Chapter 1

Introduction
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After heart disease, cancer is the leading cause of death in Europe. Of all cancers, lung cancer has the highest incidence of cancer related deaths worldwide. In the Netherlands, a total of 11,889 new cases of lung cancer were diagnosed in 2012, and an almost equal number of patients, 10,322, died that year as a consequence of this disease. In men there is a trend towards a decrease in mortality from lung cancer while in women, it is increasing and predicted to increase even further (Figure 1).

The poor prognosis of lung cancer is reflected in an overall 5-year survival rate of approximately 13 to 16%. This finding can partly be explained by the fact that 65% of all new patients are diagnosed with locally advanced or metastatic disease, which is less amenable to cure. In addition, patients with lung cancer are increasingly older, and frequently have several comorbidities, often smoking-related.

In recent decades, both the diagnostic procedures and therapies used for lung cancer have evolved. Examples of improved diagnostic techniques include higher resolution CT-scanning techniques for the thorax, FDG-PET/CT-scans...
and endobronchial and esophageal ultrasound-guided aspiration, all of which allow for more accurate, minimally invasive staging of patients. Evolving therapeutic options and scenarios are discussed in more detail below.

Evolving in therapeutic options and scenarios

For early stage lung cancer, the standard therapy in fit patients has been surgery, with post-operative mortality rates decreasing in the last decade. This is partly due to better patient selection and improved post-operative care. However, not all patients are candidates for surgery due to comorbidity, and some patients elect not to have an operation. For such patients, the introduction of stereotactic ablative radiotherapy (SABR) has led to a good alternative, with excellent local tumor control and without the risks of surgical morbidity or mortality.

Advances have also been made in the delivery of conventional radiotherapy, which is frequently used in the treatment of patients with locally-advanced disease. This includes the use of intensity modulated radiotherapy (IMRT), and arc-IMRT delivery which is referred to as volumetric modulated arc therapy (e.g. RapidArc). These techniques have made it possible to reduce the amount of high dose delivered to the surrounding normal, healthy tissue, which allows for lower toxicity risks, while still delivering a high dose to the tumor. In addition, techniques like RapidArc have reduced the delivery time. Another treatment advance has been the move towards combined chemotherapy and radiation in patients with locally advanced lung cancer, with the concurrent administration of both modalities preferred to sequential administration. Nonetheless, despite improvements in the treatment of locally advanced lung cancer, improvements in overall survival and progression free survival have been modest.
For patients with metastatic disease, changes in systemic therapy have come about with greater knowledge of genetic mutations in lung cancer, along with the ability to specifically target these driver mutations with so-called ‘targeted therapies’. In a large trial (NCT01014286), set up to determine the frequency of oncogenic mutations in patients with an advanced adenocarcinoma of the lung, 64% had an identifiable mutation. Progress is also being made in characterizing the mutations in squamous cell carcinomas, and improvements in targeted therapies for this sub-type are also expected in the near future. The frequency of oncogenic alterations in NSCLC are shown in Figure 3.

Figure 2. Prevalence and univariate analysis of 2-dimensional radiation therapy (2D-RT), 3-dimensional conformal RT (3D-CRT), and intensity modulated RT (IMRT) for stage III non-small cell lung cancer. (A) RT technique by year of diagnosis. Kaplan-Meier analysis of IMRT, 3D-CRT and 2D-RT. (B) 2D-RT results in inferior overall survival on proportional hazards models (p<.0001), whereas IMRT is superior to 3D-CRT (hazard ratio [HR] 0.90, p=.02). (C) 2D-RT results in inferior cancer specific survival (p<.0001) and IMRT is superior to 3D-CRT (HR 0.89, p=.02). (Derived from 12)

One example of a targeted therapy is the group of drugs known as tyrosine kinase inhibitors (TKI), targeting mutations in the epidermal growth factor receptor (EGFR). These have resulted in improved progression-free survival (PFS) in prospective studies for patients with such a mutation \(^{16}\). Such innovations have resulted in changes to the guidelines for treating patients with lung cancer \(^{17,18}\). However, so far the gains in overall survival for such patients appear to be modest, as most patients with “druggable” mutations eventually have disease progression \(^{19}\).

**Topics investigated in this thesis**
Against this background, this thesis explores the application of advanced radiotherapy techniques, in specific situations: 1) for patients at high risk of developing a tumor recurrence or second primary in the lung, 2) for patients in whom radical treatment is not currently considered a standard option and 3) for patients who may benefit from new technologies to reduce treatment-related toxicity. Each group poses its own challenges and is described in more detail below.

**Managing survivorship**
Patients, who survive lung cancer, continue to face challenges. Smoking is the leading cause of lung cancer, and the associated field cancerization by smoking renders patients prone to the development of other tumors \(^{20}\). Lung cancer survivors are at risk of developing metachronous (new) lung cancers on longer follow-up, with one estimate indicating a risk of developing a second primary lung cancer (SPLC) at between 3-6% per person year \(^{21}\). In this scenario, it can be a challenge to determine if a new lung lesion represents another primary lung cancer or a lung metastasis, which may have implications for subsequent therapy. Differentiating a new primary tumor from a metastasis has been made easier due to the availability of molecular techniques like comparative genomic hybridization (CGH) or using a chromosomal rearrangement-based approach \(^{22,23}\). However, histology is not always easily available in peripheral lung lesions and taking a biopsy places patients at risk for complications such as pneumothorax or hemorrhage \(^{24}\). Although outcomes after surgery for patients with metachronous early stage lung cancers appears promising \(^{25}\), as we have previously noted, many patients may be unfit or may prefer a non-surgical treatment option. With SABR now an established therapy for such
patients presenting with a single lung cancer, we evaluated our outcomes following SABR in patients with metachronous lung cancers (Chapter 2).

Patients with other smoking-related tumors like squamous cell carcinoma of the head and neck region (HNSCC) are also at increased risk for developing lung cancer, both synchronously (at the same time) and metachronously (at different times). In patients diagnosed with HNSCC, 0.8% have a synchronous lung cancer 26 and the risk of second primary lung cancer (SPLC) following HNSCC is estimated to be about 6%, 11.5%, and 16.5% at 5, 10, and 15 years, respectively 27. Population-based studies have shown that survival of SPLC following HNSCC is poor (8-10 months) compared to other patients with primary lung cancer who do not have a history of HNSCC 28. As detailed information on lung cancer following prior HNSCC is limited, we evaluated disease presentation and treatment outcomes for lung cancer in a recent cohort of patients at our center (Chapter 3).

In patients with locally advanced disease who are treated using chemoradiotherapy, up to 35% develop a local recurrence 11. Such recurrences can be an important cause of morbidity and mortality. Re-growth of the tumor can cause central airway obstruction, tracheo-oesophageal fistula, haemoptysis or a superior vena cava syndrome. In addition, long-term survivors remain at risk for developing a second primary cancer, which may be located within the previously irradiated region. Curative options for a new or recurrent tumors located in a previously irradiated area are limited. Surgery after prior chemo-radiation may be associated with a higher risks of complications 29 and salvage resection is infrequently performed 30. A repeat course of high-dose radiation has been considered to be risky due to previous doses delivered to critical organs at risk (OAR). However, improvements in radiation techniques may allow for better OAR sparing. Recently, various authors have reported their experience with high dose reirradiation, using either SABR, protons or conventional radiotherapy 31, 32. We analyzed our outcomes following a second course of high-dose radiation to the chest (Chapter 4).

**Extending limits for radical treatment: multiple primary tumors and oligometastases**

In part due to improvements in thoracic imaging, multiple primary lung cancers (MPLC) are increasingly being identified, with an incidence ranging
from 3.7–8% \(^{33}\). The diagnostic challenges in differentiating between multiple primary tumors or metastasis have been mentioned. Nonetheless, in the latest revision of the TNM staging system (from 6\(^{th}\) to 7\(^{th}\)), two ipsilateral lesions in one lobe have been ‘downstaged’ to T3 (formerly T4), two ipsilateral lesions in different lobes to T4 (formerly M1), and a new classification was added to describe patients with two bilateral lesions, which are now classified as M1a. For the latter, only lesions with different histology are classified as separate tumors \(^{34}\). These changes in the TNM staging system reflect the fact that the survival of patients presenting with more than one lesion is better than was previously believed to be the case. Consequently, the ESMO Clinical Practice Guidelines for metastatic NSCLC recommend that after appropriate staging, a solitary lesion in the contralateral lung should be considered a synchronous secondary primary lung tumor, and treated as such \(^{35}\). As a consequence, more patients are now considered for aggressive local therapies, particularly if staging reveals no nodal or distant metastases. Outcomes after surgery for patients with synchronous lung cancers are promising\(^{36}\). However, surgery to both lesions is not always feasible, and, therefore, we evaluated our outcomes following SABR in patients presenting with synchronous primary lung tumors (Chapter 5).

About 50% of lung cancer patients have metastatic disease at presentation, a situation usually associated with a poor prognosis. Although most of such patients are treated with palliative intent, the approach in selected patients has evolved from symptom relief alone, to life-extension and optimizing quality of life \(^{37, 38}\). However, patients with ‘oligometastases’ have a limited volume (or number) of metastases and may represent a distinct patient group, perhaps associated with a better prognosis \(^{39}\). We studied outcomes after radical treatment of both the lung tumor and the oligometastases (Chapter 6), and reviewed the role of radiotherapy in the treatment of oligometastases (Chapter 7).

**Reducing treatment toxicity using advances in technology.**

In palliative care, there is a growing focus on maintaining quality of life, which can justify the use of improved radiotherapy delivery to limit toxicity. For example, in patients who have undergone previous radiotherapy, the risk of toxicity can be of concern when retreating lesions in a previously irradiated
field (discussed in Chapter 4). The ability to limit toxicity is also increasingly important given the emergence of new targeted therapies, which sometimes have an unpredictable interaction with radiation. As more patients undergo long-term treatment with such targeted agents, the frequency of unexpected toxicity may rise, even after conventional palliative radiotherapy doses. In this setting, new approaches to reconstructing previous dose distributions, and evaluating the cumulative doses from re-treatment may facilitate safer re-irradiation. For this reason, we studied the use of deformable image registration in re-irradiation (Chapter 8). We also studied the use of volumetric modulated arc therapy (VMAT) to improve normal organ sparing during palliative radiotherapy of large-volume pelvic bone metastases, with the aim of better sparing the abdominal organs, to try and reduce the likelihood of side-effects and problematic interactions between radiation and systemic therapy (Chapter 9).
References


