Chapter 1

Introduction and outline of the thesis

Lung cancer: Introduction

Despite growing public awareness of the correlation between smoking and lung cancer, attempts to influence public health (including by legislation) faces considerable challenges in the Netherlands. Globally, the lung cancer epidemic continues to be a major source of concern, with a worldwide incidence of 1.6 million cases in 2008 [1]. In addition, a 52% increase in incidence of lung cancer is expected between 2010 and 2030 in the USA, mainly caused by an increase of older adults and minorities [2]. In the Netherlands, more than 10,000 lung cancer cases were diagnosed in 2010, representing an increase in incidence of 28% compared to the start of the 21th century, with a further increase expected because of the 'babyboom generation' after World War II, as the latter are now reaching the age where lung cancer most commonly manifests (median age of 70 for males and 64 for females [3]). In addition, Dutch statistics also reflect previous trends in smoking, with an 80% increase of lung cancer in women between 2000 and 2010.

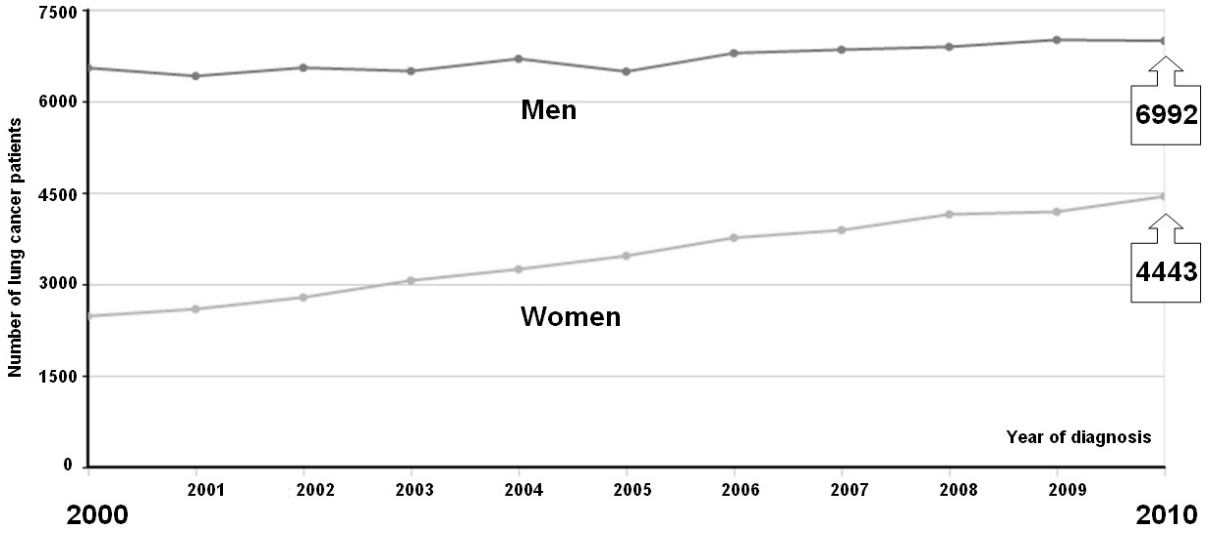

Figure 1. Incidence of lung cancer in the Netherlands between 2000 and 2010 according to gender (derived from www.iknl.nl, http://www.cijfersoverkanker.nl, accessed on 1-9-2012).

Between 6 to 18% of all lung cancer patients are alive at 5 years after diagnosis, a figure which varies between countries [4]. Treatment still remains a big challenge, not only because most lung cancer patients suffer from other comorbid diseases, but also because the majority of patients already present in an (locally-) advanced stage of disease.

For practical purposes, lung cancer used to be divided into two main types: non-small-cell and small-cell. About 80 to 89% of lung cancer patients are diagnosed with the non-small-cell type [5]. This thesis reports on studies in locally-advanced stage non-small-cell lung cancer (NSCLC) patients, representing a very heterogeneous subgroup in which the primary tumor has invaded other structures than the involved lung and/or cancer cells have spread to the mediastinal lymph nodes. Primary radical surgery or (stereotactic) radiotherapy is not an option for the overwhelming majority of these patients. Therefore, combinations of chemotherapy, radiotherapy and surgery are applied to achieve maximum loco-regional as well as distant disease control. These combinations are called “combined modality treatment”.

Diagnosis and staging of (locally-advanced) NSCLC

About one third of patients presenting with NSCLC have locally-advanced disease, also known as stage III [3]. New and improved imaging techniques have led to more accurate diagnosing and staging of lung cancer. Next to computed tomography (CT) and magnetic resonance imaging (MRI), the introduction of fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) has made an important contribution in determining whether cancer cells have spread to lymph nodes or other organs. However, pathological proof of lung cancer and involvement of suspected lymph nodes or metastases in other organs are necessary for staging and subsequent treatment purposes. Lymph node biopsy by means of cervical or parasternal mediastinoscopy is currently the standard, but less invasive, outpatient procedures to obtain pathological proof are increasingly used, for example transbronchial needle aspiration (TBNA) with or without using endobronchial ultrasound (EBUS) guiding, and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), which passes through the esophagus to reach lymph node areas.

These staging methods lead to a diagnosis in which the primary tumor (T), regional lymph node status (N) and distant metastasis (M) are characterized. In 2009, the staging system for lung cancer has been adapted. The most important changes concerning stage III

NSCLC are: 1) Pleural effusion is considered in the new staging system (7^{th}) as stage IV disease in contrast to stage IIIB in the old staging system (6^{th}). 2) Multiple tumor lesions in the same lung lobe was considered stage IIIB disease in the old system (T4), where it is now staged as T3, stage IIB when no lymph node involvement is present. 3) Additional tumor lesions in another lung lobe but in the ipsilateral lung used to be staged as stage IV disease, but is now considered stage IIIB. For all studies in this thesis the old staging system (6^{th}) was used because treatment decisions were still based on this classification.

Evolution of combined modality treatment

From a historical perspective, stage III unresectable lung cancer has been treated with radiotherapy only until the 1990s, leading to a median survival of 10-11 months and 3-year survival of <10% when radical doses were administered (≥60 Gy) [6].

The value of chemotherapy was established in 1995, when the non-small-cell lung cancer collaborative group published a meta-analysis of all randomized clinical trials in NSCLC performed between 1965-1991, showing that treatment with chemotherapy, using mainly cisplatin-based regimens leads to an absolute survival benefit of 10% at 1 year compared to best supportive care and an absolute survival benefit of 4% and 2% at respectively 2 and 5 years when combined with radical radiotherapy [7].

In 2004, guidelines by the American Society of Clinical Oncology (ASCO) stated that chemoradiotherapy for unresectable stage III NSCLC with a good performance status (PS) (Eastern Cooperative Oncology Group) 0-2 should consist of two to four cycles of platinum-based chemotherapy and no more than 60 Gy of radiotherapy in once-daily fractions of 1.8 to 2.0 Gy [8]. With the recognition of the need to optimize both local and systemic therapies for locally-advanced NSCLC, use of chemoradiotherapy became established as the standard of care for this disease.

However, many questions surrounding optimal chemoradiotherapy remain unresolved, and the overall survival gains are relatively modest. In 2010, a meta-analysis found the outcome of concurrent chemoradiotherapy (CCRT) superior when compared to sequential chemoradiotherapy. The former results in an absolute survival benefit of 5.7% and 4.5% at respectively 3 and 5 years. Median overall survival for CCRT was approximately 18 months, and the benefit of CCRT was only due to improved loco-regional control, while rate of distant failure was comparable to sequential treatment [9].

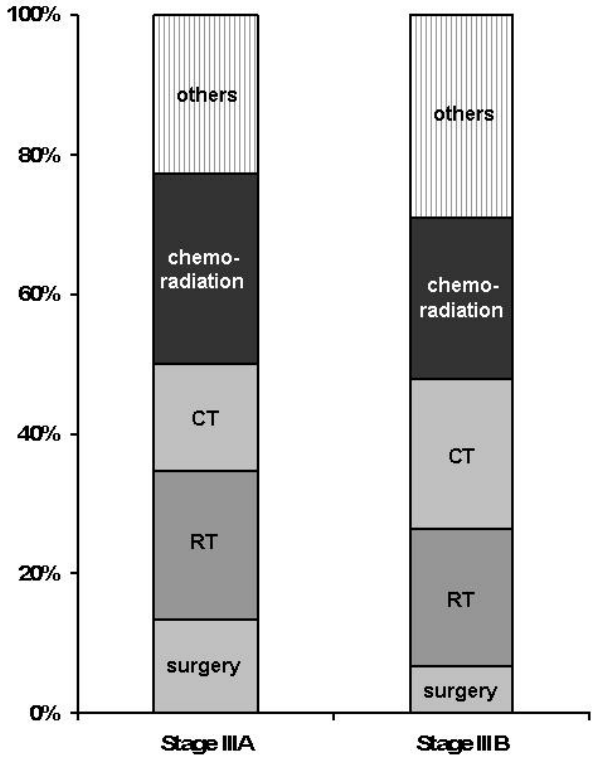

Figure 2. Treatment (combinations) used for stage III NSCLC patients in Dutch hospitals in the time period from 2001 to 2006 (derived from [10]). CT, chemotherapy; RT, radiotherapy.

Radiotherapy

High dose radiotherapy has long been the mainstay in the treatment of stage III NSCLC. In recent years, rapid progress in planning and treatment delivery has been made [11]. For example, four-dimensional (4D) treatment techniques have become standard due to image-guiding with 4D-CT-scans. By taking tumor motion into account, respiration-gated delivery can be used to limit radiation fields. The present policy of irradiating only tumor-bearing nodes in stage III NSCLC, the so-called involved-field technique, reduces field sizes without compromising local control rates [12]. Improvements in daily imaging at the treatment unit allow for use of smaller 'safety margins', with the ability to further reduce normal tissue irradiation. Routine use of dosimetric contraints such as the V_{20} (percentage of normal lung tissue receiving a dose ≥20 Gy), V_5 (percentage of normal lung tissue receiving a dose ≥5 Gy) and mean lung dose can allow for reduction in radiation pneumonitis [13].

Chemotherapy

At present, the optimal chemotherapy regimen/doublet to be used in combination with concurrent thoracic radiotherapy is unclear. As the rate of distant metastases after 3 years is reported to be as high as 40% in stage III NSCLC patients initially treated with CCRT [9], there is a clear need for more effective systemic treatments to tackle distant tumor cells which are not detected by present staging techniques. Cisplatin-based chemotherapy combinations have been shown effective in this so-called micrometastatic disease, and cisplatin is also known to have a radiosensitizing effect [14], enhancing the (loco-regional) effect of radiotherapy, in contrast to carboplatin [15, 16].

Surgery

Two large phase III trials have been published on surgery after induction treatment in stage III NSCLC. The European Organisation for Research and Treatment of Cancer (EORTC) 08941 trial applied chemotherapy before radiotherapy (arm 1) or surgery (arm 2) [17]. The North American Intergroup 0139 trial randomized between CCRT alone (arm 1) or CCRT followed by surgery (arm 2) [18]. In both trials, a survival benefit for the surgical arm could not be confirmed. Although surgery is not recommended in stage III NSCLC, consideration can be given to maximum local control by means of resection after induction treatment, while loco-regional progression with CCRT alone can be expected in 28% of stage III NSCLC patients after 3 years [9]. However, only those patients with technically/medically operable disease and pathologically proven ‘downstaging’ of mediastinal lymph nodes after induction treatment are eligible for resection, preferable by lobectomy [18].

Outline of the thesis

Although concurrent chemoradiotherapy (CCRT) has evolved to become the standard treatment strategy for stage III (locally-advanced) NSCLC patients during the time period of studies reported in this thesis (2001 to 2010), many treatment-related issues still remain unsolved. This thesis describes outcomes from different combined modality strategies used in stage III NSCLC patients at the VU University Medical Center, and addresses important treatment issues in order to provide a better insight in treatment toxicity and patient selection. In **Chapter 2**, the efficacy of using induction chemotherapy schemes was investigated in a multicenter phase II trial performed between 2001 and 2004. As was common in that period, patients showing either a response or stable disease to induction cisplatin-epirubicin, underwent thoracotomy, with the remainder proceeding to radiotherapy. **Chapter 3** describes work evaluating a trimodality treatment strategy consisting of CCRT followed by surgical resection. The main focus of this work was to limit delays between completion of induction treatment and restaging/surgery or continuing radiotherapy to a radical dose, in order to limit the adverse effect of treatment splits. Most patients with locally-advanced NSCLC are treated outside clinical trials and outcomes of CCRT as definitive treatment strategy in a cohort of 89 patients are described in **Chapter 4**. The main goal of this work was to provide more insight on characteristics and outcomes of patients from a general population, in contrast to clinical trials in which patients are selected on basis of strict inclusion criteria. CCRT is often associated with nausea, vomiting, diarrhea, anorexia, and esophagitis, causing malnourishment which may adversely influence treatment outcomes. **Chapter 5** describes a study of nutritional parameters in patients who underwent surgical resection after CCRT. A commonly reported and potentially lethal treatment-related toxicity after CCRT is radiation pneumonitis. Prediction and scoring of radiation pneumonitis is difficult and subjective, therefore we evaluated a new method in **Chapter 6** to quantitatively measure density changes on serial CT-scans of 25 eligible patients derived from the study cohort of Chapter 4. Finally, the incidence of primary tumor cavitations at diagnosis and complications of this phenomenon during or after CCRT was studied in a patient cohort treated at our hospital from 2003 to 2010 in **Chapter 7**.

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