Towards Optimization of Treatment and Patient Selection in Stereotactic Body Radiotherapy for Lung and Oropharynx cancer

This thesis has been prepared at the Department of Radiation Oncology, Erasmus Medical Center - Cancer Institute, Rotterdam, The Netherlands.

ISBN: 978-94-6361-665-2

Towards Optimization of Treatment and Patient Selection in Stereotactic Body Radiotherapy for Lung and Oropharynx cancer

Op weg naar een Optimale Behandeling en Patiëntselectie bij Stereotactische Radiotherapie voor Long- en Orofarynxkanker

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus

Prof.dr. A.L. Bredenoord

and in accordance with the decision of the Doctorate Board.
The public defence shall be held on

Tuesday 19 April 2022 at 13.00 hrs by

Sarah Pettit Baker
born in British Columbia, Canada

Erasmus University Rotterdam

Doctoral Committee:

Promotor:	**Prof. dr. M.S. Hoogeman**
Other members:	**Prof. dr. R. Nout** **Prof. dr. E. Lartigau** **Prof. dr. H. Takkenberg**
Copromotors:	**Dr. J.J.M.E. Nuyttens** **Dr. W. D. Heemsbergen**

Contents

Chapter 1:	Introduction	7
Chapter 2:	A critical review of recent developments in radiotherapy for non-small cell lung cancer	13
Chapter 3:	Prediction of early mortality following stereotactic body radiotherapy for peripheral early-stage lung cancer.	35
Chapter 4:	Development and external validation of a nomogram to predict overall survival following stereotactic body radiotherapy for early-stage lung cancer.	49
Chapter 5:	Endovascular coils as lung tumor fiducial markers for real-time tumor tracking in stereotactic radiotherapy.	69
Chapter 6:	Long term outcomes following stereotactic body radiotherapy boost for oropharyngeal squamous cell carcinoma	85
Chapter 7:	Locoregional failures and their relation to radiation fields following stereotactic body radiotherapy boost for oropharyngeal squamous cell carcinoma.	107
Chapter 8:	Discussion	129
	References	143
	Summary	165
	Samenvatting	169
	List of Publications	173
	PhD Portofolio	177
	Curriculum Vitae	179
	Acknowledgements	181

Chapter 1

General Introduction

Stereotactic radiotherapy

Stereotactic body radiotherapy (SBRT) is a method of external beam radiotherapy which accurately delivers a high dose of radiation in one or a few treatment fractions to an extracranial target [1,2]. This technique was made possible only in recent decades with advancements in radiotherapy technologies. Improved image-guidance, such as cone beam computed tomography, has allowed for reduced margins for positional uncertainty. Organ motion-management strategies including gating, tumor-tracking or 4-dimensional computed tomography have also improved treatment accuracy. Finally, more conformal delivery is now possible with multiple conformal or intensity modulated beams or arcs. This can reduce dose to normal structures and potentially reduce treatment toxicity. Increased treatment accuracy and precision has allowed for safe dose escalation, such that with SBRT, ablative doses can safely be delivered to the tumor. Delivery of higher dose per treatment fraction results in a higher biologically effective dose and potentially improved tumor control.

After its introduction first in Sweden for the treatment of lung and liver tumors in 1991, followed by Japan in 1994 and centers in the USA and Europe a few years later [3], early clinical results were published and showed promising rates of local control with low toxicity [4,5]. Over the next three decades, it would become widely adopted, despite a paucity of level I evidence to support its use. With its subsequent expansion to diverse anatomic sites, yet lack of supporting randomized data, evaluation of outcomes and prognostic factors through comparative effectiveness research is required. Cohort and

database studies may provide much-needed guidance for patient selection and an improved understanding of prognostic factors for this resource-intensive treatment.

This thesis investigates SBRT for tumors in two anatomical sites: lung and oropharynx. SBRT treatment of these sites requires further optimization due to lack of current knowledge regarding appropriate patient selection criteria and, in the case of oropharyngeal tumors, clinical outcomes.

SBRT in lung cancer

Lung cancer is the most common cancer worldwide, with the highest associated mortality [6]. Due to risk factors of cigarette smoking and increasing age, lung cancer patients typically have a high burden of comorbid illness. Many patients are not fit to undergo primary surgical resection. The introduction of SBRT has provided a potentially curative and non-invasive alternative to surgery for patients with early stage disease. SBRT has become the first-line treatment option for medically inoperable early stage lung cancer and for patients refusing surgery [7]. The two small randomized trials published to date have shown SBRT to be superior to conventional RT in terms of local control [8] and toxicity [9].

SBRT in oropharynx cancer

Oropharyngeal squamous cell carcinomas are relatively uncommon malignancies, however, the incidence of HPV-associated disease has substantially increased in recent years [10].
To date, SBRT for head and neck malignancies has primarily been used in the setting of re-irradiation [11-13], or occasionally, for small nasopharyngeal carcinomas [14,15].

At our institution, SBRT boost has been used for treating oropharynx cancer since 2005 when it evolved to try to emulate the dose distribution provided by the long-used technique of brachytherapy boost.

Scope of this thesis

The treatment of lung and oropharynx cancers with SBRT can be improved upon by gaining a better understanding of prognostic factors, which can be used to optimize treatment and patient selection. In early stage lung cancer, accurate prognostic models are lacking. Similarly, prognostic factors and overall outcomes following SBRT boost for oropharynx cancer have not been studied. This thesis investigates prognostic factors in lung and oropharynx SBRT.

Overview of chapters

Lung SBRT: Chapter 2-5

Chapter 2 introduces SBRT as one of the key recent developments in lung cancer radiotherapy. This chapter reviews defining features of SBRT and discusses recent technological advances in RT delivery.
It also introduces the theme of patient selection, and tailoring the application of advanced radiotherapy technologies to those patients most likely to benefit.

In early stage lung cancer, patient selection for SBRT remains challenging. The early stage lung cancer population is characterized by a high burden of comorbid illness and consists largely of patients ineligible for surgery due to advanced age and cardiopulmonary disease. Based on current literature and prognostic models, we cannot reliably identify patients who should not receive lung SBRT due to competing mortality risk [16]. Appropriate patient selection is important in order to utilize this resource-intensive technique judiciously. SBRT requires more time-intensive treatment planning and more rigorous quality-assurance compared to conventional radiotherapy techniques [1]. Although recent consensus guidelines from the European Society for Radiotherapy and Oncology (ESTRO) identify short estimated life expectancy as a contraindication for treatment [7], prognostic factors for short-term survival have not been determined. This

is the objective of Chapter 3. Additionally, the Chapter compares two common indices for measuring patient comorbidity (Charlson Comorbidity Index and Cumulative Illness Rating Scale) with respect to their ability to predict early mortality following SBRT.

Chapter 4 expands on the theme of prognostic factors and survival prediction. A nomogram is developed and validated, which can be used to generate survival predictions at the individual patient level.

Due to the high burden of comorbidity, lung SBRT patients are at high risk should they develop treatment-related toxicity. While a number of SBRT delivery platforms are available, the CyberKnife is advantageous in that it provides real-time tumor tracking and enables very precise and accurate treatment delivery [17]. However, fiducial markers are often required for treatment of lung tumors on the Cyberknife. Patients with underlying cardiopulmonary comorbidity may be at high risk of complications from fiducial markers such as pneumothorax. Chapter 5 investigates complication rates following fiducial marker placement.

Oropharynx SBRT: Chapter 6-7

Despite increasing implementation of SBRT for the treatment of head and neck tumors [11], large cohort studies reporting on outcomes are currently lacking. Survival and tumor control rates are needed in order to evaluate this treatment strategy against the current standard treatments, conventional (chemo)radiotherapy or surgical resection.

Since its introduction at our institution for oropharynx cancer treatment in 2005, a large cohort of patients with small (T1- small T3) tumors have been treated with SBRT as a boost following conventional IMRT. Early studies suggested potentially improved swallowing function and quality of life compared to conventional RT [18,19]. Long-term outcomes, including cancer-specific survival, toxicity, and locoregional patterns of failure, have not been studied. Evaluation of late severe toxicity is needed, as a major

challenge in the application of SBRT to head and neck tumors has been the potential for severe late toxicity including soft tissue necrosis and carotid blow out [20-23].

Indeed, due to the high dose per fraction in SBRT regimens, there is a risk of severe late toxicity following SBRT. Chapter 5 investigates rates of severe late toxicity in oropharynx cancer patients treated with SBRT boost. Prognostic factors for late toxicity are investigated as well.

Local control and prognostic factors for locoregional failure are examined in Chapter 7. Due to the highly conformal nature of SBRT dose delivery, there is a theoretical increased risk of marginal miss and accurate tumor delineation is of increasing importance. However, patterns of failure with respect to the radiotherapy field has not been studied. This is investigated in Chapter 7.

A discussion and summary of conclusions of this thesis is provided in Chapter 8.

Chapter 2

A critical review of recent developments in radiotherapy for non-small cell lung cancer

S Baker[1], M Dahele[2], FJ Lagerwaard[2], S Senan[2]

1 Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands
2 Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands

Published: Radiation Oncology. 2016;11(1):115

Abstract

Lung cancer is the leading cause of cancer mortality, and radiotherapy plays a key role in both curative and palliative treatments for this disease. Recent advances include stereotactic ablative radiotherapy (SABR), which is now established as a curative-intent treatment option for patients with peripheral early-stage NSCLC who are medically inoperable, or at high risk for surgical complications. Improved delivery techniques have facilitated studies evaluating the role of SABR in oligometastatic NSCLC, and encouraged the use of high-technology radiotherapy in some palliative settings. Although outcomes in locally advanced NSCLC remain disappointing for many patients, future progress may come about from an improved understanding of disease biology and the development of radiotherapy approaches that further reduce normal tissue irradiation. At the moment, the benefits, if any, of radiotherapy technologies such as proton beam therapy remain unproven. This paper provides a critical review of selected aspects of modern radiotherapy for lung cancer, highlights the current limitations in our understanding and treatment approaches, and discuss future treatment strategies for NSCLC.

2.1 Background

Lung cancer is the most frequently diagnosed cancer worldwide and the leading cause of cancer mortality, accounting for over 1.6 million deaths annually [24]. The role of curative-intent radiotherapy (RT) is well established in locally advanced [25] and early stage [26] non-small cell lung cancer (NSCLC). Nonetheless, the thorax remains a challenging anatomical site for RT delivery, due to the low electron density of lung, respiratory- and cardiac-induced tumor motion, and proximity of critical structures such as the esophagus and spinal cord. While advanced RT technologies can address many of these challenges [27–30], in most cases, the clinical benefit of such technology still needs to be demonstrated, especially since radiation oncology was the medical specialty generating the greatest increase in Medicare expenditures between 2003 and 2009 [31]. However, the evaluation of new technologies remains challenging. This review will discuss the current state of modern RT for NSCLC, limitations, and strategies to improve clinical outcomes in the future.

2.2 Early stage, localized disease: lung SABR

The impact of advanced RT technology is perhaps most evident in the setting of early-stage NSCLC. Stereotactic ablative radiotherapy (SABR) is now considered the standard of care for medically inoperable patients with peripheral early-stage NSCLC [26]. SABR utilizes small margins for positional uncertainty, facilitated by 4-dimensional computed tomography (4DCT), multiple conformal or intensity modulated beams or arcs and volumetric image-guidance [32]. While peripheral lung SABR can also be delivered without these technologies, newer techniques can increase treatment efficiency and user confidence. Treatment-related toxicity with peripheral lung SABR is modest [33–35]. As SABR is not universally available, it is reassuring that data from the randomized SPACE study in patients with peripheral NSCLC suggest similar tumor outcomes with conventionally fractionated 3-dimensional conformal radiotherapy to 70 Gy [36].

There is an ongoing debate about the role of SABR in patients who are fit to undergo surgery [32]. A pooled analysis of two randomized trials of operable patients which closed prematurely due to slow accrual, showed a 16 % higher 3-year survival with SABR compared to surgery ($p = 0.037$). This was due to the higher rate of peri-operative mortality in the surgical group [37]. A propensity score matched analysis revealed that rates of treatment associated mortality and severe toxicity were lower with SABR for stage I-II NSCLC than with lobectomy performed by minimally-invasive video-assisted thoracoscopic surgery (VATS) [38]. Data from both retrospective [39, 40] and prospective phase II studies of SABR suggest survival outcomes similar to surgery [35, 41]. Shared decision-making tools may assist operable patients and their clinicians to arrive at a management plan based on a patient's preferences and values [42,43]. The role of SABR in surgical patients continues to be examined in 3 studies (NCT02468024, NCT02629458, NCT01753414), with a fourth (VALOR study) due to open this year. Both the SABRTooth and STABLE-MATES trials focus on high-risk patients.

Further improvements in SABR outcomes may come from strategies to reduce the rates of local-regional and distant failure, and from technology improvements that facilitate SABR in challenging scenarios such as central tumors (Table 1).

Table 1. Challenges and solutions for difficult SABR scenarios

	Clinical Scenario	Challenges	Potential Solutions Being Explored
Pre Treatment	Incorporating patient preferences for treatment	Choice of SABR in operable NSCLC	• Shared decision-making [19, 20] • Comparative effectiveness research (including patient-reported outcomes, QOL and cost-effectiveness analyses) with "big data" strategies to facilitate data mining • RCTs underway (NCT02629458, NCT01753414 , NCT02468024, VALOR study)
	Obtaining a diagnosis	Risks of treating benign disease Risks of biopsy in frail patients	• Use validated models for cancer risk determination in a given population [9] • Exploring blood biomarkers [119]
Treatment	Central tumors Multiple primary lung cancers	Proximity to OARs Uncertainty in OAR location Uncertainly in OAR dose constraints Higher pneumonitis risk	• "Big data" strategies to establish more reliable OAR dose constraints • MRI-guided adaptive RT [44] • Protons [41]
	Oligometastases	Identify molecular and clinical characteristics of patients likely to benefit from ablative local therapies Optimize sequencing of RT and new systemic treatments	• Phase I-II trials, and well as randomized trials
Follow-up	Detection of recurrences	Distinguishing post-RT fibrosis vs recurrent disease	• Radiomic approaches [24]
	Survivorship issues	Loco-regional recurrences and second lung tumors Smoking cessation	• Survivorship clinics [120] • Patient-reported outcomes, including financial impact

Abbreviations: QOL quality of life; RT radiotherapy; SABR stereotactic ablative body radiotherapy; NSCLC non-small cell lung cancer; OAR organ at risk; PTV planning target volume

2.3 Recurrences

Local failures following SABR include recurrences in the treated lesion or involved lobe, which are in the order of 9–20 % at 5 years [35, 39]. True rates of local control can be

difficult to ascertain due to post treatment fibrosis, and radiologic changes can continue to evolve many years after treatment [44]. So-called ‘high-risk features’ on serial computed tomography (CT) scans may allow post-SABR fibrosis to be distinguished from local recurrence [45, 46] and image texture analysis merits investigation for the early identification of disease recurrence [47]. Radiological follow-up in accordance with ESMO guidelines may enable early identification of salvageable local/regional failures [48–50].

Regional lymph node failures have been observed in between 13–15 % of SABR patients at 5 years [35, 39] which appears comparable to lobectomy [38, 51, 52]. The role of routine endoscopic mediastinal and hilar nodal staging in patients without suspicious findings on positron emission tomography (PET)-CT studies is currently the subject of prospective studies [NCT01786590; NCT02719847]. When isolated hilar or mediastinal nodal failures occur, salvage radiotherapy may be possible in more than 50 % of patients, and appears well tolerated [53].

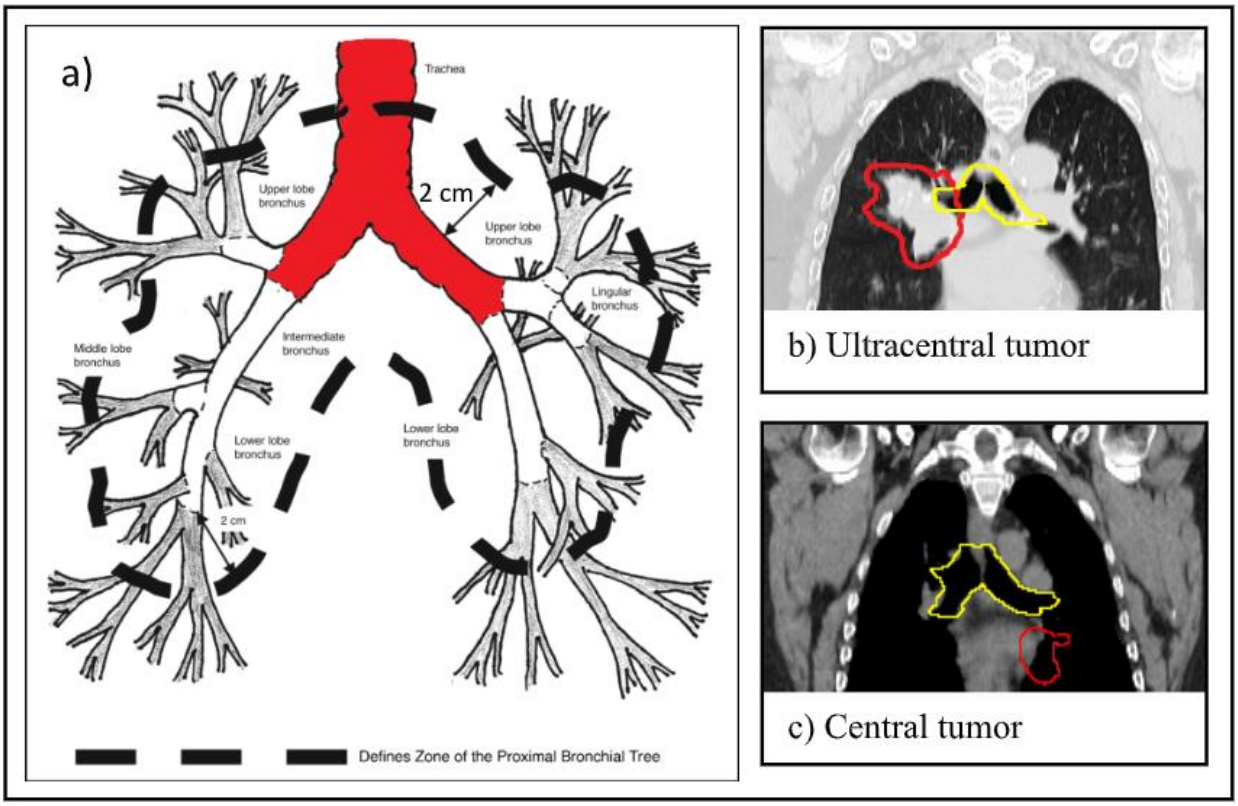
Approximately 20 % of patients develop distant disease recurrence following SABR [54, 55], which is once again similar to that observed after surgery. This suggests that systemic therapies could be of benefit in selected patients, although the recruitment of medically inoperable, elderly patients into studies exploring combined SABR and cytotoxic chemotherapy has proven to be challenging (NCT01300299).

2.4 Central early-stage NSCLC

The Advanced Radiation Technology Committee of the International Association for the Study of Lung Cancer (IASLC) has defined ‘central tumors’ as those located within 2 cm in all directions of any mediastinal critical structure, including the bronchial tree, esophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve, and recurrent laryngeal nerve [56]. It is notable that severe toxicity was reported following delivery of SABR in 3 fractions to doses of 60–66 Gy to central tumors [57], but not when ‘risk-adapted’ dosing strategies were used [35]. Both a systematic review [58], and a recent update [59], suggest that risk-adapted SABR delivered in 8 fractions is an

effective treatment for moderately central tumors. However, tumor location may help to explain some of the differences between reports. It is important to distinguish ‘moderately central’ tumors from lesions immediately adjacent to central airways, so-called ‘ultracentral lesions’ (Fig. 1). The latter term has been used to describe a PTV that overlaps the trachea or main bronchi [60], with increased toxicity reported for this subgroup after both conventional and hypo-fractionated radiotherapy schemes [60–62]. A retrospective study reported that likely or possibly treatment-related deaths occurred in 7.5 % of patients with moderately central tumors [59]. The recent Radiation Therapy Oncology Group (RTOG) 0813 trial aimed to establish the safest dose that can be delivered in 5 fractions for central lesions [63]. Preliminary data reported that patients treated with the highest dose level (60 Gy in 5 fractions) had a 23 % rate of grade 3–5 toxicity. It should be acknowledged that the true radiation tolerance for central organs at risk (OARs) remains unknown, and uncertainty in tumor and OAR positions during treatment adds to our inability to determine true cumulative doses.

Figure 1. Definitions and examples of central and ultra-central lung tumor



a) Diagram of the central airways of the lung.
Reprinted with permission. ©2006. American Society of Clinical Oncology. All rights reserved. Timmerman, R et al: J Clin Oncol 24(30), 2006: 4833-9.
The black dashed line defines the location of tumors that are central relative to the proximal bronchial tree. The term central has been widened to include the region within 2 cm in all directions of any mediastinal critical structure, including the bronchial tree/trachea, esophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve, and recurrent laryngeal nerve. The region shaded red shows the trachea and main bronchi, and lesions with a PTV which overlaps this region are considered as ultracentral.
b) Example of ultracentral tumor (planning target volume in red and main bronchi/trachea in yellow).
c) Example of central tumor.

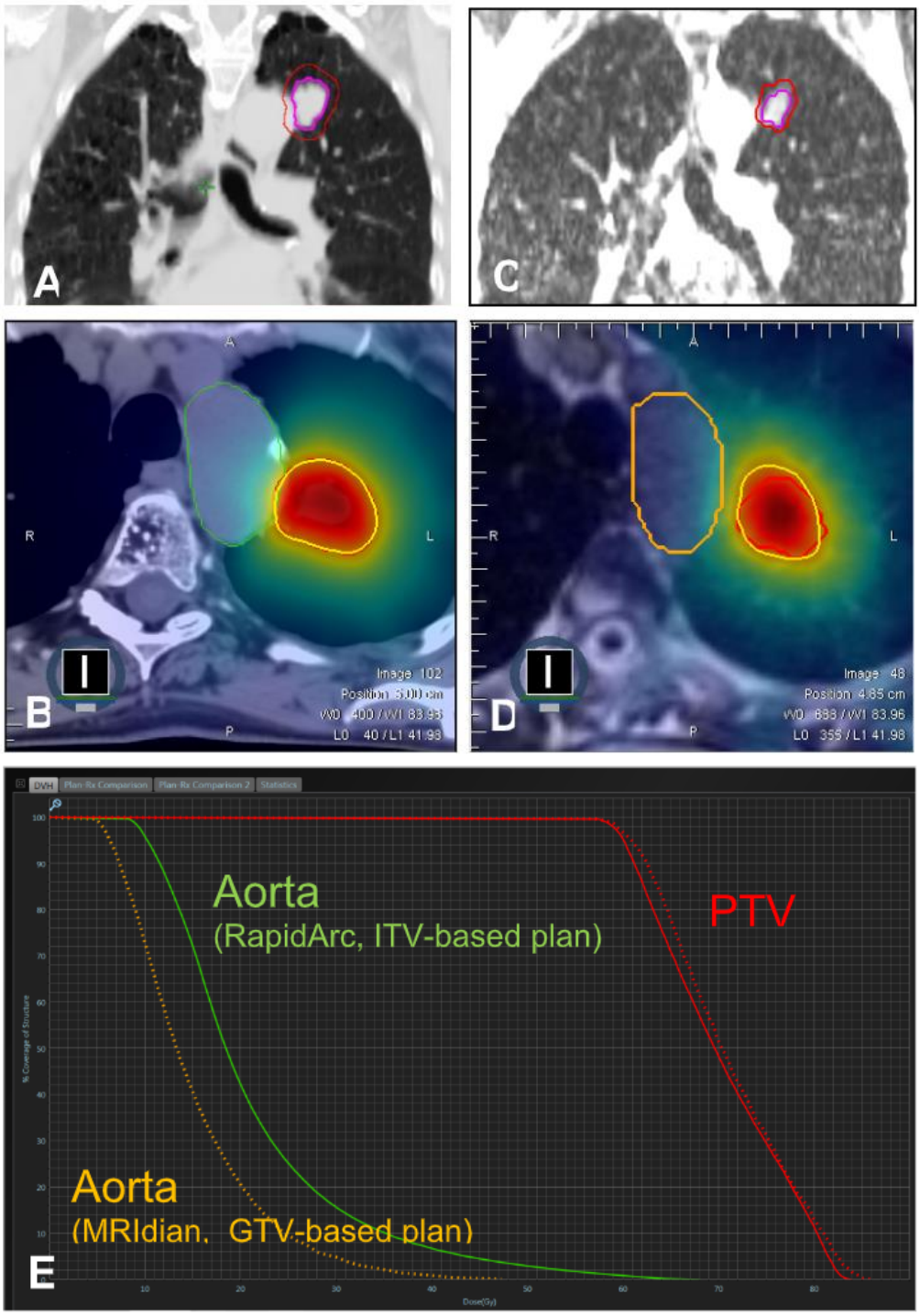
It has been suggested that proton beam therapy (PBT) can allow for dose reduction to central structures [64], although the benefits of PBT may be questionable given its susceptibility to anatomic and positional variations [65]. Although on-line matched cone beam CT scans can be used to image OARs prior to irradiation [66], the field has been advanced by the recent introduction of magnetic resonance imaging (MRI) -guided RT delivery (MRIdian System, Viewray Inc, Cleveland, OH). The MRIdian platform

facilitates online adaptive radiotherapy, and allows for direct tumor visualization during treatment delivery at 4 frames per seconds in the sagittal plane [44]. During gated radiotherapy using breath-hold mode, the system automatically shuts-off radiation delivery with a lag-time of 0.4 s (or less) when the target is outside pre-specified safety margins (Fig. 2). A number of other linac-MR delivery platforms are in development [68–70] and may contribute to advances in the practice of central SABR.

2.5 Multiple primary lung cancers

The incidence of multiple synchronous primary lung cancers (MPLCs) can be as high as 4–8 % [71], and second primary lung cancers occur at a rate of approximately 3 % per year [50]. Several studies report excellent local control and modest toxicity following SABR for MPLCs [72–74]. As larger volumes of some OAR's are irradiated in this situation, strategies designed to reduce tumor motion and dose to OARs are warranted.

Figure 2. Comparative treatment plans for MRI-guided radiotherapy using breath-hold versus a standard free-breathing internal target volume (ITV)-based approach for a central tumor in a patient with interstitial lung disease.



Panel **a** shows the ITV (7.8 cc) for a RapidArc (volumetric modulated arc therapy) plan, to which a 5 mm margin was added to derive a planning target volume (PTV, 26 cc).
Panel **b**: the corresponding dose color-wash for an 8 fraction stereotactic ablative radiotherapy scheme to 60 Gy. Treatment was delivered using on-line MRI guided breath-hold on the MRIdian in which the target was the gross tumor volume (6.9 cc, Panel **c**), to which a 3 mm setup PTV margin was added (PTV 13.6 cc). Panel **d** shows the MRIdian dose color-wash, and Panel e the dose volume histograms fro the adjuacent aorta for both plans.

In a randomized trial, surgical resection of a single brain metastasis combined with whole brain RT, more than doubled median survival from 15 to 40 weeks, and lengthened functional independence compared to RT alone [75]. More than three-quarters of patients in the study by Patchell et al. consisted of patients with NSCLC. In unselected oligometastatic patients, however, rates of progression-free survival (PFS) are highly variable, suggesting that many have more widely disseminated occult disease. In retrospective studies, rates of 5-year survival may approach 50 % in highly select patients, namely those with metachronous lesions, lower number of metastases and a good performance status [76]. A recent multi-centre phase II trial randomized NSCLC patients with ≤ 3 metastases who did not progress after first line systemic treatment to either local consolidative therapy (surgery, RT or chemo-RT to all metastases, with or without systemic therapy) or to systemic therapy alone [77]. The study was closed early after only 49 patients were enrolled when interim analysis found the median PFS in the consolidative therapy arm to be 14.4 months compared to 3.9 months in standard arm. Although these findings are provocative, the limited patient numbers mean that additional studies will be required. The interest in exploring ablative treatments for oligometastatic disease will increase following the proposed revision in the 8th Edition of the TNM lung cancer classification system, where the current M1b category is subdivided into a new M1b, comprising a single extra-thoracic metastasis in a single organ, and M1c, encompassing multiple extra-thoracic metastases [78].

Another area of investigation is the use of SABR in the setting of oligo-progression, where disease that has initially responded to systemic treatment, subsequently demonstrates limited progression [79]. In patients with stage IV disease who receive molecular targeted therapy for an activating mutation of the EGFR receptor, or an ALK-translocation, and who subsequently develop progression at limited sites, the use of local ablative therapies is now recommended in the European Society for Medical Oncology (ESMO) guidelines [80].

2.7 Locally advanced NSCLC

Stage III NSCLC remains a challenging disease to treat. In randomized trials, the addition of surgery has not been shown to be of benefit to overall survival (OS), compared to definitive concurrent chemoradiotherapy (CRT) (Table 2). In a phase III trial of concurrent CRT, radiation dose escalation to 74 Gy had a detrimental effect on survival [81]. Rates of local and distant failure after CRT have remained constant over time (approximately 30–40 and 40–50 %, respectively) however median OS has improved modestly, by approximately 10 months (Table 3). The reasons for this improvement in OS are uncertain, but stage migration due to improved imaging may be one contributory factor [82]. In addition, the incidence of high-grade radiation pneumonitis and esophagitis has decreased significantly in the past decade [83]. Survival improvements may also reflect the availability of effective systemic therapies for the 50 % of patients who relapse with systemic disease [84], although the use of such therapies is not routinely captured in trials.

Table 2. Outcomes from randomized trials with a surgical arm in stage III non-small cell lung cancer.

Trial	Inclusion	Staging PET or PET/CT	Study question	RT[a]	Chemotherapy	N (randomized)	Answer	Treatment related mortality	5-year OS
EORTC 08941 [125]	Unresectable IIIA (N2)	Not mandatory	CT-S vs CT-RT	60–62.5 Gy to primary and involved mediastinum; 40–46 Gy to uninvolved mediastinum	Platinum-based with at least one other agent	332	No significant difference	4 % within 30 days of surgery 1 patient died of RP, timing NR	16 % 14 %
INT 0139[b] [126]	Potentially resectable IIIA (N2)	Not mandatory	CRT-S vs CRT	45 Gy in CRT-S arm 61 Gy in CRT arm	Cisplatin-etoposide	429 (396 eligible)	No significant difference	8 % 2 % (No deaths during induction)	27 % 20 %
ESPATUE[c] [127]	Resectable IIIA (N2) and selected IIIB	97 %	CT-CRT-S vs CT-CRT-CRTboost	Both arms: induction 45 Gy delivered as 1.5 Gy BID In definitive CRT arm: risk-adapted CRTboost to 65–71 Gy	Induction: cisplatin-paclitaxel Concurrent: cisplatin-vinorelbine	161	No significant difference, but closed early and was under- powered with respect to the primary end-point of OS	6 % in surgical arm 3 % in definitive CRT arm (2 additional patients died during induction)	44 % 40 %
SAKK 16/00 [128]	Resectable IIIA (N2)	Required (rate NR)	CT-RT-S vs CT-S	44 Gy (in 22 fractions over 3 weeks)	Cisplatin-docetaxel	232	No difference	0 % within 30 days of surgery 3 % within 30 days of surgery	40 % 34 %

Courtesy of Prof. Rafal Dziadziuszko. Discussant ESMO 2014 Madrid. Modified to update subsequent publication

CT induction chemotherapy, *CRT* concurrent chemoradiotherapy, *RT* radiotherapy; S surgery, *CRTboost* concurrent chemoradiotherapy boost, *RP* radiation pneumonitis, *NR* not reported, *BID* twice daily, *OS* overall survival

[a]RT doses in standard fractionation unless otherwise indicated

[b]Increased disease-free survival in surgery arm (12.8 vs 10.5 months; $p = 0.017$); unplanned analysis showed longer median OS in lobectomy subgroup vs matched CRT subgroup (33.6 vs 21.7 months; $p = 0.002$)

[c]246 enrolled (out of 500 planned). After induction treatment, patients with resectable tumors ($n = 161$, 65 %) randomized. In all 246 patients, 5 year OS 34 %

Table 3. Outcomes with definitive chemoradiotherapy for stage III non-small cell lung cancer.

Trial	Inclusion	Staging PET-CT	Histology	Treatment regimen in standard CRT arm[a]	RT technique	N	PTV (mean)	Toxicity in standard CRT arm	Outcomes
RTOG 0617 [58]	Unresectable III	91 %	42/47 % squamous in 60/74 Gy arms	60 Gy Concurrent carboplatin-paclitaxel, followed by 2 cycles consolidation	46/47 % IMRT in 60/74 Gy arms (Remainder 3DCRT)	424 analyzable for radiation end-point	495/510 mL in the 60/74 Gy arm	In 60 Gy arm: Grade ≥ 3 RP 7 % Grade ≥ 3 esophagitis 7 % Grade 5 toxicity 3 %	In 60 Gy arm: Median OS 29 months 2-year OS 58 % 2-year LF 31 % 2-year DF 47 %
PROCLAIM [78]	Nonsquamous III	82 %	Non-squamous only	60–66 Gy Arm A: pemetrexed-cisplatin, pemetrexed consolidation Arm B: etoposide-cisplatin, non-pemetrexed consolidation	25 % IMRT (Remainder 3DCRT)	598	607/585 mL	Grade ≥ 3 RP 1.8/2.6 % Grade ≥ 3 esophagitis 15.5/20.6 % Grade 5 toxicity 1.7/1 %	Median OS 27/25 months Median PFS 11.4/9.8 months IFF (site of 1st failure) 42 % DF (site of 1st failure) 48 %
KCSG-LU05-04 [79]	Unresectable III	92 %	32 % squamous	66 Gy Concurrent docetaxel-cisplatin Arm A: CRT-observation Arm B: CRT-docetaxel-cisplatin consolidation	NR	437 eligible	NR	Grade ≥ 3 RP 1.2 % Grade ≥ 3 esophagitis 9.5 % Grade 5 toxicity 3.6 % during CRT, 2.9 % during consolidation	Median OS 20.6/21.8 months Median PFS 8.1/9.1 months After median follow-up time of 51 months: DF 25 % LRR 25 % DF and LF 3 %
RTOG 9410 [129]	Inoperable stage II-III	0 %	38 % squamous	63 Gy Cisplatin-Vinblastine	2DRT	610	N/A	For CRT with early RT arm: Grade ≥ 3 esophagitis 22 % Grade ≥ 3 acute RP 4 % Grade 5 toxicity 2 % (as worst overall toxicity)	For CRT with early RT arm: 5-year OS 16 % Median OS 17 months IFF only 25 % Out of field only 37 % Both IFF and out of field 10 %
Meta-analysis of 6 trials comparing CRT vs sequential CT/RT [130]	Unresected stage III	0 %	46 %	60 Gy (2 trials), 66 Gy, (1 trial), 66 Gy in 24 fractions (1 trial), 56 Gy split course (1 trial), 48.5 Gy (split course of 36 Gy in 12 fractions, 7 days rest, 12.5 Gy in 5 fractions) Single agent low-dose cisplatin (2 trials), cisplatin-based doublet (3 trials), carboplatin (1 trials)	3DCRT in 1 trial Remainder 2DRT	603/602 in concurrent/sequential groups	N/A	Grade ≥ 3 esophagitis 18 % (concurrent CRT) Rates of acute RP and Grade 5 toxicity NR	For concurrent CRT patients: 3-year OS 24 % 5-year OS 15 % 3-year LRF 28 % 5-year LRF 29 % 3-year DF 40 % 5-year DF 41 %

Abbreviations *CRT* chemoradiotherapy, *CT* chemotherapy, *RT* radiotherapy, *IMRT* intensity modulated radiotherapy, *PTV* planning target volume, *mL* milliliters, *N/A* not applicable, *RP* radiation pneumonitis, *OS* overall survival, *DFS* disease free survival, *IFF* in-field failure, *LF* local failure, *DF* distant failure, *LRR* locoregional recurrence, *NR* not reported, *3DCRT* three- dimensional conformal radiotherapy, *2DRT* two-dimensional radiotherapy

[a]All RT standard fractionation

Currently, ESMO recommends conventionally fractionated CRT to 60–66 Gy, with two to four concomitant cycles of chemotherapy to treat locally advanced NSCLC, with no evidence for induction or consolidation chemotherapy [2]. In patients unfit for concurrent CRT, accelerated RT delivery is suggested. In practice, significant numbers of patients are not fit to undergo CRT; 20 % or more of patients with stage IIIA receive only palliative treatment, with another 12 % receiving RT as a single modality [85]. In patients eligible only for RT, image-guided hypofractionated RT is a strategy that merits investigation, although it should be acknowledged that competing causes of mortality in such patients may limit major improvements in OS.

2.8 Post-operative RT

The role of post-operative RT (PORT) in patients with completely resected N2 disease remains unclear [86]. An earlier meta-analysis using older radiotherapy techniques failed to show a survival benefit for this patient group [87]. More recent population studies have suggested a survival benefit with PORT for pN2 disease [88, 89]. However, pre-operative mediastinal lymph node staging has improved significantly in the past decade, with the use of FDG-PET scans and endoscopic staging, resulting in N2 disease that is discovered only at the time of surgery being a less common scenario. Definitive conclusions of the role of PORT in N2 disease must await the results of an ongoing phase III trial, in which both surgical procedures and RT techniques are clearly specified (LungART, NCT00410683).

2.9 Have newer RT technologies improved survival in stage III NSCLC?

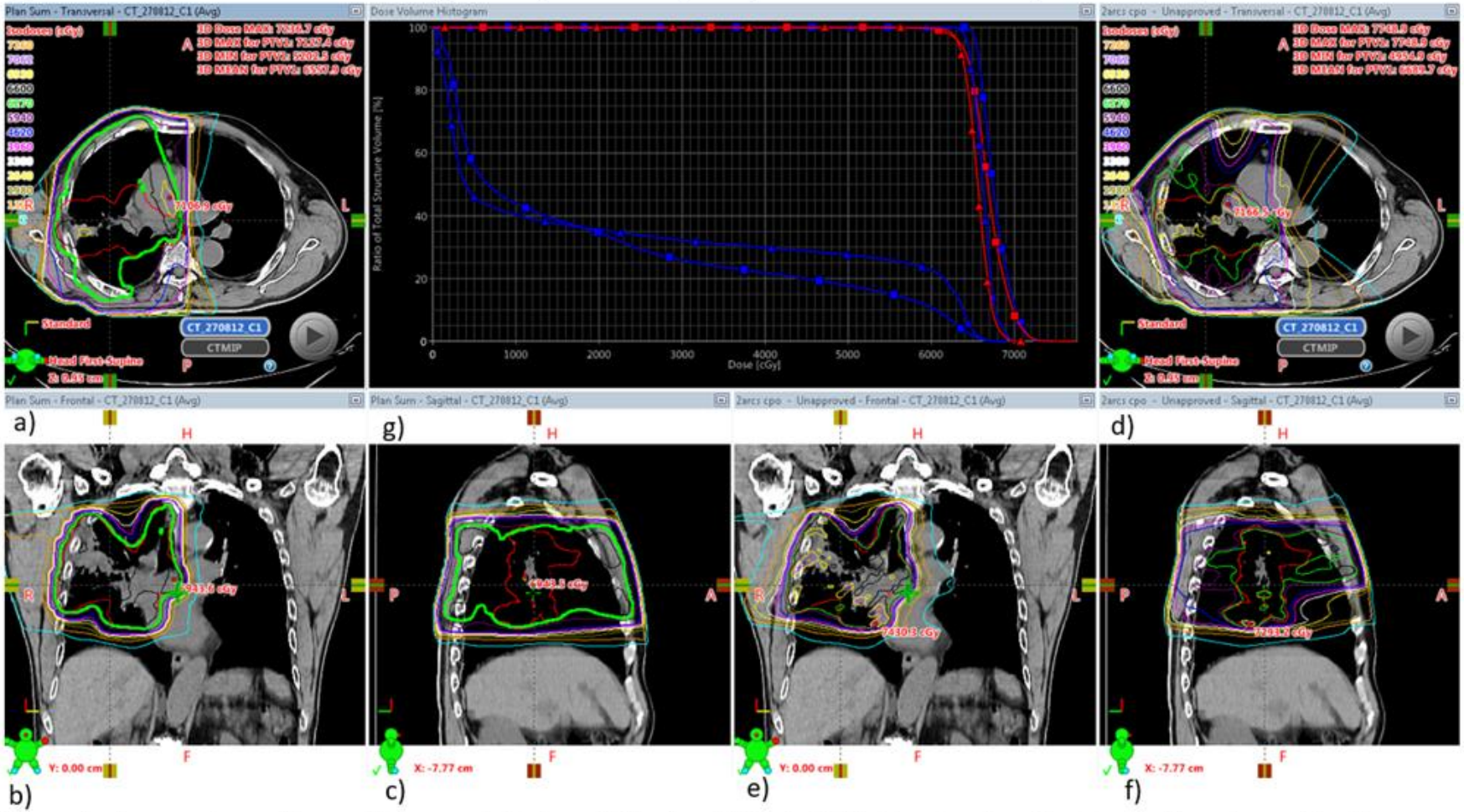
A number of innovations in RT have been introduced in the past two decades [90]. The replacement of conventional treatment simulation with CT simulation has been associated with a survival advantage in the SEER population [29]. Guidelines now recommend 4DCT simulation, and cone beam CT (CBCT) for image-guidance which has reduced planning target volume (PTV) margins [91]. More accurate dose calculation algorithms are in clinical use [27], and more conformal radiation delivery can be achieved with intensity-modulated RT (IMRT) and PBT [30, 92]. Improved OAR sparing

with more conformal dose distributions, and on-line image-guidance, may have contributed to the approximately 10 % reduction in acute esophagitis rates seen in recent years (Table 2).

2.10 Intensity-modulated RT

Planning studies have consistently demonstrated gains with IMRT compared with 3-dimensional conformal RT (3DCRT), for metrics including mean lung dose, lung V20, spinal cord dose, and heart doses [30, 93]. However volumes of low-dose irradiation may increase with some IMRT delivery approaches [94] (Fig. 3). IMRT has been rapidly adopted for lung cancer despite a paucity of evidence [95]. A SEER analysis suggested that the main predictors of IMRT utilization were geographical location, and freestanding versus hospital-based center, rather than disease factors such as tumor size or stage [96]. Most comparisons of IMRT and 3DCRT for locally advanced NSCLC come from retrospective single-institution and registry-based analyses, all with well-recognized limitations. A National Cancer Data Base (NCDB) analysis found that the use of 3DCRT or IMRT improved survival in stage III patients, versus those treated with CRT using 2-dimensional RT(2DRT) [96]. However, when 3DCRT and IMRT were evaluated separately, there was no added survival with IMRT. Other analyses have also reported no survival or toxicity improvement with IMRT [96, 98, 99], although these studies were conducted across heterogeneous patient groups. It is possible that the gains from IMRT are limited to specific patient groups, and another NCDB analysis suggested improved median and 5-year survival with IMRT for T3 and T4 tumors [100]. Unfortunately, many databases lack the comprehensive clinical and dosimetric data necessary to study the nature of the relationship between technology and outcomes.

Figure·3.·A·comparison·of·two·radiotherapy·techniques·delivering·66·Gy·in·33·fractions·to·a·locally·advanced·lung·tumor.·



Figure·4.··A·comparison·of·two·radiotherapy·techniques·delivering·66·Gy·in·33·fractions·to·a·locally-advanced·lung·tumor.·Panels·a-c·show·axial,·coronal,·and·sagittal·views·of·a·hybrid-intensity-modulated·radiotherapy·(IMRT)·plan;·panels·d-f·show·the·corresponding·views·of·a·volumetric·modulated·arc·therapy·(VMAT)·plan·for·the·same·tumor.·Panel·g·shows·the·dose-volume·histogram·of·the·hybrid·IMRT·plan·(triangles)·and·VMAT·plan·(squares);·the·red·and·blue·lines·to·the·right·represent·the·planning·target·volume·(PTV)·and·internal·target·volume·(ITV)·respectively;·the·remaining·pair·of·blue·lines·represent·the·lung·volume·(lung·tissue·outside·the·PTV).·PTV·and·ITV·coverage·is·comparable·for·both·techniques·(g).·The·VMAT·plan·has·a·more·conformal·95%·isodose·(green·line)·around·the·PTV·(d/e/f·compared·with·a/b/c),·however·the·maximum·dose·in·the·PTV·is·higher·(g).·The·amount·of·lung·receiving·≤20·Gy·is·very·similar·with·both·techniques·(g),·but·the·VMAT·plan·has·a·lower·mean·lung·dose·(19.5·Gy·vs·22·Gy·with·hybrid-IMRT)·and·the·hybrid-IMRT·plan·has·more·contralateral·lung·sparing,·as·seen·by·the·position·of·low-dose·isodose·lines·(orange·[1320·cGy]·and·light·blue·[660·cGy].

It is notable that in recent trials in which half or more of patients were treated with 3DCRT, the rates of grade ≥ 3 pneumonitis following doses of up to 66 Gy, were only in the range of 1.2–7 % [81, 101, 102]. Data from the recent RTOG 0617 dose escalation study merit closer inspection [81]. Approximately equal numbers of patients were treated with 3DCRT or IMRT contemporaneously, avoiding the confounding time factor present in retrospective analyses. Despite the IMRT group having a mean PTV about 15 % larger and more stage IIIB tumors, rates of grade ≥ 3 pneumonitis were reduced from 7.9 to 3.5 %. Furthermore, the IMRT cohort was more likely to receive full-dose consolidative chemotherapy [53], and reported less decline in quality of life at 12 months [103]. However, patients treated at higher accruing centers experienced a striking 10 % survival advantage at 2 years [104]. These centers had higher rates of IMRT utilization, which was not independently predictive of survival, raising the question of whether the benefits attributed to IMRT in earlier analyses were in fact due to other, unrecognized factors associated with treatment at high accruing centers. Although the heart V5 and V30 were reported as predictive of survival in RTOG 0617, the lung dose, a well-recognized predictor of severe toxicity, was not included in the multivariate analysis. A subsequent analysis in an independent cohort found mean lung dose, but not heart doses, to be predictive of survival; there was a strong correlation between mean heart dose and heart V5 with the mean lung dose [105].

A number of groups are investigating if the IMRT delivery of higher doses to tumor regions that show high or persistent ^{18}F-flurodeoxyglucose (FDG)-PET uptake, will lead to improved survival [NCT01024829; NCT02788461; NCT01507428; NCT02790190]. A common underlying hypothesis for these trials is that local relapses may be more frequent in the high FDG uptake regions of primary tumors. Outcomes of the ongoing trials are awaited.

2.11 Proton beam therapy

Facilities for PBT have grown rapidly in recent years, even though limited data exists for its cost-effectiveness in NSCLC [106, 107]. Highly conformal high dose distributions can theoretically be achieved, allowing for further reduction in doses to normal structures

compared to IMRT [92, 108]. PBT is currently delivered either in passively scattered proton therapy (PSPT) mode, or pencil-beam scanning (PBS), which can deliver intensity-modulated proton therapy (IMPT). Planning studies have suggested that PBS can allow greater sparing of critical structures than PSPT [109, 110], but it may be more sensitive to changes in position or anatomy [64, 111].

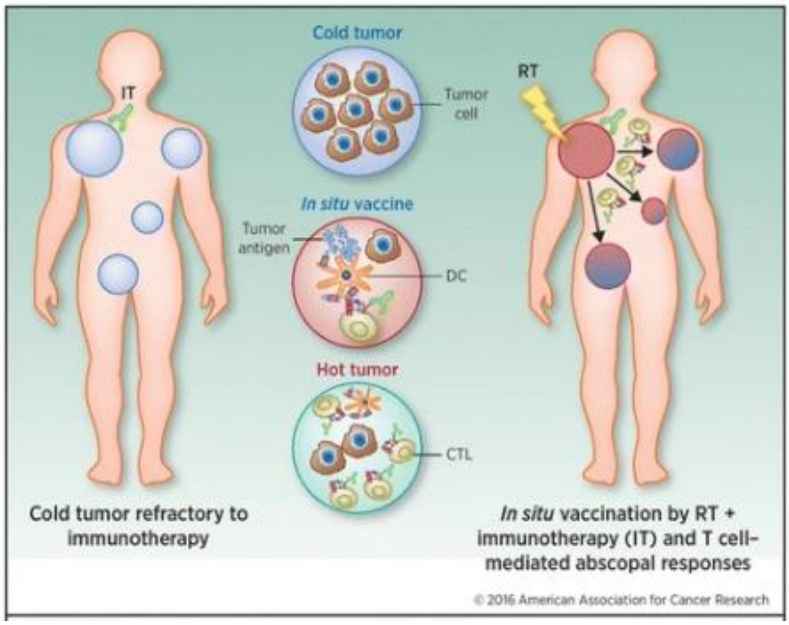
A single-institution retrospective comparison of three treatment techniques (3DCRT, IMRT and PSPT) in locally advanced NSCLC, reported that proton delivery resulted in lower rates of grade 3 or higher pneumonitis and esophagitis (2 and 5 %, respectively; 3DCRT, 30 and 18 %; IMRT, 9 and 44 %; $p < 0.01$ for all) [112]. However, the rates of esophagitis are inconsistent with findings observed in recent phase III studies. A prospective randomized trial led by the MD Anderson Cancer Center compared photon IMRT versus PSPT, and reported no differences in treatment failures, which were defined as either grade ≥3 pneumonitis or local failure at 1 year [113, 114]. A second phase III trial with a target accrual of 560 stage II-IIIB NSCLC patients is now underway (RTOG 1308). Both PSPT and PBS are still permitted in this study. While the improved OAR sparing with PBT makes it a seemingly attractive option for treating large tumors, a large volume has consistently been associated with poorer survival [115 - 117], which suggests that survival gains may be modest, at best. There is, therefore, currently no high-level evidence to support the routine use of proton therapy in locally advanced NSCLC, and evidence supporting IMRT is based on population-based analysis of patient sub-groups. 3DCRT therefore remains an important treatment option, especially as access to radiotherapy is limited in many countries, and escalating costs are of concern [118, 119].

2.12 Radiation and immunity

RT can have an immune stimulatory effect by generating tumor antigens, promoting a T-cell mediated anti-tumor response, and potentially causing immune-mediated abscopal effects where distant non-target lesions can regress [120] (Fig. 4). However, abscopal effects are very uncommon [121]. Radio-immunotherapy is a field of active research, and much remains unknown regarding the optimal sequencing of treatments,

as well as optimal RT dose/fractionation schedules [122, 123]. Some data suggests that large doses per fraction used in SABR may be more effective, but the potential for unexpected toxicity exists, suggesting a need for careful treatment planning and delivery. More safety data will be forthcoming from ongoing clinical trials in this field [124].

Figure 4. Schematic representation of immune-mediated abscopal effects. The systemic proinflammatory effects of irradiating a tumor mass results in it being 'hot,' and acting as an 'in-situ tumor vaccine' against distant non-irradiated tumors. Such a local response could be enhanced by administering immunostimulatory antibodies in order to attain an enhanced systemic effect, thereby exploiting the immune effects of radiotherapy. CTL cytotoxic T cell; RT radiotherapy.



Reprinted with permission. Theresa L. Whiteside et al. Clin Cancer Res 2016; 22: 1845 – 1855.

2.13 Challenges in evaluating new RT technologies

While classic RCTs remain the gold standard for generating evidence, their applicability for evaluating RT technology has been challenged [125, 126]. The high costs involved, the potential for a learning curve with new technology [127], and ethical concerns with a

perceived lack of equipoise between older and new technologies, are all potential impediments. The extended duration of follow-up required to assess long-term toxicities precludes study completion in a timely manner, and by the time trial results are published, they may be considered invalid due to the interval evolution of technology.

In certain situations, comparative effectiveness research may be a more practical and financially feasible approach for evaluating treatments [128, 129]. Prospective multi-center registries provide access to large patient numbers and extensive data, which may be integrated and analyzed using a ‘big data’ approach [130]. Some authors have suggested that dosimetric/complication probability models may help identify patients most likely to benefit from advanced technologies [131], but there remains much uncertainty associated with such models [132]. Similarly, patient-reported outcomes (PROs) are being increasingly considered as important clinical endpoints, but PROs can be difficult to select and interpret as they may be influenced by diverse patient factors [133, 134]. The potential of PROs for evaluating radiotherapy research may be significant, as suggested by a mobile app interface for reporting patient-reported clinical symptoms in advanced NSCLC, that was shown to improve quality of life and survival [135].

By focusing on incremental improvements in technology, radiation oncologists may risk ignoring the fact that clinicians’ overall knowledge base and the patient’s health are often a more important determinant of patient outcome [136]. For example, a poor forced expiratory volume in one second (FEV1), and large gross tumor volumes, have been associated with a 3-fold increase in early mortality following CRT [137]. Interstitial lung abnormalities, as well as severe chronic obstructive pulmonary disease (COPD), are associated with high all-cause mortality [138, 139], and a higher risk of toxicity after CRT [140, 141]. Other patient factors, including weight loss during the first three weeks of CRT may also profoundly affect survival [142]. An improved understanding of what drives poor outcomes in patients with factors like large tumors and co-morbid illness is needed. If RT delivery is considered in isolation, measures such as the optimization of

fractionation schedules for a given patient, or spatiotemporal optimization of radiation dose, are unlikely to result in large improvements in outcomes [143].

Furthermore, more accurate distinction between toxicity related to treatment versus symptoms related to comorbidities is needed. Common COPD symptoms which may be present in patients at baseline can easily be mislabeled as a grade 3 pulmonary toxicity. Simply correlating observed toxicities with OAR dose-volume parameters is insufficient, due to uncertainty in delivered dose [144,145], and lack of anatomical and functional information. This means that more robust and comprehensive dosimetry reporting is needed in the future.

2.14 Conclusion

Although innovations in treatment planning and delivery have led to more precise and accurate RT delivery, for the majority of NSCLC patients, further improvements in treatment outcomes are likely to come about from an integration of novel biological treatment strategies based on an understanding of cancer and radiotherapy at the molecular level. Understanding which patients may benefit most from a given RT technology, as well as identifying those who are at high risk of treatment toxicity, may help tailor the application of advanced technologies to those most likely to benefit and promote a personalized approach to lung cancer radiotherapy.

Chapter 3

Prediction of early mortality following stereotactic body radiotherapy for peripheral early-stage lung cancer

S Baker[1], A Sharma[2], R Peric[3], WD Heemsbergen[1], JJ Nuyttens[1]

1 Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands
2 Department of Radiotherapy and Oncology, Regional Cancer Centre, Indira Gandhi Medical College, Shimla, India
3 Department of Pulmonary Medicine, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

Published: Acta Oncologica. 2019; 58(2):237

Abstract

Background/purpose: To investigate prognostic factors for death within 6 months of stereotactic body radiotherapy (SBRT) for patients with peripheral early-stage non-small cell lung cancer (NSCLC).

Materials and methods: This analysis included 586 NSCLC patients with peripheral tumors treated with SBRT. Potential patient and tumor prognostic factors, including the Charlson Comorbidity Index (CCI) and Cumulative Illness Rating Scale (CIRS), were analyzed by logistic regression analysis for association with early mortality (death <6 months after SBRT). Additionally, CCI and CIRS were compared with respect to their predictive ability for early mortality by comparing multivariate models with each comorbidity index, and assessing their respective discriminatory abilities (C-index).

Results: A total of 36 patients (6.1%) died within 6 months of the start of SBRT. With a median follow-up of 25 months, 3-year overall survival was 54%. CIRS and tumor diameter were significant predictors of early mortality on multivariate analysis ($p = .001$). Patients with a CIRS score of 8 or higher and a tumor diameter over 3 cm had a 6-month survival of 70% versus 97% for those lacking these two features ($p < .001$). CCI was not predictive for early mortality on univariate nor multivariate analysis; the model containing CCI had a C-index of 0.65 versus 0.70 for the model containing CIRS.

Conclusion: CIRS and tumor diameter predict for early-mortality in peripheral early-stage NSCLC treated with SBRT. CIRS may be a more useful comorbidity index than CCI in this population when assessing short-term life expectancy

3.1 Introduction

Stereotactic body radiotherapy (SBRT) provides a curative-intent treatment option for patients with inoperable early-stage non-small cell lung cancer (NSCLC). In years preceding the advent of SBRT, the majority of patients with severe comorbidities or advanced age were managed with palliative treatment or supportive care alone [154]. Studies in the Netherlands have demonstrated increased utilization of curative-intent treatment since the introduction of SBRT, with a corresponding improvement in survival rates [155].

Due to a high burden of comorbid illness in the lung SBRT population, rates of overall survival lag behind those for cancer-specific survival [156, 157]. Previously, we reported that more than two-thirds of deaths in a population of early-stage NSCLC patients were from non-cancer causes [158]. Indeed, a proportion of patients will not benefit from SBRT due to competing mortality and limited life expectancy. These patients may be better served with a supportive care approach, sparing patients the inconvenience and potential cost of SBRT, and utilizing the resource-intensive treatment more judiciously. As more reports emerge describing the favorable toxicity profile in octogenarians [159] and patients with severe COPD [160, 161], the decision between SBRT and best supportive care may become an increasingly frequent clinical dilemma.

Short-term survival outcomes in this population, however, remain largely unstudied [16, 156]. Although recent consensus guidelines from the European Society for Radiotherapy and Oncology (ESTRO) identify short estimated life expectancy as a contraindication for treatment [7], prognostic factors for short-term survival have not been elucidated. The primary objective of this study was to identify factors associated with early mortality, defined as death within 6 months of SBRT, in order to assist patients and clinicians with weighing the different management options for early-stage NSCLC. Secondarily, we aimed to compare two well-known comorbidity indices, the Charlson Comorbidity Index (CCI) and the Cumulative Illness Rating Scale (CIRS), with respect to their ability to predict early mortality.

3.2 Materials and methods

Patients

Consecutive peripheral early-stage NSCLC patients treated with 4-dimensional SBRT at the Department of Radiotherapy at Erasmus MC between August 2005 and January 2017 were identified. Patients lacking histologic confirmation were recommended for SBRT based on positron emission tomography (PET)-CT scan findings and multidisciplinary tumor board review. Details regarding treatment protocol have been previously described [158, 162]. In brief, the gross tumor volume plus a 5 mm margin to account for microscopic tumor extension and geometric positional uncertainty was irradiated, typically in three fractions, on the Cyberknife radiosurgery system (Accuray Inc., Sunnyvale, CA). The following exclusion criteria were applied: central location (within 2 cm of the proximal bronchial tree), synchronous intrapulmonary lesions, histology other than NSCLC, delivered biologically effective dose (BED) < 100 Gy assuming an α/β ratio of 10, and follow-up time less than 6 months from the start of radiotherapy. Tumor staging was performed based on PET-CT scan, while mediastinal staging was based on PET-CT, mediastinoscopy, and/or endobronchial ultrasound (EBUS). For the present study, patients were re-staged according to American Joint Committee on Cancer (AJCC) 8th edition. Global Initiative for Chronic Obstructive Lung Disease (GOLD) scores were obtained [163] and were not reclassified to reflect 2017 criteria, since these incorporate comprehensive symptom assessment with validated questionnaires [164] and these data were not available retrospectively. Clinical and imaging follow-up was performed as previously described [158].

Comorbidity was assessed retrospectively using both CCI and CIRS, based on the electronic medical record. The CCI is a widely used metric to assess comorbidity and consists of 19 clinical conditions weighted for the relative risk of death. It was first developed in 1987 based on the 1-year mortality of patients admitted to a medical hospital service for a variety of reasons, and externally validated in a cohort of breast cancer patients [165]. The CIRS was developed in 1968 and scores the severity of disease in 13 organ systems from 0 (no problem) to 4 (extremely severe) [166]. Both CCI and CIRS have been used to study comorbidity burden in a variety of oncologic

populations with reliable results and good interrater reliability [167, 168]. For the present study, CCI and CIRS were scored as previously described [165, 166].

Statistics

The primary endpoint was early mortality, defined as death within 6 months of the start of SBRT. Univariable analysis of potential prognostic factors for early mortality was performed using binary logistic regression analysis. Covariates included age, gender, Karnofsky Performance Status (KPS), operability, CCI, CIRS, smoking status (current/former versus never), GOLD score, previous malignancy, previous lung cancer, maximum axial tumor diameter, and lower lobe location. Tumor diameter was dichotomized based on size criteria for AJCC TNM T-staging (≤3 cm versus >3 cm). Other continuous variables were dichotomized based on the median value (≤median versus >median). CIRS and CCI were additionally analyzed as continuous variables. Variables with a p-value ≤.2 on univariable analysis were analyzed in a multivariate logistic regression analysis using the forward selection method.

To compare the predictive ability of CCI and CIRS, two separate multivariate models were constructed and the discriminatory ability of each model assessed by the C-index. Each multivariable model was constructed by including all co-variates with a p-value ≤.2 on univariable analysis, plus the comorbidity index in question. Overall survival (OS) was estimated using the Kaplan–Meier method. Log rank tests assessed for differences in OS when stratifying by prognostic factors selected by the model building procedure. All statistical analyses were performed in SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Center (MEC2016-729).

3.3 Results

A total of 586 patients were included in analysis. Median age was 75 years (range 44–91) and 93.2% of patients were deemed medically or surgically inoperable upon multidisciplinary tumor board review. Additional baseline patient and tumor

characteristics are provided in Table 1. The median CCI score was 3 (range 1–14) while the median CIRS was 5 (range 0–15).

Table 1. Baseline clinical and treatment characteristics of 586 patients with peripheral early stage non-small cell lung cancer treated with stereotactic body radiotherapy.

Variable	*N*	Value
Age	586	75 (44–91)
Gender	586	
Female		224 (38%)
Male		362 (62%)
KPS	586	
100		25 (4%)
90		92 (16%)
80		213 (36%)
70		186 (32%)
60		60 (10%)
50		10 (2%)
Operable	586	40 (7%)
CCI	586	
≥ 4		171 (29%)
< 4		415 (71%)
Median (range)		3 (0–10)
CIRS	586	
≥ 6		374 (64%)
< 6		212 (36%)
Median (range)		5 (0–15)
Current/former smoker	520	480 (92%)
GOLD score	580	
0–2		399 (69%)
3–4		181 (31%)
Previous malignancy	586	237(40%)
Previous lung cancer	586	120 (21%)
T stage	586	
T1		441 (70%)
T2		147 (25%)
T3		28 (5%)
Tumor diameter	586	2.3 cm (0.7–7.7)
Pathology	586	
Unknown		328 (56%)
Squamous cell carcinoma		94 (16%)
Adenocarcinoma		103 (18%)
Large cell carcinoma		51 (9%)
Other		10 (2%)
Dose fractionation	586	
60 Gy/3		209 (36%)
54 Gy/3		15 (3%)
51 Gy/3		353 (60%)
40 Gy/2		1 (0.2%)
60 Gy/5		8 (1%)

For continuous variables, the median and range are given; for categorical variables, the number of patients and percentages are given.
CCI: Charlson Comorbidity Index score; CIRS: Cumulative Illness Rating Score; GOLD: Global Initiative for Chronic Obstructive Lung Disease; KPS: Karnofsky Performance Status

Respiratory disease was the most frequent CIRS comorbidity (80.0%) followed by vascular and cardiac (49.8% and 44.5%, respectively) (Table 2).

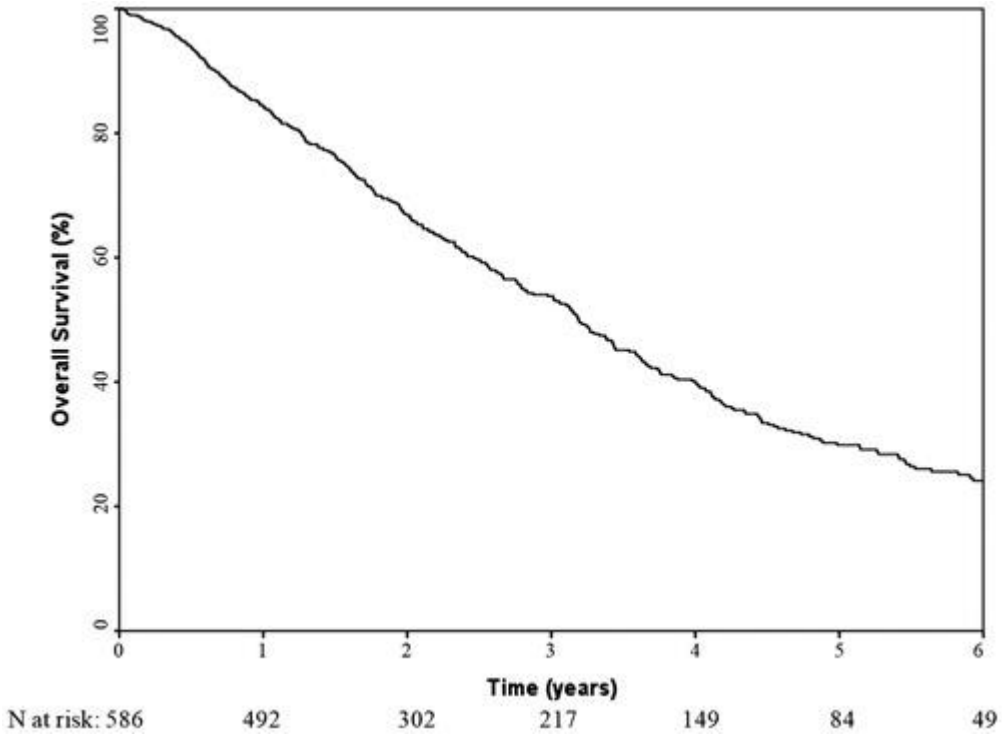
Table 2. The frequency of comorbidities within the 14 organ systems comprising the Cumulative Illness Rating Scale.

CIRS comorbidity	1	2	3	4	Any
Heart	124 (21.2%)	111 (18.9%)	25 (4.3%)	1 (0.2%)	261 (44.5%)
Vascular	180 (30.7%)	98 (16.7%)	14 (2.4%)	0 (0%)	292 (49.8%)
Respiratory	79 (13.5%)	210 (35.8%)	146 (24.9%)	34 (5.8%)	469 (80.0%)
ENT	19 (3.2%)	11 (1.9%)	3 (0.5%)	1 (0.2%)	34 (5.8%)
Upper GI	78 (13.3%)	8 (1.4%)	4 (0.7%)	0 (0%)	90 (15.4%)
Lower GI	52 (8.9%)	9 (1.5%)	1 (0.2%)	0 (0%)	62 (10.6%)
Liver	10 (1.7%)	5 (0.9%)	1(0.2%)	0 (0%)	16 (2.7%)
Renal	29 (4.9%)	26 (4.4%)	4 (0.7%)	1 (0.2%)	60 (10.2%)
GU	41 (7.0%)	12 (2.0%)	2 (0.3%)	0 (0%)	55 (9.4%)
MSK	69 (11.8%)	18 (3.1%)	2 (0.3%)	0 (0%)	89 (15.2%)
Neurologic	42 (7.2%)	16 (2.7%)	1 (0.2%)	0 (0%)	59 (10.1%)
Endocrine	200 (34.1%)	12 (2.0%)	0 (0%)	0 (0%)	212 (36.2%)
Psychological	73 (12.5%)	16 (2.7%)	3 (0.5%)	0 (0%)	92 (15.7%)

CIRS: Cumulative Illness Rating Scale; ENT: ear nose throat; GI: gastrointestinal; GU: genitourinary; MSK: musculoskeletal

A total of 36 patients (6.1%) died within 6 months of the start of SBRT. Among these patients, eight had experienced disease progression: four had distant metastases alone, three had regional (mediastinal lymph nodes) and distant recurrences, and 1 had local, regional, and distant recurrences. The median follow-up time for surviving patients was 26.1 months (range 10.4–124.6). The median overall survival was 38.3 months (95% confidence interval 34.2–42.3). Rates of 6-month, 1-year, 3-year and 5-year overall survival were 93.7%, 84.5%, 53.8% and 29.9%, respectively (Figure 1).

Figure 1. Kaplan–Meier curve showing the overall survival of the 586 early-stage lung cancer patients treated with stereotactic body radiotherapy.



Only tumor diameter (>3 cm vs ≤3 cm) and CIRS score were significantly associated with early mortality in univariable analysis (Table 3). In multivariable analysis, both tumor diameter (odds ratio [OR] 3.45, 95% CI 1.72–6.92; $p < .001$) and CIRS score (OR 1.27, 95% CI 1.10–1.45; $p < .001$) were significant predictors of early mortality. Patients with both a CIRS score of 8 or more (the highest quartile of CIRS score in the population) and a tumor diameter >3 cm had a Kaplan–Meier estimated 6 month OS of 70%, compared to 97% in patients with neither of these adverse prognostic features present ($p < .001$) (Figure 2); 1-year OS rates were 63% and 90%, respectively. The C-index for the multivariable model containing CIRS as a co-variate was 0.70 versus 0.65 for the multivariable model containing CCI.

Figure 2. Kaplan–Meier curve showing the overall survival of the 586 early-stage lung cancer patients treated with stereotactic body radiotherapy, stratified by Cumulative Illness Rating Scale (CIRS) score and tumor diameter. (Log rank $p < .001$).

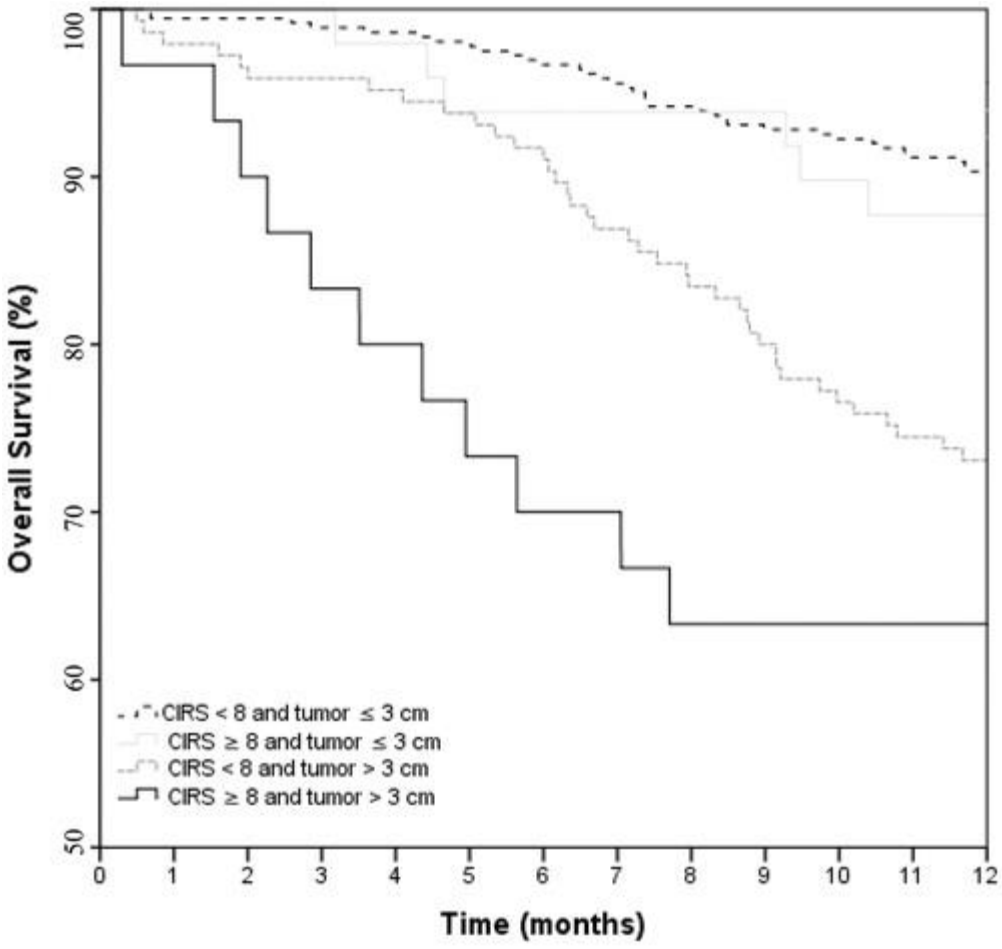


Table 3. Variables associated with early mortality (death within 6 months of stereotactic body radiotherapy).

	Univariate analysis		Multivariate analysis		
	OR	*p*-value	OR	*p*-value	95% CI
Age (≥ 75 vs <75)	1.16	.664			
Gender (male vs female)	1.93	.097			
KPS (≤ 70 vs >70)	1.68	.136			
Current or former smoker (vs never smoker)	2.33	.414			
GOLD 3-4 (vs 1–2)	1.01	.977			
Inoperable (vs operable)	2.67	.339			
Lower lobe tumor location (yes vs no)	1.00	.999			
Previous cancer (yes vs no)	0.47	.056			
Previous lung cancer (yes vs no)	0.47	.160			
Tumor diameter (> 3 cm vs ≤3 cm)	3.60	**<.001**	3.45	**.001**	1.72-6.92
CCI ≥4 vs <4	1.07	.851			
CCI (per unit increase)	1.08	.422			
CIRS ≥6 vs <6	2.33	**.015**			
CIRS (per unit increase)	1.28	**<.001**	1.27	**.001**	1.10-1.45

CCI: Charlson comorbidity score; CI: confidence interval; CIRS: Cumulative illness rating scale; GOLD: Global Initiative for Chronic Obstructive Lung Disease; OR: odds ratio; KPS: Karnofsky performance status. Significant *p* values (<0.05) are in bold.

3.4 Discussion

Short-term survival outcomes are an important and under-studied endpoint in early-stage NSCLC. Here, we have identified CIRS score, as well as tumor diameter, as important prognostic factors for early mortality. Furthermore, we have provided a quantitative assessment of the two factors on survival time, in order to assist patients and clinicians in making informed treatment decisions.

The importance of CIRS score for short-term survival is not surprising, given the high burden of comorbidity in the inoperable NSCLC population. CCI, however, was not prognostic for early mortality. This is an important finding, given that CCI is currently the most frequently used comorbidity metric in NSCLC, and may influence the therapeutic choice between definitive treatment and supportive care [169]. Indeed, recent lung

SBRT practice guidelines mention CCI as a comorbidity measure when considering appropriate patient selection for treatment [7]. Additionally, studies comparing surgical and SBRT outcomes commonly utilize CCI for propensity-score matching [170–172]. CIRS, however, may be a more appropriate metric for these purposes. While previous studies have found CCI to predict for OS in the lung SBRT population [173–175], one study which examined death within 6 months of treatment as an endpoint found that while CCI was predictive of OS, it was not significantly associated with early mortality [16]. Of note, CIRS was not included as a potential prognostic factor.

This discrepancy between CIRS and CCI for early mortality may be due to several factors. By grading diseases in each organ system from zero to four, CIRS is more sensitive to disease severity, which may be an important determinant of short-term survival. One study reported CIRS, and not CCI, was associated with length of hospital admission, suggesting CIRS may detect acute comorbidities that CCI does not [176]. Indeed, the predictive ability of CCI may progressively decline with shorter survival endpoints [167]. Conversely, the greater emphasis of CCI on chronic conditions may make it a more suitable metric for long term survival outcomes. Furthermore, CIRS may capture additional comorbidities that CCI does not. Extermann et al. [168] reported the prevalence of comorbidity in an elderly cancer population to be 36% with CCI compared to 94% with CIRS. The finding that CCI may underestimate comorbidity prevalence was also reported in a study on prognostic factors for OS in stage I NSCLC [177]. While CIRS was prognostic for both patients treated with conventional RT or surgery, CCI was only prognostic in the radiotherapy cohort, which consisted of patients with a higher comorbidity burden.

The importance of tumor diameter as a prognostic factor for early mortality is consistent with previous studies examining OS. Kopek et al. [173] reported that lung SBRT patients with T2 tumors had poorer OS than those with T1 tumors. Other studies have reported similar findings [173, 178–180]. It is perhaps surprising, however, that tumor diameter is strongly associated with early mortality. Indeed, it is notable that 8 patients with early mortality had developed recurrent disease, and in all cases, this included distant metastases. This finding highlights the early metastatic potential of NSCLC, and

suggests the need to for improved detection of occult metastases at the time of diagnosis. Of note, all patients in the present study had undergone staging with PET-CT scan.

The factors which lacked association with early mortality warrant comment. Advanced age is commonly perceived as an adverse prognostic feature, and elderly patients with lung cancer may be less likely to receive active treatment than younger patients after controlling for other adverse features [181, 182]. Similarly, GOLD score was not associated with early mortality, despite the known impact of COPD severity on OS [183]. Given the demonstrated safety of SBRT for these patients [159–161], it is reassuring that they do not experience poor short-term survival; age and COPD severity should not preclude curative-intent treatment.

Death within 6 months of SBRT was defined as early mortality, as this represents the scenario where patients do not live long enough to benefit from treatment. The appropriate definition of early mortality is dependent on the natural history of untreated NSCLC, and the timeframe in which cancer-related morbidity and mortality commonly occur. A systematic review reported a mean survival of 11.94 months (95% CI 10.07–13.8) for untreated early stage NSCLC [184]. We acknowledge that the minimum life expectancy to warrant definitive treatment is somewhat controversial [7], however, we chose the 6-month time point as a life expectancy for which most patients and clinicians would not favor radical treatment.

Previous studies on short-term survival in lung SBRT patients have focused almost exclusively on 30- and 90-day mortality, in order to facilitate comparison with surgical perioperative mortality [170]. In this context, a comprehensive assessment of prognostic factors for short-term morality in lung SBRT has not been conducted. One previous study did examine death within 6 months of SBRT as an endpoint [16]. Interestingly, only Eastern Cooperative Oncology Group (ECOG) performance status was associated with early mortality, although CIRS and tumor diameter were not included as covariates. It is surprising that performance status was not predictive of early mortality in the present study. One possible explanation is the low number of patients with very poor

performance status (only 10 patients with KPS 50). It is notable, however, that other studies on prognostic factors in lung SBRT patients have found performance status to lack prognostic significance [173, 178], although conflicting reports exist [174, 177, 179].

Limitations of the study include its retrospective nature, and the small number of events observed. Retrospective scoring of CIRS and CCI may not have captured all comorbidities. However, detailed clinical notes were available for all patients, and the majority of clinically relevant comorbidities were likely documented. Additionally, there were a small number of events observed. It is encouraging that only 6% of patients experienced death within 6 months of SBRT. However, low event number may have reduced statistical power for detecting potential prognostic factors. Of note, patients in the present study had been deemed suitable SBRT candidates after tumor board review. Investigating the survival times and prognostic factors for patients who are not referred for SBRT due to short anticipated life expectancy would yield valuable insights. An additional limitation of the analysis is that the prognostic factors identified cannot in isolation identify patient groups with very poor short-term survival; even patients with tumor diameter greater than 3 cm and CIRS scores of 8 or higher had a 6-month OS of 70%. This relatively high 6-month survival is an important observation, highlighting that patients with high CIRS score and large tumor diameter should not be excluded from SBRT on the basis of these characteristics alone. Whether additional adverse prognostic features may be identified which in combination reliably predict for very poor short term survival such that forgoing SBRT is warranted remains to be elucidated. Finally, we were unable to report the cause of death, as this information was not available for the majority of patients. Hence, short-term cancer-specific survival could not be assessed, nor treatment-related mortality. However, it is reassuring that we previously observed no grade 4–5 toxicity in peripheral early stage lung cancer patients treated with this regimen [158]. Further study into the cause of early mortality might yield valuable insight, such as whether comorbidities captured on CIRS and their severity are related to the specific cause of death. Nevertheless, the survival estimates here, as well as the identification of CIRS as an important determinant of short-term survival, provide useful information for patients and clinicians when discussing the cost-benefit analysis for definitive treatment.

Chapter 4

Development and external validation of a nomogram to predict overall survival following stereotactic body radiotherapy for early-stage lung cancer

S Baker[1], K Bakunina[1], M Duijm[1], MS Hoogeman[1], R Cornelissen[2], I Antonisse[1], J Praag[1], WD Heemsbergen[1], JJ Nuyttens[1]

1 Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

2 Department of Pulmonary Medicine, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

Published: Radiation Oncology. 2020; 15(1):89

Abstract

Background

Prognostication tools for early-stage non-small cell lung cancer (NSCLC) patients treated with stereotactic body radiotherapy (SBRT) are currently lacking. The purpose of this study was to develop and externally validate a nomogram to predict overall survival in individual patients with peripheral early-stage disease.

Methods

A total of 587 NSCLC patients treated with biologically effective dose > 100 Gy_{10} were eligible. A Cox proportional hazards model was used to build a nomogram to predict 6-month, 1-year, 3-year and 5-year overall survival. Internal validation was performed using bootstrap sampling. External validation was performed in a separate cohort of 124 NSCLC patients with central tumors treated with SBRT. Discriminatory ability was measured by the concordance index (C-index) while predictive accuracy was assessed with calibration slope and plots.

Results

The resulting nomogram was based on six prognostic factors: age, sex, Karnofsky Performance Status, operability, Charlson Comorbidity Index, and tumor diameter. The slope of the calibration curve for nomogram-predicted versus Kaplan-Meier-estimated overall survival was 0.77. The C-index of the nomogram (corrected for optimism) was moderate at 0.64. In the external validation cohort, the model yielded a C-index of 0.62.

Conclusions

We established and validated a nomogram which can provide individual survival predictions for patients with early stage lung cancer treated with SBRT. The nomogram may assist patients and clinicians with treatment decision-making.

4.1 Background

Stereotactic body radiotherapy (SBRT) is the standard of care for medically inoperable early-stage non-small cell lung cancer (NSCLC) [185]. It is increasingly utilized also in the high risk operable patient population [157]. Survival outcomes, however, are variable, and predicting survival in this patient population has proven challenging [16, 186].

A major contributor to survival variability is the potentially high rate of competing non-cancer mortality. For example, severe chronic obstructive pulmonary disease (COPD), common in the SBRT lung population, is associated with a 70% mortality rate at 5 years in those with 3 or more acute exacerbations [183]. The proven safety of SBRT in elderly patients [159] and those with severe COPD [160, 161] has promoted an inclusive stance to patient eligibility. Consequently, despite high rates of local control and cancer-specific survival, overall survival (OS) remains poor and in the order of 40% at 5 years [157].

There is currently a paucity of accurate prognostic models for the early lung SBRT population. One study in the United Stated suggested the decision between curative-intent treatment and observation may be driven largely by institutional factors (academic vs non-academic) and patient financial or racial disparities rather than clinical factors or prognosis [187]. The ability to accurately predict survival on the individual patient level would be highly valuable. Not only would it assist patients with future planning and facilitate shared decision-making with clinicians, but it would also allow for judicious resource-allocation and potentially identify patients better served by a supportive care approach. Finally, it would allow for more accurate risk-stratification for clinical trials and comparative outcomes research.

Nomograms are a practical tool which incorporate prognostic factors for a given patient to calculate the expected probability of a clinical event such as 5-year overall survival. In resected early-stage NSCLC [188] as well as in a diverse lung cancer population undergoing a variety of treatments [189], nomograms have proven more accurate than

TNM staging for survival prediction. The purpose of this study was to identify prognostic factors for survival in early lung cancer patients treated with SBRT and to build a nomogram to predict 6-month, 1-year, 3-year and 5-year overall survival.

4.2 Methods

Patients and Treatment

Consecutive NSCLC patients treated between August 2005 and January 2017 with 4-dimensional SBRT at Erasmus MC were identified. Patients lacking histologic confirmation had findings on positron emission tomography (PET)-CT scan consistent with early-stage NSCLC, and had been recommended for SBRT by a multidisciplinary tumor board. Treatment planning protocols and follow-up schedule have been previously described [158, 162]. Inclusion criteria included peripheral early-stage disease (T1-T3 N0M0). Exclusion criteria included central location (within 2 cm of the proximal bronchial tree), synchronous intrapulmonary lesions, a diagnosis of small cell lung cancer, and delivered biologically effective dose (BED) < 100 Gy assuming an α/β ratio of 10. Tumor staging was originally performed according to AJCC 7th edition based on PET-CT scan (all patients received a staging PET scan) and patients were re-staged by AJCC 8th edition criteria for the present study. Mediastinal staging was performed by PET-CT, mediastinoscopy, and/or endoscopic ultrasound (EBUS and/or EUS).

Endpoints and covariates

The primary endpoint was OS at 5 years, calculated from first day of treatment until death, and patients still alive were censored at the date of last follow-up visit. Variables analyzed for association with survival included age, sex, Karnofsky Performance Status (KPS), operability, Charlson Comorbidity Index score (CCI), Cumulative Illness Rating Score (CIRS), smoking status (current/former vs never), Global Initiative for Chronic Obstructive Lung Disease (GOLD) score [163], previous malignancy, previous lung cancer, maximum axial tumor diameter, histology, and lower lobe location. GOLD

scores were not reclassified to reflect 2017 criteria, which incorporate a comprehensive assessment of symptoms by validated questionnaires [164], as this data was not available retrospectively. Operability was determined by criteria as outlined in recently published clinical practice guidelines by the European Society for Medical Oncology (based primary on cardiac assessment and pulmonary function) [190].

Statistical analysis

Model building

The nomogram was based on a Cox proportional hazards model, using the following step-wise model building procedure. Variables with more than 1% missing values (histology 57% and smoking status 11%) were omitted from the initial model, and the decision regarding imputation (and then inclusion in the model) made subsequently based on assessment of their potential added predictive value with Cox univariate and multivariate analyses. Complete case analysis was used for variables with less than 1% missing values. The data provided evidence for interaction between the variables GOLD score, age and sex ($p = 0.001$) with the results difficult to interpret and depict in a nomogram (see further description within Results: Nomogram), and therefore GOLD score was not initially included. Thus, an initial model was built using the prognostic factors sex, age, KPS, operability, previous malignancy, previous lung cancer, lower lobe tumor location, and tumor diameter.

The model building steps were formulated as strict programmable decision rules aimed at arriving at the most parsimonious model with maximum predictive ability, so that the model building procedure could be internally validated. Initially, the prognostic factors were modeled flexibly, e.g. allowing highly non-linear relationships. Subsequently, following a predefined grid, less flexible functions were applied. The simplification was thus stopped once it began to come at the price of compromised model fit as compared to the most flexible model. Depending on the distribution of the prognostic factor, suitable measures of fit were used. Age and tumor diameter were modelled flexibly using restricted cubic splines (RCS) with 5 degrees of freedom (d.f.), and KPS was

modelled as a nominal variable to allow maximum flexibility. To this model, in turn, RCS functions of CCI and CIRS of 4 d.f. each were added. Goodness-of-fit of each of these models was evaluated with respect to the initial model using a likelihood ratio test (LRT). The comorbidity index (CCI or CIRS) which resulted in a smaller p-value was selected (and the resulting model referred to as the full model henceforth). Subsequently, a gradient of RCS functions with d.f. ranging between 2 and 4 and a linear function of the comorbidity score were compared with a LRT to the full model. The functional form with the smallest p-value was selected. The effect of age and tumor diameter were modelled simultaneously and evaluated using Akaike's Information Criteria (AIC) as the compared models are not nested, as suggested by Harrel [191]. The range of RCS of 5 d.f. to linear effect was evaluated. The model with the smallest AIC was selected. The variables previous malignancy and previous lung cancer were also assessed simultaneously using LRT with a p-value cut-off point of 0.1 for inclusion in the model. Sex, lower lobe tumor location, and operability were evaluated independently against a threshold for model inclusion of $p = 0.1$ from a LRT, a cut-off value chosen so that the model building procedure could be automated and then validated. Alternative functional forms of KPS score were also evaluated (linear and RCS with 2 and 3 d.f.) and compared to nominal variable modelling using AIC. The model with the smallest AIC is the final model.

Internal validation of the model building procedure

The model building procedure was validated by applying it to 1000 bootstrap samples and predicting the original sample based on the resulting model. Discriminative ability of the model was measured with the concordance index (C-index). Internal validation was also used to assess the degree of overfitting to the sample at hand (calibration slope), and the resulting optimism in C-index. The estimated optimism-corrected calibration slope was then used to shrink model predictions and thus increase their external validity [191]. Calibration plots in 1000 bootstrap samples were used to compare Kaplan-Meier-estimated and nomogram-predicted 6-month, 1-year, 3-year and 5-year OS.

External validation

An independent cohort of 124 NSCLC patients with centrally located tumors treated with SBRT at Erasmus MC between September 2004 – November 2016 was used for external validation.

The final model underlying the nomogram was used to predict 6-month, 1-year, 3-year, and 5-year OS of the patients in the external validation cohort. The model's discriminative ability in this cohort was measured using the C-index. For the construction of the calibration plots, the predicted survival probabilities were grouped in four equally sized groups.

Statistical analyses were performed using IBM SPSS statistics version 22.0 software package (SPSS Inc., Chicago, IL, USA) and R software, version 3.4.1 (open source; www.r-project.org).

The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Center (MEC201679).

4.3 Results

Patients

A total of 587 patients met inclusion criteria. Baseline clinical and treatment characteristics are shown in Table 1. Median age was 75 years (range 44–91) with median CCI of 3 (range 0–10). Two-hundred and fifty-eight patients had biopsy confirmation of disease, while the remaining 329 had an FDG-avid lesion on PET deemed highly suspicious of NSCLC upon multidisciplinary tumor board review. Mediastinal staging was by PET for the majority of patients (n = 478) and invasive staging (mediastinoscopy, EBUS or EUS) was performed in 109 patients.

Table 1. Baseline clinical and treatment characteristics of the primary cohort and validation cohort.

	Primary cohort		Validation cohort	
Variable	Total N	N or Median (% or range)	Total N	N or Median (% or range)
Age	587	75 (44 – 91)	124	77 (48 – 90)
Sex	587		124	
Female		224 (38%)		46 (37.1%)
Male		363 (62%)		78 (62.9%)
KPS	581		124	
≥ 90		117 (20%)		54 (43.5%)
70-80		395 (68%)		62 (50.0%)
≤ 60		69 (12%)		8 (6.5%)
Operable	581	40 (7%)	124	10 (8.1%)
CCI	587	3 (0-10)	124	2 (0-9)
CIRS	587	5 (0-15)	124	5 (0-16)
Current/former smoker	521	481 (92%)		
GOLD score	580			
1		97 (17%)		
2		240 (41%)		
3		144 (25%)		
4		37 (6%)		
Previous malignancy	587	237 (40%)		
Previous lung cancer	587	120 (20.4%)		
T stage	587		124	
T1		412 (70%)		13 (10.5%)
T2		147 (25%)		55 (44.4%)
T3		28 (5%)		42 (33.9%)
T4		0 (0%)		14 (11.3%)
Tumor diameter	587	2.3 cm (0.7 – 7.7)	124	4.6 cm (1.4 – 10.5)
Pathology	587		124	
Unknown		329 (56%)		
Squamous cell		94 (16%)		
carcinoma		103 (18%)		
Adenocarcinoma		51 (9%)		
Large cell carcinoma		10 (2%)		
Other				
Dose fractionation	587		124	
60 Gy/3		209 (36%)		
54 Gy/3		15 (3%)		
51 Gy/3		354 (60%)		
40 Gy/2		1 (0.2%)		
60 Gy/5		8 (1%)		
55 Gy/5				48 (38.4%)
48 Gy/6				19 (15.2%)
49 Gy/7				17 (13.7%)
60 Gy/5				18 (14.4%)
Other				22 (17.6%)

Abbreviations: CCI Charlson Comorbidity Index, CIRS cumulative Illness Rating Score, GOLD Golbal initiative for Chronic Obstructive Lung Disease, KPS Karnofsky Performance Status

The external validation set consisted of 124 NSCLC patients with centrally located tumors treated with SBRT to a median dose of 55 Gy in 5 fractions. Baseline patient and tumor characteristics were similar to those of the primary patient cohort, however, median tumor diameter was larger and several patients had T4 tumors in the validation cohort (Table (Table11).

Survival

At the time of analysis, 252 patients (42.9%) were alive. Median follow-up time was 23.8 months (range 0.3–124.6) for all patients and 28.5 months (range 4.5–124.6) for surviving patients. Median OS was 38.4 months (95% confidence interval [CI] 34.2–42.6). Three-year and 5-year OS were 54.2 and 29.9%, respectively (Fig. 1). Median follow-up time in the validation cohort was 22.3 months (range 1.9–121.2) and median OS was 26.0 months (95% CI 19.5–32.5) (Fig. 1).

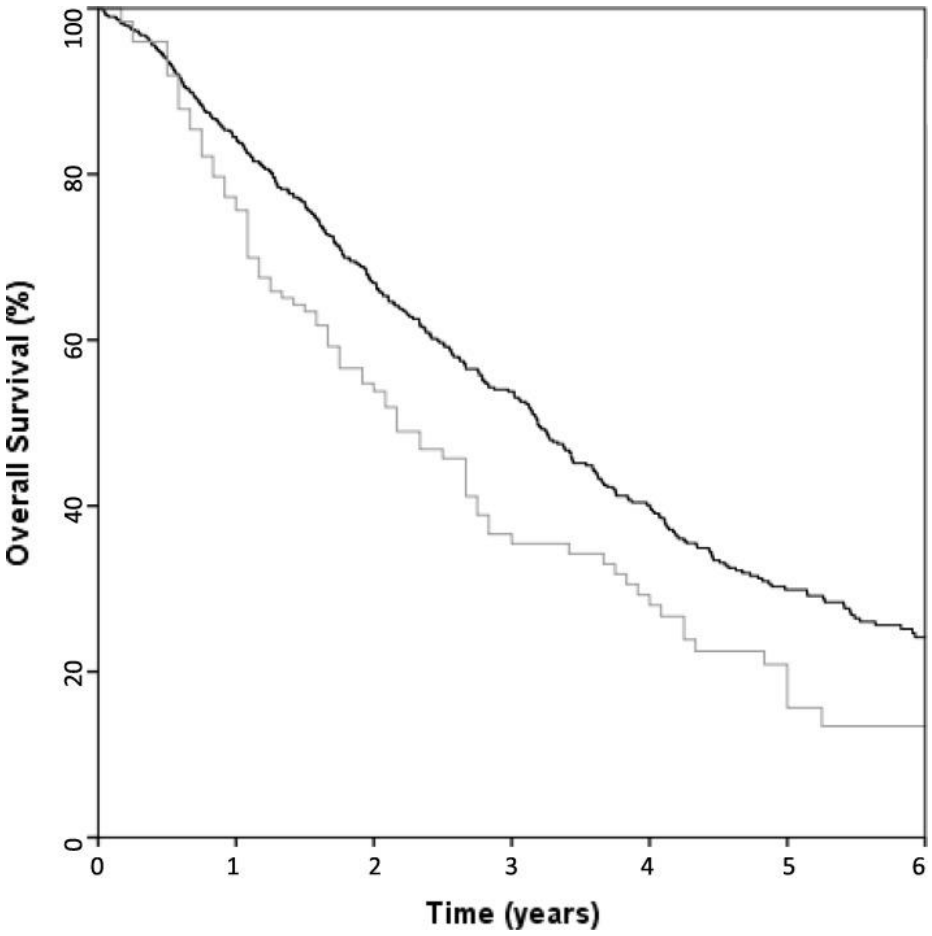


Figure 1. Kaplan-Meier curves showing the overall survival of the original cohort (black line) and validation cohort (grey line).

Nomogram

Six patients with unknown KPS score were omitted from the nomogram building procedure. Application of the model building procedure to the remaining 581 patients resulted in a final model based on the variables age, sex, operability, KPS, CCI and tumor diameter. The resulting nomogram is presented in Fig. 2. While age, CCI and tumor diameter were modelled as linear functions, KPS was best modelled as a quadratic function with restriction to linearity at both extremes of the scale, i.e. RCS function with 2 d.f. (Fig. 3). Univariate analysis demonstrated no additional predictive value from including histology, smoking status or GOLD score (*p*-values 0.38, 0.39, and 0.16, respectively). When added to the final model, histology and smoking remained insignificant and thus these variables were not included in the model. Conversely, GOLD score proved significant (p-value 0.004) when modeled as a nominal variable, however, survival effects were paradoxical: with respect to GOLD 0, GOLD 4 had a nearly identical effect on OS (HR 1.01 $p = 0.76$) while GOLD 1–3 showed favorable effects on survival with respect to GOLD 0 (HR 0.68, 0.57 and 0.63, and *p*-values 0.066, 0.002, and 0.022, respectively). When trying to understand these findings, we performed interaction tests with age and sex, which were significant (Chi2 43.7, 19 d.f., $p = 0.001$). In order to preserve greater parsimony and nomogram readability, and given the paradoxical effect of GOLD score severity on survival, GOLD score was not included in the model. The parameter estimates of the final model are shown in Table 2.

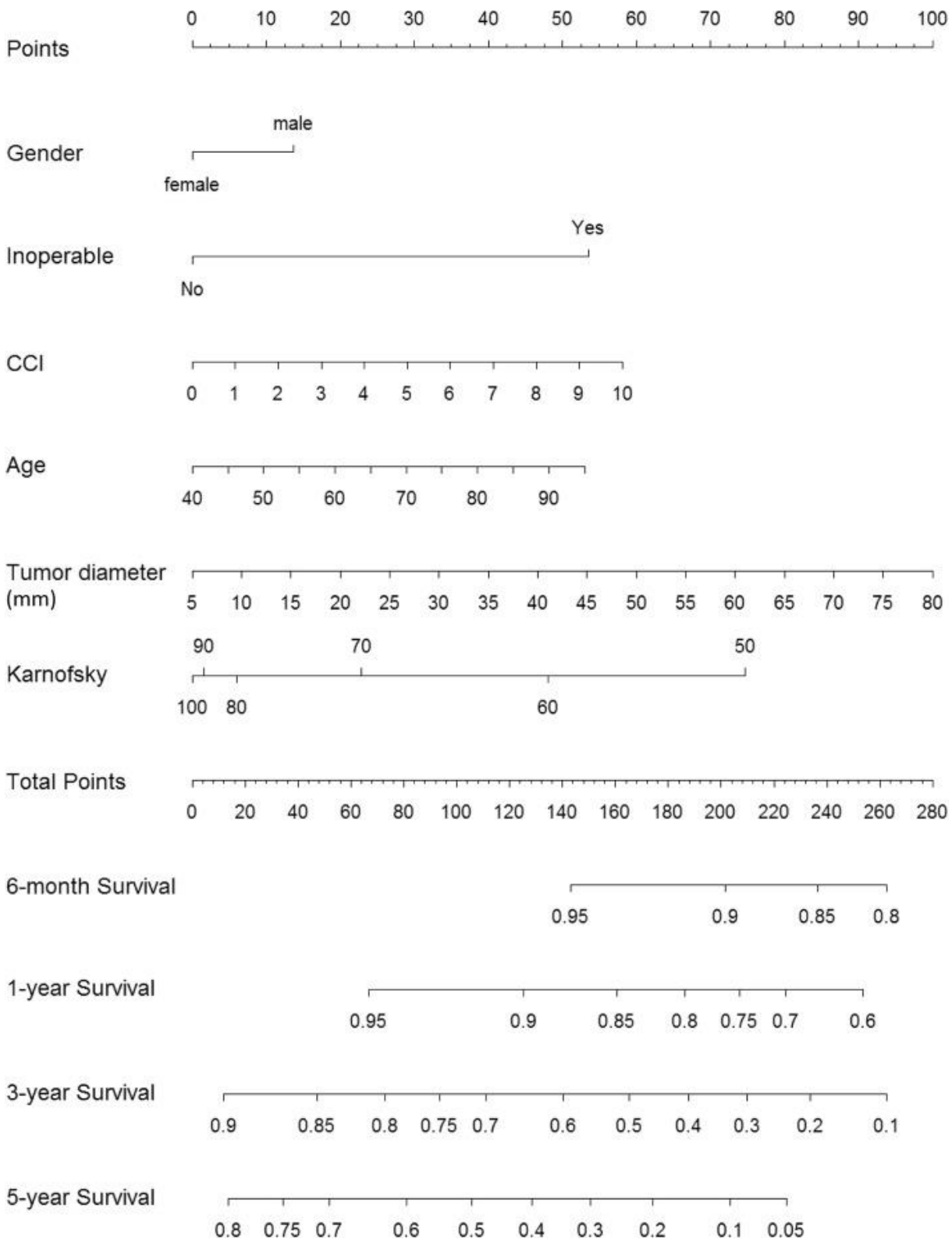


Figure 2. Nomogram for prediction of 6-month, 1-year, 3-year and 5-year survival.

Abbreviations: CCI Charlson Comorbidity Index score

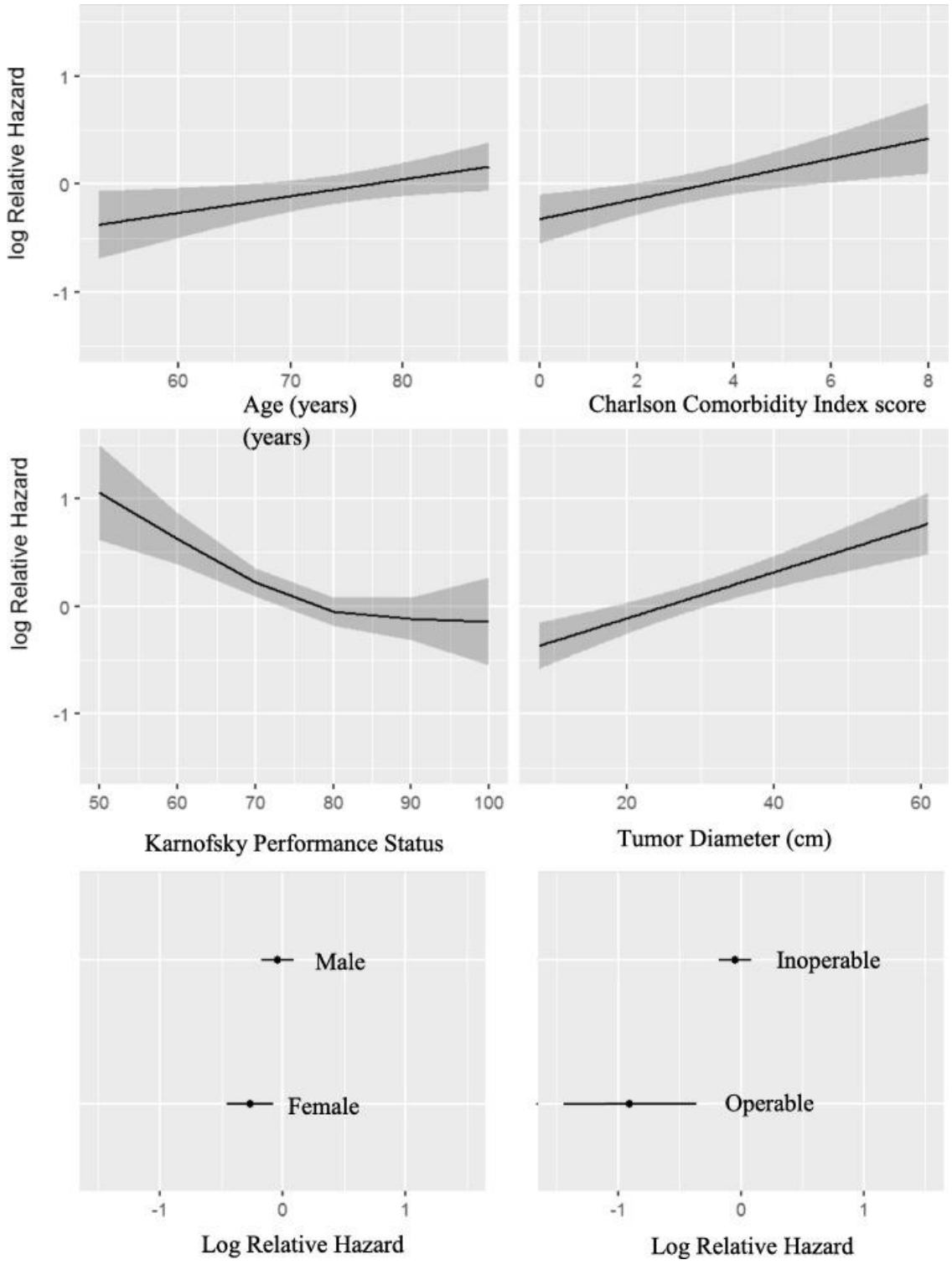


Figure 3. Relative hazard of death modelled for each variable included in the nomogram. The gray areas (first 4 panels) and the horizontal black bars (last 2 panels) depict the 95% confidence intervals.

Table 2. Parameter estimates of the final model used to generate the nomogram.

	HR	SE	*p*-value
Sex (male vs female)	1.245	0.124	0.079
Inoperable (yes vs No)	2.361	0.285	0.003
CCI[a]	1.098	0.031	0.002
Age[a]	1.016	0.007	0.023
Tumor diameter[a]	1.022	0.004	< 0.001
KPS[a,b] (linear effect)	0.958	0.011	< 0.001
KPS[a,b] (quadratic effect)	1.020	0.011	0.057

[a] Per unit increase
[b] Restricted cubic splines function parameters
Abbreviations: CCI Charlson Comorbidity Index score, KPS Karnofsky performance status, HR hazard ratio, SE standard error of the log-hazard ratio

Validation

The frequencies of prognostic factor selection in 1000 bootstrap samples are presented in Supplementary Table 1. KPS, age and tumor diameter were selected in 100% of samples, while operability was selected in 96%. The results of validating the model building procedure are presented in Supplementary Table 2. The C-index in the original sample was 0.66, and corrected for optimism through bootstrap sampling to 0.64. The optimism-corrected calibration slope was estimated at 0.766. Nevertheless, calibration plots demonstrated high correlation between observed and predicted probability of 6-month, 1-year, 3-year and 5-year OS (Fig. 4).

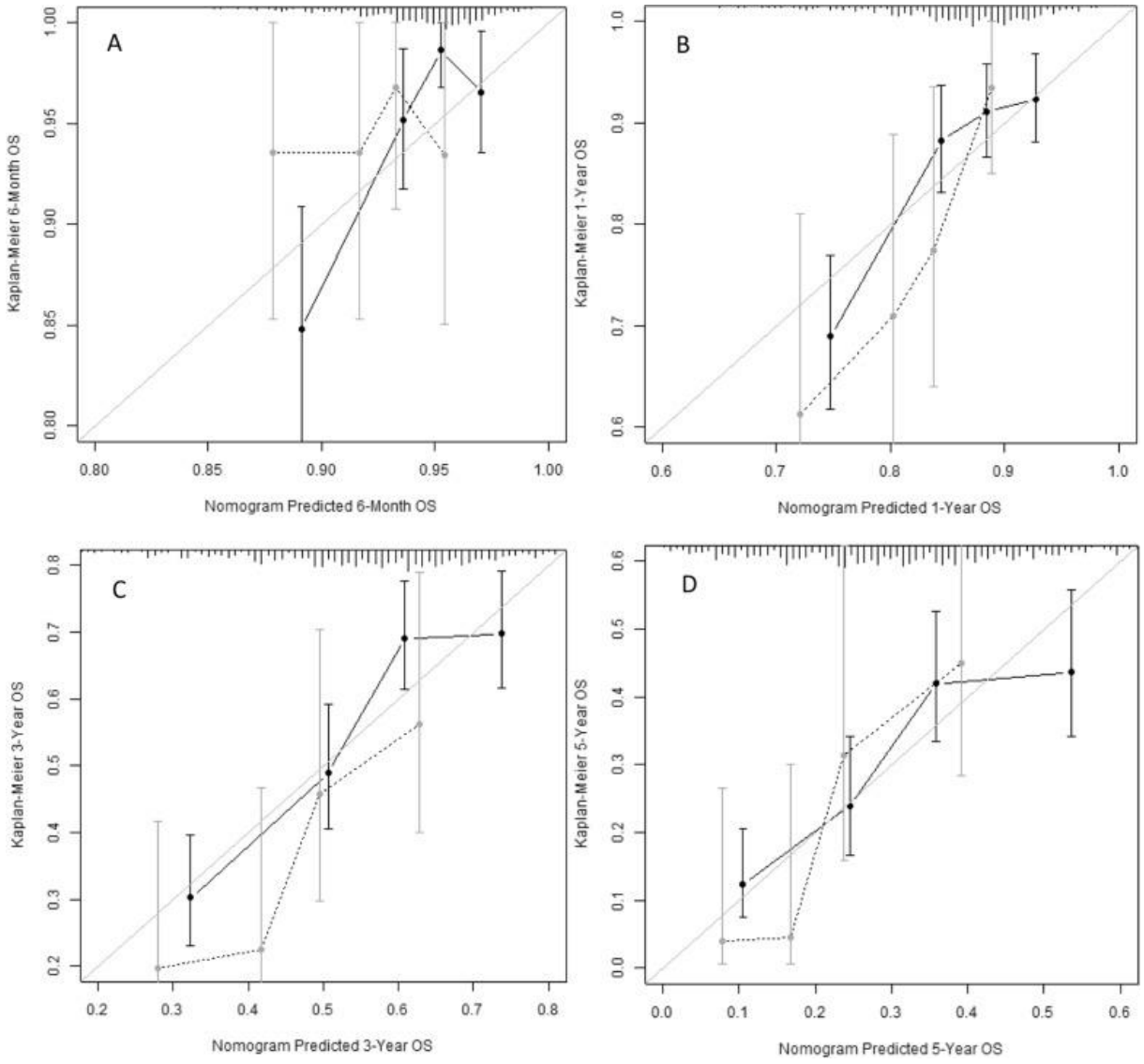


Figure 4. Calibration plots of Kaplan Meier vs nomogram predicted survival for the original patient group (black solid line) and the validation cohort (dotted grey line) for a) 6-month b) 1-year c) 3-year and d) 5-year overall survival. The error bars indicate the 95% confidence intervals. A plot along the 45-degree line would indicate perfect agreement between predicted and actual survival.

The model underlying the nomogram was used to predict OS of the patients from the external validation cohort. Its discriminative ability in this cohort as measured by C-index was assessed at 0.62, which is highly comparable with the results in the sample used to

build the model. Fig. 4 presents calibration plots of the internal as well as the external validation.

4.4 Discussion

Survival prediction at the individual patient level can facilitate informed treatment decisions for patients and clinicians. Here, we have developed a nomogram to predict OS, with moderate discriminatory ability (C-index 0.64), and good predictive accuracy based on calibration plots. The model displayed good external validity, with a C-index only slightly lower than that of the original cohort (C-index 0.62). Survival outcomes and baseline characteristics of the studied population are similar to those reported elsewhere [157, 173, 174], suggesting applicability of our model to other early NSCLC SBRT populations.

The prognostic importance of the six variables included in the final nomogram is corroborated by previous investigations. Age [188, 175, 192], sex [175, 178, 188, 192, 193], performance status [16, 174, 194], operability [16, 195], tumor diameter [191, 178–180] and Charlson Comorbidity Index [16, 173, 175] have previously been reported as significant predictors of survival in the early NSCLC population. Interestingly, in the present sample smoking status was not significantly associated with survival, a finding reported previously [16, 173] although conflicting reports exists [174, 194].

Matsuo et al. [178] investigated prognostic factors in 101 patients with early stage lung cancer treated with SBRT and identified only male sex (HR 3.40, $p = 0.004$ on multivariate analysis) and tumor diameter (HR 1.60 per 10 mm increase, $p = 0.013$ on multivariate analysis) as adverse prognostic features for 3-year OS. The population was of atypically high performance status (94% World Health Organization performance status [WHO PS] 0–1) and operability (37% of patients) which may have accounted for the lack of association of age, performance status, and operability with survival. Of note, Matsuo et al. did not evaluate comorbidity as a potential predictor. Kopek et al. [173] did

include Charlson Comorbidity score as a prognostic variable and found it to be a powerful predictor of survival: those with a CCI score of 6 or more had a median survival of only 11 months compared to 41 months in patients scoring 3 or less. T stage was also significant on multivariate analysis, and contrary to our findings, sex and performance status were not prognostic. Other variables lacking significance included histology and GOLD classification, consistent with our results.

The nomogram of the present study is one of only a few published for the early stage lung cancer population. A multi-institutional Chinese study developed a nomogram for OS in early stage lung cancer patients, however this was in the setting of resected disease [188]. Nevertheless, it shares similarities with the present nomogram, including incorporation of age, sex, and tumor size as prognostic variables. Although the C-index indicated good discriminatory ability at 0.71, the nomogram is not a useful predictive tool for patients undergoing lung SBRT for several reasons. It relies on surgical variables such as volume of blood loss and pathologic N stage. Additionally, comorbidity was not found to be significantly associated with survival and thus was not incorporated into the nomogram, but because it was coded in the model only as present or absent, if lacked the sensitivity of more established metrics such as CCI.

In the early lung SBRT population, Louie et al. also developed a nomogram for predicting OS, with a C-index similar to the present nomogram (0.66), however, it showed a lower degree of external validity (C-index 0.55 and 0.52 in two external validation cohorts) [174]. Our nomogram differs from that of Louie et al. in several key features. Only the nomogram presented here incorporates operability as a prognostic variable. As SBRT is increasingly applied to the operable setting, incorporating this important variable confers particular utility to our nomogram. Indeed, operability has previously been reported as an important prognostic factor [16, 157,195]. Onishi et al. [195] reported 5-year overall survival for medically operable patients as 64.8%, compared to 35.0% in inoperable patients ($p < 0.001$). An additional distinction of the present nomogram is incorporation of KPS rather than WHO PS as a performance status metric. Performance status is perhaps the variable which most consistently

appears as a prognostic factor for OS in early lung cancer, and with one of the greatest magnitudes of effect [16, 174, 194]. By utilizing KPS, which has a greater number of categories than WHO PS, our nomogram has greater discriminative ability for small differences in performance status which may significantly affect overall survival. Finally, our nomogram may also be used to predict 1-year and 3-year OS, and these shorter-term survival estimates may be particularly useful for treatment decision-making. The 5 year survival estimates generated by the nomogram, however, should be interpreted with caution, as the median follow up of the study was 24 months.

The nomogram's short-term survival estimates warrant particular consideration. Very poor short-term prognosis may tip the balance in favor of a supportive care approach, sparing a patient the unnecessary inconvenience and potential cost of curative treatment. Due to the aggressive natural history of NSCLC, cancer-related morbidity and mortality can reasonably be anticipated within an approximately 1-year timeframe [184]. Hence, survival longer than 6 months likely warrants active treatment. Conversely, a low probability of 6-month survival may support a palliative approach. The present nomogram, however, generates a minimum 6-month survival estimate of 80%; adverse prognostic factors including advanced age and high CCI score did not confer a very low probability of short-term survival. This suggests that age and comorbidity burden are not sufficient to justify withholding curative-intent SBRT. It also highlights the need to better identify patient and disease factors predictive of early mortality [196]. Klement et al. [16] aimed to develop a model to predict early mortality in early-stage NSCLC patients undergoing SBRT, and similarly found that patients at high risk of early mortality could not be reliably identified: 6-month mortality was only 8.8% for the group of patients at highest risk, compared to 4.1% for those with the lowest risk.

Weaknesses of the study include its retrospective nature. Additionally, the external validation cohort consisted of patients treated also at our institution, while validation in a cohort from a distinct centre would better demonstrate generalizability of our nomogram. Finally, the majority of patients lacked a histopathologic diagnosis of lung cancer, such that this could not be included as a potential prognostic factor in the nomogram. Previous studies have suggested inferior outcomes for squamous cell carcinoma lung

tumors treated with SBRT [197]. It is also possible that some benign tumors were included. However, the incidence of benign disease following surgery for Dutch patients with a clinical diagnosis of NSCLC is generally less than 5% [198], and SBRT outcomes in one study were no different with versus without pathologic confirmation of malignancy [198]. Molecular tumor markers were also not available. Strengths of the study include the relatively large patient population, homogenous treatment, and completeness of data and long-term follow-up. Calibration plots showed good agreement between nomogram-predicted and Kaplan-Meier-estimated survival, with excellent agreement for 3-year OS, suggesting high reliability of the nomogram. The nomogram was externally validated in a distinct patient population with central tumors, and despite difference from the original study population, the nomogram performed well in the external validation cohort. Development of a distinct nomogram for central lung tumors could be an avenue of future investigation, and could assess additional prognostic factors unique to central lung tumors such as potential tumor under-dosing in order to respect normal tissue tolerance. Future investigations may incorporate novel biomarkers and metabolomics signatures which are emerging as prognostic in the early NSCLC population [199].

4.5 Conclusions

Here we present a validated a nomogram to predict OS in patients with early-stage NSCLC undergoing SBRT. The discriminatory ability is moderate and incorporation of emerging prognostic factors (for example molecular markers) may increase predictive ability for future models. Nevertheless, this prognostic tool may assist patients and clinicians in generating individual survival predictions.

4.6 Supplementary Information

Table S1. Frequency of variable selection in 1000 bootstrap samples.

	Frequency of variable selection
KPS	1000
Age	1000
Tumor diameter	1000
Operability	959
CIRS	552
Sex	531
CCI	448
Previous malignancy	461
Previous lung cancer	461
Lower lobe location	201

Table S2. Results of internal validation of the model building procedure through 1000 bootstrap samples.

	Original sample	Training	Test	Optimism	Optimism-Corrected
C-index	0.663	0.675	0.647	0.028	0.635
Slope	1.000	1.000	0.766	0.234	0.766

Chapter 5

Endovascular Coils as Lung Tumor Fiducial Markers for Real-Time Tumor Tracking in Stereotactic Body Radiotherapy: Comparison of Complication Rates with Transthoracic Fiducial Marker Placement

S Baker[1], A Sharma[2], I Antonisse[1], R Cornelissen[3], A Moelker[4], JJ Nuyttens[1]

1 Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

2 Department of Radiotherapy and Oncology, Regional Cancer Centre, Indira Gandhi Medical College, Shimla, India

3 Department of Pulmonary Medicine, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

4 Department of Radiology, Erasmus University Medical Center, Rotterdam, The Netherlands

Published: Journal of Vascular and Interventional Radiology. 2019; 30(12):1901

Abstract

Purpose: To evaluate safety of endovascular coil fiducial placement and compare complication rates with transthoracic fiducial placement in patients with peripheral early-stage lung cancer receiving fiducial markers for stereotactic body radiotherapy (SBRT).

Materials and methods: This retrospective study included consecutive patients who received endovascular coils (n = 416 patients, n = 1,335 coils) or transthoracic fiducials (n = 30 patients, n = 80 fiducials) for SBRT between August 2005 and January 2017. During the first 3 years of the study period, patients preferentially received cylindrical platinum fiducial markers by percutaneous transthoracic placement; only patients with contraindications received endovascular coils. Thereafter, patients received endovascular fiducials as the first-line procedure. Endovascular embolization coils were placed via the femoral vein into subsegmental pulmonary artery branches near the tumor. Complications were scored by SIR criteria.

Results: The success rate of endovascular coil placement was 99.8%. One patient developed grade 2 hemoptysis requiring procedure discontinuation. Following placement, 1 patient (0.2%) developed grade 3 cardiac arrhythmia. A total of 36 patients (9%) developed grade 1 complications: mild hemoptysis (n = 4; 1%), small asymptomatic pulmonary infarction or hemorrhage (n = 30; 7%), hypoglycemia (n = 1; 0.2%), and vasovagal episode (n = 1; 0.2%). Following transthoracic marker placement, 4 patients (13%) developed a pneumothorax requiring hospital admission and chest tube (grade 2), 6 patients (20%) developed pneumothorax requiring no intervention (grade 1), 2 patients (7%) experienced asymptomatic pulmonary bleeding, and 1 patient (3%) developed persistent pain.

Conclusions: Endovascular coil fiducial placement for lung SBRT is associated with high procedural success rates and lower rates of clinically relevant complications than transthoracic marker placement.

5.1 Introduction

Stereotactic body radiotherapy (SBRT) has become the standard of care for medically inoperable early-stage lung cancer and is becoming increasingly common for patients at high risk for surgical resection [185, 7]. Intrafraction changes in tumor position due to respiratory and cardiac motion present a challenge to safe and accurate treatment delivery. A variety of strategies for management of respiratory motion exist [28, 200]. One strategy involves real-time tumor tracking on the CyberKnife Robotic Radiosurgery System (Accuray Inc, Sunnyvale, California). Real-time tumor tracking with the CyberKnife can be performed in 2 ways: 1) tracking of the tumor itself (Xsight Lung Tracking System; Accuray Inc) or 2) tracking of fiducials in the proximity of the tumor (fiducial tracking). The Xsight Lung Tracking System uses software based on the contrast difference between tumor and adjacent pulmonary parenchyma to track the tumor [201]. This system is suitable only for peripherally located tumors measuring at least 1.5 cm in diameter and requires a certain tumor density for visualization, and as a consequence, this technique is not suitable for many patients [202]. Therefore, most patients still require fiducial marker implantation for tumor tracking.

The percutaneous transthoracic method of fiducial marker placement has traditionally been the standard method of marker placement [203]. However, it has several limitations. Most notably, it is associated with a 22%–67% rate of iatrogenic pneumothorax [203–208], which can be potentially fatal, especially in patients with severe cardiopulmonary comorbidity. To reduce the risk of pneumothorax, a method of transfemoral vascular placement of platinum embolization coils has been developed [209, 210, 158]. Previously, preliminary results in the first 25 patients were reported [210]. Results were encouraging, with only minor complications observed. Since then, 2 other studies have reported successful endovascular placement of embolization coils for tumor tracking in 14 [211] and 15 [205] patients. These studies also reported low rates of complications. Complication rates following endovascular coil placement have been analyzed in only small patient cohorts to date. The goal of this study was to report complication rates in a large patient population following placement

of endovascular coils as fiducial markers for real-time tumor tracking and to compare complication rates with rates following transthoracic marker placement.

5.2 Materials and Methods

Patients

The Medical Ethical Committee of our institution approved this retrospective study and waived the requirement for informed consent (MEC201679). This study included all consecutive patients with early-stage (cT1-T3N0M0) peripherally located non-small cell lung carcinoma (NSCLC) who underwent endovascular coil fiducial placement (n = 416 patients, n = 1,335 fiducials) or transthoracic placement of fiducials (n = 30 patients, n = 80 fiducials) for treatment with four-dimensional SBRT at a university medical center between August 2005 and January 2017. Between 2005 and 2008, the transthoracic method of fiducial placement was the first-line method of marker placement; only patients considered at too high risk for transthoracic placement (patients with severe chronic obstructive pulmonary disease or previous pneumonectomy) underwent endovascular fiducial placement. However, preliminary results in the first 25 patients receiving endovascularly placed fiducials suggested low complication rates [210]. After 2008, the endovascular method was used as the first-line procedure for patients requiring fiducials. There were no contraindications to endovascular fiducial placement. For 270 patients (61%), the diagnosis was established on the basis of fluorodeoxyglucose positron emission tomography/computed tomography (CT) findings consistent with early-stage NSCLC, and no biopsy was performed. Global Initiative for Chronic Obstructive Lung Disease scores were based on forced expiratory volume in 1 second [163]. Additional patient and tumor characteristics are shown in Table 1.

Table 1. Baseline Patient and Tumor Characteristics of 416 Patients Undergoing Endovascular Coil Placement and 30 Patients Undergoing Transthoracic Marker Placement.

Variable	Endovascular Coils (n = 416 Patients)	Transthoracic Markers (n = 30 Patients)
Age, y	74 (44–91)	77 (51–89)
Sex		
Female	162 (39%)	11 (37%)
Male	254 (61%)	19 (63%)
KPS score	80 (60–100)	80 (60–100)
CCI score	3 (0–9)	2 (0–5)
GOLD score	2* (0–4)	2 (0–4)
Tumor diameter, cm	2.2 (0.7–7.7)	3.4 (1.3–6.6)
Pathology		
Unknown	263 (63%)	7 (23%)
SCC	55 (13%)	6 (20%)
Adenocarcinoma	59 (14%)	6 (20%)
Large cell	32 (8%)	10 (33%)
Other	7 (2%)	1 (3%)
Dose fractionation		
60 Gy/3	162 (39%)	29 (97%)
54 Gy/3	6 (1%)	—
51 Gy/3	243 (58%)	1 (3%)
60 Gy/5	5 (1%)	—

Note–Continuous variables are reported as median (range), and categorical variables are reported as number (%).
CCI = Charlson Comorbidity Index; GOLD = Global Initiative for Chronic Obstructive Lung Disease; KPS = Karnofsky performance scale; SCC = squamous cell carcinoma.
*Missing GOLD score for 6 patients.

The preliminary study [210] that reported on the first 25 patients receiving endovascular coil fiducials included 5 patients with lung metastases and 20 patients with primary NSCLC treated between May 2005 and November 2006. Owing to overlapping study periods, the present study included patients in the preliminary study who had primary NSCLC treated after August 2005. The preliminary study included 25 patients who received transthoracic fiducial placement; however, the proportion of patients with

primary NSCLC versus metastases was not reported. Also, complication rates were not reported in patients receiving transthoracic fiducials.

Details regarding treatment planning and SBRT delivery have been described previously [158, 162]. Tumor tracking was successfully accomplished during SBRT delivery for all patients with fiducial markers, with no patients requiring additional marker placement.

Endovascular Coil Placement

The benefits and potential risks for the procedure were explained to each patient, and verbal informed consent was obtained. The procedure was performed by interventional radiologists (10 different individuals with 1–10 years of experience) using fluoroscopic guidance in the interventional suite under continuous electrocardiography monitoring. Local anesthesia was used at the insertion site, and no sedation was used. Platinum embolization microcoils, such as Tornado 0.018-inch (Cook, Inc, Bloomington, Indiana) or similar microcoils, were placed into subsegmental end branches of the pulmonary artery near the tumor via a transfemoral approach. During the first 3 years of the present study (which included 45 of 416 patients receiving endovascular coil fiducials), 0.035-inch coils were used. Subsequently, 0.018-inch coils were adopted to allow for placement in closer proximity to the tumor and to reduce injury to surrounding lung parenchyma. A 5-F sheath was inserted into the right common femoral vein and navigated to the pulmonary artery with a standard multipurpose 100-cm 4-F catheter and 0.035-inch guide wire (Radifocus; Terumo Medical Corp, Tokyo Japan) (Fig 1).

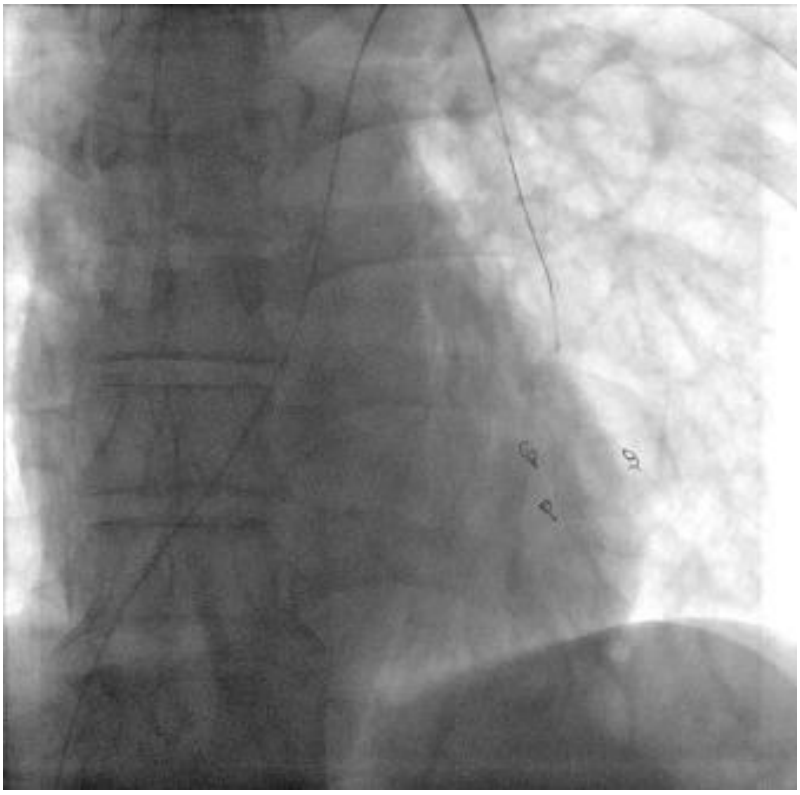


Figure 1. Three endovascular embolization coils placed near a lung tumor, with the 4-F catheter and microcatheter still in place in the left lower lobe pulmonary artery. Another (unfolded) coil is present in the distal end of the microcatheter.

Minor electrocardiography changes (asymptomatic, no wide QRS complexes) were accepted when the catheter was passing through the right atrium and ventricle. After passing the right ventricle, navigation with the catheter alone was preferred rather than using the guide wire, when possible, to minimize trauma to vasculature and parenchyma. Catheter placement in the pulmonary artery was confirmed using contrast agent. The catheter was advanced into the right or left main pulmonary artery and into 1 of the subsegmental pulmonary artery branches near the lung tumor. A 2.7-F microcatheter (Terumo Medical Corp) was then inserted through the 4-F catheter to navigate closer to the tumor. A microcoil was introduced by flushing or pushing it (with a 0.021-inch microwire) through the microcatheter into the pulmonary artery branch. Large tumors were well visualized during the procedure with fluoroscopy. The position of tumors too small to be seen with fluoroscopy was inferred from a CT scan of the

chest performed before the procedure, and microcoils were placed based on subsegmental pulmonary artery anatomy. When there was uncertainty regarding the position of microcoils relative to the tumor, a cone-beam CT scan was performed.

Ideally, 3 coils were implanted to allow for rotational motion adjustment during radiotherapy. Translational adjustments were accomplished with only 1 fiducial. Coils were placed as close to the tumor as possible. A maximum distance of 4 cm between the tumor and coil was considered a successful placement and allowed for the coil to be used for tumor tracking. A single fiducial was sufficient for tumor tracking during radiotherapy; however, migration of the fiducial could not be detected if only 1 fiducial was placed, as the CyberKnife calculates the distance between 2 markers. If there was only 1 reliable fiducial (eg, if the other fiducials were too far from the tumor or did not move synchronously with the tumor), a CT scan was performed before the start of treatment to detect potential fiducial migration.

Highly peripheral tumors required less procedure time, owing to numerous surrounding subsegmental pulmonary artery branches of sufficiently small diameter to lodge coils, compared with more central tumors. The catheter navigated more easily superiorly and posteriorly, such that tumors in the upper lobe and tumors located posteriorly required less procedure time. When difficulty was encountered navigating the 4-F catheter toward anterior tumors, a reverse curve catheter (eg, a mammary artery catheter) was sometimes used. After the procedure, manual compression was applied to the access site at the femoral vein for 5 minutes. Patients were kept on bed rest for 1 hour, with blood pressure and heart rate monitored every 15 minutes. They were permitted to mobilize thereafter, but they were kept on the ward under supervision for an additional 1 hour.

Transthoracic Fiducial Placement

Transthoracic fiducial placement involved percutaneous placement of platinum markers into the lung under fluoroscopic or CT guidance [209, 158, 162] using an 18-gauge coaxial introducer needle under local anesthesia (Fig 2). The patient’s position and the site and direction of needle entry were chosen to minimize the amount of lung tissue

traversed and to avoid fissures and bullae. The markers were smooth and cylindrical in shape, 4.0 mm in length and 0.9 mm in diameter, and were manufactured from platinum thread (obtained from Drijfhout, Amsterdam, Netherlands), which was cut, smoothed, and sterilized locally. Once the tip of the needle had reached the tumor, the fiducial was deployed. A minimum of 2 additional fiducials were placed, approximately 2 cm apart, around or in the tumor. An anteroposterior inspiratory chest radiograph was obtained 1 hour after the procedure to ensure no pneumothorax had developed.

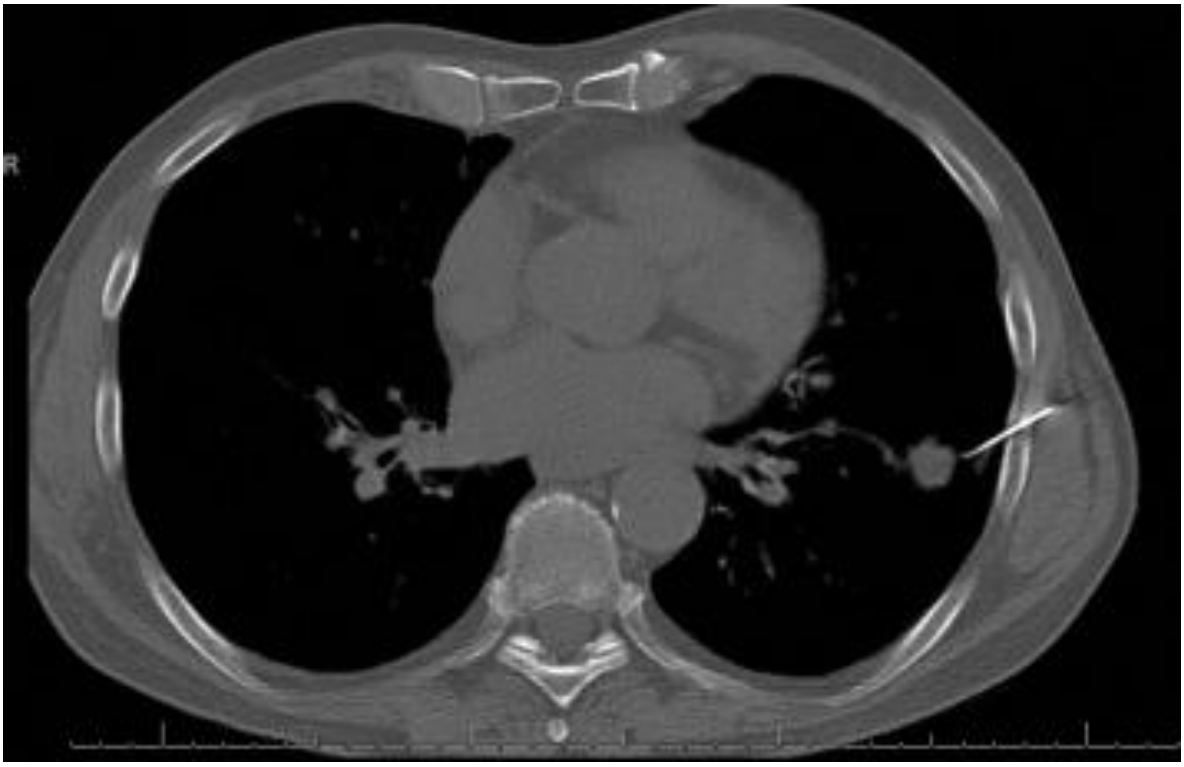


Figure 2. Transthoracic fiducial placement with 18-gauge coaxial introducer needle. The tumor is visible at the tip of the needle.

Complication Scoring

Complications were scored retrospectively according to Society of Interventional Radiology (SIR) reporting standards [212], based on procedure notes, radiographic findings on treatment planning CT, and documentation of clinical follow-up visits with the radiation oncologist. Procedure notes included any complications encountered during the procedure (eg, hemoptysis or arrhythmia) or during the 2 hour period following placement (eg, access site bleeding or symptoms suggestive of pneumothorax).

Treatment planning CT scans (contrast-enhanced four-dimensional planning CT) were obtained approximately 4–7 days after the procedure. The planning CT scans were assessed for intraparenchymal bleeding or infarction. Finally, potential clinical complications from marker placement were assessed and documented during visits with the radiation oncologist, which always included evaluation of access site and patient clinical respiratory status. These visits occurred weekly during radiotherapy and then at 3 weeks after SBRT. Subsequent follow-up entailed clinical visits and CT scans at 3, 6, 9, 12, 18, 24, and 30 months following treatment.

Statistics

Overall survival from the start of SBRT to date of death was estimated using the Kaplan-Meier method. Patients alive at last follow-up were censored from analysis. Statistical analyses were performed using IBM SPSS Version 22.0 (IBM Corp, Armonk, New York).

5.3 Results

Endovascular Coil Markers

Endovascular coil placement was attempted in 416 patients. The procedure was unsuccessful in 1 patient (0.2%) who developed hemoptysis during the procedure and was subsequently admitted for observation (grade 2 complication). This patient later underwent successful SBRT treatment using a motion-encompassing treatment approach (irradiation of the internal target volume). For the remaining 415 patients, a median of 3 coils (range, 1–6) per tumor was placed. Procedure documentation was available for 410 (99%) patients, and these patients were included in the analysis of potential complications (Table 2). Planning CT scans and documentation of clinical follow-up visits with the radiation oncologist were available for all patients. There were no grade 4 or 5 complications. There was only 1 grade 3 complication (0.2%); a patient developed a third-degree atrioventricular block during the procedure, requiring pacemaker placement (grade 3 complication). Notably, this patient had a pre-existing arrhythmia (first-degree atrioventricular block and left bundle branch block). Of 416 patients, 36 (9%) developed grade 1 complications. Thirty patients (7%) had small

asymptomatic radiographic changes distal to the vascular coil evident on radiation planning CT scan: small areas of pulmonary infarction occurred at 17 coils in 15 patients, and small areas of pulmonary bleeding were seen at 16 coils in 15 patients. Four patients (1%) developed self-limited hemoptysis requiring no further treatment. Two patients (0.5%) developed other complications; the first patient, who had diabetes, experienced hypoglycemia, and the second patient experienced a vasovagal episode. Complication rates are summarized in Table 2.

Table 2. Complications following Endovascular and Transthoracic Marker Placement as Scored by SIR Reporting Standards.

Marker Placement Technique	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Endovascular (n = 410 patients)					
Hemoptysis	4 (1%)	1 (0.2%)	—	—	—
Arrhythmia	—	—	1 (0.2%)	—	—
Asymptomatic pulmonary infarction∗	15† (3.6%)	—	—	—	—
Asymptomatic pulmonary bleed∗	15‡ (3.6%)	—	—	—	—
Other	2 (0.5%)	—	—	—	—
Total	36 (9%)	1 (0.2%)	1 (0.2%)	—	—
Transthoracic (n = 30)					
Pneumothorax	6 (20%)	4 (13%)	—	—	—
Asymptomatic pulmonary bleed	2 (7%)	—	—	—	—
Persistent pain	1 (3%)	—	—	—	—
Total	9 (30%)	4 (13%)	—	—	—

Note–Dash (—) indicates no complication.
∗ Evaluated in 409 patients, as the radiotherapy treatment planning scan was not available for 1 patient.
† Occurred at 17 markers in 15 patients.
‡ Occurred at 16 markers in 15 patients.

Transthoracic Markers

Procedure notes, planning CT scans, and documentation of clinical follow-up visits were available for all 30 patients who underwent transthoracic marker placement to assess for potential complications (Table 2). There were no grade 4 or 5 complications. Ten patients developed a pneumothorax (33%). Four patients (13%) developed a pneumothorax requiring hospital admission and chest tube placement (grade 3). There were no grade 2 complications. Nine patients (30%) experienced grade 1 complications; 6 patients developed a pneumothorax requiring no further intervention, 2 patients experienced small volume intrapulmonary bleeding (asymptomatic radiographic air space opacity consistent with small local pulmonary hemorrhage), and 1 patient developed mild persistent pain (Table 2).

Treatment Outcomes

The 5-year overall survival was 30.1% (3% 1 SE), and median overall survival was 38.9 months (95% confidence interval, 35.3–42.5). There were 285 patient deaths. Median follow-up time was 28.9 months (range, 0.5–124.6 months).

5.4 Discussion

In this large cohort of patients receiving transvascular fiducial markers for lung SBRT, complication rates were low, and the procedure was completed successfully in all but 1 patient (99.8% technical success rate). Complication rates were lower than rates following transthoracic marker placement. Iatrogenic pneumothorax occurred in 10 patients (33%) receiving markers via transthoracic puncture, with 4 patients (13%) requiring hospital admission and chest tube placement. This is consistent with the literature, where pneumothorax rates of 22%–67% are reported [204–208] making this method a poor option for patients with severe chronic obstructive pulmonary disease or prior pneumonectomy. Additionally, major pulmonary bleeding may develop in up to 3% of patients following the transthoracic approach [208, 213]. In contrast, complication rates following endovascular coil placement were very low. The only complications with rates > 1% were small subclinical radiographic changes on radiotherapy planning CT. Although 1 patient experienced grade 3 toxicity, specifically, arrhythmia during the

procedure requiring subsequent pacemaker placement, this patient had a pre-existing cardiac arrhythmia and was thus likely at greater risk than the general population. Patients with pre-existing left bundle branch block may benefit from temporary endovenous pacemaker placement during the procedure. Whereas cardiac arrhythmia is a recognized risk for coronary angiography that entails a similar procedure of intracardiac catheter manipulation, this risk has been shown to be largely negated with modern techniques and equipment (risk quoted at < 0.1%) [214, 215]. Similarly, it is likely that the risk of arrhythmia following endovascular marker placement is very low, owing to advanced techniques and image guidance employed during the procedure. Two other studies have reported on endovascular coil placement for lung tumor markers with low complication rates consistent with the present study. Mongeon et al [205] reported 15 patients who had contraindications to percutaneous marker placement. One patient (7%) developed self-limited shoulder pain, and no other patients experienced complications (asymptomatic radiographic changes were not included). Karaman et al [211] reported outcomes in 14 patients. No complications requiring medication or hospitalization > 1 night occurred (minor complications were not reported).

Endobronchial placement is an alternative method for fiducial marker placement. Disadvantages of this technique include potential difficulty in accessing peripherally located tumors [217] and frequently requirement for moderate sedation, which can be a risk or contraindicated in patients with severe comorbidities [217, 218]. Newer endoscopic methods for marker placement, including electromagnetic navigation bronchoscopy [218–220] and radial endobronchial ultrasonography [221], may allow for improved peripheral access. Whereas 1 of the main advantages of endobronchial marker placement is that the procedure may be performed at the time of tumor biopsy and mediastinal nodal sampling, this is not relevant for many patients, who undergo a biopsy before SBRT; 61% of patients in the present study underwent biopsy before SBRT, which is consistent with other SBRT series [222]. Additionally, complication rates following bronchoscope placement appear to be higher than the rates following

endovascular coil placement and may include an up to 3% rate of hemoptysis requiring hospital admission [218] and 6% rate of pneumothorax [218, 219].

The preliminary study reported successful coil placement in 23 of 25 patients in which it was attempted [210]. The procedure was stopped in 2 patients owing to difficulty navigating the angiography catheter through the pulmonary valve, which resulted in transient ventricular arrhythmia. Notably, arrhythmia requiring procedure termination was not encountered in the present patient cohort. Only 1 patient required early termination of the procedure due to development of hemoptysis. Similarly, complication rates have improved since the preliminary study [210], in which 2 patients (9%) experienced minor complications (hemoptysis and fever and pain) and 5 patients (22%) developed asymptomatic infiltrative radiographic changes. The higher procedural success rate and lower complication rates here may reflect improvements in equipment and technique.

The Xsight Lung Tracking System has reduced the percentage of patients requiring fiducial placement. This system relies on the contrast difference between tumor and adjacent lung and requires tumors to measure at least 1.5 cm in diameter (Fig 3a, b) [201].

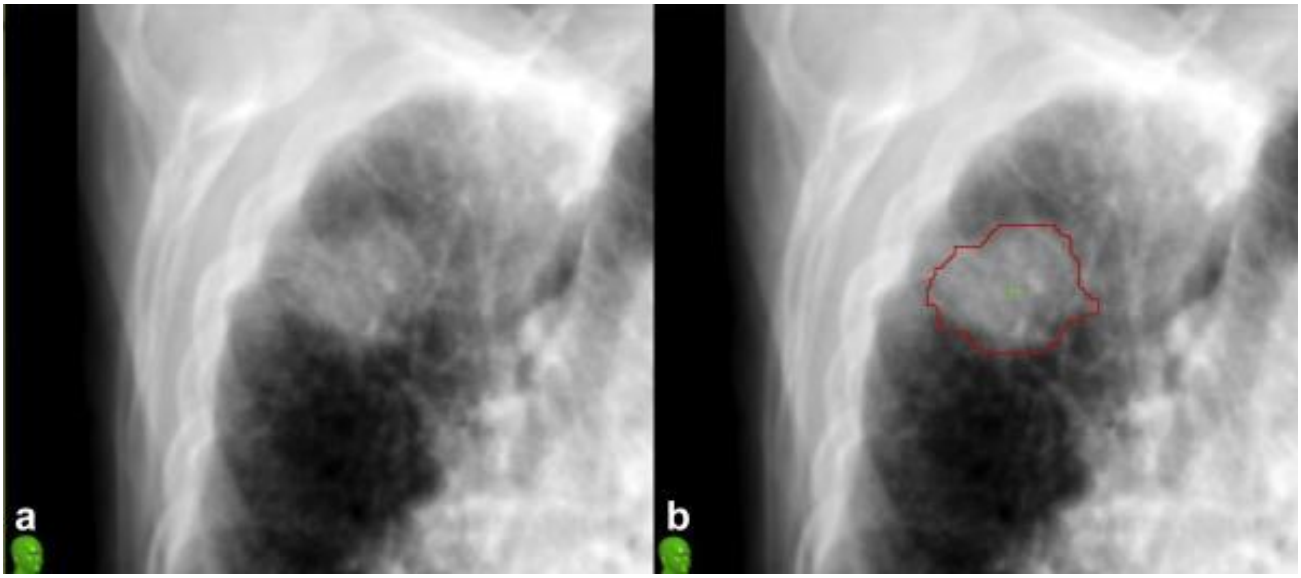


Figure 3. Digitally reconstructed radiograph in the radiotherapy treatment planning system showing a lung tumor, without contour **(a)** and with contour **(b)**, which was suitable for the Xsight Lung Tracking System. The Xsight system does not require fiducial markers for tumor tracking. Tumors must be of sufficient density for visualization by the system and must measure at least 1.5 cm in diameter.

When initially released in 2007, the estimated percentage of patients with lung cancer undergoing SBRT for whom Xsight would be applicable was 30% [40]. However, up to 34% of lung tumors preselected for Xsight based on manufacturer size and density recommendations may not be visualized sufficiently by the system to allow for tumor tracking [202]. Although the tracking software is continuously being improved by the manufacturer, the proportion of patients with lung cancer presenting with tumors < 1.5 cm will likely continue to increase with the implementation of recent lung cancer screening guidelines and with the promising results of stereotactic treatment of lung metastases. Indeed, a large percentage of patients will likely continue to require fiducial marker placement for treatment with CyberKnife.

SBRT for early-stage NSCLC may also be delivered on a conventional linear accelerator rather than CyberKnife. However, the tumor tracking enabled by the CyberKnife and fiducial markers results in a substantial reduction of geometric error caused by respiratory motion compared with cases where no tumor tracking is used [17]. Additionally, tumor tracking results in irradiation of less normal lung parenchyma compared with motion-encompassing methods (eg, irradiation of the entire volume in which a lung tumor moves through the respiratory cycle). Even when tumor tracking is not implemented and treatment is delivered on a conventional linear accelerator, fiducial markers are sometimes placed to reduce the risk of geographical miss or when the linear accelerator is not equipped with a cone-beam CT scanner.

Limitations of this study include its retrospective nature, such that it is possible that not all minor complications were documented. Based on results following endovascular coil placement for pulmonary arteriovenous malformations, one might anticipate a 3% rate of groin hematoma [222, 223], and this was not observed in the present study.

Additionally, the cohort of patients who underwent transthoracic fiducial placement was relatively small compared with the endovascular fiducial cohort, owing to the adoption of the endovascular technique as the first-line method for fiducial placement during the early years of the study.

In conclusion, endovascular placement of embolization coils for lung tumor markers is safe and effective. This may be the preferred method of fiducial marker placement for patients undergoing lung SBRT.

Chapter 6

Long-term outcomes following stereotactic body radiotherapy boost for oropharyngeal squamous cell carcinoma

S Baker[1], GM Verduijn[1], S Petit[1], A Sewnaik[2], H Mast[3], S Koljenovic[4], JJ Nuyttens[1], WD Heemsbergen[1]

1 *Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands*

2 Department of Otorhinolaryngology Head and Neck Surgery, Erasmus MC, Rotterdam, The Netherlands

3 Department of Oral and Maxillofacial Surgery, Erasmus MC, Rotterdam, The Netherlands

4 Department of Pathology , Erasmus MC , Rotterdam , The Netherlands

Published: Acta Oncologica. 2019; 58(6):926

Abstract

Background/purpose: To determine the efficacy and toxicity profile of a stereotactic body radiotherapy (SBRT) boost as a first line treatment in patients with oropharyngeal squamous cell carcinoma (OPSCC).

Materials and methods: We performed a retrospective cohort study in 195 consecutive OPSCC patients with T1-small T3 disease, treated at Erasmus MC between 2009 and 2016 with a SBRT (3 × 5.5 Gy) boost after 46 Gy IMRT. Primary endpoints were disease-specific survival (DSS) and Grade ≥3 toxicity (Common Terminology Criteria). The Kaplan-Meier method and Cox regression model were applied to determine rates and risk factors.

Results: The median follow-up was 4.3 years. Treatment compliance was high (100%). Rates of 5-year DSS and late grade ≥3 toxicity were 85% and 28%, respectively. Five-year overall survival was 67%. The most frequently observed toxicities were mucosal ulceration or soft tissue necrosis (*n* = 30, 5 year 18%), dysphagia or weight loss (*n* = 18, 5 year 12%) and osteoradionecrosis (*n* = 11, 5 year 9%). Current smoker status (hazard ratio [HR] = 2.9, *p* = .001) and Charlson Comorbidity Index ≥2 (HR = 1.9, *p* = .03) were was associated with increased toxicity risk. Tooth extraction prior to RT was associated with increased osteoradionecrosis risk (HR = 6.4, *p* = .006).

Conclusion: We reported on outcomes in the largest patient series to date treated with a hypofractionated boost for OPSCC. Efficacy was good with survival rates comparable to conventionally fractionated (chemo)radiotherapy. Grade ≥3 toxicity profiles showed high rates of soft tissue necrosis and osteoradionecrosis. Strategies to mitigate severe toxicity risks are under investigation to improve the tolerability of the SBRT boost.

6.1 Introduction

Stereotactic body radiotherapy (SBRT) allows for precise delivery of ablative radiation doses to the target with improved sparing of surrounding organs at risk [222, 223]. SBRT may theoretically be beneficial in the primary treatment of oropharyngeal squamous cell carcinoma (OPSCC), as the oropharynx has critical structures in close proximity. Additionally, SBRT offers greater convenience to patients and radiotherapy departments because of reduced number of fractions. Finally, biological dose escalation may be achieved through SBRT regimens, which theoretically may overcome the intrinsic radioresistance of less radiosensitive disease [226]. Highly hypofractionated regimens, however, may be associated with greater risk of late toxicity, particularly necrotic processes [20–22, 227–229].

Despite the potential advantages of SBRT for head and neck malignancies and a growing interest internationally [11], there is sparse literature in the setting of newly diagnosed disease. To date, SBRT has been used primarily for re-irradiation [11–13] or rarely, for nasopharyngeal carcinoma [15, 230]. The few series on SBRT in the primary setting have either included fewer than 40 patients and diverse head and neck sites [6,15] or median follow-up times less than 18 months [21, 23]. In order to evaluate SBRT as a primary treatment modality, studies with long-term follow-up consisting of homogenous patient groups are required.

At our institution, SBRT as a boost following external beam RT has been a standard treatment option for select OPSCC patients since the introduction of a frameless radiosurgery system (Cyberknife; Accuray Inc., Sunnyvale, CA, USA) in 2005. Prior to this, these patients received the boost by brachytherapy. While both techniques deliver a similar highly conformal dose distribution [225], the SBRT boost is advantageous as it is noninvasive and not limited by the strict patient eligibility criteria of brachytherapy or the requirement for specifically trained personnel.

Previously, we reported favorable quality-of-life and toxicity outcomes with SBRT boost up to 24 months post treatment [224,232]. In the current study, we felt it prudent to

investigate long-term outcomes especially given the potential for highly hypofractionated RT schedules to increase the risk of late toxicities [20–22, 227–229].

6.2 Material and methods

Patients

Consecutive OPSCC patients treated at the Department of Radiotherapy at Erasmus MC were identified from a prospective radiotherapy planning database which started in 2009. Eligibility criteria for the present study included: treatment with SBRT boost, T1 - “small” T3 (no defined size criterion, but at the discretion of the multidisciplinary tumor board), N0–N2c, M0 primaries. The following exclusion criteria were applied: diagnosis with another primary malignancy within 6 months, previous oropharyngeal cancer or previous head and neck RT. Patients were staged with a CT or MRI for the primary site, ultrasound of the neck, and in the case of N2 disease, thoracic CT.

During the early years of the inclusion period, patients with T1–T2 tumors preferentially received brachytherapy when eligible (n = 58) [232] and the remaining T1–T2, and small T3 tumors, received SBRT boost when eligible (i.e. tumors not adjacent to the thyroid cartilage). Since 2012, patients could receive SBRT boost first line, since our early experience with the SBRT boost regimen was favorable [232]. In total, 195 patients were treated with SBRT boost and fulfilled the in- and exclusion criteria. Patients with poorer performance status (Eastern Cooperative Oncology Group [ECOG] ≥ 2) who were eligible for curative-intent treatment received conventional 70 Gy IMRT. ECOG ≥2 patients may find it challenging to remain still for the 30 min required for delivery of each SBRT fraction, and thus conventional IMRT may be a more suitable treatment option.

Treatment and follow-up

The treatment regimen consists of 46 Gy accelerated IMRT (23 daily fractions, 6 fractions per week) to the primary tumor and neck, followed by a sequential SBRT boost to the primary tumor of 16.5 Gy in 3 daily fractions. The timing is such that total weekly dose during the boost phase never exceeds 16.5 Gy. Thus, the total treatment time for

the regimen is approximately 5 weeks. We regard this SBRT boost treatment schedule as a local dose intensification since the calculated biologically effective dose (including reduced treatment time) delivers up to 30.3 Gy (α/β = 10) higher biologically effective dose than a 7-week conventional IMRT regimen for rapidly proliferating tumors [233, 234] (equation provided in supporting information). However, transforming this schedule into an equivalent dose in 2-Gy fractions, which does not account for overall treatment time, EQD2 is 67 Gy (α/β = 10). Patients with T3 or N2c disease without contraindication for systemic treatment received two cycles of cisplatin (100 mg/m2) on day 1 and 22 of the IMRT phase. Our early experience with the SBRT boost regimen suggested good outcomes treating patients with N2a-b without chemotherapy, and thus chemotherapy was not given to patients with earlier nodal classification [232]. Patients with positive lymph nodes at the time of diagnosis underwent a neck dissection two weeks following RT, as previously described [235]. The target volume for the accelerated IMRT phase consists of the gross tumor volume (GTV), plus a 1 cm margin on the primary and a 5 mm margin on positive lymph nodes to account for subclinical disease, and an additional 5 mm margin (PTV) to account for set-up error/positional uncertainty. The target coverage objective was PTV V95 > 98%. Following the IMRT phase, a second planning CT scan is obtained. This is rigidly co-registered with the planning CT for the IMRT phase, and the GTV and CTV volumes are transposed. The SBRT PTV consists of the CTV of the primary tumor only, plus a 3 mm margin. The dose is prescribed to the 80% isodose line. The dose constraints for the total plan (EQD2 with α/β = 2) are: spinal cord Dmax <50 Gy and brain stem Dmax <60 Gy (both hard planning constraints); parotid glands Dmean <26 Gy, submandibular glands Dmean <39 Gy, oral cavity Dmean <50 Gy, constrictor muscles Dmean <55 Gy (when achievable). The SBRT boost is delivered on the Cyberknife radiosurgery system [1,17]. Follow-up visits (head-and-neck multi-disciplinary team) were planned every 2 months for the first year, gradually reduced to every 6 months, for a minimum of 5 years.

Endpoints

The primary endpoints were disease specific survival (DSS) and late grade ≥3 toxicity. For DSS, both tumor-related death and toxicity-related death was included as events. Secondary endpoints were overall survival (OS) and locoregional control (LRC). Disease-free survival (DFS) (events: local, regional, distant failure, and death) and progression-free survival (events: local, regional, or distant failure) were also assessed to facilitate comparison of outcomes with the literature.

Toxicity

Acute grade ≥3 dysphagia was scored as requirement for a feeding tube within the first 90 days after RT, according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v.4.0). Systematic data on acute dermatitis and mucositis were not available and therefore not scored.

Late toxicity (> 90 days after completion of RT) was scored retrospectively based on CTCAE v.4.0. Of note, CTCAE v.4.0 does not mention hyperbaric oxygen (HBO) for toxicity grading of soft tissue necrosis or osteoradionecrosis (ORN). Version 3 designates HBO as grade 3, as do most recent studies [236–238]; thus, it was scored as grade 3 toxicity for the present study also. In case of recurrent disease, further toxicity scoring was omitted. For patients requiring tube feeding >90 days post-treatment, we evaluated whether this was related to dysphagia (scored as grade 3 dysphagia) or dry mouth (grade 3 xerostomia). Grade 3 trismus was scored as maximal mouth opening <1 cm.

Statistical analysis

Statistical analyses were performed using SPSS software (version 24, IBM Corporation, Armonk, NY). p-Values <.05 were considered statistically significant. The Kaplan-Meier method was used to calculate survival and cumulative incidences of toxicity. OS and DSS were calculated from the first fraction of RT until death from any cause or death from OPSCC, respectively. Patients alive were censored at the date of last follow-up

visit. Follow-up time for toxicity endpoints was calculated from the last radiotherapy fraction. Patients were censored from toxicity analysis at time of disease recurrence, death, or last follow-up, whichever came first. Prognostic factors for toxicity were evaluated in univariable Cox regression models, and multivariable models using the forward selection method (entry $p < .1$, removal $p > .1$). Covariates assessed included: sex, age (>65 vs. ≤65 years), ECOG performance status (0 vs. 1), smoking (> 10 pack-years vs. ≤ 10, and smoker vs. nonsmoker at diagnosis), Charlson Comorbidity Index score (CCI) (≥2 vs. <2), T stage (T3 vs. T1/T2), N stage (N2 vs. N0–N1), tooth extraction prior to RT, current or previous alcohol abuse, body mass index (BMI) (≤ 22 vs. > 22), disease subsite (tonsil vs other, base of tongue vs other), and bilateral vs unilateral neck RT.

The study protocol was reviewed by the Medical Ethical Committee of the Erasmus Medical Center (EMC17404), and permission was obtained for retrospective anonymized data collection, in accordance with local and national regulations.

6.3 Results

Patients

All 195 study patients successfully completed the treatment regimen. Of the 195 study patients, one was lost to follow-up, two died prior to the late toxicity period, and 10 had residual or recurrent disease less than 90 days after RT, leaving 182 (93%) available for late toxicity assessment.

A majority of patients (n = 116, 60%) had stage III-IVA disease according to AJCC 7th edition staging, and 113 (58%) has tonsil primaries. A total of 27 patients had T3 and/or N2c disease (one patient had both). Twelve patients received concurrent chemotherapy, and the additional patients with T3 and/or N2c disease did not (n = 15) due to contraindications to chemotherapy (e.g. comorbidities). A total of 93 patients (48%) had p16 status determined, and among these, 29 (31%) were p16 negative and 64 (69%) were p16 positive. Notably, during the years of study, patients were generally

only tested for p16 if they were suspected of having HPV-associated disease (young age, lack of smoking history). For 14 patients p16 status was established retrospectively. The median age was 61 years (range 34–86), and 33 patients (17%) were over the age of 70 years. A total of 103 (53%) were smokers at the time of diagnosis. Additional baseline patient and tumor characteristics are shown in Table 1.

Survival

The 2-year and 5-year OS were 87% (2% 1 standard error [SE]) and 67% (4% 1SE), respectively (Figure 1), while for DFS, these rates were 81% (3% 1SE) and 62% (4% 1SE), respectively. There were 53 deaths (25 OPSCC-related, 12 other malignancy, 2 toxicity-related, 9 other causes, 5 unknown cause). Rates of 2-year and 5-year DSS were 89% (2% 1 SE) and 85% (3% 1SE), respectively (Figure 1). Median follow-up for surviving patients was 50.6 months (15.0–98.6) and for all patients, 42.8 months (2.1–98.6).

Table 1. Baseline characteristics of the study population (n = 195).

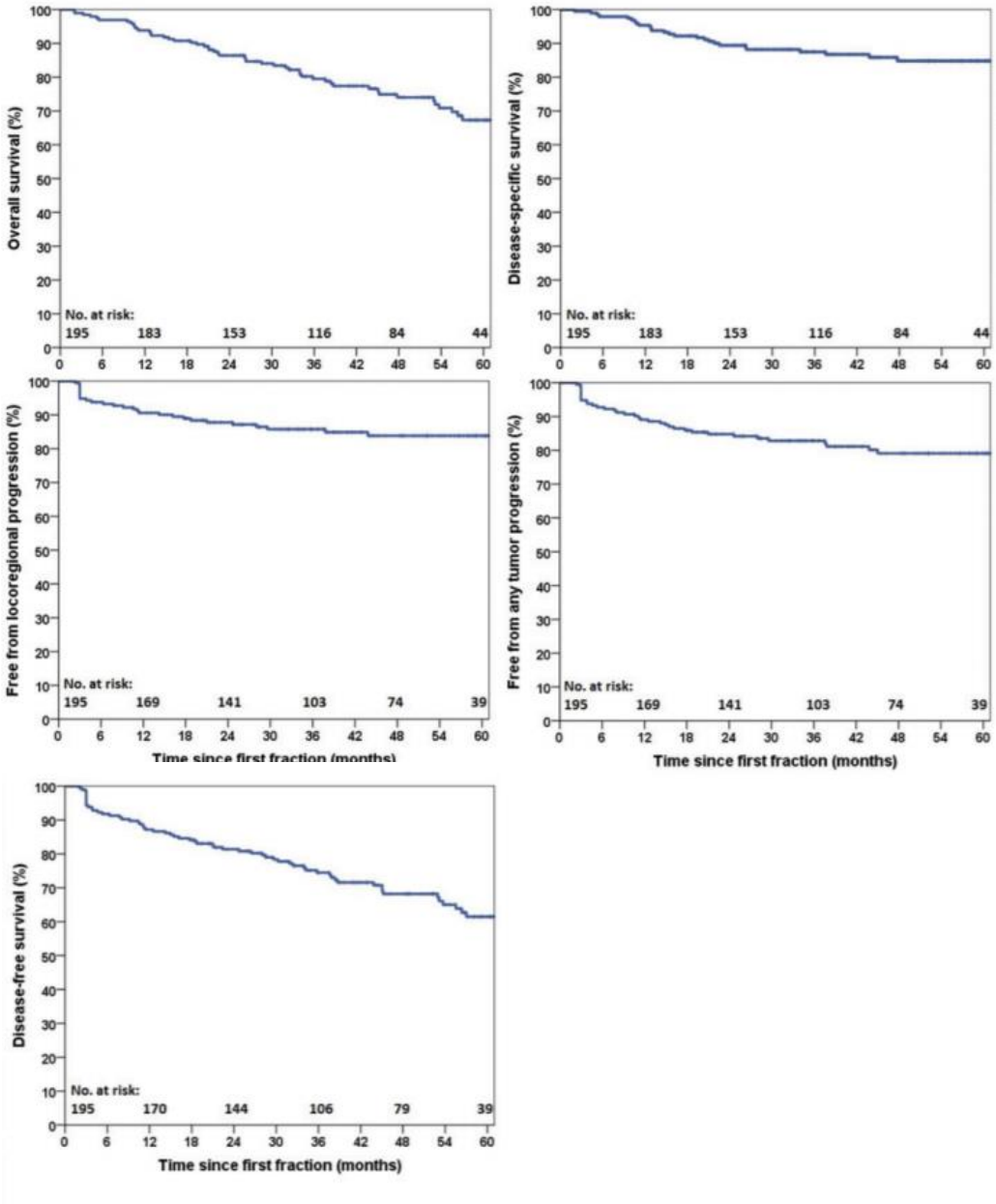
	Value*
Age (years)	61 (34–86)
Gender	
Male	122 (63%)
Female	73 (37%)
ECOG performance status	
0	151 (77%)
1	44 (23%)
Smoking >10 pack-years	147 (75%)
Smoker at diagnosis	103 (53%)
Current or previous alcohol abuse	59 (30%)
CCI	
0	54 (28%)
1	44 (23%)
≥2	97 (50%)
Baseline BMI	
>22	152 (78%)
≤ 22	43 (22%)
Tooth extraction prior to RT	64 (33%)
T stage classification	
T1	39 (20%)
T2	136 (70%)
T3	20 (10%)
N Stage classification	
N0	91 (47%)
N1	32 (16%)
N2a	15 (8%)
N2b	49 (25%)
N2c	8 (4%)
Stage grouping (AJCC 7th Edition)	
Stage I	11 (5.6%)
Stage II	68 (34.9%)
Stage III	44 (22.6%)
Stage IVa	72 (36.9%)
Oropharynx subsite	
Base of tongue	35 (18%)
Soft palate	23 (12%)
Tonsil	113 (58%)
Oropharynx wall	11 (6%)
Other	13 (7%)
P16 status	
Positive	63 (32%)
Negative	30 (15%)
Unknown	102 (52%)
Concurrent systemic treatment	
Cisplatin	10 (5%)
Cetuximab	2 (1%)
Accelerated radiotherapy	192 (99%)
Neck dissection	101 (52%)
Unilateral neck radiotherapy	82 (42%)

Abbreviations: CCI: Charlson Comorbidity Index; ECOG: Eastern Cooperative Oncology Group.

*Median and range are provided for continuous variables while n and percent are provided for categorical variables.

Three patients with lymph node metastases did not undergo neck dissection due to advanced age and inclusion of the involved lymph node in the SBRT boost ($n = 1$), complete excision of the lymph node with excisional biopsy ($n = 1$), and involvement of a retropharyngeal lymph node which was included in the SBRT boost ($n = 1$).

Figure 1. Kaplan-Meier plots showing freedom from locoregional progression, freedom from any progression, disease-specific survival, overall survival, and disease-free survival.



Locoregional control and disease recurrence

The 2-year and 5-year LRC were 88% (2% 1SE) and 84% (3% 1SE), respectively. A total of 37 patients (19%) experienced local, regional, and/or distant disease recurrence. Among the 29 patients (16%) with local and/or regional recurrences, 7 underwent successful salvage surgery. The 5-year local and regional control were 90% and 93%, respectively. A description of disease recurrences and subsequent treatment is provided in supporting information Table S1. A detailed analysis of the location of local and regional recurrences with respect to the radiotherapy fields has previously been published [233].

Acute toxicity

Two patients required a break in treatment due to aspiration/pneumonia, and subsequently completed treatment. During the acute toxicity period, 65 patients (33%) required a feeding tube. One patient had a feeding tube at baseline, and was not included in this assessment.

Late grade ≥3 toxicity

Among the 182 patients available for late toxicity assessment, 47 experienced grade ≥3 late toxicity with an estimated cumulative incidence of 28% (4% 1SE) at 5 years (Figure 2). Median time to onset of grade ≥3 late toxicity was 10.0 months (3.0–77.6) after RT. The 5-year cumulative incidence of grade ≥3 mucosal ulcers or soft tissue necrosis was 18% (3% 1SE) (Figure 3). This included one patient with grade 4 toxicity (carotid blow-out which was treated successfully with surgical ligation) and one grade 5 toxicity in a patient who died from tracheal necrosis/bleeding. Among the total 30 patients who experienced grade ≥3 mucosal ulcers or soft tissue necrosis, the time from occurrence until healing was <6 months in 14 patients (47%), 6–12 months in 9 patients (30%), and > 12 months in 6 patients (20%), with one patient (3%) lost to follow-up. The 5-year cumulative incidence of grade ≥3 osteoradionecrosis (ORN) was 9% (3% 1SE) (Figure 3). Among the total 11 cases of ORN, 5 experienced fracture and/or required surgery

(grade 4), and an additional one died from surgical complications (grade 5). The 5-year cumulative incidence of grade ≥3 dysphagia or weight loss was 12% (3% 1SE) (Figure 3). For comparison with the literature, crude rates of grade ≥3 dysphagia (tube feeding dependence) at 1 and 2 years were 2% (n = 4) and 2% (n = 3), respectively. Additional grade ≥3 toxicities are provided in Table 2.

Figure 2. Kaplan-Meier plots showing cumulative incidence of late grade ≥3 toxicity in 182 patients.

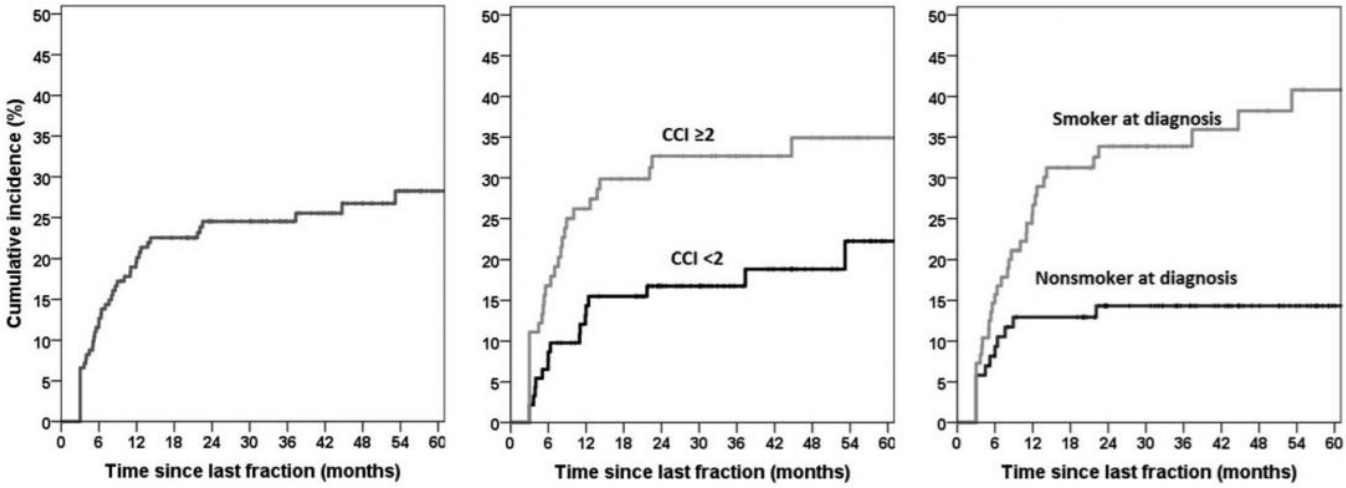


Figure 2. Kaplan-Meier plots showing cumulative incidence of late grade ≥3 toxicity in 182 patients.

Figure 3. Kaplan-Meier plots showing cumulative incidence of specific late grade ≥3 toxicity in 182 patients.

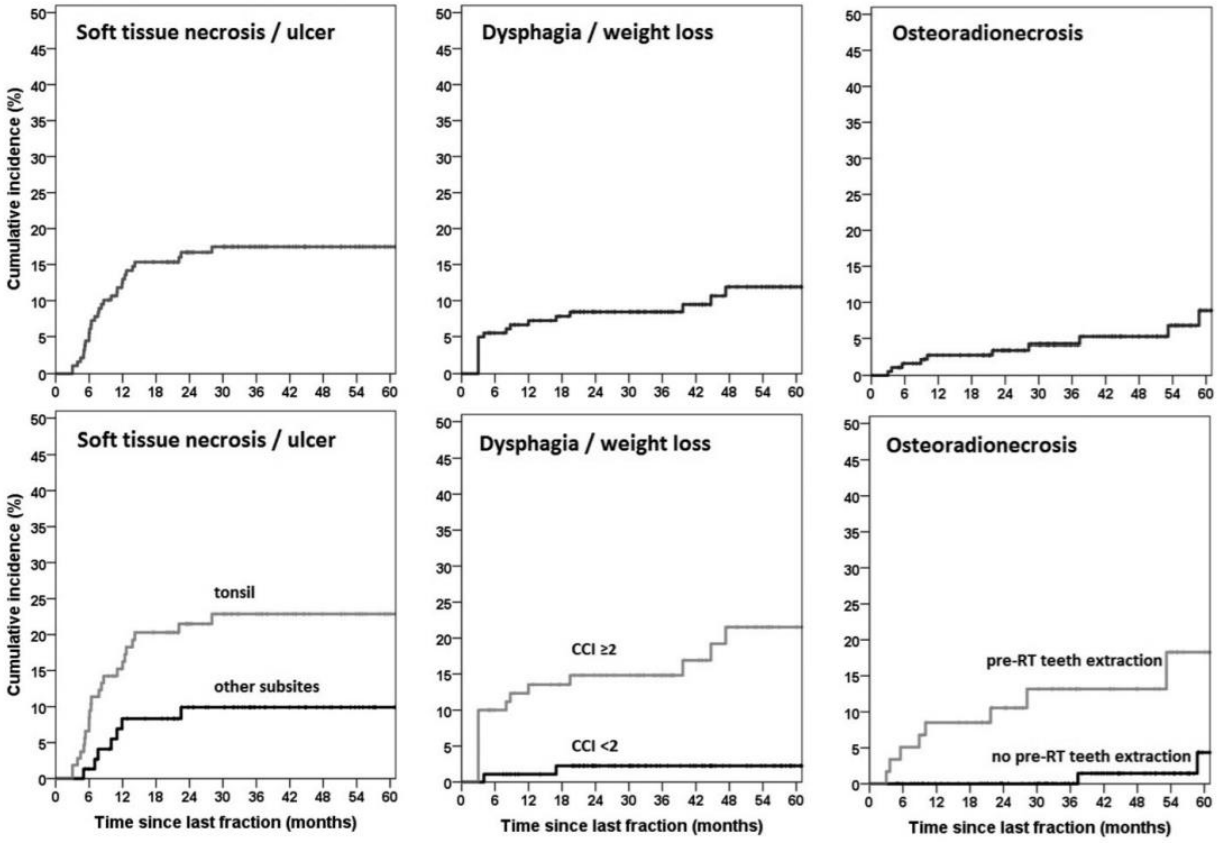


Table 2. Distribution of maximum toxicity scores in 182 evaluated patients (crude numbers).

Endpoint	Grade 3 *n* (%)	Grade 4 *n* (%)	Grade 5 *n* (%)
Overall max score	39* (21.4%)	6 (3.2%)	2 (1.1%)
Mucosal ulcer/soft tissue necrosis	28 (15.4%)	1 (0.5%)	1 (0.5%)
Dysphagia	15 (9.0%)	0	0
Weight loss	7 (3.8%)	0	0
Osteoradionecrosis	3 (1.6%)	5 (2.7%)	1 (0.5%)
Trismus	4 (2.2%)	0	0
Aspiration	1 (0.5%)	0	0
Xerostomia	0	0	0

*Including 12 patients with 2 or more grade 3 events.

Prognostic factors for toxicity

Smoking status (smoker at diagnosis) and a CCI ≥2 were associated with higher risk of grade ≥3 late toxicity on both uni- and multivariable analysis (Table 3). Current smokers had a 41% (6% 1SE) cumulative 5-year incidence of grade ≥3 late toxicity compared to 14% (4% 1SE) in nonsmokers ($p < .01$) (Figure 2).

Table 3. Prognostic factors for grade ≥3 late toxicity.

	Univariable			Multivariable		
	HR	95% CI	*p*	HR	95% CI	*p*
Sex (male vs. female)	0.61	0.34–1.08	.089			
Age (>65 vs. ≤65)	1.05	0.56–1.97	.9			
ECOG (1 vs. 0)	1.00	0.49–2.08	1.0			
Pack years (>10 vs. ≤10)	1.93	0.86–4.29	.11			
Smoker at diagnosis (yes vs. no)	2.84	1.47–5.49	**.002**	2.91	1.51–5.51	**.001**
History of alcohol abuse (yes vs. no)	1.37	0.75–2.51	.3			
CCI (≥ 2 vs. < 2)	1.84	1.02–3.31	**.042**	1.90	1.06–3.43	**.032**
BMI at start of RT (≤22 vs. >22)	1.67	0.89–3.11	.11			
Tumor subsite tonsil (vs other)	1.17	0.65–2.11	.6			
Tumor subsite BOT (vs other)	0.42	0.15–1.17	.095			
T stage (T3 vs. T1–T2)	1.49	0.63–3.50	.4			
Bilateral vs. unilateral neck RT	1.09	0.61–1.95	.8			
Tooth extraction prior to RT	1.09	0.60–2.00	.8			

BMI: body mass index; BOT: base of tongue; CCI: Charlson Comorbidity Index; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; RT: radiotherapy. Bold values indicate statistical significance ($p<0.05$).

Tooth extraction prior to RT was predictive for grade ≥3 ORN (HR 6.4, p < .01) (supporting information Table S2 and Figure 2). Only univariate analysis was undertaken for ORN due to the low total number of events. Median time from extraction to start of RT was 18 days, and was not associated with ORN (≤ vs > median time, HR 1.9, p = .4). Smoker at diagnosis and tonsil subsite were significantly associated with increased mucosal ulcers/soft tissue necrosis (p < .05) on multivariable analysis whereas CCI showed a trend towards statistical significance (p < .1) (supporting information Table S2). CCI ≥2 and smoker at diagnosis were associated with severe late dysphagia/weight loss on multivariable analysis (supporting information Table S2).

HPV-related disease

Patients with tumors positive for p16 (n = 63), compared to those with tumors negative for p16 (n = 30), were more likely to have lower CCI scores (p < .01), fewer pack-years (p < .01), nonsmokers (p < .01), higher BMI (p < .01), younger of age (p = .04), and better performance status (p < .01). The cumulative overall grade ≥3 toxicity rate was 15% (5% 1SE) at 5 years in the p16 positive group.

Tumor p16-positive status was strongly associated with lymph node positivity (N1–N2c vs N0) (Spearman's correlation of 0.45, p < .001). Neck dissection (which was performed for patients with lymph node positivity) was associated with lower risk of grade ≥3 toxicity (hazard ratio = 0.27, p < .001), likely due to the association with p-16 positivity (hence neck dissection was not included in the multivariable toxicity analysis).

Prognostic factors for overall survival

Prognostic factors for overall survival on multivariable analysis (forward model with entry <0.05, removal <0.1) included performance status (ECOG 1 vs 0, HR = 2.6, p < .01), pack years (>10 vs ≤10, HR = 2.2, p = .055), and CCI (CCI ≥2 vs 0–1, HR = 1.9, p = .04). Age, N stage, T stage, current smoking, and tumor subsite did not reach significance. Among the patient subset with known HPV status (n = 93, result of

selective HPV testing), the final multivariable model only selects HPV positivity as a prognostic factor (HR = 5.1, p = .001), and all other factors do not reach significance.

6.4 Discussion

In this single institution series, we report the long-term outcomes of 195 OPSCC patients treated with IMRT plus a SBRT boost, constituting the largest series in the literature of SBRT in the primary setting for head and neck malignancies. We observed a 5-year disease-specific survival and overall survival of 85% and 67%, respectively. Cumulative incidence of Grade ≥3 toxicity at 5 years was 28%. A previous analysis of the SBRT boost regimen at our center reported only 5% late grade ≥3 toxicity. However, this was in a smaller patient cohort (n = 102), with shorter follow-up, and only included T1–T2 tumors [224].

Overall, oncologic outcomes following SBRT boost are similar to those following conventional radiotherapy [238–240]. Few studies with similar patient populations (early T-stage OPSCC, early to advanced nodal disease) are available for meaningful comparison, and rates of HPV-associated disease have not been reported in these studies [239–241]. Nevertheless, one series of early T-stage tumors reported a 5-year OS of 67% [241], identical to the 5-year OS here. Our 2-year DFS of 81% is also consistent with previous studies, which report rates between 82 and 90% [239, 241] in T1–T2 tumors with earlier nodal classification (N0–N1) than the present study.

The apparent high rate of p16 positivity among those tested in the present study is partly a reflection of selective p16 testing practices (more often in those lacking a significant smoking/alcohol history). The rate of HPV-associated disease in the Netherlands during the years of study was 40–50% [243, 243], although in this population of early T-stage tumors, many with advanced nodal disease, this rate may be higher.

Advantages of the regimen include its tolerability and high compliance rate: all patients completed treatment and only two required short treatment breaks. Conversely, 70 Gy

conventional regimens typically require treatment breaks in 10–20% of patients due to acute toxicity, which are associated with worse oncologic outcomes [244, 245]. Additionally, the SBRT boost regimen may be a definitive treatment option for patients with advanced disease (stage III–IV) who are not eligible for conventional chemoradiotherapy due to advanced age and comorbidities which preclude concurrent chemotherapy; notably, 33 (17%) of patients in our study were over the age of 70 years. Finally, by avoiding concurrent chemotherapy, ototoxicity, renal dysfunction, and other chemotherapy-related toxicities are avoided.

The major limitation of the SBRT boost regimen is the high rate of severe late toxicity. Notably, 30 patients (16%) developed mucosal ulcers/soft tissue necrosis. Following conventional RT, late mucosal ulceration is relatively rare, occurring in 1–8% of patients [238, 239, 246, 247]. Our 9% rate of ORN is also higher than in the literature (<3% with modern radiation techniques) [228, 236, 248] with many grade 4 ORN cases which are rare following conventional RT [236, 240, 248]. The rates of severe late dysphagia we observed (crude rates of 2% at both 1 and 2 years) are slightly lower than those following conventional IMRT in early stage disease (crude 1- and 2-year rates of 7% and 4%, respectively) [249]. ”These findings are consistent with historical data showing increased late toxicity with hypofractionation in head and neck cancers [227, 228]. The majority of head and neck SBRT studies in the literature are in the setting of re-irradiation for recurrent disease, and while some of these have reported high incidence (10–17%) of necrotic processes such as soft tissue necrosis and carotid blow-out [20–23], others have not found this to be the case, with total late grade ≥3 toxicity rates of 3–6% [12, 13]. Different dose fractionation regimens as well as patient selection criteria may largely account for this difference. One other study evaluating SBRT boost (10–25 Gy in 3–5 fractions) following conventionally-fractioned RT (median 50.4 Gy) reported grade ≥3 toxicity in 35% (soft tissue necrosis in 27%) [229].

Risk factors for severe late toxicity were identified, and smoking at the time of diagnosis was the factor which emerged most consistently. This was predictive for total grade ≥3 late toxicity, and also for mucosal ulceration/soft tissue necrosis, and dysphagia/weight loss. The cumulative incidence of severe late toxicity in current smokers was 41%,

versus 14% in nonsmokers. This is consistent with the vasoconstrictive and thrombotic microvascular effects of cigarette smoking [250], which likely compound the microvascular injury from radiation which can lead to late toxicity. A less pronounced effect has been demonstrated following conventional RT, where an 18% increase in late grade ≥3 toxicity has been observed in smokers compared to nonsmokers [251].

Tooth extraction prior to RT was strongly associated with ORN. This was despite a median interval of 18 days before the start of treatment, an interval which has been associated with low ORN risk in conventional radiotherapy [252]. Comorbidity as measured by the CCI was significantly associated with general grade ≥3 late toxicity and late grade ≥3 dysphagia/weight loss, and with a trend ($p < .1$) for increased mucosal ulcers/soft tissue necrosis. Greater comorbidity burden may reduce general physiologic reserve, and increase susceptibility to toxicity. To our knowledge, comorbidity has not previously been examined as a potential prognostic factor for toxicity in head and neck cancer. Finally, tonsil primaries were at higher risk of severe late mucosal ulcers/soft tissue necrosis, potentially due to close proximity to the oropharyngeal wall. It is notable that patients with tumors positive for p16 experienced less grade ≥3 toxicity (5 year 15%), likely because they tend to be nonsmokers, younger, and with fewer comorbidities.

In summary, the regimen of accelerated IMRT and SBRT boost generated good long-term OS and DSS, but with high rates of severe late tissue necrosis, ORN, and overall late grade ≥3 toxicity. To improve the risk-benefit ratio, the protocol for tooth extraction will need evaluation with the goal of reducing rates of osteoradionecrosis. Further study will be needed to determine dose constraints for normal structures, particularly the mandible.

6.5 Supplemental material

Equation 1.

$$Biologically\ Effective\ Dose\ (BED) = D * \left(1 + \frac{d}{\alpha/\beta}\right) - \frac{0.693}{\alpha} * \frac{t - Tk}{Tp}$$

Where:

- D is the total dose (Gy)
- $\boldsymbol{\alpha}$ (Gy^{-1}) and $\boldsymbol{\beta}$ (Gy^{-2}) are the linear and quadratic constants, respectively, in the linear quadratic cell-survival equation
- t is the total treatment time (days)
- Tk is the lag or onset time until tumor repopulation
- Tp is the tumor doubling time

To calculate BED from Equation 1 for the current regimen and for a standard fractionated 70 Gy regimen, the following values were utilized[19]:
$\boldsymbol{\alpha/\beta}$ = 10 Gy, $\boldsymbol{\alpha}$ = 0.3 Gy^{-1}, Tk (for rapidly proliferating head and neck tumors) = 2, Tp = 18 days.

Supplementary Table 1. Disease recurrences and subsequent treatment.

	n	Treatment
Isolated local recurrence	17	Successful surgical salvage n=6 Surgical salvage, subsequent recurrence and death n=2 Palliative treatment/supportive care n=9
Isolated regional recurrence	7	Successful surgical salvage n=1 Surgical salvage, subsequent recurrence and death n=2 Palliative treatment/supportive care n=4
Local and regional recurrence	1	Palliative treatment/supportive care n=1
Regional and distant recurrence	4	Palliative treatment/supportive care n=4
Isolated distant recurrence	8	Palliative treatment/supportive care n=8

Supplementary Table 2. Univariable analysis for factors associated with grade ≥ 3 osteoradionecrosis.

	Univariable		
	HR	95% CI	p
Sex (male vs female)	1.00	0.29 – 3.41	1.0
Age (> 65 vs ≤ 65)	0.92	0.24 – 3.48	0.9
ECOG (1 vs 0)	0.47	0.06 – 3.66	0.5
Pack years (> 10 vs ≤ 10)	3.23	0.41 – 25.3	0.3
Smoker at diagnosis (yes vs no)	3.72	0.80 – 17.4	0.095
History of alcohol abuse (yes vs no)	0.60	0.13 – 2.78	0.5
CCI ≥ 2	0.82	0.25 – 2.69	0.7
BMI at start of RT (≤ 22 vs > 22)	1.44	0.38 – 5.43	0.6
Tumor subsite tonsil (vs other)	0.53	0.16 – 1.75	0.3
Tumor subsite BOT (vs other)	1.21	0.26 – 5.60	0.8
T stage (T3 vs T1-2)	2.03	0.44 – 9.40	0.4
Bilateral vs unilateral neck RT	1.75	0.46 – 6.67	0.4
Tooth extraction prior to RT	6.42	1.70 – 24.3	**0.006**

BMI body mass index; BOT base of tongue; CCI Charlson Comorbidity Index; CI confidence interval; ECOG Eastern Cooperative Oncology Group; HR hazard ratio; RT radiotherapy

Supplementary Table 3. Univariable and multivariable analyses for factors associated grade ≥ 3 mucosal ulceration/soft tissue necrosis, and for grade ≥ 3 dysphagia/weight loss.

	Mucosal ulceration/soft tissue necrosis					**Dysphagia/weight loss**				
	Univariable		Multivariable			Univariable		Multivariable		
	HR	p	HR	95% CI	p	HR	P	HR	95% CI	p
Sex (male vs female)	0.43	**0.023**				0.59	0.3			
Age (> 65 vs ≤ 65)	0.90	0.8				0.95	0.9			
ECOG (1 vs 0)	0.80	0.6				2.22	0.11			
Pack years (> 10 vs ≤ 10)	2.15	0.16				2.67	0.19			
Smoker at diagnosis (yes vs no)	2.63	**0.019**	2.95	1.31 – 6.65	**0.009**	3.21	**0.040**	3.38	1.11 – 10.3	**0.032**
History of alcohol abuse (yes vs no)	1.43	0.3				3.20	**0.014**			
CCI ≥ 2	1.87	0.099	1.95	0.93 – 4.09	0.079	8.72	**0.004**	9.02	2.07 – 39.3	**0.003**
BMI at start of RT (≤ 22 vs > 22)	1.96	0.083				2.49	**0.060**			
Tumor subsite tonsil (vs other)	2.52	**0.032**	2.83	1.21 – 6.63	**0.016**	0.44	0.092			
Tumor subsite BOT (vs other)	0.33	0.13				0.57	0.5			
T stage (T3 vs T1-2)	0.60	0.5				3.87	**0.010**			
Bilateral vs unilateral neck RT	0.61	0.2				3.76	**0.036**			

BMI body mass index; BOT base of tongue; CCI Charlson Comorbidity Index; CI confidence interval; ECOG Eastern Cooperative Oncology Group; HR hazard ratio; RT radiotherapy

Chapter 7

Locoregional failures and their relation to radiation fields following stereotactic body radiotherapy boost for oropharyngeal squamous cell carcinoma

S Baker[1], GM Verduijn[1], S Petit[1], JJ Nuyttens[1], A Sewnaik[2], A van der Lugt[3], WD Heemsbergen[1]

1 Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands
2 Department of Otorhinolaryngology Head and Neck Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands
3 Department of Radiology & Nuclear Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands

Published: Head and Neck. 2019; 41(6):1622.

Abstract

Background: To investigate the location of recurrences with respect to the radiation fields in oropharynx cancer after intensity-modulated radiotherapy and stereotactic body radiotherapy (SBRT) boost.

Methods: Local and regional recurrences were delineated on diagnostic scans which were rigidly coregistered with treatment planning scans, then classified based on the location of the center of mass (COM) as well as volumetrically.

Results: In 195 patients, the 5-year local and regional control were 90% and 93%, respectively. By COM, 76% of local recurrences were in-field; 24% were out-of-field, significantly higher than 0%-5% in the literature for conventional regimens ($P < 0.01$). Regional recurrences (19 in 12 patients) were largely within unirradiated neck levels (47%) and electively irradiated regions (42%).

Conclusions: The regimen with biological equivalent dose intensification provides excellent overall and in-field local control. The highly conformal boost technique was, however, associated with increased out-of-field local failure.

7.1 Introduction

Radiotherapy (RT) provides a functional organ preservation strategy for definitive treatment of oropharyngeal squamous cell carcinoma (OPSCC). However, locoregional recurrences remain problematic and are a significant source of morbidity and mortality. The majority of local recurrences occur within the high-dose RT region [253-255], suggesting that strategies to overcome radioresistance are needed. Overall dose intensification, however, is challenging as regimens are already near patient tolerance.

Highly conformal dose escalation may potentially improve in-field control while sparing swallowing structures, salivary glands, and other organs at risk. Brachytherapy has been recommended as one such strategy; however, it is technically demanding with strict patient eligibility criteria [256]. At our institution, a regimen consisting of accelerated intensity-modulated radiotherapy (IMRT) followed by stereotactic body radiotherapy (SBRT) boost was developed, initially as an option for those ineligible for brachytherapy, but later used standardly for eligible patients with T1-small T3, N0-N2 OPSCC. The SBRT boost delivers a highly conformal dose with steep dose gradients outside the target. Previously, we reported improved swallowing function, xerostomia, and qualify-of-life in patients following SBRT boost compared to conventional IMRT [232]. An additional advantage over a conventional schedule includes greater convenience for both patients and RT departments, as hypofractionation allows for fewer fractions delivered and reduced overall treatment time.

Several studies have reported overall oncologic outcomes of an SBRT boost for head and neck malignancies, but without detailed analysis of patterns of failure with respect to RT fields, and in only a minority of patients with OPSCC [229, 231]. The biologically effective dose intensification accomplished with an accelerated schedule and a hypofractionated boost may be advantageous for in-field local control. With highly conformal dose distributions and small margins around the clinical target volume (CTV), there is theoretically a greater risk of missing the target. When more conformal IMRT techniques began replacing three-dimensional conformal RT for OPSCC two decades ago, concern of potentially higher rates of marginal recurrences prompted numerous

studies evaluating locoregional recurrence location. These studies, however, found marginal and out-of-field recurrences to be uncommon [253-255, 257, 258]. Stereotactic RT planning and dose delivery take conformality one step further and place greater importance on accurate target contouring and disease delineation, a known area of potential weakness in the RT planning process [259]. The effect of a highly conformal dose distribution and steep dose gradients on marginal and out-of-field failure is uncertain and of particular relevance in the era of increasingly conformal dose distributions and the increasing utilization of proton beam therapy [260]. The primary objective of this study was to assess patterns of locoregional failures with respect to RT fields following SBRT boost for OPSCC. Secondary objectives were to determine prognostic factors for local and regional recurrences, and overall rates of local and regional control.

7.2 Patients and methods

Patient selection

Patients for the study were selected from a prospective RT planning database of consecutive patients with OPSCC treated at the Department of Radiotherapy at Erasmus MC. The database was implemented in March 2009. Between March 2009 and July 2016, 557 patients with OPSCC started curative intent treatment. Eligibility criteria for the current study were treatment with SBRT boost, T1, T2, or small T3 (as evaluated by multidisciplinary tumor board, with no defined size criterion), N0-N2c, and M0 primaries. Exclusion criteria included T4 primaries, non-SCC histology, and diagnosis with another primary malignancy within 6 months, previous oropharyngeal cancer, or previous head and neck RT. All patients had biopsy-confirmed SCC involving one or more oropharyngeal subsites. Staging investigations included a CT or MRI of the primary site, ultrasound of the neck, and a thoracic CT (if N2).

The protocol for first-line definitive treatment of T1-T2 tumors at our center changed over time, such that the percentage of patients receiving SBRT boost was not stable during the study period. During the early years of the study, patients with T1-T2 tumors received brachytherapy (when eligible [232] eg, no contraindication for general

anesthesia) and the remaining patients with T1-T2, and small T3 tumors received SBRT boost when eligible (ie, tumors not adjacent to the thyroid cartilage). Due to our positive early experience with the SBRT boost regimen,5 after approximately 2012, patients could receive SBRT boost first line. Furthermore, treatment of small T3 tumors with SBRT was stopped in 2013. Patients with large T3 or T4 tumors were treated with concomitant chemoradiation with 70 Gy in 35 fractions. During the years of study, approximately 50% of patients with T1-T3 N0-2c OPSCC received SBRT boost, 10% brachytherapy boost, 35% IMRT chemoradiotherapy, and 5% other regimens (generally more palliative treatment regimens due to comorbidities or poor performance status).

Treatment regimen

Treatment with the SBRT regimen consisted of 46 Gy accelerated IMRT (23 daily fractions, 6 fractions per week) to the primary tumor and neck, followed by an SBRT boost to the primary tumor of 16.5 Gy in 3 daily fractions. Patients with T3 or N2c disease who were eligible for systemic therapy received two cycles of cisplatin (100 mg/m^2) on days 1 and 22 of the IMRT phase. Chemotherapy was not given to patients with earlier nodal classification (eg, N2a-b) because favorable outcomes have been demonstrated at our center with treating these patients without concurrent chemotherapy [232]. The boost was delivered following the IMRT phase but such that the weekly dose never exceeded 16.5 Gy. Patients with node-positive disease underwent a selective neck dissection 2 weeks after the SBRT boost, as previously described [235].

IMRT target delineation and treatment

The gross tumor volume (GTV) was delineated on contrast-enhanced treatment planning CT, which was coregistered with the diagnostic scan (in the majority of cases, an MRI). The CTV consisted of the GTV plus a 1 cm volumetric expansion, cropped to exclude air cavities and uninvolved bone. In N0 and N1 disease, the elective nodal CTV consisted of bilateral neck levels II-IV. In N2 disease (biopsy-confirmed and/or short-axis diameter >1 cm and/or necrotic lymph nodes), ipsilateral levels Ib and V, and bilateral retropharyngeal lymph nodes were also included, whereas for N1 disease,

levels Ib and V were also included if adjacent lymph node levels were involved. Lymph node levels were contoured according to international expert consensus guidelines [261]. In well-lateralized primaries (small primaries of the tonsil, soft palate, or base of tongue 1 cm away from midline) with ≤N2b nodal disease, unilateral neck irradiation was performed. The planning target volume (PTV) consisting of the CTV plus a 5-mm volumetric expansion was constructed.

Target coverage objectives included delivery of at least 95% of the prescription dose to 95% of the PTV. Treatment was delivered with a 7-field IMRT technique. Patient immobilization was achieved with a thermoplastic head mask. Image guidance was performed with pretreatment cone beam CT for the first three fractions and weekly thereafter.

SBRT boost

A second planning CT scan was obtained following the IMRT phase and rigidly coregistered with the original planning CT, and GTV and CTV volumes transposed. Manual adjustment of the CTV based on tumor response to the IMRT phase as assessed on the planning CT scan performed just before the SBRT boost occurred at the discretion of the treating physician. The PTV consisted of the CTV plus a 3-mm margin. Dose was prescribed to the 80% isodose line. PTV coverage objectives, as well as patient immobilization, were identical to the IMRT phase. Treatment was delivered on the Cyberknife (Accuray Inc, Sunnyvale, California) as previously described [224]. Direct spinal tracking with two orthogonally positioned X-ray cameras was used for position verification and real-time adjustment for intra-fraction motion during treatment.

Follow-up visits

Patients were followed by the head-and-neck multidisciplinary team. Follow-up visits were planned every 3 months for the first year following RT, with frequency gradually reduced to every 6 months for a minimum of 5 years. Locoregional control was assessed at each visit with physical examination including flexible laryngoscopy. When

disease recurrence was suspected, examination under anesthesia and/or diagnostic imaging was performed (ultrasound, MRI, fluorodeoxyglucose (FDG)-positron emission tomography (PET), and/or CT).

Recurrence analysis

All local and regional recurrences were delineated on follow-up diagnostic MRI or CT based on consensus of two radiation oncologists. The follow-up scans were rigidly coregistered with treatment planning CT scans, optimized for the region of recurrence. Local recurrences were classified with respect to the SBRT target volumes (the volumes receiving the full prescribed dose). Regional recurrences were classified with respect to the IMRT target volumes. Classification was performed using the center-of-mass (COM) approach,1 in which the geometric center of the recurrence volume was determined using the centroid localization tool in MIM 6.6 (MIM Software Inc, Cleveland, Ohio) and localized as within the GTV, CTV, or PTV, or outside the PTV. To facilitate comparison with the literature, volumetric classification was also performed. In-field, marginal, and out-of-field were defined as ≥95%, 20%-94%, and <20% of the recurrence volume within the CTV and PTV [253, 255, 257, 258]. An example is shown in Figure 1.

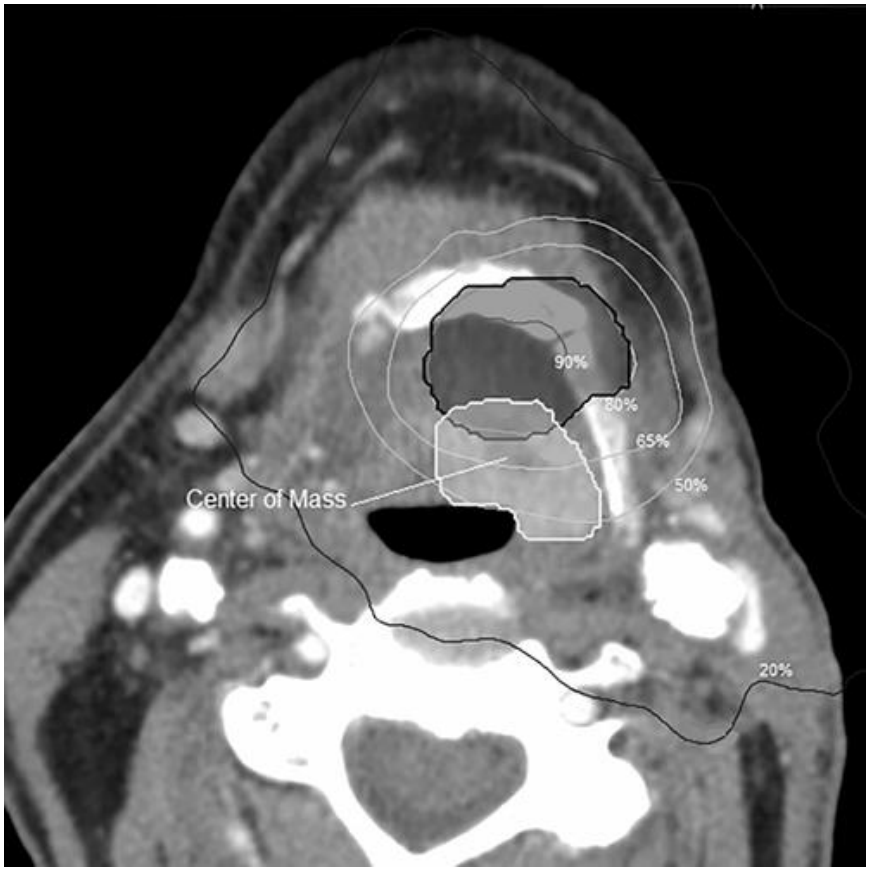


Figure 1. Local out-of-field recurrence of T1 N1 tumor of the left vallecula (patient 16). The planning target volume (PTV) of the original tumor (black) was projected onto the recurrence CT scan after image coregistration. The recurrence volume is delineated (white). Its center of mass (COM) is outside the PTV and thus “out-of-field.” Volumetrically, 17% of the recurrence volume overlaps the PTV and 5% overlaps the clinical target volume (CTV); hence, the recurrence is classified as out-of-field PTV and CTV. Isodose lines from the original radiotherapy plan are labeled. The original gross tumor volume and CTV were superior to the recurrence COM and not visible in the image.

Statistical analysis

Overall survival (OS), local control, and regional control were estimated using the Kaplan-Meier method. Time of recurrence was based on the first sign of disease (clinical or imaging). For local and regional control, patients were censored at the time of first event. Residual disease evident at the time of first follow-up visit or planned follow-up scan was classified as local failure 12 weeks after the start of RT. Comparison of out-of-field failure rates with the literature was undertaken using the nonbinomial test

with test proportion of 6%, a conservative estimation of out-of-field failure rates from the literature in which rates <1%-5% have been reported [253-255, 257, 258]. Univariate and multivariate analyses of potential variables associated with local and regional recurrences were performed using the Cox proportional hazards model. Variables assessed included age (>65 vs ≤65 years), sex, Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1), current or past alcohol abuse, smoking (current or former vs never), primary subsite (tonsil vs other), tumor grade (poor vs other), p16 status, T stage (small T3 vs T1/T2), and N stage (N+ vs N0, and N2 vs N0-1). Covariates with a *P*-value ≤0.20 were assessed in multivariate analysis (forward conditional method). A *P*-value ≤0.05 was considered significant. All statistical analyses were performed in SPSS version 22.0 (SPSS Inc., Chicago, Illinois).

The study was reviewed by the Medical Ethical Committee of Erasmus Medical Center (EMC17404), and permission to conduct the retrospective study was obtained.

7.3 Results

Patients and disease outcomes

A total of 195 patients with OPSSC fulfilled the inclusion criteria. Patient, tumor, and treatment characteristics are shown in Table 1. One hundred sixteen patients (60%) had stage III-IVa disease. All patients completed treatment.

Table 1. Patient, tumor, and treatment characteristics of 195 patients with oropharyngeal squamous cell carcinoma.

	Number of patients (range or %)
Age (years)	61 (34 – 86)
Gender	
Male	122 (63%)
Female	73 (37%)
ECOG performance status	
0	151 (77%)
1	44 (23%)
Previous or current alcohol abuse	56 (29%)
Previous or current smoking	170 (87%)
T stage	
T1	39 (20%)
T2	136 (70%)
T3	20 (10%)
N Stage	
N0	91 (47%)
N1	32 (16%)
N2a	15 (8%)
N2b	49 (25%)
N2	8 (4%)
Stage grouping (AJCC 7th Edition)	
Stage I	11 (5.6%)
Stage II	68 (34.9%)
Stage III	44 (22.6%)
Stage IVa	72 (36.9%)
Oropharynx subsite	
Base of tongue	35 (18%)
Soft palate	23 (12%)
Tonsil	113 (58%)
Oropharynx wall	11 (6%)
Other	13 (7%)
Grade	
1	9 (5%)
2	86 (44%)
3	67 (34%)
Unknown	33 (17%)
P16 status	
Positive	63 (32%)
Negative	30 (15%)
Unknown	102 (52%)
Concurrent systemic treatment	
Cisplatin	10 (5%)
Cetuximab	2 (1%)
Accelerated radiotherapy	192 (99%)
Neck dissection	101 (52%)
Unilateral neck radiotherapy	82 (42%)

Continuous variables are given as median and range, while categorical variables are given as number and percentage.
Abbreviations: ECOG Eastern Cooperative Oncology Group; AJCC American Joint Committee on Cancer

The median follow-up for all patients was 42.8 months (range 2.1-98.6 months) and for patients alive at the time of analysis (n = 169) was 50.6 months (range 18.0-98.6 months). There were 26 deaths from oropharyngeal cancer, yielding a 5-year disease-specific survival of 85.2%. Estimated five-year OS was 66.7%. There were 17 patients with local recurrences, 11 with regional recurrences, and 1 with both local and regional recurrence. Median time to local and regional recurrence was 5.5 months (range 3.0-37.8 months) and 17.0 months (range 3.0-73.1 months), respectively. Estimated 2-, 3-, and 5-year local control rates were 92.6%, 91.2%, and 90.0%, respectively (Figure 2). Estimated 2-, 3-, and 5-year regional control rates were 94.8%, 94.0%, and 92.8%, respectively (Figure 2). Distant metastases were the first site of relapse in 11 patients (3 of whom also had concurrent regional recurrence).

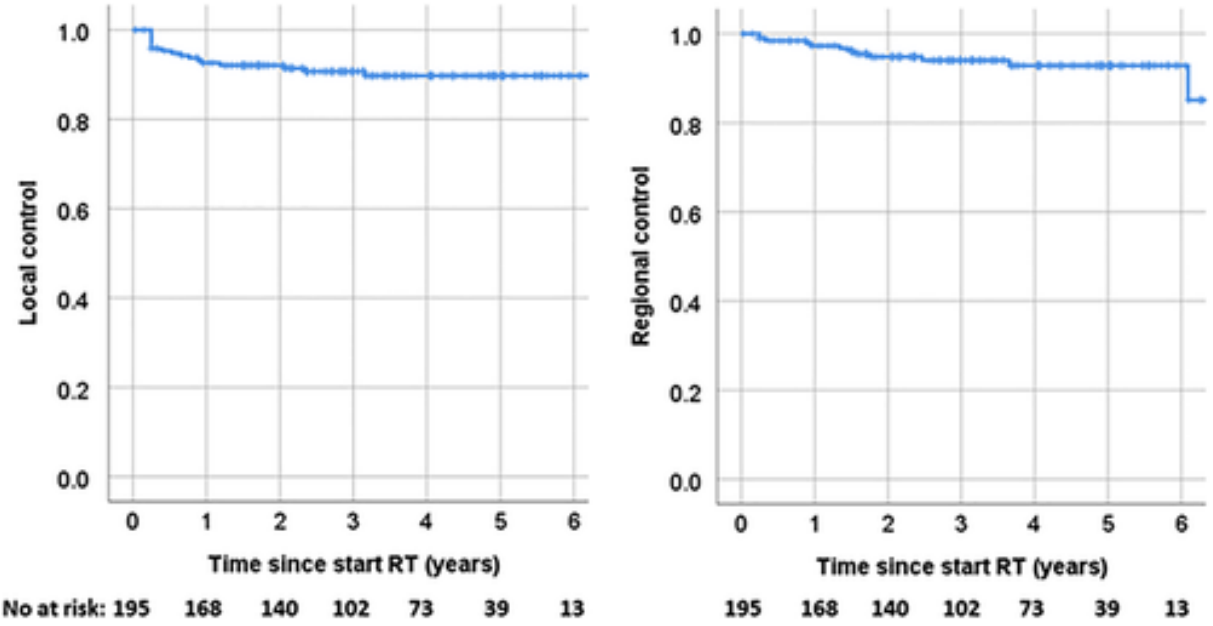


Figure 2. Kaplan-Meier plots of local and regional control.

Patterns of failure analysis

Twenty-seven of 29 patients with local and/or regional recurrences (93%) had follow-up imaging available and were included in the recurrence location analysis.

Local recurrences

The COM of local recurrences with follow-up imaging available (n = 17) was within the SBRT GTV in 12 patients (71%), outside the GTV but within the SBRT CTV in 1 patient (6%) and outside the SBRT PTV in 4 patients (24%) (Table 2). In 4 cases (Table 2, patients 2, 5, 6, and 17), the CTV was reduced between the IMRT and boost phases, with a median volume reduction of 30% (range 21%-34%). In these cases, location of the recurrence by COM classification did not change whether classification was with respect to the IMRT CTV vs boost CTV. The 24% of out-of-field local failures in the current study represents a statistically higher percentage compared to the test proportion of 6% ($P = 0.009$).

Table 2. Characteristics and location analysis of local recurrences.

					Recurrence					
								Type		
	Site	TN	Grade	p16	Time[a] (mo)	Location	Volume (mL)	COM	Volumetric CTV (% in CTV)	Volumetric PTV (% in PTV)
1	R tonsil	T2N0	3	NR	3.0	R BOT/FOM[b]	11.7	In-field	Marginal	Marginal
								Within CTV	75%	82%
2	R tonsil	T2N2b	NR	NR	3.0	R BOT/PP space[b]	53.4	In-field	Marginal	Marginal
								Within GTV	42%	54%
3	R BOT	T2N2a	NR	NR	3.0	R BOT[b]	18.2	In-field	In-field	In-field
								Within GTV	96%	100%
4	Tonsil	T3N0	2	NR	3.0	L BOT[b]	4.9	In-field	In-field	In-field
								Within GTV	100%	100%
5	R BOT	T2N1	3	NR	3.0	R tonsil/BOT[b]	12.0	In-field	Marginal	Marginal
								Within GTV	65%	81%
6	R BOT	T2N0	2	NR	3.0	R BOT[b]	6.9	In-field	Marginal	In-field
								Within GTV	95%	100%
7	R SP	T2N0	2	NR	3.0	R SP[b]	3.2	In-field	In-field	In-field
								Within GTV	100%	100%
8	L BOT	T1N1	NR	Neg	6.3	L tonsil/BOT	8.1	In-field	Marginal	Marginal
								Within GTV	77%	95%
9	L tonsil	T2N2b	NR	NR	11.2	BOT/OT	33.4	In-field	Marginal	Marginal
								Within GTV	74%	87%
10	R SP/tonsil	T2N0	2	NR	4.6	R FOM/RMT	7.0	In-field	Marginal	Marginal
								Within GTV	67%	83%
11	L tonsil	T3N1	2	NR	24.7	PP space	25.9	In-field	Marginal	Marginal
								Within GTV	59%	75%
12	R SP	T2N0	2	NR	14.3	R tonsil	3.3	In-field	Marginal	In-field
								Within GTV	88%	100%
13	R tonsil	T3N0	NR	NR	3.0	R tonsil[b]	7.7	In-field	In-field	In-field
								Within GTV	99%	100%
14	L SP	T2N0	3	NR	7.8	R SP	No imaging available			
15[c]	R BOT	T3N2c	3	NR	10.6	R tonsil	16.2	Out-of-field	Marginal	Marginal
								Outside PTV	21%	34%
16	L vallecula	T1N1	2	Neg	28.0	L vallecula	4.3	Out-of-field	Out-of-field	Out-of-field
								Outside PTV	5%	17%
17	R tonsil	T2N2c	3	Pos	9.2	R tonsil	118.2	Out-of-field	Out-of-field	Marginal
								Outside PTV	18%	24%
18	L SP/tonsil	T3N0	NR	NR	37.8	R BOT	6.9	Out-of-field	Out-of-field	Out-of-field
								Outside PTV	0.03%	9.9%

Abbreviations: BOT, base of tongue; COM, center of mass; CTV, clinical target volume; FOM, floor of mouth; GTV, gross tumor volume; L, left; mo, months; Neg, negative; NR, not reported; OT, oral tongue; Pos, positive; PP, parapharyngeal; PTV, planning target volume; R, right; RMT, retromolar trigone; SP, soft palate.

[a] Time from radiotherapy to relapse

[b] Residual disease.

[c] Patient 15 is the same individual as patient 25 in Table 4.

Regional recurrences

Regional recurrences occurred in 19 distinct lymph nodes levels in 12 patients. These 19 regional recurrences occurred in 9 unirradiated neck levels (47%) 8 elective regions (42%), and 2 times in the originally involved nodal levels (11%) (Table 3). Four of the 84 patients (4.9%) treated with unilateral neck irradiation experienced contralateral regional recurrences. All recurrences in electively irradiated levels had the COM within the elective CTV. Similarly, all recurrences within the originally involved nodal levels had the COM within the previous nodal GTV. Details of both COM and volumetric classification are provided in Table 3.

Table 3. Characteristics and location analysis of regional recurrences.

	Primary site	TN stage	Grade	p16	Time[a] (mo)	Location	Volume (mL)	COM	Volumetric CTV (% in CTV)	Volumetric PTV (% in PTV)
19	R tonsil/SP	T2 N1	2	NR	3.0	Contra unirradiated neck	9.7	Out-of-field	Out-of-field	Out-of-field
						L II x 1		Outside PTV	0%	0%
20	L tonsil	T2 N0	NR	Pos	17.7	Contra unirradiated neck	7.2	Out-of-field	Out-of-field	Out-of-field
						R II x 1		Outside PTV	0%	0%
21	R tonsil	T2 N0	2	NR	21.0	Contra unirradiated neck	7.1	Out-of-field	Out-of-field	Out-of-field
						L Ib/II x 1		Outside PTV	0%	0%
22	L tonsil	T2 N0	2	NR	3.0	Contra unirradiated neck	13.6	Out-of-field	Out-of-field	Out-of-field
						R II x 1		Outside PTV	0%	0%
						Unirradiated level	1.3	Out-of-field	Out-of-field	Out-of-field
						L Ib x 1		Outside PTV	0%	0%
23	L SP	T2 N1	2	Neg	73.1	Unirradiated level	1.2	Out-of-field	Out-of-field	Out-of-field
						R Ib x1		Outside PTV	0%	0%
						Elective neck	0.4	In-field	In-field	In-field
						R II x 2	0.6	Within eCTV	100%	100%
24	Central BOT	T1 N1	3	Neg	16.2	Unirradiated level	No imaging available			
						L V x 1				
						Elective neck				
						L II x 1				
25[b]	R BOT	T3N2c	3	NR	10.6	Elective neck	21.2	In-field	In-field	Marginal
						L II/III x 1		Within eCTV	Within eCTV	53%
						Elective neck	0.9	In-field	In-field	In-field
						R RP x 1		Within eCTV	Within eCTV	100%
26	R tonsil	T3 N0	2	NR	29.6	Elective neck	6.0	In-field	In-field	In-field
						R II x 1		Within eCTV	Within eCTV	98%
27	L BOT	T1N2b	NR	NR	3.0	Elective neck	0.01	In-field	In-field	In-field
						L IV[c]		Within eCTV	Within eCTV	100%
28	R tonsil	T2N2b	3	Pos	18.7	Unirradiated level	1.0	Out-of-field	Out-of-field	Out-of-field
						L Ib x 1		Outside PTV	Outside PTV	0%
						Elective neck	2.2	In-field	In-field	In-field
						L II x 2		Within eCTV	Within eCTV	100%
						Unirradiated level	15.4	Out-of-field	Out-of-field	Out-of-field
						R periparotid x 4		Outside PTV	Outside PTV	0%
						Elective neck	1.0	In-field	In-field	In-field
						R V x 2		Within eCTV	Within eCTV	100%
29	R tonsil	T2N2a	1	Pos	11.4	Involved neck level	8.8	In-field	In-field	In-field
						R II x 1		Within GTV	Within GTV	100%
30	R tonsil	T2N2b	3	Pos	43.8	Involved neck level	2.9	In-field	In-field	In-field
						R IV x 1		Within GTV	Within GTV	100%

Abbreviations: BOT, base of tongue; COM, center of mass; Contra, contralateral; eCTV, elective clinical target volume; GTV, gross tumor volume; L, left; Neg, negative; NR, not reported; Pos, positive; PTV, planning target volume; R, right; SP, soft palate.

[a] Time from radiotherapy to relapse.

[b] Patient 25 is the same individual as patient 15 in Table 3.

[c] Residual disease immediately following neck dissection.

Prognostic factors

Variables associated with local and regional recurrence are shown in Table 4. On univariable analysis, ECOG performance status, history of alcohol abuse, and T3 primary were significantly associated with an increased risk of local recurrence. Performance status remained significant on multivariable analysis ($P = 0.005$), with a trend for T3 ($P = 0.05$). Because p16 status was missing for many patients and testing was performed in a nonrandom manner (more frequently performed in younger, nonsmoking patients suspected of having HPV-associated disease), p16 was not included in the model. With the available data, however, p16 positivity (vs negative/unknown) was associated with a reduced risk of local recurrence on univariable analysis (hazard ratio, 0.24; $P = 0.09$). In order to assess if performance status might be serving as a surrogate for p16 status in the multivariable model (because patients positive to p16 could potentially be of better performance status), correlation between p16 positivity and better performance status (ECOG, 0 vs 1) was assessed: there was a statistically significant correlation (Spearman's rho, −0.41; $P < 0.001$). None of the covariates examined was significantly associated with the risk of regional recurrence.

Table 4. Prognostic factors for local recurrence and regional recurrence.

Prognostic factors	Local failure					Regional failure	
	Univariate		Multivariate			Univariate	
	HR	*P*	HR	95% CI	*P*	HR	*P*
Patient factors							
Sex (male vs female)	1.17	0.75				1.24	0.73
Age (>65 vs ≤ 65) (y)	0.50	0.27				1.32	0.65
ECOG (1 vs 0)	4.16	**0.003**	3.82	1.50-9.77	**0.005**	1.05	0.96
Alcohol abuse history	3.16	**0.015**				1.34	0.63
Current smoker	1.85	0.21				25.00	0.39
Tumor factors							
Subsite (tonsil vs other)	0.45	0.096				1.39	0.59
T stage (T3 vs T1-2)	3.31	**0.023**	2.81	0.99-7.95	0.05	1.77	0.46
N positive (N1-2 vs N0)	0.82	0.82				2.02	0.26
N stage (N2 vs N0-1)	0.49	0.21				1.36	0.61
Grade[a] (poor vs other)	0.99	1.00				1.01	0.99

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.
For regional recurrence univariate analysis, none of the variable had *P*-value less than 0.20 and thus multivariate analysis was not performed.
[a] Tumor grade available for n = 162. For all other variables, data available for all patients (n = 195).
Significant *p* values (<0.05) are in bold.

7.4 Discussion

Excellent rates of locoregional control were attained in our OPSCC population with a high proportion (60%) of stage III-IV disease, using accelerated IMRT followed by an SBRT boost. Five-year local and regional control rates of 90% and 93%, respectively, compare favorably to brachytherapy outcomes in similar patient populations.4 Previously, we reported a 3-year local control rate of 94% following brachytherapy boost and 97% following SBRT boost, with no statistical difference in local control between the two modalities; however, this included only patients with T1-T2 tumors [224]. Similarly, our results compare favorably to those following external beam RT; in a series of patients with oropharynx cancer with T1-T2 tumors, 5-year local control was similar to ours at 91%,15 despite our inclusion of small T3 tumors. A study from the same institution reported 5-year local control dropped to 67% in T3 tumors [262]. Although a small number of previous studies have reported outcomes following an SBRT boost, these have been in the setting of more advanced and/or inoperable disease with a minority of patients with oropharynx cancer, precluding meaningful

comparison [229, 231]. Of note, during the time frame of the study, p16 testing was selective and not on a routine basis; based on previous research in Dutch patients with OPSCC, the true incidence of human papilloma virus (HPV)-associated OPSCC in the study population is approximately 40%-50% [235, 242, 243].

Previous analyses of the location of recurrences with respect to RT fields have reported nearly all local recurrences to occur within the site of the previous GTV, suggesting radioresistance as the underlying mechanism [253-255, 257, 258]. Here, we observed a shift in this classic recurrence pattern: only 76% of local recurrences occurred with COM in-field (n = 12 within GTV and n = 1 within CTV), whereas 24% occurred out-of-field (n = 4 outside PTV). Low rates of in-field recurrence may have resulted from biological dose intensification. The accelerated schedule of the IMRT phase coupled with the hypofractionation of the boost phase reduced overall treatment time to 5 weeks from the traditional 7 weeks of a conventionally fractionated 70 Gy regimen. This may potentially reduce tumor cell repopulation and confer improved in-field control, in keeping with the known benefit of accelerated fractionation in head and neck tumors [263]. Based on the linear quadratic equation and experimentally determined values for the onset of tumor repopulation (Tk) and repopulation time (Tp) in head and neck tumors,21 the difference in biologically effective dose (BED) between a standard 70 Gy regimen and the current regimen is a minimum of 6.0 Gy_{10} for more slowly proliferating tumors (Tk = 35 days and Tp = 3 days) and up to 30.3 Gy_{10} for rapidly proliferating tumors (Tk =18 days and Tp = 2 days) (equation provided in Supplementary Material). Acknowledging that patients with stage III-IV cancer would commonly receive concurrent chemotherapy with an estimated benefit of 9.3 Gy_{10} [264] and that tumors vary with respect to proliferation rate, this benefit in BED is somewhat individualized but likely of significant magnitude on a population level for patients treated with this regimen.

Despite high overall local control, the percentage of local failures which were out-of-field was higher than reported in the literature. Indeed, previous studies utilizing a conventional IMRT approach in patients with OPSCC have found 1%-5% of local recurrences to be out-of-field [253-255, 257, 258] significantly lower than the 24% here. All out-of-field recurrences occurred within 4 years of treatment, involved the site of the

original tumor (although some were centered at different locations), and in all but one case, a biopsy was performed and was histologically consistent with the original tumor. Using COM classification, Raktoe et al. [253] reported none of the 20 local failures in 131 patients with OPSCC occurred outside the PTV, with only 1 occurring outside the CTV. Studer et al. [255] found all 46 local failures to be in-field PTV. Due et al. [254] found that only 1 of 48 locoregional recurrences occurred out-of-field (4%). Other studies using a volumetric approach have reported similar findings [257, 258].

Potential causes of higher relative out-of-field failure rates warrant consideration. With highly conformal treatment and steep dose gradients, accurate target delineation becomes more critical. Given the known interobserver variability of target delineation [259] it may be that in some cases, all disease was not encompassed within GTV/CTV targets and rapid dose fall-off resulted in insufficient dose to these areas. Rigorous quality assurance of both target delineation and delivery remain critical particularly with advanced technology such as stereotactic RT. CTV construction by 1 cm volumetric expansion of the GTV was likely sufficient in the vast majority of cases and is consistent with recently published international consensus guidelines [265]; pathology studies have found nearly all microscopic tumor infiltration within 10 mm of the tumor [265, 266]. Similarly, target delineation was consistent with recommended guidelines [265] (contrast-enhanced planning CT fused with a diagnostic MRI) and image-guidance was state-of-the-art (cone beam CT, and for the SBRT boost, spinal tracking using orthogonal X-rays), such that these were not likely factors in the high out-of-field recurrence rates. Although reduction of the CTV for the SBRT boost based on tumor response following the IMRT phase may theoretically increase out-of-field failures, this is not likely a contributing factor to the out-of-field failures in the present study. Only one of the local out-of-field failures had the CTV adjusted between the IMRT and SBRT phases. Due to lack of availability of RT plans for patients treated during the earlier years of the study, formal evaluation of the impact of CTV modification on local control could not be undertaken. However, given that tumor regression at the microscopic level may not be concentric and may be difficult to predict from observed GTV response, our institution has revisited this practice and has now implemented standardized CTV margins (1 cm for the IMRT phase and 0.5 cm for the SBRT boost phase).

The discrepancy between COM and volumetric classification is consistent with previous studies, with volumetric methods typically classifying many recurrences as marginal rather than in-field due to the very broad range of percentages (20%-94%) constituting marginal recurrences [253, 267]. Due to the effect of timing of assessment on classification, with all recurrences eventually growing such that the majority of tumor volume is outside the target, volumetric classification was felt to be less accurate than COM and its cutoff points lacking biological rationale. Limitations of the COM approach, however, include scenarios of recurrence multifocality and nonsymmetrical growth, as might occur near anatomical boundaries such as bone.

The variables identified as prognostic for local recurrence warrant comment. ECOG performance status 1 was associated with a nearly four times greater risk of local recurrence than ECOG 0. Although previous reports have also noted an association of performance status with local recurrence risk [268-270], it was unique that this emerged as the sole prognostic factor in the present study. Interestingly, worse performance status has been associated with lower rates of treatment response in OPSCC [271]. Although mechanisms underlying this finding are uncertain, one possible explanation might be an association of poor performance status with reduced hemoglobin levels or impaired immune function, factors implicated in worse oncologic outcomes [272, 273]. There was a significant association of p16 positivity with ECOG 0 performance status, which likely contributed to the effect of performance status on local recurrence risk. However, this finding is complicated by the fact that p16 testing was nonrandom, and the patients with HPV-related disease who had worse performance status (along with older age and smoking history) were likely not tested for p16. There was a trend for T3 tumors to be associated with worse local control, consistent with the known association of T stage with local control [268-270].

Limitations of the analysis include its retrospective nature and the modest number of recurrences such that the study lacked power to accurately assess the effect of tumor characteristics on recurrence pattern. P16 testing was not available for many patients (48% of total study population tested, with only 63 patients [32%] positive for p16). Based on previous studies showing improved local control in HPV-associated disease

[274, 275], this was likely also the case in our population (and is suggested by the univariate analysis for p16), but unfortunately this could not be reliably analyzed due to nonrandom missing p16 date. Strengths of this study include the availability of recurrence imaging and RT plans for most patients, the comprehensive recurrence location analysis by both COM and volumetric approaches, and the completeness of patient follow-up.

7.5 Conclusion

Treatment of OPSCC with accelerated IMRT and SBRT boost provided excellent tumor control outcomes with a shift in the typically observed pattern of in-field and out-field local failures. The highly conformal dose distribution with steep dose gradients requires precise and accurate target delineation with a potential risk of marginal and out-of-field local failures.

Chapter 8

Discussion

8.1 Introduction

Compared to conventional radiotherapy, SBRT provides more conformal and accurate treatment delivery allowing for higher, ablative radiation doses with potentially improved tumor control and reduced dose to normal structures. With the lack of data from randomized trials, however, database studies are needed to evaluate and improve upon current treatment outcomes.

This thesis aimed to provide an improved understanding of prognostic factors and clinical outcomes for SBRT for two anatomical sites, lung and oropharynx. The studies here successfully established prognostic factors associated with poor short-term survival following lung SBRT (Chapter 3), and provide a prognostic tool for individual patient survival prediction in the form of a nomogram (Chapter 4). An improved method of fiducial marker placement is established as a safer alternative to the traditional method for this high-risk population (Chapter 5). This thesis also reports 5-year survival, toxicity and cancer-specific outcomes following SBRT boost treatment for oropharynx cancer (Chapters 6 and 7), as well as prognostic factors for severe late toxicity (Chapter 6). Together, these studies provide an improved understanding of prognostic factors and outcomes in lung and oropharynx SBRT which can be used to improve patient selection and in the case of oropharynx cancer, may allow for toxicity mitigating strategies in the future.

8.2 Optimizing patient selection

Lung SBRT patient selection

In the inoperable early stage lung cancer population, the benefits of SBRT for patients in poor general condition and with severe medical comorbidities are uncertain. It is likely that some patients do not benefit from SBRT due short survival time, and intense local treatment to the tumor does not translate into clinical benefit. However, the studies here suggest that patients should not be excluded from lung SBRT due to advanced age, comorbidities, or other factors (Chapter 3). Previous studies have shown no higher risk of toxicity in patients with advanced age or severe COPD [159, 276]. The number of patients that do not live long enough to benefit from SBRT is low; rates of early mortality (death within 6 months of RT) were 6% (Chapter 3), consistent with the one previous study on the topic which also reported a rate of 6% [16]. Rates of 1-year mortality were also low (15%; Chapter 3). These figures raise the question of whether patient selection for lung SBRT is currently too restrictive. Could additional patients who are perceived as too frail or burdened with comorbidity, potentially benefit from treatment? Further study investigating survival time in patients not referred or declined for SBRT would be informative. It is reassuring that fiducial marker placement via a transfemoral endovascular approach appears to be well-tolerated in this patient group, with very few severe complications (Chapter 5). The nomogram for overall survival (Chapter 4) provides an estimate for prognosis at an individual patient level and can aid in decision making for lung SBRT.

For the present studies (Chapters 3-5), patient selection criteria for lung SBRT included recommendation for SBRT after discussion at multidisciplinary tumor board. All patients were deemed medically inoperable or had refused surgery. In general, patients with very poor performance status were not recommended to undergo SBRT (e.g. KPS ≤ 40 or ECOG 4, which signify a state of being bed-bound and incapable of self-care) and this is consistent with recent ESTRO ACROP consensus guidelines which recommend a minimum performance status of ECOG 3 [7]. Although it is possible that additional

patients could benefit from SBRT, this is likely not the case for ECOG 4/KPS ≤ 40 patients, due to very poor prognosis and potential challenges with treatment delivery due to stringent immobilization requirements which may not be possible for such patients.

The primary objective of Chapter 3 was met, and prognostic factors for early mortality were identified. Tumor size and Cumulative Illness Rating Scale (CIRS) were prognostic for death within 6 months of SBRT, a finding which has not been previously reported in the literature. However, a main limitation of Chapter 3 was that patients with a very low rate of 6-month survival could not be identified. Even patients in the most unfavorable prognostic category (tumor diameter greater than 3 cm and CIRS scores of 8 or higher) had 6-month survival of 70%, which is not sufficiently poor to consider forgoing curative-intent treatment in favour of best supportive care alone. This limitation is partly attributable to the low total event number (only 36 deaths within 6 months of SBRT). Larger, potentially multi-center trials will be required. Investigation of additional factors which have shown promise in short-term prognostication in the setting of advanced malignancy, such as frailty index score [277], comprehensive geriatric assessment [278], and parameters such as C reactive protein and albumin levels [279], may allow for more accurate early mortality prediction in combination with CIRS and tumor size.

Chapter 4 achieved the goal of generating a nomogram to predict overall survival following lung SBRT, and improves upon currently available prognostic tools for this population [174]. The nomogram performed particularly well for predicting 3-year overall survival, with excellent agreement between nomogram- and Kaplan-Meier-estimated survival on calibration plots. It demonstrated very similar discriminatory ability in both the original cohort, and in a validation cohort consisting of early stage lung cancer patients with centrally located tumors. A limitation of the nomogram however is that it could not reliably identify patients with very poor estimated survival. The nomogram generates a minimum 6-month survival estimate of 80%. Additionally, the nomogram has moderate discriminatory ability with C-index 0.64, and improved discriminatory ability would be desirable. In the future, incorporating newly emerging prognostic factors such as presence of genomic alterations [280], circulating tumor DNA [281], or radiomic tumor

features [282] may allow for improved predicative ability. External validation in a geographically distinct population would also be valuable.

Future studies: cost-saving alternatives to lung SBRT

Alternative strategies may be investigated to mitigate the high cost and system strain of the application of SBRT to an increasing number of inoperable early stage lung cancer patients. With increasing implementation of lung cancer screening programs [283, 284], the incidence of early-stage lung cancer will continue to rise. Active surveillance may be a viable option for some patients, but factors associated with indolent tumors and low metastatic potential (e.g. small tumors with low percent solid component, adenocarcinoma spectrum lesions) will need further clarification [285]. Although SBRT may be cost-effective compared to conventionally fractionated radical radiotherapy for early stage lung cancer [286], it is more costly and time-intensive than palliative radiotherapy of simple field design (e.g. parallel opposed pair) due its requirement for advanced planning techniques, trained personnel, quality-assurance, and delivery technologies. Indeed, an alternative option to SBRT for some patients may be a short course of palliative radiotherapy. Whether this may provide sufficient tumor control to limit cancer-related morbidity and mortality for poor life expectancy patients could be evaluated, for example in patients with high CIRS score and large tumor diameter.

Oropharynx SBRT patient selection: mitigating late toxicity

In contrast to SBRT for peripheral early stage lung cancer, oropharynx SBRT has high potential for severe late toxicity and patient selection criteria hinge largely on toxicity considerations. Indeed, patients treated with IMRT followed by SBRT boost had an estimated cumulative incidence of grade ≥3 late toxicity of 28% at 5 years (Chapter 6). Previous studies, consisting of diverse SBRT regimens in diverse head and neck tumor sites, have reported variable rates of late toxicity, but many as high or higher than the present study [21-23].

Smoking at time of radiotherapy was the greatest risk factor at baseline for severe late toxicity (HR 2.9, p=0.001). In current smokers, cumulative incidence was 41%, compared to 14% in previous/never smokers. It is uncertain if smoking cessation prior to initiation of radiotherapy may sufficiently mitigate this risk. While there is plausible biological rationale [250], further study will be needed to verify this hypothesis and to determine the feasibility and efficacy of various smoking cessation programs in the head and neck cancer population [287]. Tooth extraction prior to RT was strongly associated with grade ≥3 osteoradionecrosis (HR 6.4, $p < .01$), despite a median interval of 18 days before the start of treatment. A more conservative approach to pre-RT tooth extraction may be required. Dose constraints for the mandible, as well as oropharyngeal wall (16% cumulative incidence of late mucosal ulcers/soft tissue necrosis) may also help mitigate late toxicity.

Chapters 6 and 7 accomplish the objective of determining long-term survival and toxicity outcomes in a large cohort of oropharynx cancer patients following the SBRT boost regimen. Limitations include the
the lack of dosimetric data for organs such as mandible and oropharyngeal wall. The regimen could potentially be made less toxic if reliable constraints for theses organs were established. Due to great heterogeneity in head and neck SBRT studies in the literature in terms of dose-fractionation regimens, head and neck tumor subsites, and primary indication (re-irradiation versus primary treatment), dose constraints are currently unknown. A recent meta-analysis of studies on previously untreated head and neck cancers treated with SBRT found only 2 of 9 studies reported dose constraints [288].

The most important limitation of Chapters 6 and 7, however, was the absence of p16 status for many patients. The p16 immunostain is a marker for human papilloma virus (HPV)-related disease and is the single most important prognostic factor in oropharynx cancer, more heavily weighing AJCC staging than either T or N classification [289]. Because patients with HPV-related cancer have a significantly more favorable prognosis than those with HPV-negative disease and are generally younger and healthier [290],

long term toxicity is of particular concern. An area of intense research currently is the evaluation of treatment de-escalation strategies in patients with HPV-related disease in order to limit late toxicity [291]. Some strategies involve reduction of radiotherapy dose. Whether the SBRT boost regimen can be de-intensified in terms of radiotherapy dose in these favorable prognosis HPV-positive patients may be an area for future research.

Weighing the SBRT boost regimen against conventional (chemo)radiotherapy

The SBRT boost regimen has a number of advantages over conventionally fractionated (chemo)radiotherapy including shorter overall treatment time (5 weeks versus 7 weeks), higher treatment compliance (Chapter 6), and reduced dose to swallowing structures and possibly lower rates of permanent xerostomia [232]. Strategies to mitigate late toxicity are required, as detailed above. In weighting SBRT versus conventional treatment, complications and long-term toxicity (e.g. neck fibrosis) following neck dissection will need to be taken into account; planned neck dissection is required for node-positive patients with this regimen, whereas neck dissection is generally only performed as salvage for residual nodal disease following conventional treatment. Chapter 6 establishes the good 5-year cancer-specific and overall survival rates with the regimen of 85% and 67%, respectively. However, benefits over conventional (chemo)radiotherapy in terms of tumor control and survival remain yet to be proven, as the absence in our cohort of rates of HPV-related disease hampered comparison with studies on conventional RT outcomes in the literature. While the SBRT boost regimen provides biologically effective dose intensification, whether this translated into superior tumor control compared to conventional chemoradiotherapy cannot be determined without knowing relative rates of HPV-related cancer in respective study populations. The high rate of in-field locoregional control is promising (Chapter 7), but a matched pair analysis with patients receiving conventional chemoradiotherapy would yield valuable insight.

8.3 Improving accuracy of tumor targeting

Due to the highly conformal dose delivery and sharp dose gradients outside of the target, SBRT is less forgiving to small errors in tumor delineation or variation in tumor position due to physiologic organ motion or set-up variability.

Risk of out-of-field local failure following oropharynx SBRT

While an excellent 5-year local control rate of 90% was attained following the SBRT boost regimen, the rate of out-of-field failure was higher than expected (Chapter 7). Out-of-field local failure is rare following conventional (chemo)radiotherapy in oropharynx cancer, with typically 0 – 5% of local failures occurring outside of radiotherapy fields [254-257]. It was therefore a surprising finding that 24% of 17 local failures in the present study were out-of-field. This was potentially due to the submucosal pattern of disease spread in oropharyngeal cancers, which can make precise and accurate tumor delineation more challenging. The interobserver variability in tumor contouring in head and neck cancers is well described [259]. The larger PTV margins and less rapid dose fall-off with conventional radiotherapy can likely compensate to a degree for less precise and accurate tumor delineation. One previous study assessed patterns of failure with respect to radiotherapy fields in head and neck SBRT, but in the setting of recurrent disease. This study corroborates the present study, with many local failures on or near PTV borders rather than within the PTV [293].

An additional point of consideration is that the CTV for the SBRT boost was sometimes (at the discretion of the treating physician) manually adjusted based on tumor response to the IMRT phase. This could potentially increase out-of-field failures as tumor regression at the microscopic level may not be concentric and may be difficult to determine from observed GTV response. However, only one of the 17 local out-of-field failures had the CTV adjusted between the IMRT and SBRT phases and was not likely a major contributor to local failures. Nevertheless, our institution has revisited this practice and has now implemented standardized CTV margins (1 cm for the IMRT phase and 0.5 cm for the SBRT boost phase).

Reducing out-of-field failure may come about by improvements in imaging. Performing MRI scans in the radiotherapy position has been found to result in significant improvements in target definition and PTV dose coverage in oropharynx cancer [294]. Improvements in accuracy of GTV definition have been observed by incorporating both PET and MRI [295, 296].

Improvements in tumor targeting in lung SBRT

Tumor delineation in lung SBRT is less problematic due to distinct attenuation features of tumor versus lung parenchyma, and previous studies have shown low inter-observer variability in gross tumor volume contouring [297]. Improvements in tumor targeting may come about through advancements in image guidance and motion-management strategies.

Recent consensus guidelines from ESTRO ACROP outline the minimum recommended requirements for lung SBRT planning and delivery (including 3D conformal treatment planning, respiration correlated 4D-CT imaging, ITV based motion management strategy, daily pre-treatment volumetric image-guidance) as well as recommendations for “best practice” (dynamic IMRT planning/VMAT, daily pre-treatment 4D volumetric image-guidance such as in-room 4D-CT or 4D-CBCT) [7]. Future advances in available technologies may allow for further improvements in tumor targeting and reducing dose to surrounding organs at risk (OARs).

Real-time tumor motion monitoring is advantageous, as the commonly employed ITV approach may not fully capture tumor motion during treatment; both 4-dimensional CT and cone-beam CT may underestimate tumor motion during lung SBRT [298]. Indeed, there may be variability in breathing during treatment that is not captured at the time of the 4DCT [299]. Lung SBRT patients included in the present studies were treated with the CyberKnife Robotic Radiosurgery System (Accuray Inc, Sunnyvale, California) and the majority received treatment with real-time tumor tracking based on the tracking of fiducial markers placed in or around the tumor. Previously, there have been concerns

about complications with the standard method of transthoracic marker placement [207, 208]. Chapter 5 provides a detailed analysis of complications following a novel method of endovascular fiducial placement and shows the method to be highly safe with high rates of procedural success. Prior to this, only preliminary results had been published from our center [210] and only two other reports existed, based on 14 and 15 patients, respectively [211, 205]. Adoption of this method of marker placement may encourage treatment with real-time tumor tracking using fiducials.

The emerging technology of MRI-guided radiotherapy is a second method for real-time tumor motion monitoring [300] and is reviewed in Chapter 1. This technique allows for direct tumor visualization during treatment and can facilitate online adaptive radiotherapy for lung SBRT. During gated radiotherapy using breath-hold mode, the system can automatically shut-off radiation delivery when the target is outside pre-specified safety margins [69].

Improvements in image guidance/motion-management may lead to more accurate dose delivery, improvements in local control, reduced toxicity for central tumors and more reliable dose constraints (Chapter 1). Greater confidence in SBRT accuracy will likely facilitate adoption of single-fraction lung SBRT regimens, which have previously shown similar outcomes to multi-fraction SBRT regimens [301] but have not been widely adopted due to concerns about accuracy of SBRT delivery.

8.4 Prognostic factors following SBRT

Further advances in lung and oropharynx SBRT may come about through gaining an improved understating of prognostic factors. The studies here identified prognostic factors for overall survival following lung SBRT, including age, sex, performance status, tumor diameter, operability, and Charlson Comorbidity Index (CCI), and in Chapter 4, these six factors were incorporated into a nomogram. For oropharynx SBRT patients, performance status, CCI, and smoking pack years were prognostic for survival (Chapter 6).

In both lung and oropharynx SBRT, performance status and comorbidity (CCI) emerged as common factors prognostic for overall survival. Performance status is a well-known global predictor of survival in oncology and provides an overall picture of a patient's level of function with respect to physical activities and self-care. Its prognostic value for lung and oropharynx SBRT was therefore not a surprising finding, and consistent with the lung cancer [174] and oropharynx cancer [268] literature. In the lung SBRT population, death from non-cancer causes commonly exceeds cancer-related mortality [156] and comorbidity was an expected prognostic factor for overall survival. Comorbidity also plays a role in oropharynx cancer prognosis, both in HPV-related and non-HPV-related disease [302].

As SBRT and the field of radiotherapy in general continue to advance in the form of incremental improvements in imaging and treatment delivery technologies (Chapter 1), it will be critical to keep in mind that overall health status of the patient -- performance status and comorbidity -- remain important determinants of outcome. While advanced technologies may generate small improvements in accuracy and dosimetry, it is not certain whether these will translate into clinically relevant improvements in treatment outcomes for all patients.

Future developments in lung SBRT and the importance of prognostic factors

Improved understanding of prognostic factors will be important for the future of lung SBRT.

A current major controversy in thoracic oncology is the comparison of lung SBRT versus surgery for operable patients (Chapter 1). Attempted randomized trials to date have failed due to poor accrual and we will likely need to rely on retrospective cohort studies comparing surgical and SBRT patients with propensity score matching and matched pair analyses, which rely on baseline patient and tumor prognostic factors. The identification of prognostic factors for short-term mortality may be particularly useful. The one study consisting of prospective data published to date (pooled results of two randomized trials

which closed due to insufficient accrual) found higher survival following SBRT than lobectomy, despite similar recurrence-free survival and disease control [37]. Critics speculate that patients at higher mortality risk were randomized by chance to the surgery group, with an imbalance of baseline patient/tumor characteristics [303]. Improved understanding of short-term prognostic factors can help with interpretation of such comparisons in the future, so that any differences in baseline characteristics can be identified. The finding in Chapter 3 that CIRS was better predictive of early mortality than the more commonly used CCI provides a stepping stone towards more accurate short-term prognostication.

A second avenue of further investigation includes strategies to reduce disease recurrence following lung SBRT. Rates of 5-year locoregional and distant failures remain in the order of approximately 20-30% and 20%, respectively (Chapter 1), and trials investigating adjuvant immunotherapy are underway [304]. Likely only a subset of patients will benefit from adjuvant treatment, and identifying prognostic factors for disease recurrence will allow for appropriate patient selection for adjuvant treatment. Tumor radiomic features [282] and levels of circulating tumor DNA [281] are showing promise in this regard. It will be important to identify patients at risk of disease recurrence but with low risk of competing mortality. Future work may look at developing nomograms to predict cancer recurrence. The absence of data on disease recurrence and cause of death was a limitation of the present studies.

Finally, further understanding of prognostic factors will be essential to define the emerging role of SBRT for the treatment of oligometastases. Recent randomized phase II trials have reported improvements in progression-free survival [305, 306] and overall survival [305] with SBRT to all sites of disease in NSCLC patients with limited (3 or fewer [305] or 5 or fewer [306]) metastatic foci after induction systemic therapy, compared to systemic therapy or observation alone. A third randomized phase II trial (SABR-COMET) similarly found an overall survival benefit with SBRT in a variety of primary cancers with up to 5 metastatic lesions [307]. Confirmatory phase III trials, however, are needed before definitive conclusions can be drawn. These are currently

underway, including the NRG-LU002 trial (NCT03137771) and SABR-COMET-3 (NCT03862911). In the meantime, much uncertainty exists regarding appropriate patient selection. Because oligometastatic cancers may show an indolent course even without aggressive local treatment such as SBRT, it can be difficult to ascertain if favorable outcomes are due to aggressive local treatment or disease biology [79]. It will be essential to identify which patients with oligometastatic cancers benefit from SBRT, in terms of disease features (e.g. number and size of lesions, primary tumor histology) as well as patient-related prognostic factors. Similarly, prognostic factors for toxicity will be needed; while the above trials in NSCLC reported no severe toxicities in the SBRT groups [305, 306], a provocative finding in SABR-COMET was that three (5%) of 66 patients in the SABR group experienced treatment-related death [307].

8.5 Conclusion

For peripheral early stage NSCLC, SBRT should be offered to patients regardless of age and comorbidity. Very few patients die within with first 6 months following SBRT. This is important knowledge, as a large proportion of patients are elderly and have severe comorbidities; exclusion of these patients would represent unnecessary withholding of potentially curative treatment for a large number of individuals.
Comorbidity as measured by CIRS and tumor size are prognostic for death within 6 months of SBRT, and this finding will be important for subsequent study to identify patients at high risk of early mortality who could benefit from less aggressive treatment approaches. The nomogram here can also assist in prognostication and generates survival prediction at an individual patient level. In this way, these studies provide an improved understanding of prognosis which can help patients and clinicians with treatment decision making.

The SBRT boost regimen for the treatment of oropharynx cancer is a promising regimen with good long-term survival outcomes. While rates of late toxicity are high, the identification of risk factors for toxicity may allow for toxicity mitigation strategies in the future. The rate of HPV-related disease will require further study in order to facilitate

comparison with conventional chemoradiotherapy. While rates of local control were excellent overall, the rate of out-of-field local failures was higher than anticipated and highlights the need for caution when applying SBRT to diverse anatomical regions due to potentially higher rates of marginal miss.

Together, these studies provide an improved understanding of prognostic factors for lung and oropharynx SBRT and will allow for further improvements in treatment and patient selection in the future.

References

1. Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys. 2010;37:4078-101.
2. Guckenberger M, Andratschke N, Alheit H, et al. Definition of stereotactic body radiotherapy: principles and practice for the treatment of stage I non-small cell lung cancer. Strahlenther Onkol. 2014;190:26-33.
3. Nagata Y. (2015) Introduction and History of Stereotactic Body Radiation Therapy (SBRT). In: Nagata Y. (eds) Stereotactic Body Radiation Therapy. Springer, Tokyo https://doi.org/10.1007/978-4-431-54883-6_1.
4. Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. Chest. 2003;124:1946-55.
5. Wulf J, Haedinger U, Oppitz U, et al. Stereotactic radiotherapy of targets in the lung and liver. Strahlenther Onkol. 2001;177:645-55.
6. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.
7. Guckenberger M, Andratschke N, Dieckmann K, et al. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. Radiother Oncol. 2017;124:11-17.
8. Ball D, Mai GT, Vinod S, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. Lancet Oncol. 2019;20:494-503.
9. Nyman J, Hallqvist A, Lund JÅ, et al. SPACE - A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. Radiother Oncol. 2016;121:1-8.
10. Chaturved AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol 2011;29:4294-301.
11. Karam I, Yao M, Heron DE, et al. Survey of current practices from the International Stereotactic Body Radio- therapy Consortium (ISBRTC) for head and neck cancers. Future Oncol. 2017;13:603-13.
12. Rwigema JC, Heron DE, Ferris RL, et al. The impact of tumor volume and radiotherapy dose on outcome in previously irradiated recurrent squamous cell carcinoma of the head and neck treated with stereotactic body radiation therapy. Am J Clin Oncol. 2011;34:372-9.
13. Vargo JA, Ferris RL, Ohr J, et al. A prospective phase 2 trial of reirradiation with stereotactic body radiation therapy plus cetuximab in patients with previously irradiated recurrent squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys. 2015;91:480-8.

14. Liu F, Xiao JP, Xu GZ, et al. Fractionated stereotactic radiotherapy for 136 patients with locally residual naso- pharyngeal carcinoma. Radiat Oncol. 2013;8:157.
15. Hara W, Loo BW, Jr, Goffinet DR, et al. Excellent local control with stereotactic radiotherapy boost after external beam radiotherapy in patients with nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys. 2008;71:393-400.
16. Klement RJ, Belderbos J, Grills I, et al. Prediction of early death in patients with early-stage NSCLC-can we select patients without a potential benefit of SBRT as a curative treatment approach? J Thorac Oncol. 2016;11:1132-9.
17. Hoogeman M, Prévost JB, Nuyttens J, et al. Clinical accuracy of the respiratory tumor tracking system of the cyberknife: assessment by analysis of log files. Int J Radiat Oncol Biol Phys. 2009;74:297-303.
18. Al-Mamgani A, Van Rooij P, Sewnaik A, et al. Brachytherapy or stereotactic body radiotherapy boost for earlystage oropharyngeal cancer: comparable outcomes of two different approaches. Oral Oncol. 2013;49:1018-24.
19. Al-Mamgani A, van Rooij P, Tans L, et al. A prospective evaluation of patient-reported quality-of-life after (che- mo)radiation for oropharyngeal cancer: which patients are at risk of significant quality-of-life deterioration?. Radiother Oncol. 2013;106:359-63.
20. Cengiz M, Özyiğit G, Yazici G, et al. Salvage reirradiaton with stereotactic body radiotherapy for locally recurrent head-and-neck tumors. Int J Radiat Oncol Biol Phys. 2011;81:104-9.
21. Kodani N, Yamazaki H, Tsubokura T, et al. Stereotactic body radiation therapy for head and neck tumor: disease control and morbidity outcomes. J Radiat Res. 2011;52:24-31.
22. Siddiqui F, Patel M, Khan M, et al. Stereotactic body radiation therapy for primary, recurrent, and metastatic tumors in the head-and-neck region. Int J Radiat Oncol Biol Phys. 2009;74:1047-53.
23. Owen D, Iqbal F, Pollock BE, et al. Long-term follow-up of stereotactic radiosurgery for head and neck malignancies. Head Neck. 2015;37:1557-62.
24. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:E359-86.
25. Eberhardt WE, De Ruysscher D, Weder W, et al. 2nd ESMO consensus conference in lung cancer: locally advanced stage III non-small-cell lung cancer. Ann Oncol. 2015;26:1573-88.
26. Vansteenkiste J, De Ruysscher D, Eberhardt WEE, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24:vi89-98.
27. Chetty IJ, Devpura S, Liu D, et al. Correlation of dose computed using different algorithms with local control following stereotactic ablative radiotherapy (SABR)-based treatment of non-small-cell lung cancer. Radiother Oncol. 2013;109:498-504.
28. Keall PJ, Mageras GS, Balter JM, et al. The management of respiratory motion in radiation oncology report of AAPM task group 76. Med Phys. 2006;33:3874-900.
29. Chen AB, Neville BA, Sher DJ, et al. Survival outcomes after radiation therapy for stage III non-small-cell lung cancer after adoption of computed tomography-based simulation. J Clin Oncol. 2001;29:2305-11.

30. Chun SG, Hu C, Choy H, et al. Comparison of 3-D conformal and intensity modulated radiation therapy outcomes for locally advanced non-small cell lung cancer in NRG oncology/ RTOG 0617. Int J Radiat Oncol Biol Phys. 2015;93 Suppl 3:S1-2.

31. Alhassani A, Chandra A, Chernew ME. The sources of the SGR “hole.”. N Engl J Med. 2012;366:289–91.

32. Louie AV, Palma DA, Dahele M, et al. Management of early-stage non-small cell lung cancer using stereotactic ablative radiotherapy: controversies, insights, and changing horizons. Radiother Oncol. 2015;114:138-47.

33. Lagerwaard FJ, Haasbeek CJ, Smit EF, et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2008;70:685-92.

34. Ricardi U, Filippi AR, Guarneri A, et al. Stereotactic body radiation therapy for early stage non-small cell lung cancer: results of a prospective trial. Lung Cancer. 2010;68:72-7.

35. Timmerman R, Paulus R, Pass H, et al. RTOG 0618: stereotactic body radiation therapy (SBRT) to treat operable early-stage lung cancer patients. J Clin Oncol. 2013;31 suppl 15:7523.

36. Hallqvist A, Lund J, Brustugun O, et al. The SPACE study: a randomized phase II trial comparing SBRT and 3DCRT in stage I NSCLC patients; final analysis including HRQL. J Thorac Oncol. 2015;10 Suppl 2:S209.

37. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol. 2015;16:630-7.

38. Verstegen NE, Oosterhuis JW, Palma DA, et al. Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. Ann Oncol. 2013;24:1543-8.

39. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys. 2011;81:1352-8.

40. Lagerwaard FJ, Verstegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2012;83:348-53.

41. Nagata Y, Hiraoka M, Shibata T, et al. Prospective trial of stereotactic body radiation therapy for both operable and inoperable T1N0M0 Non-small cell lung cancer: Japan clinical oncology group study JCOG0403. Int J Radiat Oncol Biol Phys. 2015;93:989-96.

42. Hopmans W, Damman OC, Timmermans DR, et al. Communicating cancer treatment information using the web: utilizing the patient’s perspective in website development. BMC Med Inform Decis Mak. 2014;14:116.

43. Hopmans W, Damman OC, Senan S, et al. A patient perspective on shared decision making in stage I non-small cell lung cancer: a mixed methods study. BMC Cancer. 2015;15:959.

44. Dahele M, Palma D, Lagerwaard F, et al. Radiological changes after stereotactic radiotherapy for stage I lung cancer. J Thorac Oncol. 2011;6:1221-8.

45. Huang K, Senthi S, Palma DA, et al. Highrisk CT features for detection of local recurrence after stereotactic ablative radiotherapy for lung cancer. Radiother Oncol. 2013;109:51-7.

46. Peulen H, Mantel F, Guckenberger M, et al. Validation of high-risk computed tomography features for detection of local recurrence after stereotactic body radiation therapy for early-stage non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2016;96:134-41.

47. Mattonen SA, Palma DA, Johnson C, et al. Detection of local cancer recurrence after stereotactic ablative radiation therapy for lung cancer: physician performance versus radiomic assessment. Int J Radiat Oncol Biol Phys. 2016;94:1121-8.

48. Vansteenkiste J, Crinò L, Dooms C, et al. 2nd ESMO consensus conference on lung cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. Ann Oncol. 2014;25:1462-74.

49. Huang K, Palma D. Follow-up of patients after stereotactic radiation for lung cancer a primer for the nonradiation oncologist. J Thorac Oncol. 2015;10:412-9.

50. Verstegen NE, Lagerwaard FJ, Hashemi SM, et al. Patterns of disease recurrence after SABR for early stage Non-small-cell lung cancer: optimizing follow-up schedules for salvage therapy. J Thorac Oncol. 2015;10:1195-200.

51. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. J Clin Oncol. 2010;28:928-35.

52. Crabtree TD, Denlinger CE, Meyers BF, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. J Thorac Cardiovasc Surg. 2010;140:377-86.

53. Ward MC, Oh SC, Pham YD, et al. Isolated nodal failure after stereotactic body radiotherapy for lung cancer: the role for salvage mediastinal radiotherapy. J Thorac Oncol. 2016;11:1558-64.

54. Senthi S, Lagerwaard FJ, Haasbeek CJ, et al. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. Lancet Oncol. 2012;13: 802-9.

55. Robinson CG, Dewees TA, El Naqa IM, et al. Patterns of failure after stereotactic body radiation therapy or lobar resection for clinical stage I non-small-cell lung cancer. J Thorac Oncol. 2013;8:192-201.

56. Chang JY, Bezjak A, Mornex F. IASLC advanced radiation technology committee stereotactic ablative radiotherapy for centrally located early stage non-small-cell lung cancer: what we have learned. J Thorac Oncol. 2015;10:577-85.

57. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol. 2006;24:4833-9.

58. Senthi S, Haasbeek CJ, Slotman BJ, et al. Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. Radiother Oncol. 2013;106:276-82.

59. Tekatli H, Senan S, Dahele M, et al. Stereotactic ablative radiotherapy (SABR) for central lung tumors: plan quality and long-term clinical outcomes. Radiother Oncol. 2015;117:64-70.

60. Tekatli H, Haasbeek N, Dahele M, et al. Outcomes of hypofractionated high-dose radiotherapy in poor-risk patients with “ultracentral” Non-small cell lung cancer. J Thorac Oncol. 2016;11:1081-9.

61. Huber RM, Fischer R, Hautmann H, et al. Does additional brachytherapy improve the effect of external irradiation? a prospective, randomized study in central lung tumors. Int J Radiat Oncol Biol Phys. 1997;38:533-40.

62. Cannon DM, Mehta MP, Adkison JB, et al. Dose-limiting toxicity after hypofractionated dose-escalated radiotherapy in non-small-cell lung cancer. J Clin Oncol. 2013;31:4343-8.

63. Bezjak A, Paulus R, Gaspar L, et al. Primary study endpoint analysis for NRG oncology/RTOG 0813 trial of stereotactic body radiation therapy (SBRT) for centrally located non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys. 2016;94:5-6.

64. Chang JY, Jabbour SK, De Ruysscher D, et al. Consensus statement on proton therapy in early-stage and locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2016;95:505-16.

65. Zenke Y, Umemura S, Motegi A, et al. Acute and Progressive Tracheal Stenosis after Proton Beam Therapy with Concurrent Chemotherapy for Non–Small Cell Lung Cancer. J Thorac Oncol. 2016;11:1181-3.

66. Dahele M, van Sörnsen de Koste JR, Verbakel WF, et al. An analysis of planned versus delivered airway doses during stereotactic lung radiotherapy for central tumors. Acta Oncol. 2016;55:934-7.

67. Acharya S, Fischer-Valuck BW, Kashani R, et al. Online magnetic resonance image guided adaptive radiation therapy: first clinical applications. Int J Radiat Oncol Biol Phys. 2016;94:394-403.

68. Fallone BG. The rotating biplanar linac-magnetic resonance imaging system. Semin Radiat Oncol. 2014;24:200.

69. Lagendijk JJ, van Vulpen M, Raaymakers BW. The development of the MRI linac system for online MRI-guided radiotherapy: a clinical update. J Intern Med. 2016;280:203-8.

70. Whelan B, Gierman S, Holloway L, et al. A novel electron accelerator for MRI-linac radiotherapy. Med Phys. 2016;43:1285.

71. Gazdar AF, Minna JD. Multifocal lung cancers – clonality vs field cancerization and does it matter? J Natl Cancer Inst. 2009;101:541-3.

72. Griffioen GH, Lagerwaard FJ, Haasbeek CJ, et al. Treatment of multiple primary lung cancers using stereotactic radiotherapy, either with or without surgery. Radiother Oncol. 2013;107:403-8.

73. Murray PF, Spencer K, Snee M, et al. Is stereotactic ablative radiotherapy (SABR) a safe treatment for multiple primary lung cancer (MPLC) non-small cell lung cancer (NSCLC)? Lung Cancer. 2016;91 Suppl 1:S48.

74. Owen D, Olivier KR, Mayo CS, et al. Outcomes of stereotactic body radiotherapy (SBRT) treatment of multiple synchronous and recurrent lung nodules. Radiat Oncol. 2015;10:43.

75. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med. 1990;322:494-500.

76. Ashworth AB, Senan S, Palma DA, et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. Clin Lung Cancer. 2014;15:346-55.

77. Gomez D, Blumenschein G, Lee J, et al. Local consolidative therapy (LCT) to improve progression-free survival (PFS) in patients with oligometastatic non-small cell lung cancer (NSCLC) who receive induction systemic therapy (IST): results of a multi-institutional phase II randomized study. J Clin Oncol. 2016;34 Suppl 15:9004.

78. Eberhardt WE, Mitchell A, Crowley J, et al. The IASLC lung cancer staging project: proposals for the revision of the M descriptors in the forthcoming eighth edition of the TNM classification of lung cancer. J Thorac Oncol. 2015;10:1515-22.

79. Palma DA, Salama JK, Lo SS, et al. The oligometastatic state - separating truth from wishful thinking. Nat Rev Clin Oncol. 2014;11:549-57.

80. Besse B, Adjei A, Baas P, et al. 2nd ESMO consensus conference on lung cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease. Ann Oncol. 2014;25:1475-84.

81. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomized, two-by-two factorial phase 3 study. Lancet Oncol. 2015;16:187-99.

82. Decker RH, Lynch TJ. Unmet challenges in the use of novel agents in locally advanced non-small-cell lung cancer. J Clin Oncol. 2012;30:582-4.

83. Senan S. Treatment of stage IIIA non-small cell lung cancer: charting the next steps. J Oncol Pract. 2016;12:609-10.

84. Masters GA, Temin S, Azzoli CG, et al. Systemic therapy for stage IV non-small-cell lung cancer: American society of clinical oncology clinical practice guideline update. American society of clinical oncology clinical practice. J Clin Oncol. 2015;33:3488-515.

85. Dickhoff C, Dahele M, de Langen AJ, et al. Population-based patterns of surgical care for stage IIIA NSCLC in the Netherlands between 2010 and 2013. J Thorac Oncol. 2016;11:566-72.

86. Le Péchoux C, Dunant A, Pignon JP, et al. Need for a new trial to evaluate adjuvant postoperative radiotherapy in non-small-cell lung cancer patients with N2 mediastinal involvement. J Clin Oncol. 2007;25:e10-1.

87. PORT Meta-analysis Trialists Group. Post-operative radiotherapy in non-small cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. Lancet. 1998;352:257-63.

88. Lally BE, Zelterman D, Colasanto JM, et al. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. J Clin Oncol. 2006;24:2998-3006.

89. Robinson CG, Patel AP, Bradley JD, et al. Postoperative radiotherapy for pathologic N2 non-small-cell lung cancer treated with adjuvant chemotherapy: a review of the national cancer data base. J Clin Oncol. 2015;33:870-6.

90. De Ruysscher D, Faivre-Finn C, Nestle U, et al. European organisation for research and treatment of cancer recommendations for planning and delivery of high-dose, high-precision radiotherapy for lung cancer. J Clin Oncol. 2010;28:5301-10.

91. Grills IS, Hugo G, Kestin LL, et al. Image-guided radiotherapy via daily online cone-beam CT substantially reduces margin requirements for stereotactic lung radiotherapy. Int J Radiat Oncol Biol Phys. 2008;70:1045-56.

92. Roelofs E, Engelsman M, Rasch C, et al. Results of a multicentric in silico clinical trial (ROCOCO): comparing radiotherapy with photons and protons for non-small cell lung cancer. J Thorac Oncol. 2012;7:165-76.

93. Murshed H, Liu HH, Liao Z, et al. Dose and volume reduction for normal lung using intensity-modulated radiotherapy for advanced-stage non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2004;58:1258-67.

94. Blom GJ, Verbakel WF, Dahele M, et al. Improving radiotherapy planning for large volume lung cancer: a dosimetric comparison between hybrid-IMRT and RapidArc. Acta Oncol. 2015;54:427-32.

95. Chen AB, Li L, Cronin A, et al. Comparative effectiveness of intensitymodulated versus 3D conformal radiation therapy among medicare patients with stage III lung cancer. J Thorac Oncol. 2014;9:1788-95.

96. Shirvani SM, Jiang J, Gomez DR, et al. Intensity modulated radiotherapy for stage III non-small cell lung cancer in the United States: predictors of use and association with toxicities. Lung Cancer. 2013;82:252-9.

97. Sher DJ, Koshy M, Liptay MJ, et al. Influence of conformal radiotherapy technique on survival after chemoradiotherapy for patients with stage III nonsmall cell lung cancer in the national cancer data base. Cancer. 2014;120:2060-8.

98. Ling DC, Hess CB, Chen AM, et al. Comparison of toxicity between intensity-modulated radiotherapy and 3-dimensional conformal radiotherapy for locally advanced non-small-cell lung cancer. Clin Lung Cancer. 2016;17:18-23.

99. Harris JP, Murphy JD, Hanlon AL, et al. A population based comparative effectiveness study of radiation therapy techniques in stage III non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2014;88:872-84.

100. Jegadeesh N, Liu Y, Gillespie T, et al. Evaluating Intensity-Modulated Radiation Therapy in Locally Advanced Non-Small-Cell Lung Cancer: Results From the National Cancer Data Base. Clin Lung Cancer. 2016;17:398-405.

101. Senan S, Brade A, Wang LH, et al. PROCLAIM: randomized phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. J Clin Oncol. 2016;34:953–62.

102. Ahn JS, Ahn YC, Kim JH, et al. Multinational randomized phase III trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage III non-small-cell lung cancer: KCSG-LU05-04. J Clin Oncol. 2015;33:2660–6.

103. Movsas B, Hu C, Sloan J, et al. Quality of life analysis of a radiation dose-escalation study of patients with non-small-cell lung cancer: a secondary analysis of the radiation therapy oncology group 0617 randomized clinical trial. JAMA Oncol. 2016;2:359–67.

104. Eaton BR, Pugh SL, Bradley JD, et al. Institutional enrollment and survival among NSCLC patients receiving chemoradiation: NRG oncology radiation therapy oncology group (RTOG) 0617. J Natl Cancer Inst. 2016;108:djw034.

105. Tucker SL, Liu A, Gomez D, et al. Impact of heart and lung dose on early survival in patients with non-small cell lung cancer treated with chemoradiation. Radiother Oncol. 2016;119:495-500.

106. Verma V, Mishra MV, Mehta MP. A systematic review of the cost and cost-effectiveness studies of proton radiotherapy. Cancer. 2016;122:1483–501.

107. Lievens Y, Verhaeghe N, De Neve W, et al. Proton radiotherapy for locally-advanced non-small cell lung cancer, a cost-effective alternative to photon radiotherapy in Belgium? J Thorac Oncol. 2013;8 suppl 2:S839–40.

108. Chang JY, Zhang X, Wang X, et al. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional conformal or intensity-modulated radiation therapy in stage I or stage III non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2006;65:1087–96.

109. Register SP, Zhang X, Mohan R, et al. Proton stereotactic body radiation therapy for clinically challenging cases of centrally and superiorly located stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2011;80:1015–22.

110. Zhang X, Li Y, Pan X, et al. Intensitymodulated proton therapy reduces the dose to normal tissue compared with intensity-modulated radiation therapy or passive scattering proton therapy and enables individualized radical radiotherapy for extensive stage IIIB non-small-cell lung cancer: a virtual clinical study. Int J Radiat Oncol Biol Phys. 2010;77:357–66.

111. Albertini F, Bolsi A, Lomax AJ, et al. Sensitivity of intensity modulated proton therapy plans to changes in patient weight. Radiother Oncol. 2008;86:187–94.

112. Sejpal S, Komaki R, Tsao A, et al. Early findings on toxicity of proton beam therapy with concurrent chemotherapy for nonsmall cell lung cancer. Cancer. 2011;117:3004–13.

113. Liao Z, Lee J, Komaki R, et al. A Bayesian randomisation trial of IMRT vs. PSPT for locally advanced non-small cell lung carcinoma. Radiother Oncol. 2016;119 Suppl 1:S65.

114. Liao Z, Lee J, Komaki R, et al. Bayesian randomized trial comparing intensity modulated radiation therapy versus passively scattered proton therapy for locally advanced non-small cell lung cancer. J Clin Oncol. 2016;34 suppl 15:8500.

115. Zhang J, Gold KA, Lin HY, et al. Relationship between tumor size and survival in non-small cell lung cancer (NSCLC): an analysis of the surveillance, epidemiology, and end results (SEER) registry. J Thorac Oncol. 2015;10:682–90.

116. Basaki K, Abe Y, Aoki M, et al. Prognostic factors for survival in stage III non-small-cell lung cancer treated with definitive radiation therapy: impact of tumor volume. Int J Radiat Oncol Biol Phys. 2006;64:449–54.

117. Wiersma TG, Dahele M, Verbakel WF, et al. Concurrent chemoradiotherapy for large-volume locally-advanced non-small cell lung cancer. Lung Cancer. 2013;80:62–7.

118. Sullivan R, Peppercorn J, Sikora K, et al. Delivering affordable cancer care in high-income countries. Lancet Oncol. 2011;12:933–80.

119. Atun R, Jaffray DA, Barton MB, et al. Expanding global access to radiotherapy. Lancet Oncol. 2015;16:1153–86.

120. Salama AK, Postow MA, Salama JK. Irradiation and immunotherapy: from concept to the clinic. Cancer. 2016;122:1659–71.

121. Reynders K, Illidge T, Siva S, et al. The abscopal effect of local radiotherapy: using immunotherapy to make a rare event clinically relevant. Cancer Treat Rev. 2015;41:503–10.

122. Whiteside TL, Demaria S, Rodriguez-Ruiz ME, et al. Emerging opportunities and challenges in cancer immunotherapy. Clin Cancer Res. 2016;22:1845–55.

123. Kim JM, Chen DS. Immune escape to PD-L1/PD-1 blockade: seven steps to success (or failure). Ann Oncol. 2016;27:1492-504.

124. Johnson C, Jagsi R. The promise of the abscopal effect and the future of trials combining immunotherapy and radiation therapy. Int J Radiat Oncol Biol Phys. 2016;95:1254–6.

125. van Loon J, Grutters J, Macbeth F. Evaluation of novel radiotherapy technologies: what evidence is needed to assess their clinical and cost effectiveness, and how should we get it? Lancet Oncol. 2012;13:e169–77.

126. IOM (Institute of Medicine). Delivering high-quality cancer care: charting a new course for a system in crisis. Washington, DC: The National Academies Press; 2013.

127. Bonastre J, Noel E, Chevalier J, et al. Implications of learning eff ects for hospital costs of new health technologies: the case of intensity modulated radiation therapy. Int J Technol Assess Health Care. 2007;23:248–54.

128. Lyman GH, Levine M. Comparative effectiveness research in oncology: an overview. J Clin Oncol. 2012;30:4181–4.

129. Chavez-MacGregor M, Giordano SH. Randomized clinical trials and observational studies: is there a battle? J Clin Oncol. 2016;34:772–3.

130. Kessel K, Combs S. Review of developments in electronic, clinical data collection, and documentation systems over the last decade – are we ready for big data in routine health care? Front Oncol. 2016;6:75.

131. Langendijk JA, Lambin P, De Ruysscher D, et al. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. Radiother Oncol. 2013;107:267–73.

132. Bentzen SM, Constine LS, Deasy JO, et al. Quantitative analyses of normal tissue effects in the clinic (QUANTEC): an introduction to the scientific issues. Int J Radiat Oncol Biol Phys. 2010;76 Suppl 3:S3–9.

133. Mukesh MB, Qian W, Wilkinson JS, et al. Patient reported outcome measures (PROMs) following forward planned field-in field IMRT: results from the Cambridge breast IMRT trial. Radiother Oncol. 2014;111:270–5.

134. Mukesh MB, Qian W, Wah Hak CC, et al. The Cambridge breast intensity-modulated radiotherapy trial: comparison of clinician- versus patient-reported outcomes. Clin Oncol (R Coll Radiol). 2016;28:354–64.

135. Denis F, Lethrosne C, Pourel N, et al. Overall survival in patients with lung cancer using a web-application-guided follow-up compared to standard modalities: results of phase III randomized trial. J Clin Oncol. 2016;34 suppl 15:9006.

136. Glatstein E. Distinguishing “controversy” from conflict of interest: the wrong image for radiation oncology. Int J Radiat Oncol Biol Phys. 2010;76:1283–4.

137. Warner A, Dahele M, Hu B, et al. Factors associated with early mortality in patients treated with concurrent chemoradiation therapy for locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2016;94:612–20.

138. Putman RK, Hatabu H, Araki T, et al. Association between interstitial lung abnormalities and All-cause mortality. JAMA. 2016;315:672–81.

139. Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax. 2012;67:957–63.

140. Ohe Y, Yamamoto S, Suzuki K, et al. Risk factors of treatment-related death in chemotherapy and thoracic radiotherapy for lung cancer. Eur J Cancer. 2001;37:54–63.

141. Donington J, Ferguson M, Mazzone P, et al. American college of chest physicians and society of thoracic surgeons consensus statement for evaluation and management for high-risk patients with stage I non-small cell lung cancer. Chest. 2012;142:1620–35.

142. Sanders KJ, Hendriks LE, Troost EG, et al. Early weight loss during chemoradiotherapy Has a detrimental impact on outcome in NSCLC. J Thorac Oncol. 2016;11:873–9.

143. Kim M, Craft DL. Within the next five years, most radiotherapy treatment schedules will be designed using spatiotemporal optimization. Med Phys. 2016;43:2009–11.

144. Webb S. Does elastic tissue intrafraction motion with density changes forbid motion-compensated radiotherapy? Phys Med Biol. 2006;51:1449–62.

145. Li HS, Zhong H, Kim J, et al. Direct dose mapping versus energy/mass transfer mapping for 4D dose accumulation: fundamental differences and dosimetric consequences. Phys Med Biol. 2014;59:173–88.

146. Best MG, Sol N, Kooi I, et al. RNA-Seq of tumor-educated platelets enables blood-based Pan-cancer, multiclass, and molecular pathway cancer diagnostics. Cancer Cell. 2015;28:666–76.

147. Huang J, Logue AE, Ostroff JS, et al. Comprehensive long-term care of patients with lung cancer: development of a novel thoracic survivorship program. Ann Thorac Surg. 2014;98:955–61.

148. van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst. 2007;99:442–50.

149. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet. 2009;374:379–86.

150. Eberhardt WE, Pöttgen C, Gauler TC, et al. Phase III study of surgery versus definitive concurrent chemoradiotherapy boost in patients with resectable stage IIIA(N2) and selected IIIB non-small-cell lung cancer after induction chemotherapy and concurrent chemoradiotherapy (ESPATUE). J Clin Oncol. 2015;33:4194–201.

151. Pless M, Stupp R, Ris HB, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. Lancet. 2015;386:1049–56.

152. Curran Jr WJ, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst. 2011;103:1452–60.

153. Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol. 2010;28:2181–90.

154. Haasbeek CJ, Palma D, Visser O, et al. Early-stage lung cancer in elderly patients: a population-based study of changes in treatment patterns and survival in the Netherlands. Ann Oncol. 2012;23:2743–7.

155. Palma D, Visser O, Lagerwaard FJ, et al. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. J Clin Oncol. 2010;28:5153–9.

156. Murray P, Franks K, Hanna GG. A systematic review of outcomes following stereotactic ablative radiotherapy in the treatment of early-stage primary lung cancer. Br J Radiol. 2017;90:20160732.

157. Zheng X, Schipper M, Kidwell K, et al. Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: a meta-analysis. Int J Radiat Oncol Biol Phys. 2014;90:603–11.

158. van der Voort van Zyp NC, Prévost JB, Hoogeman MS, et al. Stereotactic radiotherapy with real-time tumor tracking for non-small cell lung cancer: clinical outcome. Radiother Oncol 2009;91:296–300.

159. Cassidy RJ, Patel PR, Zhang X, et al. Stereotactic Body Radiotherapy for Early-stage Non-small-cell Lung Cancer in Patients 80 Years and Older: A Multi-center Analysis. Clin Lung Cancer. 2017;18:551–8.

160. Baumann P, Nyman J, Hoyer M, et al. Stereotactic body radiotherapy for medically inoperable patients with stage I non-small cell lung cancer - a first report of toxicity related to COPD/CVD in a non-randomized prospective phase II study. Radiother Oncol. 2008;88:359-67.

161. Takeda A, Enomoto T, Sanuki N, et al. Reassessment of declines in pulmonary function ≥1 year after stereotactic body radiotherapy. Chest. 2013;143:130–7.

162. Nuyttens JJ, van de Pol M. The Cyber Knife radiosurgery system for lung cancer. Expert Rev Med Devices 2012;9:465–75.

163. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007;176:532–55.

164. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med 2017;195:557–82.

165. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373–83.

166. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc. 1968;16:622–6.

167. Extermann M. Measurement and impact of comorbidity in older cancer patients. Crit Rev Oncol Hematol. 2000;35:181–200.

168. Extermann M. Measuring comorbidity in older cancer patients. Eur J Cancer. 2000;36:453–71.

169. Gould MK, Munoz-Plaza CE, Hahn EE, et al. Comorbidity Profiles and Their Effect on Treatment Selection and Survival among Patients with Lung Cancer. Ann Am Thorac Soc. 2017;14:1571–80.

170. Stokes WA, Bronsert MR, Meguid RA, et al. Post-Treatment Mortality After Surgery and Stereotactic Body Radiotherapy for Early-Stage Non-Small-Cell Lung Cancer. J Clin Oncol. 2018;36:642–651.

171. Varlotto J, Fakiris A, Flickinger J, et al. Matched-pair and propensity score comparisons of outcomes of patients with clinical stage I non-small cell lung cancer treated with resection or stereotactic radiosurgery. Cancer. 2013;119:2683–91.

172. Matsuo Y, Chen F, Hamaji M, et al. Comparison of long-term survival outcomes between stereotactic body radiotherapy and sublobar resection for stage I non-small-cell lung cancer in patients at high risk for lobectomy: A propensity score matching analysis. Eur J Cancer. 2014;50:2932–8.

173. Kopek N, Paludan M, Petersen J, et al. Co-morbidity index predicts for mortality after stereotactic body radiotherapy for medically inoperable early-stage non-small cell lung cancer. Radiother Oncol. 2009;93:402–7.

174. Louie AV, Haasbeek CJ, Mokhles S, et al. Predicting Overall Survival After Stereotactic Ablative Radiation Therapy in Early-Stage Lung Cancer: Development and External Validation of the Amsterdam Prognostic Model. Int J Radiat Oncol Biol Phys. 2015;93:82–90.

175. Rosen JE, Keshava HB, Yao X, et al. The Natural History of Operable Non-Small Cell Lung Cancer in the National Cancer Database. Ann Thorac Surg. 2016;101:1850–5.

176. Rochon PA, Katz JN, Morrow LA, et al. Comorbid illness is associated with survival and length of hospital stay in patients with chronic disability. A prospective comparison of three comorbidity indices. Med Care. 1996;34:1093–101.

177. Firat S, Bousamra M, Gore E, et al. Comorbidity and KPS are independent prognostic factors in stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2002;52:1047–57.

178. Matsuo Y, Shibuya K, Nagata Y, et al. Prognostic factors in stereotactic body radiotherapy for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2011;79:1104–11.

179. Allibhai Z, Taremi M, Bezjak A, et al. The impact of tumor size on outcomes after stereotactic body radiation therapy for medically inoperable early-stage non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2013;87:1064–70.

180. Dunlap NE, Larner JM, Read PW, et al. Size matters: A comparison of T1 and T2 peripheral non-small-cell lung cancers treated with stereotactic body radiation therapy (SBRT). J Thorac Cardiovasc Surg 2010;140:583–9.

181. Owonikoko TK, Ragin CC, Belani CP, et al. Lung cancer in elderly patients: an analysis of the surveillance, epidemiology, and end results database. J Clin Oncol. 2007;25:5570–7.

182. Blanco JA, Toste IS, Alvarez RF, et al. Age, comorbidity, treatment decision and prognosis in lung cancer. Age Ageing. 2008;37:715–8.

183. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, et al. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax. 2005;60:925–31.

184. Wao H, Mhaskar R, Kumar A, et al. Survival of patients with non-small cell lung cancer without treatment: a systematic review and meta-analysis. Syst Rev 2013;2:10.

185. Videtic GMM, Donington J, Giuliani M, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. *Pract Radiat Oncol*. 2017;7:295–301.

186. Young KA, Efiong E, Dove JT, et al. External Validation of a Survival Nomogram for Non-Small Cell Lung Cancer Using the National Cancer Database. Ann Surg Oncol. 2017;24:1459–1464.

187. Koshy M, Malik R, Spiotto M, et al. Disparities in treatment of patients with inoperable stage I non-small cell lung cancer: a population-based analysis. J Thorac Oncol. 2015;10:264–271.

188. Liang W, Zhang L, Jiang G, et al. Development and validation of a nomogram for predicting survival in patients with resected non-small-cell lung cancer. J Clin Oncol. 2015;33:861–869.

189. Xiao HF, Zhang BH, Liao XZ, et al. Development and validation of two prognostic nomograms for predicting survival in patients with non-small cell and small cell lung cancer. Oncotarget. 2017;8:64303–64316.

190. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv1-iv21.

191. Harrell FE, Jr. Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis, 2nd ed. Switzerland: Springer; 2015.

192. Ou SH, Zell JA, Ziogas A, Anton-Culver H, et al. Prognostic factors for survival of stage I nonsmall cell lung cancer patients: A population-based analysis of 19,702 stage I patients in the California Cancer Registry from 1989 to 2003. Cancer. 2007;110:1532-1541.

193. McGovern SL, Liao Z, Bucci MK, et al. Is sex associated with the outcome of patients treated with radiation for nonsmall cell lung cancer? Cancer. 2009;115:3233–3242.

194. Firat S, Bousamra M, Gore E, et al. Comorbidity, and KPS are independent prognostic factors in stage I non-small cell lung cancer. Int J Radiat Biol Phys. 2002;52:1047–1057.

195. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol. 2007;2:S94–S100.

196. Baker S, Sharma A, Peric R, et al. Prediction of early mortality following stereotactic body radiotherapy for peripheral early-stage lung cancer. Acta Oncol. 2019;58:237–242.

197. Baine MJ, Verma V, Schonewolf CA, et al. Histology significantly affects recurrence and survival following SBRT for early stage non-small cell lung cancer. Lung Cancer. 2018;118:20–26.

198. Verstegen NE, Lagerwaard FJ, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy following a clinical diagnosis of stage I NSCLC: comparison with a

contemporaneous cohort with pathologically proven disease. Radiother Oncol. 2011;101:250–254.

199. Burotto M, Thomas A, Subramaniam D, et al. Biomarkers in early-stage non-small-cell lung cancer: current concepts and future directions. J Thorac Oncol. 2014; 9:1609–1617.
200. Cole AJ, Hanna GG, Jain S, et al. Motion management for radical radiotherapy in non-small cell lung cancer. Clin Oncol (R Coll Radiol). 2014;26:67-80.
201. Schweikard A, Shiomi H, Adler J. Respiration tracking in radiosurgery. Med Phys. 2004;31:2738-41.
202. Bahig H, Campeau MP, Vu T, et al. Predictive parameters of CyberKnife fiducial-less (XSight Lung) applicability for treatment of early non-small cell lung cancer: a single-center experience. Int J Radiat Oncol Biol Phys. 2013;87:583-9.
203. Whyte RI, Crownover R, Murphy MJ, et al. Stereotactic radiosurgery for lung tumors: preliminary report of a phase I trial. Ann Thorac Surg. 2003;75:1097-101.
204. Hong JC, Yu Y, Rao AK, et al. High retention and safety of percutaneously implanted endovascular embolization coils as fiducial markers for image-guided stereotactic ablative radiotherapy of pulmonary tumors. Int J Radiat Oncol Biol Phys. 2011;81:85-90.
205. Mongeon M, Thibault F, Chartrand-Lefebvre C, et al. Safety and Efficacy of Endovascular Fiducial Marker Insertion for CyberKnife Stereotactic Radiation Therapy Planning in Early-Stage Lung Cancer. J Vasc Interv Radiol. 2017;28:1090-7.
206. Patel A, Khalsa B, Lord B, et al. Planting the seeds of success: CT-guided gold seed fiducial marker placement to guide robotic radiosurgery. J Med Imaging Radiat Oncol. 2013;57:207-11.
207. Bhagat N, Fidelman N, Durack JC, et al. Complications associated with the percutaneous insertion of fiducial markers in the thorax. Cardiovasc Intervent Radiol. 2010;33:1186-91.
208. Trumm CG, Häussler SM, Muacevic A, et al. CT fluoroscopy-guided percutaneous fiducial marker placement for CyberKnife stereotactic radiosurgery: technical results and complications in 222 consecutive procedures. J Vasc Interv Radiol. 2014;25:760-8.
209. Nuyttens JJ, Prévost JB, Praag J, et al. Lung tumor tracking during stereotactic radiotherapy treatment with the CyberKnife: Marker placement and early results. Acta Oncol. 2006;45:961-5.
210. Prévost JB, Nuyttens JJ, Hoogeman MS, et al. Endovascular coils as lung tumour markers in real-time tumour tracking stereotactic radiotherapy: preliminary results. Eur Radiol. 2008;18:1569-76.
211. Karaman K, Dokdok AM, Karadeniz O, et al. Intravascular Placement of Metallic Coils as Lung Tumor Markers for CyberKnife Stereotactic Radiation Therapy. Korean J Radiol. 2015;16:626-31.
212. Khalilzadeh O, Baerlocher MO, Shyn PB, et al. Proposal of a New Adverse Event Classification by the Society of Interventional Radiology Standards of Practice Committee. J Vasc Interv Radiol. 2017;28:1432-1437.
213. Yousefi S, Collins BT, Reichner CA, et al. Complications of thoracic computed tomography-guided fiducial placement for the purpose of stereotactic body radiation therapy. Clin Lung Cancer. 2007;8:252-6.

214. Chen J, Gao L, Yao M, Chen J, et al. Ventricular arrhythmia onset during diagnostic coronary angiography with a 5F or 4F universal catheter. Rev Esp Cardiol. 2008;61:1092-5.

215. Tavakol M, Ashraf S, Brener SJ. Risks and complications of coronary angiography: a comprehensive review. Glob J Health Sci. 2012;4:65-93.

216. Reichner C, Collin B, Gagnon G, et al. The placement of gold fiducials for cyberknife stereotactic radiosurgery using a modified transbronchial needle technique. J Bronchol. 2005;12:193-5.

217. Nabavizadeh N, Zhang J, Elliott DA, et al. Electromagnetic navigational bronchoscopy-guided fiducial markers for lung stereotactic body radiation therapy: analysis of safety, feasibility, and interfraction stability. J Bronchology Interv Pulmonol. 2014;21:123-30.

218. Schroeder C, Hejal R, Linden PA. Coil spring fiducial markers placed safely using navigation bronchoscopy in inoperable patients allows accurate delivery of CyberKnife stereotactic radiosurgery. J Thorac Cardiovasc Surg. 2010;140:1137-42.

219. Anantham D, Feller-Kopman D, Shanmugham LN, et al. Electromagnetic navigation bronchoscopy-guided fiducial placement for robotic stereotactic radiosurgery of lung tumors: a feasibility study. Chest. 2007;132:930-5.

220. Lachkar S, Guisier F, Roger M, et al. Assessment of Per-Endoscopic Placement of Fiducial Gold Markers for Small Peripheral Lung Nodules < 20 mm Before Stereotactic Radiation Therapy. Chest. 2018;153:387-94.

221. Loo BW Jr, Kavanagh BD, Meyer JL. Motion management and image guidance for thoracic tumor radiotherapy: clinical treatment programs. Front Radiat Ther Oncol. 2011;43:271-291.

222. Prasad V, Chan RP, Faughnan ME. Embolotherapy of pulmonary arteriovenous malformations: efficacy of platinum versus stainless steel coils. J Vasc Interv Radiol. 2004;15(2 Pt 1):153-60.

223. Mager JJ, Overtoom TT, Blauw H, et al. Embolotherapy of pulmonary arteriovenous malformations: long-term results in 112 patients. J Vasc Interv Radiol. 2004;15:451-6.

224. Al-Mamgani A, Van Rooij P, Sewnaik A, et al. Brachytherapy or stereotactic body radiotherapy boost for early-stage oropharyngeal cancer: comparable outcomes of two different approaches. Oral Oncol. 2013;49:1018-24.

225. Teguh DN, Levendag PC, Noever I, et al. Treatment techniques and site considerations regarding dysphagia-related quality of life in cancer of the oropharynx and nasopharynx. Int J Radiat Oncol Biol Phys. 2008;72:1119-27.

226. Baliga S, Kabarriti R, Ohri N, et al. Stereotactic body radiotherapy for recurrent head and neck cancer: A critical review. Head Neck. 2017;39:595-601.

227. Maciejewski B, Withers HR, Taylor JM, et al. Dose fractionation and regeneration in radiotherapy for cancer of the oral cavity and oropharynx. Part 2. Normal tissue responses: acute and late effects. Int J Radiat Oncol Biol Phys. 1990;18:101-11.

228. Fletcher GH. Hypofractionation: lessons from complications. Radiother Oncol. 1991;20:10-5.

229. Lee DS, Kim YS, Cheon JS, et al. Long-term outcome and toxicity of hypofractionated stereotactic body radiotherapy as a boost treatment for head and neck cancer: the importance of boost volume assessment. Radiat Oncol. 2012;7:85.

230. Liu F, Xiao JP, Xu GZ, et al. Fractionated stereotactic radiotherapy for 136 patients with locally residual nasopharyngeal carcinoma. Radiat Oncol. 2013;27;8:157.

231. Yamazaki H, Ogita M, Himei K, et al. Hypofractionated stereotactic radiotherapy using CyberKnife as a boost treatment for head and neck cancer, a multi-institutional survey: impact of planning target volume. Anticancer Res. 2014;34:5755–9.

232. Al-Mamgani A, van Rooij P, Tans L, et al. A prospective evaluation of patient-reported quality-of-life after (chemo)radiation for oropharyngeal cancer: which patients are at risk of significant quality-of-life deterioration? Radiother Oncol. 2013;106:359-63.

233. Baker S, Verduijn G, Petit S, et al. Locoregional failures and their relation to radiation fields following stereotactic body radiotherapy boost for oropharyngeal squamous cell carcinoma. Head Neck. 2019;41:1622-31.

234. Fowler JF. Correction to Kasibhatla et al. How much radiation is the chemotherapy worth in advanced head and neck cancer? (Int j radiat oncol biol phys 2007;68:1491-1495). Int J. Int J Radiat Oncol Biol Phys. 2008;71:326–329.

235. Dronkers EAC, Koljenovic S, Verduijn GM, et al. Nodal response after 46 Gy of intensity-modulated radiotherapy is associated with human papillomavirus-related oropharyngeal carcinoma. Laryngoscope. 2018;128:2333–2340

236. Tsai CJ, Hofstede TM, Sturgis EM, et al. ORN and radiation dose to the mandible in patients with oropharyngeal cancer. Int J Radiat Oncol Biol Phys. 2013;85:415-20.

237. Ward MC, Ross RB, Koyfman SA, et al. Modern Image-Guided Intensity-Modulated Radiotherapy for Oropharynx Cancer and Severe Late Toxic Effects: Implications for Clinical Trial Design. JAMA Otolaryngol Head Neck Surg. 2016;142:1164-70.

238. Nguyen-Tan PF, Zhang Q, Ang KK, et al. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. J Clin Oncol. 2014;32:3858-66.

239. Eisbruch A, Harris J, Garden AS, et al. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). Int J Radiat Oncol Biol Phys. 2010;76:1333-8.

240. de Almeida JR, Byrd JK, Wu R, et al. A systematic review of transoral robotic surgery and radiotherapy for early oropharynx cancer: a systematic review. Laryngoscope. 2014;124:2096-102.

241. Garden AS, Asper JA, Morrison WH, et al. Is concurrent chemoradiation the treatment of choice for all patients with Stage III or IV head and neck carcinoma? Cancer. 2004;100:1171-8.

242. Melchers LJ, Mastik MF, Samaniego Cameron B, et al. Detection of HPV-associated oropharyngeal tumours in a 16-year cohort: more than meets the eye. Br J Cancer 2015;112:1349-57.

243. Henneman R, Van Monsjou HS, Verhagen CV, et al. Incidence Changes of Human Papillomavirus in Oropharyngeal Squamous Cell Carcinoma and Effects on Survival in the Netherlands Cancer Institute, 1980-2009. Anticancer Res 2015;35:4015-22.

244. Thomas K, Martin T, Gao A, et al. Interruptions of Head and Neck Radiotherapy Across Insured and Indigent Patient Populations. J Oncol Pract. 2017;13:e319-28.

245. Russo G, Haddad R, Posner M, et al. Radiation treatment breaks and ulcerative mucositis in head and neck cancer. Oncologist. 2008;13:886-98.

246. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010;363:24-35.

247. Selek U, Garden AS, Morrison WH, et al. Radiation therapy for early-stage carcinoma of the oropharynx. Int J Radiat Oncol Biol Phys. 2004;59:743-51.

248. Nabil S, Samman N. Risk factors for ORN after head and neck radiation: a systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113:54-69

249. Setton J, Lee NY, Riaz N, et al. A multi-institution pooled analysis of gastrostomy tube dependence in patients with oropharyngeal cancer treated with definitive intensity-modulated radiotherapy. Cancer. 2015;121:294–301.

250. Silverstein P. Smoking and wound healing. Am J Med. 1992;93:22S-24S.

251. Chen AM, Chen LM, Vaughan A, et al. Tobacco smoking during radiation therapy for head-and-neck cancer is associated with unfavorable outcome. Int J Radiat Oncol Biol Phys. 2011;79:414-9.

252. Koga DH, Salvajoli JV, Alves FA. Dental extractions and radiotherapy in head and neck oncology: review of the literature. Oral Dis. 2008;14:40-4.

253. Raktoe SA, Dehnad H, Raaijmakers CP, et al. Origin of tumor recurrence after intensity modulated radiation therapy for oropharyngeal squamous cell carcinoma. Int J Radiat Oncol Biol Phys 2013;85:136-141.

254. Due AK, Vogelius IR, Aznar MC, et al. Recurrences after intensity modulated radiotherapy for head and neck squamous cell carcinoma more likely to originate from regions with high baseline [18F]-FDG uptake. Radiother Oncol 2014;111:360-365.

255. Studer G, Luetolf UM, Glanzmann C. Locoregional failure analysis in head-and-neck cancer patients treated with IMRT. Strahlenther Onkol 2007;183:417–23; discussion 424-425.

256. Kovács G, Martinez-Monge R, Budrukkar A, et al. GEC-ESTRO ACROP recommendations for head & neck brachytherapy in squamous cell carcinomas: 1st update - Improvement by cross sectional imaging based treatment planning and stepping source technology. Radiother Oncol 2017;122:248-254.

257. Schoenfeld GO, Amdur RJ, Morris CG, et al. Patterns of failure and toxicity after intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2008;71:377-385.

258. Chao KS, Ozyigit G, Tran BN, et al. Patterns of failure in patients receiving definitive and postoperative IMRT for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2003;55:312-321.

259. Rasch C, Steenbakkers R, van Herk M. Target definition in prostate, head, and neck. Semin Radiat Oncol 2005;15:136-145.

260. Leeman JE, Romesser PB, Zhou Y, et al. Proton therapy for head and neck cancer: expanding the therapeutic window. Lancet Oncol 2017;18:e254-265.

261. Grégoire V, Ang K, Budach W, et al. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. Radiother Oncol 2014;110:172-181.

262. Mak AC, Morrison WH, Garden AS, et al. Base-of-tongue carcinoma: treatment results using concomitant boost radiotherapy. Int J Radiat Oncol Biol Phys 1995;33:289-296.

263. Bourhis J, Overgaard J, Audry H, et al. Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) Collaborative Group. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006;368:843-854.

264. Hartley A, Sanghera P, Glaholm J, et al. Radiobiological modelling of the therapeutic ratio for the addition of synchronous chemotherapy to radiotherapy in locally advanced squamous cell carcinoma of the head and neck. Clin Oncol (R Coll Radiol) 2010;22:125-130.

265. Grégoire V, Evans M, Le QT, et al. Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines. Radiother Oncol 2018;126:3-24.

266. Fleury B, Thariat J, Barnoud R, et al. Microscopic extensions of head and neck squamous cell carcinomas: impact for clinical target volume definition. Cancer Radiother 2014;18:666-6671.

267. Due AK, Vogelius IR, Aznar MC, et al. Methods for estimating the site of origin of locoregional recurrence in head and neck squamous cell carcinoma. Strahlenther Onkol 2012;188:671-676.

268. Agarwal JP, Mallick I, Bhutani R, et al. Prognostic factors in oropharyngeal cancer--analysis of 627 cases receiving definitive radiotherapy. Acta Oncol 2009;48:1026-1033.

269. Jeremić B, Milicić B. Pretreatment prognostic factors of local recurrence-free survival in locally advanced squamous cell carcinoma of the head and neck treated with radiation therapy with or without concurrent chemotherapy. Am J Clin Oncol 2008;31:213-218.

270. Cooper JS, Farnan NC, Asbell SO, et al. Recursive partitioning analysis of 2105 patients treated in Radiation Therapy Oncology Group studies of head and neck cancer. Cancer 1996;77:1905-1911.

271. Pedruzzi PA, Kowalski LP, Nishimoto IN, et al. Analysis of prognostic factors in patients with oropharyngeal squamous cell carcinoma treated with radiotherapy alone or in combination with systemic chemotherapy. Arch Otolaryngol Head Neck Surg 2008;134:1196-1204.

272. Hoff CM. Importance of hemoglobin concentration and its modification for the outcome of head and neck cancer patients treated with radiotherapy. Acta Oncol 2012;51:419-432.

273. Molling JW, Langius JA, Langendijk JA, et al. Low levels of circulating invariant natural killer T cells predict poor clinical outcome in patients with head and neck squamous cell carcinoma. J Clin Oncol 2007;25:862-868.

274. Sinha P, Thorstad WT, Nussenbaum B, et al. Distant metastasis in p16-positive oropharyngeal squamous cell carcinoma: a critical analysis of patterns and outcomes. Oral Oncol 2014;50:45-51.

275. Lydiatt WM, Patel SG, O'Sullivan B, et al. Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:122-137.

276. Takeda A, Enomoto T, Sanuki N, et al. Reassessment of declines in pulmonary function 1 year after stereotactic body radiotherapy. Chest. 2013;143:130–137.

277. Guerard EJ, Deal AM, Chang Y, et al. Frailty Index Developed From a Cancer-Specific Geriatric Assessment and the Association With Mortality Among Older Adults With Cancer. J Natl Compr Canc Netw. 2017 Jul;15:894-902.

278. Presley C, Lilenbaum R. The Treatment of Advanced Lung Cancer in the Elderly: The Role of a Comprehensive Geriatric Assessment and Doublet Chemotherapy. Cancer J. 2015;21:392–7.

279. Laird BJ, Kaasa S, McMillan DC, et al. Prognostic factors in patients with advanced cancer: a comparison of clinicopathological factors and the development of an inflammation-based prognostic system. Clin Cancer Res. 2013;19:5456-5464.

280. Cassidy RJ, Zhang X, Patel PR, et al. Next-generation sequencing and clinical outcomes of patients with lung adenocarcinoma treated with stereotactic body radiotherapy. Cancer. 2017;123:3681-90.

281. Zhao H, Chen KZ, Hui BG, et al. Role of circulating tumor DNA in the management of early-stage lung cancer. Thorac Cancer. 2018;9:509-515.

282. Lafata KJ, Hong JC, Geng R, et al. Association of pre-treatment radiomic features with lung cancer recurrence following stereotactic body radiation therapy. Phys Med Biol. 2019;64:025007.

283. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395-409.

284. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med. 2020;382:503-513.

285. Mitera G, Swaminath A, Rudoler D, et al. Cost-effectiveness analysis comparing conventional versus stereotactic body radiotherapy for surgically ineligible stage I non-small-cell lung cancer. J Oncol Pract. 2014;10:e130-6.

286. Scholten ET, de Jong PA, de Hoop B, et al. Towards a close computed tomography monitoring approach for screen detected subsolid pulmonary nodules? Eur Respir J. 2015;45:765–773.

287. McCarter K, Martínez Ú, Britton B, et al. Smoking cessation care among patients with head and neck cancer: a systematic review. BMJ Open. 2016;6:e012296.

288. Malik N, Kim M, Chen H et al. Stereotactic Radiotherapy for de novo Head & Neck Cancers: A Systematic Review and Meta-analysis. Advanced in Radiation Oncology 2020;6:100628.

289. O'Sullivan B, Huang SH, Su J, et al. Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study. Lancet Oncol. 2016;17:440-451.

290. Gillison ML, Chaturvedi AK, Anderson WF, et al: Epidemiology of human papillomavirus-positive head and neck squamous cell carcinoma. J Clin Oncol 2015;33:3235-3242.

291. Mirghani H, Blanchard P. Treatment de-escalation for HPV-driven oropharyngeal cancer: Where do we stand? Clin Transl Radiat Oncol. 2017;8:4-11.

292. Studer G, Luetolf UM, Glanzmann C. Locoregional failure analysis in head and-neck cancer patients treated with IMRT. Strahlenther Onkol. 2007;183:417-423. discussion 424-425.

293. Wang K, Heron, DE, Flickinger JC, et al. A retrospective, deformable registration analysis of the impact of PET-CT planning on patterns of failure in stereotactic body radiation therapy for recurrent head and neck cancer. Head Neck Oncol. 2012;4:12.

294. Hanvey S, McJury M, Tho LM, et al. The influence of MRI scan position on patients with oropharyngeal cancer undergoing radical radiotherapy. Radiat Oncol. 2013;8:129.

295. Thiagarajan A, Caria N, Schöder H, et al. Target volume delineation in oropharyngeal cancer: impact of PET, MRI, and physical examination. Int J Radiat Oncol Biol Phys. 2012;83:220-227.

296. Bird D, Scarsbrook AF, Sykes J, et al. Multimodality imaging with CT, MR and FDG-PET for radiotherapy target volume delineation in oropharyngeal squamous cell carcinoma. BMC Cancer. 2015;15:844.

297. Persson GF, Nygaard DE, Hollensen C, et al. Interobserver delineation variation in lung tumour stereotactic body radiotherapy. Br J Radiol. 2012;85:e654-60.

298. Steiner E, Shieh CC, Caillet V, et al. Both four-dimensional computed tomography and four-dimensional cone beam computed tomography under-predict lung target motion during radiotherapy. Radiother Oncol. 2019;135:65-73.

299. Chan MK, Kwong DL, Tam E, et al. Quantifying variability of intrafractional target motion in stereotactic body radiotherapy for lung cancers. J Appl Clin Med Phys. 2013;14:140-52.

300. Menten MJ, Wetscherek A, Fast MF. MRI-guided lung SBRT: Present and future developments. Phys Med. 2017;44:139-149.

301. Videtic GM, Paulus R, Singh AK, et al. Long-term Follow-up on NRG Oncology RTOG 0915 (NCCTG N0927): A Randomized Phase 2 Study Comparing 2 Stereotactic Body Radiation Therapy Schedules for Medically Inoperable Patients With Stage I Peripheral Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2019;103:1077-1084.

302. Schimansky S, Lang S, Beynon R, et al. Association between comorbidity and survival in head and neck cancer: Results from Head and Neck 5000. Head Neck. 2019;41:1053-1062.

303. Opitz I, Rocco G, Brunelli A, et al. Surgery versus SABR for resectable non-small-cell lung cancer. Lancet Oncol. 2015;16:e372-3.

304. Vansteenkiste J, Wauters E, Reymen B, et al. Current status of immune checkpoint inhibition in early-stage NSCLC. Ann Oncol. 2019;30:1244-1253.

305. Gomez DR, Tang C, Zhang J, et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. J Clin Oncol. 2019;37:1558-1565.

306. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. JAMA Oncol. 2018;4:e173501.

307. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet. 2019;393:2051-2058.

Summary

The aim of this thesis was to establish prognostic factors in lung and oropharynx SBRT, which can be used to optimize treatment and patient selection.

An overview of SBRT for early stage lung cancer is provided in **Chapter 2**. Key themes are discussed including strategies to reduce rates of locoregional and distant failure, the potential role for advanced technologies such as MRI-guidance and proton beam therapy, and ongoing studies evaluating SBRT for operable patients.

In **Chapter 3**, tumor size and comorbidity, as measured with the Cumulative Illness Rating Scale (CIRS), were found to be prognostic for early mortality (death within 6 months of SBRT) in a large population of non-small cell lung cancer patients with peripheral tumors treated with SBRT. Chapter 3 also examines the question of optimal comorbidity index in this setting. The Charlson Comorbidity Index (CCI) is currently the most frequently used metric for comorbidity in lung cancer patients. CIRS however, and not CCI, was predictive for early mortality. This is important information for clinicians and researchers, and provides a stepping stone towards more accurate short-term prognostication.

Chapter 4 further builds upon prognostication in the early stage lung cancer population. A nomogram is provided, based on six prognostic factors: age, sex, Karnofsky Performance Status, tumor diameter, operability, and Charlson Comorbidity Index (which was found to be more predictive of longer-term survival than CIRS). The nomogram was externally validated in a separate cohort of lung cancer patients treated with SBRT. This prognostication tool can be used to generate survival predictions for a given patient at specific time points. It improves upon currently available prognostication tools for this patient population [2], with predictive ability (C-index) of 0.64.

In Chapter 5, the endovascular technique of fiducial marker placement for lung SBRT was found to have very low rates of clinically relevant complications. The standard method of percutaneous transthoracic marker placement was associated with a high rate of pneumothorax (10 of the 30 patients receiving transthoracic fiducial markers). Conversely, moderate to severe complications were minimal among 416 patients receiving 1,335 endovascular fiducial coils (one patient developed grade 2 hemoptysis requiring procedure discontinuation and one patient developed grade 3 cardiac arrhythmia). This study confirms the safety and high procedural success rate in a large patient population.

Chapter 6 provides long-term outcomes and prognostic factors following SBRT boost for oropharynx cancer. Rates of 5-year disease-specific survival and overall survival were 85% and 67%, respectively, similar to those following conventional chemoradiotherapy. The regimen was well tolerated. All patients completed treatment and only two required short treatment breaks, compared to the typically 10-20% requiring treatment breaks with conventional 70 Gy regimens. Rates of severe late toxicity, however, were high. Among 195 patients, 16% developed mucosal ulcers/soft tissue necrosis and 9% developed osteoradionecrosis. The cumulative incidence of severe late toxicity in current smokers was 41%, compared to 14% in nonsmokers. The Charlson Comorbidity Index score was a significant predictor of severe late toxicity. Patients with HPV-related disease experienced less grade ≥3 toxicity (5 year 15%). Tooth extraction prior to RT was strongly associated with osteoradionecrosis, despite a median interval of 18 days before the start of treatment.

Chapter 7 examined rates of in-field, marginal and out-of-field locoregional recurrence following SBRT boost for oropharynx cancer. Overall and in-field tumor control were excellent with 5-year local and regional control rates of 90% and 93%, respectively, likely due to the biologically effective dose intensification accomplished with the accelerated schedule (treatment completed in 5 weeks rather than the 7 weeks with conventional RT). However, among local recurrences, 24% were out-of-field, significantly higher than 0%-5% in the literature for conventional regimens [7-9].

In **Chapter 8**, key results of the studies of this thesis are summarised and limitations are explored. Ongoing developments in the field and areas for future research are discussed.

Samenvatting

Het doel van dit proefschrift was om prognostische factoren voor een succesvolle behandeling in long- en orofarynx SBRT vast te stellen, die kunnen worden gebruikt om de behandeling en patiëntenselectie te optimaliseren.

Een overzicht van SBRT voor longkanker in een vroeg stadium is opgenomen in **hoofdstuk 2**. Belangrijke thema's worden besproken, waaronder strategieën om het aantal locoregionale recidieven en afstandsmetastases te verminderen, de potentiële rol voor geavanceerde technologieën zoals MRI-begeleiding en protonenentherapie, en lopende studies die SBRT evalueren voor opereerbare patiënten.

In **hoofdstuk 3** bleken tumorgrootte en comorbiditeit, gemeten met de Cumulative Illness Rating Scale (CIRS), prognostisch te zijn voor vroege mortaliteit (sterfte binnen 6 maanden na SBRT) bij een grote populatie niet-kleincellige longkankerpatiënten met perifere tumoren die met SBRT werden behandeld. Hoofdstuk 3 behandelt ook de kwestie van de optimale comorbiditeitsindex in deze setting. De Charlson Comorbidity Index (CCI) is momenteel de meest gebruikte maat voor comorbiditeit bij longkankerpatiënten. CIRS, en niet CCI, was echter het sterkst voorspellend voor vroege mortaliteit. Dit is belangrijke informatie voor clinici en onderzoekers en biedt een opstap naar een nauwkeurigere kortetermijnprognose.

Hoofdstuk 4 bouwt verder op de prognose in de populatie van longkanker in een vroeg stadium. Er wordt een nomogram voorgesteld, gebaseerd op zes prognostische factoren: leeftijd, geslacht, Karnofsky Performance Status, tumordiameter, operabelbaarheid en Charlson Comorbidity Index (die meer voorspellend bleek te zijn voor overleving op langere termijn dan CIRS). Het nomogram werd extern gevalideerd in een onafhankelijk cohort van longkankerpatiënten die met SBRT werden behandeld. Deze prognosetool kan worden gebruikt om overlevingsvoorspellingen voor een

bepaalde patiënt op specifieke tijdstippen te genereren. Het verbetert de momenteel beschikbare prognosetools voor deze patiëntenpopulatie [2], met een voorspellend vermogen (C-index) van 0,64.

In **hoofdstuk 5** bleek de endovasculaire techniek van fiducial markerplaatsing voor long SBRT een zeer laag percentage klinisch relevante complicaties te hebben. De standaardmethode voor de plaatsing van percutane transthoraïsche markers werd geassocieerd met een hoog percentage waarbij pneumothorax optrad (10 van de 30 patiënten die transthoraracische fiduciale markers kregen). Omgekeerd waren matige tot ernstige complicaties minimaal bij 416 patiënten die 1.335 endovasculaire fiduciale spoelen kregen (één patiënt ontwikkelde graad 2 hemoptysis die stopzetting van de procedure vereiste en één patiënt ontwikkelde graad 3 hartritmestoornissen). Deze studie bevestigt de veiligheid en het hoge procedurele slagingspercentage in een grote patiëntenpopulatie.

Hoofdstuk 6 biedt langetermijnresultaten en prognostische factoren na een SBRT-boost voor orofarynxkanker. De percentages van 5-jaars ziektespecifieke overleving en totale overleving waren respectievelijk 85% en 67%, vergelijkbaar met die na conventionele chemoradiotherapie. Het regime werd goed verdragen. Alle patiënten voltooiden de behandeling en slechts twee vereisten korte behandelingspauzes, vergeleken met de meestal 10-20% die behandelingspauzes nodig hadden met conventionele 70 Gy-regimes. De percentages van ernstige late toxiciteit graad ≥3 waren echter relatief hoog. Van de 195 patiënten ontwikkelde 16% mucosale ulcera/weke delen necrose en 9% osteoradionecrose. De cumulatieve incidentie van ernstige late toxiciteit bij huidige rokers was 41%, vergeleken met 14% bij niet-rokers. De Charlson Comorbidity Index score was een belangrijke voorspeller van ernstige late toxiciteit. Patiënten met HPV-gerelateerde ziekte ondervonden minder graad ≥3 toxiciteit (5 jaar 15%). Tandextractie voorafgaand aan RT werd sterk geassocieerd met osteoradionecrose, ondanks een mediaan interval van 18 dagen voor het begin van de behandeling.

Hoofdstuk 7 onderzocht de percentages locoregionale recidieven in het radiotherapieveld, marginaal en buiten het veld na SBRT-boost voor orofarynxkanker. Over het algemeen was de in-field tumorcontrole uitstekend met 5-jaars lokale en regionale controlepercentages van respectievelijk 90% en 93%, waarschijnlijk als gevolg van de biologisch effectieve dosisintensivering die werd bereikt met het versnelde schema (behandeling voltooid in 5 weken in plaats van de 7 weken met conventionele RT). Onder lokale recidieven was echter 24% buiten het veld, wat significant hoger is dan de 0%-5% out-of-field recidieven beschreven in de literatuur voor conventionele regimes [7-9].

In **hoofdstuk 8** worden de belangrijkste resultaten van de studies van dit proefschrift samengevat en worden beperkingen onderzocht. Lopende ontwikkelingen in het veld en gebieden voor toekomstig onderzoek worden besproken.

List of Publications

1. **Baker S**, Bakunina K, Duijm M, Hoogeman M, Cornelissen R, Antonisse I, Praag J, Heemsbergen W, Nuyttens JJ. Development and external validation of a nomogram to predict overall survival following stereotactic body radiotherapy for early-stage lung cancer. Radiation Oncology. 2020;15:89.

2. Murray S, Chung J, Zhang H, **Baker S**, Jha N, Scrimger R, Debenham B, Biron V, Harris J, O'Connell D, Seikaly H. Functional outcomes of the modified submandibular gland transfer procedure. Laryngoscope. 2020;130:925-929.

3. **Baker S**, Logie N, Duimering A, Paulson K, Murtha A. Radiotherapy for brain tumors: current practice and future directions. Current Cancer Therapy Reviews. 2020;16:182-95.

4. Sharma A, **Baker S**, Duijm M, Oomen-de Hoop E, Cornelissen R, Verhoef C, Hoogeman M, Nuyttens JJ. Prognostic factors for local control and survival for inoperable pulmonary colorectal oligometastases treated with stereotactic body radiotherapy. Radiotherapy and Oncology. 2019;144:23-29.

5. **Baker S**, Sharma A, Antonissea I, Cornelissen R, Moelker A, Nuyttens JJ. Endovascular coils as lung tumor fiducial markers for real-time tumor tracking in stereotactic body radiotherapy: comparison of complication rates with transthoracic fiducial marker placement. Journal of Vascular and Interventional Radiology. 2019;30:1901-7.

6. **Baker S**, Verduijn G, Petit S, Sewnaik A, Mast H, Koljenovic S, Nuyttens JJ, Heemsbergen WD. Long-term outcomes following stereotactic body radiotherapy boost for oropharyngeal squamous cell carcinoma. Acta Oncologica. 2019;58:926-33.

7. **Baker S**, Sharma A, Peric R, Heemsbergen W, Nuyttens J. Prediction of early mortality following stereotactic body radiotherapy for peripheral early-stage lung cancer. Acta Oncologica. 2019;58:237-42.

8. **Baker S**, Verduijn G, Petit S, Nuyttens JJ, Sewnaik A, van der Lugt A, Heemsbergen WD. Locoregional failures and their relation to radiation fields following stereotactic body radiotherapy boost for oropharyngeal squamous cell carcinoma. Head Neck. 2019;41:1622-31.

9. Loi M, Duijm M**, Baker S**, Rossi L, Grunhagen D, Verhoef C, Nuyttens J. Stereotactic body radiotherapy for oligometastatic soft tissue sarcoma. Radiol Med. 2018;123:871-78.

10. Martell K, Fairchild A, LeGuirre B, Sinha R, **Baker S**, Liu H, Ghose A, Olivotto I, Kerba M. Rates of cannabis use in patients with cancer. Current Oncology. 2018; 25:219.

11. Chu KP, **Baker S**, Zenke J, Morad A, McEwan AJB, Williams DC, Capelle L, Severin D, Morrish D, Ghosh S, McMullen TPW. Low-Activity Radioactive Iodine Therapy for Thyroid Carcinomas Exhibiting Nodal Metastases and Extrathyroidal Extension May Lead to Early Disease Recurrence. Thyroid. 2018 28:902-12.

12. Ghosh S, **Baker S**, Castro DG, Kepka L, Kumar N, Sinaika V, Matiello J, Lomidze D, Dyttus-Cebulok K, Rosenblatt E, Fidarova E, Roa W. Improved cost-effectiveness of short-course radiotherapy in elderly and/or frail patients with glioblastoma. Radiotherapy and Oncology. 2018;27:114-20.

13. Yip E, Yun J, Gabos Z, **Baker S**, Yee D, Wachowicz K, Rathee S, Fallone BG. Evaluating performance of a user- trained MR lung tumor autocontouring algorithm in the context of intra- and interobserver uncertainties. Medical Physics. 2018;45:307.

14. **Baker S**, Dahele M, Lagerwaard F, Senan S. A critical review of recent developments in radiotherapy for non-small cell lung cancer. Radiation Oncology. 2016;11:115.

15. **Baker S**, Fairchild A. Palliative radiation in advanced cancer patients with symptomatic bone metastases. Expert Review of Quality of Life in Cancer Care. 2016;6:449.

16. **Baker S**, Fairchild, A. Radiation-induced esophagitis in lung cancer. Journal of Lung Cancer: Targets and Therapy 2016;7:119.

17. **Baker S**, Fairchild A. Lung and central airway malignancies. In: CA Johnstone, ST Lutz (Ed.s), Handbook of Palliative Radiation Therapy. DemosMedical, New York; 2016.

18. Roa W, Ghosh S, Zhu Q, **Baker S**. Reply to H. Kim et al and T. Finazzi. [Re: International Atomic Energy Agency randomized phase III study of radiation therapy in elderly and/or frail patients with newly diagnosed glioblastoma multiforme]. Journal of Clinical Oncology. 2016;34:2192.

19. **Baker S**, Tai P, Joseph K. Radiotherapy in Gorlin syndrome: can it be safe and effective in adult patients?Journal of Cutaneous Medicine and Surgery. 2016;20:159.

20. **Baker S**, Patel S. Clinical Exercise Interventions in Pediatric Oncology: Can they reduce Late Toxicities? Journal of Yoga and Physical Therapy. 2015; 5:200.

PhD Portofolio

Name PhD student: Sarah Baker
Erasmus MC Department: Radiation Oncology
Research School: Molecular Medicine
PhD period: 2016 - 2020
Promotor: prof. dr. M.S. Hoogeman
Copromotor: dr. J.J. Nuyttens, W.D. Heemsbergen

	Year	Workload (ECTS)
General courses		
Survival Analysis Course	2018	0.6
Research Integrity	2018	0.3
Bayesian Statistics and JASP	2017	0.3
SPSS Basic Introduction Course	2017	1.0
Specific courses		
Radiation Oncology Lung Cancer Preceptorship (Princess Margaret Hospital, Toronto, Canada)	2019	0.3
Cyberknife school	2017	1.0
Radiobiology course (University of Alberta and Cross Cancer Institute, Canada)	2016	1.3
Ottawa radiation oncology clinical review course (Ottawa, Canada)	2016	1.3
Seminars and Workshops		
Lung Cancer Radiation Oncology Quality Assurance Rounds (BC Cancer Surrey, British Columbia, Canada)	2018-2020	3.7
Lung Cancer Journal Club (BC Cancer Surrey, British Columbia, Canada)	2018-2020	1.4
Stereotactic Body Radiotherapy Rounds (BC Cancer Surrey, British Columbia, Canada)	2019-2020	1.9
Radiation oncology department rounds (Erasmus MC)	2017-2018	0.4
Radiation Oncology department journal club and rounds (University of Alberta and Cross Cancer Institute, Canada)	2017	1.0
SBRT day (Alberta, Canada)	2017	0.3
SBRT rounds (Cross Cancer Institute, Alberta, Canada)	2017	0.5
Clinical physics workshop (University of Alberta and Cross Cancer Institute, Canada)	2016	5.7

Presentations

Presentation at GI symposium (The 3rd Rijnmond Symposium Gastro Intestinal Tumors, Rotterdam)	2018	0.3
Research day presentation (Department of radiation oncology, EMC)	2018	0.3
Refereeravond presentation (Department of radiation oncology, EMC)	2018	0.3

International conferences

ASTRO (poster presentation x 1)	2016	3.6
ESTRO (oral presentation x 1 and poster x 3)	2016	1.0

National conferences

Canadian Lung Cancer Conference	2020	0.5
CARO (oral presentation x 1 and poster x 4)	2016	3.6

Teaching

Preceptor for residents and medical students in lung cancer clinic (BC Cancer Surrey, British Columbia, Canada)	2019 -2020	1.0

Curriculum Vitae

Sarah Baker was born on April 15th, 1983 in Kamloops, British Columbia, Canada. She completed a bachelor of science (biology honours) at the Univeristy of Victoria in 2005. She then completed medical school at the University of British Columbia (Victoria campus) in 2012. During her 3rd year of medical school, she developed an interest in radiation oncology after a clinical rotation at BC Cancer Victoria. She started her residency in radiation oncology at the University of Alberta in Edmonton, which she developed an interest in lung cancer treatment and stereotactic radiotherapy. She received her Fellowship of Royal College of Physicians and Surgeons of Canada in 2017. She then completed a research fellowship at Erasmus MC Cancer Institute in stereotactic radiotherapy, with a focus on lung and oropharynx malignanices, under the supervision of dr. Nuyttens. Since August 2018, she has been working as a radiation oncologist at BC Cancer Surrey in British Columbia, Canada, treating lung, GI and head and neck cancers.

Acknowledgements

This PhD thesis would not be possible without the help of many people.

I would first like to thank Prof. dr. Joost J Nuyttens, as my co-promoter and fellowship adviser. From the first time we met on a Skype interview for the SBRT fellowship position at Erasmus MC, you knew I wanted to work towards a PhD, and you helped facilitate that to eventually happen. During my time in Rotterdam, I enjoyed our weekly research meetings and your guidance and patience for my lung research projects. Your optimism, energy and patience helped with trouble-shooting challenges along the way and helped carry on the projects to eventual completion.

Dr. Wilma Heemsberger, it was such a pleasure working with you during my time in Rotterdam and collaborating on the oropharynx database and publications. I learned a great deal from you and valued your guidance in statistical analysis. Your friendly nature, coupled with your critical review and feedback for our papers, made you the perfect collaborator and co-promoter for this PhD thesis.

Prof. dr. Mischa S. Hoogeman, I am grateful to you for supporting me as my PhD promoter. Your insightful feedback on publications during my fellowship year, as well as for this thesis, were invaluable. Thank you for the time you devoted to this project as my promoter.

I would like to thank all the co-authors for the publications, and in particular, Katerina Bakunina. Katerina, your patience and expertise for the nomogram statistics were much appreciated. I enjoyed working with and learning from you.

I would also like to thank my family, and in particular, my husband Richard Knowlton. Richard, you embarked on this wild adventure with me to live in Rotterdam for a year with 7 month old twins. You gave up pursuing your own interests to support me and care for our young children. I can never thank you enough. The year may have had its ups and downs (our inability to read Dutch certainly wasn't ideal, as we found out half way through the year we'd been washing our clothes with fabric softener rather than detergent) but it sure was unforgettable! Mom, Dad and Michael, I am so grateful to have you as my supportive family. Finally, Elizabeth and Thomas - your (endless) energy always picks me up and you give me more joy than you could ever

imagine. You inspire me everyday and make me aspire to be a better physician, researcher, and person.