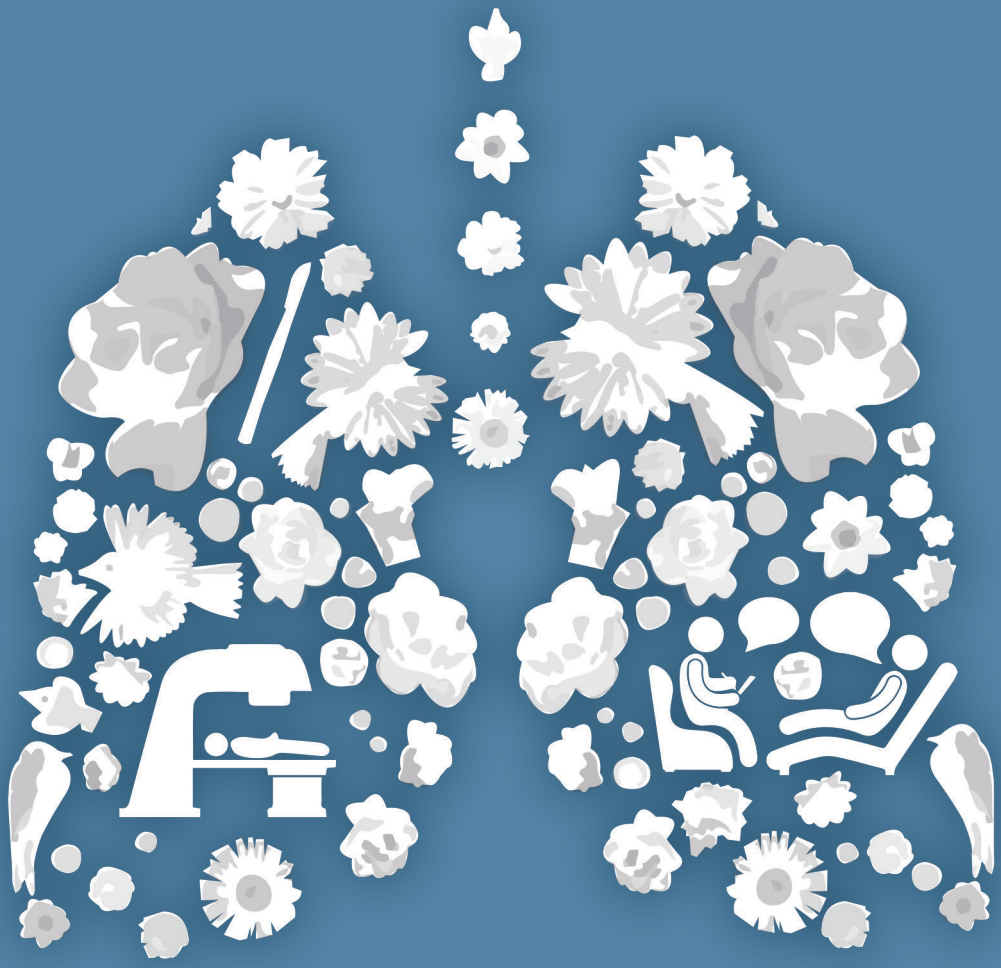
PROGNOSIS and TREATMENT DECISION MAKING

in early stage non-small cell lung cancer



SAHAR MOKHLES

PROGNOSIS AND TREATMENT DECISION MAKING IN EARLY STAGE NON-SMALL CELL LUNG CANCER

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PROGNOSE EN BESLUITVORMING BIJ VROEG STADIUM NIET-KLEINCELLIG LONGCARCINOOM

Thesis

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For my dearest mother

who taught me to walk and to read

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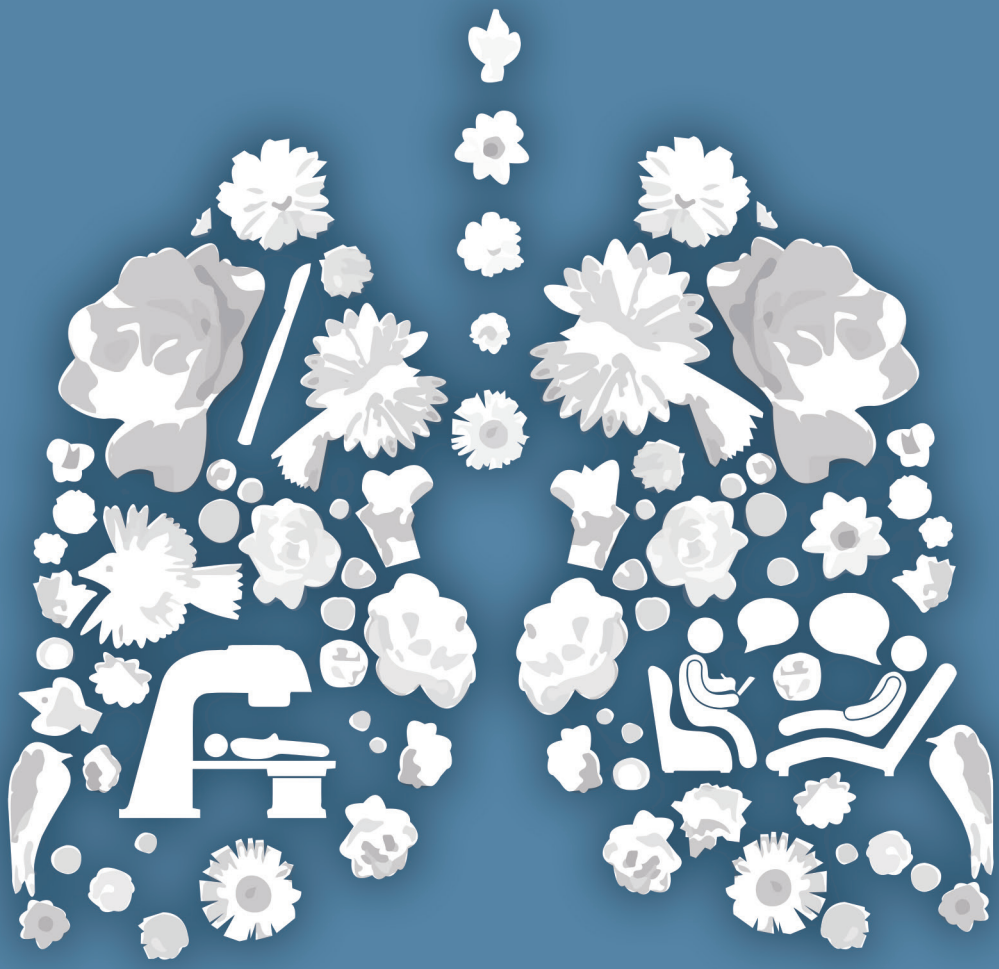

CHAPTER 1

General Introduction

LUNG CANCER

Lung cancer is one of the leading causes of death worldwide, and it is the largest contributor to new cancer diagnoses (12% of total new cancer cases) and to death from cancer (18% of total cancer deaths) (1-4). There are two major groups of lung cancer that arise from the cells of the respiratory epithelium: non-small cell lung cancer (NSCLC) and small-cell lung cancer, accounting for approximately 85% and 15% of lung cancer cases, respectively. NSCLC is further divided into three major pathologic subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, accounting for 39%, 20%, and 3%, respectively (2, 5). Squamous cell carcinoma generally develops from bronchial epithelial cells in the central airway, and it is strongly linked to smoking. Adenocarcinoma develop from basal bronchial cells and type II pneumocytes and arise in the more peripheral parts of the lung, and it is not linked to smoking which means that this type of non-small cell lung cancer can occur in patients who have never smoked. The incidence of squamous cell lung cancer is dropping, and adenocarcinoma has become the most prevalent type of NSCLC (5, 6). The distinction between different subtypes is of importance for the treatment and prognosis. The 5 year survival rate is 70-85% for localized NSCLC, and approximately 10% for metastasized NSCLC (7-9).

STAGING OF LUNG CANCER

Accurate staging of lung cancer is important to predict prognosis and assign an appropriate therapy. Currently, the clinical and pathological staging of lung cancer is based on the 7th revised Tumor, Node, and Metastases (TNM) criteria as proposed by the International Association for the Study of Lung Cancer (IASCL) (10). The staging is defined by the local extent of the primary tumor (T), involvement of associated lymph nodes (N), and whether metastases (M) exist. The revised classification of lung cancer resulted in improved prognostic stratification of the disease. Other factors that impact the prognosis, such as sex, age, comorbidities, molecular and genetic factors are not integrated into the current TNM classification. These factors will play an important role in the next TNM staging manual (11-13). The evaluation of a suspected lung cancer starts with a radiographic imaging which leads to clinical TNM stage. Following surgery a definitive TNM stage is made based on the pathological examination of lung cancer resection specimen. Despite the sophisticated techniques available for the clinical staging (e.g. FDG-PET/CT, EBUS, EUS and mediastinoscopy) (14, 15) the pathological TNM stage can differ from clinical TNM stage (16-19).

TREATMENT OPTIONS FOR EARLY STAGE NON-SMALL CELL LUNG CANCER

Although surgery is still the standard treatment for early stage lung cancer for operable patients, stereotactic body radiotherapy (SBRT) has emerged as an alternative treatment option, especially for patients in whom surgery is less desirable.

Anatomical surgical resection, in the form of lobectomy, remains the standard of care for early stage NSCLC. Depending on invasiveness of lung cancer (small, non-invasive or minimally invasive cancer) anatomical segmentectomy or wide wedge resection can also be considered (20, 21). Surgical treatment of lung cancer is important for the diagnosis, staging and curative treatment of lung cancer. First, through histological examination of resected tissue the pathological stage can be determined. Second, postoperative staging is more accurate than the clinical staging and it is the most important prognostic factor (22). Finally, the pathological stage is essential for the follow up after the surgical procedure because it provides the basis to offer adjuvant treatment, in the form of chemotherapy or radiotherapy, in upstaged patients to lower the risk of cancer recurrence (23).

Minimally invasive surgery has dramatically changed the surgical landscape by providing the same surgical result with lower risks related to the surgical procedure. At present, minimally invasive surgical procedures carried out by Video-Assisted Thoracoscopic Surgery (VATS) offer an effective alternative to conventional thoracotomy. Several studies have shown the notable benefits of the VATS procedure, in particular in older and frail patients. It has gained importance in recent years because it is less traumatic, it is associated with less postoperative pain, less postoperative morbidity, and shorter hospitalization (24, 25). In the literature, studies comparing open surgery with the VATS procedure have shown that the oncological outcomes are equivalent when a mediastinal lymph node dissection is performed (26-33).

Stereotactic radiotherapy delivers high dose radiation from many different positions around the body. Precise definition of cancer's anatomical extent is essential for accurate placement and shaping of the radiotherapy beams allowing the tumor to receive a high dose of radiation and the surrounding tissues a low dose of radiation. This technique is different from the conventional radiotherapy due to the fact that the doses between 50 and 60 Gray can be delivered in a limited number of fractions making the biological effective dose much greater (34). SBRT is the preferred choice for patients who are not candidates for surgery due to comorbidity. Good oncological outcome in these patients have resulted in an increased interest for the use of SBRT (35, 36). Several studies have been performed about the use of SBRT in potentially operable patients suggesting that SBRT may be as effective as surgery (37-45). Two randomized controlled trials comparing these treatment options in early stage NSCLC were unfortunately halted prematurely due to poor accrual (46). Chang and colleagues concluded that SBRT could be an option for treating operable

stage I NSCLC, suggesting that SBRT is not inferior to surgery. The ongoing debate about the results of SBRT versus surgery will remain until a randomized trial with larger patient population and longer follow-up will be carried out (47).

QUALITY OF LIFE

An important aim of cancer treatment is to maintain or improve patient's quality of life (QoL). Measuring the QoL is an important parameter in the treatment of lung cancer as this reflecting the balance of benefits and harms of lung cancer therapy. However, routine collection of QoL data evaluating the impact of SBRT or surgery is not common (48, 49). For the surgical population this could be explained by the fact that there is lack of validated surgical-specific questionnaires and there are no guidelines regarding the best time to evaluate QoL after surgery (49). There is limited data regarding QoL of patients treated with SBRT because the current experience has been primarily in elderly patients who are medically inoperable. Yet, recognizing factors influencing QoL related to lung cancer (e.g. fatigue, respiratory problems, pain and cough) and the treatment related complications offers the opportunity to evaluate the treatment strategy and reduce the symptoms by means of multidisciplinary approach (e.g. improving physical activity, offering pulmonary rehabilitation and psychological support) (49-52).

There are several instruments available for measuring the quality of life of lung cancer patients. The most frequently used instrument is Quality of Life Questionnaire (QLQ-C30) and Quality of Life Questionnaire with lung cancer-specific module (QLQ-LC13) developed by the European Organization for Research and Treatment of Cancer. The QLQ-C30 assesses 4 domains of QoL (functional and symptom scales, global quality of life and single items) using a 4-point Likert scale or visual analogue scales. The QLQ-LC13 contains 13 additional questions (48, 53). In addition, the Short-Form 36 (SF-36) is a generic questionnaire. The SF-36 assesses eight self-reported aspects of QoL (i.e. physical functioning, role physical functioning, role emotional functioning, mental health, vitality, social functioning, bodily pain, and general health). It also yields physical (PCS) and mental (MCS) health summary measures (54).

VALUE SENSITIVE NATURE OF THE DECISION

The preferred treatment of early stage lung cancer is not straightforward since each individual patient value the benefits and harms of treatment options in a different way. Both perioperative and postoperative complications such as longer in-hospital length of stay, risk of infection, bleeding and mortality have an impact on a patient's decision to undergo surgery. For example, identifying regional spread of lung cancer in a young patient will outweigh the fear of having an infection after surgery. The same applies to the complications after SBRT treatment (e.g. fatigue, radiation pneumonitis and inability to determine pathologic stage). No anticancer treatment is also an option if the complications are significant to the octogenarian patient with comorbidity (55). Given the value sensitive nature of the decision between surgery and SBRT or no treatment, effort should be made to involve the patient in treatment decision making so that they can make a choice consistent with their preferences.

SHARED DECISION MAKING

Shared decision making (SDM) is a process in which physician and patient work together in making a health decision after discussion the options, the benefits and harms, and considering the patients' values, preferences, and circumstances (56, 57). SDM is seen as the middle ground between informed choice, where the patient makes the decision based on information received from the physician, and traditional paternalistic decision making, where the physician makes the decision based on best available evidence (58, 59). Patient participation in decision making has been advocated for many reasons (60-62). Patients who are active participants in the process of their care, for example asking questions, expressing their opinions and preferences, have better health outcomes, more knowledge regarding the disease and they are less anxious than patients who do not participate in the decision making (57, 63-65). SDM supports the patient to understand the disease and weigh advantages and disadvantages of treatment options in their own context, which will result in an informed treatment decision with patients' needs and values incorporated. Although shared decision making has gained increased awareness among the healthcare community, it has not been widely incorporated into routine clinical practice in lung cancer care. This can be explained by the fact that there is lack of familiarity with SDM (66, 67) and also because the care of lung cancer patient can be complex due to multiple treatment types over an extended period of time and often includes a guideline-driven treatment (62). A decision for a particular treatment option is ideally driven by both scientific evidence and by patient values and preferences.

AIM

The aim of this thesis is to get an improved insight into determinants of outcome in patients with NSCLC stage I and II, and insight into current decision making from the perspective of both lung cancer patients and lung cancer physicians.

The following research questions are addressed:

- Which factors play an important role in long term clinical outcomes of patients with stage I or II NSCLC undergoing surgical treatment of SBRT (**Chapter 2-4**)
- What is the long term impact of stereotactic radiotherapy on the quality of life and what is the therapeutic value of radical mediastinal lymphadenectomy (**Chapter 5 and 6**)
- What is the role and experience of lung cancer patient in treatment decision making and what are the barriers and drivers to apply shared decision making in clinical practice (**Chapter 7-9**)
- How can we optimally combine the three questions addressed above (**Chapter 10**)

OUTLINE OF THIS THESIS

To date, there are no personalized risk prediction models to assess the risk of mortality or life expectancy for an individual lung cancer patient as it is difficult to determine each factor's predictive value when combined in individual patients. In **Chapter 2**, in a retrospective cohort study we aim to identify clinical baseline parameters for the prediction of long term survival in patients with stage I or II NSCLC undergoing surgical treatment or SBRT. The Cox proportional hazard model was used for multivariable analysis of mortality. In this chapter we used the logistic regression analysis to illustrate the extent to which the two treatment groups are comparable to each other, therefore, the results are described separately for each treatment group. Furthermore, **Chapter 3** aims to develop a prognostic model for 5 year overall survival of patients with early stage NSCLC treated with SBRT using recursive partitioning analysis and a nomogram.

In the absence of a randomized trial we performed in **Chapter 4** a propensity score matching analysis to create two similar groups in order to compare clinical outcomes of patients with clinical stage I NSCLC who underwent lobectomy, either by Video-Assisted Thoracoscopic Surgery (VATS) or by means of thoracotomy, or SBRT (68-70).

The presence of tumor metastases in lymph nodes is important for determining the optimal treatment strategy, and is one of the strongest predictor of cancer recurrence in patients with NSCLC (71). In **Chapter 5** a systematic review and meta-analysis addresses the question of whether clearing all the ipsilateral mediastinal lymph nodes at the time of surgery improves long term survival over a sampling strategy. It highlights the need for more and better trials of specific aspects of the surgery of lung cancer.

An essential goal of any cancer treatment is to maintain or improve the patients' quality of life as prolonging life cannot be viewed in isolation. Given the comorbidities of many patients with NSCLC and the limited overall survival, the quality of life is an essential component in the management of cancer. The impact of SBRT on patients' quality of life during the 5 years after the treatment will be illustrated in **Chapter 6**. In this chapter the quality of life was evaluated in patients with pathologically confirmed T1-2N0M0 NSCLC using the EORTC QLQ-C30 and QLQ-LC13. These questionnaires consist of functional scales, symptoms scales, quality of life scale, and several single items (assess additional symptoms commonly reported by cancer patients).

Chapter 7 is a letter to the editor underlining the importance of discussing the advantages and disadvantages of treatment modalities with the patient (e.g. early and late adverse events after treatment, and short-term and long-term survival outcomes), and the need of involving lung cancer patients in clinical decision making.

Patient participation in treatment decision making will be illustrated in **Chapter 8**. Patients with stage I or II NSCLC treated surgically or with SBRT were included in a prospective observational study. Using a questionnaire (with validated and non-validated parts) this chapter aim to assess among Dutch early stage NSCLC patients: (1) perceived patient knowledge of the advantages and disadvantages of treatment options, (2) experience with current clinical decision making, and (3) perceived understanding of information regarding their disease and the treatment.

Chapter 9 describes in a cross-sectional study the opinion of Dutch lung cancer physicians involved in early stage lung cancer treatment (e.g. cardio-thoracic surgeons, pulmonologists and radiation oncologists) concerning SDM. An electronic survey was conducted to assess their attitude toward patient involvement in treatment decision making, and barriers and drivers to apply SDM in clinical practice.

Chapter 10 concerns the amalgamation of 'Personalized Medicine' with 'Evidence Based Medicine' in clinical practice. The hierarchical approach of pyramid of evidence put highest value on the randomized trials and least value on surgeon opinion, however, in clinical practice a combination of the integration of the patients' values and expectations, the doctors' skills and expertise, and best available evidence is needed (72). In this chapter we illustrate that more complex methods are not always better or generalizable to all patients in clinical practice. Firstly, for each form of evidence we define the essential features and virtues. Secondly, we illustrate the method in clinical practice with examples. Finally, for each example we comment on effectiveness and its limitations in clinical practice.

The most important findings of this thesis, possible clinical implications, and future perspectives will be discussed in **Chapter 11**.

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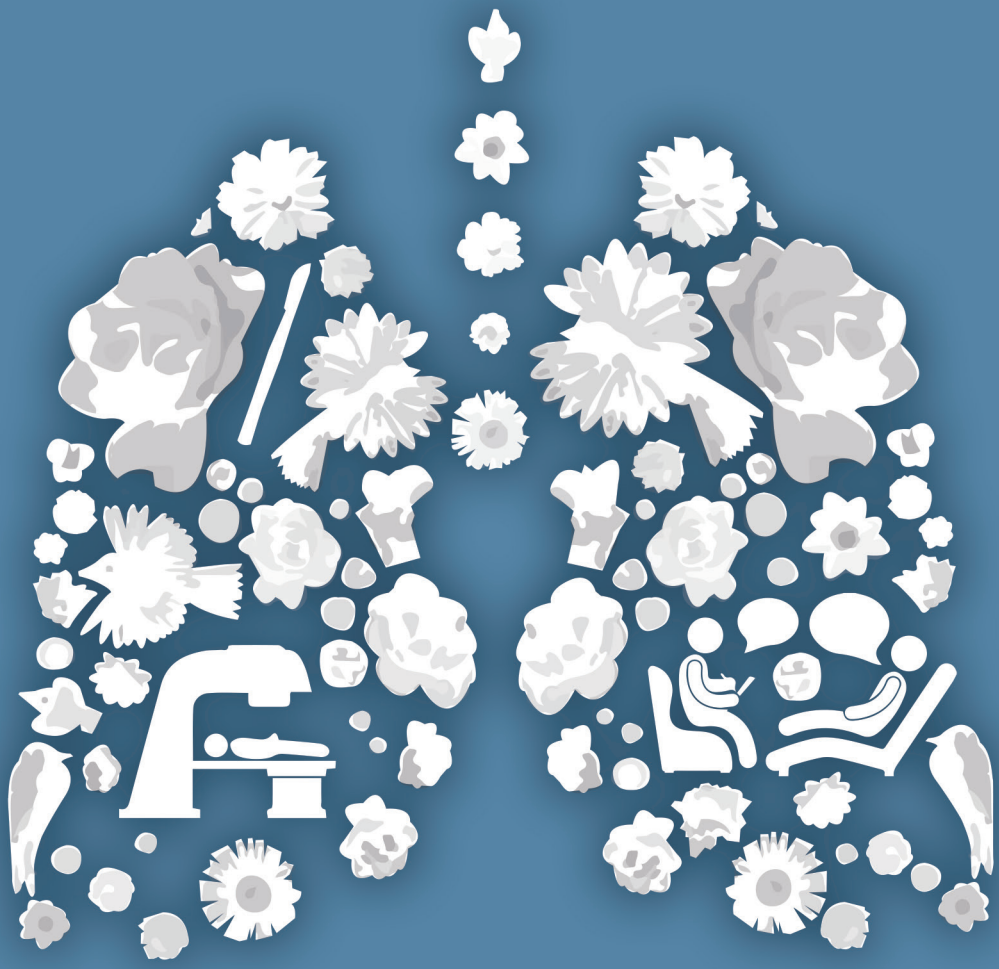

CHAPTER 2

Survival and treatment of non-small cell lung cancer stage I-II treated surgically or with stereotactic body radiotherapy :

patient and tumor-specific factors affect the prognosis

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ABSTRACT

Background. This study was designed to define clinical baseline parameters associated with impaired survival of patients with stage I or II non-small cell lung cancer (NSCLC) who underwent surgery or stereotactic body radiotherapy (SBRT).

Methods. From January 2001 to January 2011, 425 patients (216 surgery, 209 SBRT) were identified with clinical stage I or II NSCLC. Cox proportional hazards regression analyses were used to investigate risk factors for mortality.

Results. Median age of patients in the surgery and SBRT groups was 65 and 74 years, respectively. A smaller proportion of the surgical group had Charlson Comorbidity Index (CCI) score ≥1 compared with the SBRT group: 52 and 72% (*p-value*<0.001), respectively. Overall survival in the surgical group at 2 and 4 years was 79 and 65%, respectively. In the SBRT group, this was 65% at 2 years and 44% at 4 years. In the surgical group older age, CCI score 4 and clinical stage IIB were associated with long term mortality. In the SBRT group, this was CCI score≥5 and clinical stage>IA. The area under the curve was calculated for the model with clinical and tumor factors: 0.77 for the surgery and 0.85 for the SBRT group.

Conclusions. Both patient characteristics and survival of NSCLC I–II patients undergoing surgical treatment or SBRT differ considerably. Long-term survival as a result of treatment strategy of NSCLC patients might be optimized by focusing on patient and tumor specific factors. In addition to TNM staging, the consideration of patient age and CCI can be useful for prognostication of NSCLC patients.

INTRODUCTION

Lung cancer remains the most common cause of cancer-specific mortality worldwide, and more than 50% of lung cancer patients are older than 65 years at diagnosis (1-4). The rapid growth of the elderly population in the world is expected to lead to an increase in the total number of cases of lung cancer. Only a minority of lung cancer cases is detected in an early stage of disease (4-6).

The prognosis and life expectancy of non-small cell lung cancer (NSCLC) patients has nevertheless improved with the introduction of stereotactic body radiotherapy (SBRT), more precise staging, and offering (neo)adjuvant treatment to patients with advanced disease (5, 7, 8). Surgery remains the treatment of choice for fit patients with stage I and II NSCLC. SBRT is the favorable choice for patients who are not candidates for surgery due to medical comorbidities (9-11). The choice of surgical intervention or SBRT, however, has been found to depend on local practice (resection rates) (12), a variety of patient specific factors (e.g. age, comorbidity) (13, 14) and tumor characteristics (e.g. pathology, size). Uniform recommendations are therefore difficult to make. Recommendations are nevertheless necessary to optimize the course of treatment, to minimize practice variation, and to compare outcome data.

Surgical intervention has been previously compared to radiotherapy in relative cost-effectiveness (15), treatment outcomes for high-risk patients, or only patients with stage I NSCLC (16-18).

To date, there are no personalized risk prediction models to assess the risk of mortality for an individual lung cancer patient. With this study, we aim to make a first step toward this process. The objective of this retrospective cohort study was therefore to define clinical baseline parameters for the prediction of long-term survival in patients with stage I or II NSCLC who underwent surgery or SBRT.

METHODS

Study population

From January 2001 to January 2011, in EMC Rotterdam 425 consecutive patients (216 surgery, 209 SBRT) were identified with clinical stage I or II NSCLC, and subsequently treated surgically or with SBRT. Selection of patients with clinical stage I or II was based on the American Joint Committee in Cancer (AJCC) 7th edition staging manual (19). Clinical staging of patients treated surgically or with SBRT was done with CT-scan, 18FDG-PET imaging, or using minimally invasive endoscopic techniques when appropriate. All patients were discussed in a multidisciplinary team before treatment. Tumors classified according to the 6th edition of TNM classification were retrospectively reclassified into the TNM 7 staging classification. Exclusion criteria were: stage III-IV NSCLC, small-cell lung cancer, or

other cancers that had metastasized to the lung. Patients who received SBRT were treated with 20 fractions of 3 Gy (n=188), 15 fractions of 3 Gy (n=12), 5 fractions of 10 Gy (n=2), and 12 fractions of 5 Gy (n=7), as described previously (20).

Data collection

Data of patients, who were treated for NSCLC at our institution, were collected by reviewing the patients' medical records and the hospital information system. Comorbidity scores were recorded using the Charlson Comorbidity Index (CCI) and Cumulative Illness Score (CIS) (21, 22). Chronic obstructive pulmonary disease (COPD) was defined according to the GOLD criteria (23). In the surgery group, 93 patients (43%) had no COPD. In the SBRT group, 28 patients (14%) had no COPD, and in 19 patients (9%) this was unknown. The severity of the decrease in diffusing capacity for carbon monoxide (DLCO) was assessed from American Thoracic Society and European Respiratory Society standards (24). Local control and the presence of metastases were defined according to the guidelines of American College of Chest Physicians and Society of Thoracic Surgeons (25). The follow up period started on the day of treatment. The overall survival time was defined as the difference between the start of treatment and the date of death or the date of last follow up. Patients lost to follow up were censored at the last date of follow up. The Dutch civil registry was consulted to assess late mortality. Approval for this study was obtained from the Ethics Committee of the Erasmus MC (MEC 2013-116). Informed consent was waived.

Statistical analysis

Continuous data are presented as mean ± standard deviation, and comparison was done using the unpaired *t-test* unless the data were not normally distributed (Kolmogorov-Smirnov); in these instances we used the Mann-Whitney U test for comparison. Categorical data are presented as proportions, and comparison was done using the χ^2 test or the Fisher exact test where appropriate. After removal of patients with a synchronous lung tumor (surgery 5 patients, SBRT 7 patients), cumulative survival was determined using the Kaplan-Meier method (26). The log-rank test was used to compare survival between different groups. Logistic regression was used to estimate patient specific probability for being in each treatment group. All clinical baseline characteristics of the patients were included in this model. The probability of being in the surgery or SBRT group was plotted in a figure to illustrate comparability between the groups. The Cox proportional hazard model was used for univariable and multivariable analysis of mortality. Patient and tumor specific factors were included in a univariable model to identify predictors of long term mortality. Several characteristics were tested for correlation before entering them into the multivariable model. Correlation between variables was assessed with Pearson or Spearman correlation coefficient, whenever appropriate.

The clinically most important variable was chosen to be included in the multivariable model if there was a significant correlation (r^2>0.4). Risk factors for the multivariable model

were selected with the *Enter*-method (required significance of multivariable *p-value* ≤0.05 for retention in the model).

The multivariable Cox proportional hazard model with tumor factors was compared with the model consisting of both clinical baseline factors and tumor factors. Model discrimination (statistical accuracy) was tested with the receiver operating characteristic (ROC) curve (27). Model calibration (statistical precision) was determined with Hosmer-Lemeshow goodness-of-fit statistic (28). All tests were two-sided, with an α-level of 0.05. The statistical software package SPSS for Windows version 20 (SPSS Inc., Chicago, IL, USA) was used for data analysis. GraphPad Prism 5.00 for Windows (GraphPad software, San Diego, CA, USA) was used to obtain life tables and corresponding Kaplan-Meier survival curves.

Missing values

In this study, some variables have missing values (Table 1). We have used a multiple imputation technique to impute missing values to avoid them being depicted as "unknown" for incomplete observations. We have used fivefold multiple imputation using SPSS for Windows version20 (SPSS Inc.) (29).

RESULTS

Baseline characteristics of all 425 patients are listed in Table 1. The median follow-up time for the whole group was 2.6 (range 1-10) years.

Comparability between groups

The patient specific probability for being in each treatment group based on clinical characteristics logistic regression is plotted in Figure 1. The following variables were included in logistic regression model: age older than 70 years, gender, smoking, FEV1<80% of predicted value, CCI score, clinical stage, and DLCO category. Figure 1 illustrates that there is little overlap in the characteristics between the two treatment groups.

Survival and Kaplan-Meier statistics

The observed overall survival of patients with CCI, clinical stage, and overall survival at 2 and 4 years is described in Figure 2. The observed overall survival at 4 years of patients with stage IIB in the surgery group was 43% (95% confidence interval (CI) 21-64%). In the SBRT group, there were no patients alive after 1 year with stage IIB. For surgical patients with COPD GOLD I, survival at 4 years was 66% (95% CI 49-79%), for GOLD II it was 57% (95% CI 4-73%), and for GOLD III it was 44% (95% CI 14-72; *p-value* 0.325). For SBRT patients with COPD GOLD I, survival at 4 years was 49% (95% CI 30-66%), for GOLD II it was 45% (95% CI 30-58%), for GOLD III it was 50% (95% CI 31-66%), and for GOLD IV it was 34% (95% CI 9-61%; *p-value* 0.247).

Table 1. Patient characteristics

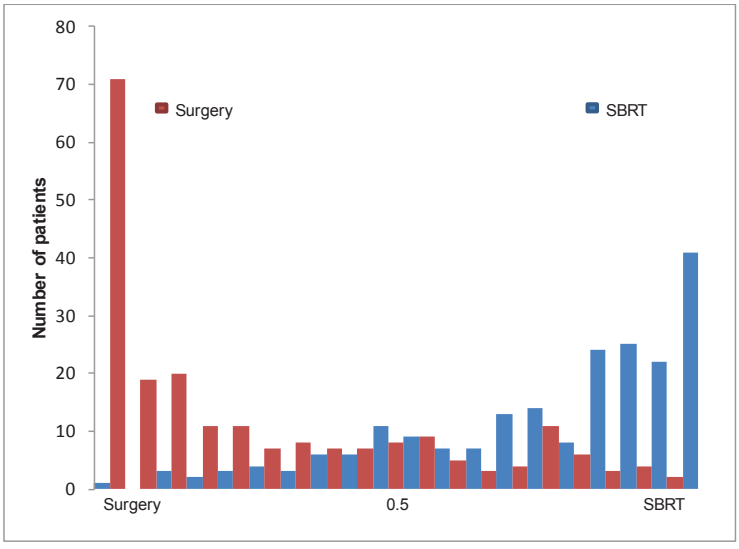
Characteristics	Surgery (*n*=216)	Radiotherapy (*n*=209)	*P-value*
Sex -Male (%) -Female (%)	 142 (66) 74 (34)	 136 (65) 73 (35)	0.919
Age, median (range)	65 (39-83)	74 (51-91)	<0.001
Median follow-up in years (range)	3.2 (0-11)	2.5 (0-6)	0.001
Smoking habits -Nonsmoker (%) -Current or former smoker (%) Unknown, n (%)	 24 (11) 192 (89) -	 31 (15) 133 (64) 45 (21)	0.039
FEV_1% mean±SD [a] Unknown, n (%)	84 (19) 2 (1)	62 (21) 32 (15)	<0.001
DLCO (%) mean±SD [b]	80 (20)	58 (26)	<0.001
DLCO (%) [b] -normal (>79 %) -mild reduction (60-79 %) -moderate reduction (40-60 %) -severe reduction (<40 %) Unknown, n (%)	 96 (44) 75 (35) 21 (10) 3 (1) 21 (10)	 31 (15) 52 (25) 56 (27) 32 (15) 38 (18)	<0.001
COPD (%) [c] - GOLD I - GOLD II - GOLD III - GOLD IV	 54 (25) 59 (27) 10 (5) -	 36 (17) 73 (35) 44 (21) 9 (4)	<0.001
Charlson comorbidity index (%) -≤1 -2-3 -4 -≥5	 103 (48) 80 (37) 15 (7) 18 (8)	 60 (28) 95 (46) 30 (14) 24 (12)	<0.001
Cumulative Illness Score (%) -0-4 -5-6 ->6	 201 (93) 8 (4) 7 (3)	 119 (57) 47 (22) 43 (21)	<0.001
Clinical stage (%) -IA -IB -IIA -IIB	 98 (45) 55 (26) 41 (19) 21 (10)	 111 (53) 72 (35) 23 (11) 3 (1)	0.001
Pathological stage (%) -IA -IB -IIA -IIB	 97 (45) 31 (14) 45 (21) 43 (20)	-	

Table 1. Patient characteristics (continued)

Characteristics	Surgery (*n*=216)	Radiotherapy (*n*=209)	*P-value*
Staging (%) -PET -CT	 158 (73) 181 (84)	 202 (97) 208 (100)	 <0.001 <0.001
Type of resection (%) -Wedge resection -Lobectomy -Bilobectomy -Pneumonectomy	 7 (3) 163 (76) 16 (7) 30 (14)		
Histology (%) -Squamous cell carcinoma -Adenocarcinoma -Large cell carcinoma -Bronchoalveolar cell carcinoma -No histology -Undifferentiated carcinoma	 78 (36) 87 (40) 42 (20) 9 (4) - -	 24 (11) 21 (10) 35 (17) - 125 (60) 4 (2)	<0.001
Clinical tumor diameter (mm), median (range) Unknown, n (%)	27.0 (4-136) 11 (5)	30.0 (10-100) -	0.079
Pathological tumor diameter (mm), median (range)	29 (5-190)	-	

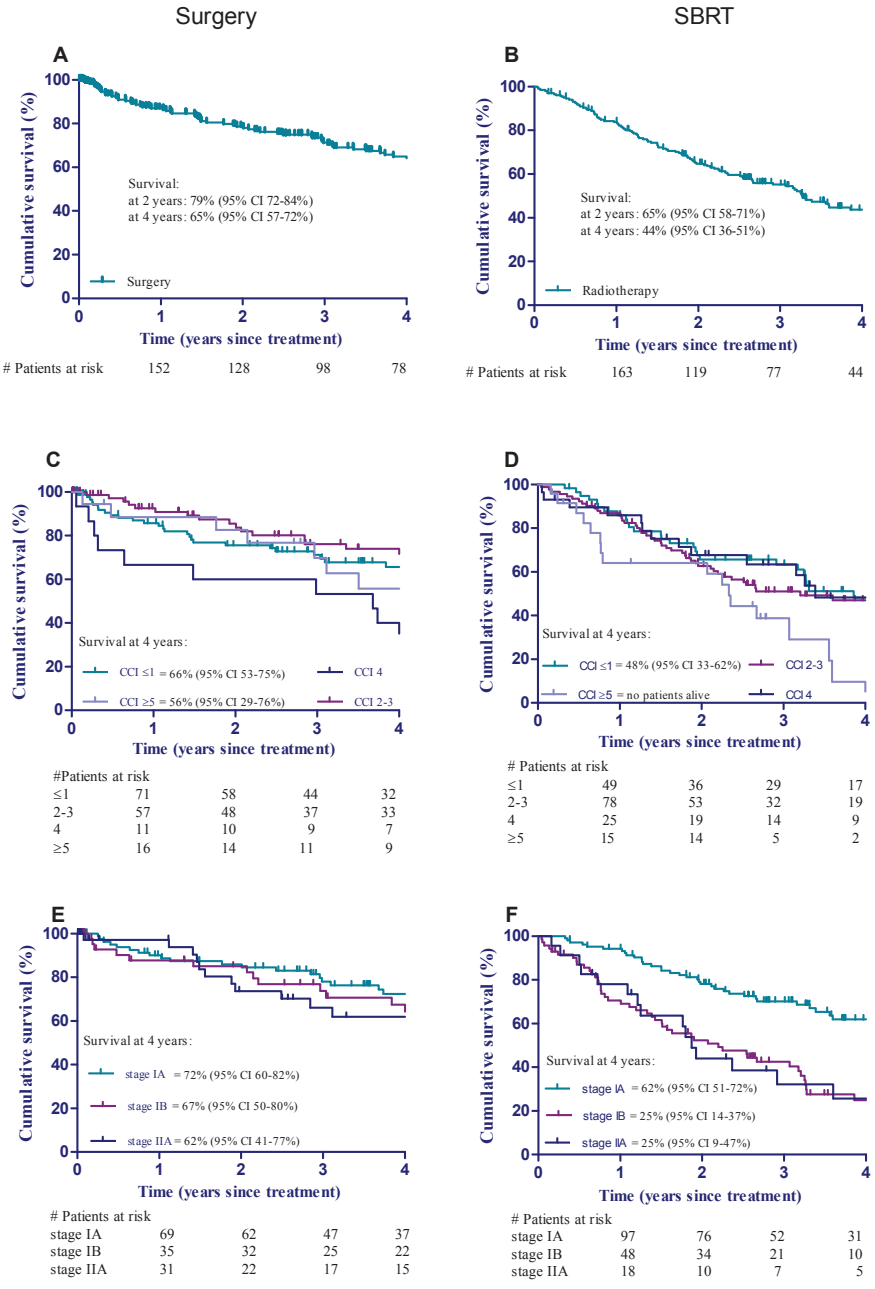
[a] FEV_1%: Forced expiratory volume in 1 s expressed as a percent of predicted. [b] Diffusion capacity of the lung for carbon monoxide. [c] COPD: chronic obstructive pulmonary disease.

Figure 1. Comparability between the groups



Representing the differences between the surgery and stereotactic body radiotherapy (SBRT) group.

Figure 2. Survival after Surgery or Stereotactic Body Radiotherapy



Kaplan-Meier figures. Survival after surgery or (SBRT); A,B) Kaplan Meier (KM) survival curve after treatment; C,D) KM survival curve stratified between different categories of Charlson Comorbidity Index (CCI); E,F) KM survival curve stratified between different stages; A,C,E represents patients undergoing surgery; B,D,F represents patients treated with SBRT.

Local control rates

Local control rates at 2 and 4 years in the surgery group were 88% (95% CI 82-92%) and 85% (95% CI 78-90%), respectively. In the SBRT group, local control rates at 2 and 4 years were 89% (95% CI 83-94%) and 83% (95% CI 73-89%), respectively.

Tumor upstaging and treatment due to surgery

Fifty-two patients (24%) were upstaged. Unsuspected N1 disease was detected in 22 patients (10%). Thirty patients were upstaged due to size of the tumor, with six patients (3%) upstaged from IA to IB, two patients (1%) from stage IA to IIA, five patients (2%) from stage IB to IIA, eight patients (4%) from stage IB to IIB, and nine patients (4%) from stage IIA to IIB. Seventeen upstaged patients received adjuvant treatment: nine patients (4%) received chemotherapy, six patients (3%) were treated with radiotherapy, and two patients (1%) were treated with radiotherapy and chemotherapy. Eleven patients (5%) did not received adjuvant treatment due to poor performance status or because they refused adjuvant treatment. Twenty-four patients (11%) did not receive adjuvant treatment, because there was no indication for further treatment.

Univariable and multivariable regression analysis

In the surgical group, univariable Cox regression analysis revealed that older patient age, CCI score 4, and clinical stage IIB were significantly associated with impaired survival. In the SBRT group, severe COPD, CCI≥5, clinical stage (IB, IIA, IIB), and larger tumor size were significantly associated with impaired survival. Correlations between factors were tested before entering them into the multivariable model. The following factors were positively correlated: FEV1 and COPD category, FEV1 and DLCO category, CCI and CIS, clinical tumor stage and clinical tumor diameter. After multidisciplinary agreement, the following factors were included into multivariable model: age>70 years, gender, smoking, FEV1<80%, CCI score, and clinical stage. We identified that age, CCI score 4, and clinical stage IIB were associated with long term mortality in patients undergoing surgery. In the SBRT group, we identified that CCI≥5 and clinical stage IA, stage IIA, and stage IIB were associated with long term mortality. Details of the univariable and multivariable Cox regression analysis can be found in Table 2.

Predictive value of model with clinical and tumor factors

Area under receiver operating characteristic curve (AUC) was calculated to illustrate the predictive value of the model with clinical and tumor factors versus the model with tumor factors. For the surgery group, the AUC for the model with tumor factors was 0.58 (95% CI 0.48-0.68), and for the model with clinical and tumor factors, the AUC was 0.77 (95% CI 0.7-0.84). For the SBRT group, the AUC for the model with tumor factors was 0.66 (95% CI 0.58-0.73), and for the model with clinical and tumor factors, the AUC was 0.85 (95% CI 0.79-0.9). Calibration of the model resulted in Hosmer-Lemeshow *p-value* of 0.65 for the model with clinical and tumor factors in both treatment groups.

DISCUSSION

Our study shows that the patients in the surgery group differ significantly from the patients in the SBRT group. Furthermore, we have shown that for NSCLC patients there are clinical baseline parameters that can help to determine survival of patients with stage I or II. Statistical accuracy (AUC) revealed that the model with clinical and tumor factors has more predictive value than the model with only tumor factors. Although numerous articles have been written on NSCLC patients treated with SBRT or surgery, to our knowledge little research has been done on the differences between the surgical and SBRT groups. It is important to appreciate that these two groups of patients differ and cannot always properly be compared. This is evidenced by the results presented in Figure. 1. In the present study, SBRT patients were older, had higher CCI score, and lower FEV1. Therefore, we have chosen in this study to describe survival and predictors of mortality separately for each treatment group. Survival rates and local control rates after 2 and 4 years are comparable with other studies (30, 31).

There is a growing discussion about the use of SBRT in potentially operable patients (32, 33). However, as we have shown in this study there is little overlap in the characteristics between the two treatment groups. Patient and tumor specific factors should be taken into account to find an appropriate treatment for patients with early stage NSCLC.

We found that in multivariable analyses older age, CCI score 4, and clinical stage IIB are significant predictors of survival in patients undergoing surgery. Significant predictors for patients treated with SBRT for early stage of NSCLC are CCI≥5 and clinical stage>IA. These results are comparable with findings of other published data (13, 14, 34, 35). While a CCI≥5 is not a predictor of survival in the surgical group, this is a valid predictor in the SBRT group. This could be explained by the small number of patients in the surgical group with CCI≥5. Not unexpectedly, all clinical stages are predictors in the SBRT group (7). However, only clinical stage IIB is a predictor in the surgical group. The pathological stage is a better predictor of long term survival in patients undergoing surgery, therefore, the other clinical stages are not the predictors of long-term survival (36, 37).

We have examined the predictive value of the model with clinical and tumor factors versus the model with tumor factors. Both statistical accuracy (discrimination) and statistical precision (calibration) were good in our series of patients. The model with clinical and tumor factors has more predictive value than the model with tumor factors. This means that the addition of clinical factors leads to better discrimination between patients with and patients without impaired survival.

An important advantage of surgery in early stage NSCLC is the ability to offer adjuvant treatment in upstaged patients to achieve curative treatment. In this study, 52 patients were upstaged after surgery, and 17 patients received adjuvant treatment. Adjuvant treatment in these patients is intended to reach better results in outcome of patients, and it forms a curative

treatment together with surgery. In the group of SBRT patients, it is not possible to upstage the patients after treatment. The fact that the potential benefit of adjuvant treatment is not present in the group of SBRT patients may partially explain the survival differences between the treatment groups. Several trials illustrated the (modest) benefits in overall survival at 5 years of postoperative radiation therapy and chemotherapy (38). However, further research is needed to give personalized treatment to each patient with NSCLC.

Our univariable analyses indicated mild COPD in the surgery group as a protective variable on long term mortality. This could be explained by the fact that the presence of COPD is associated with an increased incidence of lung cancer (39).

Limitations

The data of the current study must be interpreted within the context of the study design and population. Our study population was relatively large in size, but in some categories of variables there were not enough patients to make a reasonable statement. Due to small patient numbers, we have chosen not to include clinical tumor stage IIB and COPD categories in Kaplan-Meier analysis. However, we have described survival of these patients in the result section. Survival of patients with COPD GOLD III (in surgical group) and GOLD IV (in SBRT group) must be interpreted carefully, because these results are not completely reliable due to small patient numbers. In this study, we did not assess genetic factors, molecular markers, and biomarkers. If these genetic and epigenetic factors were to be included in the Cox proportional hazard model, then the estimation of long-term survival could be potentially improved (40). Future multicenter studies should exploit by means of larger cohorts a possibly predictive value of all those parameters that did not reach significance in our study in order to provide better prognostic index for NSCLC patients. External validation of the AUC results also is needed for evaluating prediction models.

CONCLUSIONS

Both patient characteristics and survival of NSCLC stage I and II patients undergoing surgical treatment or SBRT differ considerably. Long-term survival of lung cancer patients can be determined by focusing on patient and tumor specific factors. In addition to TNM, the consideration of patient age and CCI score may improve prognostication of NSCLC patients and assist in selecting an appropriate treatment strategy. Our findings offer a tool that can be useful in better defining the prognosis.

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Disclosures

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Table 2. Cox proportional hazard model

Variable	Surgery						Radiotherapy					
	Univariable model			Multivariable model			Univariable model			Multivariable model		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age>70 year	1.672	1.052-2.659	0.030	1.742	1.054-2.878	0.030	1.529	0.993-2.354	0.054			
Gender												
- female	0.844	0.520-1.370	0.492				0.750	0.494-1.140	0.178			
- male	1.185	0.730-1.924	0.492				1.333	0.877-2.025	0.178			
Smoking	1.365	0.626-2.977	0.435				0.729	0.456-1.165	0.185			
FEV <80	1.235	0.781-1.953	0.366				0.710	0.433-1.164	0.172			
COPD [b]												
- mild	0.753	0.364-1.558	0.438				1.044	0.484-2.253	0.913			
- moderate	1.094	0.579-2.067	0.778				1.275	0.645-2.520	0.485			
- Severe	1.186	0.433-3.253	0.739				2.064	1.022-4.169	0.043			
-Very severe	-	-	-				1.395	0.484-4.019	0.538			
CCI												
-2-3	1.088	0.641-1.847	0.754				1.310	0.819-2.096	0.260			
-4	2.613	1.296-5.270	0.007	2.607	1.183-5.746	0.017	0.986	0.508-1.915	0.968			
-≥5	1.539	0.747-3.172	0.242				2.482	1.344-4.582	0.004	2.710	1.362-5.390	0.005
CIS [d]												
- 5-6	1.197	0.436-3.287	0.727				0.998	0.614-1.623	0.995			
- >6	1.513	0.607-3.772	0.374				1.359	0.858-2.154	0.191			
Clinical stage												
- IB	1.202	0.6870-2.105	0.519				2.586	1.701-3.930	<0.0001	2.465	1.562-3.891	<0.0001
- IIA	1.015	0.499-2.064	0.967				2.411	1.331-4.369	0.004	2.647	1.381-5.074	0.003
-IIB	2.450	1.198-5.013	0.014	2.830	1.229-6.516	0.015	5.956	1.822-19.462	0.003	4.362	1.197-15.888	0.026
Tumor size	1.011	1.000-1.023	0.057				1.026	1.014-1.037	<0.0001			
DLCO	1.003	0.991-1.015	0.672				0.994	0.987-1.001	0.077			
DLCO												
-mild red	1.284	0.779-2.116	0.327				1.009	0.531-1.918	0.978			
-moderate red	1.099	0.489-2.469	0.820				1.165	0.591-2.296	0.654			
-severe red	1.144	0.291-4.504	0.843				1.325	0.701-2.508	0.385			

[a] FEV_1%: Forced expiratory volume in 1 s expressed as a percentage of predicted value, COPDChronic Obstructive Pulmonary Disease, CCI Charlson Comorbidity Index, CIS Cumulative Illness Score, DLCO Diffusion capacity of the lung for carbon monoxide (%), [a] Clinical tumor diameter (mm).

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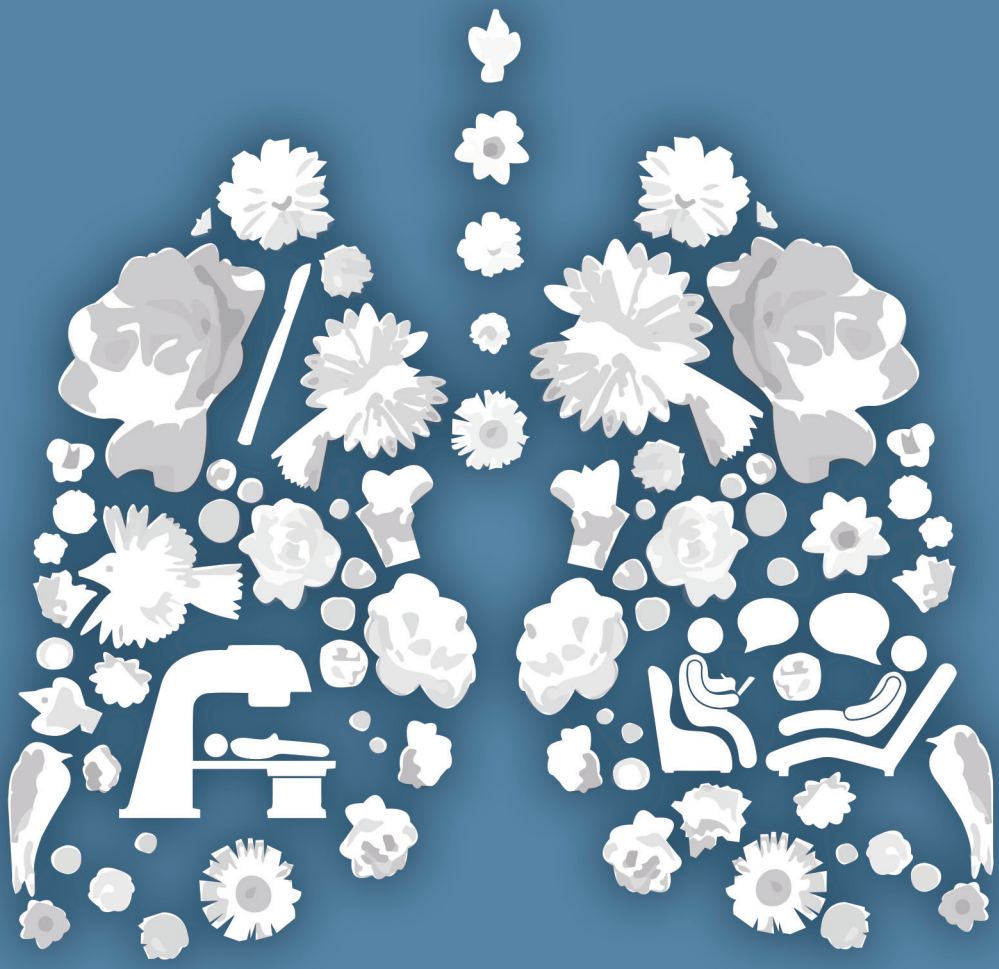

CHAPTER 3

Predicting overall survival after stereotactic ablative radiation therapy in early-stage lung cancer:

development and external validation of the Amsterdam Prognostic Model

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ABSTRACT

Purpose. A prognostic model for 5 year overall survival (OS), consisting of recursive partitioning analysis (RPA) and a nomogram, was developed for patients with early stage non-small cell lung cancer (ES-NSCLC) treated with stereotactic ablative radiation therapy (SABR).

Methods and materials. A primary dataset of 703 ES-NSCLC SABR patients was randomly divided into a training (67%) and an internal validation (33%) dataset. In the former group, 21 unique parameters consisting of patient, treatment, and tumor factors were entered into an RPA model to predict OS. Univariate and multivariate models were constructed for RPA-selected factors to evaluate their relationship with OS. A nomogram for OS was constructed based on factors significant in multivariate modeling and validated with calibration plots. Both the RPA and the nomogram were externally validated in independent surgical (n=193) and SABR (n=543) datasets.

Results. RPA identified 2 distinct risk classes based on tumor diameter, age, World Health Organization performance status (PS) and Charlson comorbidity index. This RPA had moderate discrimination in SABR datasets (c-index range: 0.52-0.60) but was of limited value in the surgical validation cohort. The nomogram predicting OS included smoking history in addition to RPA-identified factors. In contrast to RPA, validation of the nomogram performed well in internal validation (r^2=0.97) and external SABR (r^2=0.79) and surgical cohorts (r^2=0.91).

Conclusions. The Amsterdam prognostic model is the first externally validated prognostication tool for OS in ES-NSCLC treated with SABR available to individualize patient decision making. The nomogram retained strong performance across surgical and SABR external validation datasets. RPA performance was poor in surgical patients, suggesting that 2 different distinct patient populations are being treated with these 2 effective modalities.

INTRODUCTION

The advent of stereotactic ablative radiation therapy (SABR) is a major advance in curative treatment for early-stage non-small cell lung cancer (ES-NSCLC) (1). In the Netherlands, the introduction of SABR for ES-NSCLC correlated with a population improvement in overall survival (OS) in elderly patients (>75 years), primarily due to increased use of SABR in medically inoperable patients who would otherwise have been left untreated (2). Despite this population-level benefit, survival of patients after lung SABR is variable (3).

A major challenge for the judicious use of curative treatment in ES-NSCLC is the ability to accurately predict life expectancy. This issue is compounded by the difficulty in determining each factor's predictive magnitude when combined in individual patients (4). In ES-NSCLC patients who are being considered for surgery, externally validated tools to predict perioperative mortality and OS can be used to guide clinical decision making (5-7). Just as surgeons should be careful in operating on patients with medical comorbidities (8), radiation oncologists must be careful when selecting patients most likely to benefit from SABR (9). To our knowledge, currently no validated instrument exists to assist in determining the prognosis of ES-NSCLC patients treated with SABR (10), which would be useful in maximizing benefit to the broader community and minimizing undertreatment (11).

Two types of prognostic models are commonly used in this situation. Recursive partitioning analysis (RPA) creates decision trees that stratify members of a population into different groups based on dichotomous covariates. Nomograms allow for prognostication at the individual level. In this study, we developed both an RPA model and a nomogram for OS by using a large single-institution cohort of ES-NSCLC SABR patients. In developing the Amsterdam prognostic model (APM) for ES-NSCLC SABR, we measured its performance in 2 independent datasets composed of surgical and SABR patients.

METHODS AND MATERIALS

Primary dataset for RPA and creation of the nomogram

The VU University Medical Center (VUMC) maintains a database of ES-NSCLC patients treated with SABR. All patient cases are discussed in a multidisciplinary tumor board before being accepted for treatment, and when no pathology is available, patients are treated in accordance with guidelines of the European Society for Medical Oncology (12). Details for baseline characteristics, treatment, and follow-up information are prospectively entered. SABR was delivered using a risk-adapted scheme of 54 Gy in 3 fractions, 55 Gy in 5 fractions, or 60 Gy in 8 fractions, all based on tumor size and location. Treatment planning and follow-up details have been described previously (13).

A total of 1136 patients were identified from the VUMC database between January 1, 2003, and December 31, 2012. The following patients were excluded from analysis: any diagnosis of malignancy (except for basal cell cancer of the skin) within 2 years of ES-NSCLC, metastatic lung tumors, multiple lung tumors, and small-cell lung cancer diagnosis. After excluding ineligible patients, we selected the remaining 703 patients for the primary dataset and randomly divided them into a training (n=469 (67%)) and a validation (n=234 (33%)) dataset.

External validation of RPA and the nomogram

Two independent datasets consisting of clinically staged surgical and SABR ES-NSCLC patients were used for external validation of the derived models. Diagnostic and treatment details for these patients from the Erasmus Medical Center (EMC) (surgery, n=196) and Cleveland Clinic (CC) (SABR, n=543) are summarized in Supplemental File E1 (available online at www.redjournal.com) and also have been described previously in more detail (14, 15). In both external validation datasets, descriptive statistics were generated and compared with VUMC patients, using χ^2, Fisher exact, or two-sample *t-test*, as appropriate (Supplemental Table E1; available online at www.redjournal.com).

Medical ethics review for this study was not obtained for the VUMC and EMC datasets, because in the Netherlands, retrospective studies of patient records, as in the present study, do not fall under the scope of the Medical Research Involving Human Subjects Act. Institutional Review Board approval was obtained to use the CC dataset for the purposes of this study.

Model creation

Using a random number generator, patients from the primary (VUMC) dataset were dichotomized into a training set (two-thirds) and an internal validation set (one-third) without stratification. Descriptive statistics were generated for baseline patient (age, sex, World Health Organization (WHO) performance status (PS), smoking status, chronic obstructive pulmonary disease Global Initiative for Chronic Obstructive Lung Disease (GOLD) score, Charlson comorbidity index (CCI), previous malignancy, time from previous malignancy, previous lung cancer), time from previous lung cancer, tumor (maximum tumor diameter, T stage, cancer stage, laterality, use of positron emission tomography (PET), pathology proven histology, location, lobe), and treatment (number of fractions, biological equivalent dose (BED_{10}) characteristics for all patients, and were compared between training and validating sets. BED_{10} was calculated assuming that the tumor alpha:beta ratio was 10 Gy (16). The primary endpoint was OS at 5 years and was calculated using the Kaplan-Meier method from the time of treatment initiation to the date of last follow-up or death. Follow-up was calculated using the reverse Kaplan-Meier method. Patients alive as of May 29, 2014, were censored as of that date. To examine potential discrepancies related to possible inaccurately coded deaths or death dates, patient death status was verified using the Dutch national death registry.

Statistical analysis

RPA was performed using the training dataset to predict the primary endpoint based on the inventory of 21 factors. In the RPA procedure, R software (version 3.0.3, open source; www.r-project.org) default settings were used, where a minimum number of 20 observations in a node were required to enable further splitting, followed by trimming of less important downstream branches as needed. A default of a minimum of 7 observations was required for a terminal node. Rounding of cut points to the nearest significant digit was performed to increase clinical utility. OS rates were compared between the training and validating dataset RPA risk groups, using the log-rank test.

Each RPA risk group was evaluated and compared between training and validating (internal and external) sets, using the log-rank test. Univariate Cox regression was performed to evaluate RPA risk group in terms of its ability to predict OS, separately for the training and validation datasets. Univariate Cox regression was also performed using RPA-selected factors to identify significant predictors of OS. Covariates with P values of <0.05 for the training set were entered into a multivariate model to confirm significant predictors of OS. The final multivariate model obtained based on the training dataset was also assessed using the validation dataset.

A nomogram based on the final multivariate Cox regression model for OS (using the training dataset only) was generated to calculate individual patient-level probability estimates for 5 year OS according to each patient's unique combination of baseline characteristics. Nomogram equations were created to first calculate and then assign a total number of points per patient based on known baseline characteristics. Internal and external validations of the nomogram were performed via calibration plots of Kaplan-Meier-observed estimates versus nomogram-predicted probability for 5 year OS (17). The predictive accuracy and discriminative ability of the models were measured using the concordance index (C-index) and goodness-of-fit (r^2). After creation and assessment of the RPA model and nomogram on the primary datasets, they were separately evaluated using the 2 external validation datasets.

All statistical analyses were performed using SAS version 9.3 software (SAS institute, Cary, USA) and R software, using two-sided statistical testing at the 0.05 significance level.

RESULTS

Patient demographics

The distribution of baseline patient, tumor, and treatment characteristics for RPA-selected variables stratified between training and internal/external validation datasets is summarized in Table 1. The remaining stratified factors that were entered as covariates in the RPA are summarized in Supplemental Table E1 (available online at www.redjournal.com). Compared to VUMC patients, CC patients were more likely to be female and have higher rates of pathologic confirmation, better GOLD score and T-stage, and less use of PET staging (all *p-value*<0 .001). EMC patients were more commonly T1 stage, and tended to be more fit and have lower CCI, better GOLD scores, and improved PS (all *p-value*<0 .001). EMC patients were also younger and had lower rates of previous malignancy and higher rates of pathologic confirmation of malignancy and lower lobe location of disease (all *p-value<0 .001*).

Survival results and prognostic factors

The median follow-up periods for VUMC, EMC, and CC patients were 64.2, 63.0, and 34.1 months, respectively. The median OS periods for VUMC and CC patients were 40.2 and 31.2 months, respectively, and was not reached for EMC patients. In contrast to the SABR validation datasets, EMC patients had improved OS compared to the training dataset (*p-value*<0 .001).

RPA: Model development and VUMC internal validation

Initial RPA using the VUMC training dataset resulted in a 3-class stratification; class 1 tumor diameter was <23 mm and age <75 years; class 2 had tumor diameter of ≥23 mm, WHO PS of 0-1, and CCI of 0-2; and class 3 had tumor diameter of <23 mm and were ≥75 years of age or tumor diameter of ≥23 mm, a WHO PS of 0-1, and CCI of ≥ 3, or a tumor diameter of ≥23 mm and WHO PS of 2-3. A sensitivity analysis of the RPA-selected tumor diameter was performed using cut points of 20 and 25 mm. As these did not significantly alter differences in OS for the 3 RPA stratification classes, 20 mm was selected as the tumor diameter consensus, consistent with the T1a and T1b inflection points using the American Joint Committee on Cancer (AJCC) staging system. Finally, only a trend in OS difference was noted between classes 1 and 2 in the training dataset (*p-value* 0.059), a finding that was not demonstrated in the internal validation dataset (*p-value* 0.684). Accordingly, classes 1 and 2 were collapsed into a single class. In this final recursive partitioning model for OS (Figure 1), there were significant differences in OS between RPA class 1 and 2 patients on univariate Cox analysis in the training (hazard ratio (HR, 95% confidence interval): 1.86 (1.44-2.38), *p-value*<0 .001) and internal validation (HR: 1.95 (1.34-2.84), *p-value*<0 .001) datasets. The C-index used to quantify RPA stratification discrimination demonstrated moderate performance in the training (0.58) and internal validation (0.58) datasets.

Table 1. Baseline tumor, patient and treatment characteristics of all patients, training set, and validation set for RPA/Nomogram selected factors

Characteristic	VUMC	Training Set	Validating Set	EMC	CC
Age Mean ± SD, Median	 72.9 ± 8.8 74.4	 73.3 ± 8.7 74.5	 71.9 ± 8.9 73.4	 64.6 ± 9.3 65.2	 73.2 ± 9.7 74.0
Age distribution n (%)* < 75 (y) ≥ 75 (y)	 378 (53.8) 325 (46.2)	 249 (53.1) 220 (46.9)	 129 (55.1) 105 (44.9)	 167 (85.2) 29 (14.8)	 279 (51.4) 264 (48.6)
WHO Performance Status no. (%) 0 1 2 3	 84 (12.0) 354 (50.4) 229 (32.6) 35 (5.0)	 52 (11.1) 240 (51.2) 152 (32.4) 25 (5.3)	 32 (13.7) 114 (48.9) 77 (33.1) 10 (4.3)	 131 (66.8) 56 (28.6) 8 (4.1) 1 (0.5)	 12 (2.2) 332 (61.4) 190 (35.1) 7 (1.3)
Charlson Comorbidity Index Mean ± SD	2.5 ± 1.7	2.5 ± 1.7	2.5 ± 1.9	1.6 ± 1.0	2.6 ± 1.6
Distribution of Charlson Index no. (%)* 0 – 2 ≥ 3	 418 (59.5) 285 (40.5)	 273 (58.2) 196 (41.8)	 145 (62.0) 89 (38.0)	 162 (82.7) 34 (17.4)	 279 (51.4) 264 (48.6)
No. with GOLD Score shown (%) 0 1 2 3 4	 147 (21.3) 95 (13.8) 219 (31.7) 172 (24.9) 58 (8.4)	 103 (22.3) 67 (14.5) 139 (30.0) 121 (26.1) 33 (7.1)	 44 (19.3) 28 (12.3) 80 (35.1) 51 (22.4) 25 (11.0)	 91 (46.4) 105 (53.6) -- -- --	 99 (20.8) 206 (43.3) 122 (25.6) 49 (10.3)
Mean ± SD diameter (mm)	28.9 ± 12.0	29.3 ± 12.2	28.1 ± 11.5	30.6 ± 16.1	26.0 ± 13.0
No. with diameter (mm) shown (%)* < 20 ≥ 20	 174 (24.8) 529 (75.3)	 112 (23.9) 357 (76.1)	 62 (26.5) 172 (73.5)	 50 (25.5) 146 (74.5)	 186 (34.3) 356 (65.6)
Smoker	667 (97.2)	445 (97.2)	222 (97.4)	179 (91.3)	517 (95.2)

Abbreviations: CC=Cleveland Clinic; EMC=Erasmus Medical Center; GOLD=Global Initiative for Chronic Obstructive Lung Disease; RPA=recursive partitioning analysis; VUMC=VU University Medical Center; WHO=World Health Organization.

*RPA selected cutoff point.

RPA external validation

OS differences among RPA classes remained significant in the CC dataset (HR: 1.39 (1.09-1.75), *p-value* 0.007). The RPA classes, however, failed to demonstrate significant differences for the EMC dataset (HR: 1.16 (0.70-1.92), *p-value* 0 .577). Actuarial survival estimates for OS for all datasets stratified by RPA class are shown in Figure 2. The C-indexes for CC (0.55) and EMC (0.52) datasets also demonstrated discrimination only marginally better than chance.

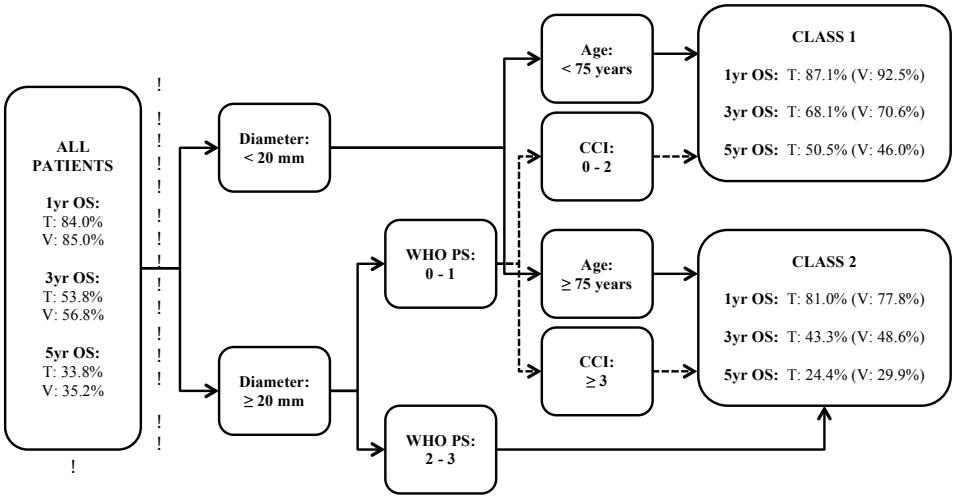

Figure 1. Two-class RPA stratification of early lung cancer patients treated with SABR. CCI=Charlson comorbidity index; OS=overall survival; T=training dataset; V=internal validating dataset.

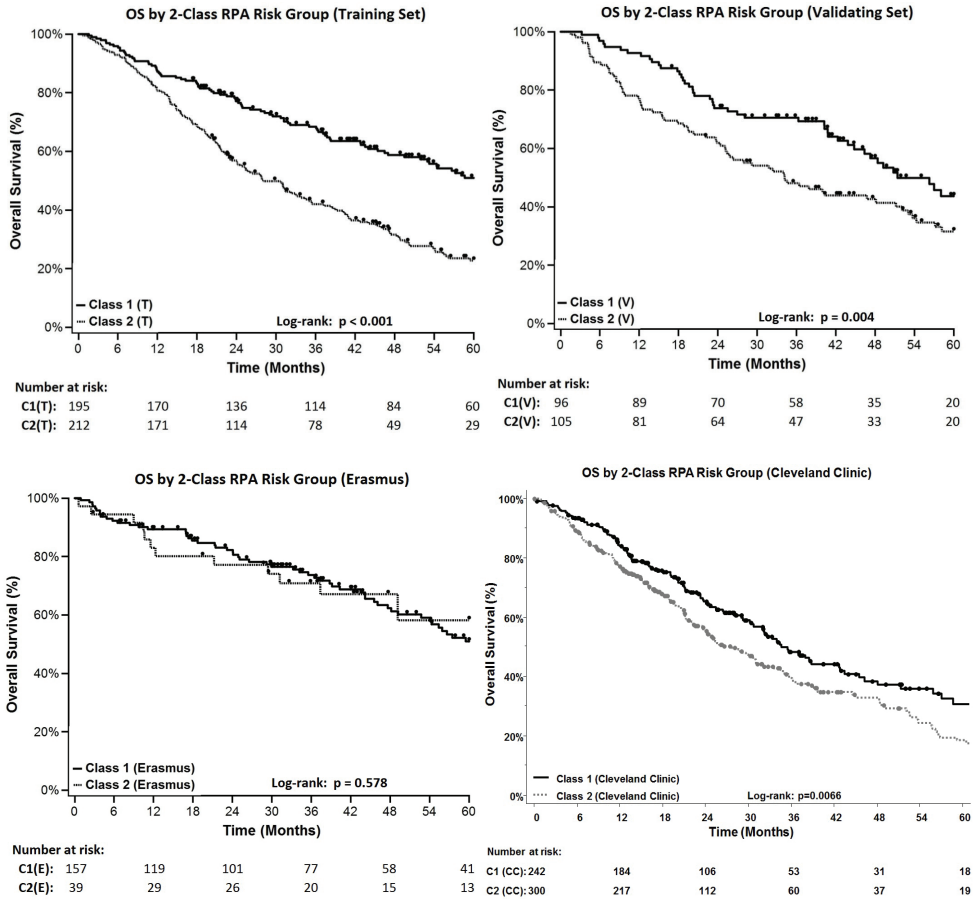

Figure 2. Kaplan-Meier curves show OS stratified by RPA classes in (top left panel) VU University Medical Center (VUMC) training set; (top right panel) Erasmus Medical Center internal validation set; Erasmus Medical Center surgical validation set (bottom left panel); and Cleveland Clinic SABR validation set (bottom right panel). OS=overall survival; RPA=recursive partitioning analysis; SABR=stereotactic ablative radiation therapy; T=training dataset; V=internal validating dataset.

Nomogram development

Results from the univariate and multivariate analyses of the training and internal validation dataset are shown in Table 2. In addition to RPA-selected factors, smoking status (HR: 4.56 (1.45-14.33), *p-value*<0.001) was found to be significant on multivariate modeling. Thus, the final clinical nomogram developed (Figure 3) was based on age, CCI, WHO PS, smoking history, and tumor diameter. The C-statistic for the multivariate training dataset model was 0.69, demonstrating good discrimination.

Table 2. Univariate and multivariable Cox regression models predictive of OS for all eligible factors entered into RPA for training and validating sets

Factor	Training dataset				Internal validation dataset			
	Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis	
Independent Variables	HR (95% CI)	*p-value*	HR (95% CI)	*p-value*	HR (95% CI)	p-value	HR (95% CI)	*p-value*
Age per 5 year increase	1.13 (1.05-1.20)	<0.001	1.13 (1.06-1.22)	<0.001	1.09 (0.99-1.21)	0.082	1.07 (0.96-1.20)	0.241
WHO PS								
1 vs. 0	1.47 (0.96-2.25)	0.073	1.41 (0.91-2.18)	0.126	0.99 (0.57-1.73)	0.977	0.88 (0.50-1.54)	0.643
2 vs. 0	1.95 (1.26-3.01)	0.003	1.90 (1.22-2.98)	0.005	2.01 (1.16-3.50)	0.013	1.69 (0.96-2.98)	0.068
3 vs. 0	3.36 (1.89-5.97)	<0.001	3.81 (2.11-6.89)	<0.001	2.16 (0.95-4.89)	0.066	1.64 (0.67-4.02)	0.278
Overall effect analysis		<0.001		<0.001		<0.001		0.004
Smoker	3.78 (1.21-11.80)	0.022	4.56 (1.45-14.33)	0.009	1.37 (0.44-4.31)	0.591	1.32 (0.41-4.28)	0.648
Charlson Index per 1 unit increase	1.09 (1.03-1.16)	0.004	1.09 (1.02-1.16)	0.011	1.19 (1.10-1.29)	<0.001	1.17 (1.07-1.27)	<0.001
Tumor Diameter per 10 mm increase	1.21 (1.11-1.32)	<0.001	1.17 (1.06-1.29)	0.001	1.16 (1.02-1.33)	0.028	1.07 (0.92-1.25)	0.364
T Stage T2 vs. T1	1.38 (1.11-1.73)	0.004	--	--	1.48 (1.07-2.06)	0.020	--	--

Table 2. Univariate and multivariable Cox regression models predictive of OS for all eligible factors entered into RPA for training and validating sets (continued)

Factor	Training dataset				Internal validation dataset			
	Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis	
Independent Variables	HR (95% CI)	*p-value*	HR (95% CI)	*p-value*	HR (95% CI)	p-value	HR (95% CI)	*p-value*
T Stage								
T1b vs. T1a	1.48 (1.08-2.02)	0.014	--	--	1.12 (0.71-1.75)	0.632	--	--
T2a vs. T1a	1.59 (1.18-2.13)	0.002	--	--	1.60 (1.05-2.42)	0.027	--	--
T2b vs. T1a	2.50 (1.59-3.93)	<0.001	--	--	1.34 (0.60-3.03	0.478	--	--
Overall effect analysis		<0.001	--	--		0.118	--	--
Fractions								
5 vs. 3	1.45 (1.12-1.86)	0.004	--	--	1.48 (1.02-2.15)	0.042	--	--
8 vs. 3	1.19 (0.87-1.64)	0.283	--	--	0.99 (0.61-1.60)	0.961	--	--
Overall effect analysis		0.017	--	--		0.062	--	--

Abbreviations; CI=Confidence interval; HR=hazard ratio; OS=overall survival; PS=performance status; RPA=recursive partitioning analysis; WHO=World Health Organization.

Nomogram validation

On univariate analysis of the internal validation dataset, WHO PS (HR: 1.69 for 2 vs 0, *p-value* 0.013), CCI (HR: 1.19 per 1 unit increase, *p-value*<0.001), and tumor diameter (HR: 1.16 per 10-mm increase, p-*value* 0.028) remained significantly prognostic. Age was of borderline significance (HR: 1.09 per 5 year increase, *p-value* 0.082), and smoking was no longer prognostic (*p-value* 0.591). Although only WHO PS (*p-value* 0.004) and CCI remained prognostic (*p-value*<0.001) for multivariate modeling of the internal validation dataset, the model continued to demonstrate good discrimination with a C-index of 0.66.

Calibration plots confirmed a high correlation between observed and predicted probability of 5 year OS for the internal, surgical, and SABR validation sets, where r^2=0.97, 0.91, and 0.79, respectively (Figure 4). As a sensitivity analysis, 4 year OS was also evaluated and demonstrated r^2 values of 0.98, 0.94, and 0.84 for the same datasets, respectively. An electronic version of the clinical nomogram is available for download (Supplemental File E2; available online at www.redjournal.com).

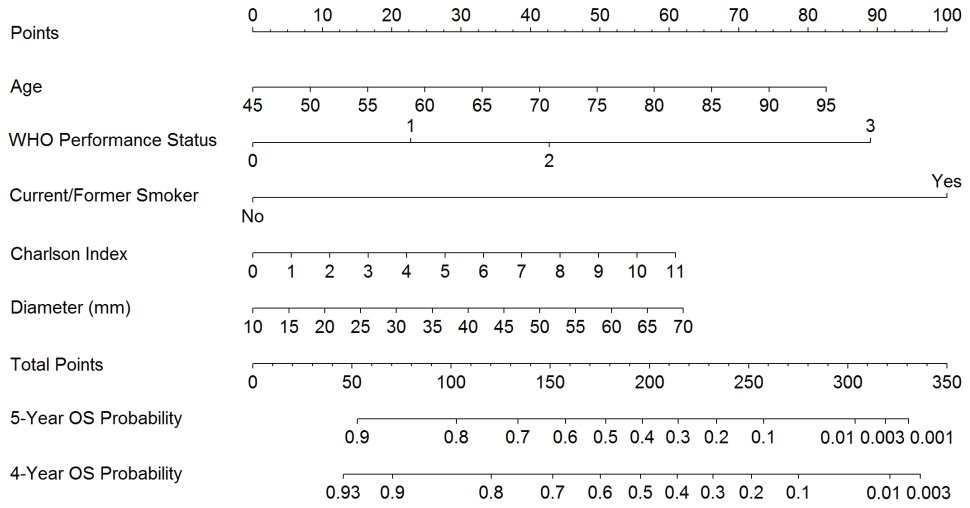

Figure 3. Nomograms predicting 5- and 4-year overall survival (OS) based on the training set from the primary dataset. WHO=World Health Organization.

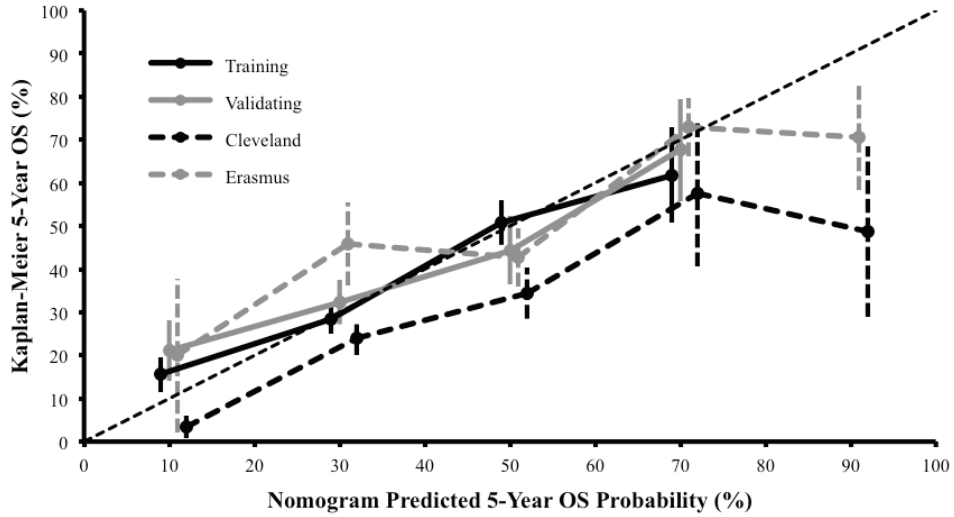

Figure 4. Calibration plots for nomograms predicting 5 year OS compared to Kaplan-Meier 5 year overall survival (OS) estimates for internal training, internal validation and Erasmus Medical Center and Cleveland Clinic datasets. Global r^2 value of 0.79 reveals a high correlation between observed and predicted probabilities.

DISCUSSION

The increasing use of SABR for ES-NSCLC is due to its low morbidity, uncommon treatment-related mortality, and convenience relative to longer radiation fractionation schemes. Despite the high rates of local control obtained, the OS in many lung SABR series are low due to other competing risks of death (1). In a review of 44 reports consisting of 3641 ES-NSCLC SABR patients with varying levels of comorbidities, 1 year OS ranged from 35% to 96%, with a weighted average of 70%. The challenges in interpreting this heterogeneous data, as well as historical fears of toxicity, may contribute to the nihilistic under-treatment of ES-NSCLC at the population level (2, 11). To assist clinicians in determining the appropriateness of radical treatment for ES-NSCLC, we report development of a novel OS prognostication tool for lung SABR patients, the Amsterdam prognostic model.

Our study is unique in that it is 1 of a few studies that uses separate training and internal validation sets for model creation, followed by external validation in a SABR and surgical cohort. The key finding was that competing risks, as measured by patient factors (age, CCI, smoking history, and WHO PS) and tumor factors (diameter), were found to be strong predictors of survival. RPA-predicted classes demonstrated modest discrimination in SABR patients but performed less favorably in surgical patients. This finding may be due to overfitting of data, which is a well-described issue in prediction modeling as a tradeoff for

practicality (18). Regarding the poorer performance of the RPA in the surgical dataset, it is important to note that EMC patients tended to be younger and fitter and have earlier stage disease and thus the low proportion of RPA class 2 patients resulted in limited statistical power. Conversely, the nomogram showed good discrimination and calibration in both surgery and SABR cohorts, suggesting that this tool warrants use in clinical practice.

The findings of this study are consistent with those of existing reports of prognostic tools for ES-NSCLC and build on those findings in several important ways. A nomogram for OS using multi-institutional Chinese registry data for patients with resected NSCLC was validated with a separate cohort from the International Association for the Study of Lung Cancer database (7). That model, based on age, sex, histology, number of lymph nodes obtained, blood loss volume, and T and N stage resulted in more precise prognostication of OS in both Chinese and IASLC datasets than the traditional TNM staging system. Although similar to our APM nomogram, that tool did not include comorbidity (coded in the model as yes/no rather than a more comprehensive metric like CCI) or smoking history (data were unavailable on greater than 10% of patients). Inclusion of these covariates may have allowed for increased discrimination and precision, as they have also been shown to be important factors in tools used to prognosticate and guide the use of adjuvant therapy for resected NSCLC (e.g. Adjvuant! Online, www.adjuvantonline.com). Other lung cancer surgical risk models include the Thoracoscore (5), the European Society Objective Score (ESOS) (19), and Society of Thoracic Surgeons (STS) models (6), created from French national, European multi-institutional, and American volunteer registry data, respectively. In addition to prognostic factors described in the APM, these models comprehensively included a number of covariates relevant to surgery, such as the extent of surgery, urgency of surgery, and American Society of Anesthesiologists score. Thoracoscore, ESOS, and STS are used to predict in-hospital mortality (STS is also used to predict major morbidity) and can be seen as complementary to the APM for lung SABR, for patients weighing the relative merits of surgery versus SABR.

Although most lung cancer patients treated with SABR worldwide are medically inoperable (20), there is an increasing trend toward treating patients who are younger and have fewer comorbidities and a better performance status (21). Indeed, there is growing equipoise for the role of SABR for these patients despite the fact that 3 randomized controlled trials comparing SABR to surgery have failed to accrue subjects (22, 23). Recently, a meta-analysis of 40 SABR and 23 surgery studies for ES-NSCLC was conducted (3). Of the 27 SABR studies reporting on proportion of patients who were potentially operable, the mean operability rate was 20.1%. The meta-analysis found that, when adjusting for age and potential operability, there were no significant differences in OS between the 2 treatment options (*p-value* 0.36), a finding that must be considered in the context of heterogeneous data and the potential bias of unmeasured confounders. Ultimately, both surgery and radiation therapy will be crucial to address the unmet therapeutic needs of ES-NSCLC.

Prognosis as determined through the APM following SABR was also found to be highly dependent on tumor size, a finding consistent with previous SABR and surgical studies (24-27). In the APM, the RPA determined a tumor diameter cutoff point of 20 mm. Although this conforms to the difference between a T1a and T1b in the most recent TNM staging system, dichotomizing tumor size may overfit the data. Tumor diameter was modeled as a continuous variable in our nomogram, similar to a recent SEER-based model, which found that incorporating data in such a manner resulted in OS predictions that were superior to those in AJCC (28).

Limitations of our model may be improved upon in the future to further guide clinical practice. While SABR populations from 2 continents performed well on validation of the models herein, the RPA did not apply to the surgical series. As the EMC dataset was mostly comprised of RPA class 1 patients (fitter, younger, with smaller tumors), a larger more heterogeneous group of patients including a larger case mix of borderline operable patients would have been more useful to evaluate the proposed stratification. In addition, the cohort of patients in this study was comprised of patients treated at academic centers, where findings may not be generalizable to community practice. Nonetheless, although a variety of methods are used worldwide for lung SABR, early multi-institutional data suggests that outcomes appear to be generalizable across various delivery platforms, image-guidance, and dose fractionations in different geographic regions, provided that a BED10 greater than 100 Gy is delivered (2, 29).

CONCLUSIONS

In conclusion, we developed the APM, consisting of a novel 2-class RPA system and 5 year OS nomogram as a prognostic tool for patients with ES-NSCLC treated with SABR. Our findings indicate that the nomogram may be used to guide individual patient decision making, and the RPA may be helpful in stratification of patients for clinical trials. The proposed models can be refined based on future work, which may include neural network analyses to evaluate the effect of potential unmeasured confounders.

Supplementary material

Supplemental File E1

At the EMC, 543 patients with ES-NSCLC were treated using a Novalis/BrainLAB system (BrainLab Inc., Feldkirchen, Germany), with a Bodyfix vacuum system and abdominal compression for immobilization, along with ExacTrac for image guidance. Treatment was delivered using either dynamic arcs or step and shoot IMRT. A variety of dose fractionations were employed over time with the vast majority having a BED10 > 100. Central (within 2 cm of the bronchial tree) tumors typically received 50 Gy in 5 fractions, while peripheral tumors received either 54 Gy in 3 fractions or 50 Gy in 5 fractions based on clinician preference. Single fraction regimens were occasionally employed.

The 196 ES-NSCLC patients treated with surgery at the CC were available for analysis from a retrospectively maintained institutional database. To facilitate comparison to SABR patients, clinical stage rather than pathologic stage was used for classification. All patients are discussed through a multidisciplinary before treatment and were staged using CT, PET and minimally invasive endoscopic techniques, where appropriate.

Supplemental File E2

This is an installation file for the Clinical Nomogram. It is accessible at: http://www.sciencedirect.com/science/MiamiMultiMediaURL/1-s2.0-S0360301615005039/1-s2.0-S0360301615005039-mmc1.zip/271185/html/S0360301615005039.

The model is available for online use at www.predictcancer.org.

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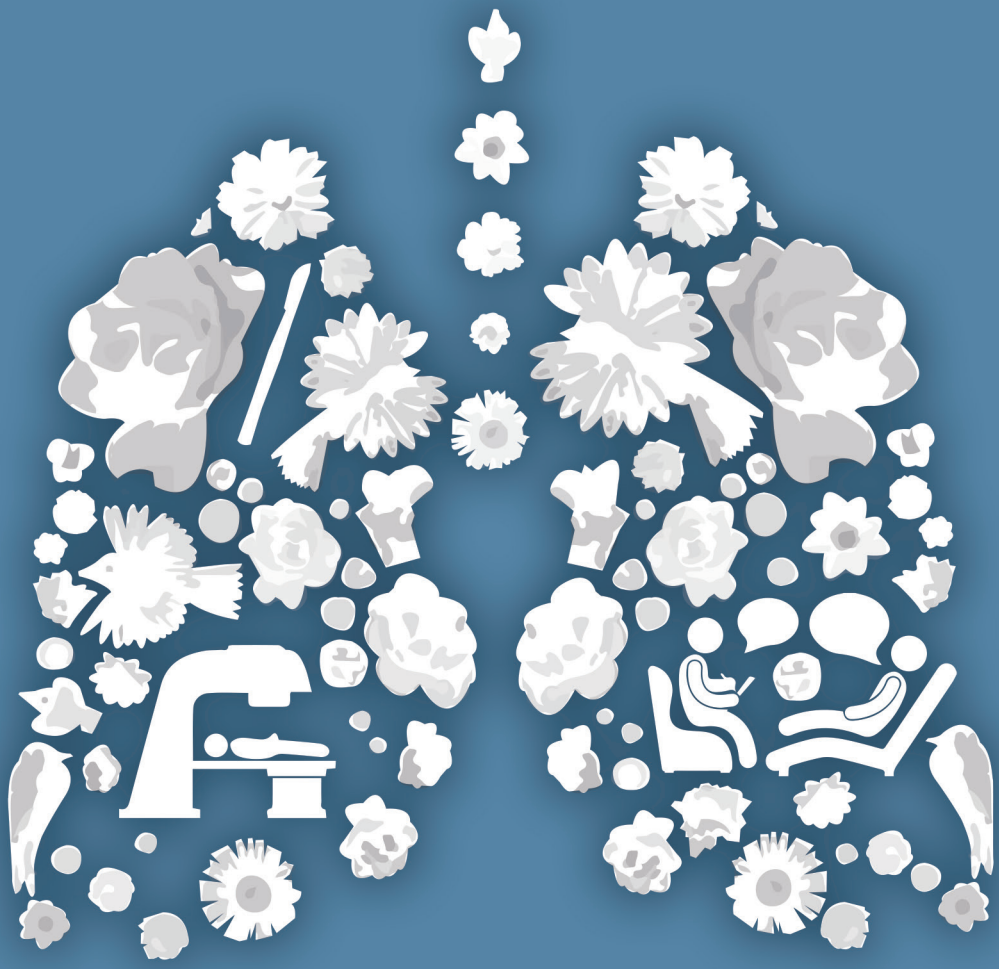

CHAPTER 4

Comparison of clinical outcome of stage I non-small cell lung cancer treated with stereotactic radiotherapy or VATS-lobectomy:

results from propensity score analysis

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ABSTRACT

Objectives. Guideline-specified curative therapies for a clinical stage I non-small cell lung cancer (NSCLC) are either lobectomy or Stereotactic Ablative Radiotherapy (SABR). As outcomes of prospective randomized clinical trials comparing these modalities are unavailable, we performed a propensity score matched analysis to create two similar groups in order to compare clinical outcomes.

Methods. We selected 577 patients, 96 VATS or open lobectomy were treated at Erasmus University Medical Center Rotterdam and 481 SABR patients were treated at VU University Medical Center Amsterdam with clinical stage I NSCLC.

Results. Matching of patients according to propensity score resulted in a cohort that consisted of 73patients in the surgery group and of 73 patients in the SABR group. Median follow up in the surgery and SABR group was 49 months and 28 months, respectively. Overall survival of patients who underwent surgery was 95% and 80% at 12 and 60 months, respectively. For the SABR group this was 94% at 12 months and 53% at 60 months. No statistical significant difference (*p-value* 0.089) in survival was found between these groups.

Conclusions. In this study we found no significant differences in overall survival in propensity matched patients diagnosed with stage I NSCLC treated either surgically or with SABR. After 3 years there seems to be a trend toward improved survival in patients who were treated surgically.

INTRODUCTION

Lung cancer is the most common cause of cancer-specific mortality worldwide (1, 2). Surgical resection is the preferred treatment for operable early stage NSCLC (3). A patient is eligible for surgery if the tumor is completely resectable, and the patient is fit to undergo surgical intervention. Surgical resection in the form of lobectomy remains the standard of care for stage I and II NSCLC as it is associated with less complications and better survival outcomes in the elderly (4). However, technical improvements have led to the development of minimally invasive surgical procedures carried out by Video-Assisted Thoracoscopic Surgery (VATS). Several studies have shown the notable benefits of VATS, in particular in older and frail patients, and it has gained importance in the last years (5, 6).

Stereotactic Ablative Radiotherapy (SABR) is an option for patients who are not candidates for surgery due to medical comorbidities or who are refusing surgery (3). Additionally, factors such as patient preferences and recommendations of the multidisciplinary team play an important role in treatment decision. Individual studies have demonstrated excellent locoregional control rates and overall survival (7, 8). Population studies reveal a longer overall survival in elderly early stage NSCLC patients following the introduction of SABR in The Netherlands (9). Due to these good results and the low toxicity profile of this treatment, in recent years a shift has been observed in patient referred for SABR from medically inoperable patients to patients potentially fit for surgery (10).

Even though both SABR and surgical resection both appear to be suitable for patients presenting with early stage NSCLC and comorbidities, currently there are no data available from randomized controlled trials comparing both treatment modalities. A few non-randomized studies comparing different surgical techniques with SABR in matched patients have been published, in which no differences in overall survival between both treatment groups were detected (11-13). However, most of these published studies of VATS and surgical techniques examined data from small groups of patients or those treated in many centers where a variety of surgical techniques were used. The goal of our study was to use databases from two tertiary cancer centers to compare the outcomes of patients who underwent lobectomy, either by VATS or by means of thoracotomy, or SABR. The outcome of this matched propensity score analysis will provide more information on treatment options for stage I NSCLC patients.

METHODS

Study population

From January 2003 to January 2012, 577 consecutive patients (96 VATS or open lobectomy treated at Erasmus Medical Center Rotterdam (EMC) and 481 SABR patients treated at VU University Medical Center Amsterdam (VUMC)) were identified with clinical stage I NSCLC. Clinical stage I was based on American Joint Committee in Cancer 7th edition

staging manual (14). Clinical staging was done with CT-scan, 18FDG-PET imaging (64 patients in surgery group and 72 patients in radiotherapy group) or using minimally invasive endoscopic techniques (53 patients in surgery group and 27 patients in radiotherapy group) when appropriate. All patients were discussed in a multidisciplinary team before treatment. Patients in surgical group underwent lobectomy, either by VATS or by means of thoracotomy. Radical lymph node dissection was performed in accordance with the guidelines (15). Furthermore, the observation of enlarged or suspicious lymph nodes intraoperative led to sampling of the different node stations. SABR was delivered using risk-adapted fractionation schemes, with amore fractionated scheme for larger tumors and those adjacent to critical normal organs, as has previously been described (16). Exclusion criteria were: previous lung malignancy, synchronous lung tumor, severe chronic obstructive pulmonary disease (COPD), other cancers five years before treatment of current lung cancer, and neo-adjuvant chemo-radiotherapy. Erasmus MC is a large tertiary hospital that provides specialized care for challenging patients. Even though there is a large database of surgically treated lung cancer patients the application of the exclusion criteria led to a cohort of only 96 surgical patients for the analysis of this study. The majority of the excluded stage I patients had a history of other cancer or synchronous lung tumor.

Data collection

All patients, who received treatment for stage I NSCLC at EMC or VUMC, were registered in a dedicated database. Comorbidity scores were recorded using Charlson Comorbidity Index (CCI) (17). COPD was defined according to the GOLD criteria (18). Toxicity in SABR group and complications in surgery group were scored according to Common Terminology Criteria for Adverse Events version 4.0 (19). The definitions of tumor recurrence for both modalities were consistent with Table 1 American College of Chest Physicians-Society of Thoracic Surgery consensus (20). Freedom from progression was defined as freedom from any tumor recurrence. The follow up period started on the first day of treatment. The overall survival time was defined as the difference between the start of treatment and the date of death or last follow up. Patients lost to follow up were censored at the last known follow up date. The Dutch civil registry was consulted to assess late mortality for surgical patients. The Ethics Committee of EMC has approved the conduct of the present study (MEC 2013-273). The Ethics Committee of VUMC waived the need for informed consent.

Propensity score matching

To reduce the bias of the retrospective nature of the study and to achieve comparable treatment groups a propensity score analysis was performed. Propensity score matching offers a way to achieve more balanced groups by matching treatment and control units based on a set of baseline characteristics (21-24). The propensity score was calculated using multivariable logistic regression to model a dichotomous outcome of surgery or SABR for the cohort of 577 patients. Patient data were anonymized and outcome data

were removed before propensity score matching was performed. The following covariates were used to match the patients: age, gender, clinical tumor stage, clinical tumor diameter, location of the tumor, histology of the tumor before treatment, pathology confirmation before treatment, FEV1, Charlson Comorbidity Index, and WHO performance score. Greedy matching technique was then used to match patients who were operated to patients that received SABR (25). A propensity score difference of 0.20 was used as a maximum caliper width for matching the two treatment groups. In order to investigate covariate balance across the groups, absolute standardized differences for all measured covariates were assessed and visualized by constructing a Love-plot (24, 26).

Study outcome

The main outcome of interest was overall survival, occurrence of distant metastasis, and loco-regional failure after treatment for stage I NSCLC either with SABR, lobectomy by VATS, and lobectomy by means of thoracotomy. Every recurrence was confirmed with biopsy or 18FDG-PET-imaging and discussed in a multidisciplinary team. All SABR patients who were suspected of having a local recurrence, but without pathological confirmation, were scored as having a recurrence.

Statistical analysis

The group comparison in the unmatched cohorts of continuous data (baseline and follow up duration) was done using the unpaired *t-test* unless the data were not normally distributed (Kolmogorov-Smirnov test); in these instances, we used the Mann-Whitney *U-test* for comparison. The group comparison in the unmatched cohort of categorical data was done with the χ^2 *test* or the Fischer exact test when appropriate. Comparison in the matched cohort was done using the McNemar test and paired sample *t-test* or Wilcoxon signed-rank test when appropriate. Overall survival of patients and time-to-event outcomes were determined using the Kaplan-Meier method (27). Kaplan-Meier plots were truncated at the point in time when 10% of the original population was still at risk (28, 29). To correct for differences in follow up time the Kaplan-Meier curves were compared using the Tarone-Ware test. All tests were 2-sided, with an α-level of 0.05. Propensity matching was done using SAS 9.2 (SAS®, Cary, NC). Statistical software SPSS for Windows version 20 (SPSS Inc., Chicago, IL) was used to construct descriptive tables. GraphPad Prism 5.00 for Windows (GraphPad software, San Diego, CA) was used to construct the Kaplan-Meier survival curves.

RESULTS

Patient characteristics

A total of 577 patients with stage I NSCLC were selected for matching (96 operated and 481 SABR). Before matching patients in the SABR group were older, with higher CCI and lower FEV1%. Median follow up time in the surgery and SABR group was 54 and 30 months, respectively. Baseline characteristics of unmatched patients can be found in Table 1.

Matching of patients according to propensity score resulted in a cohort that consisted of 73 patients in the surgery cohort and of 73 patients in the SABR cohort. Absolute standardized differences for all measured covariates were <10%, suggesting substantial covariate balance across the groups (Figure 1) (26). Median follow-up time in the surgery and SABR group was 49 and 28 months, respectively. Baseline characteristics of matched patients can be found in Table 2.

The surgery group consisted of 32 patients (44%) who underwent VATS-lobectomy and 41 patients (56%) who underwent lobectomy by means of thoracotomy. Lymph node dissection was performed in 62 patients (85%). The median number of dissected lymph node zones was 2 (range 0-5), and the median dissected number of lymph per zone was 4 (range 0-20). In 27 patients (37%) six or more nodes were dissected. Nineteen patients (26%) were upstaged due to the size of the tumor or unsuspected nodal involvement. Unsuspected nodal involvement was detected at surgery in 8 patients (11%). Eleven patients were upstaged due to size of the tumor, with 6 patients (8%) upstaging from stage IA to stage IB and 5 patients (7%) upstaging from stage IB to stage IIA. Patients upstaged at surgery received adjuvant treatment, with 5 patients (7%) receiving chemotherapy and 7 patients (10%) treated with radiotherapy (nodal disease in 1 patient and positive surgical margins in 6 patients (in 4 patients the cancer cells extended to the edge of the removed tissue and 2 patients had close margin with growth in surrounding lymph node or extension to the pleura). Seven patients (10%) did not received adjuvant treatment due to poor performance status or they refused adjuvant treatment.

The total radiation dose delivered to SABR patients ranged from 54 to 60 Gy, delivered in 3 (38%), 5 (44%) or 8 (18%) fractions. Overall treatment time in the SABR group was 1.7 weeks. Median duration of hospital stay after surgery was 8 days (range 1-68 days).

Table 1. Baseline characteristics: Unmatched patients

Characteristics	Cohort (n=577)	VATS or open lobectomy (n=96)	SABR (n=481)	*P*
Age, mean (range)±SD	72 (39-91) ± 10	65 (39-83) ± 10	74 (47-91) ± 9	<0.001
Gender, n (%) -Male -Female	 333 (58) 244 (42)	 57 (60) 39 (40)	 276 (57) 205 (43)	0.718
cTNM, n (%) -stage IA -stage IB	 238 (57) 249 (43)	 71 (74) 25 (26)	 257 (53) 224 (47)	<0.001
Tumor diameter (mm), mean (range) ±SD Missing, n (%)	29 (1-107) ± 13 9 (2)	23 (1-66) ± 13 5 (5)	30 (8-107) ± 13 4 (1)	<0.001
Location, n (%) -Right upper lobe -Right lower lobe -Right middle lobe -Left upper lobe -Left lower lobe	 204 (35) 104 (18) 27 (5) 163 (28) 79 (14	 33 (34) 22 (23) 4 (4) 25 (26) 12 (13)	 171 (36) 82 (17) 23 (5) 138 (29) 67 (13)	0.746
Pathology pretreatment, n (%) -Yes -No	 361 (63) 216 (37)	 45 (47) 51 (53)	 171 (36) 310 (64)	0.066
Histology pretreatment, n (%) -No -Squamous cell -Adenocarcinoma -other NSCLC	 362 (62) 68 (12) 72 (13) 75 (13)	 51 (53) 17 (17) 11 (12) 17 (18)	 311 (64) 51 (11) 61 (13) 58 (12)	0.316
FEV1 (*L*) mean ± SD Missing, n (%) FEV1 *(%)* mean ± SD Missing, n (%)	1.83 ± 0.78 5 (1) 71 ± 24.4 5 (1)	2.41 ± 0.84 2 (2) 83.59 ± 21.09 2 (2)	1.72 ± 0.72 3 (1) 68.54 ± 24.29 3 (1)	<0.001 <0.001
WHO performance score, n (%) -0 -1 -2 -3	 106 (18) 277 (48) 172 (30) 22 (4)	 56 (58) 30 (32) 7 (7) 3 (3)	 50 (11) 247 (51) 165 (34) 19 (4)	<0.001
Charlson comorbidity score, n (%) -0 -1 -2 -3 -4 -≥5	 56 (10) 180 (30) 150 (26) 104 (18) 43 (8) 44 (8)	 28 (29) 30 (31) 21 (22) 10 (11) 4 (4) 3 (3)	 28 (6) 150 (31) 129 (26) 94 (20) 39 (8) 41 (9)	<0.001

VATS indicates video-assisted thoracoscopic surgery, SABR indicates stereotactic ablative radiotherapy.

Table 2. Baseline characteristics: Matched patients

Characteristics	Cohort (n=146)	VATS or open lobectomy (n=73)	SABR (n=73)	*P*
Age, mean (range) ±SD	67 (39-89) ± 10	67 (39-83)± 9	67 (47-89) ± 10	0.592
Gender, n (%) -Male -Female	 86 (59) 60 (41)	 44 (60) 29 (40)	 42 (58) 31 (42)	0.868
cTNM, n (%) -stage IA -stage IB	 105 (72) 41 (28)	 54 (74) 19 (26)	 51 (70) 22 (30)	0.690
Tumor diameter (mm), mean (range) ± SD Missing, n (%)	 25 (1-70) ± 13 5 (3)	 24 (1-66) ± 13 5 (7)	 25 (8-70) ± 12 -	0.231
Location, n (%) -Right upper lobe -Right lower lobe -Right middle lobe -Left upper lobe -Left lower lobe	 47 (32) 33 (23) 10 (7) 37 (25) 19 (13)	 22 (30) 19 (26) 4 (6) 17 (23) 11 (15)	 25 (34) 14 (20) 6 (8) 20 (27) 8 (11)	0.796
Pathology pretreatment, n (%) -Yes -No	 62 (43) 84 (58)	 34 (47) 39 (53)	 28 (38) 45 (62)	0.405
Histology pretreatment, n (%) -No -Squamous cell -Adenocarcinoma -other NSCLC	 84 (58) 18 (12) 19 (13) 25 (17)	 39 (53) 10 (14) 10 (14) 14 (19)	 45 (62) 8 (11) 9 (12) 11 (15)	0.300
FEV1 (*L*) mean ± SD Missing, n (%) FEV1 *(%)* mean ± SD Missing, n (%)	2.29 (0.82) 2 (1.4) 80.88 (21.19) 3 (2)	2.30 (0.83) 2 (2.7) 80.37 (20.11) 2 (3)	2.27 (0.81) - 81.38 (22.33) 1 (2)	0.834 0.860
WHO performance score, n (%) -0 -1 -2 -3	 63 (43) 67 (46) 13 (9) 3 (2)	 36 (49) 27 (37) 7 (10) 3 (4)	 27 (37) 40 (55) 6 (8) -	0.776
Charlson comorbidity score, n (%) -0 -1 -2 -3 -4 -≥5	 28 (19) 51 (35) 36 (25) 16 (11) 10 (7) 5 (3)	 15 (20) 24 (33) 18 (25) 9 (12) 4 (6) 3 (4)	 13 (18) 27 (36) 18 (25) 7 (10) 6 (8) 2 (3)	0.844

VATS indicates video-assisted thoracoscopic surgery, SABR indicates stereotactic ablative radiotherapy.

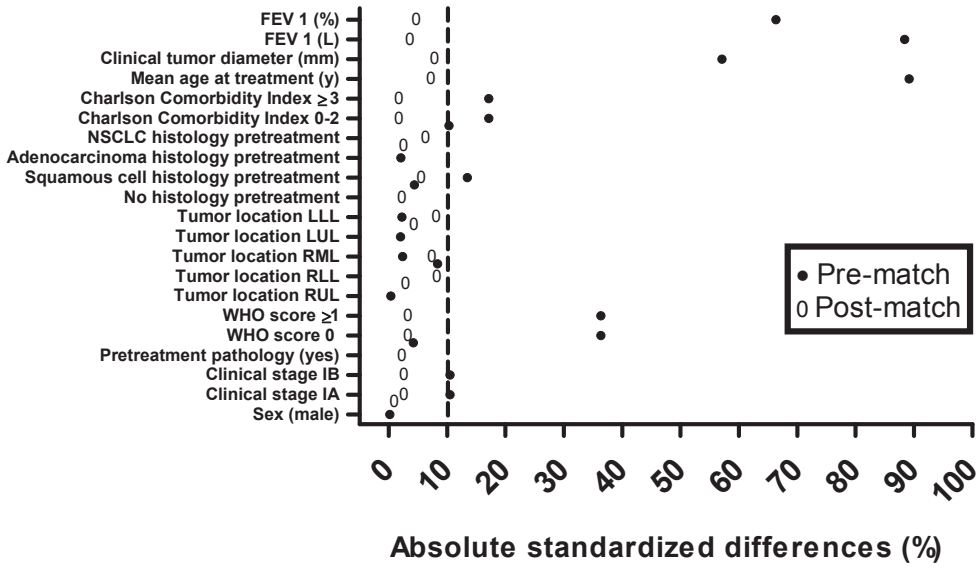

Figure 1. Love plots for absolute standardized differences for baseline covariates between patients treated surgically or with stereotactic ablative radiotherapy, before and after propensity score matching. LLL: left lower lobe; LUL: left upper lobe; RML: right middle lobe; RLL: right lower lobe; RUL: right upper lobe.

Treatment toxicity

Complications after surgery were observed in 31 patients (42%) with Common Terminology Criteria for Adverse Events (CTCAE) grade 1 observed in 13 patients (18%), grade 2 in 13 patients (18%), and grade 3 in 5 patients (7%). After six weeks, a single patient (1%) developed grade 5 side effects. This patient developed pseudomonas pneumonia and renal failure, and died 68 days after surgery. Four patients (5%) needed reoperation due to hemothorax, thoracic empyema or persistent air leak. In the SABR patients, no mortality was observed after 90 days of treatment. Complications within 6 weeks after SABR were observed in 34 patients (47%), with grade 1 toxicity observed in 28 patients (38%) and grade 2 in 7 patients (10%). Side effects after 6 weeks were observed in 24 patients (33%). Late side effect grade 1 was observed in 16 patients (22%), grade 2 in 7 patients (10%), and grade3 in 1 patients (1%) due to central stenosis.

Survival

The observed overall survival of patients who underwent surgery was 95% (95% Confidence Interval (CI) 86-98%) at 12 months and 80% (95% CI 66-88%) at 60 months. For SABR group this was 94% (95%CI 85-98%) at 12 months and 53% (95%CI 35-68%) at 60 months. The survival between the two patient groups was not statistically significant

(Tarone-Ware *p-value* 0.089) (Figure 2a). The median follow up time to any recurrence was 10 months in both treatment groups. Freedom from progression was not significantly different between the two treatment groups (*p-value* 0.903). Among surgical patients freedom from progression at 12 and 60 months was 93% (95% CI 84-97%) and 76% (95% CI 62-85%), respectively. This was in SABR group 93% (95% CI 83-97%) at 12 months, and 70% (95% CI 52-82%) at 60 months (Figure 2b).Distant metastasis occurred in 24 patients (10 patients in surgery group, 12 patients in SABR group). Distant control rates were not

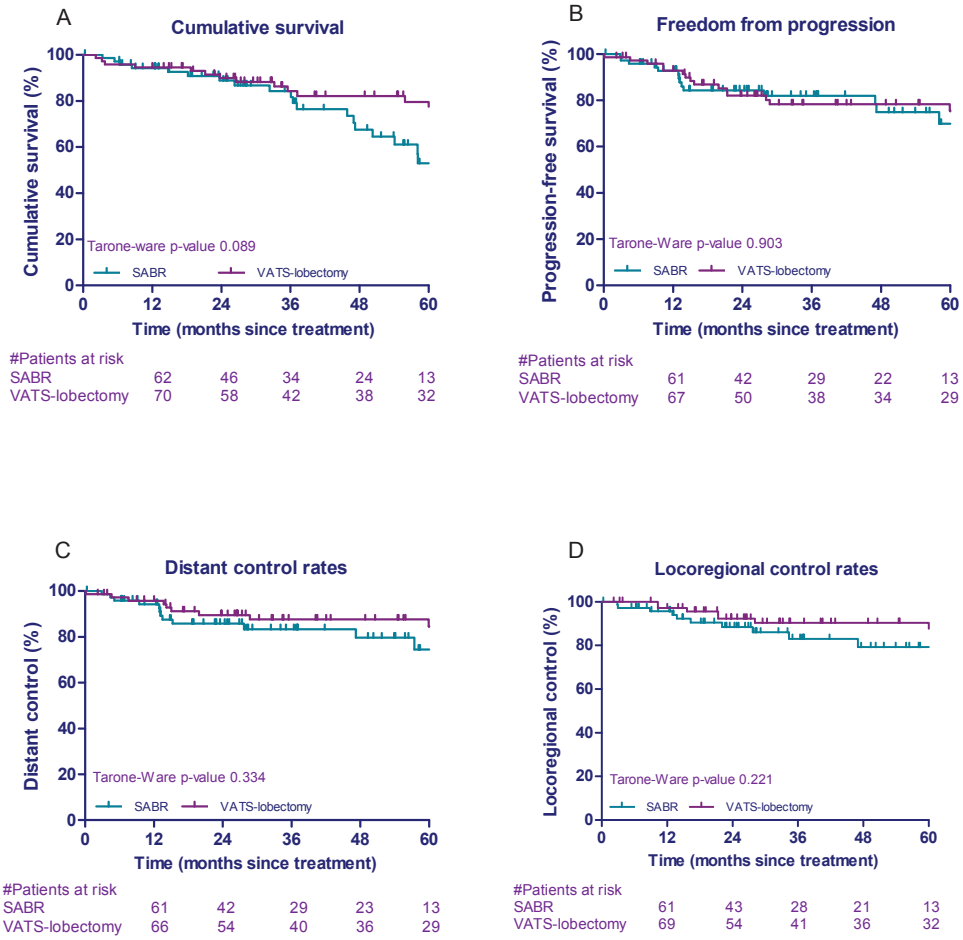

Figure 2. Kaplan-Meier plot of: a) Cumulative survival after stereotactic ablative radiotherapy. (SABR), lobectomy by means of video-assisted thoracoscopic surgery (VATS) or thoracotomy; b) Freedom from progression after SABR, lobectomy VATS or thoracotomy; c) Distant control after SABR, lobectomy by VATS or thoracotomy; d) Loco-regional control after SABR, lobectomy by VATS or thoracotomy.

significantly different between the two groups (*p-value* 0.334). Among surgical patients, the distant control rates at 12 and 60 months were 96% (95% CI 87-99%) and 85% (95% CI 72-92%), respectively. This was in the SABR group 94% (95% CI 85-98%) at 12 months, and 74% (95% CI 56-86%) at 60 months (Figure 2c). Loco-regional control rates were also not significantly different between the two groups (*p-value* 0.221). Corresponding 12- and 60 months loco-regional control rates in the surgery group were 97% (95% CI 89-99%) and 90% (95% CI 80-96%), respectively. This was in the SABR group 97% (95% CI 87-99%) at 12 months, and 79% (95% CI 63-89%) at 60 months (Figure 2d).

DISCUSSION

This propensity score matched analysis reveals that overall survival of patients with clinical stage I NSCLC treated surgically or with SABR is similar up to 3 years. After 3 years there seems to be a trend toward better survival for surgical patients. Loco-regional control rates, distant metastasis and freedom from progression did not differ significantly between treatment groups.

An important advantage of surgery in early stage NSCLC is the possibility of lymph node staging through lymph node dissection pre-operatively and during the operation. With optimal lymph node staging, patients with microscopic lymph node metastasis can be identified to receive adjuvant treatment. A possible explanation of the trend toward better survival for surgical patients after 3 years could be the practice variation in removal of suspicious lymph node zones during surgery. For example Verhagen et al. previously reported that in four hospitals in the Netherlands in only 4% of patients a complete lymph node dissection was performed (30). However, it remains controversial whether complete lymph nodes dissection and upstaging after surgery improves survival of patients with early stage NSCLC (31, 32).

A limitation of surgical approach is that adjuvant therapy is usually needed in patients with incomplete excision of cancer. In this study 6 patients received adjuvant treatment in the form of radiotherapy due to positive surgical margin.

Another explanation for the observed better outcome after surgery could be that patients treated with SABR are patients who were not eligible for a surgical treatment due to (patient and tumor) characteristics that were not included in the propensity score matching. There are many causes of death in lung cancer patients but Nichols et al. concluded that respiratory failure is by far the most frequent immediate cause of death in lung cancer patients (after tumor burden) (33). Radiation therapy damages the lungs and blood vessels which could led to respiratory failure over time. This may explain the observed increased mortality in this patient group. Unfortunately, we were not able to provide cancer specific survival in this study. More research is needed to illustrate the causes of death and types of specific comorbidities contributing to the death.

Overall survival rates and loco-regional control rates in both groups are within the range reported previously for both treatment modalities (11, 34). Theories of improved immunological response following SABR have been postulated (35, 36). These theories might help to explain the similar freedom from progression in both treatment groups, even though SABR patients with microscopic lymph node metastasis are not identified with lymph node dissection. It remains unclear what the mechanism of tumor immune response (of combination immune-radiation therapy) is and how long the effect is maintained (37).

The type and severity of complications observed after treatment differ between the SABR group and the surgery group. In SABR patients no treatment related deaths were observed. Furthermore, late side effect grade 3 was observed in one SABR patient. In the surgical group one patient died due to renal failure and pseudomonas infection and 5 patients needed additional intervention. These differences in complications are important to address when treatment options are discussed with the patient. The observed treatment related toxicity and mortality is comparable with rates published previously (5, 38).

One of the strengths of present study is that patients in both treatment groups were treated in a single tertiary academic institution, with few variability in techniques and surgical team. In a previous study, published by Verstegen and colleagues, comparing SABR and VATS-lobectomy in stage I-II NSCLC using propensity score matching, similar overall survival was observed in both patient groups, with improved loco-regional control in the SABR group (11). However, the surgical outcome of the latter study might have been inferior due to the fact that surgical patients were treated in a number of different hospitals, by surgeons who may not have completed their learning curve.

The data of the present study must be interpreted within the context of the study design and population. Even with the accurate matching there are still some differences between patients in two treatment groups. Patients with WHO score>2 were not accurately matched; this may cause differences in outcomes of patients. Furthermore, not all differences between both patient groups might be captured, as matching was done with only a limited number of variables. Staging procedure was not included as a covariate in propensity model. Before matching 36% of SABR patients (n=171) were staged using minimal invasive endoscopic techniques, in surgery group this was 75% (n=72). Using this technique in propensity model would limit the number of SABR patients for the analysis. Majority of patients were staged using CT-scan and/or 18FDG-PET imaging, adding these covariates would not have added value. Also, other factors not taken into account in the matching process may be responsible for the observed differences in outcome.

SABR has become a standard treatment option for patients unable or unwilling to undergo surgical resection. Good oncological outcome in these patients, has resulted in an increased interest for the use of SABR for potentially operable patients. No data on clinical trials comparing surgery and SABR for early stage NSCLC are currently available,

but there are several published studies comparing both treatments, in which SABR seems to achieve at least comparable results to surgery, with a milder toxicity profile. However, it is important to realize that this is a propensity matched study of 2 selected subgroups of surgical and SABR patients. In the unmatched population patients in the surgery group were younger and had less comorbidity.

In conclusion, in propensity-matched clinical stage I NSCLC patients who underwent SABR or surgery no difference in survival is observed up to 3 years, suggesting comparable effectiveness of treatment options with regard to patient survival. The observation that overall survival diverged after 3 years requires further research to elucidate the determinants of prognosis in relation to treatment options for patients with stage I NSCLC, in order to facilitate patient-tailored treatment selection and optimize clinical decision making.

Conflict of interest statement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. S. Senan received speakers honoraria from Varian Medical Systems. For the remaining authors none were declared.

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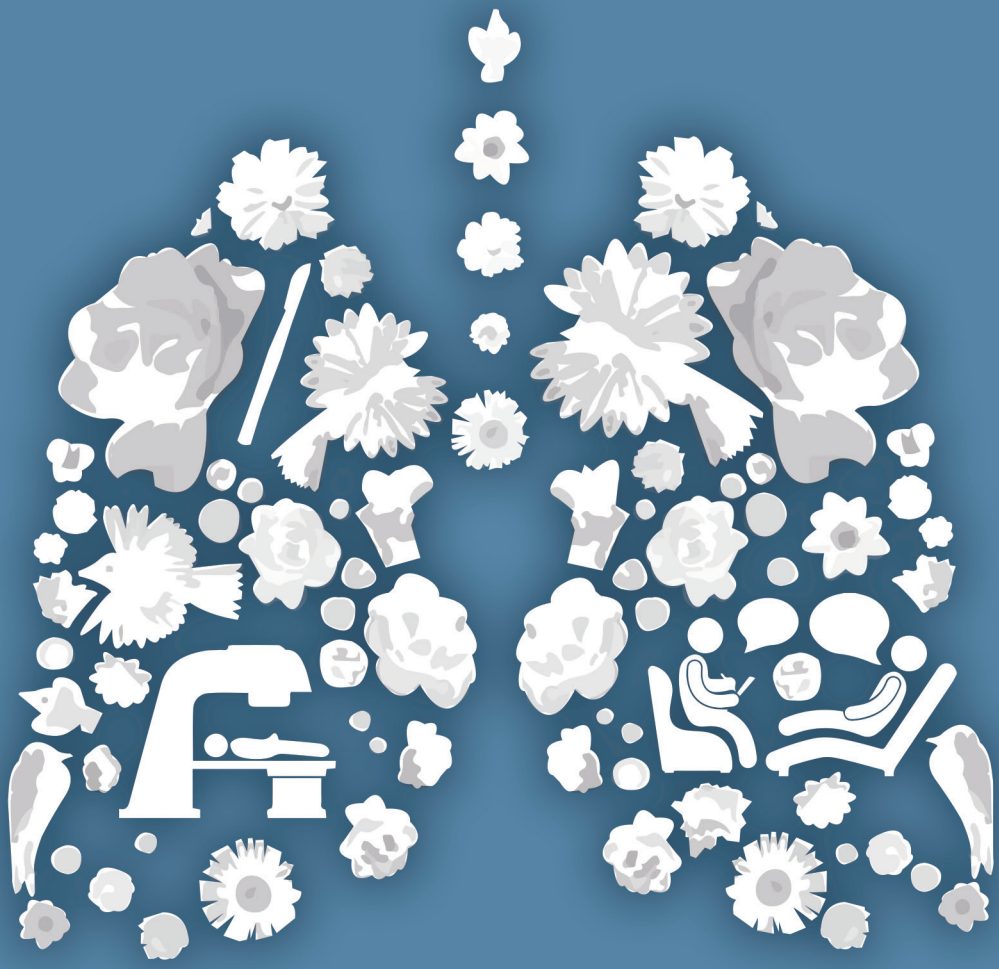

CHAPTER 5

Systematic lymphadenectomy versus sampling of ipsilateral mediastinal lymph-nodes during lobectomy for non-small cell lung cancer:

a systematic review of randomized trials and a meta-analysis

Mokhles S, Macbeth F, Treasure T, Younes, RN, Rintoul R, Fiorentino F, Bogers AJJC, Takkenberg JJM

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ABSTRACT

Objectives. To re-examine the evidence for recommendations for complete dissection versus sampling of ipsilateral mediastinal lymph nodes during lobectomy for cancer.

Methods. We searched for randomized trials of systematic mediastinal lymphadenectomy versus mediastinal sampling. We performed a textual analysis of the authors' own starting assumptions and conclusion. We analysed the trial designs and risk of bias. We extracted data on early mortality, perioperative complications, overall survival, local recurrence and distant recurrence for meta-analysis.

Results. We found five randomized controlled trials recruiting 1980 patients spanning 1989-2007. The expressed starting position in 3/5 studies was a conviction that systematic dissection was effective. Long-term survival was better with lymphadenectomy compared with sampling (Hazard Ratio 0.78; 95% CI 0.69-0.89) as was perioperative survival (Odds Ratio 0.59; 95% CI 0.25-1.36, non-significant). But there was an overall high risk of bias and a lack of intention to treat analysis. There were higher rates (non-significant) of perioperative complications including bleeding, chylothorax and recurrent nerve palsy with lymphadenectomy.

Conclusions. The high risk of bias in these trials makes the overall conclusion insecure. The finding of clinically important surgically related morbidities but lower perioperative mortality with lymphadenectomy seems inconsistent. The multiple variables in patients, cancers and available treatments suggest that large pragmatic multicentre trials, testing currently available strategies, are the best way to find out which are more effective. The number of patients affected with lung cancer makes trials feasible.

INTRODUCTION

The surgical approach to ipsilateral mediastinal (N2) nodes at the time of lobectomy for lung cancer has long been a subject of interest. The European Society of Thoracic Surgeons Guidelines in 2006 stated 'adherence to these guidelines will standardize the intraoperative lymph node staging and pathologic evaluation, and improve pathologic staging, which will help decide on the best adjuvant therapy ' (1). The opening statement of the International Association for the Study of Lung Cancer staging project's proposals for the revision of the N Descriptors in the eighth Edition of the tumour node metastasis (TNM) Classification for Lung Cancer reads: 'Nodal status is considered to be one of the most reliable indicators of the prognosis in patients with lung cancer and thus is indispensable in determining the optimal therapeutic options' (2). The extent of nodal dissection and the number of nodes removed and sent to the pathology laboratory is used as a quality standard in some jurisdictions.

Arguments in favour of more extensive lymph nodes dissection fall into three groups.

1. More accurate N staging makes research comparisons between treatment effects more reliable.
2. More complete N staging provides more information on which to plan already available and novel adjuvant treatments.
3. Removal of unsuspected or microscopic cancer by complete lymphadenectomy maximizes the possibility of cure.

There can be little doubt that systematic ipsilateral mediastinal lymphadenectomy, rather than lymph node sampling protocols, maximizes the information available for pathological staging as far as the ipsilateral mediastinum is concerned. However, in the era of modern imaging and less invasive biopsies, how much it actually adds to staging is open to question (3, 4). Furthermore, an operation for lung resection through either thoracotomy or videothoracoscopy, offers no opportunity to sample nodes on the other side of the chest. These can and, if necessary, should be assessed preoperatively by imaging and one or more of the minimally invasive biopsy techniques now available.

The argument that the chance of additional cures by removal of otherwise undetected lymph node metastases has prompted recent discussion. Lim and eminent European colleagues have argued cogently that if low volume N2 disease does not preclude lung resection then mediastinal dissection at the time of thoracotomy spares the patient preoperative biopsies (5). There appear to be substantial transatlantic differences as outlined by Rocco and colleagues: 'North American surgeons are more likely to surgically stage the mediastinum before operation, are less likely to offer surgical treatment when N2 disease is identified preoperatively, and are more likely to use induction therapy before resection. By contrast, European surgeons may offer operation as the initial treatment followed by adjuvant therapy in selected cases of N2 disease, and they may perform a more aggressive intraoperative nodal dissection' (6)

Furthermore with pressure to reduce the burden of surgery in frail elderly patients or in the presence of comorbidities there is increasing interest in treatment with stereotactic ablative radiotherapy (7). Full pathological N2 staging is not possible, at least not as part of the therapeutic intervention, making it not equivalent to surgery. The same argument has been raised against videothoracoscopy but has largely been resolved by evidence that surgeons experienced in VATS can achieve the required nodal clearance standards (8, 9). If mediastinal dissection is used as a reason for not moving to less invasive means of treating lung cancer, this should be based on sound evidence in the interests of patients.

The use of protocols for mediastinal lymph node dissection (MLND) and mediastinal lymph node sampling (MLNS) have been studied in randomized controlled trials. Four RCTs (10–13) were included in a meta-analysis reported in late 2014 (14). The authors concluded 'Results for overall survival, local recurrence rate, and distant metastasis rate were similar between MLND and MLNS in early stage non-small cell lung cancer (NSCLC) patients. There was no evidence that MLND increased complications compared with MLNS. Whether or not MLND is superior to MLNS for stage II–IIIA remains to be determined.' We have added a fifth study (15) and performed a detailed analysis of the text and the data.

MATERIALS AND METHODS:

Search strategy and selection of studies

A systematic review of literature on surgical policy with respect to mediastinal lymph node sampling or radical lymph node dissection in patients with primary lung cancer was conducted according to the PRISMA guidelines (16, 17). This selection of studies for inclusion was based on predefined eligibility criteria and conducted according to a predefined methodological approach.

Search strategy

An extensive search for published articles was conducted on 1 May 2015 in collaboration with a medical librarian, using among others the electronic databases Medline (Ovid), Embase.com, the Cochrane library and Web of Science. A total of ten databases were searched from inception until May 2015 and updated in April 2016. The main search terms were chosen to identify 'non-small-cell lung cancer' and 'mediastinal lymph node dissection or sampling'. Appropriate thesaurus terms (for Medline, Embase and CINAHL) and words and phrases in title and/or abstract were combined by Boolean logical operators and adapted to the appropriate syntax of each databases. (Full details of databases used, and the syntax for each database, are available as Supplementary Material S1).

Selection of studies

The resulting articles were then screened manually for relevance by two independent investigators (SM and TT). Any disagreement about including an article was to be resolved

by discussion with RY. Studies were included if they reported comparisons of randomly assigned groups of patients undergoing mediastinal lymph node dissection or sampling for NSCLC. We limited our search to studies that were conducted in humans, published in the last 35 years and written in English. We excluded studies not providing analysable data on survival. To ensure that no potentially valid studies were missed, the reference lists of relevant reviews and included studies were cross-checked (SM and TT).

Data extraction

Data were extracted by two of the investigators (SM and TT) using standardized tables developed for this purpose and independently checked by another investigator (RY). From each study, we collected the number of patients, patient baseline characteristics, recurrence rates and overall survival. The risk of bias was assessed (by SM and FM) using the Cochrane Handbook (18) and from information available in the publications. The authors' prior position, the vulnerability of the study design to bias, and the authors' own interpretation of their results were extracted from the text.

Statistical analysis

Overall survival data were extracted as event rates following systematic mediastinal lymph node dissection versus mediastinal lymph node sampling of all randomized comparisons. Where possible hazard ratios (HR) were derived from Kaplan–Meier curves. The method described by Williamson et al. (19) was used to estimate a logarithmic HR with corresponding variance when the number of patients at risk was given at each time frame. If these data were not provided, the method described by Parmar et al. (20) was used. For each study, we used a spreadsheet programmed to estimate the overall HR with 95% confidence intervals (CI) using an inverse variance-weighted average (21). Whereas OR was derived from the percentages of deaths in each arm at the time of reporting (early mortality), the HR gives an estimate of the overall relative survival which is more relevant when considering a time-to-event endpoint. HR was used to calculate absolute mortality risk reduction at 5 years. To illustrate early mortality and complications we used OR as these outcomes are not time-to-event outcomes and therefore differences in length of follow up, the number and timing of events does not have to be taken into account (21).

Reported study characteristics are presented as numbers or percentages in tables. The linearized occurrence rate (LOR) for each late mortality was calculated by dividing the number of deaths by the total follow-up time in patient-years, and then pooled on a logarithmic scale using the inverse variance method within a random-effects model. The pooled LOR was used to estimate the absolute mortality risk reduction at 5 years. Heterogeneity among the included studies was analysed with the I2 measure with values of 25%, 50% and 75% taken to represent, respectively, low, moderate and high heterogeneity (18). Statistical analyses were performed using Review Manager for Windows (22).

RESULTS

Figure 1 illustrates the literature search process. After removal of duplicates, 2489 titles and abstracts were screened. After successive exclusions there were nine articles (10–13, 15, 23–26) reporting five randomized trials from which data were extracted for meta-analysis.

Technical definitions of the procedures in all included studies are provide in Supplementary Material S2 and surgical procedures in Supplementary Material S3.

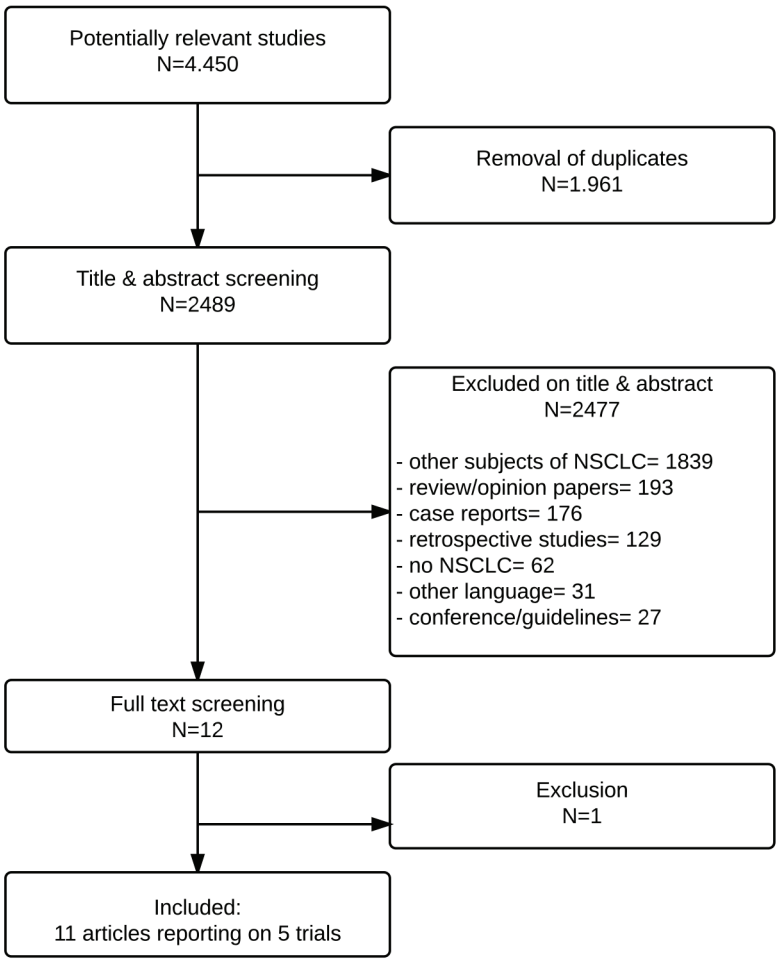

Figure 1. Flow chart of searches

There are variations in the words used and hence in the abbreviations. In the authors' abbreviations S variably stands for either 'sampling' or 'systematic' which are opposites in the context of this analysis. The essential difference under test is between 'systematic' mediastinal lymph node dissection to achieve complete lymphadenectomy, identified in our analysis as (MLND) and lymph node 'sampling' abbreviated to (MLNS). D for dissection, when used, signifies a systematic lymphadenectomy.

In Table 1, we have extracted from the text an indication of the authors' prior position and a summary of their own conclusions.

Table 1. Trialists starting position and conclusions

First author	Start	End	Starting position	Authors' Interpretation of the results
Izbiki	1989	1991	'To what extent (MLND) contributes to the chance of cure remains controversial' (23).	'... (MLND) is a safe operation that can be performed with acceptable morbidity and mortality rates' (23). '(MLND) did not improve survival ... hazard ratio 0.78 95% CI 0.47-1.24' (11).
Sugi	1985	1998	'... pulmonary resection without mediastinal lymph node dissection has been considered a palliative operation' (12).	'... peripheral non-small-cell carcinomas smaller than 2 cm in diameter do not require (MLND)' (12).
Wu	1989	1995	'The usefulness of (MLND) ... is still a matter of controversy in the field of thoracic surgical oncology ' (13).	'As compared with (MLNS) ... (MLND) can improve survival in resectable NSCLC.' (13)
Darlin	1999	2004	'Unfortunately, despite the fact that surgical staging of mediastinal lymph nodes is thought to be important, most surgeons do not perform a complete lymphadenectomy at the time of lung cancer resection' (26)	'...no difference in local (P=0.52), regional (P=0 .10), or distant (P=0.76) recurrence between the two groups.' (MLNS)(MLND) (10) There was no difference in survival (P=0.25) (10).
Zhang	2006	2007	'Compared (MLNS), (MLND) carries the potential advantage of accurate staging and survival benefit. But it may also be associated with increased surgical risks by prolonging operation time, increasing blood loss, and resulting in more complications' (15).	'(MLND) and (MLNS) have similar surgical risks and mediastinal staging effect in patients with NSCLC' (15). '(MLND) had significantly better five-year survival than (MLNS) (55.7% vs. 37.7%, P=0.005)' (15)

MLND: mediastinal lymph node dissection; MLNS: mediastinal lymph node sampling.

Risk of bias

Table 2 shows that all five trials were at risk of bias with the method for sequence generation and allocation concealment. Three trails failed to carry out an intention to treat analysis.

Table 2. Risk of bias assessment based on information presented in the publications

STUDY	Sequence generation	Allocation concealment	Blinding	Incomplete outcome reporting	Selective outcome reporting
Izbicki et al	Clear	Unclear	Not possible	Yes: No ITTA	No
Sugi et al	Unclear	Unclear	Not possible	Unclear	No
Wu et al	Unclear	Unclear	Not possible	Yes: No ITTA	No
ACOSOG	Unclear	Unclear	Not possible	Yes: No ITTA	No
Zhang et al	Unclear	Unclear	Not possible	Unclear	No

ITTA: intention to treat analysis.

Results of the meta-analysis

For perioperative survival (Figure 2A) there was an overall nonsignificant difference in favour of the more radical arms (MLND) compared with sampling (MLNS) (Odds Ratio for death 0.59 (95% CI 0.25-1.36)). This was largely due to the ACOSOG Z0031 trial. Overall survival (Figure 2) was greater after mediastinal dissection than after sampling (HR 0.78 (95% CI 0.69-0.89) Absolute mortality risk reduction at 5 years was calculated using the LOR calculated from the HR. For the (MLND) group the pooled LOR was 0.0688 (i.e. late mortality of 6.88% per year) and for the (MLNS) group this was 0.578 (i.e. late mortality of 5.78% per year). We have considered these LOR from three studies in the MLND and MLNS groups as the most reliable estimate of late mortality (10–12). Absolute mortality risk at 5 years for the MLNS group was 34.4%. A HR of 0.78 (Figure 2B) was considered as the baseline risk for overall mortality, and this information was used to calculated the relative mortality risk reduction (MLND compared to MLNS) of 0.22. The relative mortality risk reduction and 5 year risk of death in the MLNS group resulted in absolute mortality risk reduction of 7.6% in favour of MLND group.

Local recurrence (Figure 2C) was non-significantly lower after MLND (55/900; 6.1%) than sampling (75/878; 8.5%. P=0.12). Distant recurrence (Figure 2D) was also non-significantly lower after MLND (191/900; 21.2%) rather than sampling (219/878; 24.9%. P=0.07). However, complications (Figure 3) were generally higher after dissection than after sampling. Bleeding 4% vs 2.8%; bronchial secretions 12.1% vs 7.7%; chylothorax 1.8% vs 0.7%; recurrent

laryngeal nerve injury 2.4% vs 1.1%. As expected, the burden of complications (Figure 3) is greater for MLND due to the more extensive dissection. These included bleeding, chylothorax and recurrent nerve injury.

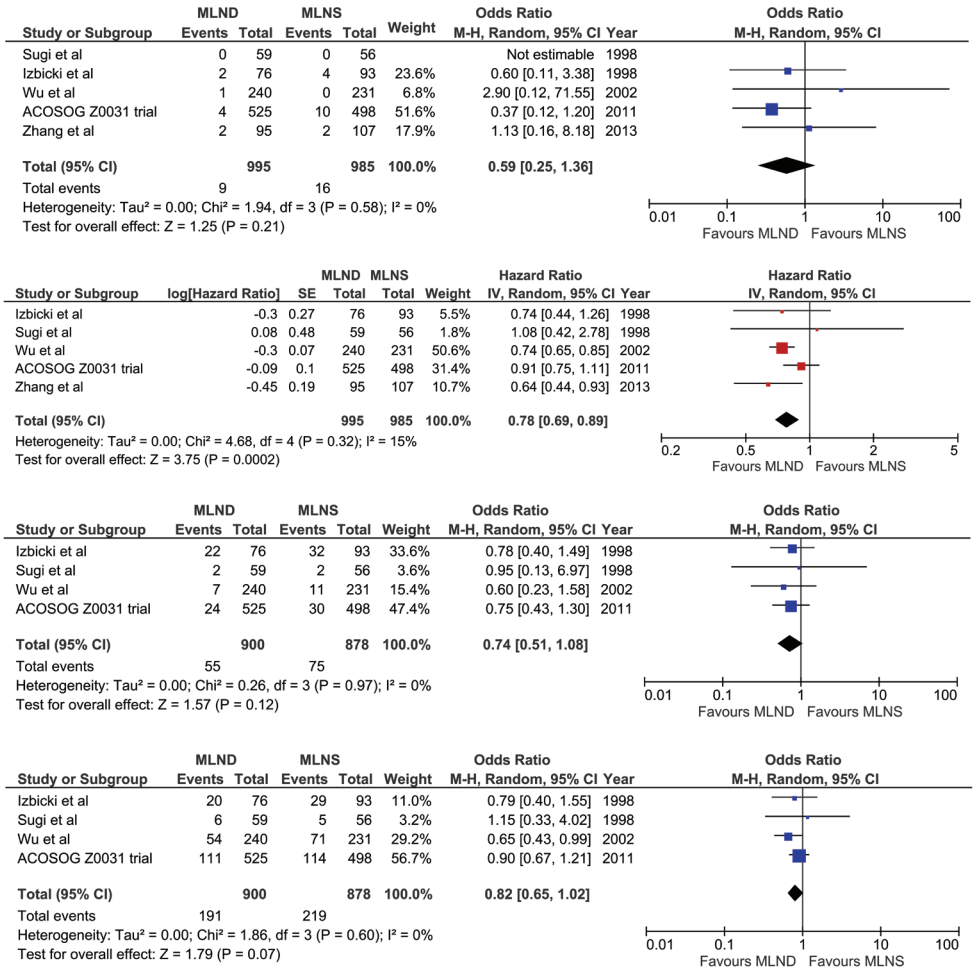

Figure 2 a to d. Forest plots of comparison in meta-analysis. (A) Early mortality odds ratio. (B) Late mortality hazard ratio. (C) Local recurrence odds ratio. (D) Distant recurrence odds ratio.

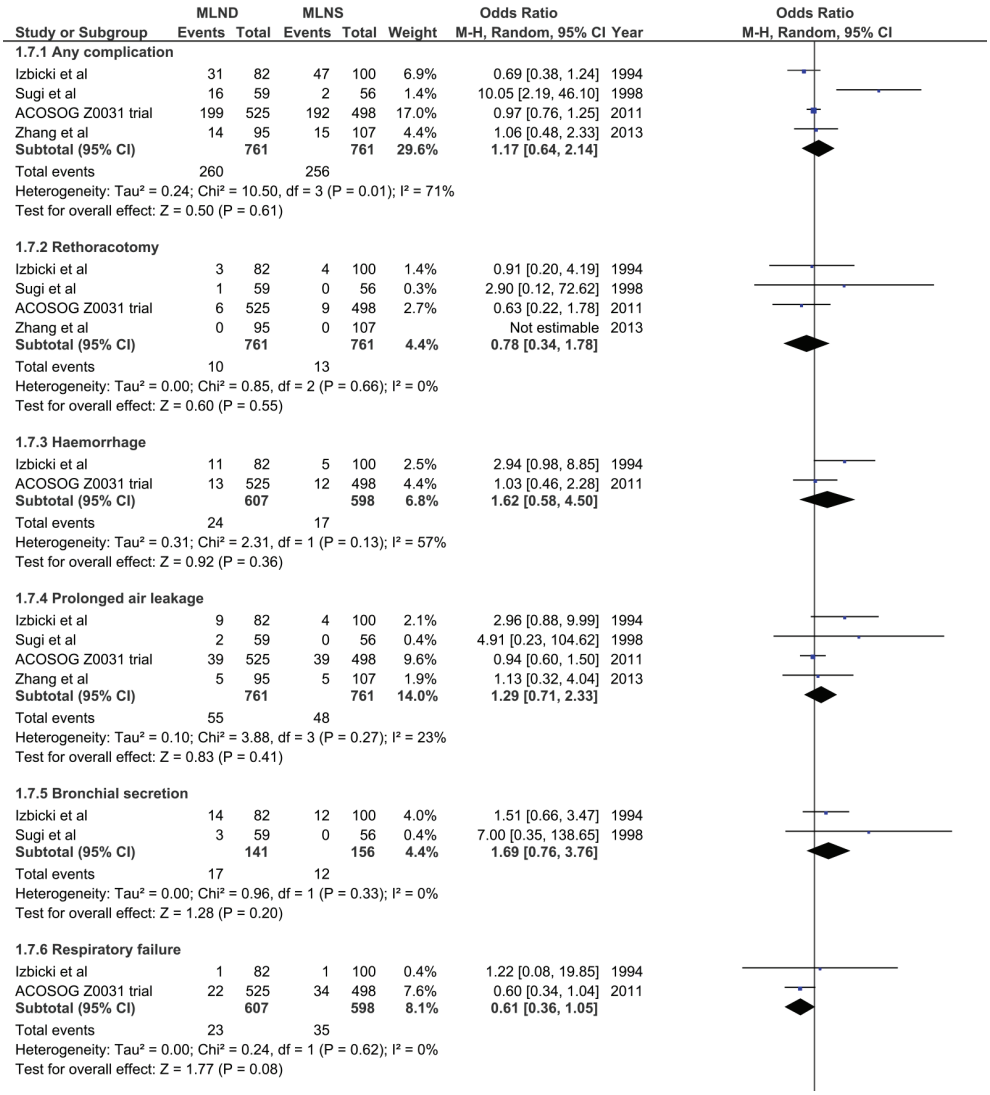

Figure 3. Perioperative complications with Odds Ratio.

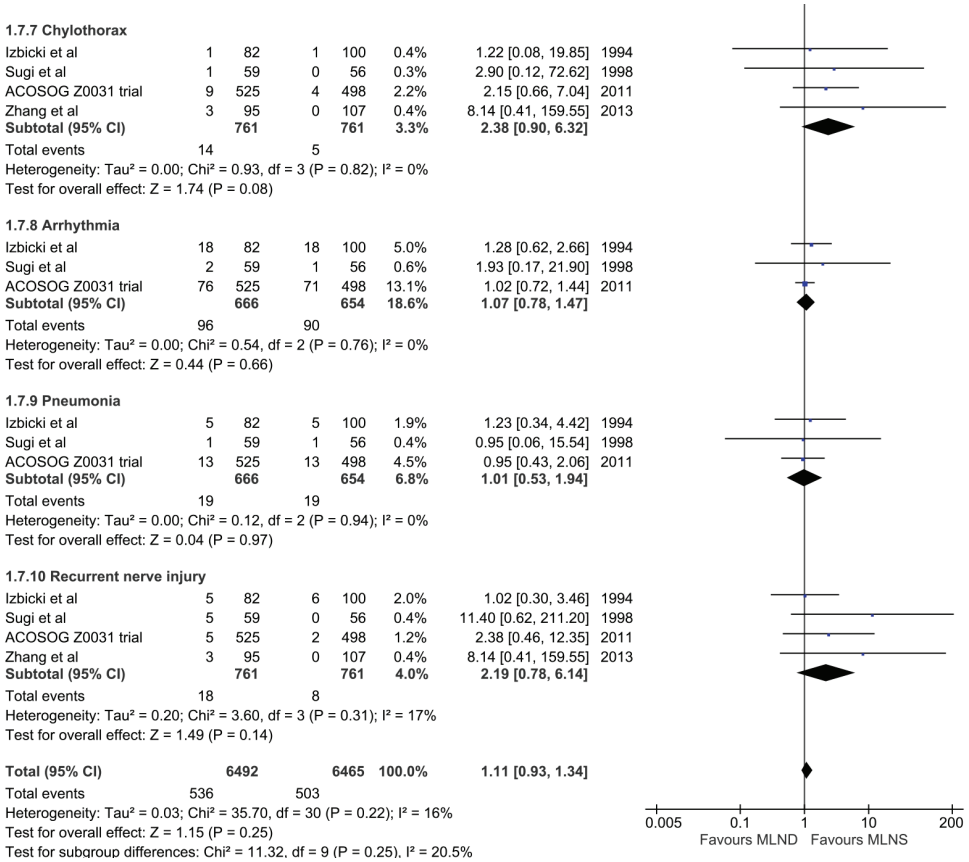

Figure 3. Continued.

DISCUSSION

The main objective of additional, more complex surgery is to provide a benefit that outweighs any additional risk. In this meta-analysis of 1980 patients, the HR for overall survival was 0.78 (95% CI 0.69-0.89) favouring systematic lymphadenectomy (MLND) rather than sampling (MLNS) and this equates with an absolute reduction in risk of death at 5 years of 7.6%. (Figure 2B) If these data are reliable this would be clinically significant confirming this procedure as standard. It would also provide a caveat about equivalence of stereotactic ablative radiotherapy instead of surgery for primary lung cancer. There are however, a number of things that reduce confidence in the validity of this conclusion.

How do we explain the better perioperative survival (Figure 2A) associated with the more extensive lymphadenectomy (MLND)? This is counterintuitive and is made more so by the tally of complications (Figure 3). As might be expected, bleeding (P=0.36), chylothorax

(P=0.08) and recurrent nerve injury (P=0.14) were all more frequent with the more extensive surgery; although not statistically significant in this analysis they are anticipated complications of more extensive surgery in the mediastinum. Despite the excess morbidity with (MLND) the early mortality was lower. In unblinded trials, run by doctors with a vested interest in the outcome, there are opportunities for reassignment or exclusion of patients in trials. The exercise of bias may be unintentional but later we will discuss data which suggest it may have happened.

These five trials were intended to test in survival terms the 'effectiveness' of extending the surgery performed at the time of lobectomy to include lymphadenectomy. This has direct bearing on three distinct drives for change in clinical practice.

1. When stereotactic radiotherapy is used as treatment for primary lung cancer rather than lobectomy (28) lymphadenectomy is precluded.
2. When videothoracoscopic surgery is used instead of open lobectomy, the prior assumption is that lymphadenectomy is less often complete (8).
3. An increasing role of lymphadenectomy will be to provide more tissue and more complete staging to guide multimodality therapy (29).

Despite a difference in overall survival, lymphadenectomy was not associated with a significant reduction in the rates of either local or distant recurrence and we cannot infer from the trials whether the apparent effect on survival is due to removal of more involved nodes having a beneficial effect on survival or the information from more accurate nodal staging guiding adjuvant treatment with consequent benefit. Only three studies mention the use of postoperative radiotherapy and it is not clear if the rates of use varied. Chemotherapy is not mentioned in the any of the reports of three of the trials (11, 13, 15, 23, 24). Use of preoperative chemotherapy was an exclusion criterion in one of the trials (26) and was used in a few cases where small-cell lung cancer or a non-lung primary was the cause of mediastinal nodal metastases (12). It is not clear whether or not adjuvant chemotherapy was given to patients with N2 disease in any of the studies; this might have made a different in outcomes.

It is also possible that the additional knowledge concerning staging obtained during the study influenced the composition of the reported trial arms in two of the studies. In the ACOSOG Z0030 trial, all patients had sampling and frozen section and the protocol required patients with any positive nodes to not be randomized (26). We are not told how many patients were excluded in this process and we cannot estimate what effect, if any that would have on the conclusions. After randomization and presumably in the knowledge of findings during the trial 'retrospective review found 155 patients to be ineligible for participation'. It appears that this was a decision which included knowledge of pTNM thus nullifying the intention to treat principle. This revision of the assigned arms

took out 14% of randomized patients (155/1111) and overall there was an imbalance of 5% between the arms.

In the table of staging provided in the report by Wu and colleagues (13) the distribution between stages I, II and III was 42%, 30% and 28% for patients having sampling but was 24%, 28% and 48% for patients having systemic nodal dissection. In the design of the trial, these should have been according to clinical staging (cTNM). We suspect that the intraoperative findings may have been used to restage the patients by pTNM thus inadvertently violating the randomization process by reassigning the patients on the basis of trial findings. The revised staging has subsequently been used to make stage specific comparisons which are therefore erroneous (13). If there is a 20% stage shift between the three stages, occult N2 disease, undiscovered by sampling is very common. What we cannot deduce is whether mediastinal nodal dissection will then alter the outcome for the patient. This illustrates the distinction to be made between 'efficacy' and 'effectiveness' as used in evidence based medicine. The 'efficacy' of removing more nodes in discovering more microscopic metastases was not the question and indeed was never in doubt: the harder you look the more you see.

The textual analysis reveals potentially important information. The authors of two studies state a prior conviction concerning the value of MLND (12, 26) There are sources of potential bias in these trial reports which are summarized in Table 2. In particular, in three of the five do not provide an intention to treat analysis and significant numbers of patients were excluded postrandomization. In the other two reports, it was not clear whether there was an intention to treat analysis and in Wu et al. (15) there was >10% imbalance between the two arms, which was not explained.

The clinical context has changed over time. Four out of five trials predate the routine use of positron emission and computerized tomography (PET/CT) scanning in the preoperative staging of patients with NSCLC. No authors mention the use of postoperative adjuvant chemotherapy which is considered standard for those with Stage III disease. So any conclusions drawn are less applicable to current practice.

The assessment of risk of bias (Table 2) shows that there are methodological uncertainties for all the studies. Of particular concern is the lack of intention to treat analysis in three of them and uncertainty about it in the other two. There are few randomized studies of the effectiveness of surgery in lung cancer and the RCTs which we have found and analysed here show poor reliability. Four of these RCTs were included in a previous meta-analysis reported in late 2014 (14). We have added a fifth study and performed a detailed analysis of the text and the data. A further meta-analysis including four RCTs and eight nonrandomized studies has been completed. The limitations we have indicated above have not been overcome (30). The claimed survival benefit from mediastinal dissection is not supported by reliable evidence and ideally its overall value should be tested in a large

pragmatic randomized trial involving contemporary diagnostic, surgical and oncological practice as has been proposed as a trans-Atlantic collaboration (6). It would have to run by an independent clinical trials unit. Until and unless the results of such a trial are available, patients should be made aware of the risks and benefits of each of the approaches and participate in a shared decision making discussion with their physician/surgeon on the best option for their individual situation. The authors are willing to work towards setting up such a trial and between us we have a track record in being involved in and leading multicenter clinical trials of oncology and surgery.

Supplementary material

Supplementary material is available at EJCTS online.

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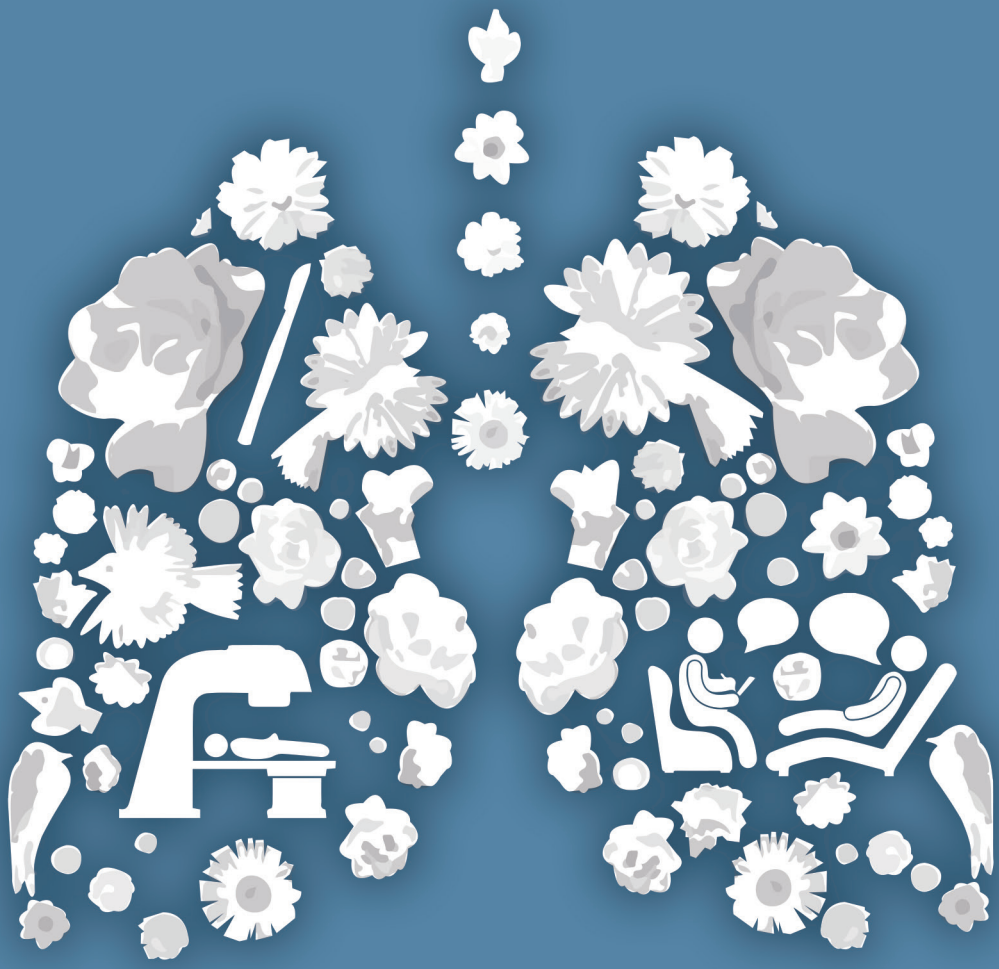

CHAPTER 6

Quality of life during 5 years after stereotactic radiotherapy in stage I non-small cell lung cancer

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ABSTRACT

Purpose. To determine the long term impact of stereotactic radiotherapy (SRT) on the quality of life (QoL) of inoperable patients with early-stage non-small cell lung cancer (NSCLC).

Methods and materials. From January 2006 to February 2008, 39 patients with pathologically confirmed T1-2N0M0 NSCLC were treated with SRT. QoL, overall survival and local tumor control were assessed. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 and the lung cancer specific questionnaire QLQ-LC13 were used to investigate changes in QoL. Assessments were done before treatment, at 3 weeks, every 2-3 months during the first two years, and then every 6 months until 5 years after the treatment or death or progressive disease. The median follow up was 38 months.

Results. During the 5 years after treatment with SRT for stage I NSCLC, the level of QoL was maintained: There was a slow decline (slope: -0.015) of the global health status over the 5 years (*p-value*<0.0001). The physical functioning and the role functioning improved slowly (slope: 0.006 and 0.004, respectively) over the years and this was also significant (*p-value*<0.0001). The emotional functioning (EF) improved significantly at 1 year compared to the baseline. Two years after the treatment dyspnea slowly increased (slope: 0.005, *p-value* 0.006). The actuarial overall survival was 62% at 2 years and 31% at 5 years.

Conclusion: QoL was maintained 5 years after SRT for stage I NSCLC and EF improved significantly. Dyspnea slowly increased 2 years after the treatment.

INTRODUCTION

Stereotactic radiotherapy (SRT) has proved to be a good alternative treatment to surgery for medically inoperable patients with early stage non-small cell lung cancer (NSCLC). Prospective trials evaluating the use of SRT showed excellent local tumor control rates (78%–97%) (1). Overall survival, while more variable, has improved compared to historical controls (1, 2). The treatment is well tolerated, even in elderly patients (3, 4). An essential goal in any cancer treatment is to maintain or improve the patients' quality of life (QoL). However, only a few publications have evaluated the impact of treatment on the patients' QoL. SRT does not lead to significant worsening of health related quality of life (HRQoL) in the first year after treatment. Patients referred for SRT have substantially worse baseline HRQoL scores than those reported in the surgical literature and clinically relevant deteriorations in HRQoL subscale scores were not observed after SRT (5). QoL was evaluated in medically inoperable patients with NSCLC treated either with SRT or conventional three-dimensional conformal radiotherapy. At one year patients treated with SRT had a stable global QoL and physical functioning (PF) and dyspnea, while patients treated with 3D-CRT had a decreased PF approaching clinical significance (6). In 2009 we published the results of the QoL one year after treatment with SRT, using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) C30 and lung cancer-specific supplementary questionnaire QLQ-LC13. QoL was maintained and the emotional functioning (EF) improved significantly. Other function scores and QLQ-C30 and QLQ-LC13 lung symptoms (such as dyspnea and coughing) showed no significant changes (7). To our knowledge, this is the first study to report the outcome of QoL 5 years after SRT for patients with stage I NSCLC.

METHODS

Patients and treatment

Between January 2006 and February 2008, 43 patients who refused surgery or had an inoperable stage T1-2N0M0 NSCLC entered our prospective phase II trial. The trial was accepted by the Medical Ethical Committee of the Erasmus Medical Center (METC Erasmus MC number: 2005-300) and was in agreement with the Declaration of Helsinki. Pathological confirmation of malignancy was obtained for all patients. Diagnostic staging included computed tomography (CT) scanning of all patients and positron emission tomography (PET) scanning for all but 4 patients. Four patients were excluded from analysis due to a lack of pretreatment assessment (n=2), progressive disease 3 weeks after treatment (n=1), and 1 patient declined to participate after inclusion. Comorbidity was registered using the Charlson Comorbidity Index and the Cumulative Illness Ranking Score (8, 9). Patient characteristics are listed in Table 1. One patient included in this analysis had a T2 tumor at the time of inclusion but a T3 tumor at the time of treatment.

Table 1. Patient and tumor characteristics*

Characteristic	No. of patients (% of total)
Medically inoperable	33 (85)
Refused surgery	6 (15)
Charlson Comorbidity Score	
0-2	20 (51)
0-3	13 (33)
<3	6 (15)
Median Cumulative	6 (2-16)
Illness Ranking (range)	
Incidence of COPD	22 (56)
Tumor location	
Peripheral	33 (85)
Central	6 (15)
T-classification	
T1	17 (44)
T2	21 (54)
T3	1 (3)
Histology	
Squamous cell carcinoma	14 (36)
Large cell carcinoma	13 (33)
Adenocarcinoma	8 (21)
Other	4 (10)
PTV median (cc) (range)	46 (7–609)

* Median age, 77 years (range, 55–87 years). No=number; PTV=Planning Target Volume.

All patients were treated with real-time tumor tracking using the CyberKnife (10). The technique has been described previously (11). Treatment consisted of 60 Gy in 3 fractions for 30 patients. A risk-adaptive treatment schedule consisting of 48 to 50 Gy in 5 to 6 fractions was used to treat 6 patients with central tumors and 1 patient with a large T2 tumor. Two patients were treated with 45 Gy in 3 fractions by choice of the treating physician. Treatment dose was prescribed to the 78 to 87% isodose line, covering at least 95% of the planning target volume (PTV). The maximum dose was defined by the 100% isodose line. Treatment planning was done with the On Target treatment planning

system version 3.4.1 (Accuray Inc., Sunnyvale, CA). Correction for tissue inhomogeneity was achieved by using the equivalent path length algorithm. None of the patients were treated with chemotherapy prior to treatment or in an adjuvant setting.

QoL instruments

QoL assessments were performed before treatment, at 3 weeks, and at 2, 4, 6, 9, 12, 15, 18, 21 and 24 months after the treatment. After 24 months, the assessments were performed every 6 months until 5 years after the treatment or death or progressive disease. Patients with evidence of progressive disease were excluded from further analysis to prevent bias caused by disease progression or treatment of progressive disease. QoL was evaluated by means of the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire, Quality of Life Questionnaire (QLQ) C30 (version 3.0), and supplementary lung cancer-specific module QLQ-LC13. The QLQ-C30 is a 30-item questionnaire composed of five functional scales, three symptom scales, a global health status/QoL scale, and six single items. The single items assess additional symptoms commonly reported by cancer patients. This questionnaire has proven to be a valid and reliable tool when used among a wide range of cancer patient populations, including lung cancer patients (12). The lung cancer module is designed for patients with various disease stages treated with chemotherapy and/or radiotherapy. It consists of 13 questions assessing lung cancer-associated symptoms, treatment-related side effects, and pain medication. The EORTC QoL and symptom measures were rescaled to percentages (scores 0 to 100%) through linear transformation. A high score for the function and QoL scales represents a high level of functioning/high QoL, whereas a high symptom score represents a high level of symptoms. The questionnaires have been translated and validated for use in a Dutch population.

Follow up and toxicity scoring

The first clinical examination was performed 3 weeks after SRT. Clinical follow up was performed every 3 months, and a CT scan was performed at 2, 4 and 6 months, and every 3 months thereafter. After 2 years it was performed every half year up to 5 years. The patient's physician scored the toxicity at each-out patient visit, using common terminology criteria for adverse events version 3.0. There was acute toxicity if it occurred within 4 months and late toxicity if it occurred thereafter.

Statistical analyses

The data in the present study were analyzed with mixed-effects models to evaluate changes over time in the mean QoL and symptom scores. Mixed-effects models are an appropriate tool for the analysis of dependent data such as data collected in a hierarchical manner, e.g. when a number of observations are collected over time on the same patient (13, 14). The advantage of using mixed-effects models is that they model the evolution of a longitudinal outcome over time while accounting for the correlation between repeated

measurements in each patient. Moreover, these models are able to deal with unbalanced data, that is when the number of observations per individual is not the same, or when time between repeated measurements of each individual varies. Specifically, mixed-effects models consist of the fixed and the random effects. The fixed effects describe the average evolution in time of a specific longitudinal outcome (e.g. one of the five functional scales), while the random effects describe the evolution in time of each patient. Due to heterogeneity in the residuals plot, the logarithmic scale was used for some variables. Missing values due to non-response of questionnaire were assumed to be missing at random, which means that the missing value was assumed to be independent of the unobserved measurement (14, 15). All analyses were performed with the R statistical software (version 2.13.2, 2011. R Development Core Team 2011, R Foundation for Statistical Computing, Vienna, Austria). All statistical tests with a *p-value* of 0.05 or lower were considered significant. Overall survival was measured from the start of radiotherapy until death by any cause. Patients still alive at the date of last contact were censored. Local tumor control was calculated from the first day of treatment until the diagnosis of a local recurrence. Patients without a local recurrence were censored on the last day of contact. In the absence of biopsy confirmed viable carcinoma, local recurrence was defined as a 20% increased longest-tumor dimension on the CT scan compared to the previous CT scan. In addition, a corresponding avid lesion on the PET scan was required.

RESULTS

Compliance with QoL assessments

QoL was assessed in 39 patients. The mean compliance over the 5 years was more than 93% (range 78-100%). At 5 years 10 patients were still alive without progression. The details are shown in Table 2.

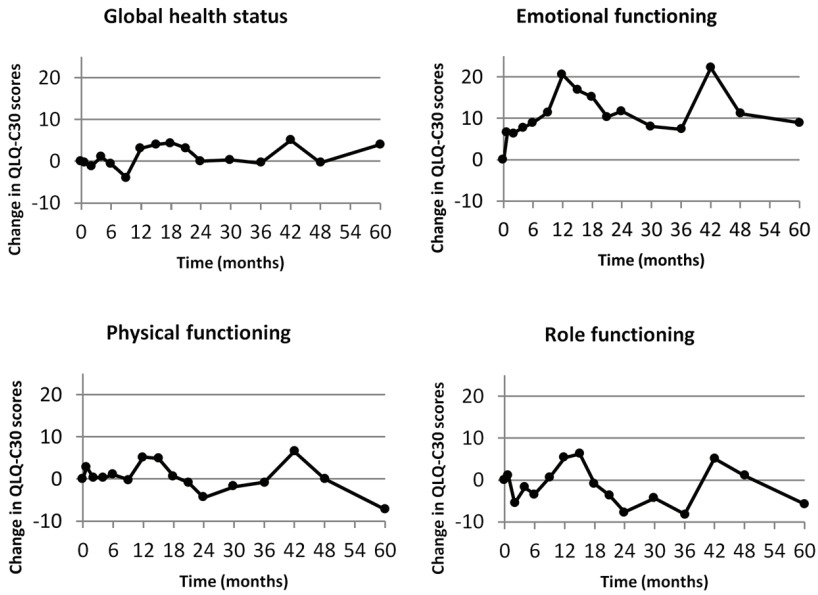
QoL and baseline symptoms

Changes in QLQ-C30 mean global health status (GH) and function scores (EF, PF and RF) during follow up are shown in Figure 1. Changes in QLQ-LC13 mean symptom scores (dyspnea, coughing and fatigue) are shown in Figure 2. During the first year, the global health status was near the baseline value, improved to a score of 4 at 18 months and then significantly declined (slope: -0.015) to the baseline value during the next years. The PF score as well as the role functioning (RF) significantly improved slowly (slope: 0.006 and 0.004, respectively) over the years. Due to the fluctuation of the EF score over the 5 years, the changes over time were not significant, but the mean EF score at 1 year was significantly different compared to the pretreatment score (*p-value* 0.0003). The small rise (slope: 0.004) over time in the cognitive functioning was also significant (*p-value* 0.004), but not the social functioning.

Table 2. Compliance with QoL assessments

Time (months)	Compliance (%)	Number of patients still alive without progression
0.75 (3 weeks)	90	35/39
2	95	35/37
4	95	35/37
6	100	36/36
9	96	27/28
12	95	20/21
15	95	19/20
18	100	20/20
21	95	19/20
24	95	19/20
30	95	18/19
36	78	14/18
42	87	13/15
48	86	12/14
60	100	10/10

Figure 1. Change in mean global health and functional scores



The dyspnea score increased during the first 6 months to a score of 6, then ameliorated after the 1st year. During the following years, the dyspnea score gradually increased to a score of 17 at 5 years. This increase (slope: 0.005) over time was significant (*p-value* 0.006) for the data from the QLQ-C30 but not for the data from the QLQ-LC13. The coughing score increased to 4 at 3 weeks after the treatment and slowly decreased during the first 2 years to -11. After the first 2 years, the score increased to a score of 8 at 5 years (*p-value* 0.57). The fatigue score at one year decreased to a score of -10, but raised thereafter to a score of -0.6 at 5 years. This slow increase (slope: 0.003) over the 5 years (*p-value* 0.05) was significant.

Overall survival and local tumor control

The overall survival rate was 62% at 2 year and 31% at 5 years. Twenty-seven patients died; 12 patients died from metastatic disease, and 15 patients died from intercurrent disease. Causes of intercurrent death are shown in Table 3. Local tumor control was 97% at 2 years and 93% at 5 years. Two patients had a local recurrence. The disease free survival was 69% at 2 years and 52% at 5 years. Fourteen patients had distant metastases. Of the 14 patients with distant metastases, 6 patients had mediastinal lymph nodes. There were no patients with isolated regional recurrence. The median follow up was 38 months (range 4-71 months).

Toxicity

Treatment related grade 4 or 5 toxicity didn't occur. Twelve patients had no acute side effects at all. The most common grade 1 and 2 toxicities were respiratory (dyspnea and coughing). Acute grade 2 toxicity involved 12 patients, of which 6 with dyspnea, 1 with esophageal pain, 1 with thoracic pain and 4 with coughing. There were 14 patients with late grade 2 toxicity: dyspnea and thoracic pain occurred both in 6 patients and chronic cough in 2. Two patients had acute grade 3 toxicity, 1 with dyspnea and 1 with thoracic pain. Late grade 3 toxicity occurred.

Figure 2. Change in mean QLQ-LC13 dyspnea, coughing and fatigue scores

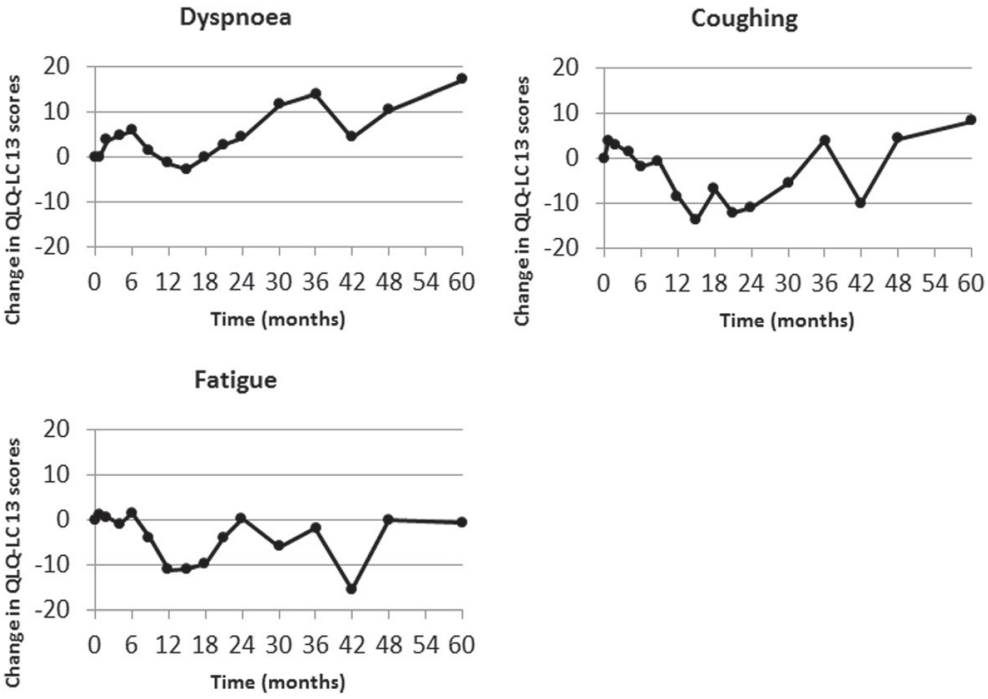


Table 3. Causes of death

Cause of death	Number of patients (N=27)
Metastatic disease	12
Intercurrent	15
Cardiovascular	3
Mortality during surgery (AAA)	1
Sudden death of unknown cause	3
General deterioration	6
Pulmonal infection	2

DISCUSSION

We observed that QoL was maintained 5 years after SRT. The global health increased during the first 1.5 years but decreased thereafter to the baseline. The PF and RF significantly improved slowly, although the improvements were small. The EF improved significantly in the first year, but declined thereafter. Respiratory symptoms (dyspnea and coughing) did not get worse in the first two years, although it slowly increased in the next years after SRT.

Four other studies have reported health related quality of life outcomes (HRQoL) after SRT in patients with early stage NSCLC (2, 5, 6, 16). These studies report on the QoL one to three years after the SBRT. Widder et al. investigated changes of HRQoL parameters after SRT (202 patients) and 3-D treatment (27 patients) in two prospective cohorts of inoperable patients. In all studies, global QoL and PF were stable after treatment, no statistically or clinically significant worsening of any of the HRQoL functioning or symptom scores at any follow up time point was observed in our and other mentioned studies (5, 6, 16). Most noticeable difference is that our study showed a statistically significant improvement of the EF at 1 year. Mathieu et al. did report a trend in QLQ-C30 emotional score improvement of 14 at 36 months (16).

A prospective study with patients diagnosed with early stage lung cancer undergoing 3D-CRT showed a gradual and significant increase in dyspnea, fatigue, and appetite loss, together with a significant deterioration of RF compared to the baseline measurement. The global QoL did not deteriorate, EF did not improve. Their hypothesis for worsening of dyspnea and fatigue was because of preexisting, slowly progressive chronic obstructive pulmonary disease (COPD) and radiation-induced pulmonary changes (17).

Langendijk et al. investigated the effect of respiratory symptoms on QoL in patients with stage I-III lung cancer during the first 2 years after the treatment. At the baseline, dyspnea was the most important and significant respiratory symptom affecting all EORTC scales, with the exception of EF (18).

In comparison with surgery, the HRQoL after stereotactic radiotherapy compared to HRQoL after the surgery is at 3 or 6 months after the treatment in general better. Poghosyan et al. reviewed 19 out of 337 studies and concluded that participants had worse physical function at 6 months after surgery and had decreased physical function up to 2 years after surgery, compared to the pre-surgical status. Pain, fatigue, dyspnea and coughing were the most prevalent symptoms. Increased levels of dyspnea and fatigue persisted for at least 2 years after surgery. Kenny at al. who studied the HRQoL in 173 patients with stage I and II NSCLC reported that surgery substantially reduced HRQoL across all dimensions except emotional functioning. HRQoL improved in the 2 years after surgery for patients without disease recurrence, although approximately half continued to experience symptoms and functional limitations.

There is not much known about the quality of life more than 2 years after the treatment in patients with early stage lung cancer. It is generally known that patients with COPD have a decline of their long function over time. This is mainly based on the study of Fletcher and Peto (19). More than 35 years ago, they did report on the natural history of tobacco smoke-related chronic airflow obstruction. Fletcher and Peto measured the forced expiratory volume in 1 second (FEV1) every 6 months for an 8 year follow up period in a cohort of 792 working men and concluded that a lower FEV1 declined greater for similar intervals of time in COPD patients who smoked. However recent research found that patients with COPD GOLD stage I had a decline of about 40 ml/year, patients with COPD GOLD stage II a decline of 47-79 ml/year, patients with COPD GOLD stage III, a decline of 56-59 ml/year, and patients with COPD GOLD stage IV a decline of <35 ml/year (20, 21). Many of our patients had COPD. The dyspnea score increased during the first 6 months to a score of 6, then ameliorated after the 1st year (score -3). During the following years, the dyspnea score gradually increased to a score of 17 at 5 years. So the increase of the dyspnea score after the 1st year can be related to decline of the lung function over time or due to the radiotherapy. Probably it is caused by both. Several studies did report on the QoL in patients with COPD. Carrasco Garrido et al. did report on the HRQoL in 10711 patients and concluded that patients with stable COPD stages 2-4 did show a reduction of their HRQoL, even in mild stages of the disease. The factors determining the HRQoL include sex, FEV1, use of oxygen therapy, and number of visits to emergency rooms and hospital admissions (22). Bridevaux et al. studied 519 patients with COPD GOLD stage I and concluded also that these patients have a lower QoL than the 3627 asymptomatic subjects with normal lung function. The slow decline of the global health (GH) score over the last 3 years is maybe caused by the decrease of the lung function and increase of dyspnea in our patients, but the PF score as well as the RF ameliorated slowly over the years. However, the impact in COPD in patients with lung cancer is not completely clear (23). Mohan et al. studied 160 patients with COPD and stage III and IV lung cancer and concluded that no significant differences were found in clinical profile, Karnofsky performance status, or QoL scores between patients with and without COPD (24). On the other hand, Gore et al. compared the QoL in end-stage COPD patient with NSCLC patients and concluded that the end-stage COPD patients experienced a poor HRQoL comparable to or worse than that of advanced NSCLC patients (25).

The actuarial overall survival of our study was 62% at 2 years and 31% at 5 years. The actuarial local tumor control was 97% at 2 years and 93% at 5 years. This is in agreement with other studies: Widder et al. reported estimates at two years for 3D-CRT versus SRT of 48% versus 72% for overall survival (OS), and 78% versus 95% for local control (LC), respectively (6). In the patient-report of Lagerwaard et al. HRQoL data were collected prospectively in 382 consecutive patients treated with SRT. The median survival was 40 months, with a 2 year OS of 66% (5).

In our study the overall compliance was more than 93%, so the missing data of QoL assessments is minimal. Though, the major limitation of this study was the small number of patients with increasing follow up time. Therefore the study has not enough power and should be seen as descriptive, as this is the first report about QoL during 5 years. More research will be needed, especially a bigger number of patients for more data.

CONCLUSIONS

During the 5 years after treatment with stereotactic radiotherapy for stage I NSCLC, the level of QoL was maintained. There was a slow decline of the Global Health status over the 5 years (*p-value*<0.0001). The physical functioning score as well as the role function score did ameliorated slowly over the years and this was also significant (*p-value*<0.0001). The emotional functioning improved significantly at 1 year compared to the baseline. Two years after the treatment, the dyspnea slowly increased.

Abbreviations

SRT: Stereotactic radiotherapy; QoL: Quality of life; NSCLC: Non-small cell lung cancer; EORTC: European organization for research and treatment of cancer; QLQ: Life questionnaire; EF: Emotional functioning; HRQoL: Health related quality of life; PH: Physical functioning; METC: Medical ethical committee; CT: Computed tomography; PET: Positron emission tomography; PTV: Planning target volume; RF: Role functioning; FEV1: Forced expiratory volume in 1 second; GH: Global health; OS: Overall survival; LC: Local control.

Competing interests

Erasmus MC Cancer Institute has a research collaboration with Accuray Inc.

Authors' contributions

JU: Contribution to acquisition data, analysis and interpretation data, drafting the article, final approval. SM: acquisition data, interpretation data, revising article, final approval. EA: statistics, interpretation data, revising article, final approval. CB: acquisition data, revising article, final approval. NV: acquisition data, interpretation data, revising article, final approval. SA: interpretation data, revising article, final approval. JA: interpretation data, revising article, final approval. JN: Contribution to conception and design, acquisition data, analysis and interpretation data, drafting the article, revising article, final approval. All authors read and approved the final manuscript.

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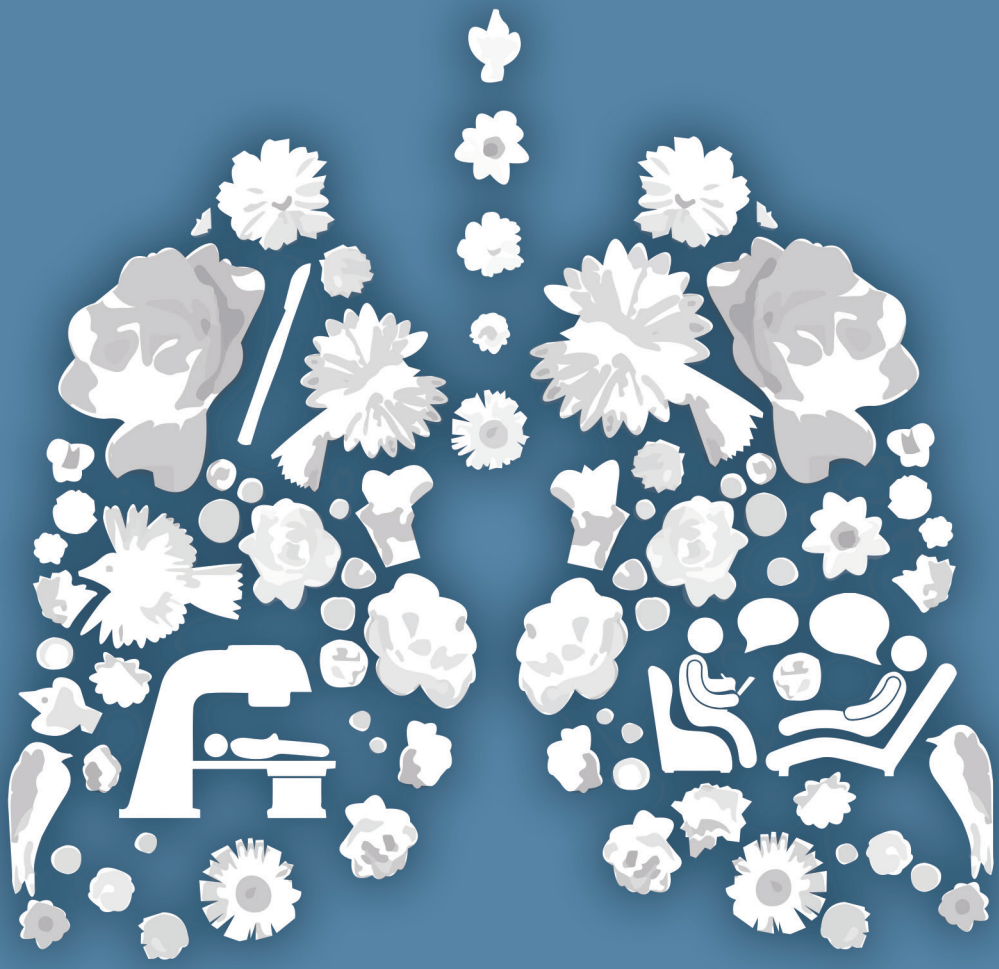

CHAPTER 7

Letter by Mokhles et al:

Surgery versus Radiation Therapy in Stage I Lung Cancer

Mokhles S, Takkenberg JJM and Bogers AJJC

Ann Thorac Surg 2015 Nov;100(5):1968

To the Editor,

We read with great interest the recent article by Hamaji and colleagues (1). The authors concluded that video-assisted thoracoscopic surgery (VATS) lobectomy may offer significantly more favorable long-term outcomes than stereotactic ablative radiotherapy (SABR) in potentially operable patients with stage I non-small cell lung cancer (NSCLC).

We have some minor concerns regarding the methodology of this study. The 10 year overall survival (OS) was reported while 1 patient was at risk. It is important to curtail the plot when only 10% to 20% of patients are still in follow up (2). Furthermore, the follow up periods differed significantly between the treatment groups in the unmatched cohort. For that reason, the Tarone-Ware test would be an appropriate statistical test for comparison. Moreover, in the comparison of two treatment modalities, it is important to describe the incidence and severity of adverse events.

Nevertheless, this study prompted us to write this letter because it contributes to the discussion about offering SABR to operable patients and emphasizes the need of involving patients in clinical decision making.

In this study the 3 year and 5 year rates of OS in the VATS lobectomy group were 80.1% and 68.5%, respectively. In the SABR group, they were 52.7% and 37.3%, respectively. In Figure 2a, OS diverges after 2 years. We have recently published a report comparing a comparable patient population with propensity score matching (3). We observed no significant differences between the treatment groups regarding freedom from progression, locoregional control rates, and distant metastasis. However, after 3 years we observed a trend toward better survival for surgical patients. The 3 year and 5 year rates of OS in the VATS lobectomy group were 84.3% and 80%, respectively. In the SABR group, they were 81.7% and 53%, respectively. Although we observed better OS rates, and the OS curve diverged later, both studies observed a possible survival benefit for surgically treated patients. The question is whether a possible survival benefit after surgical procedures outweighs the risks and discomfort that are associated with them. Given the value-sensitive nature of the decision between SABR and operation, it is important that doctors and patients engage into shared decision making. Discussing all the pros and cons of both treatment modalities with the patient (e.g. early and late adverse events after treatment, and short term and long term survival outcomes) will enable them to consider the evidence along with their values and preferences, make informed treatment decisions, and avoid overtreatment. To guarantee optimal quality of cancer care and empower the patient, transparency is required in giving patients access to all data on treatments and clinical outcomes before the start of treatment.

In conclusion, both reports observe a possible survival benefit for surgically treated patients and underline the importance of shared decision making and of involving lung cancer patients in therapy selection to meet their preferences and expectations about treatment options and prognosis.

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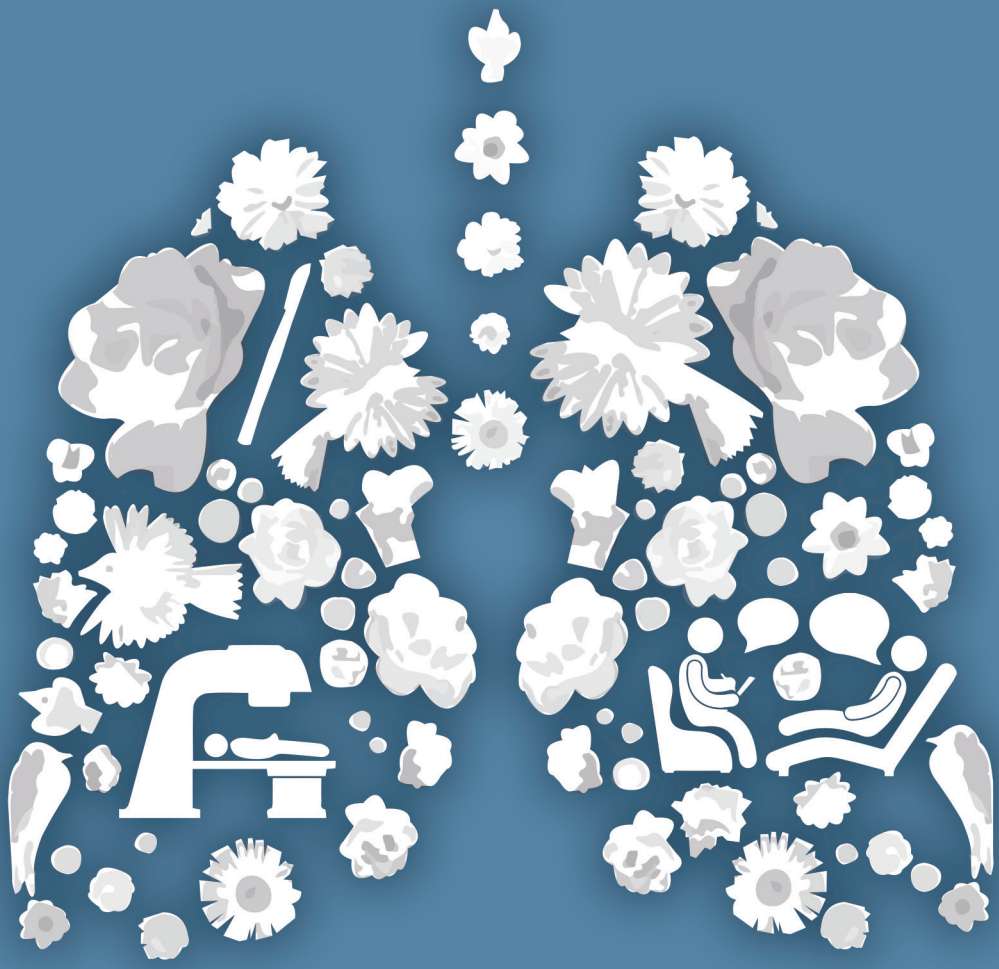


CHAPTER 8

Treatment Selection of Early Stage Non-Small Cell Lung Cancer:

The Role of the Patient in Clinical Decision Making

Mokhles S, Nuyttens JJME, de Mol M, Aerts JGJV, Maat APWM, Birim O, Bogers AJJC, Takkenberg JJM

Submitted

ABSTRACT

Objective. To Investigate the role and experience of early stage non-small cell lung cancer (NSCLC) patients in the decision making process concerning treatment-selection in the current-clinical-practice.

Methods. Stage I-II NSCLC-patients (surgery 55 patients, SBRT 29 patients, median age 68) completed a questionnaire that explored: (1) perceived patient knowledge of the advantages and disadvantages of the treatment options, (2) experience with current clinical decision making, and (3) the information that the patient received from their treating physician. This was assessed by multiple-choice, 1-5 Likert-Scale, and open questions. The Decisional Conflict Scale was used to assess the decisional-conflict.

Results. In 19% of patients, there was self-reported perceived lack of knowledge about the advantages/disadvantages of the treatment options. Seventy-four percent of patients felt that they were sufficiently involved in decision-making, and 81% found it important to be involved in decision-making. Forty percent experienced decisional-conflict, and one in five patients to such an extent that it made them feel unsure about the decision. Subscores with regard to feeling uninformed and on uncertainty, contributed the most to decisional-conflict, as 36% felt uninformed and 17% of patients were not satisfied with their decision.

Conclusion/practice implications. Dutch early-stage NSCLC patients find it important to be involved in treatment-decision-making. Yet a substantial proportion experiences decisional-conflict and feels uninformed. Better patient information and/or involvement in treatment decision making is needed in order to improve patient knowledge and hopefully reduce decisional-conflict.

INTRODUCTION

Surgical resection is considered the preferred treatment for patients with early stage non-small cell lung cancer (NSCLC). A less invasive option for patients with comorbidities is stereotactic body radiotherapy (SBRT) (1, 2). Several studies have demonstrated that SBRT may be as effective as surgery in potentially operable patients, however, randomized trials with larger patient populations and longer follow-up are still lacking (3-5). In this setting it is important to provide adequate information to allow patients to take an active role in treatment decision. Shared decision making (SDM), where patients are involved as active partners with the physician in treatment decisions, is an important part of patient-centered cancer care as it weighs the pros and cons of treatment options while taking patients values and preferences into account (6-8). However, there are a number of factors that complicate the implementation of SDM in current clinical practice such as guideline based treatments, patient knowledge, time constrains and care settings (7). Therefore, in the field of lung cancer treatment SDM has not been widely incorporated into routine clinical practice.

This study assesses among Dutch early-stage NSCLC patients: (1) perceived patient knowledge of the advantages and disadvantages of treatment options, (2) experience with current clinical decision-making, and (3) perceived understanding of information regarding their disease and the treatment.

METHODS

Patient population

Between December 2012 and December 2014, 155 consecutive patients with stage I or II NSCLC were recruited for this prospective observational study. These patients were subsequently treated surgically or with SBRT at Erasmus University Medical Center, Erasmus MC-Cancer Institute, or Amphia Hospital Breda. Consecutive patients were contacted by telephone to explain the purpose of the study and obtain their consent to receive a questionnaire. Only patients who agreed to participate and provided written informed consent were eligible for the inclusion in this study (n=84). The overall response rate was 54%. No significant differences were found between responders and non-responders in terms of baseline characteristics. This study was approved by the institutional review board of Erasmus University Medical Center (MEC 2012-462).

Clinical staging of patients treated surgically (n=55) or with SBRT (n=29) was done with CT-scan, ^{18}FDG-PET imaging and/or using (minimally invasive) endoscopic techniques when appropriate. Clinical and pathological staging was based on American-Joint-Committee-in-Cancer 7th-edition staging manual (9). Chronic obstructive pulmonary disease (COPD) was defined according to the GOLD criteria (10). Comorbidity-scores were recorded using the Charlson Comorbidity Index (CCI) (11). Treatment planning of patients who received

SBRT have been described previously (12). All patients were discussed in a multidisciplinary team meeting before the treatment.

Data collection

Baseline characteristics of patients were collected by reviewing the patients' medical records and hospital information system. After the treatment decision was made but before the actual start of the treatment, patients completed a questionnaire. The aim of this questionnaire is to investigate: (1) perceived patient knowledge of the advantages and disadvantages of treatment options, (2) experience with current clinical decision-making (this includes the preferences, patient experience and involvement in treatment decision-making using Decisional Conflict Scale (DCS) and Control Preferences Scale (CPS), and (3) perceived understanding of information regarding their disease and the treatment. These components are measured at baseline using multiple-choice questions, a 1-5 Likert Scale, and open questions. Health related quality of life (HRQoL) was measured before the treatment, 6 months and 12 months after the treatment using the Short-Form 36-Item Health Survey (SF-36).

Control Preference Scale

The patients' preferred decisional role was assessed using a modified version of the CPS. The CPS is an instrument that assesses preferences regarding patient participation in health care decisions. Patients were asked to select one of the five statements on roles in treatment decision-making; (A) the physician makes the decision about the treatment alone, (B) the physician makes the decision after considering the patient's opinion, (C) the patient makes the decision together with the clinician, (D) the patient makes the decision after considering the doctor's opinion, and (E) the patient makes the decision about the treatment alone (13-15). This scale has been widely used in previous studies (16, 17). To investigate the potential association between education level and CPS patients were asked to indicate their educational attainment.

Decisional Conflict Scale

The DCS was used to assess the level of 'decisional conflict' that patients experience while making health care decisions. This scale has been extensively validated and has been widely used. The DCS measures decision uncertainty that leads to decision delay, and quantifies modifiable factors which contribute to uncertainty. It contains 16 items, each using a five-point Likert response format (i.e. completely agree, agree, neither agree nor disagree, disagree, completely disagree). These items are combined to form total score and five subscales (i.e. uncertainty, informed, values clarity, support, and effective decision subscore). Scores lower than 25 are associated with implementing decisions and scores exceeding 37.5 are associated with delay or feeling unsure about implementation (18, 19). In case of missing values (<6%) we used a multiple imputation technique to impute missing

values in order to avoid them being depicted as 'unknown' in incomplete observations. We have used 5-fold multiple imputation using SPSS for Windows version 21 (20).

Health related quality of life assessment

HRQoL was measured with the SF-36. The SF-36 is the most extensively used and evaluated health outcomes measure and has shown to be valid and reliable in multiple populations. The SF-36 assess eight self-reported aspects of HRQoL (i.e. physical functioning, role physical functioning, role emotional functioning, mental health, vitality, social functioning, bodily pain, and general health). It also yields physical (PCS) and mental (MCS) health summary measures. Scale scores are obtained by summing the items together within a domain, dividing this outcome by the range of scores and then transforming the scores to a scale from 0 to 100 (21). The mean score of the PCS and MCS is 50 with a standard deviation of 10 and wherein a higher score means a better health status. Furthermore, a higher score on the SF-36 subdomains represents a better functioning; a high score on the bodily pain scale indicates the absence of pain. The scale has good reliability, with Cronbach α ranging from 0.65 to 0.96 for all subscales (22). We used the Dutch adaptation of the SF-36 health status scale (23). Patients were asked to complete the SF-36 form after treatment decision was made but before the treatment (baseline), at 6 and 12 months to all surviving patients. In case of missing values we applied simple imputation (24, 25). HRQoL was assessed in 84 patients at baseline (surgery=55, SBRT=29). In the surgery group 32 and 19 patients were alive at 6 and 12 months without tumor progression, respectively. In the SBRT group this was 9 and 4 patients at 6 and 12 months, respectively. Due to the low response rates at 6 and 12 months the effect of time could not be analyzed.

Local control and the presence of metastases were defined according to the guidelines of ACCP and STS (26). Twelve patients were diagnosed with tumor recurrence after the treatment, four of these patients had both loco-regional and distant recurrence.

Statistical Analysis

Continuous data are reported as mean±SD or median with range, and categorical data are reported as proportions. Normally distributed continuous variables were compared by using Student *t* tests, and not normally distributed (Kolmogorov-Smirnov) data were compared by using the Mann-Whitney-U-test. Discrete variables were compared by using the Chi-Square test or the Fisher Exact test where appropriate.

A general linear model (GLM) with the bootstrap method was used to assess the association between HRQoL measured at baseline and 1) patient experience with involvement in treatment selection, 2) patient preferences for SDM, and 3) patients' preferred decisional role in treatment decision-making (assessed with CPS). The purpose behind the use of bootstrapping is to account for skewed distribution of residuals of SF-36 variables (27, 28) and to obtain valid and reliable *p*-values.

All statistical tests were two-tailed and a *p*-value of <0.05 was regarded as statistical significant. The statistical software package SPSS for Windows version 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used for data analysis. GraphPad Prism5.00 for Windows (GraphPad software,San Diego,CA) was used to obtain graphs of QoL.

RESULTS

The baseline characteristics of all 84 patients are listed in Table 1. In 55 patients surgical treatment was chosen (median age=65), in 29 patients SBRT (median age=73). In this cohort of patients the education level was in accordance with the education level of the general Dutch population (29, 30).

Perceived patient knowledge regarding the treatment

Self- reported lack of knowledge about the advantages and disadvantages of the treatment options was present in 18% of patients in the surgery group and in 22% of patients in the SBRT group. Self-reported lack of knowledge about the treatment risks was present in 6% of patients in the surgery group and in 21% of patients in the SBRT group.

Experience with current clinical decision-making

Patient preferences for SDM

The majority (85%) of patients agreed that ideally decision-making should be done together with the physician. Twelve percent of patients wanted to leave the decision about the appropriate treatment to their treating physician and three percent indicated that the decision should be done mainly by the patient. No association was found between the education level and the control preference scale.

Experience in treatment decision-making

On average, patients in this cohort discussed their treatment with three physicians. The majority of patients in the surgery and SBRT group involved a family member in making the choice for a treatment, 75% and 68%, respectively. Most of the patients thought that they had enough time to make an informed decision (80% in the surgery group and 79% in the SBRT group). Patients indicated that several subjects were discussed during the conversation with their treating physician. Two percent of patients in the surgery group had the feeling that not every aspect of the treatment was discussed during the conversation with their treating physician. This was 11% in the SBRT group.

Table 1. Patient characteristics

Characteristics	Total (*n*=84)	Surgery (*n*=55)	Radiotherapy (*n*=29)	*P-value*
Sex				0.406
-Male (%)	44 (52)	27 (49)	17 (59)	
-Female (%)	40 (48)	28 (51)	12 (41)	
Age, median (range)	68 (50-87)	65 (50-81)	73 (52-87)	*0.001*
Education level (%):				0.875
-Primary education	12 (14)	8 (15)	4 (14)	
-Secondary education	21 (55)	29 (53)	17 (59)	
-Higher education	46 (27)	15 (27)	8 (27)	
-other	3 (4)	3(5)	-	
Smoking habits				
-Nonsmoker (%)	3 (4)	2 (4)	1 (3)	*0.588*
-Current or former smoker (%)	60 (71)	38 (69)	22 (76)	
-Unknown, n (%)	21 (25)	15 (27)	6 (21)	
FEV_1% mean±SD [a]	80 (24)	87 (20)	67 (26)	*0.001*
-Unknown, n (%)	3 (4)	2 (4)	1 (3)	
DLCO (%) mean±SD [b]	76 (24)	83 (22)	61 (22)	*<0.001*
COPD (%) [c]				0.001
-No COPD	38 (45)	31 (56)	7 (24)	
-GOLD I	17 (20)	10 (18)	7 (24)	
-GOLD II	19 (23)	13 (24)	6 (21)	
-GOLD III	8 (10)	1 (2)	7 (24)	
-GOLD IV	2 (2)	-	2 (7)	
Charlson comorbidity index (%)				0.026
-≤1	47 (56)	33 (60)	14 (48)	
-2-3	26 (31)	17 (31)	9 (32)	
-4	6 (7)	3 (5)	3 (10)	
-≥5	5 (6)	2 (4)	3 (10)	
Clinical stage (%)				0.001
-IA	47 (56)	22 (40)	25 (86)	
-IB	14 (17)	12 (22)	2 (7)	
-IIA	17 (20)	15 (27)	2 (7)	

Table 1. Patient characteristics (continued)

Characteristics	Total (*n*=84)	Surgery (*n*=55)	Radiotherapy (*n*=29)	*P-value*
-IIB	6 (7)	6 (11)		
Pathological stage (%)				
-IA	17 (31)	17 (31)	-	
-IB	18 (33)	18 (33)	-	
-IIA	9 (16)	9 (16)	-	
-IIB	7 (13)	7 (13)	-	
-IIIA/B	4 (7)	4 (7)	-	
Histology (%)				0.262
-Squamous cell carcinoma	18 (21)	14 (26)	4 (14)	
-Adenocarcinoma	21 (25)	15 (27)	6 (21)	
-Large cell carcinoma	8 (10)	6 (11)	2 (7)	
-NSCLC	37 (44)	20 (36)	17 (58)	
Clinical tumor diameter (mm), median (range) Unknown, n (%)	25 (7-130)	29 (7-130) 11 (5)	22 (9-41) -	*<0.001*
Pathological tumor diameter (mm), median (range)	28 (1-90)	28 (1-90)	-	

[a] FEV_1%: Forced expiratory volume in 1 s expressed as a percent of predicted. [b] Diffusion capacity of the lung for carbon monoxide. [c] COPD: chronic obstructive pulmonary disease.

In the surgery group, 40% of patients experienced decisional conflict (score >25), and 22% to such an extent that they felt unsure about their decision (score >37.5). Thirty-two percent felt uncertain about the best choice, and 39% felt uninformed. Twenty-nine percent felt unclear about personal values for benefits and side effects of the treatment. Twenty-one percent felt unsupported in decision-making, and 21% of patients were not satisfied with their decision.

In the SBRT group, 48% of patients experienced decisional conflict, and 7% to such an extent that they felt unsure about their decision. Thirty-five percent felt uncertain about the best choice, and 29% felt uninformed. Thirty-two percent felt unclear about personal values for benefits and side effects of the treatment. Fourteen percent felt unsupported in decision-making, and 7% of patients were not satisfied with their decision. Subscores on feeling uninformed and on uncertainty contributed the most to decisional conflict. Scores exceeding 37.5 are described here, details of the total score and five subscales for the two treatment groups are illustrated in Figure 1.

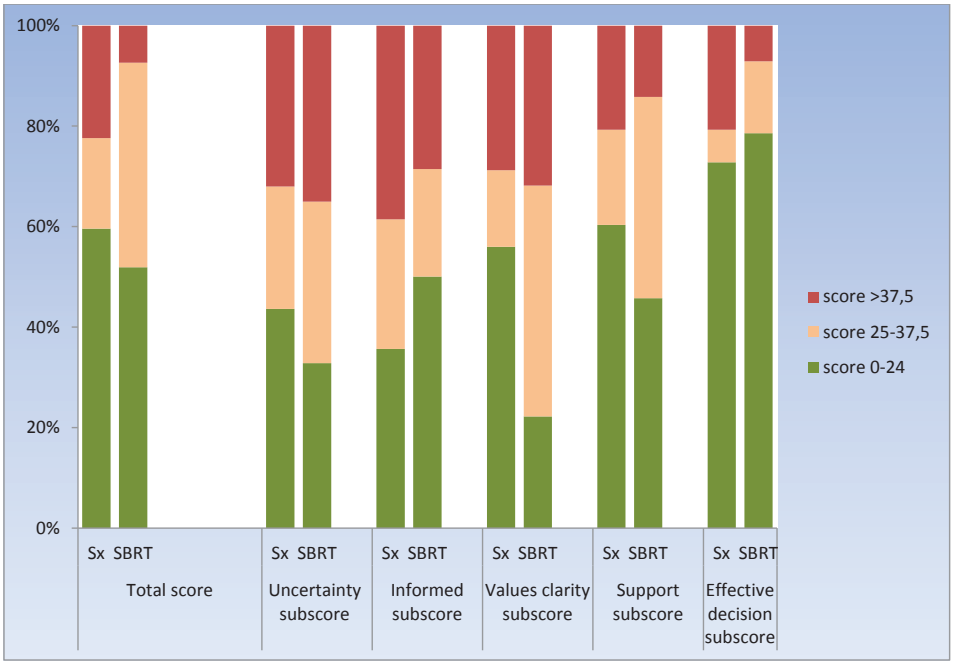


Figure 1. Decisional conflict in patients treated surgically or with stereotactic body radiotherapy (SBRT). Scores <25 (green color) are associated with implementing decisions and scores <37.5 (red color) are associated with delay or feeling unsure about implementation. Orange color represent scores between 25 and 37.5.

Involvement in treatment decision-making

Seventy-four percent of patients felt that they were sufficiently involved in decision-making by their physician, 73% felt that they had a choice between different treatment options, 81% found it important to be involved in decision-making, Six percent reported that alternative treatment options and complementary treatments were not discussed during the conversation about their treatment. Patients mentioned immunotherapy, diet and vitamin supplements as an example. Involvement in treatment decision-making for the two treatment groups can be found in Table 2.

Perceived understanding of information regarding the disease and the treatment

Patients were asked to report which topics were discussed during the conversation about their treatment. Figure 2 illustrates that the minority of patients who undergone surgery or radiation therapy received information about the survival, 24% and 18%, respectively.

Health related quality of life assessment

At baseline, patients in the surgery group scored higher on physical component summary (mean 42.4±12.3) than patients in the SBRT group (mean 34.4±10.1), Figure 3. No major differences could be found between the HRQoL in the surgery and SBRT group for the other measured SF-36 scales, except for physical functioning and general health (Figure 4). Recurrence rates and death rates are illustrated in Table 3.

SDM and HRQoL at baseline

No significant association could be found between HRQoL and patient experience with involvement in treatment selection (PCS *p*-value 0.398, MCS *p*-value 0.341), patient preferences for SDM (PCS *p*-values=0.439, MCS *p*-value 0.580), and final decision in lung cancer treatment selection (PCS *p*-value 0.402, MCS *p*-value 0.662).

Table 2. Involvement in treatment decision making for the two treatment groups

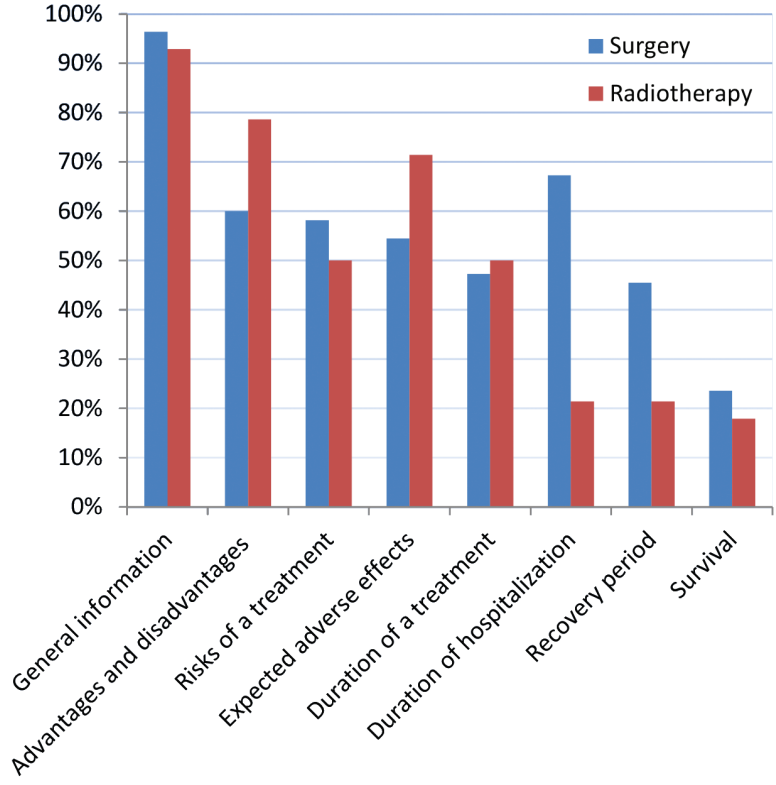
Involvement in decision making	Surgery (%)	Radiotherapy (%)
Felt sufficiently involved	78	68
Found important to be involved	78	89
Having a choice	71	79
Not having a choice	18	7

Table 3. Recurrence rate of patients treated surgically or with SBRT

	Surgery (%)	Radiotherapy (%)
All recurrence	9 (16)	3 (10)
Time till all recurrence(mean±SD)	1.1±0.7 months	0.4±0.06 months
Local recurrence	1 (2)	-
Loco-regional recurrence	4 (7)	1 (3)
Distant recurrence	9 (16)	2 (7)
Death	5 (9)	8 (28)

Four patients had both loco-regional recurrence and distant recurrence.

Figure 2. Information that the patient received during the consultation



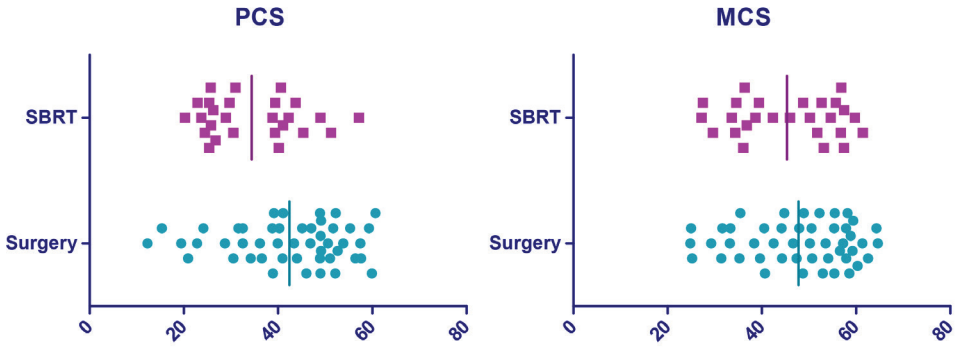


Figure 3. Scatterplot of physical component summary (PCS) and mental component summary (MCS) at baseline in the surgery and stereotactic body radiotherapy (SBRT) group.

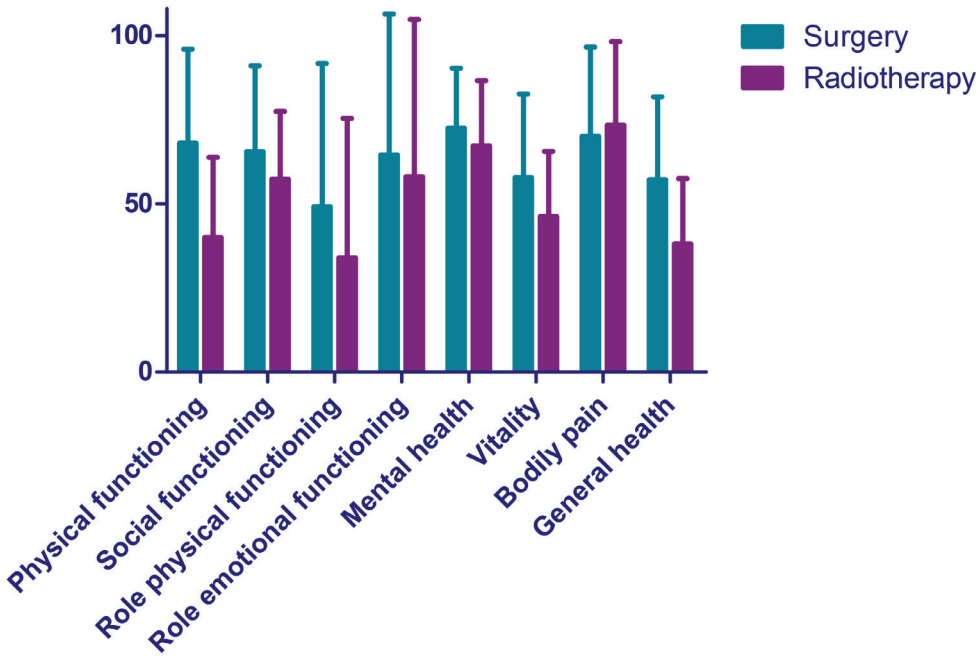


Figure 4. Eight self-reported aspects of HRQoL measured at baseline. The scores are expressed as the mean score with a standard deviation stratified by treatment group. A high score indicates better HRQoL, with a high score on bodily pain representing absence of pain.

DISCUSSION AND CONCLUSION

This study illustrates that in the current clinical practice lung cancer patients experience decisional conflict and suboptimal information provision regarding the treatment and survival which highlights the need of improvement of information conveyance, and involvement of patients with early-stage NSCLC in treatment decision-making.

Perceived patient knowledge regarding the treatment and communication with the patient

Up to one-fifth of the patients reported lack of knowledge about the advantages and disadvantages of the treatment options and one-tenth of patients reported lack of knowledge about the treatment risks. These results illustrate that providing information needs to improve, particularly in an early stage of diagnosis and treatment because lung cancer patients are emotionally unstable and overloaded with information about their disease. Numerous studies explored different strategies to improve and adopt

SDM in clinical practice (31). One of the main topics of improving cancer communication is 'health literacy' which involves the ability of the patient to read, understand, and use health information to make an appropriate decision. In order to achieve an effective communication it is essential to describe health state in language that is accessible to the patient and discuss the benefits and risks of treatment options in a balanced way (32, 33). In the field of breast cancer it is illustrated that by deciding on a cancer treatment without fully understanding the associated risks and benefits could lead to overuse or underuse of cancer treatments (34, 35).

Additionally, the majority of patients felt sufficiently involved in treatment decision-making and indicated that they had enough time to make an informed decision. It was interesting to see that the minority of patients reported to have received information on survival. It is crucial to discuss survival and prognosis with the patient in a way that the patient will understand this information because previous studies have shown that the cancer patients overestimate their life expectancy and probabilities of cure when compared to their physicians' perspective (36-38). This will lead to unrealistic high expectations about the medical treatment which is a common phenomenon in oncology patients (39, 40).

Experience with current clinical decision-making

The majority of patients had a strong desire to participate in treatment decision-making and preferred the decision to be the outcome of a SDM process. This is in line with the previous studies showing that more patients preferred to participate rather than delegate decisions (41). One of the challenges of SDM is knowing how much involvement a patient wants and needs. It is even more difficult when patients vary in the amount of control that they prefer to have over the treatment decision-making at the time of diagnosis (17). Using tools such as decision aids prior to the consultation or during the visit will improve the communication between the patient and physician and there will be more time for the patient to absorb health care information and ask questions during the consultation (42, 43).

Forty percent of patients experienced decisional conflict, and one in five patients to such an extent that it made them feel unsure about the decision. Decisional conflict was most evident in the uncertainty and informed subscale, suggesting that improvement of patient uncertainty and better informing the patient before the treatment will improve the quality of decision-making (18). In our previous study we have illustrated that patients who receive SBRT differ significantly from the surgical patients (44). It is important to appreciate these differences and realize that SBRT patients do not always have a choice between treatment options. Although decisional conflict is about what patients go through when confronted with a difficult decision, the idea of decisional conflict is also to help patients to think about participation in decision-making and motivate them to engage in treatment decision-making (45). Furthermore, these scales also illustrate how the patients are informed and where the improvements are needed.

Health related quality of life and shared decision making

In general, lung cancer patients have poor HRQoL compared to the general population or patients without lung cancer (46, 47). In this study, patients in the SBRT group scored at baseline lower on physical component summary compared to the patients treated surgically. No differences could be found regarding the mental component summary. An explanation for the observed differences in HRQoL between the two groups could be the significant differences in baseline characteristics (2, 44). No association could be found between HRQoL and different aspect of SDM meaning that in this study HRQoL was not positively or negatively influenced by patient experiences with SDM. Our findings are comparable with a number of studies concluding that there is weak evidence that aspects of SDM are positively or negatively associated with QoL outcomes (48).

Strengths and Limitations

The present study is a prospective observational cohort study allowing for new insights into the process of SDM and information conveyance in lung cancer patients. Although many articles have been written on SDM and patient participation in treatment decision-making in cancer patients, to our knowledge little research has been done on the role of early-stage lung cancer patients -treated surgically or with SBRT- in treatment decision-making and patients experiences and preferences regarding SDM. Also, the lung cancer patients were surveyed after diagnosis but before the treatment which allow us to investigate the unbiased perception of the patient regarding the treatment decision-making.

Potential limitations need to be addressed regarding the present study. First, the conceptual design of this study was not built on a specific theory. We explicitly chose to include all patients with stage I or II NSCLC who were planned for a surgical treatment or SBRT. We wanted to illustrate the patient participation in treatment decision-making, since there is little research about the role of early stage lung cancer patients -treated surgically or with SBRT- in treatment decision-making. Second, overall response rate was 54% thus making the sample size of this study small. The non-responders were contacted to ask why they would not be part of the study. The following major reasons were given: 1) they were shocked by the diagnosis and therefore they did not want to complete the questionnaire; 2) they were too preoccupied with their illness and therefore they had no time for the questionnaire; 3) the questionnaire was too confrontational. However, no significant differences were found between responders and non-responders in terms of baseline characteristics. Third, we are aware of the shortcomings of using GLM. By using the bootstrap method we have tried to account for this inadequacy. However, no differences were observed between the results of GLM and results of GLM with bootstrapping. Finally, the response rate at 6 and 12 months was low due to recurrences rates and death rates in both treatment groups making analyses of HRQoL at 6 and 12 months difficult.

Conclusions and practice implications

Dutch early stage NSCLC patients find it important to be involved in treatment decision-making. The majority of patients in this study found it important to be involved in decision-making and reported that they felt sufficiently involved by their treating physician. Yet a substantial proportion of patients experiences decisional conflict and feels uninformed. HRQoL was not influenced by patient experiences with SDM. Better patient information, and patient involvement in treatment decision-making is needed in order to improve patient knowledge and hopefully reduce decisional conflict.

Abbreviations:

ACCP, American College of Chest Physicians; CCI, Charlson-Comorbidity-Index; COPD, chronic obstructive pulmonary disease; CPS, Control Preferences Scale; DCS, Decisional Conflict Scale; GLM, general linear model; HRQoL, health related quality of life; MCS, mental component summary; NSCLC, non-small cell lung cancer; PCS, physical component summary; SBRT, stereotactic body radiotherapy; SDM, shared-decision-making; SF-36, Short-Form 36-Item Health Survey; STS, Society of Thoracic Surgeons.

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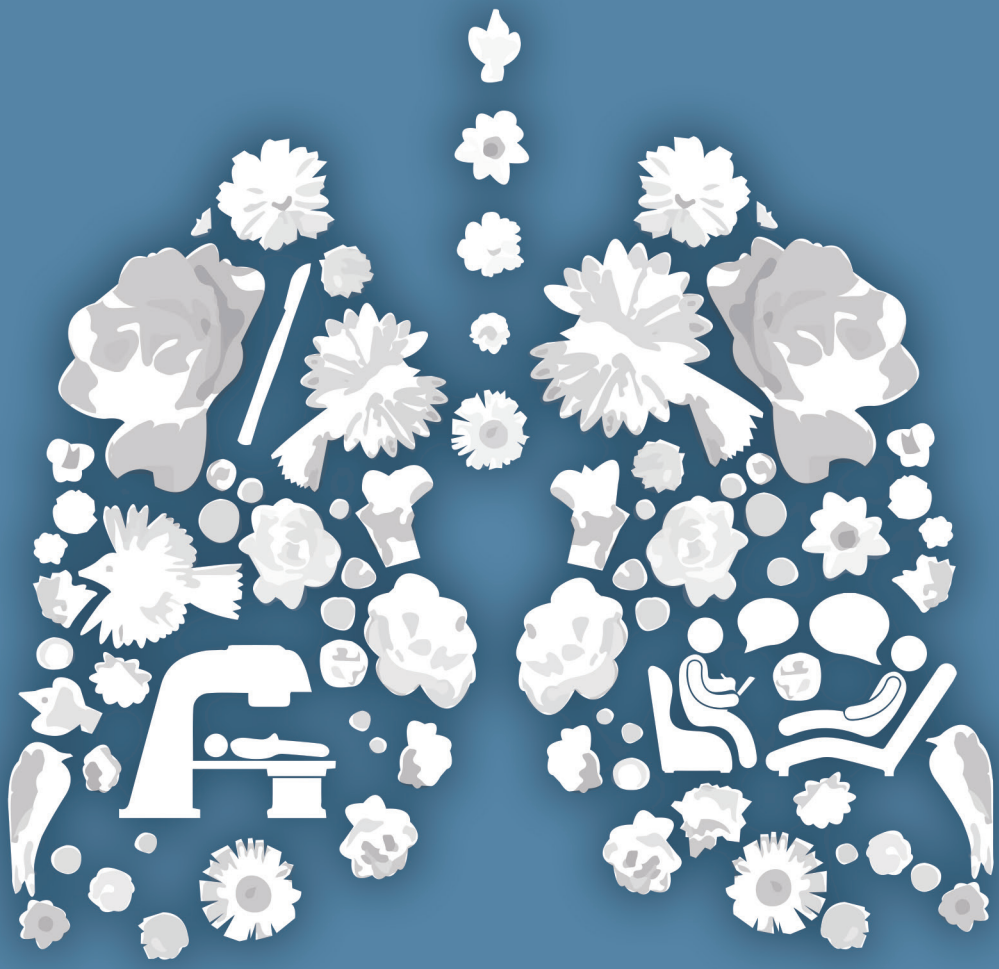

CHAPTER 9

Lung Cancer Clinician Opinion on Shared Decision Making in Early stage Non-Small Cell Lung Cancer

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Interactive Cardiovascular and Thoracic Surgery, in press

ABSTRACT

Objectives. To investigate the opinion of lung cancer clinicians concerning shared-decision-making (SDM) in early stage lung cancer patients.

Methods. A survey was conducted among Dutch cardio-thoracic-surgeons/lung-surgeons, pulmonologists and radiation oncologists. Clinician opinion on involvement of patients in treatment decision making was assessed by using 1-5-Likert-scale. Through open-questions we queried barriers and drivers to apply SDM in clinical practice. Opinion on choice of treatment strategies was assessed by seven hypothetical-cases in which the clinician rated the likelihood of choosing a particular treatment using 1-7-Likert-scale.

Results. Twenty-six percent of surgeons, 20% of pulmonologists and 12% of radiation oncologists indicated that they always apply SDM (missing 16%; *p-value* 0.10). Most respondents found that ideally doctors and patients should decide together (surgeons 52%, pulmonologists 67%, and radiation oncologists 35%; p-*value* 0.005). Thirty percent of surgeons, 27% of pulmonologists, and 44% of radiation oncologists indicated that doctors are not properly trained to implement SDM in clinical practice (p-*value* 0.37). SDM may not always be feasible due to low patient-education-level and little knowledge concerning lung cancer. Wide variation in clinicians' lung cancer treatment preferences was observed in the hypothetical cases.

Conclusions. In current clinical decision making in lung cancer treatment there is consensus among a majority of clinicians that it is important to involve lung cancer patients in treatment decision making but important barriers are time constraints and inability of some patients to make a weighted decision. The observed variation in lung cancer treatment preferences among clinicians suggests that for most patients both surgery and radiotherapy are suitable, and it underlines the value sensitive nature of treatment choices in early stage NSCLC.

INTRODUCTION

Lung cancer remains a global health problem, accounting for 27% of all cancer deaths (1). Cancer decisions are very personal and dependent on fears about the side effects of various treatments and concerns about cancer recurrence (2, 3). Applying SDM is important regardless of stage of the disease. It has been shown that by informing the patient about their disease and its prognosis, and involving the patient in treatment decision making by means of shared decision making (SDM), the quality of treatment decision making improves and overtreatment can be reduced (4, 5).

SDM is a process in which the physician and patient work together in making a health decision after discussing the options, the benefits and harms, and considering the patients' values, preferences, and circumstances (6). The main reason why SDM has become the hallmark of patient-centered care is that it supports patients to better understand their disease and weigh advantages and disadvantages of treatment options in their own context, which will result in informed treatment decisions that incorporates patient needs and values. Informing the patient adequately and according to their educational background and giving them the opportunity to address their preferences will lead to an increased patient knowledge, less patient anxiety, improved health outcomes and reductions in care and cost variation (4, 7). Although SDM has gained increased awareness among the healthcare community, it has not been widely incorporated into routine clinical practice in lung cancer care. This can be explained by the current lack of familiarity with SDM among physicians and patients, and also because the care of lung cancer patients can be complex due to multiple treatment types over an extended period of time(8). Furthermore, lung cancer treatment can be guideline-driven. These guidelines are based on evidence-based research and occasionally they strongly support a single treatment option (9).

Even though the treatment options for non-small cell lung cancer (NSCLC) are based on cancer stage and overall health of the patient (10), numerous articles have been written about the use of stereotactic body radiotherapy (SBRT) in potentially operable patients suggesting that SBRT may be as effective as surgery (11). Two randomized-trials comparing SBRT with surgery for early stage NSCLC were halted early because of slow recruitment (12). In this setting it is important to provide adequate information to allow patients to take an active role in treatment decision making.

With this study we aim to assess the opinion of Dutch clinicians involved in early stage lung cancer treatment (cardio-thoracic surgeons, general surgeons with special training in thoracic surgery (lung surgeons), pulmonologists, and radiation oncologists) concerning SDM in patients with early stage NSCLC, by querying (1) their attitude toward patient involvement in treatment decision making, (2) exploring perceived barriers and drivers to apply SDM in clinical practice, and (3) assessing clinician preferences for early stage NSCLC treatment strategies.

MATERIALS AND METHODS

Study population

An electronic survey was conducted among Dutch cardio-thoracic surgeons, lung surgeons, pulmonologists, and radiation oncologists between February and June 2015. Lung cancer clinicians who specifically provide care for early stage lung cancer patients were invited to complete a self-administrated anonymous questionnaire. The relevant mailing lists were obtained from the Netherlands Association for Cardiothoracic Surgery, Society of Lung Surgeons of the Netherlands, the Dutch Society for Radiotherapy and Oncology, the Dutch Society of Physicians for Lung Disease and Tuberculosis, and Netherlands Comprehensive Cancer Organization.

Questionnaire

To assess clinician opinion concerning SDM in patients with early stage NSCLC a four-part questionnaire was developed. Part one consisted of seven general questions: clinician age, specialty (cardio-thoracic surgeon, lung surgeon, pulmonologist or radiation oncologist), resident or registered medical specialist, hospital, years of working experience, annual number of surgical lung resections in their institution, and information regarding weekly multidisciplinary team meetings.

Part two of the questionnaire was designed to assess the opinion of the lung cancer clinicians on involvement of patients in decision making. This part consisted of seven questions using a 1-5 Likert scale ranging from never to always (13) and five questions using the Control Preference Scale (14).

Part three of the questionnaire explored the perspective of the clinicians on advantages and disadvantages of applying of shared decision making in clinical practice and was assessed using 6 open questions.

The preferences of the clinicians for treatment strategies was assessed in part four using seven hypothetical cases in which the clinician rated the likelihood of choosing a particular treatment using a 1-7 Likert-scale ranging from 1 (always surgery) to 7 (always radiotherapy). The WHO performance score was described to quantify patients' general well-being and activities of daily life. For a detailed description of the questionnaire, see supplementary data (available as online-only content).

Statistical analysis

Continuous data are presented as mean, standard deviation and range. Categorical data are presented as counts or proportions. Group responses regarding the clinician opinion on choice of treatment strategies are presented as median, interquartile range, and total range. To compare responses between surgeons, pulmonologists, and radiation oncologists the Kruskal-Wallis test or Chi-square test was used when appropriate with

p-*values* representing the differences between cardio-thoracic surgeons/lung surgeons, pulmonologists, and radiation oncologists.

All tests were two-sided, with an α-level of 0.05. The statistical software packages SPSS for Windows version 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used for data analysis. GraphPad Prism 5 for Windows (GraphPad software, San Diego, CA, USA) was used to plot Box & Whiskers to illustrate clinician opinion on choice of treatment strategies.

RESULTS

Demographics of lung cancer clinicians are listed in table 1.

Table 1. Demographics of medical specialists

	Total	**Surgeons***	**Pulmonologists**	**Radiation oncologists**
Total, N (%)	110	46	30	34
Age, mean (years)	45(range:27-64),SD=10	49(range:36-62),SD=8	44(range:29-64),SD=11	42(range:27-58),SD=10
Resident	17(15)	2(4)	9(30)	6(18)
Registered medical specialist	93(85)	44(96)	21(70)	28(82)
Work experience, mean (years)	13(range:1-35),SD=9	14(range:2-35),SD=9	12(range:1-35),SD=9	12(range:1-29),SD=10
Surgical resections per year, N (%)				
No resections	8(7)	0	4(13)	4(12)
<50	26(24)	15(33)	7(23)	4(12)
50-100	45(41)	27(59)	11(37)	7(20)
100-150	9(8)	1(2)	6(20)	2 6)
>150	4(4)	1(2)	2(7)	1(3)
Not known	17(15)	2(4)	0	15(44)
missing	1(1)	0	0	1(3)
Weekly multidisciplinary team meetings#, N (%)				
Yes	106(95)	45(98)	29(97)	32(94)
No	4(4)	1(20	1(3)	2(6)

*Thoracic surgeons and lung surgeons, #Multidisciplinary team meetings every week with surgeons, pulmonologists, pathologists and radiation oncologists.

Clinician opinion on patient participation in treatment decision making

Twenty-six percent of surgeons, 20% of pulmonologists and 12% of radiation oncologists indicated that they always apply SDM (missing 16%; *p-value* 0.10) and 20% of surgeons, 37% of pulmonologists and 9% of radiation oncologists think that a clinician should always try to involve the patient in treatment decision making even if the patient does not want to be involved (missing 16%; *p-value* 0.04). Fifty-two percent of surgeons, 57% of pulmonologists and 53% of radiation oncologists agreed that the lung cancer patients should always be involved in SDM (missing 16%; *p-value* 0.67). Eleven percent of surgeons, 17% of pulmonologists, and 3% of radiation oncologists indicated that patients often have questions about complementary treatments in addition to their standard treatment (*p-value* 0.15). Twenty-two percent of surgeons, 20% of pulmonologists and 29% of radiation oncologists think that all treatment options should be discussed with the patient even if the patient does not have a choice (p-*value* 0.28). Thirty-eight percent of surgeons, 37% of pulmonologists and 48% of radiation oncologists thought that the clinician can often decide for patients how risks and benefits should be weighed (*p-value* 0.85). Details of this part of the questionnaire can be found in Figure 1.

Thirty percent of surgeons, 27% of pulmonologists, and 44% of radiation oncologists indicated that doctors are not properly trained to implement SDM in clinical practice (p-*value* 0.37) (figure 2).

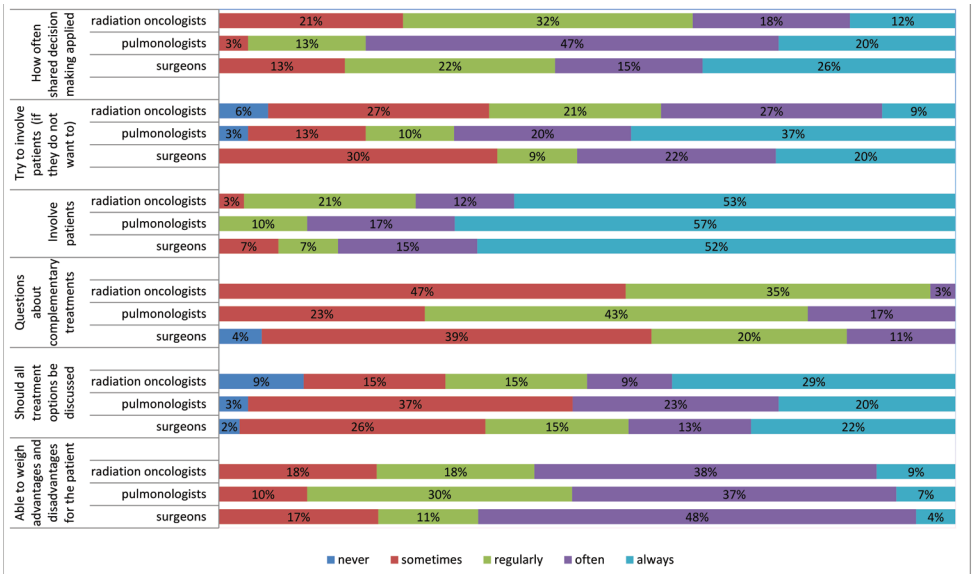

Figure 1: Clinician opinion on patient participation and decision making in clinical practice. Various colors present the various responses of Dutch cardio-thoracic-surgeons/lung-surgeons, pulmonologists and radiation oncologists to the questions.

Most respondents found that ideally doctors and patients should decide together (surgeons 52%, pulmonologists 67%, and radiation oncologists 35%; p-*value* 0.005). Radiation oncologists were more inclined to let the patient take the lead, see Figure 3.

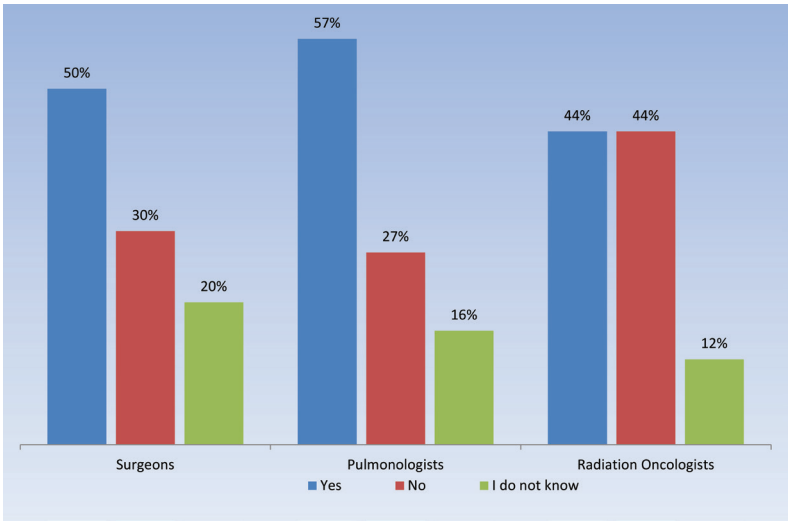

Figure 2: Opinion of Dutch cardio-thoracic-surgeons/lung-surgeons, pulmonologists and radiation oncologists on whether they think that doctors are trained properly to implement SDM in clinical practice.

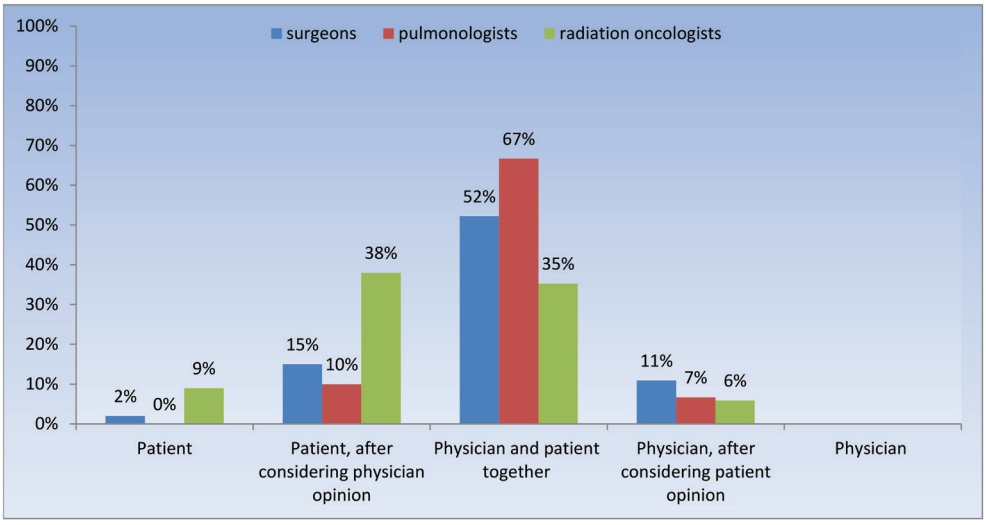

Figure 3: Clinician preference for patient involvement in final decision for lung cancer treatment.

Clinician perspective on advantages and disadvantages of SDM in clinical practice

Table 2 illustrates the answers to open questions regarding the barriers and drivers of applying SDM in clinical practice.

Clinician preferences for treatment strategies

The answers to the seven hypothetical patient cases are illustrated in the box-and-whiskers plot in Figure 4. It illustrates a wide variation in responses and that surgeons are leaning more toward a surgical procedure, while pulmonologists and radiation oncologists are leaning more toward radiotherapy. A detailed description of the answers with corresponding p-values can be found in figure 4.

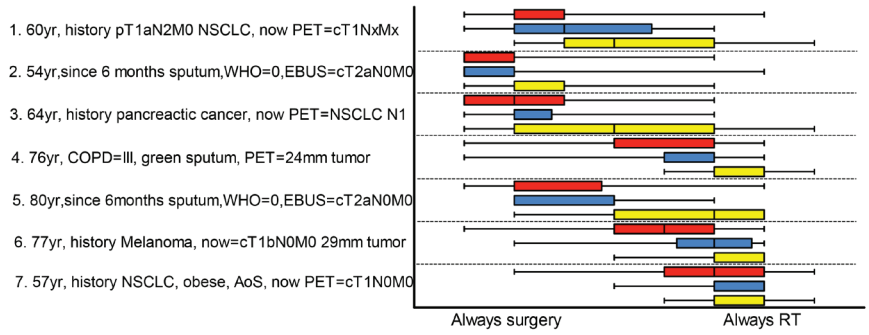

Figure 4: Clinician preference for a treatment strategy in 7 hypothetical cases. Red box=surgeons, blue box=pulmonologists and green box=radiation oncologists. Box represent 50% of the clinician preferences and the whiskers illustrate the minimum and maximum value. *P-value* for case 1-5 ≥0.001, case 6=0.005, case 7=0.013.

Table 2. Response to open ended questions regarding and barriers and drivers to apply shared decision making (SDM) in clinical practice

	Total, N(%)	Surgeons, N(%)	Pulmonologists, N(%)	Radiation oncologists, N(%)
Benefits of SDM:				
Patient is motivated	17 (16)	7 (15)	4 (13)	6 (18)
Well-informed	15 (14)	4 (9)	5 (17)	6 (18)
Compliance	11 (10)	6 (13)	2 (7)	3 (9)
Will benefit the physician-patient relationship	23 (21)	11 (24)	7 (23)	5 (15)
Autonomy and control over treatment	24 (22)	10 (22)	4 (13)	10 (29)
Patient will support the treatment decision	31 (28)	13 (28)	10 (33)	8 (24)
Objections to SDM:				
No objections	26 (24)	9 (20)	8 (27)	9 (27)
Time consuming	19 (17)	8 (17)	4 (13)	7 (21)
Low patient education-level	7 (6)	4 (9)	2 (7)	1 (3)
Not able to make a weighted decision	36 (33)	16 (35)	11 (37)	9 (27)
More health care costs	10 (9)	0	2 (7)	8 (24)
No choice between treatments	5 (5)	1 (2)	2 (7)	2 (6)
Conditions that are less suitable to apply SDM:				
No conditions	9 (8)	3 (7)	2 (7)	4 (12)
Neuro-cognitive conditions/legally incapable	33 (30)	10 (22)	13 (43)	10 (29)
Not able to make a decision	31 (28)	14 (30)	9 (30)	8 (24)
No choice between treatments	13 (12)	8 (17)	2 (7)	3 (9)
Acute situations/time pressure	10 (9)	3 (7)	2 (7)	5 (15)
In what circumstances would you like to apply SDM:				
Always apply SDM	59 (54)	26 (57)	21 (70)	12 (35)
If there is a choice	18 (16)	5 (11)	4 (13)	9 (27)
If the patient is able to make a choice	13 (12)	6 (13)	2 (7)	5 (15)
What makes it difficult to apply SDM:				
No problems	12 (11)	7 (15)	2 (7)	3 (9)
Time pressure/high work pressure	40 (36)	16 (35)	14 (47)	10 (29)
Patient do not want to be involved	6 (6)	2 (4)	2 (7)	2 (6)
Understanding of the information	22 (20)	9 (20)	5 (17)	8 (24)

Table 2. Response to open ended questions regarding and barriers and drivers to apply shared decision making (SDM) in clinical practice

	Total, N(%)	Surgeons, N(%)	Pulmonologists, N(%)	Radiation oncologists, N(%)
Not able to participate in SDM	14 (13)	4 (9)	8 (27)	2 (6)
No choice between treatments/MTB meeting	8 (7)	4 (9)	0	4 (12)
No decision aids	4 (4)	1 (2)	0	3 (9)
Are patients burdened by SDM:				
No	57 (52)	22 (48)	16 (53)	19 (56)
Yes	22 (20)	10 (22)	5 (17)	7 (21)
Depending on the personality of the patient	9 (8)	2 (4)	2 (7)	5 (15)

DISCUSSION

The current study illustrates that Dutch lung cancer clinicians agree that participation of lung cancer patients in treatment decision making is important, while they recognize in current practice several areas of improvement for effective SDM, and interestingly their own therapeutic preferences vary widely.

The majority of respondents agreed that lung cancer patients should always be involved in SDM as this process will lead to better knowledge of treatment options and more realistic perceptions of treatment effects. The respondents in this study indicated that it is important to try to involve the patient in treatment decision making even if the patient does not want to be involved. This can be particularly challenging in older patients and women since they tend to take a more passive role in cancer treatment decision making: in older patients the passive role is determined by low literacy and numeracy, while women tend not to report the differences between their actual and desired roles in decision making (3, 15). To the best of our knowledge, no studies have previously reported on these outcomes in patients with early stage lung cancer.

Interestingly, most respondents indicated that the clinician can often decide for patients how risks and benefits should be weighed. However, several studies have shown a potential mismatch between the information that the patient needs and the information that is given by the clinician and the difference of the clinicians' perception of patient preferences from actual patient preferences (16-18). Surely, some patients will prefer that the clinician takes a guiding role in treatment decision making and do not want or need to know every detail of their disease and/or treatment as some of these patients have difficulty understanding the health information (19). However, previous studies illustrate that even patients who

initially do not want to be involved in decision making, do want to be involved once they are well informed (20) and want to play an active role when educational materials exist (21).

Most respondents found that doctors and patients should make a treatment decision together, with radiation oncologists being more inclined to let the patient take the lead. In preference sensitive situations, as in this study the choice of surgical versus radiotherapeutic intervention, it is important to motivate the patient to engage in SDM. Even after considering the stage of tumor, the age of patient and the comorbidities a patient might still have personal perspectives of illness, treatment options and prognosis that deviate from their lung cancer clinician. Previous studies in other fields illustrate that cancer patients value the balance between survival and quality of life differently than clinicians (15, 18, 22). In the present study, approximately 20% of respondents recognize that there is discrepancy between the views of patients and clinicians regarding patient preferences and therefore, they believe that all treatment options should be discussed with the patient even if the patient does not have a choice. Of course, every patient will balance the risks, benefits and consequences of treatments in their own unique way (23). For that reason, it is important to be aware of between- and within-patient variability in weighing the trade-offs of different cancer treatments as treatment choices are personal and can change over the course of treatment (24). In this respect it is important for clinicians to realize that choice preferences regarding cancer treatments can also vary among clinicians themselves (15).

Fifteen percent of the respondents were residents in training. One can argue that the point of view of highly experienced physician is not comparable to the physician just starting the residency. However, we decided to include the residents in training in our analysis because these young group of physicians are exposed to trends towards increased patient involvement in current clinical practice. Due to the sample size of this study we decided to describe the data and not stratify or adjust for age and/or years of working experience.

In this study, lung cancer clinicians point out that SDM will benefit the physician-patient relationship and will give the patient more control over treatment which will result in more compliance. However, they recognize that there are several areas of improvement for effective SDM, such as increasing patient knowledge, resolving time constraints, and adequate implementation of SDM in the care path (25). It is not just the clinician who needs training to apply SDM in clinical practice, but the conditions should also permit it. Firstly, it is challenging to involve lung cancer patients in SDM because they find themselves in a very emotional situation obstructing them to absorb information about the disease and treatment options. In this regard, the lung cancer clinicians indicated that decision aids to support SDM could improve patient knowledge and save time on consultation because patients would be able to read the information prior to the hospital visit. As patients seek medical information online, it is important to offer a reliable up to date decision aid with good quality of information. Secondly, MTB meetings form the foundation of the treatment plan and contribute to the logistical and medical management of cancer patients (26, 27).

However, patient preferences regarding the treatment options and the quality of life are not yet integrated into the meeting recommendation as the patient is not present at the MTB meeting (28). To improve the effectiveness of the meeting it must be ensured that the physician responsible for the patient is present at this meeting. Thirdly, clinicians think that SDM is associated with more health care costs, which is however not in line with previously published studies (4, 5). On the contrary, the theory is that better informed patients are less likely to choose an extensive treatment (29).

An important finding of this study is the observed variation in clinician preferences for a particular treatment for early stage lung cancer. For the hypothetical case number 2 the clinicians prefer a surgical treatment while they prefer radiotherapy for the case number 4, 6 and 7. There is a wide variation in clinician preferences for the case number 1, 3 and 5. Also, it was interesting to notice that medical specialty was associated with treatment preferences which may be explained by the fact that the clinicians recommend treatments that are in line with their specialty, as was previously observed in the field of prostate cancer (30). Potential differences in between-clinician expectations regarding treatment outcomes will complicate effective communication and involvement in treatment decision making because cancer patients discuss their diagnosis, treatment, and the follow up with multiple lung cancer clinicians (2). Working as a team and good communication between the clinicians during the MTB meeting will optimize communication with the patient and improve treatment decision making. This is especially important in health care systems similar to Dutch health care. The general practitioner redirects a patient with symptoms to a pulmonologist. If it appears to be lung cancer the patient will be presented during the weekly MTB meeting and the recommendations of the multidisciplinary team will play an important role in treatment decision making.

In conclusion, this questionnaire illustrates that in current clinical decision making in lung cancer treatment there is consensus among a majority of clinicians that it is important to involve lung cancer patients in treatment decision making but that time constraints and inability of some patients to make a weighted decision are important barriers. Even if there is little discussion about the treatment choice it is still important to involve the patient in order to improve patients' knowledge about their disease and treatment options, improve commitment to the treatment and autonomy of the patient. The variation in lung cancer treatment preferences among clinicians suggests that for most patients both treatment options are suitable, and it underlines the value sensitive nature of the treatment choices in early stage NSCLC. The use of patient decision aids may be helpful for lung cancer clinicians and patients to improve patient information and patient participation in decision making. Furthermore, our study highlights the need to improve the implementation of SDM in clinical practice as lung cancer clinicians report that doctors are not properly trained to implement SDM, and there is not enough consultation time to properly engage the patient with limited health literacy in treatment decision making. Implementation studies are

needed to investigate the integration of SDM in clinical practice in order to help clinicians integrate SDM into their work.

Abbreviations:

MTB,multidisciplinary tumour board; NSCLC,non-small cell lung cancer; SBRT,stereotactic body radiotherapy; SDM,shared-decision-making.

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SUPPLEMENTARY DATA

1. Do you think lung cancer patients should be involved in choosing a treatment?

Never Sometimes Regularly Often Always I don't know

Comments.....

2. If a patient doesn't want to be involved in choosing a treatment, do you think that clinicians should try to involve the patient in the decision?

Never Sometimes Regularly Often Always I don't know

Comments.....

3. The final decision in treatment choice should be made by:

The patient

The patient, after considering clinician opinion

The patient and clinician together

The clinician, after considering patient opinion

The clinician

Comments.....

4. To choose a treatment for lung cancer, the advantages and disadvantages of treatment options are taken into consideration. Do you think clinicians can decide for patients how risks and benefits should be weighted?

Never Sometimes Regularly Often Always I don't know

Comments.....

5. Do you think that *all* treatment options should be discussed with the patient (even if the patient does not have a choice)?

Never Sometimes Regularly Often Always I don't know

Comments.....

6. Have you noticed that the patients have questions about complementary treatments?

Never Sometimes Regularly Often Always I don't know

Comments.....

7. Do you believe that doctors are adequately trained to implement shared decisions in clinical practice?

Yes No

Comments.....

8. How often do you apply shared decision making when consulting lung cancer patients?

Never Sometimes Regularly Often Always I don't know

Comments.....

10. What are the benefits of shared decision making according to you?

.....

11. What do you find problematic in shared decision making?

.....

12. What conditions do you think are less suitable to apply shared decision making?

.....

13. In what circumstances would you like to apply shared decision making?

.....

14. What makes it difficult to apply shared decision making in current clinical practice?

.....

15. Do you think that patients are burdened when they are involved in treatment decision making?

.....

Case 1. Female, 60 years. History of pT1aN2M0 NSCLC (stage IIIA) which was treated with concurrent chemo-radiotherapy. Now on PET scan cT1NxMx right lower lobe. Conclusion of pathology report is adenocarcinoma. It is not possible to perform EBUS.

Surgery 1 2 3 4 5 6 7 Stereotactic radiotherapy

Comments.....

Case 2. Male, 54 years. Productive cough with white sputum for the past 6 months, his weight is stable and WHO classification is 0. The clinical stage of the tumor is determined by EBUS procedure which resulted in cT2AN0M0 in right middle lobe.

Surgery 1 2 3 4 5 6 7 Stereotactic radiotherapy

Comments.....

Case 3. Female, 64 years. History of pancreatic cancer. Now NSCLC in right upper lobe with positive N1 lymph node which was seen on PET scan. There are no other suspicious lymph nodes seen on CT scan. Brush cytology showed a small number of malignant cells suspicious for adenocarcinoma.

Surgery 1 2 3 4 5 6 7 Stereotactic radiotherapy

Comments.....

Case 4. Male, 76 years. Patient is ill, with COPD GOLD III, shortness of breath and productive cough with green sputum. PET scan show a tumor of 24 mm in left upper lobe.

Surgery 1 2 3 4 5 6 7 Stereotactic radiotherapy

Comments.....

Case 5. Male, 80 years. Productive cough with white sputum for the past 6 months, his weight is stable and WHO classification is 0. The clinical stage of the tumor is determined by EBUS procedure which resulted in cT2AN0M0 in right middle lobe.

Surgery 1 2 3 4 5 6 7 Stereotactic radiotherapy

Comments.....

Case 6. Male, 77 years. The patient is known with melanoma (metastatic to the liver and to an axillary lymph node). During the follow up of this disease a suspicious node in left lower lobe of his lung was seen. Further diagnostics shows squamous cell tumor of 29 mm, cT1bN0M0.

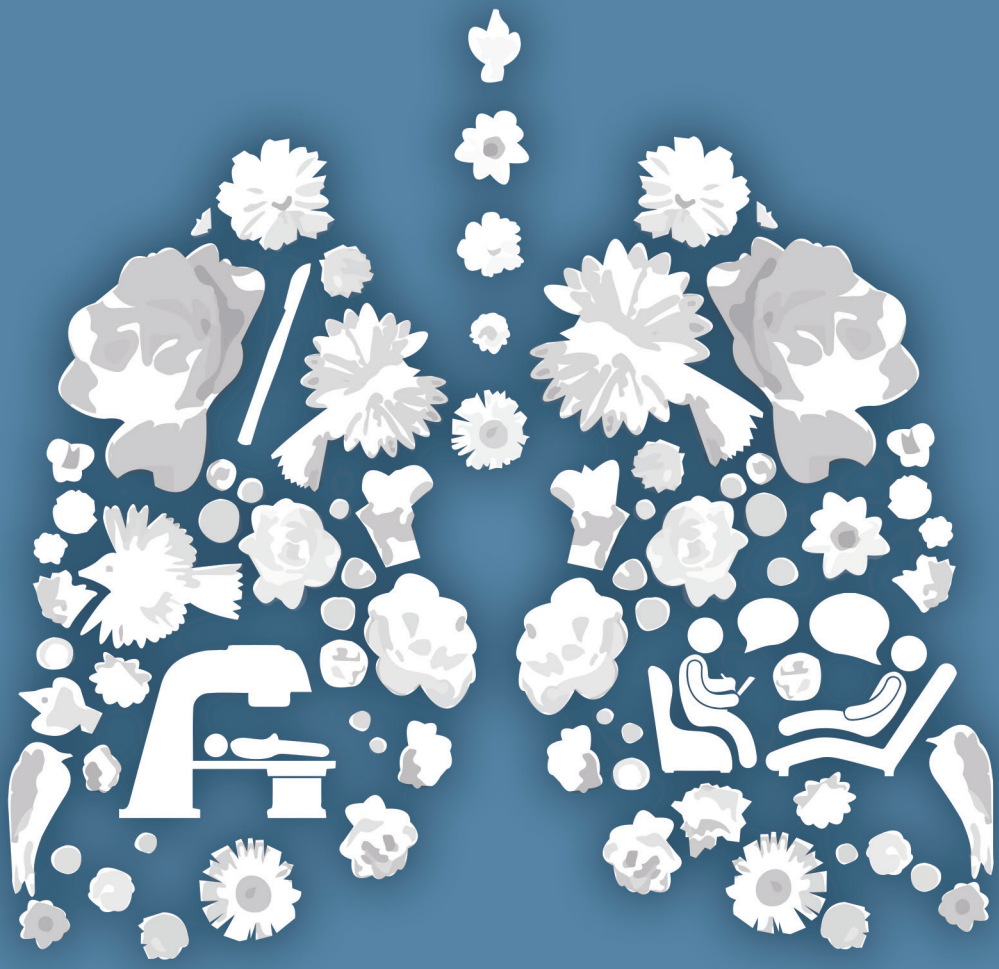
Surgery 1 2 3 4 5 6 7 Stereotactic radiotherapy

Comments.....

Case 7. Female, 57 years. History of complete resection of the tumor in left lower lobe, pT1bN0M0 adenocarcinoma. Now PET scan show a tumor in right lower lobe with cT1N0M0. Pathological confirmation of the tumor stage could not be obtained. The patient has now severe aortic stenosis, reduced lung function and morbid obesity.

Surgery 1 2 3 4 5 6 7 Stereotactic radiotherapy

Comments.....



CHAPTER 10

Evidence-Based and Personalized Medicine. It's [AND] not [OR].

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Annals of Thoracic Surgery 2017 Jan;103(1):351-360

ABSTRACT

Good clinical practice is an amalgamation of personalized medicine with evidence-based medicine in the best interests of patient. Hence, our title uses Boolean operators to indicate that it is [AND] not [OR]. This is the syntax of formal searching for systematic reviews, ensuring that all the evidence is found. Comprehensive evidence-based guidance can thus be formulated. Many residents and fellows around the world, and their chiefs, are now exposed to consensus documents, white papers, levels of appropriateness, and guidelines and are in many jurisdictions expected to comply with them. However, they are the summation of many forms of evidence, each of which has its place, and we consider them in turn in this article.

INTRODUCTION

An aptitude for surgery has two components: manual ability and mind-set. Surgery demands technical skill; that is, an innate ability honed by practice and attention to detail. The surgical mind-set has admirable components: decisiveness, self-reliance, the ability to keep going in adversity, clarity of purpose, optimism. However, it is that very same mind-set that makes, for some, the trappings of evidence-based medicine (EBM) hard to bear. We hope to make it better understood in this article. The pyramid of evidence was introduced in the early 1990s as a new paradigm for improving patient care. Running through this article is the distinction in EBM between efficacy (does it work under ideal circumstances?) and effectiveness (does it benefit the patient in daily clinical practice?). The words are interchangeable in most English usage, but in EBM a simple example might be that in an anemic patient a blood transfusion can be relied on to raise the hemoglobin (it works, it has efficacy) but in moderate chronic anemia it would not generally be the most clinically effective line of treatment. Finally, we touch on efficiency (does it contribute to more efficient use of resources?), a growing determinant in health care expenditure.

There are three components to any clinical encounter.

1. The patient's values and expectations. These vary between cultures and throughout history. Faced with illness or injury, all sentient beings would prefer to remain alive and to avoid suffering. The treatment may heighten as well as reduce fears.

2. The doctor's skills and experience. These also vary with place and time, but modern civilizations have come to rely on the attention of physicians, but only relatively recently has medicine made a large impact on disease (1).

3. Best available evidence. Even more recently medical practice has comes under close scrutiny, and evidence is expected to inform decisions.

These three components are illustrated by the three legged milking stool analogy (Figure 1). A three-legged stool will sit on even the roughest floor. You need to have all three legs for it to work, but they can vary in length and breadth and still give support. The analogy is attributed to the late David Sackett (1934–2015) who wrote:

Evidence based medicine is not "cookbook" medicine. Because it requires a bottom up approach that integrates the best external evidence with individual clinical expertise and patients' choice, it cannot result in slavish, cookbook approaches to individual patient care. External clinical evidence can inform, but can never replace, individual clinical expertise, and it is this expertise that decides whether the external evidence applies to the individual patient at all and, if so, how it should be integrated into a clinical decision (2).

Figure 1: The three-legged stool of which 'best available evidence' is just one leg

The Pyramid of Evidence Versus the Best Available Evidence

The EBM movement introduced doctors to the pyramid of evidence which ranked the value of evidence from highest to lowest (Figure 2). In present day surgical practice this ranking may be used in the levels of evidence for clinical practice guidelines (3), but it is a subject of debate and change. Although helpful in categorizing types of studies, it has become clear that it is too simplistic to rank evidence by methodologic sophistication. There are times when accurate observation is most or all that we need (4). Furthermore, it is not what happens in practice, as seen in Figure 3 derived from an analysis of the forms of evidence used in more than 250 articles in the 50th Anniversary Volume 100 *of The Annals of Thoracic Surgery*.

We ground this article in the reality of cardiothoracic surgery teaching and training, starting with the simpler methods and progressing to those of increasing complexity. We want to convey the message that more complex methods are not always better. Less sophisticated methods have often served as evidence enough, but they should be tested for their appropriateness as evidence for clinical practice.

Figure 2: The pyramid of evidence

The practice of EBM involves five essentials steps (five A's) (5): (1) ask: formulate the question; (2) acquire: search for answers by acquiring the evidence; (3) appraise: evaluate the evidence for quality, relevance, and clinical significance; (4) apply: apply the results; and (5) assess: assess the outcome.

These steps are developed to overcome automatic decision making and to deliver optimal patient care. However, there are a number of possible features of a research method that would contribute unbiased and more trustworthy evidence.

- Was the question prespecified?
- Was the outcome clearly defined from the outset?
- Was there was a protocol?
- Was there independent allocation?
- Was a formal comparison made?
- Was there was a power calculation?

Not all of the features are achievable and not all are essential, but absence of one of these criteria may lead to a weakness in the conclusion and hence in the evidence. In surgery it is difficult to satisfy all of the features of research method, but the fewer that are satisfied,

the less reliable is the conclusion. Many studies that are trusted as guiding practice will pass only some of them.

In this article, for each form of evidence, first, we define the method and set out its essential features and virtues. Second, we illustrate the method in practice with one or more examples. We accentuate the positive by choosing examples that have provided evidence for practice. Finally, for each example, we comment on whether we think the method worked well (and that involves our judgments and opinions) and its limitations.

Case Reports

Humans have evolved as a successful species by observation and experimentation with the world around us. Having discovered which berries are nourishing and which are poisonous, how to hunt and kill an animal, how to catch a fish, how to make a controlled fire and to cook with it, man's instinct is to stick with what he knows works. In medicine we love case reports as can readily be gathered from the tally of published items in *The Annals of Thoracic Surgery* volume 100 (Figure 3).

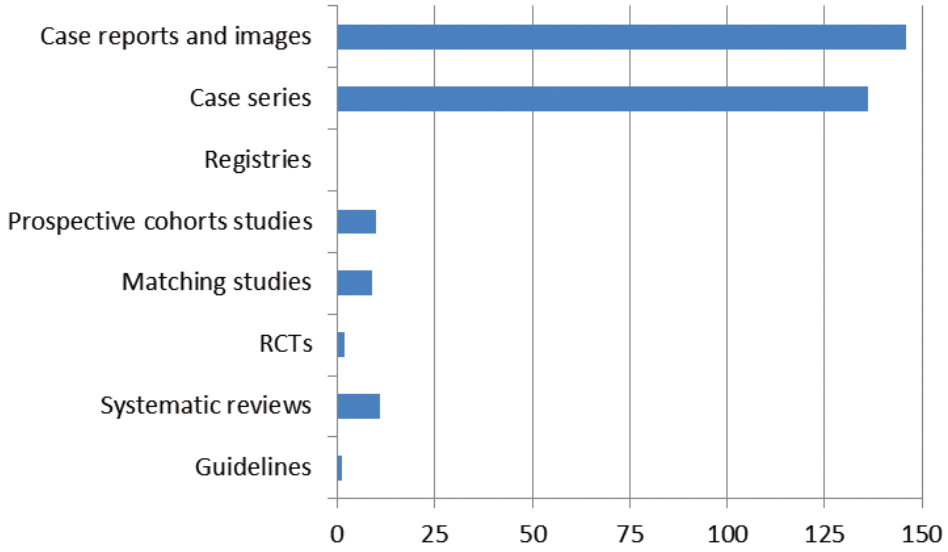

Figure 3: Annals of Thoracic Surgery Volume 100, July to December 2015, the 50th Anniversary of The Society of Thoracic Surgeons, 526 articles were categorized by title, abstract and full text. In addition to the 362 included in this chart there were 106 educational articles, 59 commentaries, 38 related to modelling and risk scores, 27 reporting clinical science and 10 on bench or animal laboratory studies. (RCT=Randomized controlled trial)

A case report is an original and personal experience of the authors. Writing of a single clinical case has been the way for young surgeons to start their publishing career; often that is also where it stops. However, the clinical case report, if we are to judge by publications in *The Annals of Thoracic Surgery*, is as popular as ever. Cases are often used to start of teaching rounds or for student presentations. For teaching cases they are not chosen to be unusual; they should be representative of what is to be taught. Then the case is an exemplar or a parable. In contrast, cases for publication are rarities or even cautionary tales: "We'll never do this again!" It was interesting that as extrapleural pneumonectomy for mesothelioma went into decline, a case report appeared of a single patient who may indeed have been cured by extrapleural pneumonectomy (6). Its very publication in 2014 was an indicator that this was not the routinely experienced outcome (7).

Example: Composite Root Replacement for Marfan Aortic Root Aneurysm

In 1968 Bentall at The Hammersmith Hospital operating for severe aortic regurgitation and near end-stage heart failure was confronted with the following problem: "A mid-sternal thoracotomy revealed a large globular dilatation of the ascending aorta. Its bulging inelastic wall was so thin that blood could be seen eddying within" (8).

Bentall, at the operating table, fashioned a composite valved tube graft and sewed that to the aortoventricular junction. He reconnected the coronary orifice with end face anastomoses to the tube graft (8). This is regarded as the first composite root replacement and set an important precedent.

Comments

In 1966 Cooley and colleagues (9) in Texas had reported a series of operations for patients with ascending aortic aneurysm and aortic regurgitation in which they replaced the aortic valve and most of the ascending aorta, but they made their proximal anastomosis distal to the coronary orifices. So we can see that Bentall's operation was not a shot in the dark. The theoretical desirability of replacing the sinuses in Marfan root aneurysm operation was anticipated, but the surgical risk had appeared prohibitive to date. Bentall saw no possibility of getting this patient through the operation alive with methods reported thus far. Having done it, he knew he had achieved an important landmark in the operation for root aneurysms. The main advantage of case reports is the capacity to present a first. However, many case reports, even if fascinating and popular, may inadvertently focus on misleading elements. Few are ground breaking.

Case Series

These are observational studies that report on a subject group without a comparison population. In surgery they are typically a single surgeon or an institutional report summarizing a sequence of operations of a particular type. Case series remain one of the most common forms of evidence in journals of clinical surgery (Figure 3). They are low cost and easy to conduct. They may be helpful in refining new techniques or in defining

treatment protocols. The limitations are that there was an unknown pool from which the patients were drawn so there is selection bias and limited generalizability (Table 1); therefore, they should not be used to draw inferences regarding overall treatment effect.

Example: Commissurotomy for Mitral Stenosis

In 1950 Brock reported his series of eight operations for mitral stenosis, starting in 1948, six in London, and two at Johns Hopkins (10).

Comments

There had been reports of two successful cases in the 1920s (11, 12), but there was a run of deaths thereafter (13). Surgical relief of mitral stenosis was discounted with increasingly strong statements of contrary opinion (14). The problem was revisited in late 1948 in Philadelphia (15), Boston (16), and London (17). Brock, who had scheduled three patients for operation in a fortnight in 1948, held off publishing until he had a series. After this report (17) and others, mitral valvotomy was adopted all over the world with very obvious clinical benefit and quickly reduced risk. This is why we chose mitral valvotomy as an example of the influence of a series as opposed to a case report.

Two case reports in 1923 and 1925 reported clinically successful operations for mitral stenosis (11, 12). These case reports had failed to gain traction. A subsequent case series reported that these firsts were not replicated (13). Brock held his pen until he had a run of successes. There are many instances in which case series have been proved to be all the evidence that was needed to introduce operations into practice.

Many standard operations came into practice on the basis of case series. Once the technical difficulties were overcome, hip replacement and cataract operation came into practice on the basis of surgical follow-up studies because "the lame walked and the blind recovered their sight" as in Biblical miracles (18). These operations meet the criteria for acceptance into practice on the basis of clinical observation: the intervention fixes the problem in an evident way, the effect is immediate, the effect size is great, and the benefit is maintained (4).

However, case series have short comings and are not as good evidence for cancer operations (19). The selected patients are those with the best prognostic features, at the longer surviving end of the broad spectrum of patients with these malignant diseases, statistically an example of selection bias (Table 1). The desired outcome of longer survival takes years to measure, and there is commonly reappearance of cancer, indicating mechanistic failure of the surgical intent, which was to excise all cancer.

Case series are also unreliable if the outcome being prevented has an unpredictable and relatively low occurrence rate as in carotid endarterectomy to prevent stroke. Most patients (70% to 80%) will not have a stroke in the next 3 to 5 years (20) so for any individual freedom from stroke cannot be attributed to the carotid endarterectomy; most were not destined

to have a stroke. Case series are also poor evidence for conditions with naturally varying severity of symptoms. A bad phase tends to prompt the intervention, and on average the group of patients will be better at a later time. This is a statistical effect called regression to the mean (Table 1).

Table 1. Glossary of terms

Term	Definition
Bias	In everyday English mention of bias is generally pejorative but in EBM it merely recognises a human inevitability. Surgeons rightly select the patients who will do well over those in whom our operation will fail which is selection bias. Editors prefer to publish positive and ground breaking results which is publication bias. Studies should be designed to minimize the effects of bias
Confounding	A familiar example is that there may be an apparent association between drinking alcohol and the likelihood of dying from lung cancer drinkers are more likely to smoke and vice versa. Further analysis shows that smoking is causative and that the association between drinking and lung cancer is a confounding factor
Generalizability	A word not liked by linguistic purists but a useful one expressing the idea that the evidence in a study is likely to be widely applicable
Intention to treat analysis	When advice is given to a patient about what is the likely outcome of one or another course of treatment, or of no treatment, the prediction has to take into account the range of likely outcomes at the time the treatment is assigned. Whatever happens subsequently outcomes should be reported on intention to treat
Power calculation	At an early stage in planning a controlled trial it is essential to estimate how many patients are needed in the study for a clinically important treatment effect not to be missed
Regression to the mean	Treatment of disease with variable symptoms is more likely to be started when symptoms are at their worst. Due to variation over time subsequent assessment is likely to produce measures nearer to the average and an illusion of benefit

Registries

For a recently introduced or evolving treatment there is commonly a call to set up a registry. People offering the treatment are invited to join and pool their data. Sometimes contributing data to the registry is a requirement to have access to a device or equipment. The virtue is that a large number of patients can be included.

Example 1: International Registry of Lung Metastases

The International Registry of Lung Metastases (IRLM) was published in 1997 (21, 22). The analysis of 5,206 patients showed that the favorable factors for survival were a longer interval since primary resection (>3 years) and a solitary metastasis. The IRLM authors

choose their words carefully. They call these prognostic factors which is indeed correct: these apply irrespective of treatment rather than being predictive of a beneficial effect of metastasectomy (23). The IRLM authors were also quite clear in their recommendation for further work. In their view the registry would "define areas of uncertainty concerning surgery and other therapeutic modalities to be explored by prospective randomized trials' (22).

Example 2: The TASTE Trial

The Thrombus Aspiration in ST-Elevation myocardial infarction (TASTE) trial was a multicenter, controlled clinical trial that used the infrastructure of a population-based registry in Scandinavia to facilitate patient enrollment and data collection (24). Harnessing the power of an existing and well-supported registry allowed completion of a large trial (N ¼ 7,244) without having to start the whole process from scratch.

Comments

One limitation is that the IRLM only includes patients who had metastasectomy, not patients considered for the treatment. There can be no intention-to-treat analysis (Table 1). Welcoming the registry as "the major scientific initiative during the last 20 years" Åberg commented at the time that the "inclusion in the registry of the probably few patients who abstain from operation after being advised to have it would add to the value of the registry" (25). That would have provided the critical missing piece of information: the unoperated survival for patients who are similar to those having metastasectomy. That is the natural history of the condition.

The value of registries would be enhanced if they can be used, as in the second example, as a repository of a cohort of patients who can be recruited into subsequent prospective studies of clearly defined research questions.

Prospective Cohort Studies

A cohort study is one in which a group of subjects, selected to represent the population of interest, is studied over time. A cohort study may be either retrospective or prospective. Retrospective cohort studies concern a certain exposure in the past (e.g. an operation) and then study the occurrence of an outcome (eg, death or complications) until the present time. Prospective cohort studies start in present time and include future patients with a certain exposure and then wait for prespecified outcomes to occur. Truly prospective cohort studies are more uncommon in surgery than retrospective cohort studies because they are far more costly and usually require a long follow-up time, in particular when the outcome of interest is infrequent. However, prospective cohort studies have the following advantages: they are suitable for the study of rare exposures, can measure the change in exposure and outcome over time, can be used to study more than one outcome, and gives some indication of causality (26).

Example

An example of a prospective cohort study is the study about the predictors of outcome in severe, asymptomatic aortic stenosis. The clinical outcome and management of patients with symptomatic aortic stenosis has been well known; however, the management of patients with asymptomatic aortic stenosis remains controversial, and irreversibly impaired left ventricular function and risk of sudden death are not unusual. In the study of Rosenhek and colleagues (27) a large cohort of patients with asymptomatic, severe aortic stenosis were studied prospectively to identify clinical or echocardiographic predictors of outcome. They concluded that it is relative safe to delay operation until symptoms develop.

Comments

The main disadvantage of a prospective cohort study is that if the outcome is infrequently occurring then a large cohort of patients must be followed for a long period of time before results become available. In this example, to ascertain the risk of sudden death in patients with asymptomatic aortic stenosis and to illustrate that these patients will benefit from aortic valve replacement, a large cohort of patients is needed because sudden death is not a frequent occurrence. In the study of Rosenhek and colleagues (27) six of the eight deaths were due to cardiac-related causes from which one sudden death occurred without any symptoms before death. However, being asymptomatic is not the same as being stoical and uncomplaining. Consideration of valve replacement should depend on disease characteristics, including clinical signs and measurement. The predictors of outcome in patients with asymptomatic aortic stenosis were aortic-jet velocity, aortic valve area, hypertension, diabetes mellitus, and mitral annular calcification.

Matching Studies

A comparison group is derived from existing data. Patients who did not have the treatment but might have are selected from a data set to match as many factors as are available with patients who did have the treatment. There may be more than one patient matched. They may be matched as a group. A standard method at present is to derive a propensity score based on available predictors of the risk of an adverse outcome. It only works if patients were suitable for both courses of action. If there is little or no overlap between patients having one or other course of action, this method fails because we cannot separate the effect of the treatment from the reasons for being selected for the treatment.

Example: Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting From the DELTA Registry

Coronary artery bypass grafting (CABG) is the treatment of choice for patients with multivessel or left main coronary artery disease. Numerous articles have compared CABG with percutaneous coronary intervention (PCI) using propensity score matching. The authors from the DELTA registry compared the long-term clinical outcomes of PCI with those of CABG in a substudy. Even though a total of 856 patients were ineligible for comparison (482 treated with PCI and 374 with CABG), only 209 pairs were matched (28).

Comments

Propensity score matching offers a solution for reducing bias in observational studies and offers a way to achieve more balanced groups by matching treatment and control units based on a set of baseline characteristics. So it depends on the registered or measured baseline characteristics because the calculated propensity score for each individual reflects patients' probability to receive a certain treatment based on baseline characteristics. It is impossible to record in a database all of the factors that lead to a highly skilled and experienced team choosing between PCI and CABG. Because of differences in unrecorded characteristics there may still be an imbalance between the two treatment groups. The deliberate decision whether to treat a patient by means of PCI or CABG is based on certain specific characteristics of the patient which may not have been adjusted for with propensity score matching. In the study of Naganuma and colleagues (28) 49% of patients could be matched with the calculated propensity score, creating two selected subgroups of PCI and CABG patients, and the conclusion cannot be generalized with confidence to the entire population of PCI and CABG patients.

Randomized Controlled Trials

There are several essential features of the typical two-arm randomized trial. Its design can be simplified to the acronym PICO (P for participants, patients, problem, or population; I for the intervention under test; C for the control group or comparator; and O for the outcome(s) to be reported).

The reporting of randomized trials has been standardized in the CONSORT statement (Consolidated Standards of Reporting Trials) which if adhered to greatly assists in reviewing the study and later extracting data for meta-analysis. It also sets out the information needed to assess the quality of the trial using in turn the GRADE (Grading of Recommendations Assessment, Development and Evaluation) instrument. Because systematic reviews and meta-analysis have become essential components of EBM, checklists such as CONSORT and GRADE to standardize methods of weighing the relative values of evidence have become increasingly used.

The headline requirement of a randomized controlled trial (RCT) is that patients deemed eligible for either treatment are assigned their treatment by chance.

- The trial has, of its nature, to be prospective.
- The workup of patients is by protocol, and only when all workup is complete are the patients randomly assigned.
- Randomization should be deferred to as short a time as possible before the intervention so that further decisions are not biased by the knowledge of the assigned treatments arm.

- Once assigned all patients remain in the assigned arm for analysis irrespective of dropouts and cross overs.

These steps are to reduce as far as possible any biases, however, unintended. The outcome should be objective and clinically meaningful. Full double blinding is difficult in interventional trials; both patients and practitioners know or can easily deduce which treatment has been given. Some trials have gone to great lengths to disguise which operation (or no operation) has been performed.

- In the landmark RCT of open versus laparoscopic cholecystectomy the various dummy dressings were applied and stained with blood to make them realistic (29).

- In an RCT of arthroscopic knee joint washout a placebo group had skin incisions but no arthroscopy (30).

These measures are difficult to achieve, and it is difficult to be certain that blinding really worked. More simply, it should possible to ensure that the evaluation and recording of the outcomes is best made by individuals without knowledge of which treatment the patient had. The RCT's single greatest advantage over other forms of comparative study is that it has the potential for balancing known and unknown confounding factors between the trial arms.

Example

Radical mastectomy was compared with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast (31). There was no survival advantage for women having the more radical operation.

Comment

Radical mastectomy occupied what seemed to be an unassailable position in the treatment of breast cancer from the 1890s. The story of radical mastectomy is familiar as an example of an RCT that changed practice (32). The demise of radical mastectomy is attributed to a RCT from Milan, Italy, published in the *New England Journal of Medicine* (31). The standard teaching had been that anything less than a radical mastectomy would compromise the chance of cure, and, if the patient died of breast cancer, the surgeon doing a lesser operation would be culpable for the death of this patient. Surgeons were encouraged to extend the scope of the operation. In addition to axillary lymph node clearance, they were urged to routinely dissect the lymphatics of the neck and, for medial breast cancers, the mediastinum. The story is told dramatically by Siddartha Mukherjee in *The Emperor of All Maladies* (33).

The story is however not quite that straightforward, and there are more lessons to learn. In fact considerable doubt had been raised in a 50-page treatise on the subject by Bernard Fisher in 1970 (34), and by 1978 one of the foremost teachers of clinical surgery, Harold

Ellis, wrote an article about best management of breast cancer without once mentioning radical mastectomy (35). The omission of radical mastectomy was not faulted in the correspondence columns in the following months; the practice was already waning. So here is the point: for an RCT to be possible there has to be doubt about the rightness of established practice. Confidence in radical mastectomy first had to be shaken and only then could random allocation be justified. By the time the RCT was recruiting, clinical practice was already shifting away from radical mastectomy. The RCT did not start the debate, but it played a vital role in concluding it and ensuring that within our lifetimes it has not had to be revisited.

Variations in clinical practice could theoretically be resolved by pragmatic RCTs. It would require surgeons to see variation in practice as a sign of uncertainty, to share uncertainty to reach a mutually agreed equipoise, and to put the question to the fair test of a randomized trial. That has proved remarkably difficult to do. Surgeons would also have to accept that variation in practice associated with an every man for himself spirit is best avoided.

Systematic Reviews

Before making guidelines for treatment, or embarking on a new trial to resolve a question with respect to treatment, it is best practice to systematically review all the evidence available. This is clearly preferable to nonsystematic selective citing by guidelines committees; hence, the need to a priori clearly document search terms and strategies as hinted at in the title of this article. By individually assessing studies for their sample size, patient and treatment characteristics, quality, and reliability, the standard of analysis is raised from simply considering the number of studies that support a practice versus those that do not.

As a part of a systematic review one can consider performing a meta-analysis: a statistical exercise to combine data from the individual studies in the systematic review. At first meta-analysis tended to use RCTs (36). In more recent years it has become more common to also systematically review observational studies. Although meta-analysis of observational data and multiple follow-up studies enlarges the data set, it does not overcome the absence of control groups. Furthermore, if the methodologic quality of trials or observational studies are inadequate, then the findings of systematic reviews may also be compromised, and publication bias remains a problem as significant results are more likely to get published and more likely to be cited. The methods of systematic reviews and meta-analyses have improved over the past decades by taking the essential features of the methods into account (eg, predefined inclusion and exclusion criteria for studies, performing an extensive search with a medical librarian (methodology will be more reproducible), assessment of the validity of the findings, account for the variable follow-up time between studies by using the hazard ratios, etc.) (37). Very helpful in this regard is the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement that provides a checklist to improve the quality of systematic reviews (38, 39). There is an

equivalent checklist for reviews of observational data with the acronym MOOSE (Meta-analysis of Observational Studies in Epidemiology).

The main advantage of a systematic review is that sample size is increased and therefore provides more power to identify small effect sizes or to be more confident of a no difference conclusion. Meta-analysis also improves the precision of estimates of treatment effects; may contribute to resolve uncertainty when original research, reviews, and editorials disagree; and may demonstrate the lack of adequate evidence that needs to be addressed in future studies. Here, we consider meta-analysis of randomized trials.

Example

Between 2001 and 2013 there were eight RCTs (N of 31 to 500) which addressed the question of whether there was a difference between use and nonuse of external suction to pleural drains after lung resection (40). Some found that the use of suction, which was the more common clinical preference, might be detrimental, and this was supported by meta-analysis of all available trials (41, 42).

Comments

The efficacy of a pleural drain and underwater seal was established from the outset of thoracic surgery based on mechanistic understanding and clinical observation. The efficacy of tube drainage and water seal was never in question. The life-saving benefit in tension pneumothorax is dramatic. The addition of external suction hastens evacuation of air and fluid, but a blanket policy of suction may be detrimental. Which is the more clinically effective policy? This illustrates the difference in EBM between efficacy (does it work?) and effectiveness (does it benefit the patient?).

Clinical Practice Guidelines

Ideally, we want to combine all available evidence when we attempt to provide guidance for optimal patient treatment. Although a systematic review of all relevant RCTs may provide cause–effect relationships, it is often not generalizable to all patients in clinical practice. However, observational studies may be more generalizable, but they only provide associations between patient and treatment characteristics and outcome. They are subject to reporting bias because we tend to prefer to publish our best practices and not our failures. Innovations usually start by being reported in case reports or case series and are worthwhile to be included as the basis for clinical practice guidelines. Unfortunately, current clinical practice guidelines are more often eminence based than evidence based.

Example

The European Society of Cardiology/European Association for Cardio-Thoracic Surgery 2012 guidelines on the management of valvular heart disease (3) gives recommendations on the treatment of heart valve disease based on three different levels of evidence. Level A is data derived from multiple RCTs or meta-analyses. Level B is data derived from a single

RCT or large nonrandomized studies. Level C is consensus of opinion of the experts or small studies, retrospective studies, registries.

In the guidelines recommendations for operation in aortic regurgitation, for operation in aortic root disease, and for aortic valve replacement in aortic stenosis, are nearly all based on level of evidence C. There were no trials undertaken. The guidance is nearly all based on consensus from the experts asked to formulate the guidance.

Comment

With respect to operation for aortic stenosis the natural history was well known, and the adverse features for survival (syncope, angina on minimal effort) were well characterized. Within a few years of the first technically successful operations there were asymptomatic survivors clearly restored to good health with good heart function. Survival figures of 90% at 10 years compared with a natural history of less than 2 years meant that relief of aortic stenosis met the criteria to accept observational data; there was a clear mechanistic link between the intervention and the outcome, a sustained benefit and a large effect (4).

After the initial proof of clinical effectiveness there were dozens of valve designs tried and failed. There were individual trials of mechanical versus tissue valves (43) and of the relative thromboembolic risk of disc versus caged-ball valves (44), but largely the progress was based on noncomparative studies, as is reflected in current clinical practice guidelines.

The European Society of Cardiology/European Association for Cardio-Thoracic Surgery 2012 guidelines on the management of valvular heart disease guidelines (3) may be the best one can do in the absence of RCT evidence but does not achieve what is expected overall. How can we improve guideline development in our field? The guidelines for trustworthy guidelines are themselves well defined and internationally agreed. They set the bar quite high (45). A guideline development group should include diverse and relevant stakeholders, such as health professionals, methodologists, experts on the topic, and patients. The decision-making process should be explicit and based on best-available evidence and established before the start of guideline development. Disclosure of the financial and nonfinancial conflicts of interest is essential as is the way conflicts were recorded and resolved. There should be a scope and methods defined ahead of the meetings. Systematic evidence reviews are essential, and a rating system to communicate the quality and reliability of both the evidence and the strength of its recommendations is part of the process. There should be an opportunity for review and stakeholder consultations (45). These standards are needed because otherwise it is all too easy for groups with a vested interest to issue position statements in the guise of clinical guidelines (46).

Another consideration in 21st century clinical practice (guidelines development) is the issue of efficiency: how can we benefit most from technologic innovations in our field

while at the same time contain the steadily increasing health care costs? In Britain the National Institute for Health and Care Excellence produces guidance for the National Health Service which is regularly updated and is seen internationally as a model in guideline development. However, its guidance is not always welcomed. An underlying principle is that Health Economic Evaluation underpins all decisions. Expensive treatments that, although clinically effective, consume resources for limited or short-term gains in health have to give way to treatments that gain more quality survival for the money spent. In the United States in March 2016 the division of the National Academies of Sciences, Engineering, and Medicine (the Academies) that focuses on health and medicine was renamed the Health and Medicine Division instead of using the name Institute of Medicine. There is will be an increased focus on a wider range of health matters. The process features extensive public consultation, and the change in the name signals an emphasis on public health measures that may come at the expense of high-cost interventional medicine. Cardiothoracic surgeons will be all too well aware of this changing climate in how clinical effectiveness will be considered.

As a surgical community we have the moral obligation to improve the evidence base and wherever it is feasible work toward levels of evidence A and B. This can be achieved by first of all continuing to study outstanding questions though a range of study designs and to publish all results, including the ones we tend to like less due to our prior convictions. Second, it is of utmost importance that systematic collection of all available evidence, including efficacy, effectiveness, and efficiency is implemented in the process of clinical practice guidelines development.

Table of acronyms and abbreviations	
CONSORT	Consolidated Standards of Reporting Trials
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
EBM	Evidence Based Medicine
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HMD	Health and Medicine Division
IOM	Institute of Medicine
MOOSE	Meta-analysis of Observational Studies in Epidemiology
NICE	National Institute for Health and Care Excellence
RCT	Randomised Controlled Trial
PICO	The essential features of a study.
'P' is used variably to stand for Patients, Population or Participants; 'I' for Intervention; 'C' for Control or Comparator; 'O' for Outcome	
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
STARD	Statement for reporting studies of diagnostic accuracy
STROBE	Strengthening the Reporting of Observational studies in Epidemiology.

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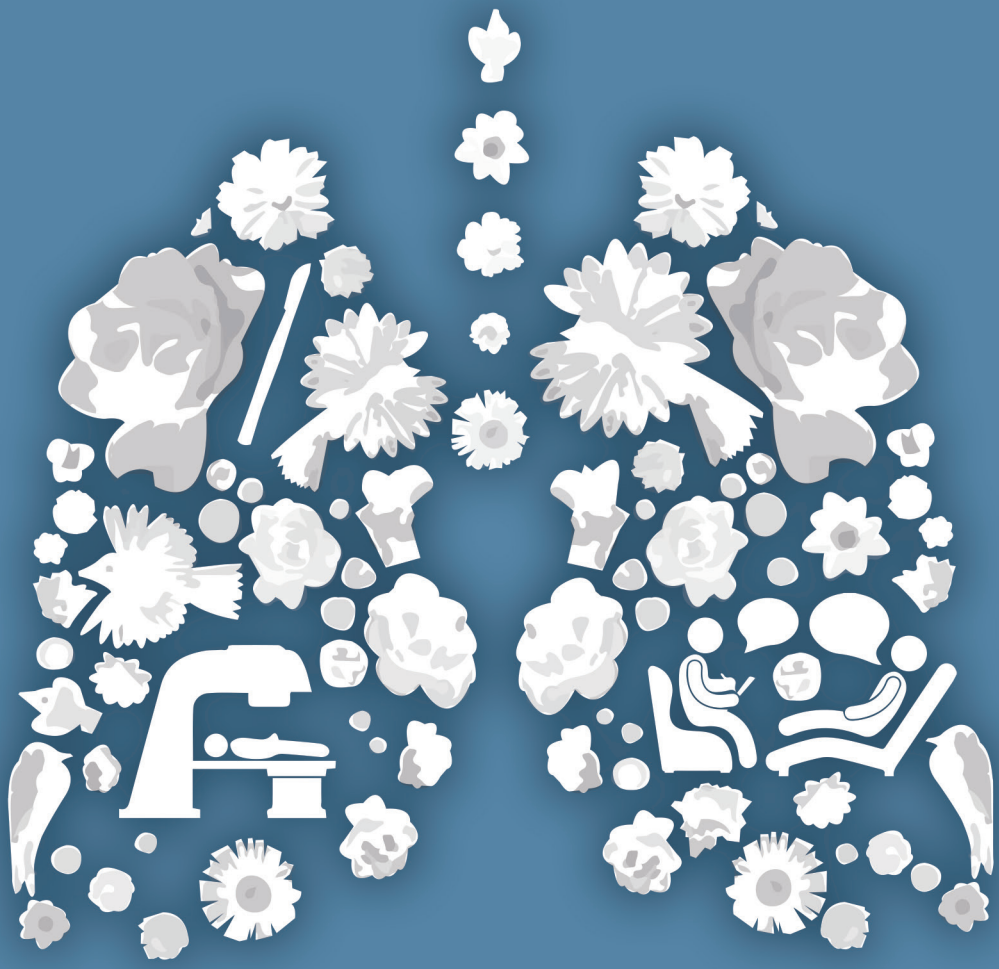

CHAPTER 11

General Discussion

The aim of this thesis was to gain an improved insight into determinants of outcome in patients with non-small cell lung cancer (NSCLC) stage I and II, and insight into current treatment decision making from the perspective of both lung cancer patients and lung cancer physicians. In this discussion chapter, I will address our research questions. The results will be put in a broader perspective and the implications for the clinical practice will be presented. First, the prognostic factors for the prediction of long term outcomes and survival of early stage NSCLC patients will be discussed. Second, the procedure related complications and the quality of life will be explored. Thereafter, the role and experience of early stage NSCLC patients in treatment decision making will be explored and the barriers and drivers to apply shared decision making in current clinical practice will be illustrated. Finally, future perspectives about the care of early stage NSCLC patient will be suggested.

Prognostic factors and clinical outcomes

Comorbidity and tnm classification

Although the revised Tumor Node Metastases (TNM) classification suggests that the nodal status is the most reliable indicator of the prognosis of lung cancer patients (1), the heterogeneity in the group of early stage lung cancer patients (e.g. age, gender, comorbidity, race-ethnicity and socioeconomic status) makes it difficult to choose the optimal treatment for an individual patient (2-7). Development of tools, such as prediction models and a nomogram to predict survival, based on patient and tumor characteristics, could potentially allow for more personalized treatment decisions (8-11). In **Chapter 2** and **3** we aimed to make a first step toward this process. In **Chapter 2** is illustrated that in addition to TNM classification, the consideration of patient age and Charlson Comorbidity Score (CCI) may improve the prognostication of NSCLC patients. Significant predictors in the surgical group were older age, CCI 4, and clinical stage IIB. While, the significant predictors in the group of patients treated with stereotactic body radiotherapy (SBRT) were CCI >5, and clinical stage IA to stage IIB. In **Chapter 3** we also observed that age, CCI, smoking history, and WHO performance score were strong predictors of survival. These observations indicate the importance of elucidating the impact of comorbidity on treatment and survival of lung cancer. When it comes to time of lung cancer diagnosis, it is not clear whether the presence of comorbidity delays the diagnosis of lung cancer or that lung cancer is diagnosed at an earlier stage of the disease. For example, chronic pulmonary disease progress over the course of years which will lead to more intensive medical care and radiographic evaluation resulting in early diagnosis of lung cancer (12, 13). On the other hand, comorbidity may be associated with a delay of lung cancer diagnosis for the reason that it can complicate the presentation of lung cancer (e.g. misinterpretation of blood tests or radiographic images) (14). Comorbidity is of prognostic value for survival, independent of TNM classification as the patients who have comorbidity are less likely to receive treatment with curative intent (15-21). Furthermore, patients with comorbidities, such as

pre-existing pulmonary conditions, have an increased incidence of treatment related adverse effects (e.g. pneumonitis or fibrosis after radiation therapy or not being eligible for pneumonectomy) (21, 22). Given the impact of comorbidities which comprises diagnosis, treatment, and survival of lung cancer it is justified to conclude that this multifaceted role of comorbidity need to be considered. Unfortunately, no comorbidity is included in TNM classification despite the evidence of its prognostic importance (23). In addition, biological parameters, molecular and genetic factors (e.g. epidermal growth factor receptor) are currently not integrated into TNM staging which could potentially increase the prognostic accuracy of lung cancer (24).

Prediction models

Prediction models are used to predict the occurrence of a certain event given a set of risk factors. Due to the growing complexity of the diagnostic and prognostic evidence that is available in the literature, prediction models are increasingly relevant for cancer patients to predict local cancer recurrence or survival. In **Chapter 3** two types of prognostic models were used: recursive partitioning analysis (RPA) and a nomogram. With RPA a decision tree can be created that stratifies members of a population into different groups based on dichotomous covariates (25). This method does not work well for continuous variables and may overfit data, but it provides a simple and intuitive method for classifying subjects (26). A nomogram is a reliable and pragmatic prediction tool as it quantifies the probability of a given outcome based on defined patient characteristics and allows for simultaneous consideration of multiple aspects of numerous variables (27). This leads to prognostication at an individual level. Nomograms have been proven to provide more precise prediction compared to the TNM classification (10), and have the advantage of being applicable for patient counseling, follow up scheduling, and research purposes. In this thesis a RPA model and a nomogram were developed in early stage NSCLC patients treated with SBRT which was subsequently externally validated in a surgical and SBRT cohort. Whereas the RPA demonstrated modest discrimination in SBRT patients, the performance in the surgical group was less favorable. This finding could be explained by the phenomena of overfitting data meaning that the statistical model is fitted with too many degrees of freedom in the modelling process resulting in being too optimistic about the performance of the model. This is a well described issue in prediction modeling as a tradeoff for practicality and may be caused by, among other factors, model complexity and smaller sample size of the training set (25). In addition, patients in the surgical group were younger and have less comorbidity. Conversely, the nomogram showed good discrimination and calibration in both surgery and SBRT group, suggesting that this tool may be useful to guide individual patient decision making in clinical practice.

The predictive accuracy of prognostic models can be improved by using a large database with high quality of individual patient data (28). For example, in **Chapter 2** the database was relative large in size, but in some categories of variables the patient number was insufficient to make a reasonable statement. It is also important to assess the performance

of a prediction model by testing model discrimination (i.e. statistical accuracy) and calibration (statistical precision) which shows how close predictions are to the actual outcome (29). In our study the model with clinical and tumor factors had a better predictive value than the model with tumor factors alone. This means that incorporating patient- and tumor factors into prediction models provides more valid and reliable predictions. Furthermore, the process of model validation is important before a prediction model can be used in clinical practice. External validation, using the patient data not used for the model development, is essential to illustrate the generalizability and the reliability of the model (30). Many prediction models are developed, but only a few are externally validated (31).

Differences between treatment groups

Several studies have investigated prognostic and predictive factors for lung cancer survival, however, little research has been done on the differences between the surgical and SBRT group (13, 32-34). In **Chapter 2** we used logistic regression with patient and tumor specific factors to illustrate the patient specific probability of being in either the surgery or SBRT group. This method shows clearly that patients in the surgery group differ significantly from the patients in the SBRT group, implying that these two groups of patients cannot always be properly compared.

In recent years there has been a steadily growing debate about offering SBRT to operable patients and whether surgery is still the optimal treatment for early stage NSCLC. Several observational studies in inoperable NSCLC patients illustrated respectable local control rates, less treatment related adverse events and less treatment related mortality (35-38). Consequently, it is an effective and well-tolerated treatment for inoperable early stage lung cancer patients with limited treatment options (39). Population-based analyses from several centers worldwide demonstrated improved overall survival for elderly patients with stage I NSCLC (36, 40, 41). Also, Palma et al demonstrated a decline of 12% in the number of untreated elderly patients with stage I NSCLC who were registered in Amsterdam Cancer Registry (36). In addition to these observational and registry studies several centers reported phase I and II studies of SBRT in early stage NSCLC (37, 42-46). Research group of Timmerman and colleagues was of the first phase I studies evaluating safety of SBRT in T1 or T1 tumors demonstrating escalation doses to levels no previously considered safe (46, 47). In this study, local control rate of 98% and overall survival of 56% at 3 years was reported.

Due to these good results there is a growing interest in offering SBRT in operable patients (48-50). However, it is important to realize that confounding and selection bias cannot be ruled out as these results were based on population based studies, retrospective studies and propensity matched analyses (51-53). Furthermore, there are some limitations in direct comparison of surgical treatment with SBRT in early stage lung cancer patients. First, the surgical group often covers a cohort of patients treated before 2000 (54), while SBRT was

widely used for the treatment of stage IA or IB inoperable NSCLC after 2005. The latter being the result of the publication of Timmerman and colleagues (46, 47). Comparing outcomes of patients enrolled at different cohort years may not adequately reflect improved surgical technology and better perioperative care in the past decades, per se. This may, for example, be biased by the large sum of other equally evolving surgical and medical techniques (e.g. video-assisted thoracic surgery (VATS)). Second, the majority of studies are comparing SBRT with pulmonary resection through thoracotomy while in more recent years minimal invasive techniques with less surgical related adverse events have emerged (55-61). In addition, patients treated with SBRT not often undergo pathological staging while the rate of hilar or mediastinal lymph node involvement range from 13% to 32%, even with a negative staging with FDG-PET scan (62-65). Finally, few studies report an overall survival beyond 5 years after SBRT because median follow up time is short (48, 66, 67). This may have an impact on evaluating survival rates beyond 3 years as no proper comparison can be done due to the limited numbers of patients who are still at risk after this point in time. In a recent propensity matched national data analysis of Paul and colleagues it is reported that cancer specific survival of NSCLC patients aged >65 years with tumor size <2cm did not differ significantly between the surgical and SBRT group (86% and 83%, respectively) at 3 years (68). Also, most deaths were not associated with cancer but with age related comorbidities. As patients who underwent in this study were older and had more comorbidities the authors reported that at the end of 3 year follow up overall survival was 53% and 73% for patients treatment with SBRT and video assisted thoracoscopic sublobar resection, respectively. The authors concluded that the overall survival was significantly higher when thoracoscopic resection was compared with SBRT.

A recently published report of combined results of two randomized trials (STARS and ROSEL) consisting of a cohort of 58 patients (31 in SBRT group and 27 in surgery group) concluded that SBRT was not inferior to surgery (62). However, these trials were halted prematurely due to poor accrual and the fact that it remained underpowered. In addition, these trials have other limitations which includes amongst others the fact that only 5 of 27 patients in the surgery group underwent lobectomy through VATS and a histologic cancer diagnosis was not required for enrollment in the ROSEL trial. Therefore, the results of these trials should be interpreted with caution as the histology before randomization was unknown in 14 patients (8 in SBRT group and 6 in the surgery group) and only a small proportion of surgical patients underwent surgery through VATS. Nonetheless, the results of SBRT in inoperable lung cancer patients have been promising and the role of SBRT in patients treated surgically continues to be studied in order to apply SBRT as primary treatment for patients with operable early stage NSCLC (e.g. NCT02468024, NCT02629458, NCT01753414, and VALOR study) (69).

Survival and propensity score matching

Although randomized controlled trials (RCT) are considered as the only way of determining whether a cause-effect relation exist between treatment and clinical outcome, and is

placed at the highest level of the pyramid of evidence based medicine (EBM), it is not always feasible to perform a RCT (70). Also, the external validity and generalizability of many RCTs have been questioned as patients eligible for inclusion are younger, fitter, and have less comorbidities than patients included in observational studies (71). Especially for lung cancer patients, who are older than 65 years at diagnosis, an RCT may not be representative or even feasible (72-75). Two randomized trials comparing SABR with surgery for early stage NSCLC were halted early because of slow recruitment (62, 76).

Given the limited feasibility and generalizability of an RCT in lung cancer patients, balancing patient characteristics for each treatment in a nonrandomized setting may offer an alternative. The propensity score, first described by Rosenbaum and Rubin, is a specific balancing score which reflects the probability of treatment assignment conditional on observed baseline characteristics (77-80). As described in publication of Blackstone (79) there are 3 types of comparison available once the propensity score is calculated for each patient. The first comparison type is including propensity score in multivariable analysis of outcome which adjusts for the influence of the comparison variable of interest. The second comparison type is stratification of the study population based on the propensity score. The third comparison type is propensity score matching. The latter could offer a way to achieve more balanced groups by matching treatment and control units based on a set of baseline characteristics. Matching according propensity score has been considered the most statistically efficient method and an effective method to reduce imbalance. Stratification is also an effective method to reduce imbalance, however, propensity score matching has been proven to be more effective in reducing treatment-selection bias (81). Adjustment method is often used because it illustrates whether all variables important for bias reduction have been incorporated into the model. However, it is not as effective in reducing bias.

In **Chapter 4** we performed a propensity score matching in order to obtain objective measure of survival probability and to compare clinical outcomes of patients treated either surgically or by SBRT. In contrast to previous publications (51, 82), we found that after 3 years there seems to be a trend toward better survival for patients treated surgically. Loco-regional control rates, distant metastases, and freedom form progression did not differ significantly. These results confirm the findings of Zhang et al. who performed a meta-analysis using propensity matched comparative studies and concluded that results from six published studies with 864 patients illustrate that surgery was associated with a better 3-year overall survival in early stage NSCLC patients (83). Also, the propensity score matched national data analysis by Paul et al illustrated that at the end of 3 year follow up overall survival was 53% and 73% for patients treatment with SBRT and video assisted thoracoscopic sublobar resection, respectively (68).

Despite the fact that propensity score analysis is a sophisticated statistical method for reducing bias in observational studies, limitations remain. It is possible that some baseline

differences between the treatment groups are not taken into account when calculating the propensity score (or when there are few variables for propensity modeling) which could result in extremely degraded propensity score (79). In our study, even with the accurate matching there were still some differences between patients in the two treatment groups. For example, patients with the WHO score >2 were not accurately matched. Also, the deliberate decision whether to treat a patient by means of surgery or SBRT is intertwined with certain specific patient characteristics which cannot be taken into account in propensity score modeling. Altogether, it is important to realize that propensity score matching has its strengths and limitations, and by creating two selected subgroups of patients the conclusion cannot be generalized with confidence to the entire population of surgical and SBRT patients.

Procedure-related complications and quality of life

Complications related to stereotactic radiotherapy and surgery

The incidence and severity of complications after SBRT is dependent on tumor localization, dose intensity and patient characteristic. Chest wall pain, rib fracture, radiation induced lung injury, toxicity to brachial plexus and esophagus are among the complications of SBRT (67, 84). Radiation induced lung injury can manifest in an early phase as an inflammatory process (known as radiation pneumonitis) or as a late-onset fibrotic process (known as radiation fibrosis). Radiation pneumonitis is one of the main toxicities after SBRT which limits the maximal radiation dose that can be delivered to lung cancer. In 30% of patients with thoracic irradiation radiation pneumonitis can develop from 1 to 3 months after SBRT. Radiation fibrosis can occur from 6 to 24 months after SBRT, and may result in pulmonary hypertension (85, 86). Most of the radiation pneumonitis is grade 1 or 2, and a high incidence of severe radiation pneumonitis has been described in patients with pre-existing pulmonary fibrosis (66, 87, 88). With regard to peripheral tumors, the rate of toxicity grade ≥3 is less than 5%, while for central tumors very high dose of SBRT is associated with significant toxicity and death (66, 89-91).

With the increasing use of minimally invasive techniques the severity of complications after lung cancer resection has reduced (59-61). Reported rates of surgical complications following pulmonary resection are in the range of 30% to 40% (92). Complications that occur from pulmonary resection can be anticipated by identifying the preoperative risk factors of patients (e.g. low FEV1/DLCO and severity of COPD). Major complications after pulmonary resection are atelectasis requiring bronchoscopy, adult respiratory distress syndrome, mechanical ventilation longer than 24h, pulmonary edema, pulmonary embolism, myocardial ischemia, cardiac failure, arrhythmia, stroke, and acute renal failure (93-95). Minor non-life-threatening complications such as air leak or pneumothorax are adverse events without requiring a specific treatment. Risk factors for major and minor

complications are age, preoperative pulmonary function, cardiovascular comorbidity, smoking and chronic pulmonary disease (9, 96). An extensive evaluation of the preoperative risk factors is necessary as it offers a tool to optimize the perioperative and postoperative care. For example, age is not a contra-indication for pulmonary resection but an extensive cardiovascular assessment is needed as majority of lung cancer patients are old with cardiovascular history (97). Furthermore, patient risk factors for complications and mortality should be used to identify the most effective treatment for an individual patient. For example, preoperative evaluation of FEV1 and DLCO is important for the determination of the extent of pulmonary resection and it is in several studies linked to morbidity and mortality (98-100).

This thesis describes that the type and severity of complications differ between the surgery and SBRT group (**Chapter 4**). These complications can vary from grade 1-2 toxicity (drain or anticoagulants in the surgery group and fatigue or sensitive skin in the SBRT group) to grade 3-5 toxicity (reoperation due to persistent air leak or chylothorax in the surgery group and radiation pneumonitis or hemoptysis in the SBRT group). These complications may have negative impact on the pulmonary rehabilitation and recovery from the treatment, therefore, it is useful to reduce these complications as much as possible. In this thesis we question whether complete dissection of ipsilateral mediastinal lymph nodes should be considered as the standard of care during lobectomy for lung cancer (**Chapter 5**). Lymph node assessment is important for accurate staging of NSCLC, however, the optimum extent of lymphadenectomy has been a subject of interest among the thoracic surgeons. Removal of one or more lymph nodes guided by preoperative or intra-operative findings through lymph node sampling is potentially associated with less postoperative complications compared to complete lymph node dissection. On the other hand, complete removal of the mediastinal tissue containing the lymph nodes by lymph node dissection leads to more accurate staging and better defining the extent of the disease leading to better informed decisions about whether or not to give adjuvant therapy in order to improve long term survival (101). In **Chapter 5** we point out that the evidence to date has been unclear as to when or for which patient complete lymph node dissection is indicated. Although our meta-analysis indicates that long-term survival is improved by mediastinal dissection, we address that in the 5 RCTs regarding this topic there were methodological flaws (e.g. no intention to treat analysis, significant number of patients were excluded after the randomization). Radical lymph node dissection is a major procedure that could potentially damage neurogenic, vascular or lymphatic structures in the mediastinum. The question is whether more complex surgery provides a benefit that outweighs the complications. Therefore, a large randomized trial involving current diagnostic, surgical and oncological practice is needed to support the evidence of potential survival benefit of complete lymph node dissection.

Quality of life

Quality of life (QoL) or health related quality of life is commonly defined as the subject's functioning and well-being in the physical, psychological, and social domains in relation to disease and treatment (102, 103). The goal of every lung cancer treatment is improved survival and QoL with the least possible toxicity. Of course, this is easier said than done. Firstly, more than half of lung cancer cases are diagnosed in patients aged >65 years (104-106) with a high prevalence of comorbidities making the treatment of these patients challenging (107, 108). Secondly, over the last few years little progress has been made in terms of survival with a median survival time of 1 year and 5 year survival rate of only 16% (109). Thirdly, even patients with an early stage lung cancer have significantly worse QoL than the general population (110, 111). Last of all, it is important to realize that QoL and survival are interrelated because it is well established that QoL is an important prognostic factor in lung cancer patients (112-115).

Until the introduction of SBRT patients with early stage lung cancer who were inoperable (due to older age or comorbidities) had limited treatment options. After the introduction of SBRT, several prospective studies reported consistently high rates of local tumor control and improved overall survival with SRBT (37, 42-44, 116-118) and it is now considered a standard of care for early stage inoperable lymph node negative NSCLC (39). However, only a few publications have evaluated the impact of SBRT on patients' QoL. Questionnaires evaluating QoL offer valuable information about the impact of cancer and therapy-related adverse events. It is also a valuable source of information as they illustrate the patient's needs and feelings which can differ from the physician's preference for choosing an extensive treatment in order to extend the survival of the patient. Of course, there are patients who want to choose a very aggressive treatment to extend their life to a maximum at the cost of often serious side effects of treatment. On the other hand, there are also patients who accept the incurable condition and are less likely to choose an extensive treatment and want a treatment to relief their symptoms and maximize the quality of the life they have left. There are several questionnaires available to evaluate QoL in lung cancer patients, each with their own evaluation of a range of factors reflecting physical, psychologic, emotional, and social well-being (119). Physical and role functioning are important for the prognosis because it has been shown in several studies that significantly lower level of physical and role functioning is associated with poorer survival. The same applies for overall QoL (112, 120, 121). In line with the literature, we did not observe decline of physical or role functioning after treatment with SBRT over a 5 year period (122-124) (**Chapter 6**). We also observed an improvement of emotional functioning 1 year after the start of treatment with SBRT (124). Despite the limited size of our cohort, we illustrate that during the 5 years after treatment with SBRT for stage I NSCLC the level of QoL was maintained, with a slow decline of the global health status.

QoL complements the clinical evaluation and is an important prognostic factor for survival (112). However, there is lack of consistent reporting of QoL in clinical cancer studies (125).

Furthermore, to our knowledge, there are no studies comparing the QoL in early stage lung cancer patients treated with either surgery or SBRT. It is reported that patients treated surgically have worse physical functioning 6 months after surgery and decreased physical functioning up to 2 years after surgery compared with pre-surgical status (126, 127). On the other hand, a major advantage of a surgical resection is the possibility of lymph node staging through lymph node dissection preoperatively and during the operation which provides the opportunity of offering adjuvant treatment leading to potentially improved long term survival. Furthermore, if malignancy is diagnosed with intraoperative frozen section then an anatomical resection with an adequate lymph node dissection can be performed. Quality of life of early stage lung cancer patients treated with SBRT is mainly reported in studies with small sample sizes. These studies report mixed outcomes. While some studies report significant clinical deterioration in fatigue and dyspnea after SBRT (123, 128). Other studies report no significant clinical deterioration of QoL after SBRT. Since many patients treated with SBRT have comorbidity these studies conclude that that preservation of baseline QoL can be regarded as the optimal result of SBRT treatment (129). On the other hand, patients who cannot be surgically treated due to the patients' performance status and comorbidities can be treated with SBRT resulting in improved survival as local control rates exceed 90% (meaning the absence of tumor progression within 1 cm of the primary tumor site (37)) (35). The use of SBRT has narrowed the gap in survival rates between patients treated surgically and patients with limited treatment options. In **Chapter 8** we illustrated the QoL of NSCLC patients before surgery and the start of the treatment with SBRT. In this chapter we observe no differences regarding the mental component score. However, we did observe differences for physical functioning and general health and this could be explained by the significant differences in baseline characteristics. This observation and the discussion above illustrate that the patient characteristics and therefore the quality of life differ between the treatment groups making a proper comparison between SBRT and surgery difficult. For this reason, we should question the value of a comparison between treatment groups as primary objective of studies. Ultimately, the focus of research should be on finding a method to enable patient-tailored treatment on the basis of cancer and patient characteristics and patient preferences. Eventually, it is up to the patient to make a tradeoff between the QoL and the quantity of life as each treatment is associated with complications and side-effects, but also has its own advantages and disadvantages.

Toward informed and shared decision making

Given the value sensitive nature of the decision between SBRT and surgery it is clear that the treatment of early stage lung cancer is complex. An example of the latter is the study of Louie et al who used a Markov model to simulate a comparison between SBRT and surgery (130). In this study a small survival advantage was illustrated at 5 years in favor of surgery, with benefit ranging from 2.2% to 3.0%. These numbers illustrate that the clinical relevance of a small survival advantage is debatable. In this condition it is up to the patient to decide whether a possible benefit after surgical procedure outweighs the

risks and discomfort that are associated with them (**Chapter 7**). Naturally, there is also an option of not getting a cancer treatment and avoiding any treatment side effects. A systematic review and meta-analysis reporting on 7 cohort studies and 15 RCTs illustrated a pooled mean survival of 7.15 months in untreated lung cancer patients, with a pooled mean survival of 12 months in cohort studies and 5 months in RCTS (131). These numbers are valuable for the comparison of treatment options, in particular when treatment options are discussed with the patient.

The majority of patients, regardless of the disease, prefers to be actively involved in treatment decision making (132). The remaining part of the patients who initially do not want to be involved, do want to be engaged in treatment decision making once they become aware that there is a choice (133). These findings are also observed in Dutch lung cancer patients (**Chapter 8**). Most Dutch patients found it important to be involved in decision making and they felt sufficiently involved by their treating physician. Yet, a substantial proportion of patients (39% in the surgery group and 29% in the SBRT group) felt uninformed and experienced decisional conflict (40% in the surgery group and 48% in the SBRT group), reflecting the difficulty that patients can experience when comparing the advantages and the disadvantages of different treatment options (134). Up to one-fifth of patients were not aware of the advantages and the disadvantages of the treatment options. In order to reach optimal decision making various obstacles need to be resolved at the level of the patient, the physician and the health care system.

With regard to the obstacles at the level of the patient it is important to communicate complex health information in an understandable way by using plain language, in order to achieve informed decision. Not only the tradeoffs between potential benefits and side effects of treatment options need to be discussed, but certainly also the consequences of not getting a cancer treatment. It has become clear that patient's level of health literacy (the ability to obtain, read, understand and use health care information to make an appropriate decision) and numeracy (the ability to understand the numbers) can affect patient communication and expressing preferences. Inadequate literacy and numeracy is an important barrier to process the information and to make an informed decision (135-137). If the patient understands the information regarding the disease, treatment options and their associated risks and benefits they can actively participate in decision making (138, 139). Patient-physician communication is an integral part of clinical practice.

Potential barriers at the physician level should also be recognized. Physicians are the ones responsible for recognizing the patient's symptoms and put these symptoms in a scientific perspective, informing the patient adequately and according to their educational background (140), they have also an important role in actively engaging patients in treatment decision making. Regarding early stage lung cancer there is no single 'best choice' in selecting a treatment since the factors regarding advantages and disadvantages and life expectancy can be valued differently by individual patient (140, 141). Therefore, the

next step toward informed and shared decision making (SDM) is to reach a decision by consensus. In the process of SDM the physician and the patient share the best available evidence when making a health care decision. SDM has been shown to improve patients' understanding of the disease and treatment options, increase proportion of patients with realistic expectations of advantages and disadvantages of treatment options and stimulate patients' involvement in treatment decision making (142). Also incorporating preferences of the patient into decision making process could also lead to improved adherence to treatment and higher satisfaction with health outcomes (143-145) . Although SDM has gained increased awareness among the healthcare community, there are several barriers to implementation into routine clinical practice (**Chapter 9**) (142, 146-149). Firstly, it is difficult to determine whether the patient have the ability to make a weighted decision when they find themselves at a crossroad of medical options. Secondly, not every physician is familiar with SDM or adequately trained to apply SDM. Finally, it may not feasible for the physician to provide information in an understandable way when there is not enough consultation time. The most commonly used model is the one by Elwyn et al (150) who proposed a three step model to support the process of SDM based on choice, option and decision talk with the aim of effectively involving patient in treatment decision making. These three steps are as follows: 1) introducing choice through offering options and justifications for those options, 2) describing options by using patient decision support tools and 3) helping patients explore preferences and make decisions. By using this model educational tools could be developed for medical students and residents in order to gain the ability to use SDM in clinical practice and allow them to improve risk communication with the patient. Engaging patient in treatment decision making is regarded as an essential part of patient-centered care, therefore, it deserves to be integrated in medical curriculum (151).

Obstacles at the level of health care system should also be resolved in order to reach optimal decision making. The barrier of patient-physician communication and time constrains could potentially be resolved with the use of decision aids (step two of Elwyn model (150)). The existence of decision support tools facilitate SDM as it supplement the conversation with the patient and give the patient the ability to find reliable information about the disease after the consultation (152). It is shown in literature the effectiveness of decision support tools for increasing knowledge and risk perception, improving patient-physician communication, reducing decisional conflict and feeling uninformed and therefore leading to less anxiety and depression (142, 153). Furthermore, there are also models concentrating on other individuals who could potentially increase the adoption of SDM. For example, Légaré et al have developed a model which includes amongst others the family of the patient, nurses and health coaches (154). Specialized nurses could act as coaches by explaining medical information and supporting the patient which could improve patient decision making by resolving barriers such as communicating complex health information and time constrains (155). Obviously, SDM has many benefits for the patients but what is the role of SDM when it comes to the cost-effectiveness of delivering health care? In the literature, SDM has been seen as a method that could potentially

prevent overtreatment and reduce health care costs because it is believed that patients who are better informed are less likely to choose an extensive treatment (144). However, little research is on done on the role of SDM and decision support tools on health care costs. Simply adding decision tools could potentially lead to higher health care cost, therefore, it is desirable that barriers are resolved at the level of health care system with the implementation of decision support tools into this system (e.g. more involvement and shift to nurse practitioners) (156). The use of decision support tools and using specialized nurses does not guarantee that process of SDM will be optimized. For the latter is a common understanding of the value of SDM and change at different levels (e.g. at the level of the physician and health care system) is needed (157).

Amalgation of evidence based medicine and personalized medicine

This thesis consists of a set of publications with various study designs. **Chapter 2, 3 and 6** are retrospective studies addressing overall survival and QoL after SBRT or surgical treatment of early stage lung cancer patients. This study design is ranked at level 3 of the evidence based medicine pyramid (**Chapter 10**) with disadvantages of incomplete or inconsistently measured data as there is limited control over data collection. However, this study design is less costly and do not require a long follow up time like a prospective study design. On the other hand, prospective cohort studies have several advantages such as measuring the change in exposure and outcome over time, can be used to study more than one outcome and gives some indication of causality. In **Chapter 8 and 9** we used a prospective study design to investigate the role and experience of early stage lung cancer patients in treatment decision making and the opinion of lung cancer physicians concerning SDM. Furthermore, prospective and retrospective study designs are less suitable for the comparison of clinical outcomes in two treatment groups. We performed propensity score matching in **Chapter 4** in order to create two similar groups. Also, this study design has its disadvantages. This method only work if patients are suitable for both treatment options (SBRT and surgery) because we cannot separate the effect of the treatment from the reasons for being selected for the treatment. As systematic reviews and meta-analysis are at the top of the EBM pyramid, we used this study design in **Chapter 5** to question whether complete dissection of ipsilateral mediastinal lymph nodes should be considered as the standard of care during lobectomy for lung cancer. The main disadvantage of the systematic reviews and meta-analysis is that the quality of this study design is dependent on a priori clearly documented search terms and strategies. The discussion above illustrates that each study design has its own advantages and disadvantages and highlight that certain type of study design is more appropriate for a particular research question than the other. While, the ranking of EBM implies that some forms of evidence are inherently superior to others. Sometimes is an observation all that is needed to address a question (**Chapter 7**). Nevertheless, currently the level of EBM is maintained when clinical guidelines are developed.

The goal of every guideline is to improve the quality of care and to offer a tool for the physicians to achieve effective and efficient health care. However, not every guideline is based on a combination of scientific evidence, knowledge gained from clinical practice and patient values and preferences (**Chapter 10**). Although guidelines are based on systematic reviews of randomized trials because they are placed at the top of the evidence pyramid, they are not necessarily tailored to an individual cancer patient as they are based on combined experience of large numbers of research participants. In addition, the eligibility criteria of most randomized trials are strict and often exclude older patients with comorbidity (158). Therefore, the results of these trials cannot be implemented in a large proportion of cancer patients. Moreover, it is not entirely clear what the effect of some clinical guidelines are on patient health outcomes (159).

Ideally, good clinical practice is an amalgamation of EBM and personalized medicine. Of course it is important, for example, to include prediction models in clinical guidelines in order to estimate the probability of developing a particular outcome in the future, but certainly patient values and preferences regarding the treatment and the effect of treatment on QoL must be taken into account. Incorporation patients' values and preferences when there is uncertainty about the best course of action will allow the physician to discuss the advantages and disadvantages associated with or without the treatment and will encourage patients to engage in treatment decision making. Besides, this method will give the patient the opportunity to think about the tradeoffs between risks and benefits and the changes in their QoL (160). Putting patients in the center of healthcare leads to more personalized care. Nevertheless, the fact that personalized medicine is important for lung cancer treatment does not mean that it is a competitor of EBM, it is complementary to the best available evidence.

Conclusion and future perspectives

This thesis provides further insight into determinants of outcome in patients with early stage NSCLC, and insight into current decision making from the perspective of both lung cancer patients and lung cancer physicians. The different studies illustrate that incorporation of patient- and tumor factors into TNM classification and prediction models provide more valid and reliable predictions of survival. This thesis also illustrates that patients with early stage NSCLC in the surgery group differ significantly from the patients in the SBRT group with regard to patient characteristics, overall survival, the procedure related complications and the QoL. These results are particularly important when treatment options are discussed with the patient and underline the importance of engaging patients in treatment decision making. In order to achieve frequent and effective application of SDM in clinical practice several barriers need to be resolved at the level of the patient, the physician and the health care system. Decision support tools and a more active role of nurse practitioners could optimize SDM and the quality of treatment decision making. Ultimately, the focus of research should be on finding a method to enable patient-tailored treatment on the basis of cancer and patient characteristic, including informed patient preferences.

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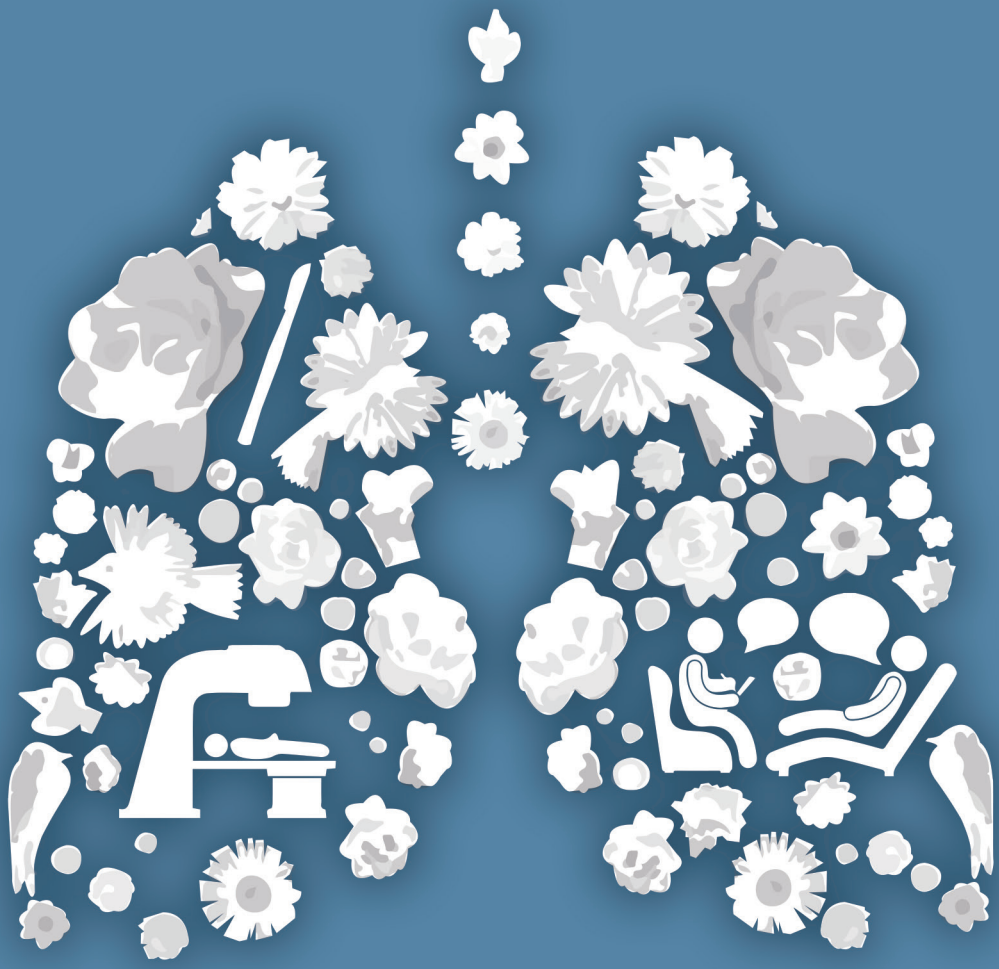

CHAPTER 12

Summary

Nederlandse Samenvatting

Dankwoord/Acknowledgements

PhD portfolio

List of publications

About the author

SUMMARY

Chapter 1 is a general introduction to this thesis. This chapter forms the background against which the aims and research questions are explained.

Chapter 2 describes patient characteristics and survival of non-small cell lung cancer (NSCLC) patients with stage I-II treated surgically or with stereotactic body radiotherapy (SBRT). The results of this study illustrate that the patients in the surgery group differ significantly from het patients in the SBRT group and therefore cannot always properly be compared. Furthermore, there are clinical baseline characteristics (patient and tumor specific factors) that can help to determine the survival of patients with stage I or II NSCLC. The consideration of these characteristics may improve prognostication of NSCLC patients and assist in selecting an appropriate treatment strategy.

Chapter 3 presents a prognostic model for 5 year overall survival, consisting of recursive partitioning analysis and a nomogram, for patients with early stage NSCLC treated with SBRT. The results illustrate that age, Charlson Comorbidity Index, smoking history, and WHO performance score are strong predictors of survival. This observation indicates the importance of elucidating the impact of comorbidity on treatment and survival of lung cancer. A clinical nomogram and recursive partitioning analysis may be clinically useful for stratification of patients into different groups and for the prediction of 5 year overall survival. This is another step toward assessing the risk of mortality for an individual lung cancer patient and may be valuable in assisting individual patient decision making.

Chapter 4 presents a propensity score matched analysis of two similar groups comparing the clinical outcomes of patients stage I NSCLC who were treated surgically (lobectomy either by video-assisted thoracoscopic surgery or thoracotomy) or with SBRT. This study shows no significant differences in overall survival in patients treated either surgically (84% at 3 years and 80% at 5 years) or with SBRT (82% at 3 years and 53% at 5 years). Overall survival was similar up to 3 years suggesting comparable effectiveness of treatment options with regard to patient survival. After 3 years there seems to be a trend toward better survival for surgical patients. Loco-regional control rates, distant metastases and freedom from progression did not differ significantly between the treatment groups. The observation that overall survival diverged after 3 years requires further research (in the form of randomized controlled trials with large sample size) to elucidate the determinants of prognosis in relation to treatment options for patients with stage I NSCLC.

Chapter 5 describes the results of a systematic review and meta-analysis of randomized controlled trials (spanning 1989 to 2007) assessing the impact of systematic lymphadenectomy versus lymph node sampling of ipsilateral mediastinal lymph nodes during lobectomy for NSCLC. In this meta-analysis of 1980 patients undergoing either systematic lymphadenectomy or lymph node sampling the hazard ratio for overall survival

was 0.78% (95% CI 0.69-0.89) favoring systematic lymphadenectomy rather than lymph node sampling and this equates with an absolute reduction in risk of death at 5 years of 7.6%. Despite the excess morbidity with systematic lymphadenectomy (e.g. bleeding, chylothorax and recurrent nerve injury) the early mortality was lower (odds ratio for death 0.59) compared to lymph node sampling. In this chapter we illustrate that there are several methodological uncertainties (e.g. no intention to treat analysis, significant number of patients were excluded after the randomization) for all the studies. Therefore, a large randomized trial involving current diagnostic, surgical and oncological practice is needed to support the evidence of potential survival benefit of complete lymph node dissection.

Chapter 6 describes the outcome of QoL 5 years after SBRT for patients with stage I NSCLC. In this chapter we did not observe decline of physical or role functioning after treatment with SBRT over a 5 year period. We observed an improvement of emotional functioning 1 year after the start of treatment with SBRT. Furthermore, respiratory symptoms such as dyspnea and coughing showed a stable trend during the first two years before showing a gradual increase in the years thereafter. Despite the limited size of our cohort, we illustrated that during the 5 years after treatment with SBRT for stage I NSCLC the level of QoL was maintained, with a slow decline of the global health status.

Chapter 7 is a letter to the Editor underlining the importance of shared decision making and of involving lung cancer patients in therapy selection to meet their preferences and expectations about treatment options and prognosis. Given the value sensitive nature of the decision between surgery and SBRT it is important to discuss al the pros and cons of both treatment modalities (e.g. early and late adverse events after treatment and short-term and long-term survival outcomes) with the patient. By doing so you are enabling the patient to consider the evidence along with their values and preferences and therefore, to make informed treatment decisions.

Chapter 8 investigates the role and experience of early stage NSCLC patients in the decision making process concerning treatment selection in the current clinical practice. Most Dutch patients found it important to be involved in decision making and they felt sufficiently involved by their treating physician. Yet, a substantial proportion of patients (39% in the surgery group and 29% in the SBRT group) felt uninformed and experienced decisional conflict (40% in the surgery group and 48% in the SBRT group), reflecting the difficulty that patients can experience when comparing the advantages and the disadvantages of different treatment options. Better patient information and involvement in treatment decision making is needed to improve patient knowledge and hopefully reduce decisional conflict.

Chapter 9 investigates the opinion of lung cancer clinicians concerning shared decision making (SDM) in early stage NSCLC patients. This chapter illustrates that in current clinical decision making in lung cancer treatment there is consensus among a majority

of Dutch lung cancer clinicians (cardiothoracic surgeons, lung surgeons, pulmonologists and radiation oncologists) that it is important to involve lung cancer patients in treatment decision making but that time constrains and inability of some patients to make a weighted decision are important barriers. Furthermore, we observed wide variation in clinician lung cancer treatment preferences suggesting that for most patients both treatment options are suitable, and it underlines the value sensitive nature of the treatment choices in early stage NSCLC.

Chapter 10 concerns the amalgamation of 'Personalized Medicine' with 'Evidence Based Medicine' in clinical practice. In this chapter we illustrate that more complex methods are not always better or generalizable to all patients in clinical practice. The hierarchical approach of pyramid of evidence put the highest value on the randomized trials and least value on surgeon opinion, however, we illustrate that in clinical practice a combination of the integration of the patients' values and expectations, the doctors' skills and expertise, and best available evidence is needed. Furthermore, this chapter underlines the important of implementing all available evidence in the process of clinical practice guidelines development.

Chapter 11, the general discussion, the results that were presented in this thesis are discussed and the research questions are answered.

SAMENVATTING

Hoofstuk 1 is de inleiding van dit proefschrift. In dit hoofdstuk wordt de achtergrond van het onderzoek beschreven en worden het doel en de onderzoeksvragen uiteengezet.

Hoofdstuk 2 beschrijft welke patiënt- en tumor karakteristieken van belang zijn voor de overleving van de patiënten met niet-kleincellig longcarcinoom (NKCLC) stadium I-II. Stadium I en II NKCLC worden lokale of vroege kankers genoemd. Bij deze stadia is de verwijdering van de tumor door een chirurgische ingreep de behandeling bij voorkeur. Stereotactische radiotherapie is een alternatief, wanneer een chirurgische ingreep niet haalbaar is of wanneer de patiënt dit weigert. In dit hoofdstuk illustreren wij dat de patiënten in de chirurgische groep significant verschillen van de patiënten in de stereotactische radiotherapiegroep. Een directe vergelijking is dan ook om verschillende redenen niet haalbaar. Daarnaast is de uitkomst van onze studie dat de verschillende klinische patiënt- en tumor karakteristieken van belang zijn om de overleving van de patiënten met NKCLC te voorspellen. Binnen de klinische praktijk moet dan ook rekening gehouden worden met deze karakteristieken om de ziektevrije interval te verbeteren en de kans op overleving te verhogen. Daarnaast, kan dit behulpzaam zijn bij het kiezen van een passende behandeling die toegespitst is op de individuele patiënt.

Hoofdstuk 3 presenteert een prognostische model voor 5-jaars overleving in stereotactisch bestraalde patiënten met vroeg stadium NKCLC, bestaande uit een 'recursive partitioning' analyse en een nomogram. Leeftijd, Charlson Comorbidity Index, rookgedrag en WHO score waren onafhankelijk geassocieerd met de overleving. Deze observatie benadrukt het belang van het ophelderen van de effecten van comorbiditeit op de behandeling en de overleving van deze groep patiënten. Een klinisch nomogram en 'recursive partitioning' analyse kan een bijdrage leveren aan een betere inschatting van de 5-jaars overleving, een betere keuze van de behandeling.

Hoofdstuk 4 betreft de resultaten van een studie waarin de overleving van de patiënten met NKCLC stadium I die een chirurgische behandeling (open procedure of kijkoperatie) hebben ondergaan vergeleken is met de overleving van de NKCLC patiënten die met stereotactische radiotherapie bestraald zijn. Deze studie is uitgevoerd door middel van de propensity score matching, waarbij gestreefd wordt naar een gelijke verdeling van confounders tussen de twee groepen. De resultaten van deze studie tonen aan dat er geen significante verschillen zijn tussen de twee behandelgroepen wat de betreft de lokale tumorcontrole, afstandsmetastase en ziektevrije interval. Daarnaast laat deze studie geen significante verschillen zien tussen de patiënten die chirurgisch behandeld zijn (84% na 3 jaar en 80% na 5 jaar) en de patiënten die stereotactisch bestraald zijn (82% na 3 jaar en 53% na 5 jaar). Hoewel de overleving op 3 jaar vergelijkbaar is tussen de twee behandelgroepen, wordt er na 3 jaar een trend tot betere overleving waargenomen in de groep van de chirurgisch behandelde patiënten. Deze observatie moet verder

onderzocht worden in gerandomiseerde studies die duidelijkheid moeten verschaffen over welke factoren voorspellende betekenis hebben voor de prognose in relatie tot de behandelopties voor NKCLC patiënten met stadium I.

Hoofdstuk 5 beschrijft de resultaten van een literatuurstudie en meta-analyse van gerandomiseerde studies met betrekking tot impact van lymfekliersampling (verwijdering van lymfeklieren op geleide van abnormale bevindingen) en complete mediastinale lymfeklierdissectie (routinematig verwijderen van al het ipsilaterale mediastinale weefsel dat lymfeklieren bevat) in NKCLC patiënten die een lobectomie (chirurgisch verwijderen van één longkwab) hebben ondergaan. In deze meta-analyse van vergelijkende studies tussen deze twee technieken werd er onder 1980 patiënten een overlevingsvoordeel (hazard ratio van 0.78%) gevonden van complete mediastinale lymfeklierdissecties. Na 5-jaar betrof het hier een absolute risicoreductie op overlijden van 7.6%. Ondanks de complicaties van complete mediastinale lymfeklierdissectie (o.a. bloeding, chylothorax, zenuwletsel) was de vroege mortaliteit laag (odds ratio van 0.59). In dit hoofdstuk illustreren wij de methodologische tekortkomingen (o.a. geen intention to treat analyse en exclusie van patiënten na de randomisatie) van de geïncludeerde studies en benadrukken wij het belang van het opzetten van grote gerandomiseerde studies. Het is hierbij essentieel dat de huidige richtlijnen omtrent diagnostiek, verbeterde chirurgische technieken en de oncologische zorg in acht worden genomen om zodoende het bewijs van het mogelijke overlevingsvoordeel van complete mediastinale lymfeklierdissectie te ondersteunen.

Hoofdstuk 6 beschrijft de invloed van stereotactische radiotherapie op de kwaliteit van leven van patiënten met NKCLC stadium I. In deze studie is over een periode van 5 jaar geen rolbeperking of achteruitgang van fysiek vermogen waargenomen. Een jaar na de stereotactische bestraling was het emotionele functioneren van de patiënten verbeterd. Daarnaast waren de respiratoire symptomen zoals benauwdheid en hoesten niet verslechterd in de eerste twee jaren na de behandeling, echter in de daarop volgende jaren namen deze klachten toe. Ondanks de beperkte grootte van deze studie illustreren wij dat over een periode van 5 jaar na stereotactische radiotherapie de kwaliteit van leven werd behouden met een geleidelijke afname van algemene gezondheidsbeleving.

Hoofstuk 7 is een brief naar de editor waarin het belang van het betrekken van de NKCLC patiënten bij het vaststellen van een behandelstrategie benadrukt wordt. Omdat de therapiekeuze voor vroeg stadium NKCLC een patient preferentie-gevoelige beslissing is, is het van belang om de afweging van voor- en nadelen van een chirurgische behandeling of stereotactische bestraling te bespreken met de patiënt. Betrekken van de patiënten bij een keuzeproces zorgt er voor dat de zorg aansluit bij de preferenties van de patiënt en stelt de patiënt in staat om een weloverwogen keuze te maken.

Hoofdstuk 8 beschrijft de rol en ervaringen van patiënten met vroeg stadium NKCLC in het proces van gezamenlijke besluitvorming in de huidige klinische praktijk. De meerderheid

van de Nederlandse NKCLC patiënten vindt het belangrijk om betrokken te zijn in het proces van gezamenlijke besluitvorming en vermeldt tevens dat ze voldoende betrokken worden door hun behandelend arts. Echter, een aanzienlijk deel van de patiënten (39% in de chirurgische groep en 29% in radiotherapiegroep) voelde zich ongeïnformeerd en ervaarde 'decisional conflict', een staat van onzekerheid over de verschillende keuzemogelijkheden, (40% in de chirurgische groep en 48% in radiotherapiegroep). Beter informeren van de patiënten en meer betrokkenheid in het proces van gezamenlijke besluitvorming is nodig om begrip omtrent hun eigen ziekte en behandeling te verbeteren en zal hopelijk leiden tot afname van 'decisional conflict'.

Hoofdstuk 9 rapporteert het perspectief van cardio-thoracale chirurgen, longchirurgen, longartsen en radiotherapeuten omtrent gezamenlijke besluitvorming bij patiënten met vroeg stadium NKCLC. Deze studie illustreert dat in de huidige klinische praktijk de meerderheid van de Nederlandse longkanker clinici het proces van gezamenlijke besluitvorming van groot belang vindt bij de therapiekeuze van vroege stadium NKCLC. Echter, ze erkennen dat verschillende barrières (o.a. tijdsmanagment en de mate waarin de patiënt in staat om een weloverwogen besluit te nemen) de effectieve toepassing van gezamenlijke besluitvorming belemmeren. Tot slot toont deze studie een grote variatie in de voorkeur voor een bepaalde behandeling onder de Nederlandse longkanker clinici. Deze observatie benadrukt dat therapiekeuze voor vroege stadium NKCLC preferentie gevoelig is.

Hoofdstuk 10 betreft de samenvoeging van 'Personalized Medicine' met 'Evidence Based Medicine' in de klinische praktijk. Dit hoofdstuk illustreert dat een complexe studieopzet niet per definitie beter is om een onderzoeksvraag te beantwoorden. Dan is er nog de vraag in hoeverre de studieresultaten generaliseerbaar zijn naar andere patiënten dan diegenen bij wie het onderzoek oorspronkelijk werd uitgevoerd. 'Evidence Based Medicine' heeft hiërarchie van bewijsvormen waarbij de gerandomiseerde studies en meta-analyses hoger geplaatst zijn in de pyramide van 'Evidence Based Medicine' en de mening van de experts zoals chirurgen het minst gewaardeerd wordt. Echter, met verschillende voorbeelden illustreren wij in deze studie dat in de praktijk een combinatie van integratie van de patiënt preferenties en verwachting, het oordeel van de professionals en de best beschikbare kennis de voorkeur heeft. Tot slot wordt er benadrukt dat het belangrijk is om alle vormen van beschikbaar wetenschappelijk bewijs te implementeren bij richtlijnontwikkeling.

Hoofdstuk 11 geeft een algemene discussie. De bevindingen die zijn beschreven in dit proefschrift worden bediscussieerd en de onderzoeksvragen worden beantwoord.

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PHD PORTFOLIO

Name PhD student:	Sahar Mokhles
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Research School:	Cardiovascular Research School (COEUR)
PhD period:	December 2013-December 2016
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Promotors:	Prof. dr. A.J.J.C. Bogers Prof. dr. J.J.M. Takkenberg
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2011-2014	Master of Science (MSc) in Public Health, NIHES, Rotterdam, The Netherlands
2009-2012	Bachelor of Science (BSc) in Medicine, Erasmus MC, Rotterdam, The Netherlands
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2010-2011	Erasmus MC Honours Class, Erasmus MC, Rotterdam, The Netherlands
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PhD Training (50 ECTS)

In-depth courses (13 ECTS)

2015	Research Integrity, Erasmus MC, Rotterdam, The Netherlands
2015	Course on R software, Molecular Medicine, Erasmus MC, Rotterdam, The Netherlands
2014	Cancer Epidemiology, The Netherlands Cancer Institute (NKI), Amsterdam, The Netherlands
2014	Introduction to Medical Decision Analysis (Decision Analytic Modeling), Society for Medical Decision Making, Antwerp, Belgium
2014	Revise and Improve your presentation for the meeting, Society for Medical Decision Making, Antwerp, Belgium
2014	Autopsy Practical Course, EUR, Rotterdam, The Netherlands
2014	Arrhythmia Research Methodology, COEUR, Rotterdam, The Netherlands
2014	Vascular Clinical Epidemiology, COEUR, Rotterdam, The Netherlands
2014	Presenting and Pitching your research, EUR, Rotterdam, The Netherlands
2013	Fundamentals of Epidemiology, Harvard School of Public Health, Boston, USA

2013	Global Health and Infectious Disease, Harvard School of Public Health, Boston, USA
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Teaching (3 ECTS)

2015	Supervision 3rd year students from Delft University of Technology, Erasmus MC, Rotterdam, The Netherlands
2014	Supervising 2nd year medical students in writing a systematic review, Erasmus MC, Rotterdam, The Netherlands
2014	Supervision 3rd year students from Delft University of Technology, Erasmus MC, Rotterdam, The Netherlands
2014	Lecture 'Diagnostic and Prognostic Tests' for Medical students, Erasmus MC, Rotterdam, The Netherlands

Oral presentations (10 ECTS)

2016	European Conference on General Thoracic Surgery, Naples, Italy
2015	European Lung Cancer Conference, Geneva, Switzerland
2014	ROTS symposium, Rotterdam, The Netherlands
2014	Society for Medical Decision Making, Antwerp, Belgium
2014	American Thoracic Society, San Diego, USA

(Moderated) Poster presentations (3 ECTS)

2015	Society for Medical Decision Making, St. Louis, USA
2015	Innovation for Health, Amsterdam, The Netherlands

Meetings (21 ECTS)

2015	Meeting of the Dutch Association for Thoracic Surgery
2014-2015	Journal Club meetings department of Cardiothoracic Surgery, Erasmus MC, Rotterdam, The Netherlands
2013-2014	Scientific meetings Master of Science in Public Health, Erasmus MC, Rotterdam, The Netherlands
2013-2016	COEUR research seminar and lectures
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Awards and grants

2015	National Research Foundation travel grant to attend the Global Young Scientists Summit@one-north 2016 (GYSS), Singapore, Singapore

2015	Top 3 Upcoming Scientists, Innovation for Health, Amsterdam, The Netherlands
2015	European Lung Cancer Conference travel grant for young scientists, Geneva, Switzerland
2014	Nijbakker-Morra Prize for promising students undertaking research in cancer, The Netherlands

LIST OF PUBLICATIONS

1. **Mokhles S**, Nuyttens JJ, Maat APWM, Birim O, Bogers AJJC, Takkenberg JJM. Survival and treatment of non-Small cell lung cancer stage I-II: patient and tumor specific factors affect the prognosis. *Annals of Surgical Oncology* 2015 Jan Jan;22(1):316-23.
2. **Mokhles S**, Verstegen N, Maat APWM, Birim O, Mokhles MM, Senan S, Lagerwaard FJ, Takkenberg JJM. Comparison of clinical outcome of stage I non-small cell lung cancer treated with stereotactic radiotherapy or VATS-lobectomy: a multi-center study with propensity score analysis. *Lung Cancer* 2015 Mar;87(3):283-9.
3. Ubels RJ, **Mokhles S**, Andrinopoulou EF, Braat C, van der Voort van Zyp N, Aluwini S, Aerts J, Nuyttens JJ. Quality of life during 5 years after stereotactic radiotherapy in stage I non-small cell lung cancer. *Radiat Oncol.* 2015 Apr 22; 10:98.
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5. **Mokhles S**, Takkenberg JJM and Bogers AJJC. Letter to the Editor: surgery versus radiation therapy in stage I lung cancer. Ann Thorac Surg. 2015 Nov;100(5):1968.
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7. **Mokhles S**, Macbeth F, Farewell V, Fiorentino F, Williams N, Younes RN, Takkenberg JJM, Treasure T. Meta-analysis of colorectal cancer follow-up after potentially curative resection. Br J Surg. 2016 Sep;103(10):1259-68.
8. **Mokhles S**, Takkenberg JJM, Treasure T. Evidence-based and personalized medicine. It's [AND] not [OR]. Ann Thorac Surg. 2017 Jan;103(1):351-360.
9. **Mokhles S**, Macbeth F, Treasure T, Younes R, Rintoul R, Fiorentino F, Bogers AJJC, Takkenberg JJM. Systematic lymphadenectomy versus sampling of ipsilateral mediastinal lymph-nodes during lobectomy for non-small cell lung cancer: a systematic review of randomized trials and a meta-analysis. (European Journal of Cardio-Thoracic Surgery 2017 Jan 30 0 (2017) 1-8.
10. **Mokhles S**, Maat APWM, Aerts JGJV, Nuyttens JJ, Bogers AJJC, Takkenberg JJM. Lung cancer clinician opinion on shared decision making in early stage non-small cell lung cancer. Interactive Cardiovascular and Thoracic Surgery, in Press.
11. **Mokhles S**, Nuyttens JJ, Mol de M, Aerts JGJV, Maat APWM, Birim O, Bogers AJJC, Takkenberg JJM. Treatment selection of early stage non-small cell lung cancer: the role of the patient in clinical decision making. Patient Education and Counseling, submitted.

ABOUT THE AUTHOR

Sahar Mokhles was born on January 13th, 1989 in Kabul, Afghanistan. At the age of 10 she moved together with her parents, brother and sister to The Netherlands as political refugees. After graduating from secondary school (Nature & Health, Openbaar Zeister Lyceum, Zeist), she started her academic career in 2007 at Erasmus School of Law. In 2009 she started with the Medical School at Erasmus University Medical Center. In 2012 she obtained her bachelor degree in Dutch Law and in the same year her bachelor degree in Medicine. During her bachelor's degrees she had the opportunity to participate in the Erasmus Honours Programme at Erasmus University and Erasmus Honours Class at Erasmus University Medical Center, an interdisciplinary academic training program to tackle crucial contemporary scientific and societal questions from various scientific perspectives. Furthermore, Sahar was during her education active in various education committees.

In 2011, Sahar was among the top 10% of medical students and was selected to participate in a special program organized by the Netherlands' Institute of Health Sciences (NIHES). This program enabled her to combine the Master of Science in Medicine with the Master of Science in Public Health. During this program she received her training in epidemiology, part of which was spent at the Harvard School of Public Health in Boston Massachusetts and University of Cambridge in United Kingdom. While pursuing this program, she became more and more interested in doing research in cancer patients and started her PhD in December 2013 at the department of Cardiothoracic Surgery, Erasmus University Medical Center, under supervision of prof. dr. A.J.J.C. Bogers and prof. dr. J.J.M. Takkenberg, which resulted in this thesis.

In 2014, Sahar was awarded with a prize of the Nijbakker-Morra Foundation and the Dutch Heart Foundation for promising students who do research in the area of fundamental or applied cancer research. This allowed her to spend part of her PhD research in the United Kingdom. Between April 2015 and September 2015 she worked as a research fellow at the department of Surgical & Interventional Trials Unit at University College London in United Kingdom. Under direct supervision of prof. dr. T. Treasure she acquired knowledge and experience in the field of cancer research.

In April 2016 she started with the clinical rotations at various hospitals in the Rotterdam area, which she expects to complete in spring 2018.

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