New radiotherapeutic approaches for improving cure and palliation of lung tumors

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New radiotherapeutic approaches for improving cure and palliation of lung tumors

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geboren te Hilversum

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copromotor:	dr. M.R. Dahele

Content

Chapter 1

Introduction

Introduction

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 [1]. 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 [2]. 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)[3].

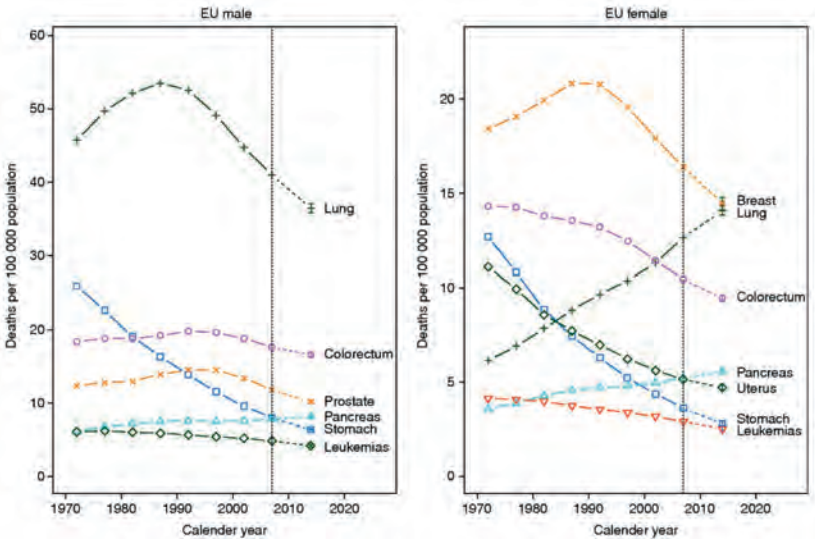

Figure 1. European cancer mortality predictions for 2014 (derived from [3])

The poor prognosis of lung cancer is reflected in an overall 5-year survival rate of approximately 13 to 16% [2]. 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[4]. 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 [5,6]. 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 [7]. This is partly due to better patient selection and improved post-operative care [8]. 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 [9].

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) [10]. 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 [11]. Nonetheless, despite improvements in the treatment of locally advanced lung cancer, improvements in overall survival and progression free survival have been modest (Figure 2) [12].

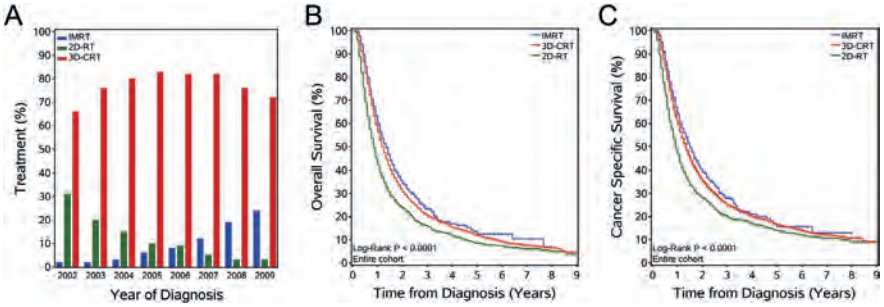

Figure 2. Prevalence and univariate analysis of 2-dimensional radiation therapy (2D-RT), 3-dimensional conformal RT (3D-CRT), and intensity modulated RT (IMRT) for stage III non-small cell lung cancer. (A) RT technique by year of diagnosis. Kaplan-Meier analysis of IMRT, 3D-CRT and 2D-RT. (B) 2D-RT results 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])

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' [13]. 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 [14]. Progress is also being made in characterizing the mutations in squamous cell carcinomas [15], 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.

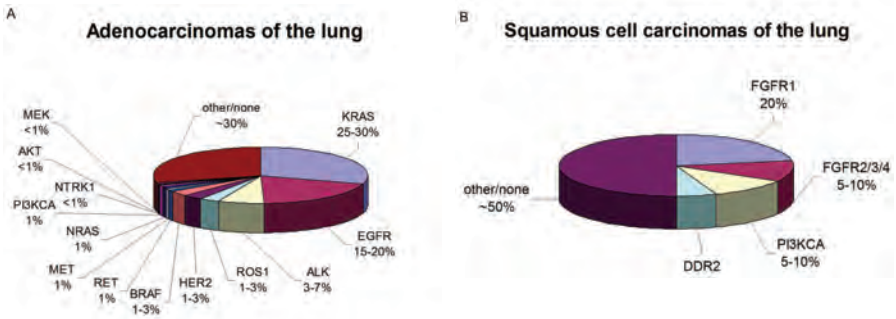

Figure 3. Frequency of oncogenic alterations in non-small cell lung cancer. A) adenocarcinoma. B) Squamous cell carcinoma. (Derived from ASCO educational book 2014 - Gerber et al - Management and future directions in NSCLC with known activating mutations.)

Chapter 6

Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): patient outcomes and prognostic factors

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Abstract

Objectives: Metastatic non-small cell lung carcinoma (NSCLC) generally carries a poor prognosis, and systemic therapy is the mainstay of treatment. However, extended survival has been reported in patients presenting with a limited number of metastases, termed oligometastatic disease. We retrospectively reviewed the outcomes of such patients treated at two centers.

Materials and methods: From September 1999 - July 2012, a total of 61 patients with 1-3 synchronous metastases, who were treated with radical intent to all sites of disease, were identified from records of two cancer centers. Treatment was considered radical if it involved surgical resection and/or delivery of radiation doses ≥ 13x3Gy.

Results: Besides the primary tumor, 50 patients had a solitary metastasis, 9 had two metastases, and 2 had three metastases. Locations of metastases included the brain (n=36), bone (n=11), adrenal (n=4), contralateral lung (n=4), extra-thoracic lymph nodes (n=4), skin (n=2) and colon (n=1). Only one patient had metastases in two different organs. Median follow-up was 26.1 months (m), median overall survival (OS) was 13.5m, median progression free survival (PFS) was 6.6m and median survival after first progression (SAFP) was 8.3m. The 1- and 2-year OS were, 54% and 38%, respectively. Significant predictors of improved OS were: smaller radiotherapy planning target volume (PTV) ($p=0.004$) and surgery for the primary lung tumor ($p<0.001$). Factors associated with improved SAFP included surgery for the primary lung tumor, presence of brain metastases, and absence of bone metastases. No significant differences in outcomes were observed between the two centers.

Conclusion: Radical treatment of selected NSCLC patients presenting with 1-3 synchronous metastases can result in favorable 2-year survivals. Favorable outcomes were associated with intra-thoracic disease status: patients with small radiotherapy treatment volumes or resected disease had the best OS. Future prospective clinical trials, ideally randomized, should evaluate radical treatment strategies in such patients.

Introduction

Almost half of patients diagnosed with non-small cell lung carcinoma (NSCLC) have distant metastases at presentation [1, 2]. Metastatic NSCLC is generally associated with a poor prognosis, and systemic therapy is the cornerstone of treatment. A number of randomized clinical trials have established a response rate of 20-30% to platinum based chemotherapy-schedules with a median survival in the order of 8-11 months [3], which is significantly better than after supportive care alone. However, sub-groups of patients with specific molecular characteristics and a better prognosis are being identified [4]. In addition, several retrospective reports have suggested that selected patients who present with only a limited number of metastases, so-called oligometastatic disease, may also have a better-than-expected survival [5].

The term oligometastasis and its significance were described by Hellman and Weichselbaum in 1995 [6], but efforts to cure patients with metastatic disease predate this by many years [7, 8]. Nonetheless, literature on outcomes in NSCLC patients with oligometastases is largely based on retrospective, single institution series and typically describes the outcomes with surgical treatment. Most reports have included patients with both synchronous and metachronous oligometastases, and have predominantly focused on brain or adrenal metastases [9]. More reports have emerged in recent years on treatment of metastases at other sites, and using other treatment modalities [10-14]. This growing body of data has been recognized in the recent ESMO guidelines (2012), which recommends consideration of radical treatment as an option for selected patients with a solitary metastasis [3]. Nonetheless, level 1 evidence supporting improved OS after aggressive treatment is lacking, apart from resection or stereotactic ablation of a single brain metastasis [15, 16] and there is limited information on outcome for the specific group of patients presenting with NSCLC and synchronous oligometastases.

The purpose of the present study was to add to the existing literature by evaluating outcomes in patients treated in routine clinical practice (i.e. outside clinical trials), who were diagnosed with NSCLC and 1-3 synchronous metastases at presentation, and had all sites of disease treated with radical intent. The goals of this study were to assess survival outcomes and determine

predictors of survival, and to better guide clinical care and the design of future clinical trials.

Materials and methods

This analysis was performed at the VU University medical center (VUmc), the Netherlands, and in the London Regional Cancer Program (LRCP), Canada. Data was pooled from these 2 large comprehensive cancer centers in order to increase the power and generalizability of the study. At both centers, details of all patients with NSCLC who had been radically treated between September 1999 and July 2012, were retrospectively identified using an institutional database, with subsequent review of individual charts. Patients who had metastases at presentation (synchronous metastases) that were also radically treated were selected for further analysis. Treatment was considered radical for primary tumors or metastases if it included surgery, or if radiotherapy (RT) was prescribed with a dose that was biologically equivalent to a treatment schedule of ≥13 fractions of 3 Gray (Gy). Baseline patient, tumor and treatment characteristics were extracted from patient charts, and where necessary other hospitals and general practitioners were contacted by the research team to minimize missing data. All patients had been discussed in a multidisciplinary tumor board, where a consensus was reached that radical treatment to all known sites of disease was clinically reasonable and feasible. To limit potential bias, including selection bias, patients were included based on the 'intention-to-treat' decision of the multidisciplinary tumor board. As such, patients who progressed or died prior to or during treatment remained within the study database. Local Research Ethics Board approval was obtained from both participating institutions prior to study initiation.

Primary endpoints were overall survival (OS), progression-free survival (PFS) and survival after first progression (SAFP). Survival was calculated from the first day of radiotherapy or surgery until the last date of follow-up or death. PFS was calculated from first day of treatment until any relapse, local or distant, or death (whichever occurred first). Survival after first progression was calculated from the date that first relapse was reported until the last date of follow-up or death. First progression was scored based on available clinical or imaging reports of any

progression (local or distant). Toxicity was a secondary end-point and was scored based on the Common Terminology Criteria for Adverse Events version 4.0.

Statistical analysis

Descriptive statistics were generated for baseline patient, tumor and treatment characteristics, stratified by cohort and compared using the Chi-square test, Fisher's exact test or T-test as appropriate. Kaplan-Meier estimates of OS, PFS and SAFP were generated and compared across a set of baseline patient, tumor and treatment characteristics using the log-rank test. Median actuarial follow-up was calculated using the reverse Kaplan-Meier method. Univariable cox regression analysis was also performed on a set of baseline patient, tumor and treatment characteristics to identify predictors of OS, PFS and SAFP respectively. p-Values were used to quantify degree of association between each of the factors and the survival-based endpoints. Recursive partitioning analysis was performed separately for OS and SAFP, based on significant factors from univariable analysis. Default settings were used (minimum number of 20 observations in a node required to enable further splitting) following by trimming of less important downstream branches as needed. All statistical analysis was performed using SAS 9.2 software (SAS institute, Cary NC), and the R language environment for statistical computing (open source, www.r-project.org, for recursive partitioning analysis only), using two-sided statistical testing at the 0.05 significance level.

Results

In the period September 1999 - July 2012 a total of 61 patients met the inclusion criteria. In total, these patients accounted for 74 metastases located at 7 different body sites. More than 70% of the patients were treated after 2009. Thirty-six of these patients were treated in the VUmc in the Netherlands, and 25 patients were treated at the LRCP in Canada. Baseline patient and tumor characteristics, for all patients and stratified by cohort, are summarized in Table I. Seventy-nine percent of all patients were staged by PET and 72% had pre-treatment brain MRI imaging. The majority of patients (62%) had locally advanced (stage III) intra-thoracic disease. Eighty-two percent had a solitary metastasis (n=50), 9 patients had two metastases and two had three metastases. Only one patient, with two metastases in total, had metastatic disease located at two different

sites. The most common site for metastases was brain (n=36 patients), followed by bone (n=11), adrenal (n=4), contralateral lung (n=4), extra-thoracic lymph nodes (n=4), skin (n=2) and colon (n=1).

Table I: Baseline patient, tumor and treatment characteristics of all patients (n=61) and stratified by cohort (LRCP versus VUmc).

Characteristic	All Patients (n=61)	LRCP (n=25)	VUmc (n=36)	p-value ***
Treatment Year – n(%):				
1999 – 2009	17 (27.9)	13 (52.0)	4 (11.1)	**< 0.001**
2010	18 (29.5)	8 (32.0)	10 (27.8)	
2011	18 (29.5)	3 (12.0)	15 (41.7)	
2012	8 (13.1)	1 (4.00)	7 (19.4)	
Age – mean ± SD, median (range)	61.7 ± 9.5 61.7 (35.2, 80.2)	61.8 ± 9.0 63.4 (38.1, 76.0)	61.5 ± 9.9 61.4 (35.2, 80.2)	0.909
Male – n(%):	31 (50.8)	14 (56.0)	17 (47.2)	0.500
ECOG Performance Status – n(%):				
0	10 (16.4)	3 (12.0)	7 (19.4)	0.775
1	44 (72.1)	19 (76.0)	25 (69.4)	
2	7 (11.5)	3 (12.0)	4 (11.1)	
Smoking Status – n(%):	56 (91.8)	24 (96.0)	32 (88.9)	0.640
Charlson Comorbidity Index (CCI)* – mean ± SD, median (range)	2.4 ± 1.6 2 (0, 7)	2.5 ± 1.6 2 (0, 5)	2.4 ± 1.7 2 (0, 7)	0.880
Pathology / Histology – n(%):				
Adenocarcinoma	48 (78.7)	15 (60.0)	33 (91.7)	**0.004**
Squamous	5 (8.2)	3 (12.0)	2 (5.6)	
NSCLC NOS	8 (13.1)	7 (28.0)	1 (2.8)	
Primary tumor/node stage – n(%):				
I	11 (18.0)	5 (20.0)	6 (16.7)	0.705
II	12 (19.7)	6 (24.0)	6 (16.7)	
III	38 (62.3)	14 (56.0)	24 (66.7)	
PET-CT Staging – n(%):	48 (78.7)	12 (48.0)	36 (100.0)	**< 0.001**
Brain MRI Staging – n(%):	44 (72.1)	12 (48.0)	32 (88.9)	**< 0.001**
Brain CT Staging – n(%):	23 (37.7)	21 (84.0)	2 (5.6)	**< 0.001**
Number of Metastases – n(%):				
1	50 (82.0)	22 (88.0)	28 (77.8)	0.553
2	9 (14.8)	3 (12.0)	6 (16.7)	
3	2 (3.3)	--	2 (5.6)	
Location of Metastases** – n(%):				
Brain	36 (59.0)	15 (60.0)	21 (58.3)	0.896
Contralateral Lung	4 (6.6)	2 (8.0)	2 (5.6)	1.00
Adrenal	4 (6.6)	2 (8.0)	2 (5.6)	1.00
Bone	11 (18.0)	4 (16.0)	7 (19.4)	1.00
Skin	2 (3.3)	1 (4.0)	1 (2.8)	1.00
Lymph Node (extra thoracic)	4 (6.6)	--	4 (11.1)	0.137
Colon	1 (1.6)	1 (4.0)	--	0.410

Table I: Continued

Characteristic	All Patients (n=61)	LRCP (n=25)	VUmc (n=36)	p-value ***
Number of Brain Metastases – n(%):				
0	25 (41.0)	10 (40.0)	15 (41.7)	0.830
1	27 (44.3)	12 (48.0)	15 (41.7)	
2	7 (11.5)	3 (12.0)	4 (11.1)	
3	2 (3.3)	--	2 (5.6)	
Chemotherapy – n(%):	51 (83.6)	21 (84.0)	30 (83.3)	1.00
Treatment Primary Lung Tumor – n(%):				
Concurrent CRT	30 (49.2)	20 (80.0)	10 (27.8)	
Sequential CRT	10 (16.4)	--	10 (27.8)	**< 0.001**
Primary RT	2 (3.3)	1 (4.0)	1 (2.8)	
Stereotactic RT	10 (16.4)	2 (8.0)	8 (22.2)	
Trimodality (Surgery + CRT)	3 (4.9)	1 (4.0)	2 (5.6)	
Surgery + CT	3 (4.9)	--	3 (8.3)	
Surgery only	3 (4.9)	1 (4.0)	2 (5.6)	
Treatment to Metastases – n(%):				
Stereotactic RT	24 (39.3)	3 (12.0)	21 (58.3)	**< 0.001**
- Intracranial	*18 (29.5)*			
- Extracranial	*6 (9.8)*			
Conventional RT (EBRT)	13 (21.3)	7 (28.0)	6 (16.7)	
Surgery	6 (9.8)	1 (4.0)	5 (13.9)	
WBRT + Boost	2 (3.3)	--	2 (5.6)	
Surgery + RT	16 (26.2)	14 (56.0)	2 (5.6)	
Primary Tumor – Radiation Dose (Gy) – mean ± SD, median (range) [n=54]	58.2 ± 9.5 60 (16, 66)	58.7 ± 11.1 61 (16, 66)	57.9 ± 8.3 60 (39, 66)	0.755
Primary Tumor ± nodes - PTV (cc) – mean ± SD, median (range) [n=46]	527 ± 323 517 (46, 1335)	529 ± 341 507 (103, 1335)	526 ± 320 528 (46, 1247)	0.981
First Metastasis – PTV (cc) – mean ± SD, median (range) [n=38]	105 ± 265 7.9 (0.1, 1502.1)	214 ± 521 25.8 (1.1, 1502.1)	76 ± 140 5.8 (0.1, 633)	0.479
Dead – n(%)	38 (62.3)	17 (68.0)	21 (58.3)	0.444

Abbreviations: LRCP = London Regional Cancer Program, VUMC = VU University Medical Center, SD = Standard Deviation, ECOG = Eastern Cooperative Oncology Group, NSCLC NOS = Non-Small Cell Lung Carcinoma Not Otherwise Specified, PET-CT = Positron Emission Tomography - Computed Tomography, MRI = Magnetic Resonance Imaging, CT = Computed Tomography, CRT = chemoradiation, RT = radiotherapy, CT = chemotherapy, Gy = Gray, PTV = Planned Target Volume

*Adjusted for Age and Metastatic Disease (CCI Score minus 6 points).

**Metastases counted per patient. Only one patient had 2 metastases in two locations.

*** p-values < 0.05 shown in **BOLD**

Treatment to the primary site included surgery in 9 patients, with (n=3) or without (n=6) pre- or postoperative radiotherapy. The majority of the remaining 52 patients were treated with concurrent chemo-radiation (n=30). For patients that received RT, the planning target volume (PTV) and dose are described in Table I. In the entire cohort, 84% received platinum-based chemotherapy

as part of their treatment for the primary tumor. Most metastases (out of a total of n=74 lesions) were treated by either stereotactic radiotherapy (intra-cranial n=18, extra-cranial n=6), the combination of surgical resection and radiotherapy (n=16) or conventional radiotherapy alone (n=13) (Table I).

A total of 4 patients did not complete the prescribed treatment: two patients died during treatment of unknown cause, making it impossible to rule out treatment related toxicity; one patient developed sepsis (grade 4) during chemo-radiation, and on resolution of the sepsis, was found to have progressed; and the fourth patient did not complete chemo-radiation of the lung tumor because of toxicity (thrombocytopenia). In one other patient, treatment of a solitary brain metastasis with stereotactic radiotherapy was delayed due to thrombo-embolic disease and severe dyspnea after thoracic chemo-radiation, without obvious radiation pneumonitis. This patient improved sufficiently to receive stereotactic radiotherapy seven months later to the (still) solitary brain metastasis. Grade 3 oesophagitis was recorded in 3 patients, and one patient had a grade 3 pneumonitis, based on a temporary need for oxygen.

Table II: Univariable cox regression models examining relationship between individual predictors of: (a) Overall Survival (n=61), (b) Progression-Free Survival (n=61), and (c) Survival after First Progression (n=43).

Dependent Variables	**Overall Survival (n=61)**		**Progression-Free Survival (n=61)**		**Survival after 1st Progression (n=43)**	
Independent Variables	**Univariable HR (95% CI)**	**p-value *****	**Univariable HR (95% CI)**	**p-value *****	**Univariable HR (95% CI)**	**p-value *****
Cohort LRCP vs. VUmc	1.49 (0.78, 2.83)	0.224	0.98 (0.57, 1.69)	0.946	0.98 (0.43, 2.25)	0.970
Treatment Year: 1999-2009 vs. 2010-2012	1.36 (0.69, 2.70)	0.377	0.58 (0.31, 1.11)	0.100	1.30 (0.55, 3.10)	0.550
Age ≥ 65 yrs vs. < 65 yrs	0.94 (0.48, 1.85)	0.857	1.02 (0.58, 1.80)	0.945	0.85 (0.38, 1.89)	0.683
Male Male vs. Female	1.79 (0.93, 3.42)	0.081	1.22 (0.71, 2.08)	0.475	1.70 (0.79, 3.64)	0.174
ECOG PS						
1 vs. 0	1.70 (0.60, 4.85)	0.318	1.11 (0.53, 2.29)	0.788	1.36 (0.40, 4.57)	0.621
2 vs. 0	1.53 (0.38, 6.17)	0.550	1.08 (0.38, 3.08)	0.884	1.08 (0.18, 6.50)	0.931
		***0.605*		***0.965*		***0.856*
CCI						
Score = 1 vs. 0	1.75 (0.38, 7.95)	0.472	0.60 (0.20, 1.81)	0.362	2.56 (0.54, 12.04)	0.235
Score = 2 vs. 0	2.55 (0.54, 11.92)	0.235	0.87 (0.28, 2.69)	0.807	2.94 (0.61, 14.21)	0.181
Score ≥ 3 vs. 0	1.87 (0.43, 8.21)	0.406	0.68 (0.23, 1.99)	0.478	1.90 (0.41, 8.84)	0.416
		***0.647*		***0.685*		***0.532*
Smoking Status Yes vs. No	1.26 (0.39, 4.09)	0.706	0.65 (0.26, 1.65)	0.367	1.37 (0.41, 4.58)	0.605
PET Staging No vs. Yes	1.47 (0.70, 3.12)	0.313	1.35 (0.72, 2.52)	0.353	0.68 (0.24, 1.98)	0.481
MRI Staging No vs. Yes	1.68 (0.84, 3.36)	0.139	1.03 (0.57, 1.88)	0.914	2.18 (0.94, 5.09)	0.071

Table II: Continued

Dependent Variables	Overall Survival (n=61)		Progression-Free Survival (n=61)		Survival after 1st Progression (n=43)	
Histology						
Squamous vs. Adeno.	1.60 (0.48, 5.34)	0.445	0.87 (0.27, 2.82)	0.817	2.37 (0.54, 10.34)	0.250
NSCLC vs. Adeno.	4.10 (1.74, 9.70)	**0.001**	2.51 (1.16, 5.45)	**0.020**	2.19 (0.49, 9.81)	0.306
		****0.006***		**0.059*		**0.345*
Tumor Stage						
II vs. I	1.77 (0.58, 5.43)	0.316	1.07 (0.44, 2.58)	0.878	4.53 (0.95, 21.46)	0.057
III vs. I	1.60 (0.61, 4.19)	0.338	1.17 (0.58, 2.37)	0.667	2.73 (0.63, 11.84)	0.181
		**0.570*		**0.902*		**0.145*
Number of Metastases 2-3 vs. 1	1.19 (0.54, 2.62)	0.662	1.55 (0.77, 3.11)	0.221	1.00 (0.40, 2.49)	1.00
Brain Metastases No vs. Yes	1.53 (0.80, 2.90)	0.197	0.99 (0.57, 1.72)	0.980	3.27 (1.47, 7.29)	**0.004**
Bone Metastases Yes vs. No	1.68 (0.76, 3.73)	0.202	1.31 (0.65, 2.62)	0.451	3.66 (1.44, 9.33)	**0.007**
Chemotherapy Yes vs. No	1.52 (0.59, 3.91)	0.382	0.77 (0.37, 1.59)	0.485	2.17 (0.73, 6.40)	0.162
Lung Surgery No vs. Yes	∞*	**< 0.001***	4.18 (1.47, 11.86)	**0.007**	11.23 (1.51, 83.56)	**0.018**
Surgery – Metastases Yes vs. No	1.54 (0.81, 2.94)	0.188	1.16 (0.67, 2.01)	0.599	1.33 (0.60, 2.92)	0.484
Lung PTV ≥ 639 cc vs. < 639 cc	2.89 (1.36, 6.17)	**0.006**	2.49 (1.28, 4.85)	**0.007**	2.01 (0.83, 4.88)	0.123

Abbreviations: HR = Hazard Ratio, CI = Confidence Interval, ECOG PS = Eastern Cooperative Oncology Group Performance Status, CCI= Charlson Comorbidity Index, PTV = Planned Target Volume

* Hazard ratio was undefined due to insufficient events

** Overall analysis of effects for variables with > 2 groups

*** p-values < 0.05 shown in **BOLD**

Median actuarial follow-up for the whole group was 26.1 months, and 38 death events occurred. Median OS was 13.5 months, with an actuarial 1 year OS of 54% and a 2 year OS of 38% (Fig. 1).

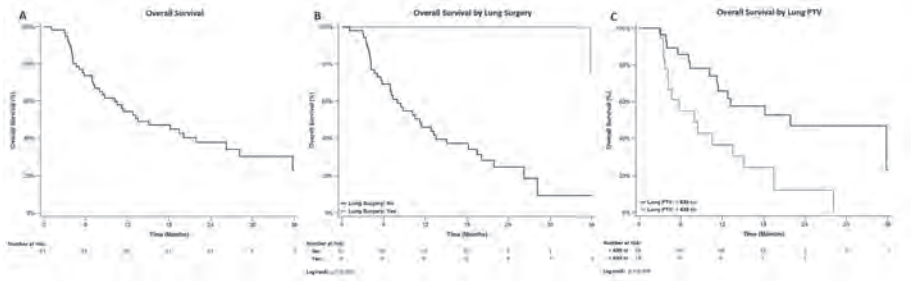

Figure 1. Kaplan-Meier curves of overall survival of all patients (A), those undergoing lung surgery (B), and by planning target volume (PTV) of the intrathoracic tumor (C)

Surgical resection of the intra-thoracic disease ($p < 0.001$) and lower PTV volume ($p = 0.004$) were associated with improved OS. Cox regression modeling is shown in Table II, with similar findings on univariable modeling as the Kaplan-Meier analyses. However, Cox modeling had two major limitations: in univariable modeling, the independent variable "lung surgery" had very few events (only 1 death event occurring 36 months post-treatment), and thus solutions for a final model could not be reached for that variable, and the hazard ratio (HR) for "lung surgery" was undefined. Secondly, for multivariable modeling, the two factors that predicted most strongly for improved OS on Kaplan-Meier analysis (Lung Surgery and PTV volume) were nearly mutually exclusive, and as such a regression model could not be built that included both factors simultaneously.

Recursive partitioning analysis (RPA) was therefore used to create risk groups, as it is not subject to these limitations. RPA resulted in identification of 3 risk groups: patients who received surgery for their intra-thoracic disease had the best prognosis (low-risk group); patients treated with radiotherapy with a PTV ≥639cc had the worst prognosis (high-risk group); patients treated with radiotherapy and having a PTV <639cc formed an intermediate group (Fig. 2).

Median PFS was 6.6 months, with actuarial 1- and 2-year PFS of 32% and 8% respectively (Fig. 3). Univariable modeling showed a positive correlation with improved PFS if patients received surgery for the intra-thoracic disease [HR (95% CI): 4.18(1.47, 11.86), $p = 0.007$].

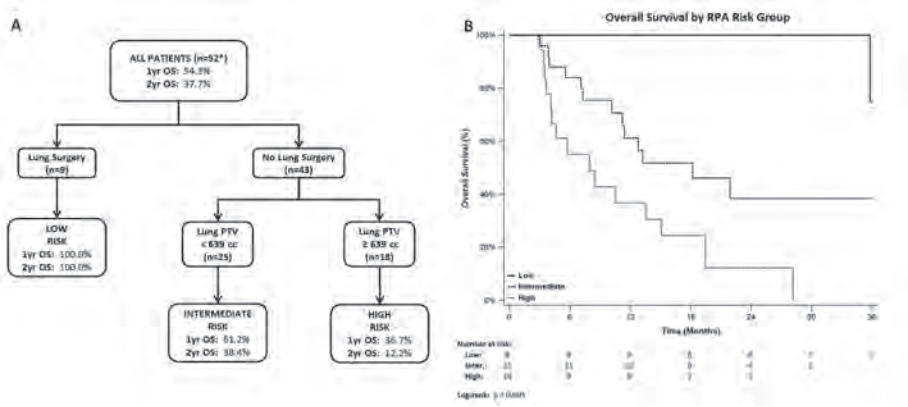

Figure 2. Recursive Partitioning Analysis (RPA) flowchart for overall survival showing characteristics of risk groups (A), with accompanying Kaplan-Meier curves of overall survival by RPA risk groups (B)

Median SAFP was 8.3 months, with a 1-year and 2-year SAFP of 34% and 26% respectively (Fig. 3). SAFP was positively associated with brain metastases at initial presentation [13.4 versus 3.3 months; log-rank p = 0.002; HR (95%CI): 3.27 (1.47-7.29)] and negatively associated with the presence of bone metastases at initial presentation [11.9 versus 3.3 months; log-rank p = 0.004; HR (95%CI): 3.66 (1.44-9.33)].

Although the LRCP and VUmc cohorts differed in several baseline factors, including year of treatment (VUmc more recent), histology, staging investigations, and treatments used, outcomes did not differ between the two cohorts. In particular, staging with PET-CT was not associated with improved OS, PFS or SAFP. The inclusion of brain MRI in staging only showed a trend towards better survival (p=0.135).

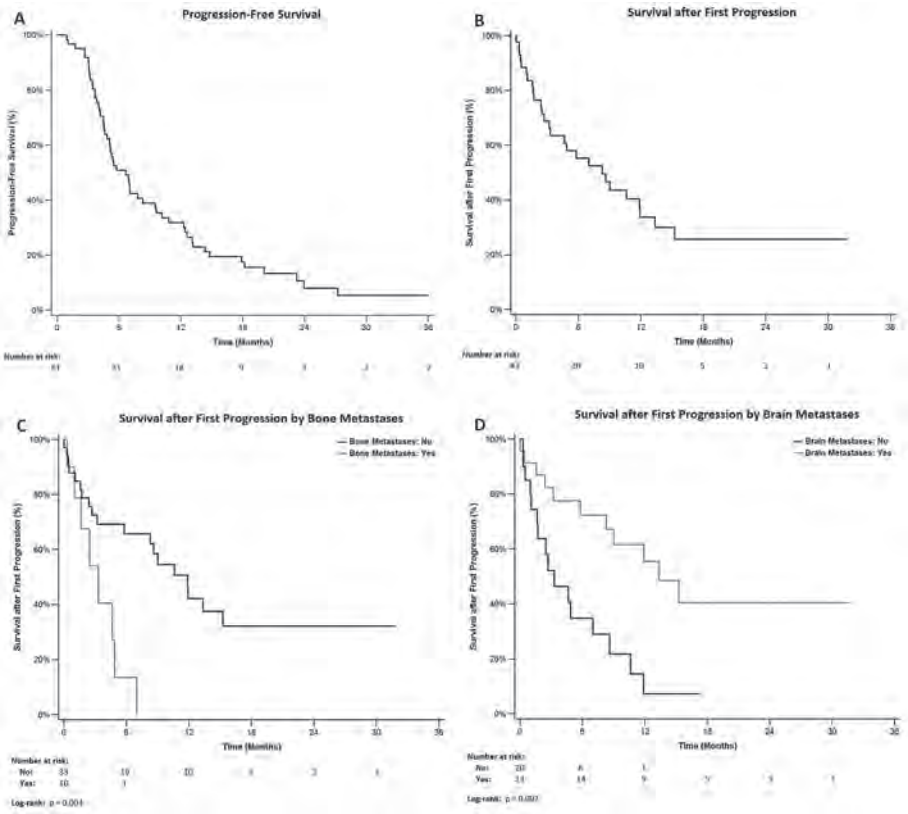

Figure 3. Kaplan-Meier curves for progression-free survival of all patients (A), survival after first progression for all patients (B), and survival after first progression, stratified by either bone metastases (C) or brain metastases (D) at initial presentation

Discussion

This two-center pooled retrospective analysis of patients undergoing radical treatment for NSCLC and 1 to 3 synchronous metastases found that over 80% of the treated patients had a solitary metastasis, most often located in the brain. Radical treatment resulted in a median overall survival of 13.5 months and a median PFS of 6.6 months. Significantly, the major predictors of OS were the extent or resection of intra-thoracic disease: a PTV ≥639cc, and the absence of surgery as part of the treatment of the primary tumor, both portended a worse prognosis. Reported high-grade toxicity rates were low in this retrospective analysis, although 2 patients died of unknown cause during initial treatment.

The data reported herein are consistent with previously published literature, and extend our understanding of oligometastatic NSCLC in several important ways. Specifically, (1) despite a small percentage of patients progressing during treatment, more than one third of the patients survived over two years after radical treatment, (2) it was observed that thoracic treatment characteristics - PTV size and whether or not surgery was performed - were the strongest prognostic factors, and (3) toxicity of a radical treatment strategy was acceptable. Overall, the reported survival data are comparable with a recently published, prospective, phase II study of 39 patients receiving radical treatment for NSCLC with synchronous oligometastases in which the primary tumor was treated with chemo-radiotherapy [14]. In that study treatment was well-tolerated, with a median overall survival of 13.5 months. Reported 1- and 2-year overall survival were 56% and 23% respectively, compared with 54% and 47% in the present study. The 1- and 2-year progression-free survival were respectively 51% and 13% in De Ruysscher et al. [14], versus 32% and 8% in the present study.

The survival rates reported herein are intermediate between stage III patients and unselected stage IV patients: for patients with stage III NSCLC treated with sequential or concurrent chemo-radiation, median survival is approximately 16-19 months [17, 18]. Overall survival for the patients in our study with synchronous brain metastases (OS 21.9 months) and the patients without bone metastases (OS of 18 months) were similar to these stage III populations. Importantly, our study confirms that although some patients achieve long-term survivorship beyond two years, most patients progress within a relatively short period, suggesting that undetectable micrometastases were likely present at the time of diagnosis in many patients.

Most surgical series reporting on patients with oligometastatic NSCLC have focused on brain or adrenal metastases. Median survival for patients undergoing resection of the primary site and their brain metastases ranges from 7 up to 27 months [9], with one of the largest series of 103 patients reporting a median survival of 12.4 months [19]. Similarly, two surgical studies describing outcomes in synchronous oligometastases reported a median overall survival of 19 and 20.5 months, with a 1-year survival of respectively 73% and 65% [10, 11]. Patient selection plays a pivotal role in these outcome data: patients eligible for surgery are generally in a better condition and have fewer comorbidities

than those who are ineligible for surgery. For instance, in a recent series of patients with synchronous solitary brain metastasis from primary NSCLC who received aggressive management of the primary lesion in the chest along with stereotactic RT to the single lesion in the brain, those patients with favorable performance status experienced significantly improved median OS compared to those with a worse performance status [20]. In our study, brain metastases represented a substantial number of the oligometastases treated, and the more favorable outcome after progression (9 vs. 3 months, p=0.003), suggests that fit patients might benefit from regular follow-up and salvage when new oligometastases arise.

The results of this study must be considered within the context of its limitations, particularly in light of its retrospective nature. The patients in this series are highly selected and the group is heterogeneous regarding intra-thoracic stage, treatment of the lung tumor and metastases and the location of the metastases. More than 80% of patients were treated for a solitary metastasis, and many had a solitary brain metastasis. Therefore, although the term oligometastases is often used in patients with up to 5 metastases, it may not be appropriate to extrapolate this data to patients with multiple metastases in various locations. Follow-up was not standardized and imaging protocols varied widely. This makes the identification and differentiation of local and distant recurrences less reliable. We acknowledge that some of our patients received a comparatively low dose of RT. The optimal dose in such patients requires further evaluation. Despite this, the similarity in survival between centers suggests that patient selection and initial treatment is perhaps most important. In addition, data on some variables of interest, such as quality of life, were not available. We also acknowledge that there was missing data, including data on PTV and on treatment after progression. Although not every patient was staged by PET-CT and brain-MRI, univariable analysis did not show a significant association between survival and staging with either of these modalities. Due to the retrospective nature and the non-standardized follow-up, assessment of toxicity was dependent on documentation in the charts, and may have been underestimated.

Without a control group of patients with oligometastatic disease who did not receive aggressive treatment, it is difficult to ascertain whether such aggressive

treatment to metastases outside the brain actually improves OS, particularly as the median OS reported herein is only a few months longer than reports from unselected patients with metastatic disease treated with chemotherapy alone. A recent meta-analysis, which included 5 randomized controlled trials comparing docetaxel-based and vinorelbine-based chemotherapy in patients with advanced NSCLC (62-100% of all patients had stage IV disease and the remainder stage IIIb), found a 1- and 2 year overall survival of approximately 40% and 20% [21], whereas in our study OS is respectively 54% and 38%. Some authors have argued that the 'better-than-expected' outcomes for patients with oligometastatic disease merely reflect the selection of patients with slow-growing tumors, good performance status, and low burden of disease, rather than the effects of any aggressive treatment [22]. Two previous randomized trials addressing this question have closed due to poor accrual. The first, a randomized phase II study conducted by the North Central Cancer Treatment Group (NCT00776100), sought to randomize patients with NSCLC and 1-3 oligometastases who achieved stable disease or partial response after 2-6 cycles of platinum-based chemotherapy to observation vs. high-dose radiotherapy to the primary and metastases. The second, conducted by the University of Chicago (NCT00887315), sought to randomize patients with NSCLC and 1-5 metastases who achieved either stable disease or partial response after two cycles of docetaxol and cisplatin to either 2 further cycles of chemotherapy vs. high-dose radiotherapy to the primary tumor and metastases. However, in the setting of metachronous oligometastases (1-5), the SABR-COMET randomized phase II trial (NCT01446744) is assessing a strategy of stereotactic radiotherapy to all sites of disease vs. standard-of-care palliative chemotherapy and/or palliative radiotherapy 23, and is accruing well in Canada and the Netherlands. For patients with synchronous oligometastases from NSCLC, the limited patient numbers suggest that a multi-center trial would be necessary to detect any potential survival benefit over chemotherapy alone. The prognostic factors indentified herein will be useful for informing the design of such a trial.

Conclusion

Radical treatment of selected NSCLC patients presenting with 1-3 synchronous metastases can result in favorable 2-year survival. Patients with resected intra-thoracic disease had the best prognosis, and patients treated with radiotherapy who had a large primary PTV had the worst prognosis. Prospective clinical trials, ideally randomized, should evaluate the role of radical treatment strategies in patients with oligometastases.

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Chapter 10

Conclusions & future directions

Conclusions & future directions

An improved understanding of the epidemiological aspects and molecular characteristics of lung cancer has led to new challenges, while the breakthroughs in molecular targeted therapies have led to new dilemmas in our daily practice. The work performed for this thesis attempts to address some of these issues.

Managing Survivorship

Even after curative treatment, lung cancer patients are faced with the risk of disease recurrence and developing new a primary lung cancer. In 1294 patients who underwent a resection for an early stage lung cancer, followed by a CT-scan of the thorax at least every 6-12 months, the risk of disease recurrence was 6-10% per person-year during the first four years, and decreased thereafter to 2% [1]. Moreover, the risk of developing a second primary was 3-6% per person-year and did not decrease over time [1]. The persistently high risk of death in lung cancer patients is illustrated by survival data from the SEER database on 31,026 patients who were still alive at least 5 years after being diagnosed with NSCLC [2]. This study revealed that both overall survival and disease specific survival keep diminishing, even after more than 15 years (Figure 1.).

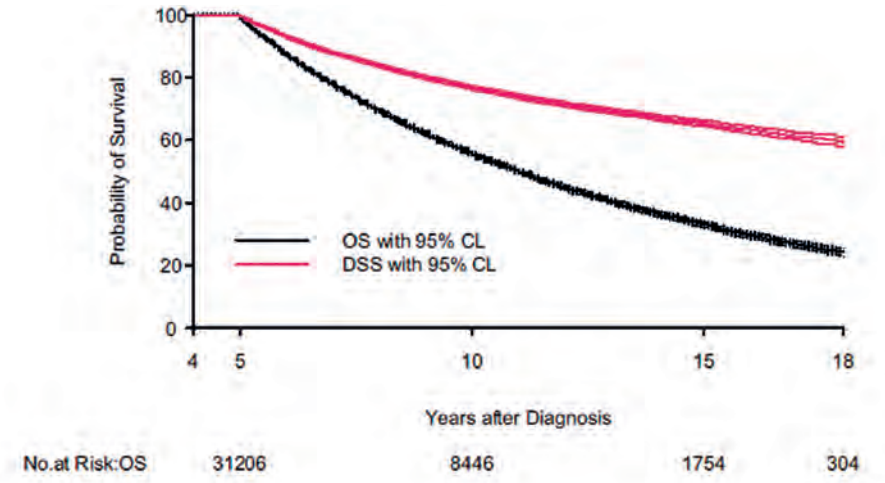

Figure 1. Graphs of DSS (top red line) and OS (bottom black line) in patients with NSCLC surviving more than 5 years. CL, Confidence limit; DSS, disease-specific survival; OS, overall survival. Derived from [2].

A similar situation is encountered in patients with head and neck cancer [3], where the risk of second primary lung cancers (SPLC) after 5, 10, and 15 years post-treatment is 6%, 11%, and 16%, respectively (Figure 2.) [4].

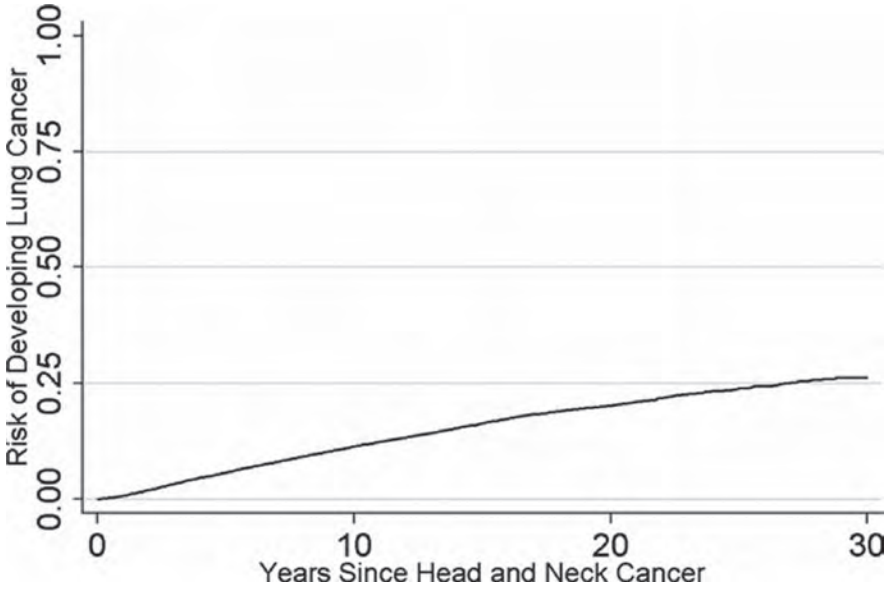

Figure 2. Kaplan–Meier risk of developing lung cancer after head and neck cancer among 61,883 patients. Derived from [4].

Our study on treatment outcomes for SPLC after HNSCC (Chapter 3), found a better prognosis if SPLC was diagnosed in an early stage. Unfortunately, more than half of the SPLC after HNSCC were found at a more advanced stage, presumably due to a lack of comprehensive surveillance.

The National Lung Screening Trial (NLST) compared the use of a low-dose CT-scan versus a chest radiograph to screen for lung cancer in high-risk patients, and showed a relative reduction in mortality from lung cancer of 20% with CT screening [5]. Given the high 5-year incidence rates of SPLC in the two patient populations studied above, and the far lower risk of developing a lung cancer in populations undergoing CT screening, low-dose CT in lung and head and neck cancer survivors deserves attention. An absolute risk-prediction model for lung-cancer mortality in the NLST's chest radiography group has been developed [6], which revealed the following quintiles for the 5-year risk of

lung-cancer death: 0.15 to 0.55% in quintile 1 (lowest risk) to more than 2.00% in quintile 5 (highest risk). Consequently, the number of participants who would need to be screened to prevent one lung-cancer death decreased from 5276 among the 20% of participants at lowest risk to 161 among the 20% of those at highest risk. Similarly, the number of stage I lung cancers increased significantly with an increasing risk of lung-cancer death (40 in quintile 1 vs. 215 in quintile 5, P<0.001 for trend). In the light of available data suggesting that the 5-year risk of SPLC exceeds 6% in survivors of both lung and H&N cancer, we would argue that secondary CT screening in these groups is justified [7,8].

Distinguishing SPLC from metastasis continues to pose a challenge. Besides using array comparative genomic hybridization (arrayCGH), the use of genomic rearrangements from mate-pair sequencing demonstrates promise in distinguishing if two lesions are related (primary-metastasis) or unrelated (two different primary tumors) [9]. However, to distinguish two lesions based on tissue samples, means that a biopsy is needed. Currently, it is not feasible to retrieve a tissue sample in every patient (Chapter 1), as a biopsy can pose risks, especially to patients with significantly impaired lung function [10]. Less invasive approaches for obtaining tissue samples are required, but if the distinction cannot be made, the decision made by a multidisciplinary tumor board should take precedence, and patients should be given the benefit of the doubt, which usually means managing them as though they have 2 separate primary tumors.

After conventional radiotherapy, and to a lesser extent, SABR, local and regional recurrences, still pose a challenging clinical problem. In patients without widespread metastases, an attempt to perform curative treatment for lesions located in a previously irradiated area appears to be reasonable. Three clinical scenarios may be encountered by radiation oncologists in clinical practice, although published data is limited:

- Stereotactic radiotherapy (SABR) followed by repeat SABR in the same area
- High-dose (chemo) radiation, followed by SABR
- Conventional (chemo) radiation followed by re-treatment with conventional radiation

In practice, re-irradiation for recurrent disease remains a challenge due to the absence of reliable data on normal organ tolerance doses in this setting. More

accurate tools that can provide data on the accumulation of doses from both courses of radiation are entering clinical use, but the problems arising due to loss of tissue and fibrosis in previously irradiated areas may limit the clinical conclusions that can be drawn from such data. In the first scenario (SABR after SABR), high rates of toxicity have been reported when repeat SABR is performed in patients with central lung tumors [11]. A recent review also suggests that using SABR for re-irradiation after previous conventional radiotherapy was associated with higher toxicity for central tumors [12]. However, the available studies comprised a very heterogeneous, and selected, patient population, receiving a range of treatment regimes, with short follow-up. We explored the third scenario (conventional after conventional), and found that the acute toxicity of re-irradiation appears to be acceptable when modern radiotherapy techniques are used. Once again, central re-irradiation may be associated with higher risks and the prognosis for patients requiring large treatment volumes was worse (Chapter 4). In-field tumor recurrences after re-irradiation remain a major problem, and the median survival in our selected patient population was only 13.5 months. Consequently, the level of evidence for a beneficial effect for high-dose re-irradiation in all three scenarios remains low, especially for lesions located centrally close to the hilar structures. Nonetheless with about 25% of patients surviving 2 years, we believe that its use is justifiable in carefully selected patients and after appropriate discussion of risks and potential benefits.

Extending limits for radical treatment: multiple primary tumors and oligometastases

Patients who present with multiple primary lung cancers (MPLC) represent an under appreciated, but clinically relevant problem, as highlighted by incidences of 5 and 9% in two recent screening studies [13,14]. Similarly, rates of MPLC were respectively 7 and 12%, following video-assisted thoracoscopic surgery (VATS) and thoracotomy in early stage lung cancer [15]. Our results revealed good local control and survival using SABR in patients presenting with MPLC (Chapter 5), findings confirmed recently by the results from the MD Anderson Cancer center [16]. An interesting observation in our study was the higher incidence of regional lymph node recurrences in patients presenting with two synchronous ipsilateral lesions. This finding suggests that minimally invasive endobronchial and esophageal endosonography (EBUS and EUS) may be indicated as a

staging procedure for this group of patients. The prospective evaluation of EUS-EBUS in addition to PET-CT scan before SABR, is the subject of our recent multicenter, prospective, diagnostic single-arm study called **ST**ereotactic **A**blative radiotherapy for lung cancer after sta**G**ing with **E**ndosonography (STAGE; NL46486.018.13). A similar trial in Canada also aims to compare the results after nodal staging with EBUS-TNA with the findings on CT and FDG-PET scans taken prior to the EBUS-procedure (NCT01786590).

The treatment of so-called oligometastases is still a controversial topic (Chapter 6 and 7). Although the idea of the existence of oligometastases can be very appealing to both physicians and patients, there is only limited data in support of this theory. In patients with lung cancer, an individual patient data meta-analysis was published recently. Using the data of 757 patients with oligometastatic lung cancer, this study identified three risk groups [17], which can guide us in our decision on how to treat patients with oligometastases. The group with the best survival ('low-risk') had a 5 year overall survival of almost 50%, and was formed by patients with metachronous oligometasases (> 6 months). The 'intermediate risk' group was formed by patients with lung cancer and synchronous oligometastases, without evidence of nodal disease (N0), and had a 5 year overall survival of 36%. The group with the worst survival ('high risk'), was formed by patients with lung cancer, synchronous oligometastases and evidence of nodal disease. Their 5 year overall survival was only 14%.

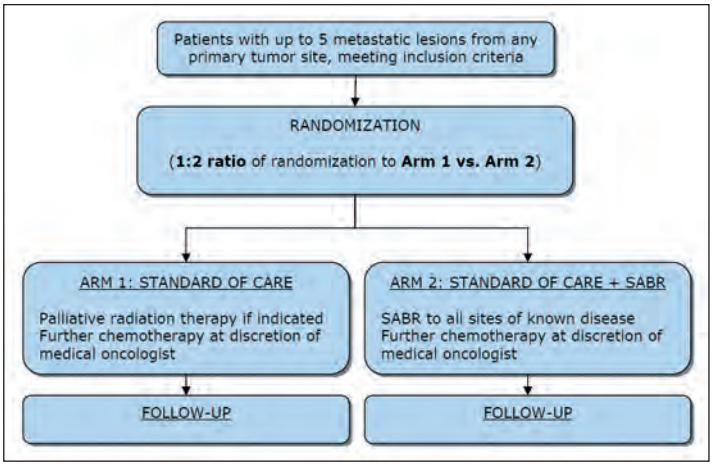

Figure 3. Flow-chart of the Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastastic Tumors (SABR-COMET): a randomized phase II trail.

Available data based on observational studies, or highly selected patient groups, that report better-than-expected outcomes cannot exclude the possibility of patients having more indolent disease [18]. Our ongoing multicenter, randomized phase II trial (NCT01446744; Figure 3) [19] will hopefully be a stepping stone towards a phase III trial for treating oligometastases, and provide higher quality data.

Reducing treatment toxicity using advances in technology

Following thoracic irradiation, changes in lung tissue, such as atelectasis and fibrosis, can become apparent [20, 21]. In addition, factors such as changes in body weight and differences in positioning on consecutive CT-scans. All these changes can make it difficult to reconstruct the doses received by specific anatomical regions in patients who present for thoracic re-irradiation. In some cases, deformable image registration may help to account for these changes and assist the planning of re-irradiation. However, validating the accuracy of DIR is a challenge. Our research (Chapter 8) showed that DIR can better account for anatomical differences than when using a rigid registration, but the technique is not without limitations. This point was illustrated when DIR was evaluated in a more favorable setting, in a study validating several DIR-algorithms using a thoracic 4D-CT-scan in which 300 anatomical landmarks were identified on both the inspiration and expiration phase of this scan [22]. The study showed that DIR performed reasonably well for small displacements, but that its accuracy quickly deteriorated when the displacement of landmarks between the two scans increased. Due to the inability to directly verify the registration, for now, DIR should be used with caution, especially when gross anatomical changes have occurred.

Improved technology for radiotherapy delivery has mainly been used for curative treatments, with an apparent reluctance to do so in a palliative setting. In part, this may be due to the perceived time and effort required to perform such treatments. However, acceptance can be facilitated when techniques can be shown to result in meaningful benefits to patients. A good example of the former in a palliative setting, is illustrated by the use of stereotactic radiosurgery (SRS) for brain metastases, for which there is level I evidence for benefit [23]. Due to concerns about the efficacy and toxicity associated with whole-brain radiotherapy (WBRT), current Dutch guidelines recommend using SRS for 1-3 brain metastases without WBRT, as it appears to reduce the

risk of neurocognitive toxicity [24]. We have recently extended this to selected patients with more lesions, again in an attempt to reduce the risks of toxicity encountered with irradiating the whole brain.

The work performed in this thesis (Chapter 9) also provided an example of where fast, bowel-sparing volumetric modulated arc therapy (VMAT) was implemented in the palliative setting for bone metastases. The use of conventional radiation fields for palliating painful metastases was associated with diarrhea in 28% of patients after a single dose of 8 Gy [25]. With the growing trend of treating patients with NSCLC with targeted therapies, such as tyrosine kinase inhibitors (TKI), it becomes more important to use advanced techniques to spare organs at risk, even in a palliative setting, in order to minimize the risk of (unexpected) toxicity and to minimize treatment interruptions.

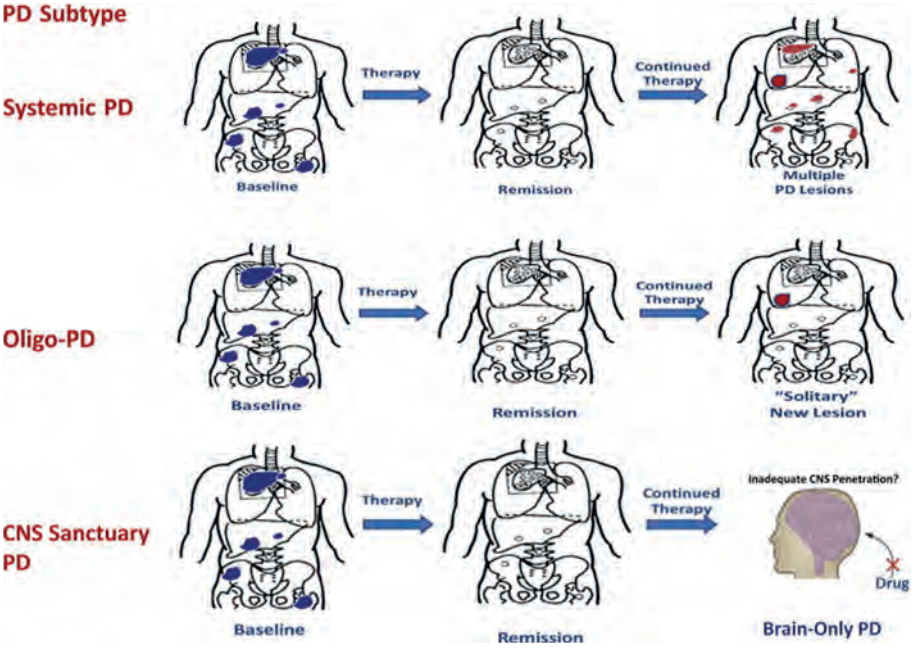

Figure 4. Subtyping Progressive disease. Abbreviations: CNS = centrals nervous system; PD = progressive disease. Derived from [26].

Most patients with lung cancer who present with oncogene-driven tumors acquire resistance to targeted therapies. This can manifest in different clinical scenarios: systemic progressive disease (progression at many sites),

oligo-progressive disease (progression in the form of a single lesion or a small number of new/existing lesions) and isolated, so-called central nervous system sanctuary progression (Figure 4.) [26].

Recent guidelines have now made recommendations to address these clinical scenarios. Updated ESMO guidelines recommend that when oligometastatic progression is detected during treatment with tyrosine kinase inhibitors (TKI's), the use of a local treatment such as surgery or radiotherapy should be considered, and TKI's 'continued or resumed' [27]. Similarly, the National Comprehensive Cancer Network (NCCN) guidelines recommend that when faced with symptomatic progression in the brain or with an isolated extra-cranial lesion, the clinician should consider local therapy and continue the TKI [28]. In practice, the decision about whether to continue with the targeted agent during high-dose radiotherapy (including SABR or stereotactic radiosurgery), should be carefully considered by the treating group. In many cases, we currently elect to stop the agent around the time of radiation therapy.

The concomitant use of chemotherapeutic and/or targeted agents with radiation may, however, cause an increase in toxicity. For example, the combination of vascular endothelial growth factor (VEGF) and radiation has been linked with serious lung and gastro-intestinal toxicity, such as pulmonary fibrosis, tracheo-esophageal fistula, bowel ulceration and even perforations, which may be fatal [29,30]. In addition, in patients treated with sorafenib (a kinase inhibitor) after prior radiation therapy, a recall effect of the radiation has been described, which can cause, for example, radiation dermatitis and pneumonitis [31]. In such cases, we recommend that the radiotherapy techniques used should be chosen carefully, and that advanced techniques be used to spare potential organs at risk, even in relatively low-dose palliative treatments. (Chapter 9 and Figure 5).

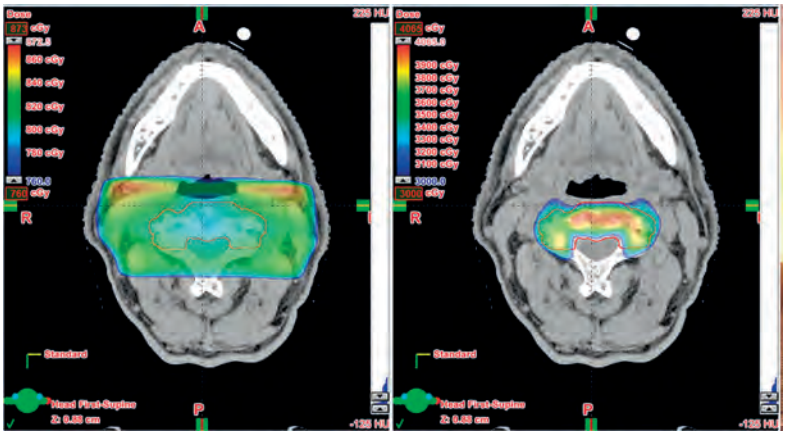

Figure 5. The plan on the left is typical of a conventional cervical spine treatment. Two lateral fields are used to treat the target volume (red line), but they also irradiate everything inbetween (including the spinal canal and esophagus) with a dose that is similar to the prescription dose (in this case the prescribed dose was a single fraction of 8Gy and the colorwash represents a dose of at least 7.6Gy). On the right is a stereotactic radiotherapy plan for the same target volume (red line). In this case, intensity modulation is used to control the dose that is delivered to different regions and discriminate between the target and organs at risk (OAR). This results in relative sparing of the OAR (e.g. spinal cord an esophagus) and enables dose-escalation in the target (in this case the colorwash represents a dose of at least 30Gy, delivered in 5 fractions). Such techniques (with or without dose escalation may be useful in trying to reduce toxicity due to interactions between radiation and targeted therapies.

Additional directions for the future

In addition to the above challenges, two other topics are worthy of mention. It is important for healthcare professionals to encourage all patients to cease smoking, as cessation at any age dramatically reduces death rates [32]. The effectiveness of systematically providing support for smoking cessation to all adult smokers admitted to the hospital, relative to usual care, is established [33]. Patients should be aware that having an initial smoking-related cancer places them at risk of developing a second malignancy [34]. In addition, current smokers with lung cancer have an increased risk of mortality, whereas former and never-smokers have comparable survival (Figure 6)[35].

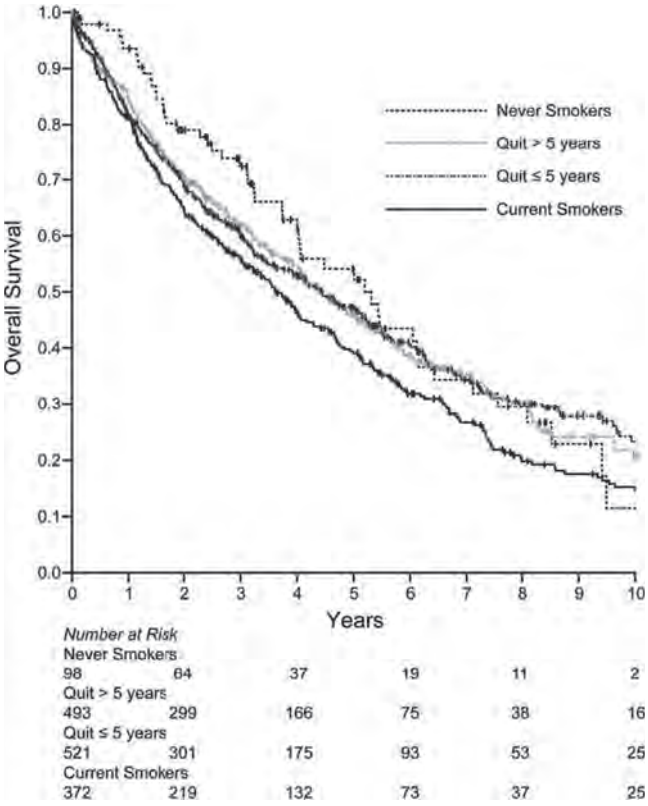

Figure 6. Kaplan-Meier graph demonstrating rates of overall survival , stratified by smoking status. Derived from [35].

In addition, more attention must be paid to the quality of life of lung cancer survivors. A systematic review on quality of life (QoL) of lung cancer patients after a surgical resection, revealed a significant incidence of pain, fatigue, dyspnea and coughing, depressive symptoms and anxiety [36]. It is interesting to note that studies describing QoL after SABR, report that the QoL is preserved, which is in marked contrast to the surgical literature [37-40]. At present, addressing psychological symptoms that may influence QoL, is not routine in the follow-up of lung cancer patients. One model for a 'survivorship program' for lung cancer patients, in which patients who have been disease free for a year are transferred to a nurse practitioner-led program, has recently been described [41]. Such an approach might help in addressing symptoms, such as depression and anxiety, more often. Together with smoking cessation programs, this might improve the lives of lung cancer patients in the future.

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Summary

Although advances in diagnostic and therapeutic options have led to a better survival in cancer patients, there remain several challenges that need to be addressed, particularly in patients with lung cancer.

In patients treated for lung cancer, survival can be influenced by recurrent disease or a second primary tumor. Following a curative treatment for lung cancer, survivors have a 3-6% risk per person year of developing a second primary lung cancer (SPLC). Consequently, several guidelines now recommend the use of CT surveillance.

Chapter 2 describes outcomes of 107 lung cancer survivors, who were diagnosed with early stage SPLC and were treated with stereotactic radiotherapy (SABR). Our analysis showed a three years overall survival (OS) (60%) and local control rate (89%), that are comparable to the outcomes for a first lung cancer. Toxicity was uncommon, despite the fact that 73% of patients had undergone a prior (bi)lobectomy. Given these promising results after SABR for SPLC, CT surveillance seems appropriate in patients who may be unfit, or unwilling, to undergo surgery after curative treatment for an initial lung cancer.

Because of a shared etiology of tobacco exposure, patients with squamous cell head and neck carcinomas (HNSCC) are also at risk of developing a SPLC. Population-based studies show that patients with SPLC after HNSCC have a poorer prognosis compared to patients with a primary lung cancer. In **chapter 3**, we describe outcomes in patients with HNSCC and SPLC treated at our institution. Of a 181 patients identified, 40 patients had a synchronous HNSCC - SPLC and 141 presented with metachronous HNSCC-SPLC. In this cohort, the survival of patients who were diagnosed with advanced disease was indeed poor; 11.0 and 4.6 months for locally advanced and metastatic disease, respectively. However, patients who were diagnosed with early stage SPLC had a significantly better survival, with a median OS of 95.4 months. CT surveillance strategies in HNSCC patients may positively influence survival, and this warrants further investigation.
If a disease recurrence or new primary lung tumor develops in a previously treated area following high-dose radiotherapy, treatment options, such as a

salvage resection or reirradiation are often considered to be limited. This is mainly due to concerns about toxicity. The availability of improved radiotherapy techniques, however, has increased options for reirradiation. In **chapter 4**, we describe our experience with 24 patients treated with high-dose conventional thoracic reirradiation. The majority of patients (63%) had stage III non-small cell lung carcinoma (NSCLC) at both initial and second treatment. Median OS after reirradiation was 13.5 months, with a 1-year survival of 51%. Three patients died with possible grade 5 toxicity (bleeding). Planning target volume (PTV) at reirradiation was the most important prognostic factor, in which a smaller volume (PTV <300cc) was associated with a significantly better survival. The magnitude of overlap between the initial and subsequent PTVs, and between dose distributions, did not appear to influence survival. Further studies are needed to confirm feasibility and prognostic factors, and to establish reliable normal tissue tolerance doses for reirradiation.

As diagnostic imaging continues to improve, the number of lung cancer patients diagnosed with multiple primary lung cancers (MPLC) is increasing. Current guidelines recommend a curative approach when early-stage MPLC is diagnosed, based on favorable outcomes have been reported after surgery. In **chapter 5**, we describe outcomes following stereotactic ablative radiotherapy (SABR) in 62 patients with MPLC. In our series, the median OS was 31 months, with an actuarial 2-year survival of 56%. No grade 4 or 5 post-SABR toxicity was observed. Two-year local and regional control rates were 84% and 87%, respectively. As toxicity is limited, we believe that SABR should be considered when patients with lung cancer present with a synchronous second lesion, and where no nodal involvement is detected.

In contrast to early-stage lung cancer, survival in most patients with metastatic lung cancer is poor. However, it has been suggested that there might be a subgroup of patients, in whom the number of metastases is limited ('oligometastases'), who have a favorable prognosis, if all lesions can be treated with radical intent. **Chapter 6** describes outcomes of 61 lung cancer patients who, at the time of diagnosis, already had 1-3 metastases. These patients were treated with radical intent to all sites of disease. The 1- and 2-year OS in this cohort were 54% and 38%, respectively. These favorable outcomes were associated with the intra-thoracic disease status: patients with small

radiotherapy treatment volumes or resected disease had the best OS.
In addition to evaluating outcomes of lung cancer patients with synchronous oligometastases, we also reviewed the literature on the use of radiotherapy for oligometastases in **chapter 7**.

Finally, improved technology for reconstructing previous doses can permit safer thoracic reirradiation. This reconstruction of the previously administered dose can be rendered difficult due to anatomic changes by tissue loss or post-irradiation fibrosis. A technique to account for anatomical changes and more accurately reconstruct prior doses, is deformable image registration (DIR). In **chapter 8** we compare the performance of DIR to rigid image registration (RIR), to evaluate accuracy.

In a palliative setting, radiation treatment often consists of just a single fraction. As a palliative radiation dose, is relatively low, the sparing of organs is often not given a high priority, and a simple technique is use, so time can be spared, and patients can be treated quickly. However, despite the low dose, it can be associated with toxicity. Furthermore, with the increased use of targeted agents, organ sparing radiotherapy might become more important, as awareness of the potential for radiation-drug interactions increases. In **chapter 9**, we describe the use of intensity modulated radiotherapy (IMRT) for large-field palliative pelvic bone treatments, which can substantially reduce the dose delivered to abdominal/pelvic organs, and show that it is possible to introduce such techniques into routine care.

Samenvatting

Hoewel vooruitgang in diagnostische en therapeutische toepassingen heeft geleid tot een betere overleving bij kankerpatiënten, zijn er nog steeds een aantal uitdagingen die moeten worden aangepakt, vooral bij patiënten met longkanker.

Bij patiënten die behandeld zijn voor longkanker kan de overleving worden beïnvloed door een recidief of een tweede primaire tumor. Na een curatieve behandeling voor longkanker hebben deze patiënten een risico van 3-6% per persoon per jaar op het ontwikkelen van een tweede primaire longkanker ("second primary lung cancer"; SPLC). Daarom bevelen verschillende richtlijnen nu ook het gebruik van CT-surveillance aan.

Hoofdstuk 2 beschrijft de resultaten van 107 behandelde longkanker patiënten, die met een vroeg stadium SPLC werden gediagnosticeerd en zijn behandeld met stereotactische radiotherapie ("stereotactic ablative radiotheray"; SABR). Onze analyse toonde een 3-jaars overleving (60%) en locale controle (89%), die vergelijkbaar zijn met de uitkomsten na een eerste longkanker. De toxiciteit bleef beperkt, ondanks het feit dat 73% van de patiënten eerder een (bi) lobectomie hadden ondergaan. Gezien de veelbelovende resultaten na SABR voor SPLC lijkt CT-surveillance ook aangewezen bij patiënten die ongeschikt of niet bereid zijn, om een operatie te ondergaan na de curatieve behandeling voor hun eerste longkanker.

Gezien de gedeelde etiologie door roken, lopen patiënten met een plaveiselcelcarcinoom van de hoofd-halsregio ook een risico op het ontwikkelen van een SPLC. Studies op basis van populatie-data tonen aan dat patiënten met SPLC na een hoofd-halstumor een slechtere prognose hebben, dan patiënten met een primaire longkanker. In **hoofdstuk 3** beschrijven we de resultaten van patiënten met een hoofd-halstumor en SPLC, welke behandeld zijn in ons ziekenhuis. Van de 181 geselecteerde patiënten hadden 40 patiënten een synchrone en 141 presenteerden zich met een metachrone hoofd-halstumor met SPLC. In dit cohort, was de overleving van patiënten, die werden gediagnosticeerd met een meer gevorderde stadium inderdaad matig; 11,0 en 4,6 maanden voor respectievelijk een lokaal gevorderd en

gemetastaseerd stadium. Echter, patiënten die werden gediagnosticeerd met een vroeg stadium SPLC hadden een significant betere overleving, met een mediane overleving van 95,4 maanden. CT-surveillance zou, daarom, bij hoofd-halskankerpatiënten een positieve invloed kunnen hebben op de overleving en dit vraagt om verder onderzoek.

Als een recidief of nieuwe primaire longtumor zich ontwikkelt in een eerder, met hoge dosis radiotherapie behandelde gebied worden de behandelopties, zoals een salvage resectie of re-irradiatie, vaak beperkt geacht. Dit, voornamelijk door zorgen over de toxiciteit. Door de beschikbaarheid van betere technieken in de radiotherapie, zijn echter de mogelijkheden voor re-irradiatie toegenomen. In **hoofdstuk 4** beschrijven we onze ervaring met 24 patiënten, die behandeld zijn met een hoge dosis conventionele re-irradiatie. De meerderheid van deze patiënten (63%) had een stadium III niet-kleincellig longcarcinoom (NSCLC) tijdens zowel de eerste als tweede behandeling. De mediane overleving na re-irradiatie was 13,5 maanden, met een 1-jaars overleving van 51%. Drie patiënten overleden door een mogelijke graad 5 toxiciteit (bloeding). De belangrijkste prognostische factor was het geplande doelgebied (PTV) voor de re-irradiatie, waarbij een kleiner volume (PTV <300cc) geassocieerd was met een significant betere overleving. De mate van overlap tussen het eerste en het tweede PTV en tussen de dosis van beide behandelingen bleek geen invloed te hebben op de overleving. Verdere studies zijn nodig om de haalbaarheid en prognostische factoren te bevestigen, en om meer betrouwbaar de tolerantie van de normale weefsels voor re-irradiatie te bepalen.

Door de continue verbetering van de diagnostische beeldvorming wordt het aantal longkanker patiënten, die met meerdere primaire longtumoren ("multiple primary lung cancers"; MPLC) gediagnosticeerd worden, steeds hoger. De huidige richtlijnen adviseren een curatieve aanpak bij een vroeg stadium MPLC, gebaseerd op de gunstige resultaten na resectie. In **hoofdstuk 5** beschrijven we de resultaten na SABR bij 62 patiënten met MPLC. In onze serie was de mediane overleving 31 maanden, met een actuariële 2-jaars overleving van 56%. Er werd geen graad 4 of 5 post-SABR toxiciteit waargenomen. De 2-jarige lokale en regionale controle bedroegen respectievelijk 84% en 87%. Aangezien de toxiciteit van deze behandeling beperkt is, zijn wij van mening

dat SABR moet worden overwogen bij longkankerpatiënten met een synchrone tweede laesie, bij wie geen pathologische lymfklieren zijn gevonden.

In tegenstelling tot de goede overleving van een vroeg stadium longkanker, is de overleving bij de meeste patiënten in een gemetastaseerd stadium zeer matig. Echter, mogelijk bestaat er een subgroep van patiënten met slechts een beperkt aantal metastasen (oligometastasen), waarbij de prognose gunstiger is, mits alle laesies radicaal behandeld kunnen worden. **Hoofdstuk 6** beschrijft de uitkomsten van 61 longkankerpatiënten die ten tijde van de diagnose 1 tot 3 metastasen hadden. In deze patiënten zijn alle ziektelocaties radicaal behandeld. De 1- en 2-jaars overleving in dit cohort waren respectievelijk 54% en 38%. Deze gunstige resultaten leken geassocieerd met de mate van intra-thoracale ziekte: patiënten met een klein radiotherapeutisch doelvolume en patiënten die geopereerd waren, hadden de beste overlevingskansen.
Naast het evalueren van de overleving van longkankerpatiënten met synchrone oligometastasen hebben we, in **hoofdstuk 7**, ook een overzicht gemaakt van de literatuur over het gebruik van radiotherapie bij oligometastasen.

Tenslotte kan de vooruitgang in de technologie voor het reconstrueren van een eerder gegeven bestralingsdosis, re-irradiatie mogelijk veiliger en vaker mogelijk maken. De reconstructie van de eerder toegediende dosis kan lastig zijn door anatomische veranderingen, zoals het verlies van weefsel of het ontstaan van radiatie-fibrose. Een techniek die rekening houdt met anatomische veranderingen om zo de voorafgaande doses nauwkeuriger te reconstrueren, is 'deformable image registration' . In **hoofdstuk 8** vergelijken we de prestaties van deformable image registration met rigide registratie, om de nauwkeurigheid te beoordelen.

Een palliatieve bestraling bestaat vaak uit slechts een enkele fractie. De dosis van deze bestraling is relatief laag en daarom heeft het sparen van organen vaak niet een hoge prioriteit en wordt een eenvoudige techniek gebruikt, zodat tijd wordt bespaard en patiënten snel kunnen worden behandeld. Ondanks de lage dosis, kan een palliatieve bestraling toch ook toxiciteit geven. Bovendien wordt met het toenemende gebruik van 'targeted agents', orgaansparende radiotherapie nog belangrijker, naarmate de kennis over mogelijke interacties tussen deze medicatie en de bestraling toeneemt. In **hoofdstuk 9** beschrijven

we het gebruik van 'intensity modulated radiotherapy' voor de palliatieve behandeling van grote bekken-velden. Hierdoor kan een aanzienlijke verlaging van de dosis op de organen in de buik en het bekken worden gerealiseerd. Wij hebben laten zien dat het mogelijk is om deze nieuwe technieken in de dagelijkse praktijk toe te passen.

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Curriculum Vitae

Gwendolyn Griffioen was born in 1983 in Hilversum, the Netherlands. She graduated from the gymnasium in 2001, after which she started medical school at the University of Amsterdam.

After reading an article about autologous breast reconstruction for breast cancer that her father passed on to her, she became interested in the speciality of oncology. During her internships, she was drawn towards the more hands-on discipline of surgery, and joined a research project at the department of surgery at the Academic Medical Center Amsterdam. After her internships, she became a resident on the surgical department of the Tergooi Hospital in Hilversum. During this stage, she realized that although she very much liked the practical side of this profession, her interest was more on the oncological cases. At that point, a colleague pointed her in the direction of the radiation oncology, which appeared to fulfill her professional interests.

During her interview at the department of radiation oncology of the VU University Medical Center, she was offered the opportunity to start with performing research at this department, supervised by professor S. Senan. She grabbed this opportunity with both hands and this resulted in not only this thesis but also, following three years of research, in a position in the medical residency program. She expects to qualify as a radiation oncologist in September 2018.

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