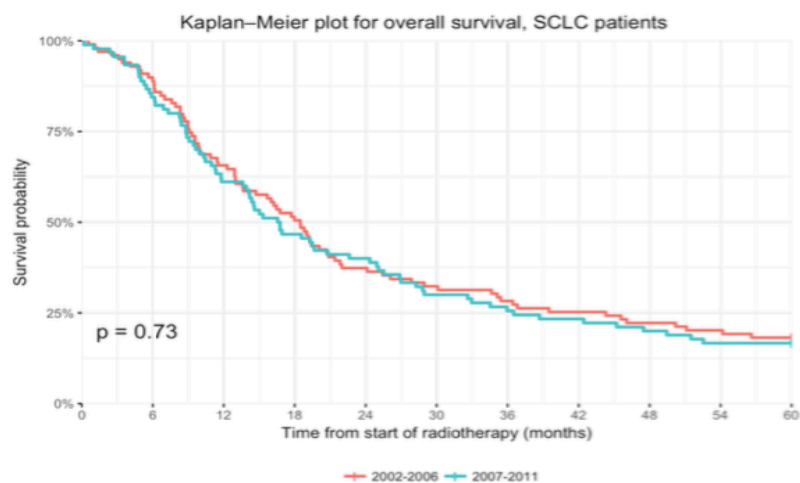
Figure 3.4, Five-year survival by time interval for SCLC patients

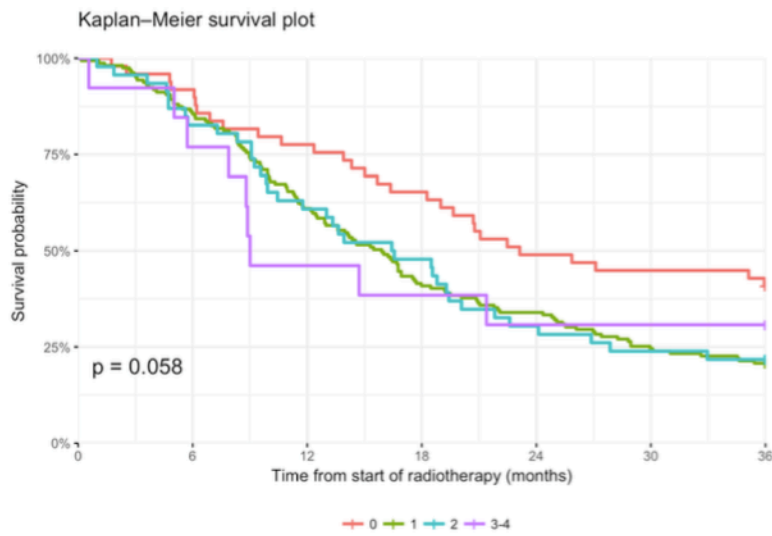*Figure 3.5, Three-year survival by total radiation dose for SCLC patients*

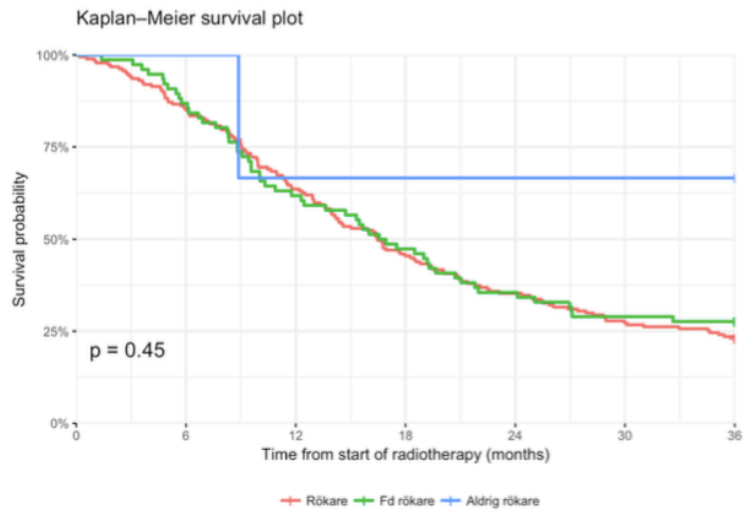*Figure 3.6, Three-year survival by ECOG performance status for SCLC patients*

Figure 3.7, Three-year survival by smoking habits for SCLC patients
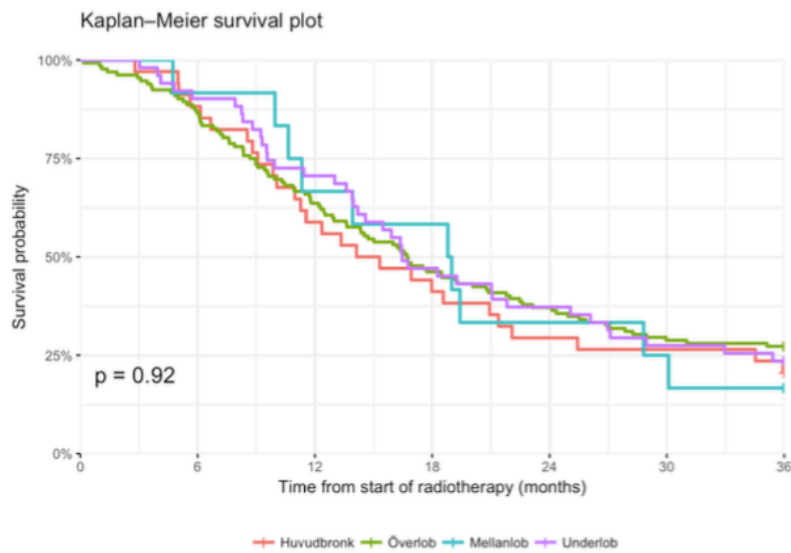

Figure 3.8, Three-year survival by lobar location for SCLC patients

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