The evolving role of stereotactic ablative radiotherapy in operable early stage non-small cell lung cancer

Verstegen, N.E.

2015

1

Introduction

Currently, cancer is the second leading cause of death in Europe[1]. Globally, lung cancer is by far the most common cause of cancer-related deaths, and is by itself the 5th leading cause of death worldwide[2,3]. In the Netherlands, incidence rates in women are increasing, and although incidences in men are declining, the total number of new patients per year is expected to continue to increase due to the aging population[4].

Lung cancer can be divided in two main histological types, small cell lung cancer and non-small cell lung cancer (NSCLC). About 80% of lung cancers are classified as NSCLC. Overall, NSCLC has a poor prognosis, with 5 year survival rates of about 17%[2].

NSCLC is staged using the TNM-classification as proposed by the International Association for the Study of Lung Cancer (IASLC)[5]. With the TNM-classification, tumors are classified based on size and extension (T), spread to regional lymph nodes (N) and the presence of distant metastases (M). This classification divides patient into different stages, which provide information on prognosis and appropriate treatment options. In 2010, the updated 7th edition of the TNM-classification came into effect. With this new edition, some changes were made in the classification, as shown in table 1 and 2[6]. Currently, about 15% of NSCLC are diagnosed at stage I[2]. Historically, the best outcome has been reported for this stage, with 5 year overall survival of 50-70%[5].

Recently, the results of the National Lung Screening Trial were published[7]. A total of 54.454 participants, aged between 55 and 74 years, who had a history of at least 30 pack years and, if former smokers, had quit in the previous 15 years, were randomly assigned to undergo three annual screenings with either low-dose CT scans or chest radiography. In the persons screened with CT scans a relative reduction of lung cancer mortality of 20.0% was observed. Guidelines in the United States now recommend lung cancer screening for adults who are at high risk for lung cancer, defined as persons 55 to 74 years of age with a minimum smoking history of ≥ 30 pack-years, who currently smoke or have quit in the past 15 years and who are in relatively good health[8,9]. The NELSON study (Nederlands Leuvens Longkanker Screenings Onderzoek) is designed to study the benefits for lung cancer screening in the Dutch and Belgian populations, and results are expected shortly[10]. A subsequent pooled analysis of European CT-screening studies will further clarify the role of CT-screening for early stage NSCLC in Europe. In the National Lung Screening Trial, 55% of lung cancers were diagnosed at stage I as compared to 15% of lung cancers detected outside screening studies[2,11]. Therefore with lung cancer screening the proportion of lung cancers diagnosed at an earlier stage is likely to increase in the future.

Table 1: *Changes in the 7th edition of the TNM-classification*

Changes in TNM-classification 7th edition			
T	T1	≤2 cm	➔ T1a
		>2 cm but ≤ 3 cm	➔ T1b
	T2	>3 cm but ≤5 cm	➔ T2a
		>5 cm but ≤7 cm	➔ T2b
		>7 cm	➔ T3
	T4	Nodules in same lobe	➔ T3
		Malignant pleural or pericardial effusion	➔ M1a
N		No changes	
M	M1	Nodules in ipsilateral lobe	➔ T4
	M1	Contralateral nodules / pleural dissemination	➔ M1a
	M1	Distant metastasis	➔ M1b

Table 2*: Staging in the 7th edition of the TNM-classification*

TNM 7th edition - staging Stage	T	N	M
IA	1a-1b	0	0
IB	2a	0	0
IIA	2b	0	0
	1a-2a	1	0
IIB	2b	1	0
	3	0	0
IIIA	1a-2b	1	0
	3	1-2	0
	4	0-1	0
IIIB	4	2	0
	1-4	3	0
IV	1-4	0-3	1a-1b

The guideline-recommended treatment for early stage (stage I-II) NSCLC is an anatomical surgical resection, preferably a lobectomy[12,13]. The evidence supporting use of surgery is mainly based on long-term experience and observational studies[13]. The 30- and 90-day mortality rates after surgery vary widely between multicenter randomized controlled trials with rates of between <2% and 3%, and Dutch national registries with rates of between 5.4% and 9.3%, respectively[14]. Furthermore, several studies on surgery for patients with early stage NSCLC have reported diminished health-related quality of life in the first 6 months after surgery in patients aged 70 years or over, with a failure to return to baseline quality of life levels, especially in patients with poorer pre-treatment quality of life[15–17].

As smoking and age are the major risk factors for development of NSCLC, many patients have co-morbidities that are tobacco-related[18]. These patients undergoing surgery for early stage NSCLC experience excess mortality in follow-up, probably related to these co-morbidities. This excess mortality can be expressed using conditional survival, which estimates the likelihood of further survival for patients who have already survived for a certain duration after treatment as compared to the general population. For all patients treated with surgery for stage I NSCLC, conditional survival was <80%, but for patients aged 60 years or older, it does it not exceed 70%. Even at 10 years after treatment, patients continue to experience excess mortality as compared to the general population[19,20]. Due to the above mentioned co-morbidities in patients diagnosed with early stage NSCLC and risks associated with surgical resection, many elderly patients do not undergo surgical resection. In the Netherlands, only 15% of patients aged 80 years or older undergo surgery as compared to 88% in patients aged 50-64 years and 67% of patients aged 65-79[18]. Until recently, the only potentially curative alternative to surgical resection was conventional radiotherapy, with daily treatment required for several weeks, and with only modest improvement of survival[21]. Consequently, many elderly inoperable patients with early stage NSCLC were left untreated[22].

Technological advances have facilitated the use of stereotactic ablative radiotherapy (SABR) for extracranial tumors. SABR involves the delivery of a high dose of radiation to precisely target the tumor, while minimizing doses to surrounding healthy tissues[23]. With SABR, doses between 50 and 60 Gy can be delivered in a limited number of fractions, compared to usually around 30 fractions used in conventional radiotherapy. This hypofractionation greatly increases the biological effective dose compared to that of conventional radiotherapy. No randomized controlled trials have been published comparing SABR with conventional radiotherapy. However, the limited studies directly comparing both treatments suggest a survival advantage of SABR over conventional radiotherapy[24,25].

Studies on the results of SABR are traditionally published on medically inoperable patients who are no candidates for the standard surgical treatment. However, even in these frail patients, excellent outcomes have been achieved. As a biologically effective dose (BED) of >100Gy_{10} has been shown to be associated with local control rates of 90% or more, guidelines of the European Society of Medical Oncology recommended the use of a BED of >100Gy_{10}[12,26,27]. Furthermore, treatment related toxicity is usually mild, with most studies reporting late toxicities ≥grade 3 in less than 10% of patients[28]. With good results reported in medically inoperable patients, SABR is increasingly being evaluated as an option in patients with operable early stage NSCLC. Three randomized controlled trials were set up in order to compare SABR to either lobectomy or sublobar resection in these patients, however all three trials closed prematurely due to poor accrual[29]. In the absence of evidence from randomized controlled trials, many questions still exist on the role SABR can play for operable patients or so-called ‘borderline’ operable patients who are at high risk for complications following surgery.

Outline of this thesis

Chapter 2 and 3 provide an overview of recent advances in radiotherapy and highlight the role of SABR in the treatment of medically inoperable patients with early stage NSCLC. An important difference between surgery and SABR is that a pathological diagnosis is always available after surgery, while this may not be the case with SABR. Although the risk of benign disease in the Netherlands is small in patients staged with ^{18}FDG PET- and CT-scans, questions have been raised whether results published in SABR patients have been inflated by the inclusion of patients with benign disease. In **Chapter 4**, we analyzed patients treated with SABR either with or without pathological confirmation of malignancy, to investigate whether or not it is likely that SABR results are biased by the inclusion of benign lesions. In **Chapter 5**, we investigated the outcomes of SABR in operable patients by retrospectively identifying patients who were potentially operable.

Propensity score matching allows the creation of groups with similar baseline characteristics, such as age and co-morbidity index. In **Chapter 6** and **7** this type of matching is used to compare outcomes in patients with early stage NSCLC treated with either SABR or lobectomy.

It is increasingly believed that patients should play an active role in their health care, so called shared-decision making[30,31]. With this increased patient engagement, objective and good quality health care information on treatment choices plays a vital role. In **Chapter 8,** we investigated the quality of online health care information on SABR in several countries. Nowadays, more fit patients undergo SABR. Therefor more emphasis is placed on follow-up after treatment, as these patients will have longer survival as they have less competing causes of mortality. Furthermore, patients might be eligible for salvage for recurrences or second primary lung cancers. In **Chapter 9** we analyze local recurrences and second primary lung cancers in patients treated with SABR in order to help determine optimal follow-up post SABR. In **Chapter 10** we describe the feasibility of salvage surgery in patients who were initially treated with SABR for early stage NSCLC and who experienced local recurrence.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9-29.
2. SEER Cancer Statistics. 2015. Available at: www.seer.cancer.gov.
3. WHO mortality estimates. 2015. Available at: www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html
4. Integraal Kankercentrum Nederland. 2015. Available at: www.iknl.nl
5. Goldstraw P, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revision of the TNM Stage Groupings in the Forthcoming (Seventh) Edition of the TNM Classification of Malignant Tumour. J Thorac Oncol. 2009;2(8):706-714.
6. Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. Chest. 2009;136(1):260-271.
7. Aberle D, Adams A, Berg C. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395-409.
8. Wender R, Fontham ETH, Barrera E, et al. American Cancer Society lung cancer screening guidelines. CA Cancer J Clin. 2013;63(2):107-117.
9. Roberts H, Walker-Dilks C, Sivjee K, et al. Screening High-Risk Populations for Lung Cancer: Guideline Recommendations. J Thorac Oncol. 2013;8(10):1232-1237.
10. Nederlands Trial Register. 2015. Available at www.trialregister.nl
11. Church TR, Black WC, Aberle DR, et al. Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med. 2013;368(21):1980-1991.
12. Vansteenkiste J, Crinò L, Dooms C, et al. 2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. Ann Oncol. 2014;25(8):1462-1474.
13. Scott WJ, Howington J, Feigenberg S, et al. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007;132(3 Suppl):234S - 242S.
14. Senthi S, Senan S. Surgery for early-stage lung cancer: post-operative 30-day versus 90-day mortality and patient-centred care. Eur J Cancer. 2014;50(3):675-677.
15. Fernando HC, Landreneau RJ, Mandrekar SJ, et al. Analysis of longitudinal quality-of-life data in high-risk operable patients with lung cancer: Results from the ACOSOG Z4032 (Alliance) multicenter randomized trial. J Thorac Cardiovasc Surg. 2014;4032.
16. Schulte T, Schniewind B, Walter J, et al. Age-related impairment of quality of life after lung resection for non-small cell lung cancer. Lung Cancer. 2010;68(1):115-120.
17. Poghosyan H, Sheldon LK, Leveille SG, Cooley ME. Health-related quality of life after surgical treatment in patients with non-small cell lung cancer: a systematic review. Lung Cancer. 2013;81(1):11-26.
18. Janssen-Heijnen MLG, Maas HAAM, Houterman S, et al. Comorbidity in older surgical cancer

patients: influence on patient care and outcome. Eur J Cancer. 2007;43(15):2179-2193.

19. Janssen-Heijnen ML, van Steenbergen LN, Steyerberg E, et al. Long-term excess mortality for survivors of non-small cell lung cancer in the Netherlands. J Thorac Oncol. 2012;7(3):496-502.
20. Palma D and Senan S. Improving outcomes of high-risk patients with early stage non small-cell lung cancer: insights from population based data and the role of stereotactic ablative radiotherapy. Clin Lung Cancer. 2013;14(1):1-5.
21. Wisnivesky JP, Halm E, Bonomi M, et al. Effectiviness of radiation therapy for elderly patients with unresected stage I and II non-small cell lung cancer. Am J Respir Crit Care Med. 2010;181(3):264-269.
22. Palma D, Visser O, Lagerwaard FJ, et al. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non–small-cell lung cancer: A population-based time-trend analysis. J Clin Oncol 2010;28(35):5153-5159.
23. Haasbeek CJA, Slotman BJ, Senan S. Radiotherapy for lung cancer: clinical impact of recent technical advances. Lung Cancer. 2009;64(1):1-8.
24. Shirvani SM, Jiang J, Chang JY, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. Int J Radiat Oncol Biol Phys. 2012;84(5):1060-1070.
25. Koshy M, Malik R, Mahmood U, et al. Stereotactic body radiotherapy and treatment at a high volume facility is associated with improved survival in patients with inoperable stage I non-small cell lung cancer. Radiother Oncol. 2015;114(2):148-54
26. Zhang J, Yang F, Li B, et al. Which is the optimal biologically effective dose of stereotactic body radiotherapy for Stage I non-small-cell lung cancer? A meta-analysis. Int J Radiat Oncol Biol Phys. 2011;81(4):e305-e316.
27. Olsen JR, Robinson CG, El Naqa I, et al. Dose-response for stereotactic body radiotherapy in early-stage non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2011;81(4):e299-e303.
28. Chi A, Liao Z, Nguyen NP, et al. Systemic review of the patterns of failure following stereotactic body radiation therapy in early-stage non-small-cell lung cancer: clinical implications. Radiother Oncol. 2010;94(1):1-11.
29. Louie A V, Senthi S, Palma DA. Surgery versus SABR for NSCLC. Lancet Oncol. 2013;14(12):e491.
30. The Salzburg Statement on Shared Decision Making. Br Med J. 2011;342:d1745
31. Lawler M, Le Chevalier T, Murphy MJ, et al. A Catalyst for Change : The European Cancer Patient ’ s Bill of Rights. Oncologist. 2014;19(3):217-224.